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ORIGINAL ARTICLE

Pembrolizumab plus chemotherapy for advanced and recurrent cervical cancer: final analysis according to bevacizumab use in the randomized KEYNOTE-826 study☆

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Background: In KEYNOTE-826 (NCT03635567), pembrolizumab plus chemotherapy (±bevacizumab) significantly improved overall survival (OS) and progression-free survival (PFS) in patients with persistent, recurrent, or metastatic cervical cancer. This exploratory analysis examined outcomes in patient subgroups defined by bevacizumab use.

Patients and methods: Eligible adult patients had persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix not previously treated with chemotherapy and not amenable to curative treatment; measurable disease per RECIST v1.1; and an Eastern Cooperative Oncology Group performance status ≤1. Patients were randomly allocated 1 : 1 to pembrolizumab 200 mg every 3 weeks or placebo for up to 35 cycles plus chemotherapy (±bevacizumab 15 mg/kg). Dual primary endpoints were OS and PFS per RECIST v1.1 by investigator assessment. Outcomes were assessed in subgroups defined by bevacizumab use. Hazard ratios (HRs) and 95% confidence intervals (CIs) were based on a stratified Cox regression model.

Results: A total of 617 patients were randomly assigned [pembrolizumab arm, $n = 308$ (63.6% with bevacizumab); placebo arm, $n = 309$ (62.5% with bevacizumab)]. The most common reason for bevacizumab exclusion was medical contraindication (75.9%). Among patients who received bevacizumab, HRs (95% CIs) for PFS favored the pembrolizumab arm in the programmed cell death-ligand 1 combined positive score ≥1 [0.56 (0.43-0.73)] and all-comer [0.57 (0.45-0.73)] populations; OS results were 0.60 (0.45-0.79) and 0.61 (0.47-0.80), respectively. Among patients who did not receive bevacizumab, HRs (95% CIs) for PFS also favored the pembrolizumab arm in the programmed cell death-ligand 1 combined positive score ≥1 [0.61 (0.44-0.85)] and all-comer [0.69 (0.50-0.94)] populations; OS results were 0.61 (0.44-0.85) and 0.67 (0.49-0.91), respectively. Among patients who received bevacizumab, grade ≥3 treatment-related adverse events occurred in 74.0% of patients in the pembrolizumab arm and 66.8% in the placebo arm.

Conclusion: Pembrolizumab plus chemotherapy prolonged PFS and OS and had manageable safety compared with placebo plus chemotherapy in patient subgroups defined by bevacizumab use.

Key words: bevacizumab, cervical cancer, chemotherapy, pembrolizumab

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INTRODUCTION

Cervical cancer was the fourth most common cancer among women worldwide in 2020, accounting for 6.5% of all cancers in this population.[1] The burden of cervical cancer is high globally, with ∼604 000 new cases diagnosed and nearly 342 000 deaths occurring in 2020 alone.[1,2] Women with metastatic cervical cancer have a poor prognosis, with a 5-year overall survival (OS) rate of only 19%.[3] Standard of care first-line treatment of patients with persistent, recurrent, or metastatic cervical cancer consists of cisplatin or carboplatin plus paclitaxel, with or without bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor.[4,5] Addition of the anti-programmed cell death protein 1 monoclonal antibody pembrolizumab represents the new standard of care for patients whose tumors express programmed cell death-ligand 1 (PD-L1) with a combined positive score (CPS) ≥1.[4,5] Antiangiogenic agents may enhance the anticancer activity of immunotherapy by normalizing the tumor vasculature, thereby improving T-cell trafficking and reducing vessel-mediated T-cell inactivation, and by interrupting aberrant immune—vascular crosstalk, thereby reducing overall immunosuppression.[6]

Approval of chemotherapy plus bevacizumab was based on results of the phase III GOG 240 study in which the combination significantly improved OS and progression-free survival (PFS) versus chemotherapy alone in patients with recurrent, persistent, or metastatic cervical cancer.[7,8] Although the addition of bevacizumab to chemotherapy did not result in significant deterioration of health-related quality of life in the GOG 240 study,[9] combination therapy was associated with greater toxicity, including a higher incidence of grade 2 hypertension (25% versus 2%; $P < 0.001$), grade ≥3 gastrointestinal fistulas (3% versus 0%; $P = 0.02$), grade ≥3 thromboembolism (8% versus 1%; $P = 0.001$), and grade 4 neutropenia (35% versus 26%; $P = 0.04$),[7] adverse events (AEs) known to be associated with bevacizumab.[10] Therefore, while bevacizumab is considered a preferred first-line regimen for patients with advanced cervical cancer, its use is determined according to local practice, physician discretion, and the presumed benefit/risk profile accounting for clinical contraindications to bevacizumab use.

Approval of the pembrolizumab-containing regimen was based on the phase III KEYNOTE-826 study, which evaluated first-line pembrolizumab plus chemotherapy (±bevacizumab) compared with placebo plus chemotherapy (±bevacizumab) in patients with persistent, recurrent, or metastatic cervical cancer.[11,12] At the first interim analysis, patients in the pembrolizumab arm had significant improvements in PFS and OS in the all-comer population (intention-to-treat) and in patients whose tumors expressed PD-L1 CPS ≥1 or PD-L1 CPS ≥10.[11] The improvements in PFS and OS were maintained at the protocol-specified final analysis of KEYNOTE-826.[12] The addition of pembrolizumab to chemotherapy with or without bevacizumab did not negatively affect health-related quality of life,[13] but was associated with a higher rate of immune-mediated AEs (34.5% versus 16.5% at final analysis).[12] The current exploratory subgroup analysis reports efficacy and safety outcomes from the final analysis of KEYNOTE-826 based on the use of bevacizumab.

METHODS

Study design and patients

KEYNOTE-826 (ClinicalTrials.gov NCT03635567) was a phase III, randomized, double-blind, placebo-controlled trial conducted at 151 sites in 19 countries. Detailed methods were previously published.[11,12] Briefly, eligible patients were women aged ≥18 years who had persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix that had not been treated with systemic chemotherapy and was not amenable to curative treatment (prior radiotherapy and chemoradiotherapy completed ≥2 weeks before randomization was permitted). Patients were also required to have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and an archival tumor tissue sample or newly obtained core or excisional biopsy for prospective determination of PD-L1 status. The study was conducted in accordance with Good Clinical Practice guidelines. The study protocol and all amendments were approved by the institutional review board or ethics committee at each site. All patients provided written informed consent before participating in the study.

Treatment

Eligible patients were randomly allocated 1 : 1 to receive pembrolizumab 200 mg i.v. or placebo once every 3 weeks for up to 35 cycles. All patients also received paclitaxel 175 mg/m^2 plus either cisplatin 50 mg/m^2 or carboplatin area under the concentration-time curve 5 mg/ml/min once every 3 weeks for up to six cycles. Patients with ongoing clinical benefit and who were tolerating chemotherapy could have continued beyond six cycles after consultation with the sponsor. Patients could also have received bevacizumab 15 mg/kg i.v. once every 3 weeks per local practice per investigator decision.

Randomization was stratified by metastatic stage at diagnosis (International Federation of Gynecology and Obstetrics 2009 stage IVB; yes versus no), planned bevacizumab use (yes versus no), and PD-L1 CPS (<1 versus 1-9 versus ≥10). Randomization occurred centrally using an interactive voice response system/integrated web response system. Treatment continued until the maximum number of treatment cycles for each treatment or until confirmed radiographic disease progression, unacceptable toxicity, intercurrent illness, patient withdrawal, or investigator decision. Patients with a confirmed complete response and who had completed eight or more cycles of treatment,

including two or more cycles beyond the initial complete response, may have discontinued treatment at the discretion of the investigator.

Endpoints

The dual primary endpoints in the KEYNOTE-826 study were PFS per RECIST version 1.1, as assessed by the investigator, and OS in the PD-L1 CPS $\geq$1, all-comer, and PD-L1 CPS $\geq$10 populations. Secondary endpoints included in this subgroup analysis were objective response rate (ORR) and duration of response (DOR) per RECIST version 1.1, as assessed by the investigator, and safety.

Assessments

Expression of PD-L1 was assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA) and measured according to the CPS [number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100]. Tumor imaging was carried out every 9 weeks after randomization through week 54 and every 12 weeks thereafter. Survival was assessed every 12 weeks during follow-up. AEs were assessed from the time of randomization through 30 days after the end of treatment (90 days for serious AEs) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

This subgroup analysis was exploratory and not controlled for multiplicity. Treatment outcomes were assessed in patient subgroups defined by bevacizumab use (yes or no). This subgroup analysis only reports efficacy results for the PD-L1 CPS $\geq$1 and all-comer populations as the subgroup sample sizes for the PD-L1 CPS $<$1 and PD-L1 CPS $\geq$10 populations were too small to draw any meaningful conclusions. Safety was assessed in all patients as treated. PFS, OS, and DOR curves were analyzed using the Kaplan–Meier method. For PFS and OS, hazard ratios (HRs) and 95% confidence intervals (CIs) were based on a stratified Cox regression model with Efron's method of tie handling and with treatment as a single covariate. The differences in ORR and their 95% CIs were assessed based on the stratified Miettinen and Nurminen's method.

RESULTS

Patients

A total of 617 patients were randomly allocated between 20 November 2018 and 31 January 2020; 389 (63.0%) received bevacizumab and 228 (37.0%) did not receive bevacizumab (Figure 1). Among the 389 patients who received bevacizumab, 196 were allocated to receive pembrolizumab plus chemotherapy (pembrolizumab arm) and 193 to placebo plus chemotherapy (placebo arm). Among the 228 patients who did not receive bevacizumab, 112 were allocated to the pembrolizumab arm and 116 to the placebo arm. Medical reasons accounted for 75.9% (173/228) of patients not being treated with bevacizumab [risk of gastrointestinal perforation or fistula (34.8% in pembrolizumab arm and 35.3% in placebo arm), hemorrhage (5.4% and 5.2%), new or worsened hypertension (2.7% and 1.7%), or other clinical conditions that may have placed the patient at undue risk (35.7% and 31.0%)]. Patient demographics and baseline clinical characteristics were generally balanced between treatment arms, with small differences in race, ECOG status, and prior therapy in patients who received bevacizumab compared with those who did not receive bevacizumab (Table 1).

Median time from randomization to the data cut-off date [3 October 2022 (final analysis)] was 39.1 months (range,

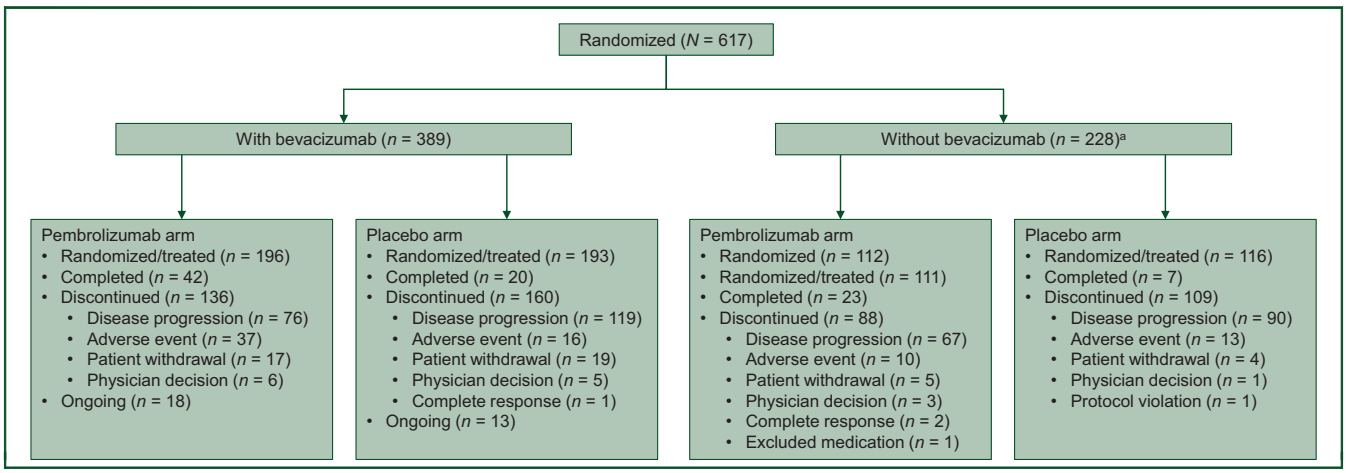

Figure 1. Patient disposition.

[a]In the pembrolizumab arm, patients did not receive bevacizumab for medical reasons (risk of gastrointestinal perforation or fistula, $n = 39$; risk of hemorrhage, $n = 6$; risk of new or worsened hypertension, $n = 3$; other clinical conditions, $n = 40$), nonmedical reasons (not approved for use in country, $n = 2$; not local standard of care, $n = 17$; lack of experience with use for cervical cancer, $n = 1$), and other reasons not specified ($n = 4$). In the placebo arm, patients did not receive bevacizumab for medical reasons (risk of gastrointestinal perforation or fistula, $n = 41$; risk of hemorrhage, $n = 6$; risk of new or worsened hypertension, $n = 2$; other clinical conditions, $n = 36$), nonmedical reasons (not approved for use in country, $n = 4$; not local standard of care, $n = 17$; lack of experience with use for cervical cancer, $n = 3$), and other reasons not specified ($n = 7$).

Table 1. Patient demographics and baseline clinical characteristics in all-comer population

	With bevacizumab			Without bevacizumab		
	Pembrolizumab arm $n = 196$	Placebo arm $n = 193$	Total $n = 389$	Pembrolizumab arm $n = 112$	Placebo arm $n = 116$	Total $n = 228$
Age, median (range), years	51.0 (25-82)	50.0 (22-77)	51.0 (22-82)	52.5 (30-82)	50.0 (31-79)	51.5 (30-82)
Race						
White	103 (52.6)	115 (59.6)	218 (56.0)	67 (59.8)	75 (64.7)	142 (62.3)
Asian	49 (25.0)	37 (19.2)	86 (22.1)	16 (14.3)	8 (6.9)	24 (10.5)
Other	44 (22.4)	41 (21.2)	85 (21.9)	29 (25.9)	33 (28.4)	62 (27.2)
ECOG PS						
0	127 (64.8)	107 (55.4)	234 (60.2)	51 (45.5)	63 (54.3)	114 (50.0)
1	68 (34.7)	86 (44.6)	154 (39.6)	60 (53.6)	53 (45.7)	113 (49.6)
2	1 (0.5)	0	1 (0.3)	0	0	0
Missing	0	0	0	1 (0.9)	0	1 (0.4)
Histologic subtype						
Squamous cell/ squamous cell carcinoma	147 (75.0)	122 (63.2)	269 (69.2)	88 (78.6)	89 (76.7)	177 (77.6)
Adenocarcinoma	37 (18.9)	59 (30.6)	96 (24.7)	19 (17.0)	25 (21.6)	44 (19.3)
Adenosquamous/ both - squamous and adenocarcinoma	11 (5.6)	12 (6.2)	23 (5.9)	4 (3.6)	2 (1.7)	6 (2.6)
Epidermoid carcinoma	0	0	0	1 (0.9)	0	1 (0.4)
Undifferentiated carcinoma	1 (0.5)	0	1 (0.3)	0	0	0
PD-L1 CPS						
<1	21 (10.7)	22 (11.4)	43 (11.1)	14 (12.5)	12 (10.3)	26 (11.4)
1 to <10	74 (37.8)	73 (37.8)	147 (37.8)	41 (36.6)	43 (37.1)	84 (36.8)
≥10	101 (51.5)	98 (50.8)	199 (51.2)	57 (50.9)	61 (52.6)	118 (51.8)
Prior therapy						
Chemoradiation only	80 (40.8)	67 (34.7)	147 (37.8)	45 (40.2)	51 (44.0)	96 (42.1)
Chemoradiation and surgery	30 (15.3)	33 (17.1)	63 (16.2)	19 (17.0)	23 (19.8)	42 (18.4)
Radiation only	19 (9.7)	13 (6.7)	32 (8.2)	12 (10.7)	11 (9.5)	23 (10.1)
Surgery only	21 (10.7)	22 (11.4)	43 (11.1)	2 (1.8)	2 (1.7)	4 (1.8)
Radiation and surgery	13 (6.6)	11 (5.7)	24 (6.2)	9 (8.0)	12 (10.3)	21 (9.2)
None	33 (16.8)	47 (24.4)	80 (20.6)	25 (22.3)	17 (14.7)	42 (18.4)
Disease stage at initial diagnosis[a]						
I	48 (24.5)	44 (22.8)	92 (23.7)	19 (17.0)	14 (12.1)	33 (14.5)
II	52 (26.5)	53 (27.5)	105 (27.0)	33 (29.5)	40 (34.5)	73 (32.0)
III	0	4 (2.1)	4 (1.0)	5 (4.5)	4 (3.4)	9 (3.9)
IIIA	4 (2.0)	8 (4.1)	12 (3.1)	0	0	0
IIIB	34 (17.3)	20 (10.4)	54 (13.9)	12 (10.7)	22 (19.0)	34 (14.9)
IVA	3 (1.5)	2 (1.0)	5 (1.3)	4 (3.6)	2 (1.7)	6 (2.6)
IVB	55 (28.1)	62 (32.1)	117 (30.1)	39 (34.8)	34 (29.3)	73 (32.0)
Disease status at study entry						
Metastatic[b]	33 (16.8)	47 (24.4)	80 (20.6)	25 (22.3)	17 (14.7)	42 (18.4)
Persistent or recurrent with distant metastases	136 (69.4)	108 (56.0)	244 (62.7)	63 (56.3)	71 (61.2)	134 (58.8)
Persistent or recurrent without distant metastases	27 (13.8)	38 (19.7)	65 (16.7)	24 (21.4)	28 (24.1)	52 (22.8)

Data cut-off date: 3 October 2022. Values are *n* (%) unless stated otherwise.

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1.

[a]Stage at initial diagnosis was determined using International Federation of Gynecology and Obstetrics 2009/National Comprehensive Cancer Network 2017 criteria.

[b]Metastatic included patients with para-aortic lymph node involvement. These patients were diagnosed with stage IVB disease and entered the study without any prior treatment of their cervical cancer.

32.1-46.5 months). Among patients who received bevacizumab, median treatment duration was 13.9 months (range, 0.03-43.7 months) in the pembrolizumab arm versus 9.7 months (range, 0.03-43.9 months) in the placebo arm. Among patients who did not receive bevacizumab, median treatment duration was 6.3 months (range, 0.03-32.1 months) versus 5.4 months (range, 0.03-26.7 months), respectively. Median number of cycles of bevacizumab was 13.0 (range, 1.0-58.0) in the pembrolizumab arm and 11.0 (range, 1.0-61.0) in the placebo arm.

Efficacy

Results for the dual primary endpoints are described below for the PD-L1 CPS ≥1 and all-comer populations. Results for the secondary endpoint of ORR (Table 2) were consistent with those of the dual primary endpoints, with pembrolizumab plus chemotherapy being associated with higher ORRs than placebo plus chemotherapy regardless of bevacizumab use, in both populations.

PD-L1 combined positive score ≥1 population. Among patients who received bevacizumab, median PFS was 15.3 months (95% CI 10.5-29.1 months) in the pembrolizumab arm versus 10.3 months (95% CI 8.4-12.3 months) in the placebo arm [HR, 0.56 (95% CI 0.43-0.73)], with 24-month PFS rates of 43.2% and 25.5%, respectively (Figure 2A). Among patients who did not receive bevacizumab, median PFS was 7.0 months (95% CI 6.2-9.1 months) in the pembrolizumab arm versus 6.0 months (95% CI 4.3-6.3 months) in the placebo arm [HR, 0.61 (95% CI 0.44-0.85)], with 24-month PFS rates of 22.7% and 6.6%, respectively (Figure 2A).

Among patients who received bevacizumab, median OS was 43.9 months (95% CI 28.6 months-not reached) in the pembrolizumab arm versus 23.0 months (95% CI 16.4-26.3 months) in the placebo arm [HR, 0.60 (95% CI 0.45-0.79)], with 24-month OS rates of 62.3% and 48.0%, respectively (Figure 3A). Among patients who did not receive bevacizumab, median OS was 17.5 months (95% CI 14.9-22.3 months) in the pembrolizumab arm versus 11.9 months (95% CI 9.7-14.8 months) in the placebo arm [HR, 0.61 (95% CI 0.44-0.85)], with 24-month OS rates of 37.8% and 25.3%, respectively (Figure 3A).

All-comers. Among patients who received bevacizumab, median PFS was 15.2 months (95% CI 10.5-23.3 months) in the pembrolizumab arm versus 10.2 months (95% CI 8.3-12.2 months) in the placebo arm [HR, 0.57 (95% CI 0.45-0.73)], with 24-month PFS rates of 41.8% and 24.0%, respectively (Figure 2B). Among patients who did not receive bevacizumab, median PFS was 6.3 months (95% CI 6.1-8.3 months) in the pembrolizumab arm versus 6.2 months (95% CI 4.4-6.3 months) in the placebo arm [HR, 0.69 (95% CI 0.50-0.94)], with 24-month PFS rates of 21.6% and 5.8%, respectively (Figure 2B).

Among patients who received bevacizumab, median OS was 37.6 months (95% CI 27.0 months-not reached) in the pembrolizumab arm versus 22.5 months (95% CI 16.6-25.0 months) in the placebo arm [HR, 0.61 (95% CI 0.47-0.80)], with 24-month OS rates of 61.2% and 46.1%, respectively (Figure 3B). Among patients who did not receive bevacizumab, median OS was 17.1 months (95% CI 14.4-21.3 months) in the pembrolizumab arm versus 12.6 months (95% CI 10.0-15.7 months) in the placebo arm [HR, 0.67 (95% CI 0.49-0.91)], with 24-month OS rates of 36.1% and 26.2%, respectively (Figure 3B).

Results for PFS and OS among patients who discontinued bevacizumab because of AEs but continued pembrolizumab are shown in Figure 4. The HRs (95% CIs) were 0.49 (0.27-0.89) and 0.40 (0.20-0.79), respectively.

Table 2. Tumor response per RECIST version 1.1 by investigator in PD-L1 CPS ≥1 and all-comer populations

	PD-L1 CPS ≥1				All-comers			
	With bevacizumab		Without bevacizumab		With bevacizumab		Without bevacizumab	
	Pembro arm $n = 175$	Placebo arm $n = 171$	Pembro arm $n = 98$	Placebo arm $n = 104$	Pembro arm $n = 196$	Placebo arm $n = 193$	Pembro arm $n = 112$	Placebo arm $n = 116$
ORR (95% CI), %	77.1 (70.2-83.1)	61.4 (53.7-68.7)	53.1 (42.7-63.2)	33.7 (24.7-43.6)	75.5 (68.9-81.4)	61.7 (54.4-68.5)	50.0 (40.4-59.6)	34.5 (25.9-43.9)
Difference, % (95% CI)[a]	16.1 (6.4-25.7)		19.3 (5.7-32.3)		14.1 (4.8-23.2)		15.5 (2.6-27.9)	
Best overall response, *n* (%)								
CR	52 (29.7)	36 (21.1)	18 (18.4)	4 (3.8)	57 (29.1)	39 (20.2)	19 (17.0)	5 (4.3)
PR	83 (47.4)	69 (40.4)	34 (34.7)	31 (29.8)	91 (46.4)	80 (41.5)	37 (33.0)	35 (30.2)
SD	29 (16.6)	43 (25.1)	28 (28.6)	43 (41.3)	35 (17.9)	48 (24.9)	33 (29.5)	49 (42.2)
PD	1 (0.6)	13 (7.6)	8 (8.2)	16 (15.4)	3 (1.5)	16 (8.3)	12 (10.7)	17 (14.7)
Unevaluable/no assessment	10 (5.7)	10 (5.8)	10 (10.2)	10 (9.6)	10 (5.1)	10 (5.2)	11 (9.8)	10 (8.6)
Time to response, median (range), months	2.1 (1.9-20.6)	2.1 (1.3-20.6)	2.2 (1.7-23.5)	2.1 (1.4-6.3)	2.1 (1.9-20.6)	2.1 (1.3-20.6)	2.2 (1.7-23.5)	2.1 (1.4-6.3)
DOR, median (range), months	27.5 (1.3+ to 40.9+)	12.6 (2.1+ to 40.7+)	8.8 (1.9+ to 40.9+)	6.3 (1.5+ to 35.2+)	26.6 (1.3+ to 40.9+)	12.9 (2.1+ to 40.7+)	8.5 (1.9+ to 40.9+)	6.3 (1.5+ to 35.2+)

Data cut-off date: 3 October 2022.

'+' indicates no PD by time of last disease assessment.

CI, confidence interval; CPS, combined positive score; CR, complete response; DOR, duration of response; ORR, overall response rate; PD, progressive disease; PD-L1, programmed cell death-ligand 1; pembro, pembrolizumab; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

[a]The between-group difference in ORR for the pembrolizumab group versus the placebo group was estimated using the Miettinen & Nurminen method stratified by metastatic stage at initial diagnosis (International Federation of Gynecology and Obstetrics 2009 stage IVB; yes or no), bevacizumab use (yes or no), and PD-L1 status (CPS <1, CPS 1 to <10, or CPS ≥10).

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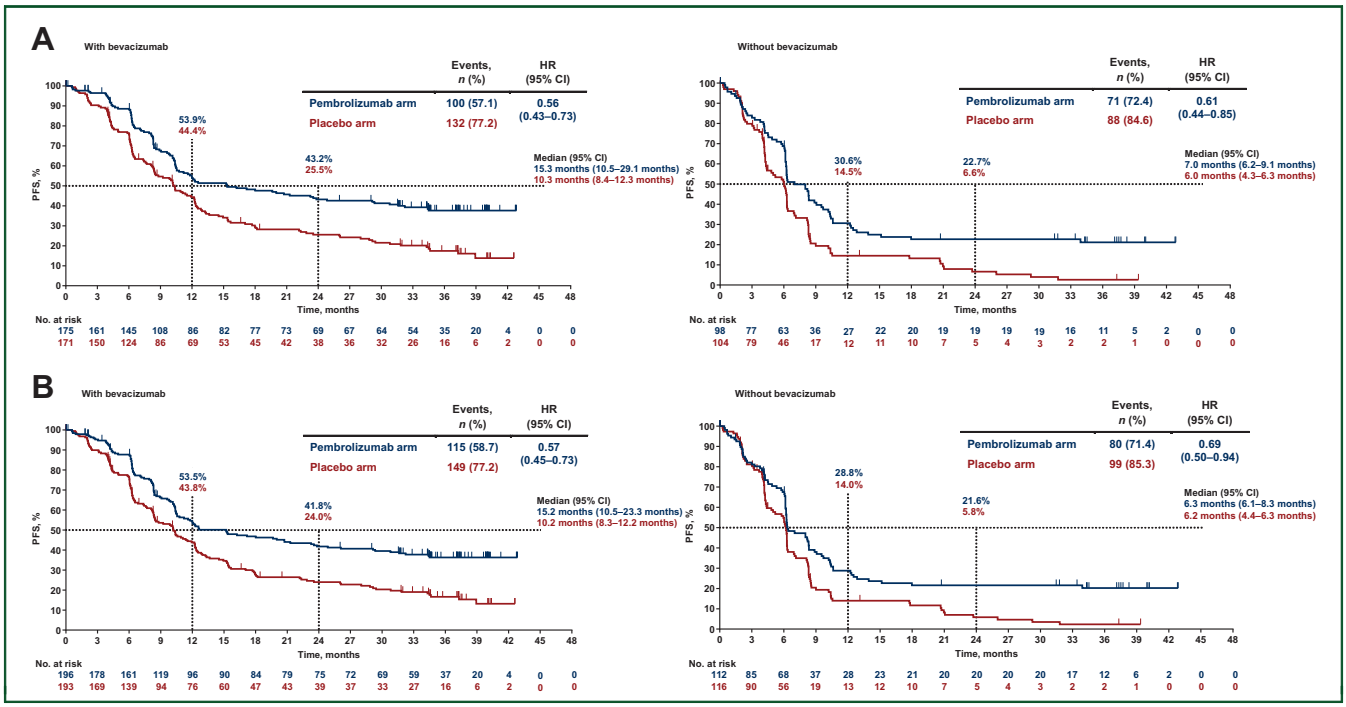

Figure 2. PFS by bevacizumab use in (A) the PD-L1 CPS ≥1 and (B) all-comer populations.
CI, confidence interval; CPS, combined positive score; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival.

Safety

Patients who received bevacizumab. Treatment-related AEs were experienced by 97.4% of patients in the pembrolizumab arm versus 98.4% of patients in the placebo arm; grade ≥3 treatment-related AEs occurred in 74.0% and 66.8% of patients, respectively (Table 3). Grade ≥3 treatment-related AEs of interest included hypertension (pembrolizumab arm, 11.7%; placebo arm, 13.0%), female genital tract fistula (2.0%; 3.6%), intestinal perforation (1.0%; 0.5%), rectal perforation (1.0%; 0.5%), pulmonary

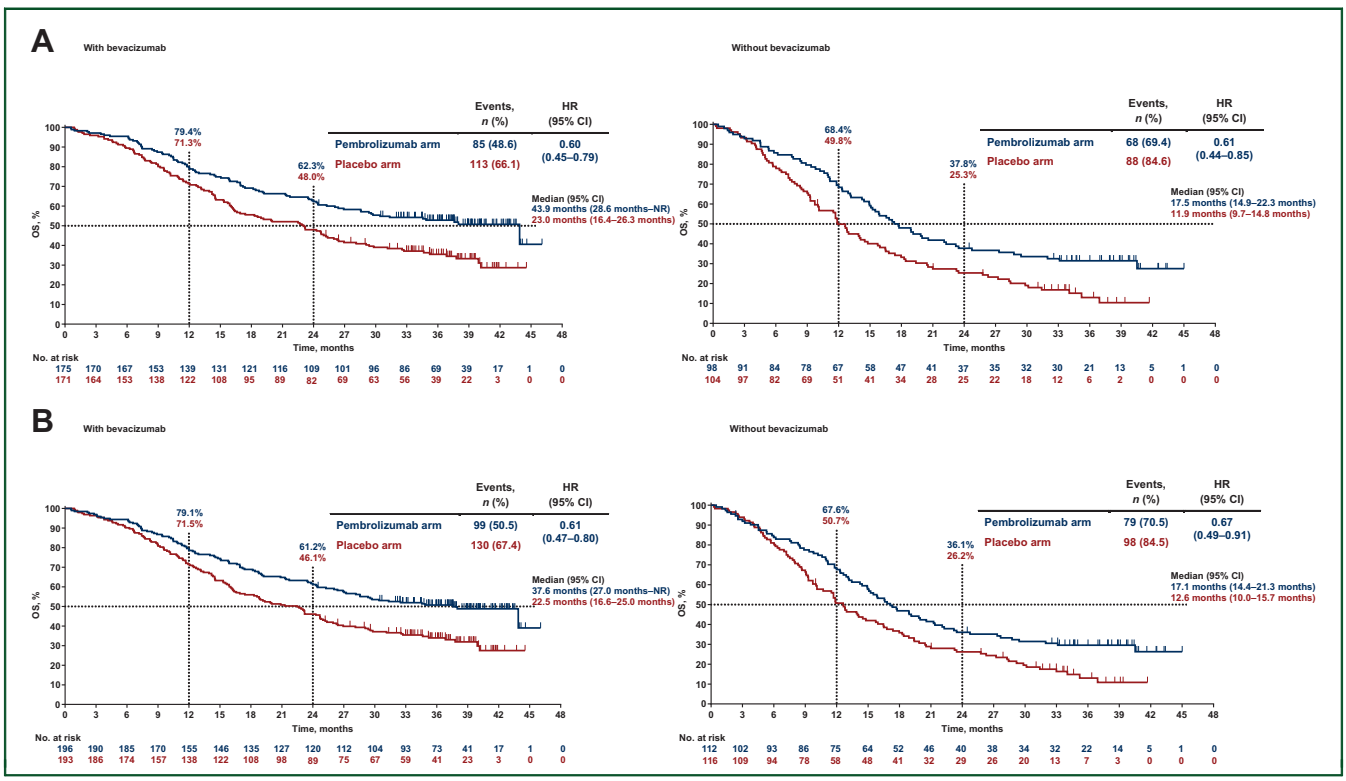

Figure 3. OS by bevacizumab use in (A) the PD-L1 CPS ≥1 and (B) all-comer populations.
CI, confidence interval; CPS, combined positive score; HR, hazard ratio; NR, not reached; OS, overall survival; PD-L1, programmed cell death-ligand 1.

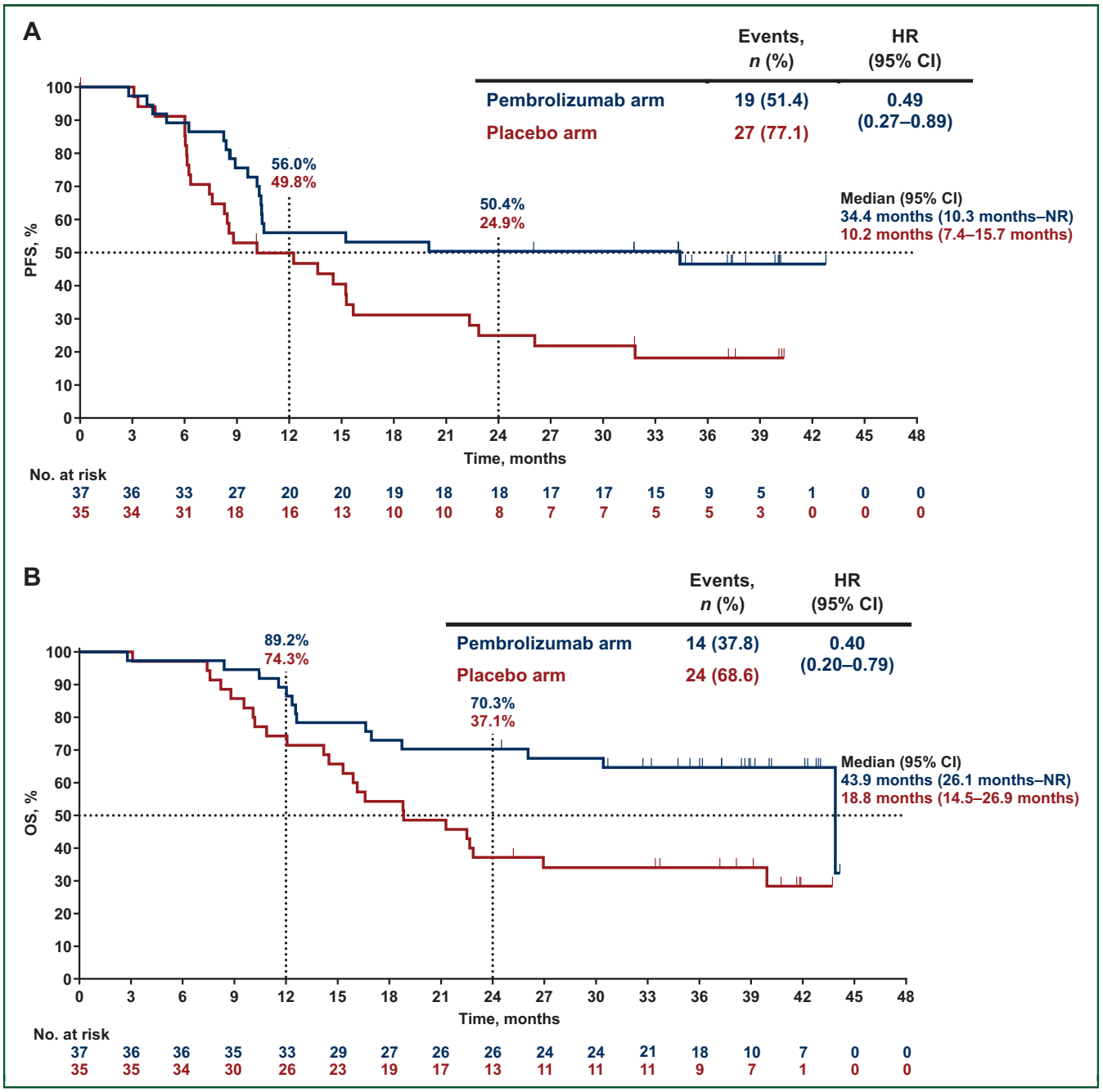

Figure 4. **(A) PFS and (B) OS in patients who discontinued bevacizumab due to an adverse event but continued pembrolizumab in the all-comer population.** CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

embolism (0.5%; 0.5%), small intestinal perforation (0.5%; 0%), urogenital fistula (0.5%; 1.0%), vaginal fistula (0.5%; 1.0%), embolism (0%; 0.5%), enterovesical fistula (0%; 0.5%), and large intestine perforation (0%; 0.5%). Treatment-related AEs led to the discontinuation of any study drug in 40.8% of patients in the pembrolizumab arm versus 32.6% of patients in the placebo arm and resulted in the death of one patient (intestinal perforation) and three patients (female genital tract fistula, large intestine perforation, and pulmonary sepsis), respectively. Immune-mediated AEs and infusion reactions occurred in 44.4% of patients in the pembrolizumab arm versus 32.1% of patients in the placebo arm; these events were grade $\geq$3 in 16.3% and 5.7% of patients, respectively. Immune-mediated AEs and infusion reactions led to the discontinuation of any study drug in 11.7% of patients in the pembrolizumab arm versus 4.7% of patients in the placebo arm and resulted in the death of one patient (acute pancreatitis) and no patients, respectively.

Patients who did not receive bevacizumab. Treatment-related AEs were experienced by 96.4% of patients in the pembrolizumab arm versus 94.8% of patients in the placebo arm; grade $\geq$3 treatment-related AEs occurred in 60.4% and

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Table 3. Safety in all-comer population

AE	With bevacizumab				Without bevacizumab			
	Pembrolizumab arm $n = 196$		Placebo arm $n = 193$		Pembrolizumab arm $n = 111$		Placebo arm $n = 116$	
Any AE	196 (100)		193 (100)		109 (98.2)		114 (98.3)	
Treatment-related AEs	191 (97.4)		190 (98.4)		107 (96.4)		110 (94.8)	
Grade 3-5[a]	145 (74.0)		129 (66.8)		67 (60.4)		72 (62.1)	
Led to discontinuation of any treatment component	80 (40.8)		63 (32.6)		22 (19.8)		14 (12.1)	
Pembrolizumab/placebo	27 (13.8)		7 (3.6)		6 (5.4)		6 (5.2)	
Any chemotherapy	45 (23.0)		40 (20.7)		19 (17.1)		13 (11.2)	
Bevacizumab	51 (26.0)		35 (18.1)		0		0	
All study treatments	7 (3.6)		2 (1.0)		2 (1.8)		4 (3.4)	
Treatment-related AEs occurring in ≥20% of patients who received bevacizumab	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Alopecia	111 (56.6)	0	118 (61.1)	0	60 (54.1)	0	54 (46.6)	0
Anemia	81 (41.3)	40 (20.4)	74 (38.3)	28 (14.5)	68 (61.3)	36 (32.4)	58 (50.0)	37 (31.9)
Nausea	66 (33.7)	1 (0.5)	72 (37.3)	2 (1.0)	38 (34.2)	3 (2.7)	48 (41.4)	2 (1.7)
Hypertension	58 (29.6)	23 (11.7)	55 (28.5)	25 (13.0)	0	0	1 (0.9)	1 (0.9)
Fatigue	54 (27.6)	3 (1.5)	50 (25.9)	7 (3.6)	16 (14.4)	5 (4.5)	27 (23.3)	6 (5.2)
Diarrhea	53 (27.0)	3 (1.5)	40 (20.7)	2 (1.0)	24 (21.6)	2 (1.8)	20 (17.2)	3 (2.6)
Peripheral neuropathy	53 (27.0)	6 (3.1)	54 (28.0)	6 (3.1)	22 (19.8)	2 (1.8)	23 (19.8)	3 (2.6)
Proteinuria	46 (23.5)	8 (4.1)	27 (14.0)	6 (3.1)	1 (0.9)	0	0	0
Peripheral sensory neuropathy	45 (23.0)	2 (1.0)	52 (26.9)	5 (2.6)	24 (21.6)	1 (0.9)	27 (23.3)	2 (1.7)
Hypothyroidism	44 (22.4)	1 (0.5)	21 (10.9)	1 (0.5)	11 (9.9)	1 (0.9)	6 (5.2)	0
Vomiting	44 (22.4)	4 (2.0)	43 (22.3)	2 (1.0)	19 (17.1)	1 (0.9)	23 (19.8)	1 (0.9)
Immune-mediated AEs and infusion reactions	87 (44.4)	32 (16.3)	62 (32.1)	11 (5.7)	41 (36.9)	11 (9.9)	22 (19.0)	5 (4.3)
Hypothyroidism	46 (23.5)	2 (1.0)	24 (12.4)	1 (0.5)	13 (11.7)	1 (0.9)	7 (6.0)	0
Infusion reactions	22 (11.2)	6 (3.1)	30 (15.5)	5 (2.6)	19 (17.1)	1 (0.9)	8 (6.9)	2 (1.7)
Hyperthyroidism	19 (9.7)	0	7 (3.6)	1 (0.5)	7 (6.3)	0	3 (2.6)	0
Severe skin reactions	10 (5.1)	8 (4.1)	1 (0.5)	1 (0.5)	4 (3.6)	4 (3.6)	0	0
Colitis	9 (4.6)	3 (1.5)	2 (1.0)	2 (1.0)	7 (6.3)	2 (1.8)	3 (2.6)	3 (2.6)
Hepatitis	5 (2.6)	4 (2.0)	1 (0.5)	1 (0.5)	0	0	0	0
Thyroiditis	8 (4.1)	2 (1.0)	1 (0.5)	0	3 (2.7)	0	0	0
Pneumonitis	5 (2.6)	2 (1.0)	0	0	2 (1.8)	0	1 (0.9)	0
Pancreatitis	3 (1.5)	2 (1.0)	1 (0.5)	0	1 (0.9)	1 (0.9)	0	0
Adrenal insufficiency	2 (1.0)	1 (0.5)	0	0	2 (1.8)	2 (1.8)	0	0
Cholangitis sclerosing	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Myositis	2 (1.0)	1 (0.5)	0	0	0	0	0	0
Nephritis	2 (1.0)	1 (0.5)	0	0	0	0	0	0
Type 1 diabetes mellitus	2 (1.0)	2 (1.0)	0	0	0	0	0	0
Vasculitis	2 (1.0)	0	0	0	0	0	0	0
Encephalitis	0	0	0	0	1 (0.9)	1 (0.9)	0	0
Myocarditis	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Hypophysitis	1 (0.5)	1 (0.5)	1 (0.5)	0	0	0	0	0

Data cut-off date: 3 October 2022. Values are *n* (%).
AE, adverse event.
[a]In patients who received bevacizumab, treatment-related AEs resulted in the death of one patient in the pembrolizumab arm (intestinal perforation) and three patients in the placebo arm (female genital tract fistula, large intestine perforation, and pulmonary sepsis). In patients who did not receive bevacizumab, treatment-related AEs resulted in the death of one patient in the pembrolizumab arm (autoimmune encephalitis) and one patient in the placebo arm (embolism).

62.1% of patients, respectively (Table 3). Treatment-related AEs led to the discontinuation of any study drug in 19.8% of patients in the pembrolizumab arm versus 12.1% of patients in the placebo arm and resulted in the death of one patient (autoimmune encephalitis) and one patient (embolism), respectively. Immune-mediated AEs and infusion reactions occurred in 36.9% of patients in the pembrolizumab arm versus 19.0% of patients in the placebo arm; these events were grade ≥3 in 9.9% and 4.3% of patients, respectively. Immune-mediated AEs and infusion reactions led to the discontinuation of any study drug in 6.3% of patients in the pembrolizumab arm versus 1.7% of patients in the placebo arm and resulted in the death of one patient (autoimmune encephalitis) and no patients, respectively.

DISCUSSION

In this subgroup analysis of the KEYNOTE-826 study, the addition of pembrolizumab to chemotherapy resulted in clinically meaningful improvements in PFS and OS compared with placebo plus chemotherapy regardless of concomitant bevacizumab use in patients with persistent, recurrent, or metastatic cervical cancer. Additionally, ORR

was higher and DOR was longer with the addition of pembrolizumab. The safety profile of pembrolizumab plus chemotherapy with or without bevacizumab was manageable, and no new safety signals were identified. The findings were consistent in patients with PD-L1 CPS $\geq$1 tumors and all-comers.

Efficacy outcomes in our study were generally consistent with those of other phase III clinical trials in which patients with persistent, recurrent, or metastatic cervical cancer were treated in the first-line setting. The atezolizumab arm of the BEATcc study[14] and the pembrolizumab arm of KEYNOTE-826 both demonstrated the PFS and OS benefits of adding immunotherapy to the treatment regimen. In BEATcc, quadruplet therapy with atezolizumab, doublet chemotherapy, and bevacizumab significantly reduced the risk of progression or death by 38% [HR, 0.62 (95% CI 0.49-0.78); $P < 0.0001$] and the risk of death by 32% [HR, 0.68 (95% CI 0.52-0.88); $P = 0.0046$] compared with doublet chemotherapy plus bevacizumab.[14] The corresponding risk reductions observed with pembrolizumab, doublet chemotherapy, and bevacizumab compared with doublet chemotherapy plus bevacizumab in KEYNOTE-826 were 43% [HR, 0.57 (95% CI 0.45-0.73)] and 39% [HR, 0.61 (95% CI 0.47-0.80)], respectively, in the all-comer population. The median OS with quadruplet therapy was 32.1 months in BEATcc (interim analysis) and 37.6 months in KEYNOTE-826 (final analysis).

Our results suggest that first-line quadruplet therapy with pembrolizumab, doublet chemotherapy, and bevacizumab may be the optimal initial treatment approach for those patients who do not have contraindications to receiving bevacizumab. The addition of pembrolizumab to doublet chemotherapy in KEYNOTE-826 provided clinical benefits irrespective of bevacizumab use and therefore, for those patients ineligible to receive bevacizumab, the combination of pembrolizumab plus doublet chemotherapy is a treatment option that provides clinical benefit. Although the sample size was small and the results must be interpreted with caution, exploratory analysis suggested that, among patients who initiated quadruplet therapy but discontinued bevacizumab because of an AE, clinical benefit may have been achieved in those who continued pembrolizumab therapy.

The types of AEs observed in the current subgroup analysis were as expected based on the individual components and generally consistent with the safety profiles reported in previous clinical trials.[7,8,14] Importantly, in KEYNOTE-826, the addition of pembrolizumab versus placebo to doublet chemotherapy plus bevacizumab did not increase the occurrence of grade $\geq$3 treatment-related AEs of interest including hypertension (11.7% versus 13.0%), perforations (2.5% versus 1.0%), pelvic fistulas (2.5% versus 4.7%), other fistulas (0.5% versus 1.5%), and embolism (0.5% versus 1.0%).

This preplanned subgroup analysis was exploratory and not controlled for multiplicity, and therefore was not powered to assess statistical significance. Planned bevacizumab use was a prespecified stratification factor to help mitigate imbalance between the treatment arms. Although KEYNOTE-826 was designed to assess the dual primary endpoints of PFS and OS, each tested sequentially in the PD-L1 CPS $\geq$1, all-comer, and PD-L1 CPS $\geq$10 populations, subgroup analysis in the latter population was not possible because of the limited sample size. The percentage of patients who were treated with bevacizumab in the first-line setting in KEYNOTE-826 (63.0%) was within the range reported in real-world studies of patients with persistent, recurrent, or metastatic cervical cancer in Europe and the USA (42.0%-72.0%).[15-17] The demographic (e.g. age, race) and clinical characteristics (e.g. ECOG performance status, histology) were also similar; thus, our patients were largely representative of the general population with cervical cancer.

In conclusion, the addition of pembrolizumab to chemotherapy resulted in clinically meaningful improvements in PFS and OS versus chemotherapy regardless of concomitant bevacizumab use. These results provide further support for pembrolizumab plus chemotherapy with or without bevacizumab as a standard of care for patients with persistent, recurrent, or metastatic cervical cancer.

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DATA SHARING

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the USA and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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