ORIGINAL ARTICLE

Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma

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ABSTRACT

BACKGROUND

First-line chemotherapy for advanced esophageal squamous-cell carcinoma results in poor outcomes. The monoclonal antibody nivolumab has shown an overall survival benefit over chemotherapy in previously treated patients with advanced esophageal squamous-cell carcinoma.

METHODS

In this open-label, phase 3 trial, we randomly assigned adults with previously untreated, unresectable advanced, recurrent, or metastatic esophageal squamous-cell carcinoma in a 1:1:1 ratio to receive nivolumab plus chemotherapy, nivolumab plus the monoclonal antibody ipilimumab, or chemotherapy. The primary end points were overall survival and progression-free survival, as determined by blinded independent central review. Hierarchical testing was performed first in patients with tumor-cell programmed death ligand 1 (PD-L1) expression of 1% or greater and then in the overall population (all randomly assigned patients).

RESULTS

A total of 970 patients underwent randomization. At a 13-month minimum follow-up, overall survival was significantly longer with nivolumab plus chemotherapy than with chemotherapy alone, both among patients with tumor-cell PD-L1 expression of 1% or greater (median, 15.4 vs. 9.1 months; hazard ratio, 0.54; 99.5% confidence interval [CI], 0.37 to 0.80; P<0.001) and in the overall population (median, 13.2 vs. 10.7 months; hazard ratio, 0.74; 99.1% CI, 0.58 to 0.96; P=0.002). Overall survival was also significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with tumor-cell PD-L1 expression of 1% or greater (median, 13.7 vs. 9.1 months; hazard ratio, 0.64; 98.6% CI, 0.46 to 0.90; P=0.001) and in the overall population (median, 12.7 vs. 10.7 months; hazard ratio, 0.78; 98.2% CI, 0.62 to 0.98; P=0.01). Among patients with tumor-cell PD-L1 expression of 1% or greater, a significant progression-free survival benefit was also seen with nivolumab plus chemotherapy over chemotherapy alone (hazard ratio for disease progression or death, 0.65; 98.5% CI, 0.46 to 0.92; P=0.002) but not with nivolumab plus ipilimumab as compared with chemotherapy. The incidence of treatment-related adverse events of grade 3 or 4 was 47% with nivolumab plus chemotherapy, 32% with nivolumab plus ipilimumab, and 36% with chemotherapy alone.

CONCLUSIONS

Both first-line treatment with nivolumab plus chemotherapy and first-line treatment with nivolumab plus ipilimumab resulted in significantly longer overall survival than chemotherapy alone in patients with advanced esophageal squamous-cell carcinoma, with no new safety signals identified. (Funded by Bristol Myers Squibb and Ono Pharmaceutical; CheckMate 648 ClinicalTrials.gov number, NCT03143153.)

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*A complete list of the sites and investigators in the CheckMate 648 trial is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Esophageal cancer causes more than half a million cancer-related deaths worldwide each year,[1] with squamous-cell carcinoma accounting for approximately 85% of cases.[2] Many esophageal cancers are unresectable at diagnosis, and most patients treated with curative intent eventually have a relapse.[3-6]

Standard fluoropyrimidine-plus-platinum–based chemotherapy for advanced or metastatic esophageal squamous-cell carcinoma often results in poor survival outcomes (median survival, <1 year).[7-9] Although chemotherapy has been a widely used first-line treatment for decades,[10-13] clinical benefit was recently reported with programmed death 1 (PD-1) inhibitors in combination with chemotherapy over chemotherapy alone.[14,15]

Tumor-cell programmed death ligand 1 (PD-L1) expression in esophageal squamous-cell carcinoma is enriched,[16] with expression of 1% or greater detected in approximately 50% of patients with advanced disease.[17] Treatment with the anti–PD-1 monoclonal antibody nivolumab has been reported to result in significantly longer overall survival than chemotherapy in previously treated patients with advanced esophageal squamous-cell carcinoma and is approved for this indication, irrespective of PD-L1 expression status.[12,17] In a phase 3 trial involving patients with gastric, gastroesophageal junction, or esophageal adenocarcinoma, first-line treatment with nivolumab plus chemotherapy resulted in a significant overall survival and progression-free survival benefit as compared with chemotherapy alone, as well as in durable objective responses and an acceptable safety profile.[18] First-line dual checkpoint inhibition with nivolumab and ipilimumab, an anti–cytotoxic T-lymphocyte antigen 4 antibody, has also been shown to lead to longer overall survival than chemotherapy or nivolumab monotherapy in multiple solid tumors.[19-21]

CheckMate 648 is a global phase 3 trial that evaluated the efficacy and safety of both an immune checkpoint inhibitor in combination with chemotherapy and a dual immune checkpoint inhibitor combination in previously untreated patients with advanced esophageal squamous-cell carcinoma. We report the results for nivolumab plus chemotherapy and for nivolumab plus ipilimumab as compared with chemotherapy alone.

Methods

Patients

Eligible patients were at least 18 years of age; had unresectable advanced, recurrent, or metastatic esophageal squamous-cell carcinoma, regardless of PD-L1 expression status; had disease that was not amenable to curative treatments; and had not received previous systemic therapy for advanced disease. Patients had histologically confirmed esophageal squamous-cell or adenosquamous-cell carcinoma and had measurable disease, according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Additional details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design and Interventions

CheckMate 648 is a global, randomized, open-label, phase 3 trial. Patients were randomly assigned in a 1:1:1 ratio to receive nivolumab (administered intravenously at a dose of 240 mg every 2 weeks) plus chemotherapy (consisting of a 4-week cycle of intravenous fluorouracil at a dose of 800 mg per square meter of body-surface area on days 1 through 5 and intravenous cisplatin at a dose of 80 mg per square meter on day 1); nivolumab (administered intravenously at a dose of 3 mg per kilogram of body weight every 2 weeks) plus ipilimumab (administered intravenously at a dose of 1 mg per kilogram every 6 weeks); or chemotherapy alone. Treatment continued until disease progression, unacceptable toxic effects, withdrawal of consent, or the end of the trial. Patients could receive nivolumab or nivolumab plus ipilimumab for a maximum of 2 years. Chemotherapy was administered according to the criteria and dosing schedule specified in the protocol, available at NEJM.org. Additional details are provided in the Supplementary Appendix.

Trial Oversight

The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board or independent ethics committee at each site. All the patients provided written in-

formed consent. An independent data monitoring committee provided oversight of safety and efficacy data.

Bristol Myers Squibb (the sponsor), in collaboration with Ono Pharmaceutical, funded the trial, provided the trial drugs, and collaborated with the academic authors on the trial design and on the collection, analysis, and interpretation of the data. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The authors had access to the trial data, participated in the development or review of the manuscript, and provided final approval to submit the manuscript for publication. Medical writing support, including development of the first draft of the manuscript under the guidance of the authors, was funded by the sponsor. The authors and their institutions were required to maintain data confidentiality during the trial.

END POINTS AND ASSESSMENTS

The primary end points were overall survival and progression-free survival, as determined by blinded independent central review on the basis of RECIST, version 1.1. The secondary end points included the percentage of patients with an objective response, which was also assessed by blinded independent central review on the basis of RECIST, version 1.1. According to the hierarchical testing procedure, the end points were assessed first in patients with tumor-cell PD-L1 expression of 1% or greater and then in the overall population (i.e., all randomly assigned patients in the trial). Key prespecified exploratory end points were the duration of response (as assessed by blinded independent central review), overall survival in subgroups defined according to tumor-cell PD-L1 expression and PD-L1 combined positive score, patient-reported outcomes, and safety. PD-L1 combined positive score was defined as the number of PD-L1–expressing tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells and multiplied by 100.

Adverse events were assessed in all the patients who had received at least one dose of the assigned treatment throughout the treatment and follow-up periods; these events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Patient-reported outcomes were evaluated with the use of the Functional Assessment of Cancer Therapy–Esophageal (FACT-E) questionnaire, which includes the item, "I am bothered by side effects of treatment" (single GP5 item). The threshold for clinically meaningful change for the FACT-E total score was 9.5 points.[22,23] Additional details are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The final analysis of progression-free survival was planned to be performed after 136 events had occurred among patients with tumor-cell PD-L1 expression of 1% or greater who had received chemotherapy alone or after a 12-month minimum follow-up, with a formal interim analysis of overall survival planned to be performed at the same time. Details regarding significance levels and sample-size considerations are described in the Supplementary Appendix.

For the analyses of overall survival and progression-free survival, the stratified two-sided log-rank test was used to compare the treatment groups,[24,25] and hazard ratios were estimated with the use of a stratified Cox proportional-hazards regression model.[26] The median overall survival and progression-free survival were estimated with the use of the Kaplan–Meier method,[27] and the corresponding confidence intervals were calculated with the use of the log–log transformation method. The percentages of patients with an objective response, and the corresponding two-sided 95% confidence intervals, were calculated with the use of the Clopper–Pearson method,[28] and the estimates of these differences between the treatment groups were calculated with the use of the Cochran–Mantel–Haenszel test, with adjustment for stratification factors.[29]

RESULTS

PATIENTS

From June 2017 through November 2019, a total of 1358 patients at 182 sites in 26 countries were assessed for eligibility. Of these patients, 970 were randomly assigned to receive nivolumab plus chemotherapy (321 patients), nivolumab plus ipilimumab (325 patients), or chemotherapy alone (324 patients) (Fig. S1 in the Supplementary Appendix). Demographic and baseline clinical characteristics were balanced across the treatment

Table 1. Demographic and Clinical Characteristics of the Overall Population at Baseline.*

Characteristic	Nivolumab plus Chemotherapy (N=321)	Nivolumab plus Ipilimumab (N=325)	Chemotherapy (N=324)
Median age (range) — yr	64 (40–90)	63 (28–81)	64 (26–81)
Male sex — no. (%)	253 (79)	269 (83)	275 (85)
Race — no. (%)†			
Asian	227 (71)	231 (71)	227 (70)
White	85 (26)	79 (24)	84 (26)
Black	1 (<1)	4 (1)	6 (2)
Other	8 (2)	11 (3)	7 (2)
Geographic region — no. (%)			
Asia	225 (70)	229 (70)	226 (70)
Region other than Asia	96 (30)	96 (30)	98 (30)
ECOG performance-status score — no. (%)‡			
0	150 (47)	151 (46)	154 (48)
1	171 (53)	174 (54)	170 (52)
Histologic type at initial diagnosis, squamous-cell carcinoma — no. (%)§	311 (97)	322 (>99)	318 (98)
Tumor-cell PD-L1 expression — no. (%)			
<1% or indeterminate¶	163 (51)	167 (51)	167 (52)
≥1%	158 (49)	158 (49)	157 (48)
Disease status at trial entry — no. (%)			
Metastatic	184 (57)	196 (60)	187 (58)
Recurrent, locoregional	21 (7)	25 (8)	25 (8)
Recurrent, distant	72 (22)	73 (22)	60 (19)
Unresectable advanced	44 (14)	31 (10)	52 (16)
Number of organs with metastases — no. (%)			
≤1	158 (49)	160 (49)	158 (49)
≥2	163 (51)	165 (51)	166 (51)
Smoking status — no. (%)			
Current or former smoker	254 (79)	268 (82)	256 (79)
Never smoked	67 (21)	57 (18)	68 (21)

* The overall population includes all the patients who underwent randomization. Randomization was stratified according to tumor-cell programmed death ligand 1 (PD-L1) expression status (≥1% vs. <1% or indeterminate), geographic region (East Asia [Japan, Korea, and Taiwan] vs. rest of Asia vs. rest of world), Eastern Cooperative Oncology Group (ECOG) performance-status score (0 vs. 1), and number of organs with metastases (≤1 vs. ≥2). Percentages may not total 100 because of rounding.

† Race was reported by the patients.

‡ ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.

§ A total of 9 patients who received nivolumab plus chemotherapy, 3 patients who received nivolumab plus ipilimumab, and 6 patients who received chemotherapy alone had adenosquamous-cell carcinoma of the esophagus. One patient who had been assigned to receive nivolumab plus chemotherapy had sarcomatoid carcinoma of the esophagus and underwent randomization but was not treated.

¶ Three patients who received nivolumab plus ipilimumab and 2 patients who received chemotherapy alone had indeterminate tumor-cell PD-L1 expression at baseline.

groups in the overall population (Table 1) and in patients with tumor-cell PD-L1 expression of 1% or greater (Table S1). Most of the patients (680 of 970 [70%]) were from Asian countries, and 473 (49%) had tumor-cell PD-L1 expression of 1% or greater (Table 1). The primary reason for treatment discontinuation was disease progression (in 184 of 310 patients [59%] who received

nivolumab plus chemotherapy, in 174 of 322 patients [54%] who received nivolumab plus ipilimumab, and in 193 of 304 patients [63%] who received chemotherapy alone) (Fig. S1).

EFFICACY

Nivolumab plus Chemotherapy as Compared with Chemotherapy Alone

After a minimum follow-up period of 13 months, overall survival was significantly longer with nivolumab plus chemotherapy than with chemotherapy alone among patients with tumor-cell PD-L1 expression of 1% or greater; the median overall survival was 15.4 months (95% confidence interval [CI], 11.9 to 19.5) and 9.1 months (95% CI, 7.7 to 10.0), respectively, with a 46% lower risk of death with nivolumab plus chemotherapy than with chemotherapy alone (hazard ratio, 0.54; 99.5% CI, 0.37 to 0.80; P<0.001) (Fig. 1A). The percentage of patients who were alive at 12 months was 58% and 37%, respectively. Similarly, nivolumab plus chemotherapy resulted in significantly longer overall survival than chemotherapy alone in the overall population; the median overall survival was 13.2 months (95% CI, 11.1 to 15.7) and 10.7 months (95% CI, 9.4 to 11.9), respectively, with a 26% lower risk of death with nivolumab plus chemotherapy than with chemotherapy alone (hazard ratio, 0.74; 99.1% CI, 0.58 to 0.96; P=0.002) (Fig. 1B).

Progression-free survival, as determined by blinded independent central review, was significantly longer with nivolumab plus chemotherapy than with chemotherapy alone among patients with tumor-cell PD-L1 expression of 1% or greater; the median progression-free survival was 6.9 months (95% CI, 5.7 to 8.3) and 4.4 months (95% CI, 2.9 to 5.8), respectively (hazard ratio for disease progression or death, 0.65; 98.5% CI, 0.46 to 0.92; P=0.002) (Fig. 1C). In the overall population, the difference in progression-free survival between the group that received nivolumab plus chemotherapy and the group that received chemotherapy alone did not meet the prespecified boundary for significance of 0.015; the median progression-free survival was 5.8 months (95% CI, 5.6 to 7.0) and 5.6 months (95% CI, 4.3 to 5.9), respectively (hazard ratio, 0.81; 98.5% CI, 0.64 to 1.04; P=0.04) (Fig. 1D).

The percentage of patients who had an objective response, as determined by blinded independent central review, was higher with nivolumab plus chemotherapy than with chemotherapy alone among patients with tumor-cell PD-L1 expression of 1% or greater (53% vs. 20%), as well as in the overall population (47% vs. 27%), and the median duration of response was longer (8.4 vs. 5.7 months and 8.2 vs. 7.1 months, respectively). The percentage of patients who received nivolumab plus chemotherapy and had a complete response was more than triple the percentage of patients who received chemotherapy alone and had a complete response (16% vs. 5%) for patients with tumor-cell PD-L1 expression of 1% or greater and more than double (13% vs. 6%) for the overall population (Table 2 and Fig. S2A and S2B).

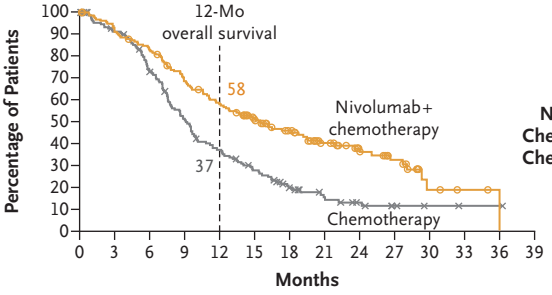
Nivolumab plus Ipilimumab as Compared with Chemotherapy

Overall survival was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with tumor-cell PD-L1 expression of 1% or greater; the median overall survival was 13.7 months (95% CI, 11.2 to 17.0) and 9.1 months (95% CI, 7.7 to 10.0), respectively, with a 36% lower risk of death with nivolumab plus ipilimumab than with chemotherapy (hazard ratio, 0.64; 98.6% CI, 0.46 to 0.90; P=0.001). The percentage of patients who were alive at 12 months was 57% and 37%, respectively (Fig. 2A). Treatment with nivolumab plus ipilimumab also resulted in significantly longer overall survival than chemotherapy in the overall population; the median overall survival was 12.7 months (95% CI, 11.3 to 15.5) and 10.7 months (95% CI, 9.4 to 11.9), respectively, with a 22% lower risk of death with nivolumab plus ipilimumab than with chemotherapy (hazard ratio, 0.78; 98.2% CI, 0.62 to 0.98; P=0.01) (Fig. 2B).

Among patients with tumor-cell PD-L1 expression of 1% or greater, the median progression-free survival, according to blinded independent central review, was 4.0 months (95% CI, 2.4 to 4.9) with nivolumab plus ipilimumab and 4.4 months (95% CI, 2.9 to 5.8) with chemotherapy, and the difference between the groups did not meet the criteria for statistical significance (hazard ratio for disease progression or death, 1.02; 98.5% CI, 0.73 to 1.43; P=0.90) (Fig. 2C). Therefore, progression-free survival was not tested in the overall population (Fig. 2D).

Among patients with tumor-cell PD-L1 expression of 1% or greater, the percentage who had an objective response, as assessed by blind-

A Overall Survival in Patients with Tumor-Cell PD-L1 Expression of ≥1%



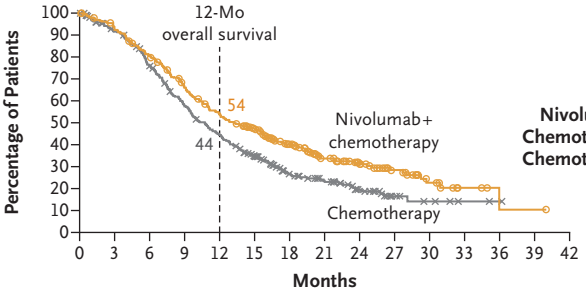
	No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+ Chemotherapy	158	15.4 (11.9–19.5)
Chemotherapy	157	9.1 (7.7–10.0)

Hazard ratio for death, 0.54 (99.5% CI, 0.37–0.80)
P<0.001

No. at Risk

Nivolumab+chemotherapy	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemotherapy	157	135	105	72	52	36	21	12	8	4	2	1	1	0

B Overall Survival in the Overall Population



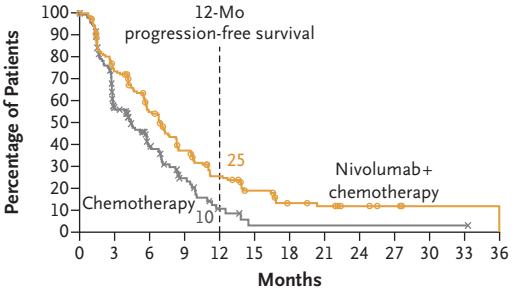
	No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+ Chemotherapy	321	13.2 (11.1–15.7)
Chemotherapy	324	10.7 (9.4–11.9)

Hazard ratio for death, 0.74 (99.1% CI, 0.58–0.96)
P=0.002

No. at Risk

Nivolumab+chemotherapy	321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
Chemotherapy	324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

C Progression-free Survival in Patients with Tumor-Cell PD-L1 Expression of ≥1%



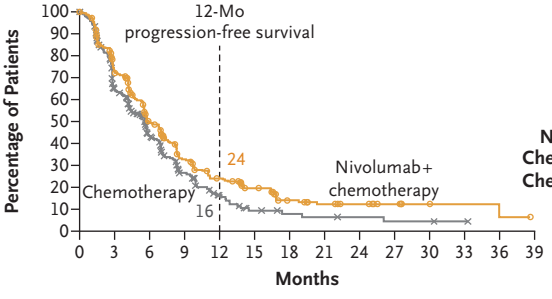
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+ Chemotherapy	158	6.9 (5.7–8.3)
Chemotherapy	157	4.4 (2.9–5.8)

Hazard ratio for disease progression or death, 0.65 (98.5% CI, 0.46–0.92)
P=0.002

No. at Risk

Nivolumab+chemotherapy	158	107	75	47	29	18	10	8	5	3	1	1	0
Chemotherapy	157	67	35	17	5	1	1	1	1	1	1	1	0

D Progression-free Survival in the Overall Population



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+ Chemotherapy	321	5.8 (5.6–7.0)
Chemotherapy	324	5.6 (4.3–5.9)

Hazard ratio for disease progression or death, 0.81 (98.5% CI, 0.64–1.04)
P=0.04

No. at Risk

Nivolumab+chemotherapy	321	216	136	81	53	35	18	13	10	6	3	2	1	0
Chemotherapy	324	170	90	43	19	8	5	4	3	2	2	1	0	0

Figure 1 (facing page). Overall Survival and Progression-free Survival with Nivolumab plus Chemotherapy as Compared with Chemotherapy Alone.

Shown are Kaplan–Meier estimates of overall survival in patients with tumor-cell programmed death ligand 1 (PD-L1) expression of 1% or greater (Panel A) and in the overall population (Panel B) and Kaplan–Meier estimates of progression-free survival (as assessed by blinded independent central review) in patients with tumor-cell PD-L1 expression of 1% or greater (Panel C) and in the overall population (Panel D). The P value for the analysis of progression-free survival in the overall population did not meet the prespecified boundary for significance. Symbols indicate censored data.

ed independent central review, was higher with nivolumab plus ipilimumab than with chemotherapy (35% vs. 20%), and the percentage of patients who received nivolumab plus ipilimumab and had a complete response was more than three times as high as the percentage who received chemotherapy and had a complete response (18% vs. 5%). The median duration of response was 11.8 months with nivolumab plus ipilimumab and 5.7 months with chemotherapy (Table 2 and Fig. S2C). In the overall population, the percentage of patients who had an objective response was similar in the two groups (28% and 27%, respectively), and the percentage of patients who had a complete response with nivolumab plus ipilimumab was nearly twice as high as the percentage with chemotherapy (11% vs. 6%). The median duration of response in the overall population was 11.1 months and 7.1 months, respectively (Table 2 and Fig. S2D).

Subgroup Analyses

Overall survival favored nivolumab plus chemotherapy or nivolumab plus ipilimumab over chemotherapy alone across multiple prespecified subgroups in both the overall population and in patients with tumor-cell PD-L1 expression of 1% or greater, including the subgroups defined according to geographic region, Eastern Cooperative Oncology Group performance-status score, and the number of organs with metastases (Fig. S3A through S3D). Hazard ratios were consistently below 1 in all the tumor-cell PD-L1 expression subgroups (1%, 5%, and 10% cutoffs), with the highest magnitude of benefit observed in the subgroup of patients with tumor-cell PD-L1 expression of 1% or greater (Fig. S3B and S3D). Among patients with tumor-cell PD-L1 expression of less than 1%, the median overall survival was approximately 12 months in each treatment group, and no progression-free survival benefit was observed with the nivolumab-containing regimens as compared with chemotherapy alone (Table S2). However, the percentage of patients who had tumor-cell PD-L1 expression of less than 1% and had an objective response was higher with nivolumab plus chemotherapy than with chemotherapy alone (42% vs. 34%), and the percentage of patients who had a duration of response of at least 12 months was higher with both nivolumab-containing regimens than with chemotherapy alone (38% for nivolumab plus chemotherapy, 47% for nivolumab plus ipilimumab, and 27% for chemotherapy alone) (Table S2). Among the patients with a PD-L1 combined positive score of 1 or higher (824 of 906 [91%]), the median overall survival was 13.8 months (hazard ratio for death, 0.69; 95% CI, 0.56 to 0.84) with nivolumab plus chemotherapy and 12.7 months (hazard ratio, 0.76; 95% CI, 0.62 to 0.93) with nivolumab plus ipilimumab as compared with 9.8 months with chemotherapy alone (Fig. S3B and S3D). Among the few patients with a PD-L1 combined positive score of less than 1 (82 of 906 [9%]), the median overall survival was 9.9 months (hazard ratio, 0.98; 95% CI, 0.50 to 1.95) with nivolumab plus chemotherapy and 11.5 months (hazard ratio, 1.00; 95% CI, 0.52 to 1.94) with nivolumab plus ipilimumab as compared with 12.1 months with chemotherapy alone.

EXPOSURE AND SAFETY

The median duration of treatment was 5.7 months with nivolumab plus chemotherapy, 2.8 months with nivolumab plus ipilimumab, and 3.4 months with chemotherapy alone (Table S3). Treatment-related adverse events are summarized in Table 3. The incidence of treatment-related adverse events of grade 3 or 4 was higher among patients who received nivolumab plus chemotherapy (147 patients [47%]) than among those who received nivolumab plus ipilimumab (102 patients [32%]) or chemotherapy alone (108 patients [36%]). Treatment-related serious adverse events of any grade were more common with nivolumab plus chemotherapy (74 patients [24%]) and nivolumab plus ipilimumab (103 patients [32%]) than with chemotherapy alone (49 patients

Table 2. Antitumor Activity, as Assessed by Blinded Independent Central Review.*

Variable	Patients with Tumor-Cell PD-L1 Expression of ≥1%			Overall Population		
	Nivolumab plus Chemotherapy (N = 158)	Nivolumab plus Ipilimumab (N = 158)	Chemotherapy (N = 157)	Nivolumab plus Chemotherapy (N = 321)	Nivolumab plus Ipilimumab (N = 325)	Chemotherapy (N = 324)
Objective response rate						
No. of patients (%)	84 (53)	56 (35)	31 (20)	152 (47)	90 (28)	87 (27)
95% CI	45–61	28–43	14–27	42–53	23–33	22–32
Best overall response — no. (%)						
Complete response	26 (16)	28 (18)	8 (5)	43 (13)	36 (11)	20 (6)
Partial response	58 (37)	28 (18)	23 (15)	109 (34)	54 (17)	67 (21)
Stable disease	40 (25)	43 (27)	72 (46)	103 (32)	103 (32)	148 (46)
Progressive disease	22 (14)	48 (30)	24 (15)	42 (13)	103 (32)	38 (12)
Could not be evaluated	12 (8)	11 (7)	30 (19)	24 (7)	29 (9)	51 (16)
Median time to response (range) — mo†	1.5 (0.6–4.3)	1.5 (1.2–8.4)	1.5 (1.3–9.7)	1.5 (0.6–6.8)	1.5 (1.2–8.4)	1.5 (1.1–9.7)
Median duration of response (95% CI) — mo†	8.4 (6.9–12.4)	11.8 (7.1–27.4)	5.7 (4.4–8.7)	8.2 (6.9–9.7)	11.1 (8.3–14.0)	7.1 (5.7–8.2)
Patients with ongoing response — no. (%)†	11 (13)	14 (25)	1 (3)	26 (17)	20 (22)	5 (6)

* Included are all patients who underwent randomization and had target-lesion measurements at baseline, as assessed by blinded independent central review. Percentages may not total 100 because of rounding.
† This analysis included only patients who had an objective response.

[16%]). The percentage of patients who had a treatment-related adverse event of any grade that led to discontinuation of any drug in the regimen was higher with nivolumab plus chemotherapy (106 patients [34%]) than with nivolumab plus ipilimumab or chemotherapy alone (57 patients [18%] and 59 patients [19%], respectively). The incidence of treatment-related deaths was similar across the groups: 5 patients (2%) with nivolumab plus chemotherapy, 8 (2%) with nivolumab plus ipilimumab, and 6 (2%) with chemotherapy alone. These included three deaths in the group that received nivolumab plus ipilimumab and two deaths in the group that received chemotherapy that were attributed to disease, other reasons, or an unknown cause for which fatal treatment-related serious adverse events were also reported by the investigator. Most of the treatment-related adverse events with potential immunologic causes were grade 1 or 2; events of grade 3 or 4 occurred in no more than 6% of the patients across the treatment groups and organ categories (Table S4). Data regarding subsequent therapies are provided in Table S5.

PATIENT-REPORTED OUTCOMES

A longitudinal mixed-model analysis of FACT-E scores through week 49 showed an overall increase in the least-squares mean change from baseline with nivolumab plus chemotherapy (4.98 points; 95% CI, 2.68 to 7.27), nivolumab plus ipilimumab (3.45 points; 95% CI, 0.96 to 5.94), and chemotherapy alone (1.54 points; 95% CI, –1.26 to 4.33) in the overall population. These improvements from baseline were not clinically meaningful, which indicates that health-related quality of life was maintained during the treatment period (Fig. S4A). Except at baseline, the percentage of patients who reported not being bothered by treatment side effects over time was higher with nivolumab plus ipilimumab than with chemotherapy, whereas percentages with nivolumab plus chemotherapy were similar to those with chemotherapy alone (Fig. S4B and S4C).

DISCUSSION

In the CheckMate 648 trial, first-line treatment with nivolumab in combination with chemotherapy or as a chemotherapy-free combination with ipilimumab resulted in a significant overall survival benefit over chemotherapy alone in pa-

tients with advanced esophageal squamous-cell carcinoma. In both the overall population and among patients with tumor-cell PD-L1 expression of 1% or greater, the median overall survival exceeded 1 year, with patients surviving 2.0 to 6.3 months longer with a nivolumab-containing regimen than with chemotherapy alone. Survival at 1 year was 10 to 21 percentage points higher in the groups that received a nivolumab-containing regimen than in the group that received chemotherapy alone. An initial increased incidence of early death among the patients who received nivolumab plus ipilimumab did not preclude long-term benefit; after the Kaplan–Meier curves crossed at approximately 6.5 months, they showed sustained separation favoring nivolumab plus ipilimumab. Nivolumab plus chemotherapy was also associated with significantly longer progression-free survival than chemotherapy alone among patients with tumor-cell PD-L1 expression of 1% or greater.

Treatment with either nivolumab-based regimen resulted in a higher percentage of patients who had a complete response, as well as in more durable responses, than chemotherapy alone. Among the three treatment regimens, nivolumab plus chemotherapy led to the highest percentages of patients with an objective response and nivolumab plus ipilimumab resulted in the longest median duration of response.

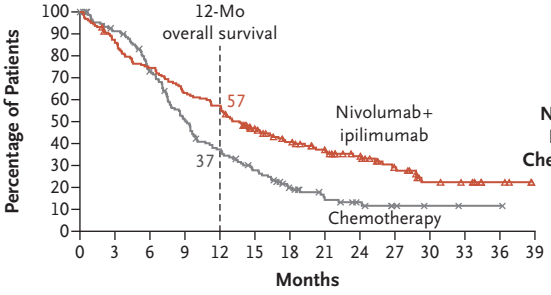
The percentages of patients who had treatment-related adverse events of grade 3 or 4 and the percentages of those who had a treatment-related adverse event of any grade that led to discontinuation of any trial drug were the highest with nivolumab plus chemotherapy and the lowest with nivolumab plus ipilimumab. Health-related quality of life was maintained over the course of the treatment period for the nivolumab-based regimens, and fewer patients who were receiving nivolumab plus ipilimumab reported being bothered by treatment side effects than did patients who were receiving a chemotherapy-based treatment.

PD-1 inhibitors have been associated with a survival benefit in previously treated patients with advanced esophageal squamous-cell carcinoma.[17,30-32] In the CheckMate 648 trial, first-line treatment with nivolumab plus chemotherapy and nivolumab plus ipilimumab showed a significant overall survival benefit. Pembrolizumab plus chemotherapy and camrelizumab plus chemotherapy have also been reported to result in longer median overall survival than chemotherapy alone in this population; these findings show the benefit of adding a PD-1 inhibitor to chemotherapy.[14,15]

In the CheckMate 648 trial, overall survival favored the nivolumab-containing regimens across most of the prespecified subgroups. Although the hazard ratios in a few subgroups were close to or exceeded 1 (e.g., female sex and locoregional recurrence), the median overall survival with chemotherapy alone was notably longer in these subgroups than the expected median of less than 12 months and the number of patients was small, both of which limited interpretation of the results.[7-9] The prevalence of tumor-cell PD-L1 expression of 1% or greater in the CheckMate 648 trial was approximately 50%, which is consistent with previous reports.[17,33] Hazard ratios for death were less than 1 across all the tumor-cell PD-L1 expression subgroups for both nivolumab-containing regimens. The magnitude of the overall survival benefit was greater in patients with tumor-cell PD-L1 expression of 1% or greater, with no further enrichment at higher cutoffs, than in patients with tumor-cell PD-L1 expression of less than 1%, in whom the hazard ratios were close to 1. The median overall survival with chemotherapy alone was 3 months longer in patients with tumor-cell PD-L1 expression of less than 1% than in those with tumor-cell PD-L1 expression of 1% or greater; these findings are consistent with results reported in an earlier trial involving previously treated patients with esophageal squamous-cell carcinoma.[17] Among patients with tumor-cell PD-L1 expression of less than 1%, the percentage of patients with responses lasting at least 1 year was higher with both nivolumab-containing regimens than with chemotherapy alone, a finding that suggests that longer follow-up may result in extended overall survival.

The preplanned exploratory subgroup analyses of overall survival that were performed according to PD-L1 combined positive score showed the overall survival benefit of the nivolumab-containing regimens in the subgroup that had a combined positive score of 1 or higher, a subgroup that accounted for more than 90% of all the patients in the trial who had a quantifiable combined positive score. Among the patients

A Overall Survival in Patients with Tumor-Cell PD-L1 Expression of ≥1%

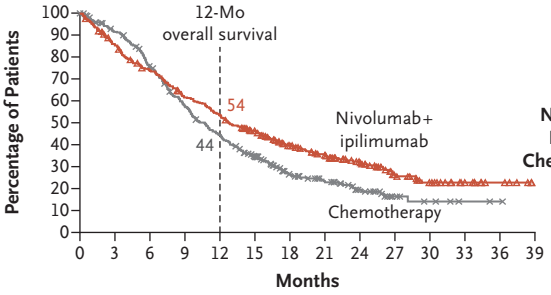


	No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+ Ipilimumab	158	13.7 (11.2–17.0)
Chemotherapy	157	9.1 (7.7–10.0)

Hazard ratio for death, 0.64 (98.6% CI, 0.46–0.90)
P=0.001

No. at Risk														
Nivolumab+ipilimumab	158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemotherapy	157	135	105	72	52	36	21	12	8	4	2	1	1	0

B Overall Survival in the Overall Population

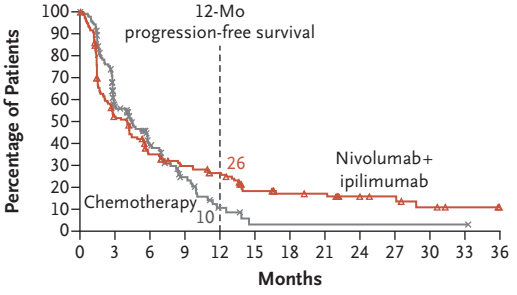


	No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+ Ipilimumab	325	12.7 (11.3–15.5)
Chemotherapy	324	10.7 (9.4–11.9)

Hazard ratio for death, 0.78 (98.2% CI, 0.62–0.98)
P=0.01

No. at Risk														
Nivolumab+ipilimumab	325	274	232	191	166	129	97	77	55	33	22	12	6	0
Chemotherapy	324	281	229	171	131	93	56	41	23	9	5	2	1	0

C Progression-free Survival in Patients with Tumor-Cell PD-L1 Expression of ≥1%

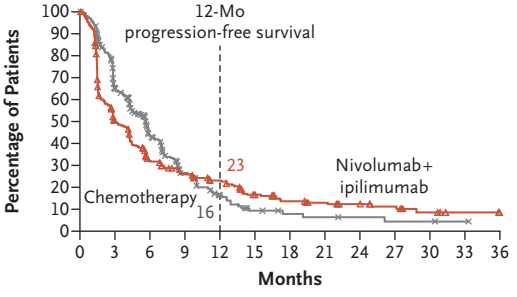


	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+ Ipilimumab	158	4.0 (2.4–4.9)
Chemotherapy	157	4.4 (2.9–5.8)

Hazard ratio for disease progression or death, 1.02 (98.5% CI, 0.73–1.43)
P=0.90

No. at Risk													
Nivolumab+ipilimumab	158	78	48	38	31	18	14	13	8	7	4	2	0
Chemotherapy	157	67	35	17	5	1	1	1	1	1	1	1	0

D Progression-free Survival in the Overall Population



	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+ Ipilimumab	325	2.9 (2.7–4.2)
Chemotherapy	324	5.6 (4.3–5.9)

Hazard ratio for disease progression or death, 1.26 (95% CI, 1.04–1.52)
P value not tested

No. at Risk													
Nivolumab+ipilimumab	325	149	86	65	52	31	22	18	13	10	5	2	0
Chemotherapy	324	170	90	43	19	8	5	4	3	2	2	1	0

Figure 2 (facing page). Overall Survival and Progression-free Survival with Nivolumab plus Ipilimumab as Compared with Chemotherapy.

Shown are Kaplan–Meier estimates of overall survival in patients with tumor-cell PD-L1 expression of 1% or greater (Panel A) and in the overall population (Panel B) and Kaplan–Meier estimates of progression-free survival (as assessed by blinded independent central review) in patients with tumor-cell PD-L1 expression of 1% or greater (Panel C) and in the overall population (Panel D). Symbols indicate censored data.

with a PD-L1 combined positive score of less than 1, the small sample size and wide confidence intervals limited data interpretation. The PD-L1 combined positive score has been shown to be a more appropriate scoring method than tumor-cell PD-L1 expression in predicting the efficacy of immune checkpoint inhibitor–based therapies for gastroesophageal adenocarcinoma.[34,35] In patients with esophageal squamous-cell carcinoma in the CheckMate 648 trial, the observed hazard ratios and corresponding confidence intervals for overall survival across the tumor-cell PD-L1 expression and exploratory PD-L1 combined positive score subgroups suggest that both scoring methods have clinical utility.

A significant progression-free survival benefit, as assessed by blinded independent central review, was observed with nivolumab plus chemotherapy over chemotherapy alone in patients with tumor-cell PD-L1 expression of 1% or greater but not in the overall population; no benefit in progression-free survival was observed in either patient population with nivolumab plus ipilimumab as compared with chemotherapy alone. A lack of progression-free survival benefit despite longer overall survival has previously been observed with immunotherapies and is probably attributable to their delayed treatment effect relative to chemotherapy.[17,36,37]

The higher percentages of patients who had objective responses and complete responses and the longer durations of response that were seen with nivolumab plus chemotherapy as compared with chemotherapy alone both in patients with tumor-cell PD-L1 expression of 1% or greater and in the overall population in the CheckMate 648 trial were consistent with reports of pembrolizumab plus chemotherapy and camrelizumab plus chemotherapy in patients with esophageal cancer.[14,15] Nivolumab plus ipilimumab was also associated with notably higher percentages of patients who had a complete response than chemotherapy, both among patients with tumor-cell PD-L1 expression of 1% or greater and in the overall population, in addition to longer median durations of response (by 6 months and 4 months, respectively). However, the percentages of patients with progressive disease were also higher with nivolumab plus ipilimumab. Longer follow-up will further elucidate the magnitude of long-term clinical benefit with nivolumab plus ipilimumab.

The safety profiles of nivolumab plus chemotherapy and nivolumab plus ipilimumab were consistent with the known profiles of the individual components at similar doses.[9,17,19,38] Among the patients who received nivolumab plus chemotherapy, adverse events were mainly driven by chemotherapy (with the most common events being nausea, decreased appetite, and stomatitis), with some immune-mediated events. In contrast, treatment with nivolumab plus ipilimumab primarily resulted in immune-mediated adverse events (the most common being rash, pruritus, and hypothyroidism) at frequencies expected with this combination.[21] Although treatment-related serious adverse events were more common with the nivolumab-based regimens than with chemotherapy alone, treatment-related adverse events of grade 3 or 4 that had potential immunologic causes occurred in no more than 6% of the patients across the organ categories. The incidence of treatment-related deaths was similar across the three treatment groups and occurred in approximately 2% of the patients in each group.

The trial was not designed to compare outcomes between nivolumab plus chemotherapy and nivolumab plus ipilimumab or to determine which treatment should be used for specific subgroups. Multiple factors may influence the choice of regimen in clinical practice, including an individual patient's need for a relatively rapid treatment effect and the occurrence of side effects associated with chemotherapy that a patient considers to be unacceptable. Additional exploratory post hoc analyses may help to identify demographic characteristics or baseline disease characteristics that could predict efficacy outcomes for each nivolumab-containing regimen.

A limitation of this trial was its open-label design. Although the primary end point of over-

Table 3. Treatment-Related Adverse Events in All the Patients Who Received Trial Treatment.*

Event	Nivolumab plus Chemotherapy (N=310)		Nivolumab plus Ipilimumab (N=322)		Chemotherapy (N=304)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	297 (96)	147 (47)	256 (80)	102 (32)	275 (90)	108 (36)
Treatment-related serious adverse event	74 (24)	57 (18)	103 (32)	73 (23)	49 (16)	38 (12)
Treatment-related adverse event leading to trial-drug discontinuation†	106 (34)	29 (9)	57 (18)	41 (13)	59 (19)	14 (5)
Treatment-related adverse event leading to death‡	5 (2)	—	8 (2)	—	6 (2)	—
Treatment-related adverse events reported in ≥10% of patients in any group						
Nausea	182 (59)	11 (4)	26 (8)	1 (<1)	158 (52)	8 (3)
Decreased appetite	132 (43)	13 (4)	19 (6)	5 (2)	130 (43)	9 (3)
Stomatitis	98 (32)	20 (6)	14 (4)	0	71 (23)	5 (2)
Anemia	93 (30)	30 (10)	12 (4)	2 (1)	67 (22)	17 (6)
Decreased neutrophil count	65 (21)	25 (8)	2 (1)	0	52 (17)	24 (8)
Fatigue	61 (20)	7 (2)	29 (9)	4 (1)	50 (16)	11 (4)
Diarrhea	60 (19)	3 (1)	32 (10)	2 (1)	46 (15)	6 (2)
Constipation	59 (19)	2 (1)	7 (2)	1 (<1)	66 (22)	1 (<1)
Vomiting	56 (18)	7 (2)	18 (6)	4 (1)	49 (16)	9 (3)
Malaise	50 (16)	1 (<1)	12 (4)	0	45 (15)	0
Decreased white-cell count	43 (14)	11 (4)	3 (1)	0	28 (9)	6 (2)
Hiccups	42 (14)	0	2 (1)	0	53 (17)	0
Increased blood creatinine level	39 (13)	1 (<1)	5 (2)	0	32 (11)	1 (<1)
Decreased platelet count	36 (12)	3 (1)	6 (2)	0	32 (11)	5 (2)
Mucosal inflammation	33 (11)	8 (3)	4 (1)	0	26 (9)	4 (1)
Alopecia	31 (10)	0	2 (1)	0	32 (11)	0
Rash	24 (8)	1 (<1)	55 (17)	7 (2)	5 (2)	0
Pruritus	23 (7)	0	43 (13)	3 (1)	2 (1)	0
Hypothyroidism	18 (6)	0	43 (13)	0	0	0

* Included are all the patients who received at least one dose of the assigned treatment. All events were reported between the first dose of treatment and 30 days after the last dose of treatment. Any relation between treatment and adverse events reported in the patients who received nivolumab plus chemotherapy was attributed to either nivolumab or any of the chemotherapies or both. Any relation between treatment and adverse events reported in the patients who received nivolumab plus ipilimumab was attributed to either nivolumab or ipilimumab or both. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and the *Medical Dictionary for Regulatory Activities*, version 23.1.

† This category refers to adverse events leading to discontinuation of any drug in the regimen.

‡ Treatment-related adverse events leading to death were reported regardless of time frame. Treatment-related deaths in the group that received nivolumab plus chemotherapy were from acute kidney injury, pneumonia, pneumonitis, pneumonitis or respiratory-tract infection, and pneumatosis intestinalis (in 1 patient each). Treatment-related deaths in the group that received nivolumab plus ipilimumab were from pneumonitis (in 2 patients) and acute respiratory distress syndrome, interstitial lung disease, and pulmonary embolism (in 1 patient each). In addition, three deaths in the group that received nivolumab plus ipilimumab (one from other reasons and two from disease) were also reported by the investigator as treatment-related serious adverse events that eventually had a fatal outcome (acute kidney injury, general physical health deterioration, and internal hemorrhage). Treatment-related deaths in the group that received chemotherapy alone were from acute kidney injury, pneumonia, sepsis, and septic shock (in 1 patient each). Two additional deaths in the chemotherapy group (one from other reasons and one from an unknown cause) were also reported by the investigator as treatment-related serious adverse events that eventually had a fatal outcome (acute respiratory failure and death).

all survival was objectively determined and therefore was not biased by the type of treatment, causality assessments of adverse events and responses to questionnaires evaluating patient-reported outcomes may have been influenced by knowledge of the assigned treatment.

First-line treatment of advanced esophageal squamous-cell carcinoma with either nivolumab plus chemotherapy or nivolumab plus ipilimumab resulted in a significant overall survival benefit and durable responses as compared with chemotherapy alone. The safety profiles of each treatment were consistent with the known safety profiles of the individual components in each regimen.

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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.

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APPENDIX

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