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Phase II study of the safety and efficacy of the anti-PD-1 antibody balstilimab in patients with recurrent and/or metastatic cervical cancer

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HIGHLIGHTS

- Balstilimab elicited promising and durable clinical activity in patients with recurrent/metastatic cervical cancer.
- Tumor responses occurred irrespective of tumor PD-L1 status or histology.
- Balstilimab is well tolerated, with a safety profile consistent with other PD-1 inhibitors.
- These findings highlight balstilimab as an attractive candidate for both single-agent and combination-based immunotherapy.

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ABSTRACT

Objective. This phase II clinical trial evaluated the safety and antitumor activity of balstilimab, an anti-PD-1 antibody, in patients with previously-treated, recurrent/metastatic cervical cancer.

Methods. Eligible patients were 18 years or older with recurrent and/or metastatic cervical cancer and who had relapsed after a prior platinum-based treatment regimen for advanced disease. Balstilimab was administered intravenously at 3 mg/kg once every two weeks, for up to 24 months. The primary endpoint was objective response rate (ORR, RECIST v1.1) as assessed by an independent review committee.

Results. At data cutoff, 161 women (median age, 53 years [range 25–81]) were enrolled and treated with balstilimab. Of these, 140 had measurable disease at baseline and one prior line of platinum-based therapy in the metastatic, persistent, or recurrent setting; these patients were included in the efficacy analyses. The ORR was 15% (95% CI, 10.0%–21.8%) and included 5 patients with a complete response and 16 with a partial response. The median duration of response was 15.4 months. In patients with PD-L1-positive tumors the ORR was 20%,

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however patients with PD-L1-negative tumors also responded to balstilimab (ORR, 7.9%). Responses were not restricted to tumors of squamous cell histology, and an ORR of 12.5% was seen in the subset of patients with cervical adenocarcinoma. The disease control rate was 49.3% (95% CI, 41.1%–57.5%). Immune-mediated enterocolitis (3.1%) and diarrhea (1.9%) were the most common grade 3 or higher treatment-related adverse events.

Conclusion. Balstilimab demonstrated meaningful and durable clinical activity, with manageable safety, in patients with previously-treated, recurrent/metastatic cervical cancer.

1. Introduction

Cervical cancer is the most common female genital tract malignancy and fourth leading cause of cancer mortality in women worldwide [1], responsible for more than 311,000 deaths annually. The prognosis for patients diagnosed with recurrent and/or metastatic disease is particularly poor, as evidenced by a 5-year overall survival (OS) rate of 17% [2]. Beyond palliative platinum-based chemotherapy, treatment options for these patients are limited and typically administered without expectation of cure. Further, optimal second-line and later regimens for the management of advanced, relapsed disease are yet to be established [3].

In this regard, agents that target the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoint pathway have emerged as promising candidates for altering the cervical cancer therapeutic landscape [4–6]. Since 2015, multiple clinical trials evaluating the potential utility of PD-1/PD-L1 antibodies for cervical cancer treatment have been conducted, and numerous others are ongoing [6]. To date, only the anti-PD-1 antibody pembrolizumab has received accelerated approval by the US Food and Drug Administration for the treatment of patients with PD-L1-positive, recurrent/metastatic cervical cancer following disease progression on or after chemotherapy. Approval was based on the results of the phase 2 KEYNOTE-158 study, in which pembrolizumab monotherapy yielded an objective response rate (ORR) of 14.3% with the median duration of response not reached (median follow-up of 10.2 months) in a PD-L1-positive cohort of 77 patients with previously treated cervical cancer [7]. While these efficacy outcomes appear relatively modest, both parameters were similar or superior to those observed with other available treatment options in the same setting [3]. This observation underscores the significant unmet clinical need for this group of patients, for whom alternative and effective treatments are urgently needed.

Balstilimab (AGEN2034) is an investigational, fully human monoclonal antibody that binds with high affinity to PD-1, designed to prevent the interaction between this receptor and its ligands PD-L1 and PD-L2 [8]. By functioning as a PD-1 antagonist, balstilimab enhances T-cell receptor (TCR) signaling and T-cell responsiveness under conditions of TCR stimulation. Here we present results of a phase II single-arm trial designed to assess the safety and efficacy of balstilimab monotherapy for patients with recurrent and/or metastatic cervical cancer who had relapsed after a prior platinum-based treatment regimen.

2. Methods

2.1. Patients

Eligible patients had a pathologically confirmed diagnosis of squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix, with metastatic, persistent, or recurrent disease at the time of enrollment. Patients were required to have at least one lesion measurable by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [9], and disease that had relapsed after a first line, platinum-based treatment regimen (subjects who received chemotherapy concurrently with primary radiation, or adjuvant chemotherapy following completion of radiation therapy and progressed within 6 months, were permitted to enroll). Patients were included regardless of PD-L1 expression status at baseline, which was analyzed in archival tumor biopsy specimens using the validated PD-L1 IHC 22C3 pharmDx assay at a central laboratory. Patients were additionally required to be ≥18 years of age; have an Eastern Cooperative Oncology Group performance status score of 0 or 1; and have adequate hematologic, renal, and hepatic function. Key exclusion criteria included prior immune checkpoint inhibitor therapy; known hypersensitivity to humanized monoclonal antibodies; or >1 systemic treatment regimen for advanced cervical cancer. All patients provided written informed consent in accordance with federal, local, and institutional guidelines.

2.2. Study design and treatment

This was an open-label, single-arm, global phase II clinical trial conducted at 60 sites throughout the United States, Europe, South America, and Australia. Patients were enrolled from November 20, 2017 to April 16, 2020 and received intravenous balstilimab at a dose of 3 mg/kg once every two weeks, given as a 60-min infusion. This dose was the recommended phase II dose determined by a run-in, phase I dose-escalation stage [10]. Treatment was permitted for up to 24 months, or until disease progression, intolerable toxicity, or investigator/patient decision. The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. The trial is registered at ClinicalTrials.gov (NCT03104699).

2.3. Endpoints and assessments

The primary efficacy endpoint was objective response rate (ORR), assessed by an independent endpoint review committee, according to RECIST version 1.1. To evaluate tumor response, computerized tomography or magnetic resonance imaging was performed at baseline and every 6 weeks on-study. Secondary efficacy outcomes included duration of response (DOR) and disease control rate (DCR). The additional secondary end points of progression-free survival (PFS) and overall survival (OS) will be reported elsewhere. The association of PD-L1 expression (positivity defined by a combined positive score [CPS] ≥1%) with clinical response was an exploratory endpoint.

Safety and tolerability were primary safety endpoints. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 and monitored continuously from the time of the first study dose until 28 days after the last dose of study drug or 10 weeks after the last dose if an adverse event was present. Immune-related adverse events (irAEs) were adverse events of special interest considered to have immune-mediated mechanisms of action, including infusion-related reactions.

2.4. Statistical considerations

The aim of this phase II study was to detect preliminary evidence of clinical activity for balstilimab in patients with metastatic cervical cancer. For this analysis, the data cutoff date was February 11, 2021. The primary end point of ORR was estimated as the binomial proportion of best overall response of a confirmed partial response (PR) or complete response (CR) and reported with two sided, 95% Wilson score confidence interval (CI). Trial enrollment was planned for approximately 150

subjects; at this sample size, the power to exclude an ORR of 5% by the lower limit of the 95% Wilson score interval was 92.2% and 96.2%, assuming a true ORR of 12% and 13%, respectively. The sample size also provided ≥77% probability to observe an AE with an underlying rate of ≥1%. Descriptive statistics were used to summarize trial results, i.e., statistics for continuous variables included medians and ranges and categorical variables were summarized by counts and percentages. DOR and duration of stable disease were analyzed using Kaplan-Meier estimates.

3. Results

3.1. Patients

Between November 20, 2017 and April 16, 2020, a total of 161 patients were enrolled and received treatment with balstilimab, thus comprising the safety population (Fig. 1). Baseline demographic and disease characteristics are summarized in Table 1. The median age was 53 years (range, 25–81) and over half had an ECOG performance status of 1 (52.2%). The distribution of cervical cancer histology was squamous cell carcinoma (62.7%), adenocarcinoma (32.3%), and adenosquamous carcinoma (4.3%). All individuals had prior platinum exposure and 47 (29.2%) had received bevacizumab as part of a previous therapeutic regimen. Ninety-nine patients (61.5%) had PD-L1-positive tumors (CPS ≥1%) and 43 (26.7%) were determined to be PD-L1-negative; the remainder of cases (11.8%) were either not evaluable or tissue was not available. Of the patients deemed PD-L1-positive, 23 (23.2%) had prior bevacizumab treatment. The median duration of follow-up (time on study from first dose to data cutoff) was 14.6 months (range, 9.9–38.8).

Table 1
Patient demographics and baseline characteristics.

Characteristic	$n = 161$
Age, years	
Median (range)	53 (25–81)
ECOG PS, *n* (%)	
0	76 (47.2)
1	84 (52.2)
2	1 (0.6)
Tumor histology, *n* (%)	
Squamous	101 (62.7)
Adenocarcinoma	52 (32.3)
Adenosquamous	7 (4.3)
Other[a]	1 (0.6)
PD-L1 tumor expression status, *n* (%)	
Positive (CPS ≥1%)	99 (61.5)
Negative (CPS <1%)	43 (26.7)
Unknown[b]	19 (11.8)
Prior therapy exposure, *n* (%)	
Platinum	161 (100.0)
Bevacizumab	47 (29.2)

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1.
[a] Poorly differentiated carcinoma with extensive necrosis.
[b] PD-L1 status not determined due to missing/insufficient biopsy tissue for analysis or samples were non-evaluable.

3.2. Clinical activity

Of the 160 patients enrolled with measurable disease at baseline, 20 subjects had received only front-line chemoradiotherapy (CRT) for locally advanced cervical cancer (with or without neoadjuvant/adjuvant chemotherapy) and progressed within 6 months prior to enrollment. Baseline characteristics and outcomes for this patient subset are listed in Supplementary Tables S1 and S2. The remaining 140 patients had received one prior line of platinum-based therapy for the metastatic, persistent, or recurrent disease (Fig. 1). This defined population of patients who had relapsed after a platinum-based treatment regimen in the recurrent/metastatic disease setting was evaluated as part of the efficacy analyses.

The confirmed ORR in these patients, as assessed by RECIST v1.1 per independent central review, was 15% (95% CI, 10.0–21.8) and included 5 complete responses (3.6%) and 16 partial responses (11.4%) (Table 2). A summary of histological breakdown, treatment history, target lesion site, and PD-L1 status in patients with a best overall response of CR or PR is provided in Supplementary Table S3. Fig. 2A plots changes in target lesion burden for these patients as a function of time, with individuals grouped according to confirmed tumor response. Responses were

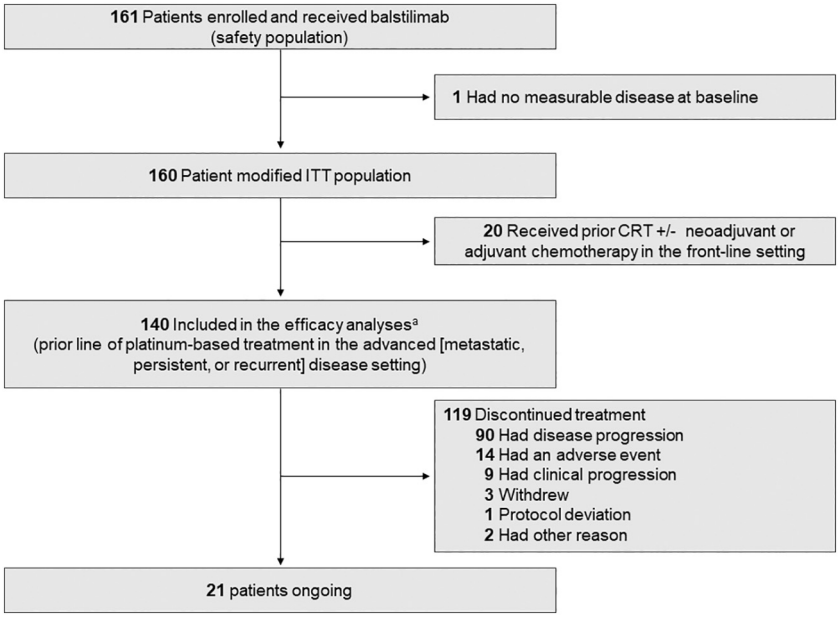

Fig. 1. Patient enrollment and disposition. [a] Patients who received ≥1 dose of study treatment, with measurable disease at baseline, and had prior line of platinum-based treatment in the metastatic, persistent, or recurrent setting (per Independent Review Committee).

Table 2
Objective response rate, disease control, and durability.

Characteristic	$n = 140$
Confirmed objective response rate, *n* (%)	21 (15.0)
95% CI	(10.0–21.8)
Best overall response, *n* (%)	
Complete response	5 (3.6)
Partial response	16 (11.4)
Stable disease	51 (36.4)
Progressive disease	56 (40.0)
Not available/evaluable[a]	12 (8.6)
Disease control rate, *n* (%)[b]	69 (49.3)
95% CI	(41.1–57.5)
Duration of response, (median) months[c]	15.4
95% CI	(5.7 – NR)
Estimated rate of response duration, %[c,d]	
≥6 mo	73.7 (12)
≥9 mo	54.6 (8)
≥12 mo	54.6 (6)
Objective response rate by PD-L1 status, *n* (%)	
Positive ($n = 85$)	17 (20.0)
Negative ($n = 38$)	3 (7.9)
Unknown ($n = 17$)[e]	1 (5.9)
Objective response rate by histology, *n* (%)	
Squamous ($n = 85$)	15 (17.6)
Adenocarcinoma ($n = 48$)	6 (12.5)

NR, not reached.
[a] Post-baseline imaging data not available or tumor measurements not adequate for best overall response evaluation.
[b] Defined as proportion of patients with a confirmed complete or partial response, or stable disease without progression for at least 12 weeks.
[c] Provided for responders only ($n = 21$).
[d] Presented as % ongoing responses (number of patients at risk).
[e] PD-L1 status not determined due to missing/insufficient biopsy tissue for analysis or samples were non-evaluable.

durable, with an observed median duration of response of 15.4 months (95% CI, 5.7 months, not reached). In patients who responded, the median time to response was 2.7 months (95% CI, 2.0–3.9). Overall, the disease control rate (defined as proportion of patients with a confirmed complete or partial response, or stable disease without progression for at least 12 weeks) was 49.3% (95% CI, 41.1–57.5). Fig. 2B plots the best percentage change from baseline in target lesion size for all patients in the efficacy evaluable population. At the time of analyses, 21 patients remained on treatment (Fig. 1).

In the subset of patients with PD-L1-positive tumors ($n = 85$) the ORR was 20.0% (95% CI, 12.9–29.7, with duration of response not reached), and confirmed responses to balstilimab were also seen in subjects who were PD-L1-negative (3/38, 7.9%) (Table 2). Responses were observed across histologic subtypes, including tumor responses that occurred in 12.5% of patients with cervical adenocarcinomas (6/48). Of note, twenty adenocarcinoma patients (41.7%) were PD-L1 positive; this compared to 62/85 (72.9%) patients with PD-L1-positive, squamous cell carcinoma tumors. Forty-seven efficacy-evaluable patients (33.6%) had received prior bevacizumab treatment; responses were seen in five of these subjects (one complete and four partial responders) for an ORR of 10.6% (Supplementary Table S4).

3.3. Safety

The most common treatment-related AEs (TRAEs) of any grade were asthenia (23%), diarrhea (12.4%), pruritis (11.8%), and fatigue (10.6%) (Table 3), the majority of which were grade 1 or 2. The incidence of ≥ grade 3 TRAEs was 11.8%, with immune-mediated enterocolitis the most frequently reported at 3.1% (five patients). A total of 12 patients (7.5%) experienced at least one serious TRAE, and immune-mediated enterocolitis again accounted for the most common event. TRAEs leading to dose interruptions or discontinuations occurred in 23 (14.3%) and 7 (4.3%) patients, respectively. Immune-mediated pneumonitis was the leading cause of treatment discontinuation (3 patients). One death deemed possibly related to treatment occurred on study in a 37-year-old patient who died 41 days after her final dose of balstilimab of an unknown cause as she had been lost to follow-up.

Treatment-related irAEs were observed in 53 patients (32.9%), and most frequently included hypothyroidism (11 patients, 6.8%), hyperthyroidism (6 patients, 3.7%), diarrhea, immune-mediated pneumonitis, and immune-mediated enterocolitis (each 5 patients, 3.1%). Other irAEs that occurred in 3 or more patients were arthralgia and pyrexia (1.9%) (Table 3). These adverse events were generally managed with appropriate supportive care (including replacement therapy), corticosteroids, or withholding treatment. The only infusion-related reactions seen were individual cases of grade 1 pyrexia or grade 1 flushing.

4. Discussion

Balstilimab monotherapy elicited promising clinical activity in patients with previously-treated, advanced cervical cancer in this study which, to our knowledge, represents the largest phase II trial to date of a PD-1 inhibitor conducted in this high-need patient population. In the full efficacy-evaluable cohort the primary end point of ORR was 15%, including five patients (3.6%) who experienced a confirmed complete response; in the subset of PD-L1-positive patients the ORR was 20%. Responses were durable, as evidenced by a median DOR of 15.4 months. With the caveat that cross-trial comparisons can be challenging, it is informative to consider these outcomes with results for other PD-1 inhibitors in similar patient populations. Accelerated approval of pembrolizumab in the second-line metastatic setting was based on the results of the KEYNOTE-158 trial where an overall ORR of 12.2% was seen; however responses only occurred in subjects with PD-L1-positive tumors, resulting in an ORR in this subpopulation of 14.6% (14.3% in the cohort of patients who had received prior chemotherapy) [7]. In the earlier KEYNOTE-028 phase Ib study that evaluated pembrolizumab in patients of similar eligibility ($n = 24$, all PD-L1-positive), an ORR of 17% was observed due to four subjects achieving a partial response [11]. Here we report confirmed responses in patients receiving balstilimab who were PD-L1 negative, suggesting possible functional differentiation from pembrolizumab and potential opportunity to provide clinical benefit to a greater proportion of cervical cancer patients.

Nivolumab is a fully human immunoglobulin G4 anti-PD-1 antibody, similar to balstilimab, and is approved for the treatment of a variety of cancers including melanoma and non-small cell lung cancer [12]. Recently, the results of two trials of nivolumab in small number cohorts of patients with recurrent/metastatic cervical cancer have been reported. As part of the CHECKMATE 358 study, an ORR of 26.3% was observed in a cohort of 19 patients with previously treated, recurrent/metastatic disease [13]. At the time of analysis, the DOR had not been reached (median duration of follow up of 19.2 months). However, in a separate phase II study of nivolumab in 24 patients with cervical cancer (NRG-GY002) only one partial response was seen, resulting in an ORR of just 4% [14]. Of note, the patient population of NRG-GY002 was comparable to the current study, with all subjects having received one prior systemic chemotherapeutic regimen for the management of persistent, recurrent, or metastatic disease. The reasons for the marked differences in nivolumab activity between the two trials is unclear. One potential contributing factor may be related to the histological composition of each trial. CHECKMATE 358 evaluated only patients with squamous cell carcinoma (i.e. those patients more likely to respond), while NRG-GY002 enrolled patients with squamous cell carcinoma, adenocarcinoma, and adenosquamous tumors (60%, 24%, 16%, respectively). Similar to the balstilimab study presented here, the NRG-GY002 patient population is more representative of the true distribution of cervical cancer histologies. However, without a prospective randomized comparison, this is hypothesis driven.

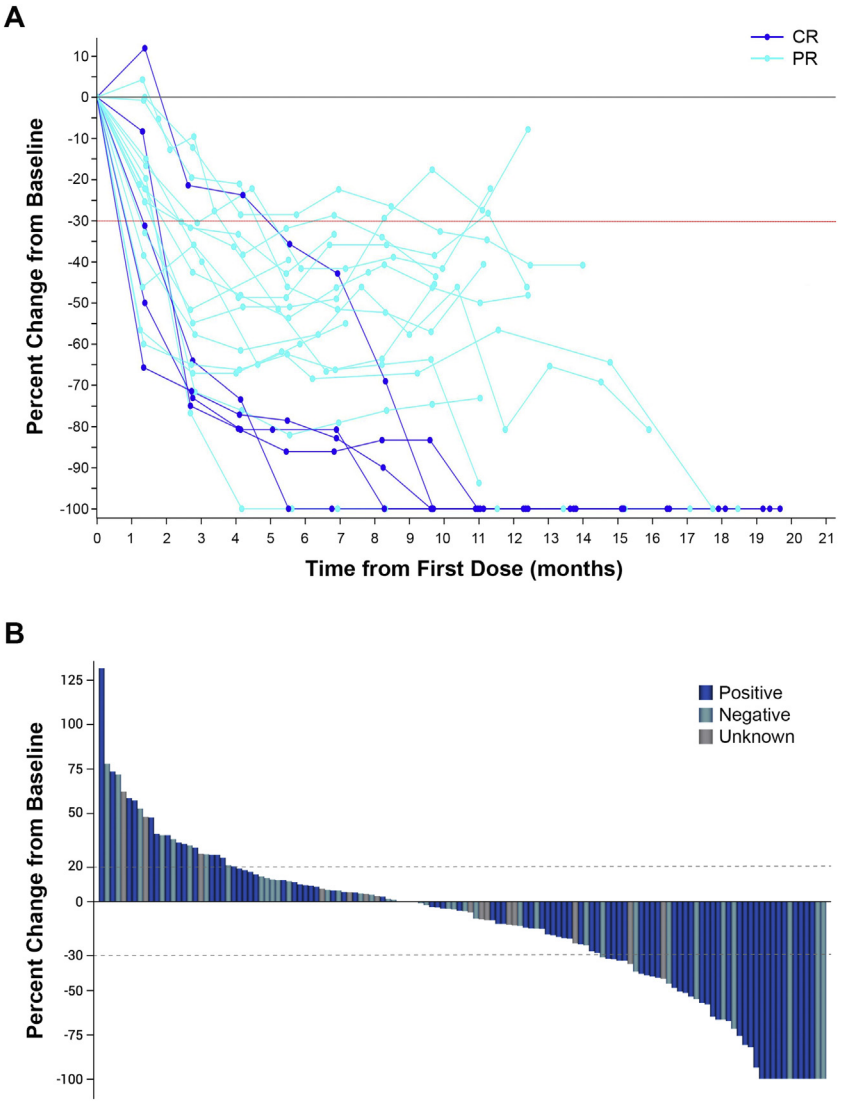

Fig. 2. (A) Percentage change in target lesion RECIST sum over time in patients with confirmed responses to balstilimab treatment. Dashed red line corresponds to 30% decrease in tumor size. (B) Best percentage change in target lesion size from baseline in the efficacy-evaluable patient population; PD-L1 status is indicated by color coding of bars. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In this regard, an intriguing finding of the present study was that balstilimab treatment induced a 12.5% response rate in patients whose tumors were of adenocarcinoma origin. The reason(s) for the activity of balstilimab in adenocarcinoma remain to be determined, but it is known that differences exist in the immunological microenvironments and tumor escape mechanisms between cervical adenocarcinoma and squamous cell carcinoma [3]. For example, and as was the case for the patient population evaluated in this study, PD-L1 is more frequently expressed by squamous-type tumors compared with adenocarcinoma [15,16]. In addition, and in contrast to squamous cell carcinomas, the presence of PD-L1-positive tumor-associated macrophages in adenocarcinoma tumors is associated with poorer disease-specific survival [16]. The relative incidence of cervical adenocarcinoma has increased over the past few decades, with the advent of long-term and widespread screening leading to the removal of more slow-growing squamous lesions [17]. Moreover, the stagnant survival rates seen in cervical cancer have been suggested, beyond the lack of major treatment advances, to in part reflect the increasing proportion of adenocarcinoma histology cases [18]. In light of these considerations, extending the therapeutic reach of immune checkpoint blockade beyond the squamous cell histotype has potentially broad clinical implications for this disease.

Balstilimab was well tolerated, with a manageable safety profile that is consistent with that of other approved agents of the PD-1 inhibitor class [19]. TRAES of grade 3 or higher occurred in 11.8% of patients, with one patient death considered possibly attributable to treatment although it occurred while the patient was lost to follow-up. The irAEs seen in the study were typical of checkpoint inhibitor therapies, which have also previously been associated with hypothyroidism, diarrhea, pneumonitis, and enterocolitis [20–26]. Further, balstilimab administration was characterized by a very low frequency of infusion-related reactions. The adverse event profile of balstilimab is both differentiated from, and compares favorably with, chemotherapies used in this patient population [3,27,28].

In conclusion, balstilimab monotherapy was associated with promising, durable clinical activity in patients with advanced cervical cancer who had progressed after prior platinum-based therapy in the setting of recurrent/metastatic disease. Notably, tumor responses occurred irrespective of tumor PD-L1 status or histology. Along with a favorable tolerability profile, balstilimab thus represents an attractive candidate for use as a backbone in combination-based therapeutic approaches. Accordingly, an ongoing phase 2 study of balstilimab in combination with the novel cytotoxic T-lymphocyte-associated protein 4 inhibitor

Table 3
Treatment-related adverse events in the safety population.

Event	$n = 161$
Any TRAE, *n* (%)[a]	115 (71.4)
Asthenia	37 (23.0)
Diarrhea	20 (12.4)
Pruritis	19 (11.8)
Fatigue	17 (10.6)
Grade ≥ 3 TRAE, *n* (%)[b]	19 (11.8)
Immune-mediated enterocolitis	5 (3.1)
Diarrhea	3 (1.9)
Hypokalemia	2 (1.2)
Anemia	2 (1.2)
Treatment-related SAE, *n* (%)	12 (7.5)
Treatment-related irAEs, *n* (%)[c]	53 (32.9)
Hypothyroidism[d]	11 (6.8)
Hyperthyroidism	6 (3.7)
Diarrhea	5 (3.1)
Immune-mediated pneumonitis[e]	5 (3.1)
Immune-mediated enterocolitis	5 (3.1)
Arthralgia	3 (1.9)
Pyrexia	3 (1.9)
TRAE leading to dose interruption, *n* (%)	23 (14.3)
TRAE leading to dose discontinuation, *n* (%)	7 (4.3)

irAE, immune-related adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event.
[a] Individual adverse events with incidence ≥10% are reported.
[b] Individual grade 3/4 adverse events occurring in 2 or more patients are reported.
[c] Investigator-assessed events occurring in 3 or more patients are reported.
[d] Includes related terms of hypothyroidism and immune-mediated hypothyroidism.
[e] Includes related terms of pneumonitis, immune-mediated pneumonitis, and interstitial lung disease.

zalifrelimab (NCT03495882) is assessing the feasibility of dual immune checkpoint blockade for further improving outcomes in this patient population.

Author contributions

Conceptualization: DMO, AO, BJM, KNM, LMR, IRC.
Data curation: DMO, AO, FS, CR, LG, DB, AL, KNM, MDPED, ACHB, JA, CPO, CRdA, LMR, IRC.
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Supervision: DMO, WOF, IRQ.
Writing - original draft: DMO, BJM, WOF.
Writing - review & editing: All authors.

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Appendix A. Supplementary data

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