ORIGINAL ARTICLE

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

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ABSTRACT

BACKGROUND

Pembrolizumab has efficacy in programmed death ligand 1 (PD-L1)–positive metastatic or unresectable cervical cancer that has progressed during chemotherapy. We assessed the relative benefit of adding pembrolizumab to chemotherapy with or without bevacizumab.

METHODS

In a double-blind, phase 3 trial, we randomly assigned patients with persistent, recurrent, or metastatic cervical cancer in a 1:1 ratio to receive pembrolizumab (200 mg) or placebo every 3 weeks for up to 35 cycles plus platinum-based chemotherapy and, per investigator discretion, bevacizumab. The dual primary end points were progression-free survival and overall survival, each tested sequentially in patients with a PD-L1 combined positive score of 1 or more, in the intention-to-treat population, and in patients with a PD-L1 combined positive score of 10 or more. The combined positive score is defined as the number of PD-L1–staining cells divided by the total number of viable tumor cells, multiplied by 100. All results are from the protocol-specified first interim analysis.

RESULTS

In 548 patients with a PD-L1 combined positive score of 1 or more, median progression-free survival was 10.4 months in the pembrolizumab group and 8.2 months in the placebo group (hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.50 to 0.77; P<0.001). In 617 patients in the intention-to-treat population, progression-free survival was 10.4 months and 8.2 months, respectively (hazard ratio, 0.65; 95% CI, 0.53 to 0.79; P<0.001). In 317 patients with a PD-L1 combined positive score of 10 or more, progression-free survival was 10.4 months and 8.1 months, respectively (hazard ratio, 0.58; 95% CI, 0.44 to 0.77; P<0.001). Overall survival at 24 months was 53.0% in the pembrolizumab group and 41.7% in the placebo group (hazard ratio for death, 0.64; 95% CI, 0.50 to 0.81; P<0.001), 50.4% and 40.4% (hazard ratio, 0.67; 95% CI, 0.54 to 0.84; P<0.001), and 54.4% and 44.6% (hazard ratio, 0.61; 95% CI, 0.44 to 0.84; P=0.001), respectively. The most common grade 3 to 5 adverse events were anemia (30.3% in the pembrolizumab group and 26.9% in the placebo group) and neutropenia (12.4% and 9.7%, respectively).

CONCLUSIONS

Progression-free and overall survival were significantly longer with pembrolizumab than with placebo among patients with persistent, recurrent, or metastatic cervical cancer who were also receiving chemotherapy with or without bevacizumab. (Funded by Merck Sharp and Dohme; KEYNOTE-826 ClinicalTrials.gov number, NCT03635567.)

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*A complete list of investigators in the KEYNOTE-826 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 18, 2021, at NEJM.org.

N Engl J Med 2021;385:1856-67.
DOI: 10.1056/NEJMoa2112435
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Standard first-line therapy for persistent, recurrent, or metastatic cervical cancer is platinum-based chemotherapy, with a preferred regimen of a platinum compound (cisplatin or carboplatin) and paclitaxel plus bevacizumab on the basis of a balance between efficacy and safety.[1-7] The anti–programmed death 1 (PD-1) monoclonal antibody pembrolizumab has shown efficacy and mainly low-grade toxic effects as monotherapy in patients with cervical cancer.[8-11] In the recurrent or metastatic cervical cancer cohort of the phase 2 KEYNOTE-158 trial, an objective response to pembrolizumab was observed in 12.2% of all patients and in 14.3% of the patients who received one or more previous chemotherapy regimens for recurrent or metastatic disease and had programmed death ligand 1 (PD-L1)–positive tumors.[10] We conducted the KEYNOTE-826 trial to assess whether adding pembrolizumab to platinum-based chemotherapy with or without bevacizumab would improve efficacy as compared with chemotherapy with or without bevacizumab as first-line therapy for persistent, recurrent, or metastatic cervical cancer.

Methods

Patients

Eligible patients were 18 years of age or older and had persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous-cell carcinoma of the cervix that had not been treated with systemic chemotherapy and was not amenable to curative treatment. Previous radiotherapy, including chemoradiotherapy, was permitted if it was completed at least 2 weeks before randomization and all associated toxic effects had resolved; a 1-week washout period was permitted for palliative radiotherapy to non–central nervous system lesions. Patients must also have had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with 0 indicating no symptoms and higher scores indicating increasing disability[12]); had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[13]; and have provided a newly obtained biopsy (preferred) or archival tumor-tissue sample collected from a nonirradiated lesion for determination of PD-L1 status. Full eligibility criteria are provided in Section 5 in the protocol, available with the full text of this article at NEJM.org.

Trial Design and Regimens

A Quick Take is available at NEJM.org

This double-blind trial was conducted at 151 sites in 19 countries. Patients were randomly assigned in a 1:1 ratio to receive pembrolizumab (200 mg) or placebo every 3 weeks for up to 35 cycles. All the patients were to receive paclitaxel (175 mg per square meter of body-surface area) and the investigator's choice of cisplatin (50 mg per square meter) or carboplatin (area under the concentration–time curve, 5 mg per milliliter per minute) every 3 weeks. At the request of a global regulatory authority, the second protocol amendment (approved on June 25, 2019) limited chemotherapy to 6 cycles, although patients with ongoing clinical benefit who were receiving chemotherapy without unacceptable side effects could continue beyond 6 cycles after consultation with the sponsor. Patients could receive bevacizumab at a dose of 15 mg per kilogram of body weight every 3 weeks according to local practice at the investigator's discretion. All trial agents were administered intravenously. Randomization was performed centrally through an integrated interactive voice-response and Web-response system and was stratified according to metastatic disease at diagnosis (yes vs. no), planned bevacizumab use (yes vs. no), and PD-L1 combined positive score (<1 vs. 1 to <10 vs. ≥10).

Treatment was continued until the maximum number of cycles for each component, radiographic progression, unacceptable toxic effects, use of prohibited therapy (e.g., new antineoplastic therapy or nonpalliative radiotherapy), a decision by the investigator to discontinue the regimen, or withdrawal of consent by the patient. Patients with a confirmed complete response could discontinue treatment if they had received at least 8 cycles of pembrolizumab, including at least 2 cycles beyond a complete response. At their discretion, investigators could interrupt or discontinue individual trial agents to manage toxic effects. Full details regarding treatment decisions and adverse-event management are provided in Sections 6.5 and 6.6 in the protocol.

Assessments and End Points

PD-L1 expression was assessed during screening at a central laboratory with the use of the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) and measured according to the combined positive score, defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable

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tumor cells, multiplied by 100.[14] Tumor imaging was scheduled for week 9, then every 9 weeks through week 54 and every 12 weeks thereafter. Adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Scores on the visual-analogue scale of the EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L VAS), a standardized instrument for measuring patient-reported general health status (on a scale from 0 to 100, with higher scores indicating better health),[15] were determined before trial treatment at cycles 1 through 14 and at every other cycle thereafter.

The dual primary end points were overall survival and progression-free survival assessed according to RECIST, version 1.1, by investigator review. Secondary end points were the percentage of patients with a confirmed complete or partial response, the duration of response, and the percentage of patients who were alive without disease progression at 12 months, all assessed according to RECIST, version 1.1, by investigator review; progression-free survival assessed according to RECIST, version 1.1, by blinded independent central review; and safety. Time to deterioration in the EQ-5D-5L VAS score and the proportion of patients with improved or stable EQ-5D-5L VAS scores were prespecified exploratory analyses in which deterioration and improvement were based on changes of at least 10 points from baseline.

TRIAL OVERSIGHT

The trial was designed by academic advisors and employees of the sponsor. An external data and safety monitoring committee oversaw the trial, periodically assessed safety, and assessed efficacy at the interim analysis. The trial protocol and all amendments were approved by the appropriate ethics body at each participating center. All the patients provided written informed consent.

The trial was conducted in accordance with Good Clinical Practice guidelines. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the authors attest that they had access to the data, participated in writing or reviewing and editing the manuscript, and approved the decision to submit the manuscript for publication. Assistance with manuscript preparation was provided by a medical writer who was employed by the sponsor.

STATISTICAL ANALYSIS

The full statistical analysis plan is available in Section 9 in the protocol. Efficacy was assessed in the intention-to-treat population (i.e., all randomly assigned patients). Safety was assessed in the as-treated population (i.e., all randomly assigned patients who received at least one dose of pembrolizumab or placebo). Overall survival, progression-free survival, and duration of response were estimated with the use of the Kaplan–Meier method. Between-group differences in overall and progression-free survival were assessed with the use of the stratified log-rank test, with the magnitude of the difference assessed with the use of the stratified Cox proportional-hazards model and Efron's method of tie handling. The randomization stratification factors were applied to all stratified analyses. Methods regarding patient-reported outcomes are provided in the Supplementary Appendix, available at NEJM.org.

The graphical method of Maurer and Bretz[16] was used to control the familywise type I error rate at a one-sided alpha level of 0.025 across six primary hypotheses, two interim analyses, and a final analysis (Fig. S1 in the Supplementary Appendix). Superiority of pembrolizumab plus chemotherapy with or without bevacizumab for overall survival and progression-free survival were each tested sequentially in patients with a PD-L1 combined positive score of 1 or more, in the intention-to-treat population, and in patients with a PD-L1 combined positive score of 10 of more. The planned enrollment was 600 patients; power calculations are shown in the Supplementary Appendix. The first interim analysis, the results of which are presented here, was planned to be performed when approximately 370 events of disease progression or death had occurred in patients with a PD-L1 combined positive score of 1 or more; at this time, it was expected that approximately 246 deaths would have occurred in this group and that approximately 22 months would have elapsed since the first patient underwent randomization. The number of events observed and the superiority boundaries for the six primary hypotheses at the first interim analysis are summarized in Table S1.

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RESULTS

PATIENTS AND TREATMENT

Between November 20, 2018, and January 31, 2020, a total of 617 patients were randomly assigned to receive pembrolizumab plus chemotherapy with or without bevacizumab (pembrolizumab group; 308 patients) or placebo plus chemotherapy with or without bevacizumab (placebo group; 309 patients), including 548 patients with a PD-L1 combined positive score of 1 or more (273 in the pembrolizumab group and 275 in the placebo group) and 317 patients with a PD-L1 combined positive score of 10 or more (158 in the pembrolizumab group and 159 in the placebo group). Bevacizumab was used by 63.6% of the patients in the pembrolizumab group and 62.5% of those in the placebo group. Demographic and disease characteristics of the patients at baseline were generally well balanced between trial groups in all analysis populations (Table 1 and Tables S2 and S3). Overall, 72.3% of the patients had squamous-cell carcinoma, 56.4% received previous chemoradiotherapy with or without surgery, and 19.8% had previously untreated metastatic disease at trial entry.

One patient who was assigned to the pembrolizumab group did not receive pembrolizumab (Fig. 1). The median follow-up, defined as the time from randomization to the May 3, 2021, data cutoff for the first interim analysis, was 22.0 months (range, 15.1 to 29.4), and 104 of 307 patients (33.9%) in the pembrolizumab group and 54 of 309 patients (17.5%) in the placebo group were continuing to receive at least one trial agent (Fig. 1). The use of trial agents in the PD-L1–selected populations is shown in Figure S2.

EFFICACY

Progression-free survival was significantly longer in the pembrolizumab group than in the placebo group in patients with a PD-L1 combined positive score of 1 or more (median, 10.4 months [95% confidence interval {CI}, 9.7 to 12.3] vs. 8.2 months [95% CI, 6.3 to 8.5]; hazard ratio for disease progression or death, 0.62; 95% CI, 0.50 to 0.77; P<0.001) (Fig. 2A), in the intention-to-treat population (median, 10.4 months [95% CI, 9.1 to 12.1] vs. 8.2 months [95% CI, 6.4 to 8.4]; hazard ratio, 0.65; 95% CI, 0.53 to 0.79; P<0.001) (Fig. 2B), and in patients with a PD-L1 combined positive score of 10 or more (median, 10.4 months [95% CI, 8.9 to 15.1] vs. 8.1 months [95% CI, 6.2 to 8.8]; hazard ratio, 0.58; 95% CI, 0.44 to 0.77; P<0.001) (Fig. 2C). The percentage of patients who were alive without disease progression at 12 months favored pembrolizumab in all populations (Table S4). Results for the analysis of progression-free survival assessed by blinded, independent central review were consistent with those based on investigator review (Table S5). The hazard ratio for disease progression or death was less than 1 in all protocol-specified subgroups analyzed, and the 95% confidence intervals for all subgroups overlapped that of the overall population (Fig. 2D and Fig. S3).

Overall survival was significantly longer in the pembrolizumab group than in the placebo group among patients with a PD-L1 combined positive score of 1 or more (24-month estimate of patients alive, 53.0% [95% CI, 46.0 to 59.4] vs. 41.7% [95% CI, 34.9 to 48.2]; hazard ratio for death, 0.64; 95% CI, 0.50 to 0.81; P<0.001) (Fig. 3A), among patients in the intention-to-treat population (24-month estimate, 50.4% [95% CI, 43.8 to 56.6] vs. 40.4% [95% CI, 34.0 to 46.6]; hazard ratio, 0.67; 95% CI, 0.54 to 0.84; P<0.001) (Fig. 3B), and among patients with a PD-L1 combined positive score of 10 or more (24-month estimate, 54.4% [95% CI, 45.5 to 62.4] vs. 44.6% [95% CI, 36.3 to 52.5]; hazard ratio, 0.61; 95% CI, 0.44 to 0.84; P=0.001) (Fig. 3C). Median overall survival was not reached in either PD-L1–selected population for pembrolizumab, it was 24.4 months in the intention-to-treat population for pembrolizumab, and it ranged from 16.3 to 16.5 months for placebo. The hazard ratio for death was no more than 1.00 in all protocol-specified subgroups, and the 95% confidence intervals for all subgroups overlapped that of the overall population (Fig. 3D and Fig. S4).

The percentage of patients with a confirmed response according to investigator review was higher in the pembrolizumab group than in the placebo group among those with a PD-L1 combined positive score of 1 or more (68.1% vs. 50.2%), among those in the intention-to-treat population (65.9% vs. 50.8%), and among those with a PD-L1 combined positive score of 10 or more (69.6% vs. 49.1%) (Table S6). More complete responses were noted in the pembrolizumab group than in the placebo group (22.7% vs.

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Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Pembrolizumab Group (N=308)†	Placebo Group (N=309)†
Age		
Median (range) — yr	51 (25–82)	50 (22–79)
≥65 yr — no. (%)	48 (15.6)	52 (16.8)
Race — no. (%)‡		
White	170 (55.2)	190 (61.5)
Non-White	138 (44.8)	119 (38.5)
ECOG performance-status score — no. (%)§		
0	178 (57.8)	170 (55.0)
1	128 (41.6)	139 (45.0)
Disease stage at initial diagnosis — no. (%)¶		
I	67 (21.8)	58 (18.8)
II	85 (27.6)	93 (30.1)
III	5 (1.6)	8 (2.6)
IIIA	4 (1.3)	8 (2.6)
IIIB	46 (14.9)	42 (13.6)
IVA	7 (2.3)	4 (1.3)
IVB	94 (30.5)	96 (31.1)
Disease status at trial entry — no. (%)		
Metastatic‖	58 (18.8)	64 (20.7)
Persistent or recurrent with distant metastases	199 (64.6)	179 (57.9)
Persistent or recurrent without distant metastases	51 (16.6)	66 (21.4)
Histologic type — no. (%)**		
Adenocarcinoma	56 (18.2)	84 (27.2)
Adenosquamous carcinoma	15 (4.9)	14 (4.5)
Squamous-cell carcinoma	235 (76.3)	211 (68.3)
PD-L1 combined positive score — no. (%)††		
<1	35 (11.4)	34 (11.0)
1 to <10	115 (37.3)	116 (37.5)
≥10	158 (51.3)	159 (51.5)
Previous therapy — no. (%)		
Chemoradiotherapy and surgery	49 (15.9)	56 (18.1)
Radiotherapy and surgery	22 (7.1)	23 (7.4)
Chemoradiotherapy only	125 (40.6)	118 (38.2)
Radiotherapy only	31 (10.1)	24 (7.8)
Surgery only	23 (7.5)	24 (7.8)
None	58 (18.8)	64 (20.7)
Bevacizumab use during the trial — no. (%)		
Yes	196 (63.6)	193 (62.5)
No	112 (36.4)	116 (37.5)

* The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding.

† The assigned regimen in both groups also included paclitaxel, the investigator's choice of cisplatin or carboplatin, and per investigator discretion, bevacizumab.

‡ Race was reported by the patient or the investigator according to local practice and where permitted by law.

§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability. In the pembrolizumab group, one patient (0.3%) had an ECOG performance-status score of 2, and one patient (0.3%) had an unknown score.

¶ Disease stage was determined with the use of International Federation of Gynecology and Obstetrics 2009–National Comprehensive Cancer Network 2017 criteria.

‖ Patients with paraaortic lymph-node involvement are included. Patients with metastatic disease received a diagnosis of stage IVB disease and entered the trial without any previous treatment for cervical cancer.

** In the pembrolizumab group, histologic type was recorded as epidermoid carcinoma for one patient (0.3%) and as undifferentiated carcinoma for one patient (0.3%).

†† The programmed death ligand 1 (PD-L1) combined positive score was defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

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13.1%, 21.4% vs. 12.9%, and 22.2% vs. 11.3%, respectively). The duration of response was longer in the pembrolizumab group than in the placebo group (median, 18.0 vs. 10.4 months, 18.0 vs. 10.4 months, and 21.1 vs. 9.4 months, respectively) (Fig. S5).

SAFETY

The median treatment duration was 10.0 months in the pembrolizumab group and 7.7 months in the placebo group (Table S7). Table S8 summarizes the number of treatment cycles overall and according to the individual trial agent.

Grade 3 to 5 adverse events occurred in 81.8% of 307 treated patients in the pembrolizumab group and in 75.1% of 309 treated patients in the placebo group (Table 2). Serious adverse events occurred in 49.8% of the patients in the pembrolizumab group and in 42.4% of those in the placebo group; the only serious adverse events that occurred in at least 5% of the patients were febrile neutropenia (6.8% and 4.2%, respectively) and urinary tract infection (5.2% and 5.8%, respectively). Adverse events led to discontinuation of any trial agent in 37.5% and 26.5% of the patients, respectively, and of all trial agents in 5.9% and 4.9%, respectively. Adverse events led to death in 14 patients in each group (4.6% and 4.5%, respectively); of these, 2 events (0.7%) in the pembrolizumab group and 4 events (1.3%) in the placebo group were considered by the investigator to be related to any trial agent (Table S9). In both groups, the most common adverse events of any grade were anemia, alopecia, and nausea and of grade 3 to 5 were anemia, neutropenia, decreased neutrophil count, and hypertension (Table 2). The only adverse events with an incidence of 10% or more in either group for which there was a greater risk in the pembrolizumab group than in the placebo group were hypothyroidism (incidence, 18.2% vs. 9.1%) and decreased white-cell count (12.1% vs. 7.1%); no grade 3 to 5 adverse events with an incidence of 5% or more in either group were of greater risk in the pembrolizumab group than in the placebo group (Fig. S6). Table S10 summarizes the most common adverse events in patients with and patients without concomitant bevacizumab use. Table S11 summarizes adverse events attributed to any trial agent by the investigator.

Potentially immune-mediated adverse events occurred in 33.9% of the patients in the pembrolizumab group and in 15.2% of those in the placebo group, including in 11.4% and 2.9%, respectively, who had grade 3 to 5 events (Table S12). One patient in the pembrolizumab group died from an immune-mediated adverse event (encephalitis). Infusion reactions occurred in 13.4% of the patients in the pembrolizumab group and in 12.6% of those in the placebo group; events were of grade 3 to 5 severity in 2.3% of the patients in each group.

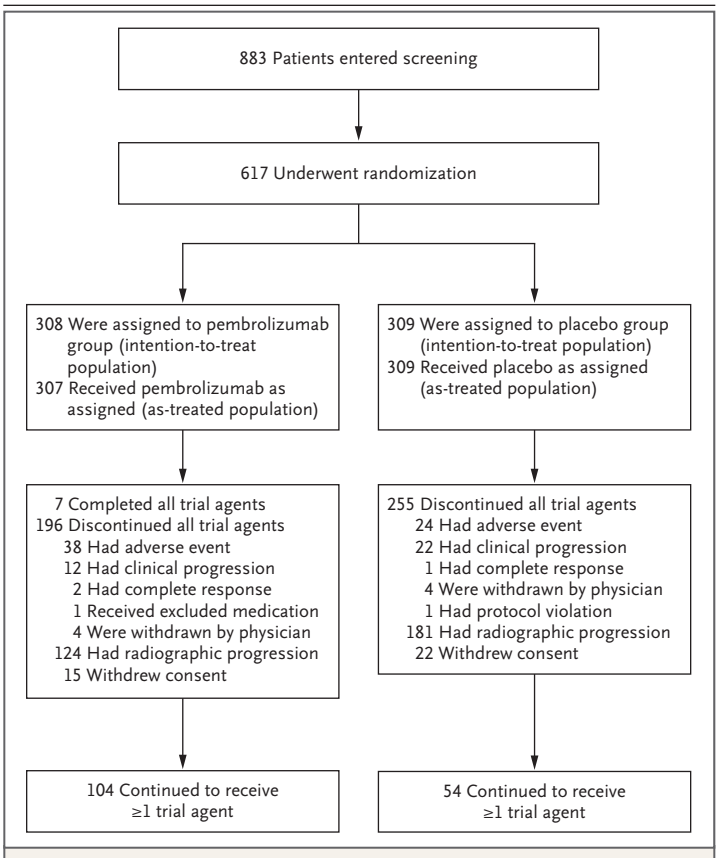

Figure 1. Trial Profile.

The assigned regimen in both groups also included paclitaxel, the investigator's choice of cisplatin or carboplatin, and per investigator discretion, bevacizumab. Patients who completed all trial agents include those who received bevacizumab and discontinued it at cycle 35 or earlier.

PATIENT-REPORTED OUTCOMES

Compliance with the EQ-5D-5L questionnaires between baseline and week 30 was 94.0% or more in the pembrolizumab group and 88.9% or more in the placebo group. Time to deterioration in the EQ-5D-5L VAS score was longer with pembrolizumab than with placebo (12-month estimate of patients free from deterioration, 58.2% vs. 44.8%; hazard ratio, 0.75; 95% CI, 0.58 to

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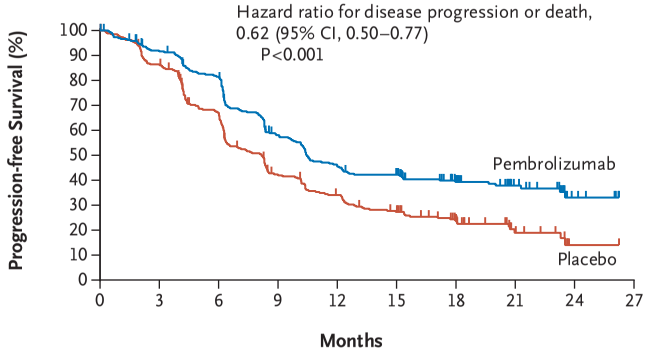
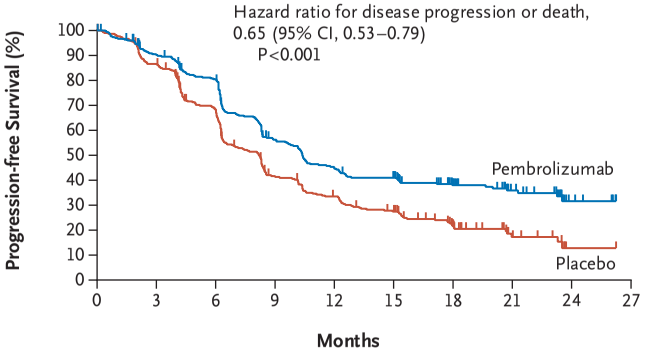
A Patients with a PD-L1 Combined Positive Score of ≥1



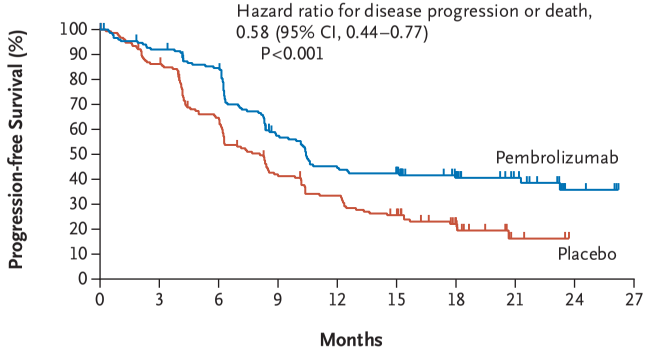
No. at Risk										
Pembrolizumab	273	238	208	143	112	101	66	34	10	0
Placebo	275	229	170	103	81	63	38	13	1	0

B Intention-to-Treat Population



No. at Risk										
Pembrolizumab	308	263	229	155	123	110	70	35	10	0
Placebo	309	259	195	113	89	71	39	13	1	0

C Patients with a PD-L1 Combined Positive Score of ≥10



No. at Risk										
Pembrolizumab	158	138	124	80	62	58	35	21	7	0
Placebo	159	131	95	60	47	35	19	3	0	0

D Subgroup Analysis in Intention-to-Treat Population

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	406/617	0.65 (0.53–0.79)
Age		
<65 yr	345/517	0.63 (0.50–0.78)
≥65 yr	61/100	0.77 (0.42–1.42)
Race		
White	239/360	0.70 (0.53–0.91)
Non-White	139/221	0.64 (0.45–0.90)
ECOG performance-status score		
0	197/348	0.65 (0.48–0.87)
1	207/267	0.69 (0.52–0.93)
PD-L1 combined positive score		
<1	51/69	0.94 (0.52–1.70)
1 to <10	152/231	0.68 (0.49–0.94)
≥10	203/317	0.58 (0.44–0.77)
Concomitant bevacizumab		
Yes	234/389	0.61 (0.47–0.79)
No	172/228	0.74 (0.54–1.01)
Metastatic disease at diagnosis		
Yes	137/190	0.92 (0.64–1.30)
No	269/427	0.58 (0.45–0.75)

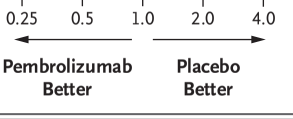


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Figure 2 (facing page). Kaplan–Meier Estimates of Progression-free Survival.

Progression-free survival was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1, by investigator review. The assigned regimen in both groups also included paclitaxel, the investigator's choice of cisplatin or carboplatin, and per investigator discretion, bevacizumab. The programmed death ligand 1 (PD-L1) combined positive score was defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability. Tick marks in Panels A, B, and C indicate censored data. CI denotes confidence interval.

0.97). During 30 weeks of follow-up, more patients who received pembrolizumab had improved or stable EQ-5D-5L VAS scores than patients who received placebo (78.3% vs. 71.7%).

DISCUSSION

In this phase 3 trial of pembrolizumab plus chemotherapy with or without bevacizumab as compared with placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer, the success criteria for all six primary hypotheses were met at the protocol-specified first interim analysis. We found that adding pembrolizumab reduced the hazard of disease progression, as assessed by investigator review, or death by 38% in patients with a PD-L1 combined positive score of 1 or more, by 35% in the intention-to-treat population, and by 42% in patients with a PD-L1 combined positive score of 10 or more; the hazard of death was reduced by 36%, 33%, and 39%, respectively. The progression-free survival benefit for pembrolizumab was similar with assessment by blinded, independent central review. All survival curves began to separate in favor of the pembrolizumab group at approximately month 3 and continued to diverge over time. The benefit in the pembrolizumab group was generally consistent across the protocol-specified subgroups, including subgroups based on concomitant bevacizumab; although the 95% confidence intervals for some subgroups crossed 1, all subgroup confidence intervals overlapped those of the respective total populations. The percentage of patients with an objective response was higher and the duration of response was longer in the pembrolizumab group than in the placebo group in all populations.

Several other PD-1 and PD-L1 inhibitors have been studied as monotherapy or as part of combination therapy for cervical cancer, including atezolizumab,[17] balstilimab,[18] camrelizumab,[19] cemiplimab,[20,21] and nivolumab.[22-25] In the phase 3 EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 trial involving patients with recurrent or metastatic cervical cancer that progressed after platinum-based chemotherapy, monotherapy with the PD-1 inhibitor cemiplimab significantly improved overall survival as compared with chemotherapy among patients with squamous-cell carcinoma and in the overall population.[21] In the overall population, cemiplimab reduced the hazard of death by 31% (median survival, 12.0 vs. 8.5 months; P<0.001). The ability of pembrolizumab to improve outcomes earlier in the course of treatment is being assessed in the ongoing phase 3 KEYNOTE-A18/ENGOT-cx11/GOG-3047 trial of chemoradiotherapy with or without concurrent and maintenance pembrolizumab in patients with high-risk, locally advanced cervical cancer.[26]

Bevacizumab has a proven overall survival benefit when added to chemotherapy in patients with persistent, recurrent, or metastatic cervical cancer.[6,7] However, some contraindications to bevacizumab are common complications of recurrent or metastatic cervical cancer.[27] Although the hazard ratios for overall and progression-free survival for the subgroup without concomitant bevacizumab were slightly higher than those for the subgroup with concomitant bevacizumab and the upper boundaries of the 95% confidence intervals for the subgroup without bevacizumab crossed 1.0, the hazard ratios fell within the 95% confidence intervals for the overall population and for the subgroup with concomitant bevacizumab.

In the phase 2 KEYNOTE-158 trial of pembrolizumab monotherapy for previously treated metastatic or unresectable cervical cancer, all responses were observed in patients with PD-L1–expressing tumors.[10] Although the benefit of pembrolizumab relative to that of placebo in our trial appeared to increase with increasing PD-L1 expression, the hazard ratios were tightly grouped and the 95% confidence intervals overlapped for

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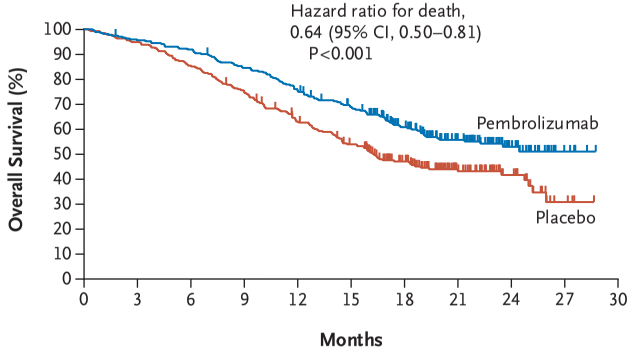
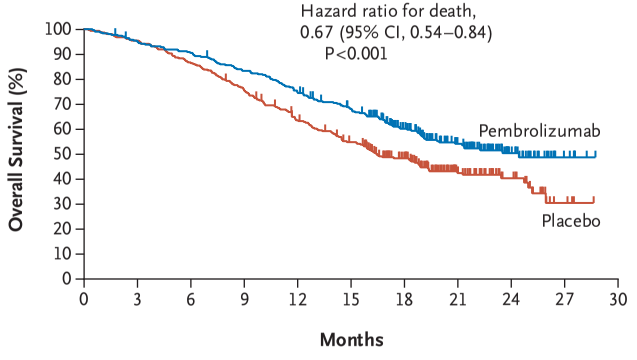
A Patients with a PD-L1 Combined Positive Score of ≥1



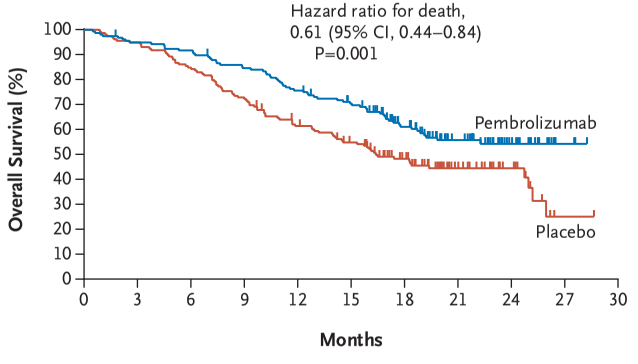
No. at Risk											
Pembrolizumab	273	260	250	229	204	181	132	82	34	6	0
Placebo	275	261	235	206	168	140	100	55	25	4	0

B Intention-to-Treat Population



No. at Risk											
Pembrolizumab	308	291	277	254	228	201	145	89	36	6	0
Placebo	309	295	268	234	191	160	116	60	28	4	0

C Patients with a PD-L1 Combined Positive Score of ≥10



No. at Risk											
Pembrolizumab	158	149	144	132	118	106	76	46	21	3	0
Placebo	159	151	135	116	95	81	56	31	15	1	0

D Subgroup Analysis in Intention-to-Treat Population

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	312/617	0.67 (0.54–0.84)
Age		
<65 yr	265/517	0.64 (0.50–0.82)
≥65 yr	47/100	0.88 (0.47–1.64)
Race		
White	189/360	0.68 (0.50–0.91)
Non-White	107/221	0.70 (0.47–1.04)
ECOG performance-status score		
0	141/348	0.68 (0.49–0.96)
1	169/267	0.68 (0.50–0.94)
PD-L1 combined positive score		
<1	40/69	1.00 (0.53–1.89)
1 to <10	118/231	0.67 (0.46–0.97)
≥10	154/317	0.61 (0.44–0.84)
Concomitant bevacizumab		
Yes	166/389	0.63 (0.47–0.87)
No	146/228	0.74 (0.53–1.04)
Metastatic disease at diagnosis		
Yes	104/190	0.84 (0.56–1.26)
No	208/427	0.61 (0.46–0.80)

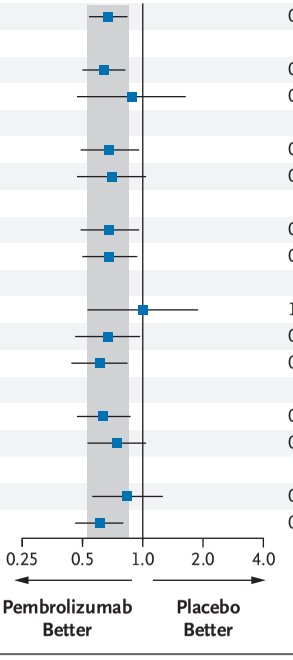


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Figure 3 (facing page). Kaplan–Meier Estimates of Overall Survival.

The assigned regimen in both groups also included paclitaxel, the investigator's choice of cisplatin or carboplatin, and per investigator discretion, bevacizumab. Tick marks in Panels A, B, and C indicate censored data.

both progression-free and overall survival. In the small subgroup of patients with a PD-L1 combined positive score of less than 1, the hazard ratios were close to 1. Given the small size of that subgroup (11.2% of the patients) and the overall KEYNOTE-826 design, it is not possible to draw clear inferences about efficacy in the subgroup of patients with a PD-L1 combined positive score of less than 1, but the effect, if any, appears small.

The safety profile in the pembrolizumab group was as expected on the basis of the profiles previously observed for pembrolizumab and platinum-based chemotherapy with or without bevacizumab in patients with persistent, recurrent, or metastatic cervical cancer.[4-8,10] No new safety signals emerged in the pembrolizumab group. In general, pembrolizumab did not exacerbate known toxic effects of chemotherapy and bevacizumab, and chemotherapy and bevacizumab did not exacerbate immune-mediated adverse events associated with pembrolizumab. As expected, the incidence of adverse events associated with pembrolizumab and another trial agent was higher in the pembrolizumab group than in the placebo group.

The results of the KEYNOTE-826 trial showed that progression-free and overall survival were significantly longer with pembrolizumab than

Table 2. Adverse Events of Any Cause with an Incidence of 20% or More in Either Group (As-Treated Population).*

Event	Pembrolizumab Group (N=307)†		Placebo Group (N=309)†	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)			
Any event	305 (99.3)	251 (81.8)‡	307 (99.4)	232 (75.1)§
Anemia	188 (61.2)	93 (30.3)	165 (53.4)	83 (26.9)
Alopecia	173 (56.4)	0	179 (57.9)	0
Nausea	122 (39.7)	6 (2.0)	135 (43.7)	5 (1.6)
Diarrhea	109 (35.5)	6 (2.0)	92 (29.8)	8 (2.6)
Fatigue	88 (28.7)	11 (3.6)	84 (27.2)	14 (4.5)
Constipation	87 (28.3)	1 (0.3)	102 (33.0)	3 (1.0)
Arthralgia	82 (26.7)	2 (0.7)	80 (25.9)	4 (1.3)
Peripheral neuropathy	81 (26.4)	8 (2.6)	79 (25.6)	9 (2.9)
Vomiting	81 (26.4)	8 (2.6)	84 (27.2)	6 (1.9)
Hypertension	74 (24.1)	29 (9.4)	71 (23.0)	33 (10.7)
Urinary tract infection	73 (23.8)	27 (8.8)	80 (25.9)	25 (8.1)
Neutropenia	72 (23.5)	38 (12.4)	60 (19.4)	30 (9.7)
Peripheral sensory neuropathy	71 (23.1)	3 (1.0)	79 (25.6)	6 (1.9)
Asthenia	63 (20.5)	11 (3.6)	66 (21.4)	5 (1.6)
Thrombocytopenia	61 (19.9)	23 (7.5)	62 (20.1)	14 (4.5)

* Shown are adverse events that occurred while patients were receiving trial agents or within 30 days after the end of the trial treatment period (or, for serious events, within 90 days after the end of trial treatment or within 30 days if the patient initiated new anticancer therapy). The as-treated population included all the patients who underwent randomization and received at least one dose of pembrolizumab or placebo. Events are listed in descending order of frequency in the pembrolizumab group. Adverse events were classified according to the *Medical Dictionary for Regulatory Activities*, version 24.0.

† The assigned regimen in both groups also included paclitaxel, the investigator's choice of cisplatin or carboplatin, and per investigator discretion, bevacizumab.

‡ The maximum grade was grade 3 for 167 patients (54.4%), grade 4 for 70 patients (22.8%), and grade 5 for 14 patients (4.6%).

§ The maximum grade was grade 3 for 176 patients (57.0%), grade 4 for 42 patients (13.6%), and grade 5 for 14 patients (4.5%).

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with placebo among patients with persistent, recurrent, or metastatic cervical cancer who were also receiving platinum-based chemotherapy with or without bevacizumab. The safety profile of the combination was consistent with the known profiles of the individual trial agents.

Supported by Merck Sharp and Dohme, a subsidiary of Merck.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families and caregivers for participating in the trial; the investigators and site personnel; and the following employees of Merck Sharp and Dohme: Gursel Aktan for input into the trial design; Cumhur Tekin for trial oversight; Amy Blum, Susan Galligan, and Karyn O'Flaherty for trial support; Ying Zhang and Jing Zhao for statistical support; Matthew J. Monberg for assistance with patient-reported outcomes; and Melanie A. Leiby for medical writing and editorial assistance with an earlier version of the manuscript.

APPENDIX

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