

ORIGINAL ARTICLE

Survival with Cemiplimab in Recurrent Cervical Cancer

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ABSTRACT

BACKGROUND

Patients with recurrent cervical cancer have a poor prognosis. Cemiplimab, the fully human programmed cell death 1 (PD-1)-blocking antibody approved to treat lung and skin cancers, has been shown to have preliminary clinical activity in this population.

METHODS

In this phase 3 trial, we enrolled patients who had disease progression after first-line platinum-containing chemotherapy, regardless of their programmed cell death ligand 1 (PD-L1) status. Women were randomly assigned (1:1) to receive cemiplimab (350 mg every 3 weeks) or the investigator's choice of single-agent chemotherapy. The primary end point was overall survival. Progression-free survival and safety were also assessed.

RESULTS

A total of 608 women were enrolled (304 in each group). In the overall trial population, median overall survival was longer in the cemiplimab group than in the chemotherapy group (12.0 months vs. 8.5 months; hazard ratio for death, 0.69; 95% confidence interval [CI], 0.56 to 0.84; two-sided $P < 0.001$). The overall survival benefit was consistent in both histologic subgroups (squamous-cell carcinoma and adenocarcinoma [including adenosquamous carcinoma]). Progression-free survival was also longer in the cemiplimab group than in the chemotherapy group in the overall population (hazard ratio for disease progression or death, 0.75; 95% CI, 0.63 to 0.89; two-sided $P < 0.001$). In the overall population, an objective response occurred in 16.4% (95% CI, 12.5 to 21.1) of the patients in the cemiplimab group, as compared with 6.3% (95% CI, 3.8 to 9.6) in the chemotherapy group. An objective response occurred in 18% (95% CI, 11 to 28) of the cemiplimab-treated patients with PD-L1 expression greater than or equal to 1% and in 11% (95% CI, 4 to 25) of those with PD-L1 expression of less than 1%. Overall, grade 3 or higher adverse events occurred in 45.0% of the patients who received cemiplimab and in 53.4% of those who received chemotherapy.

CONCLUSIONS

Survival was significantly longer with cemiplimab than with single-agent chemotherapy among patients with recurrent cervical cancer after first-line platinum-containing chemotherapy. (Funded by Regeneron Pharmaceuticals and Sanofi; EMPower-Cervical 1/GOG-3016/ENGOT-cx9 ClinicalTrials.gov number, NCT03257267.)

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DESPITE VALIDATED SCREENING programs for cervical cancer using cytologic assessment and high-risk human papillomavirus DNA detection and the availability of effective prophylactic vaccines, approximately 600,000 new cases of cervical cancer and 350,000 deaths from cervical cancer occur worldwide each year.¹ The American Cancer Society estimates that 14,100 new cases and 4280 deaths will have occurred in the United States in 2022.² Although frankly invasive early disease (International Federation of Gynecology and Obstetrics [FIGO] stage IB₁ or IB₂)³ can be treated with radical hysterectomy and lymphadenectomy with or without adjuvant therapy, patients with locally advanced carcinoma (FIGO stage IB₃-IVA)³ receive chemoradiation and high-dose-rate intracavitary brachytherapy.⁴ Patients with persistent or recurrent disease after radiotherapy that is not amenable to curative pelvic exenteration with urinary diversion, as well as those who present with metastases (FIGO stage IVB),³ are treated with platinum-based chemotherapy^{5,6} with or without bevacizumab.⁷

Despite the improvement in overall survival conferred by antiangiogenic therapy,^{7,8} most patients have progression after first-line platinum-containing therapy and have limited treatment options. Cemiplimab is a high-affinity, fully human programmed cell death 1 (PD-1)-blocking monoclonal antibody with activity in cervical cancer.^{9,10}

METHODS

TRIAL OVERSIGHT

We conducted EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9, an open-label, multicenter, phase 3 trial sponsored by Regeneron Pharmaceuticals and Sanofi, which provided cemiplimab free of charge in accordance with European Network for Gynecological Oncological Trial groups—Gynecologic Oncology Group model C.¹¹ The first draft of the manuscript was written by the first author and was critically reviewed and revised by all authors. The authors take responsibility for the accuracy and completeness of the reported data and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org.

PATIENTS

Patients with recurrent or metastatic cervical carcinoma were eligible for participation if their

tumor had progressed after platinum-containing therapy used to treat recurrence or metastases. Patients had to have previously received bevacizumab and paclitaxel therapy (unless they had declined the treatment, the treatment had been deemed unsuitable, or, in the case of bevacizumab, the patient did not have access to the drug). Previous bevacizumab treatment had to have been discontinued because of progression or toxic effects before enrollment in the trial. Candidates for pelvic exenteration were excluded. All cancers were confirmed by local pathological review. An Eastern Cooperative Oncology Group (ECOG) performance-status score¹² of 0 or 1 was required for enrollment (scores range from 0 to 5, with higher scores indicating greater disability), and patients had to have adequate renal, hepatic, and bone marrow function. Patients were required to have measurable disease.

Patients with ongoing or recent (within 5 years) evidence of moderate-to-severe autoimmune disease, as well as those who had received immunosuppressive glucocorticoid doses (>10 mg of prednisone daily or the equivalent) within 4 weeks before the first dose of trial drug and those with active bacterial, viral, fungal, or mycobacterial infection deemed to require therapy, were excluded. Squamous-cell carcinoma, adenocarcinoma, and adenosquamous carcinoma histologic types were permitted, and patients were enrolled regardless of programmed cell death ligand 1 (PD-L1) expression status. Previous anti-PD-1 or anti-PD-L1 therapy was not permitted. Treatment with other systemic immune-modulating agents within 4 weeks before the trial enrollment date was not permitted.

TRIAL DESIGN AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive either cemiplimab or the investigator's choice of chemotherapy as the control therapy (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Randomization was stratified according to histologic type (squamous-cell carcinoma or adenocarcinoma [including adenosquamous carcinoma]), geographic region (North America, Asia, or rest of the world), previous bevacizumab exposure (yes or no), and ECOG performance-status score (0 or 1). A protocol amendment was implemented to cap enrollment of patients with adenocarcinoma or adenosquamous carcinoma, with the intent to enroll a trial population that

matched the real-world distribution of histologic types.

Control therapy was determined before randomization by the investigator from protocol-specified options reflecting the availability of drugs in different regions of the world. Anti-folate therapy consisted of pemetrexed (500 mg per square meter of body-surface area administered intravenously every 21 days), with vitamin B₁₂ and folate support given as needed. Topoisomerase I inhibitors included topotecan (1 mg per square meter administered intravenously daily for 5 days) or irinotecan (100 mg per square meter administered intravenously weekly for 4 weeks). The nucleoside analogue gemcitabine (1000 mg per square meter administered intravenously on days 1 and 8 every 21 days) and the vinca alkaloid vinorelbine (30 mg per square meter administered intravenously on days 1 and 8 every 21 days) were also available. Control therapy was discontinued at the onset of disease progression or development of unacceptable toxic effects, with stopping rules for adverse events outlined in the protocol and no crossover allowed.

For patients who were randomly assigned to the cemiplimab group, cemiplimab was administered at a flat dose of 350 mg intravenously every 21 days for up to 96 weeks with an option for repeat treatment for patients who completed 16 treatment cycles and then had progressive disease in the post-treatment follow-up period. Patients receiving cemiplimab who had an unconventional response consistent with pseudo-progression were allowed to be treated beyond progression, provided the ECOG performance-status score did not increase, rapid disease progression did not occur, and severe adverse events warranting cemiplimab discontinuation were not encountered.

ASSESSMENTS AND BIOMARKER ANALYSES

Details of baseline tumor and response assessments and adverse events, including the assessment schedule (Table S1), are provided in the Supplementary Appendix. Exploratory analyses were performed on archival tumor samples to evaluate associations between efficacy end points and biomarkers, including PD-L1 expression in tumor cells, as detected with the use of the SP263 monoclonal antibody (Ventana).¹³ PD-L1 expression status (measured as the tumor cell expression score [the percentage of tumor cells

expressing PD-L1]) was categorized as either greater than or equal to 1% or less than 1% in tumor cells. Only samples stained within 6 months after slide sectioning were analyzed, in accordance with the assay manufacturer instructions for use.

Quality of life was assessed with the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (QLQ-C30), which includes five function scales, nine symptom scales, and a global health status and quality-of-life scale; results for the global health status and quality-of-life scale are included in this report. Scores on this scale range from 0 to 100 after linear transformation of the raw scores, with higher scores representing better global health status and quality-of-life. The threshold for a clinically meaningful difference was an increase by 10 or more points from baseline to cycle 8.¹⁴ Additional details are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The statistical analysis plan is available with the protocol at NEJM.org. Definitions of end points are provided in the Supplementary Appendix. The primary end point, overall survival, was analyzed with the use of the intention-to-treat principle, with patients grouped according to randomized treatment assignment, regardless of adherence. Secondary end points of progression-free survival, objective response, response duration, and quality of life were similarly analyzed with the use of the intention-to-treat principle. However, safety was analyzed in the “as-treated” population (i.e., patients who received any trial drug). Differences in overall and progression-free survival were assessed with the log-rank test with the use of geographic region and tumor histologic type as stratification factors, as prespecified in the statistical analysis plan.¹⁵ Hazard ratios and associated 95% confidence intervals were estimated with stratified Cox proportional hazards models.¹⁶ Longitudinal changes in QLQ-C30 quality-of-life scores from baseline were analyzed with the use of a mixed-effects model for repeated measures (MMRM).¹⁷⁻¹⁹ Only scheduled visits during treatment for which data were available for 10 or more patients in both treatment groups were planned for inclusion in the MMRM analysis. After the first eight cycles, the sample size became too small for robust analysis

(<10 patients in the chemotherapy group). The MMRM model was used to estimate the least-squares mean change from baseline in the quality-of-life score at each scheduled visit during treatment.

Approximately 460 patients with squamous-cell carcinoma would need to be enrolled, with approximately 340 deaths expected, to provide 90% power to detect at least a 30% lower risk of death in the cemiplimab group than in the chemotherapy group with an overall one-sided type I error of 2.5% in the population with squamous-cell carcinoma. Approximately 590 patients in the overall population (i.e., patients with either histologic subtype) were projected to be needed to complete enrollment of 460 patients with squamous-cell carcinoma. Two interim analyses were planned to be conducted after approximately 70% and 85% of deaths had occurred among the patients with squamous-cell carcinoma, in order to allow for reporting of treatment activity early in the event of dramatic results with respect to survival.^{20,21} The interim analyses were conducted by an independent statistics group and were reviewed by the independent data and safety monitoring committee.

Type I error was controlled with the use of a hierarchical testing plan that started with an analysis of overall survival in the population with squamous-cell carcinoma; if these results were significant, overall survival was then analyzed in the overall population (Table S2).²² The analyses used for secondary end points are described in the Supplementary Appendix. Confidence intervals reported for analyses outside the testing hierarchy or below the first nonsignificant result within the testing hierarchy have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Because the trial was designed to assess superiority, one-sided tests were specified for the alternative hypothesis, critical regions, and P values. However, two-sided tests are reported in the main text.

For the analysis of safety, treatment-related adverse events occurring at any time and adverse events reported until 90 days after the last dose of treatment or 1 day before the start of post-treatment therapy, whichever commenced earlier, regardless of the relationship to the trial treatment, were summarized for patients who received any trial treatment and for whom information on adverse events was submitted.

RESULTS

PATIENTS AND TREATMENT

From July 2017 through August 2020, a total of 608 patients were enrolled and randomly assigned to receive cemiplimab (304) or chemotherapy (304) (Fig. 1). The median age of the patients was 51 years (range, 22 to 87). Among the patients in the trial, 473 (77.8%) had squamous-cell carcinoma and 135 (22.2%) had adenocarcinoma or adenosquamous carcinoma. The demographic and disease characteristics of the patients at baseline were balanced between the treatment groups (Table 1). All the patients had previously had disease progression after platinum-containing therapy used to treat recurrence. Approximately 40% of the patients in each group had received more than one previous line of systemic therapy for recurrence, and approximately 50% in each group had previously received bevacizumab (Table 1). All the data reported herein are based on a data cutoff date of January 4, 2021.

In the overall population, the median duration of treatment exposure was 15.2 weeks (range, 1.4 to 100.7) for cemiplimab and 10.1 weeks (range, 1.0 to 81.9) for chemotherapy. The median duration of follow-up from randomization to the data cutoff was 18.2 months (range, 6.0 to 38.2) for all patients. As of the data cutoff, 37 patients (12.2%) were still receiving cemiplimab, 1 (0.3%) was receiving retreatment with cemiplimab, and 7 (2.3%) were receiving chemotherapy. Disease progression led to discontinuation of trial treatment in 199 patients (65.5%) receiving cemiplimab and in 229 (75.3%) receiving chemotherapy.

EFFICACY

At the second planned interim analysis (median follow-up of 16.8 months in the population with squamous-cell carcinoma), the trial was stopped on the basis of prespecified criteria for efficacy in the population with squamous-cell carcinoma. In the overall population, median overall survival with cemiplimab was 12.0 months (95% confidence interval [CI], 10.3 to 13.5), as compared with 8.5 months (95% CI, 7.5 to 9.6) with chemotherapy (hazard ratio for death, 0.69; 95% CI, 0.56 to 0.84; two-sided $P < 0.001$) (Fig. 2A). Assessment according to the type of chemotherapy chosen by the investigator showed median overall survival in the chemotherapy group

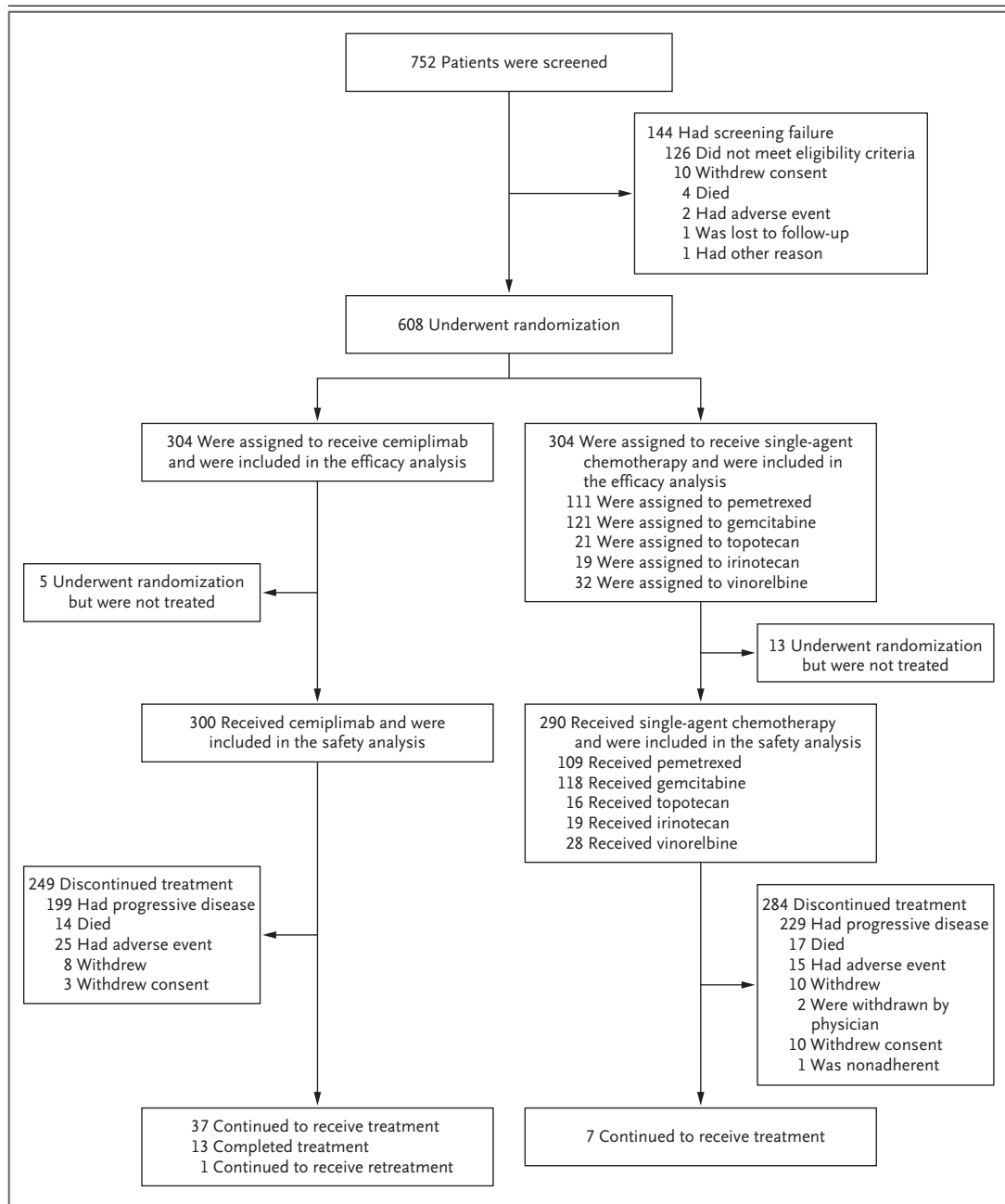


Figure 1. Screening, Randomization, and Treatment.

Of the patients who were randomly assigned to receive chemotherapy, 47 (15.5%) received post-trial treatment with immune-checkpoint inhibitors, and 46 (15.1%) received post-trial treatment with anti-programmed cell death ligand 1 (PD-L1) agents. One patient was randomly assigned to the chemotherapy group but received one dose of cemiplimab and then discontinued treatment; this patient was included in the cemiplimab group for the safety analysis. The figure shows only the primary reason for discontinuation of treatment according to the treating investigator. Treatment discontinuation could occur because of more than one reason in a single patient (e.g., an adverse event plus disease progression).

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.

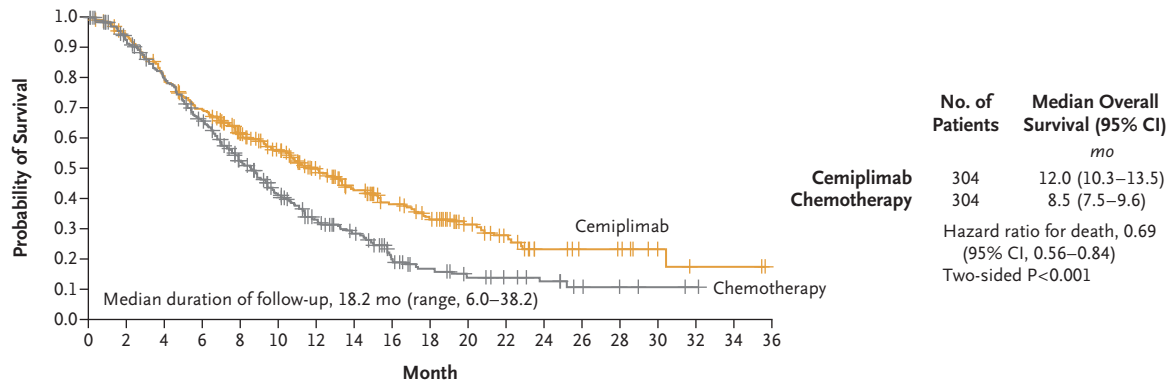
Characteristic	Cemiplimab (N = 304)	Chemotherapy (N = 304)	Overall (N = 608)
Age			
Median (range) — yr	51 (22–81)	50 (24–87)	51 (22–87)
<65 years — no. (%)	269 (88.5)	264 (86.8)	533 (87.7)
Race or ethnic group — no. (%) [*]			
White	193 (63.5)	192 (63.2)	385 (63.3)
Black	9 (3.0)	12 (3.9)	21 (3.5)
Asian	88 (28.9)	88 (28.9)	176 (28.9)
American Indian or Alaska Native	2 (0.7)	1 (0.3)	3 (0.5)
Other	8 (2.6)	4 (1.3)	12 (2.0)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)
Not reported	3 (1.0)	6 (2.0)	9 (1.5)
Hispanic or Latino			
No	251 (82.6)	250 (82.2)	501 (82.4)
Yes	47 (15.5)	44 (14.5)	91 (15.0)
Not reported	6 (2.0)	10 (3.3)	16 (2.6)
Region of enrollment — no. (%)			
North America	32 (10.5)	34 (11.2)	66 (10.9)
Asia	83 (27.3)	83 (27.3)	166 (27.3)
Rest of the world	189 (62.2)	187 (61.5)	376 (61.8)
ECOG performance-status score — no. (%) ^{*†}			
0	142 (46.7)	141 (46.4)	283 (46.5)
1	162 (53.3)	163 (53.6)	325 (53.5)
Histologic type — no. (%) ^{*‡}			
Squamous-cell carcinoma	240 (78.9)	233 (76.6)	473 (77.8)
Adenocarcinoma or adenosquamous carcinoma	64 (21.1)	71 (23.4)	135 (22.2)
Extent of disease — no. (%)			
Metastatic	284 (93.4)	290 (95.4)	574 (94.4)
Recurrent or persistent	20 (6.6)	14 (4.6)	34 (5.6)
Previous lines of therapy for recurrent or metastatic disease — no. (%)			
One	177 (58.2)	169 (55.6)	346 (56.9)
More than one	124 (40.8)	135 (44.4)	259 (42.6)
Previous bevacizumab use — no. (%) [§]			
Yes	149 (49.0)	147 (48.4)	296 (48.7)
No	155 (51.0)	157 (51.6)	312 (51.3)
Previous paclitaxel use — no. (%) [§]			
Yes	273 (89.8)	287 (94.4)	560 (92.1)
No	31 (10.2)	17 (5.6)	48 (7.9)

* Information is from the electronic data-capture system.

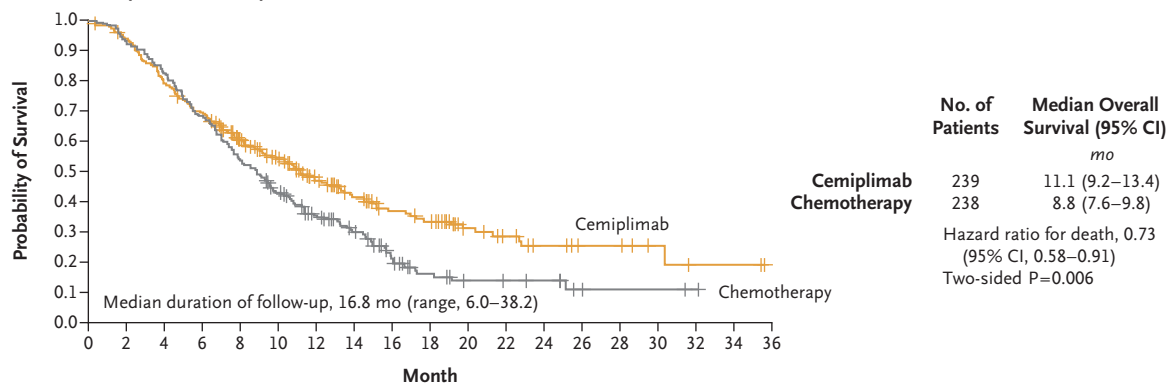
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

‡ At the time of randomization, discrepancies between the electronic data-capture system and interactive Web response system in the distribution of histologic types were introduced. According to the electronic data-capture system, 77.8% of the patients had squamous-cell carcinoma and 22.2% had adenocarcinoma or adenosquamous carcinoma. According to the interactive Web response system, 78.5% of the patients had squamous-cell carcinoma and 21.5% had adenocarcinoma or adenosquamous carcinoma.

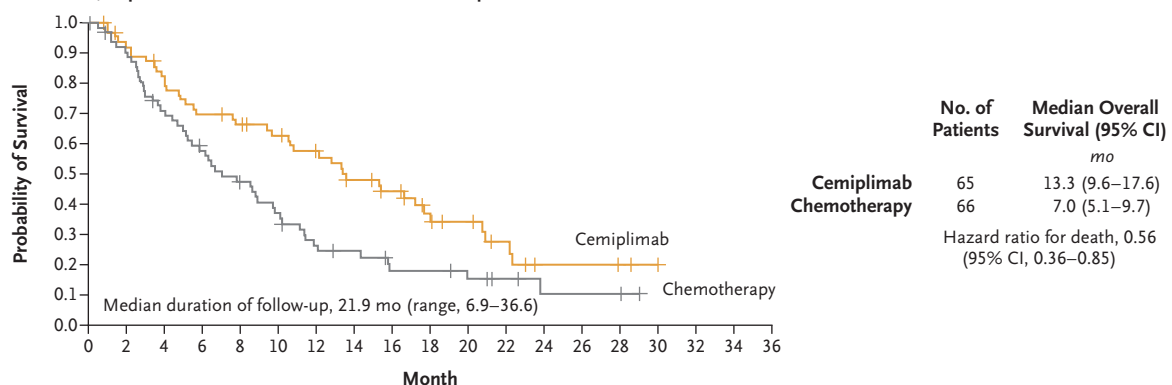
§ Information is from the interactive Web response system.

A Overall Survival, All Patients**No. at Risk**

Cemiplimab	304	281	236	206	167	139	110	83	65	52	35	26	13	10	9	4	2	2	0
Chemotherapy	304	264	224	183	132	99	70	54	32	22	15	12	9	5	3	2	1	0	0

B Overall Survival, Population with Squamous-Cell Carcinoma**No. at Risk**

Cemiplimab	239	223	188	163	127	103	79	58	44	39	24	19	10	7	7	4	2	2	0
Chemotherapy	238	209	182	149	105	78	56	42	24	14	9	8	7	3	2	2	1	0	0

C Overall Survival, Population with Adenocarcinoma or Adenosquamous Carcinoma**No. at Risk**

Cemiplimab	65	58	48	43	40	36	31	25	21	13	11	7	3	3	2	0	0	0	0
Chemotherapy	66	55	42	34	27	21	14	12	8	8	6	4	2	2	1	0	0	0	0

Figure 2 (facing page). Overall Survival.

Kaplan–Meier curves for overall survival in the overall trial population (Panel A), the population with squamous-cell carcinoma (Panel B), and the population with adenocarcinoma or adenosquamous carcinoma (Panel C) are shown. The hazard ratio in the overall trial population was assessed with a Cox regression model stratified according to geographic region (North America, Asia, or the rest of the world) and histologic type (squamous-cell carcinoma or adenocarcinoma [including adenosquamous carcinoma]) as reported in the interactive Web response system. The hazard ratio in the population with squamous-cell carcinoma was assessed with a Cox regression model stratified according to geographic region (North America, Asia, or the rest of the world) as reported in the interactive web response system. The confidence interval for the hazard ratio in the population with adenocarcinoma or adenosquamous carcinoma has not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. The duration of follow-up was defined as the time from randomization to the data cutoff date. Tick marks indicate censored data.

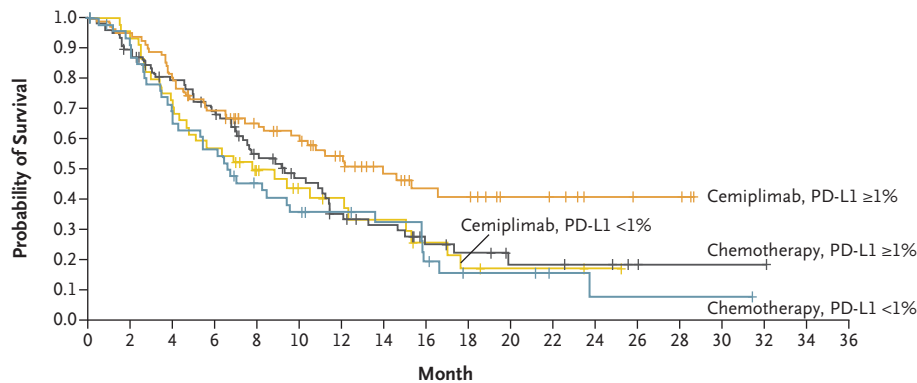
in the overall population that ranged from 6.5 months (95% CI, 4.4 to 8.8) with topotecan to 11.8 months (95% CI, 6.9 to 14.9) with irinotecan (Table S3). In the population with squamous-cell carcinoma, median overall survival was significantly longer with cemiplimab than with chemotherapy (11.1 months [95% CI, 9.2 to 13.4] vs. 8.8 months [95% CI, 7.6 to 9.8]; hazard ratio, 0.73; 95% CI, 0.58 to 0.91; two-sided $P=0.006$) (Fig. 2B). In the population with adenocarcinoma or adenosquamous carcinoma, median overall survival was 13.3 months (95% CI, 9.6 to 17.6) with cemiplimab, as compared with 7.0 months (95% CI, 5.1 to 9.7) with chemotherapy (hazard ratio, 0.56; 95% CI, 0.36 to 0.85) (Fig. 2C). The treatment benefit of cemiplimab over chemotherapy was also observed in analyses of subgroups defined according to ECOG performance-status score and previous bevacizumab exposure. Subgroup analyses according to age and previous lines of systemic therapy were limited by small numbers and although directionally consistent, the confidence interval for the hazard ratio crossed 1.0 in these subgroups (Fig. S2).

In the overall population, median progression-free survival was 2.8 months (95% CI, 2.6 to 3.9) with cemiplimab and 2.9 months (95% CI, 2.7 to 3.4) with chemotherapy (hazard ratio for disease

progression or death, 0.75; 95% CI, 0.63 to 0.89; two-sided $P<0.001$) (Fig. S3A). In the population with squamous-cell carcinoma, median progression-free survival was 2.8 months (95% CI, 2.6 to 4.0) with cemiplimab and 2.9 months (95% CI, 2.7 to 3.9) with chemotherapy (Fig. S3B). Although median progression-free survival was similar in the two groups, the hazard ratio of 0.71 (95% CI, 0.58 to 0.86; two-sided $P<0.001$) indicated significantly longer progression-free survival conferred by cemiplimab than by chemotherapy. Subgroup analysis of the population with adenocarcinoma or adenosquamous carcinoma showed median progression-free survival of 2.7 months (95% CI, 2.3 to 4.0) with cemiplimab and 2.8 months (95% CI, 2.0 to 3.2) with chemotherapy (hazard ratio, 0.91; 95% CI, 0.62 to 1.34) (Fig. S3C). The benefit with respect to progression-free survival with cemiplimab was driven by durable separation of the curves after median progression-free survival was reached (Fig. S3).

In the overall population, the percentage of patients with an objective response was 16.4% (95% CI, 12.5 to 21.1) in the cemiplimab group, as compared with 6.3% (95% CI, 3.8 to 9.6) in the chemotherapy group (two-sided $P<0.001$) (Table S4). The Kaplan–Meier estimate of the median duration of response in the overall patient population was 16.4 months (95% CI, 12.4 to not reached) for cemiplimab and 6.9 months (95% CI, 5.1 to 7.7) for chemotherapy (Table S4). In the population with squamous-cell carcinoma, an objective response occurred in 17.6% (95% CI, 13.0 to 23.0) of the patients in the cemiplimab group, as compared with 6.7% (95% CI, 3.9 to 10.7) of those in the chemotherapy group (two-sided $P<0.001$) (Table S4). In the population with adenocarcinoma or adenosquamous carcinoma, the corresponding percentages were 12% (95% CI, 6 to 23) and 4% (95% CI, 1 to 13) (Table S4).

The marked effect of cemiplimab on tumor growth was evident when individual tumor growth curves were evaluated for all patients treated with cemiplimab as compared with those treated with chemotherapy (Fig. S4A and S4B). To highlight the greater depth and duration of tumor responses in the cemiplimab group, the median percent change in target lesions over time for cemiplimab as compared with chemotherapy is shown in Figure S4C.

**No. at Risk**

Cemiplimab, PD-L1 $\geq 1\%$	82	78	65	55	45	39	30	22	16	15	10	9	4	3	3	0	0	0	0
Cemiplimab, PD-L1 <1%	44	41	30	25	18	13	11	9	6	4	3	3	1	0	0	0	0	0	0
Chemotherapy, PD-L1 $\geq 1\%$	80	69	58	50	36	28	20	16	10	8	5	5	4	2	1	1	1	0	0
Chemotherapy, PD-L1 <1%	48	40	30	26	19	15	12	10	6	4	4	2	1	1	1	1	0	0	0

Figure 3. Overall Survival According to PD-L1 Expression Status in the Overall Trial Population.

Kaplan–Meier estimates of overall survival according to PD-L1 expression status are shown. Patients with PD-L1 expression (measured as the tumor cell expression score [the percentage of tumor cells expressing PD-L1]) of 1% or greater generally had enhancement of the overall survival benefit. Patients with PD-L1 expression of less than 1% generally had an overall survival benefit as good as or slightly better than that of patients who received chemotherapy. Tick marks indicate censored data.

QUALITY OF LIFE

The percentage of patients who completed the QLQ-C30 global health status and quality-of-life scale was greater than 95% at baseline and remained high during the entire treatment period in both treatment groups, at approximately 90% among those expected to complete the questionnaire (i.e., those who were alive and still receiving trial treatment). In the overall population, the estimated least-squares mean difference between cemiplimab and chemotherapy from baseline through cycle 8 in the global health status and quality-of-life score was 7.8 points (95% CI, 3.3 to 12.3). The within-group overall least-squares mean change from baseline quality-of-life score was 1.0 (95% CI, –2.0 to 4.0) in the cemiplimab group and –6.8 (95% CI, –11.0 to –2.6) in the chemotherapy group (Fig. S5).

PD-L1 EXPRESSION

Of the 608 patients who underwent randomization, 254 had baseline tumor samples that could be evaluated for PD-L1 expression: 126 in the cemiplimab group and 128 in the chemotherapy group. This subpopulation of patients had clinical outcomes similar to those observed in the overall population. Among patients with a baseline sample that could be evaluated, PD-L1 expression of 1% or greater was more common

among the patients with squamous-cell carcinoma (70.7%, 147 of 208 patients) than among those with adenocarcinoma or adenosquamous carcinoma (32.6%, 15 of 46 patients).

The effect of cemiplimab as compared with chemotherapy on overall survival according to PD-L1 expression status is shown in Figure 3B. Among the patients with PD-L1 expression of 1% or greater, median overall survival was 13.9 months (95% CI, 9.6 to not reached) with cemiplimab, as compared with 9.3 months (95% CI, 7.0 to 11.4) with chemotherapy (hazard ratio for death, 0.70; 95% CI, 0.46 to 1.05). Among the patients with PD-L1 expression of less than 1%, median overall survival was 7.7 months (95% CI, 4.3 to 12.3) with cemiplimab and 6.7 months (95% CI, 3.9 to 9.5) with chemotherapy (hazard ratio, 0.98; 95% CI, 0.59 to 1.62). Objective responses to cemiplimab were observed in 15 of 82 patients with PD-L1 expression of 1% or greater (18%; 95% CI, 11 to 28) and in 5 of 44 patients with PD-L1 expression of less than 1% (11%; 95% CI, 4 to 25). Additional analyses of PD-L1 expression and efficacy are shown in Table S5.

SAFETY

Adverse events, regardless of attribution, occurred in 88.3% of the patients who received cemiplimab and in 91.4% of those who received

Table 2. Adverse Events Regardless of Attribution.*

Adverse Event	Cemiplimab (N=300)		Chemotherapy (N=290)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	<i>number of patients (percent)</i>			
Any	265 (88.3)	135 (45.0)	265 (91.4)	155 (53.4)
Serious	89 (29.7)	69 (23.0)	78 (26.9)	64 (22.1)
Led to treatment discontinuation	26 (8.7)	20 (6.7)	15 (5.2)	11 (3.8)
Led to death	5 (1.7)	5 (1.7)	2 (0.7)	2 (0.7)
Occurred in ≥10% in either group†				
Anemia	75 (25.0)	36 (12.0)	129 (44.5)	78 (26.9)
Nausea	55 (18.3)	1 (0.3)	97 (33.4)	6 (2.1)
Fatigue	50 (16.7)	4 (1.3)	45 (15.5)	4 (1.4)
Vomiting	48 (16.0)	2 (0.7)	68 (23.4)	7 (2.4)
Decreased appetite	45 (15.0)	1 (0.3)	46 (15.9)	2 (0.7)
Constipation	45 (15.0)	0	59 (20.3)	1 (0.3)
Pyrexia	35 (11.7)	1 (0.3)	61 (21.0)	0
Urinary tract infection	35 (11.7)	15 (5.0)	25 (8.6)	8 (2.8)
Asthenia	33 (11.0)	7 (2.3)	44 (15.2)	3 (1.0)
Back pain	33 (11.0)	4 (1.3)	25 (8.6)	2 (0.7)
Diarrhea	32 (10.7)	3 (1.0)	39 (13.4)	4 (1.4)
Arthralgia	31 (10.3)	1 (0.3)	8 (2.8)	0
Abdominal pain	29 (9.7)	3 (1.0)	33 (11.4)	3 (1.0)
Neutropenia	6 (2.0)	3 (1.0)	44 (15.2)	26 (9.0)

* Safety was assessed in all patients who underwent randomization and received at least one dose of the assigned treatment. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

† The events are listed in descending order of frequency in the cemiplimab group. The events were coded according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 23.1.

chemotherapy; events of grade 3 or higher occurred in 45.0% and 53.4%, respectively (Table 2). The most common grade 3 or higher adverse events (occurring in ≥5% of patients in either group) were anemia (12.0% with cemiplimab and 26.9% with chemotherapy), urinary tract infection (5.0% and 2.8%), and neutropenia (1.0% and 9.0%) (Tables 2 and S6).

Adverse events that resulted in discontinuation of the trial treatment occurred in 26 patients (8.7%) receiving cemiplimab and in 15 patients (5.2%) receiving chemotherapy (Table 2). Adverse events, regardless of attribution, that led to death occurred in 1.7% of patients treated with cemiplimab and in 0.7% of those treated with chemotherapy. None of the adverse events leading to death were considered by the treating investigator to be related to cemiplimab. Immune-related adverse events occurred in

15.7% of the patients in the cemiplimab group and in 0.7% of those in the chemotherapy group (Table S6).

DISCUSSION

Cemiplimab treatment led to significantly longer overall survival than chemotherapy among patients with recurrent cervical cancer who had had disease progression after first-line platinum-containing chemotherapy. As compared with the investigator's choice of chemotherapy, cemiplimab treatment resulted in a 31% lower risk of death in the overall population and a 27% lower risk of death in the population with squamous-cell carcinoma. The overall survival benefit with cemiplimab was consistent in clinically relevant subgroups, including patients with adenocarcinoma or adenosquamous carcinoma and patients

with previous bevacizumab exposure. The effect of cemiplimab on progression-free survival was less clear; medians were similar in the two groups, but the curve in the cemiplimab group had a tail suggesting that a subgroup of patients benefited. The percentage of patients with an objective response was significantly higher in the cemiplimab group than in the chemotherapy group, both in the overall population and in the population with squamous-cell carcinoma.

The survival benefit with cemiplimab was observed in patients with squamous-cell carcinoma and in those with adenocarcinoma or adenosquamous carcinoma. Among the cemiplimab-treated patients, an overall response occurred in a higher percentage of patients in the population with squamous-cell carcinoma than in the population with adenocarcinoma or adenosquamous carcinoma. Although a relatively greater magnitude of benefit with respect to median survival was observed in patients with adenocarcinoma or adenosquamous carcinoma than in those with squamous-cell carcinoma, the confidence interval was wide in the relatively small subgroup of patients with adenocarcinoma or adenosquamous carcinoma.

The safety profile of cemiplimab was consistent with that previously reported for the drug and for other PD-1 or PD-L1 inhibitors in patients with other tumor types.²³⁻²⁵ Although patients had a longer median duration of exposure to cemiplimab (15.2 weeks) than to chemotherapy (10.1 weeks), cemiplimab-treated patients had fewer adverse events of any grade, as well as fewer grade 3 or higher events. The number of deaths caused by adverse events was low in both treatment groups.

Currently, pembrolizumab is the sole anti-PD-1 agent approved in the United States as second-line therapy for patients with recurrent cervical cancer.²⁶ The approval of pembrolizumab was initially based on a single-group phase 2

trial in which antitumor activity was observed in patients with PD-L1–positive tumors (combined positive score, ≥ 1) but not in PD-L1–negative tumors. Accordingly, the approved use of pembrolizumab as monotherapy in the context of second-line and later treatment is restricted to patients whose tumors express PD-L1 with a combined positive score of 1 or higher.

In this trial, objective responses were seen in patients with PD-L1 expression of less than 1%. Unfortunately, only a subgroup of patients had samples that could be evaluated for PD-L1 expression, which made interpretation of the role of PD-L1 expression in the response to cemiplimab treatment difficult to assess. However, these results suggest that some PD-L1–negative patients may nevertheless have a response to cemiplimab.

In our randomized trial involving patients with recurrent cervical cancer who had disease progression after platinum-containing therapy, cemiplimab showed a benefit with respect to overall survival that was significant and clinically meaningful. The results suggested that some women with recurrent cervical cancer may benefit from therapy with cemiplimab.

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APPENDIX

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