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Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer

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abstract

PURPOSE Patients with advanced esophageal cancer have a poor prognosis and limited treatment options after first-line chemotherapy.

PATIENTS AND METHODS In this open-label, phase III study, we randomly assigned (1:1) 628 patients with advanced/metastatic squamous cell carcinoma or adenocarcinoma of the esophagus, that progressed after one prior therapy, to pembrolizumab 200 mg every 3 weeks for up to 2 years or chemotherapy (investigator's choice of paclitaxel, docetaxel, or irinotecan). Primary end points were overall survival (OS) in patients with programmed death ligand-1 (PD-L1) combined positive score (CPS) ≥ 10, in patients with squamous cell carcinoma, and in all patients (one-sided α 0.9%, 0.8%, and 0.8%, respectively).

RESULTS At final analysis, conducted 16 months after the last patient was randomly assigned, OS was prolonged with pembrolizumab versus chemotherapy for patients with CPS ≥ 10 (median, 9.3 *v* 6.7 months; hazard ratio [HR], 0.69 [95% CI, 0.52 to 0.93]; $P = .0074$). Estimated 12-month OS rate was 43% (95% CI, 33.5% to 52.1%) with pembrolizumab versus 20% (95% CI, 13.5% to 28.3%) with chemotherapy. Median OS was 8.2 months versus 7.1 months (HR, 0.78 [95% CI, 0.63 to 0.96]; $P = .0095$) in patients with squamous cell carcinoma and 7.1 months versus 7.1 months (HR, 0.89 [95% CI, 0.75 to 1.05]; $P = .0560$) in all patients. Grade 3-5 treatment-related adverse events occurred in 18.2% of patients with pembrolizumab versus 40.9% in those who underwent chemotherapy.

CONCLUSION Pembrolizumab prolonged OS versus chemotherapy as second-line therapy for advanced esophageal cancer in patients with PD-L1 CPS ≥ 10, with fewer treatment-related adverse events.

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INTRODUCTION

Esophageal cancer is the seventh most common cancer and the sixth most common cause of cancer-related death worldwide, with approximately 572,000 new cases and 509,000 deaths in 2018.[1] The highest prevalence of esophageal cancer occurs in Asia and Africa, where the most common subtype is squamous cell carcinoma, whereas adenocarcinoma is more common in North America and Western Europe.[1-3] Treatment options for patients with unresectable, locally advanced, or metastatic esophageal cancer are limited.[4] The prognosis is typically poor in patients with metastatic esophageal cancer, with 5-year survival rates of less than 5%.[5] Current guidelines recommend combination with fluoropyrimidine and platinum therapies in first-line chemotherapy.[2,6,7] However, after first-line chemotherapy, there is no accepted standard of care, although taxanes and irinotecan are used.[8]

Anti–programmed death 1 (PD-1)/programmed death ligand-1 (PD-L1) therapies have shown antitumor activity in patients with metastatic esophageal cancer.[9-12] Pembrolizumab is a humanized, high-affinity, monoclonal anti–PD-1 antibody that provides a survival benefit in multiple tumor types.[13] In the phase II KEYNOTE-180 study (ClinicalTrials.gov identifier: NCT02559687), pembrolizumab provided durable responses with acceptable safety in patients with esophageal cancer who had progressed after two or more prior therapies.[11] Here, we report the results from the randomized phase III, open-label KEYNOTE-181 study of pembrolizumab versus paclitaxel, docetaxel, or irinotecan in patients with advanced or metastatic

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What is the antitumor activity of pembrolizumab versus chemotherapy as second-line treatment in patients with advanced or metastatic esophageal cancer?

Knowledge Generated

Pembrolizumab provided a clinically meaningful survival benefit versus chemotherapy for patients with metastatic esophageal squamous cell carcinoma and programmed death ligand-1 (PD-L1) combined positive score (CPS) ≥ 10 tumors and also in patients with metastatic esophageal squamous cell carcinoma or PD-L1 CPS ≥ 10 tumors, in the second-line, with reduced toxicity.

Relevance

Pembrolizumab provided a clinically meaningful overall survival benefit versus chemotherapy in a global population of patients with metastatic esophageal squamous cell carcinoma and with PD-L1 CPS ≥ 10 tumors in the second-line setting.

esophageal cancer who progressed after one line of prior therapy.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ 18 years of age with histologically confirmed squamous cell carcinoma or adenocarcinoma of the esophagus including human epidermal growth factor receptor 2/neu negative Siewert type 1 adenocarcinoma of the esophagogastric junction. Selection criteria included metastatic or locally advanced, unresectable disease, measurable disease per RECIST version 1.1 by local investigator/radiology assessment, documented radiographic or clinical progression on one prior line of standard therapy, and Eastern Cooperative Oncology Group performance status of 0 or 1 (on a 5-point scale, with higher scores indicating increasing disability).[14] Patients also had to provide a newly obtained or archival tissue sample, and written informed consent. Full eligibility criteria are presented in the Protocol (online only).

Trial Design and Treatment

In this randomized, open-label, global, phase III study, patients were randomly assigned 1:1 to pembrolizumab 200 mg every 3 weeks or investigator's choice of standard-of-care chemotherapy with paclitaxel 80-100 mg/m^2 on days 1, 8, and 15 of each 28-day cycle, docetaxel 75 mg/m^2 on day 1 of each 21-day cycle, or irinotecan 180 mg/m^2 on day 1 of each 14-day cycle. Random assignment was stratified by histology (squamous cell carcinoma *v* adenocarcinoma) and geographic region (Asia *v* rest of world). Treatment with pembrolizumab or paclitaxel, docetaxel, or irinotecan was continued until documented disease progression, unacceptable toxicity or physician or patient decision to withdraw, or after up to 2 years of pembrolizumab. Additional study and treatment details are provided in the Protocol.

Assessments

PD-L1 expression was centrally assessed during screening using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA). Tumors positive for PD-L1 had a combined positive score (CPS) of 10 or more as described previously.[11] Tumor response was assessed per RECIST version 1.1 by central radiology review at week 9 and every 9 weeks thereafter. Progressive disease was verified by central imaging review. During follow-up, survival was assessed every 9 weeks. Adverse events (AEs) were assessed throughout the study and at 30 days (90 days for serious AEs and events of interest to pembrolizumab) after treatment discontinuation and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Trial Oversight

The study was designed by academic investigators and employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ. The Protocol was approved by the appropriate institutional review board or ethics committee at each participating institution. All authors attest that the trial was conducted in accordance with the Protocol and all its amendments and Good Clinical Practice standards. All authors had full access to the data and were involved in the writing or reviewing and editing drafts of the manuscript and vouch for the accuracy and completeness of the data analyses. Assistance in the preparation of the manuscript was provided by a medical writer employed by the sponsor.

End Points

The three primary end points were overall survival (OS) in patients with PD-L1 CPS ≥ 10, in patients with squamous cell carcinoma, and in all patients. Secondary end points

included progression-free survival (PFS) and objective response rate (ORR) per RECIST version 1.1 by central review in patients with PD-L1 CPS ≥ 10, in patients with squamous cell carcinoma, and in all patients, and safety and tolerability.

Statistical Analyses

The statistical analysis plan specified one interim analysis and a final analysis. The overall type-1 error rate was strongly controlled at a one-sided α of 2.5% with use of the graphical method of Maurer and Bretz (Data Supplement, online only). The Lan-DeMets O'Brien-Fleming α spending function was used to control for type 1 error. The secondary hypotheses of PFS and ORR in all patients were tested only if OS with pembrolizumab was superior to that with chemotherapy in all patients.

We determined that a global enrollment of 600 patients (280 with PD-L1 CPS ≥ 10 and 400 with squamous cell carcinoma of the esophagus) would permit comparison of superiority for pembrolizumab versus chemotherapy in patients with PD-L1 CPS ≥ 10, in patients with squamous cell carcinoma, or in all patients to have at least 90.9%, 91.3%, or 92.6% power with underlying hazard ratios (HRs) of 0.60, 0.65, or 0.70 for OS at a one-sided α level of 0.9%, 0.8%, or 0.8%, respectively. At the Protocol-specified final analysis (data cutoff date October 15, 2018), death events for two patients were not included in the data analysis because of a data reporting inconsistency. As such, a subsequent OS analysis was performed at the October 15, 2018, cutoff date to include the events for these patients. The OS results reported are based on the final analysis and the updated analysis that includes death events for these two patients. In addition, an OS analysis was performed with 4 months of additional follow-up (data cutoff date February 13, 2019). The initial multiplicity strategy is applicable only to the final

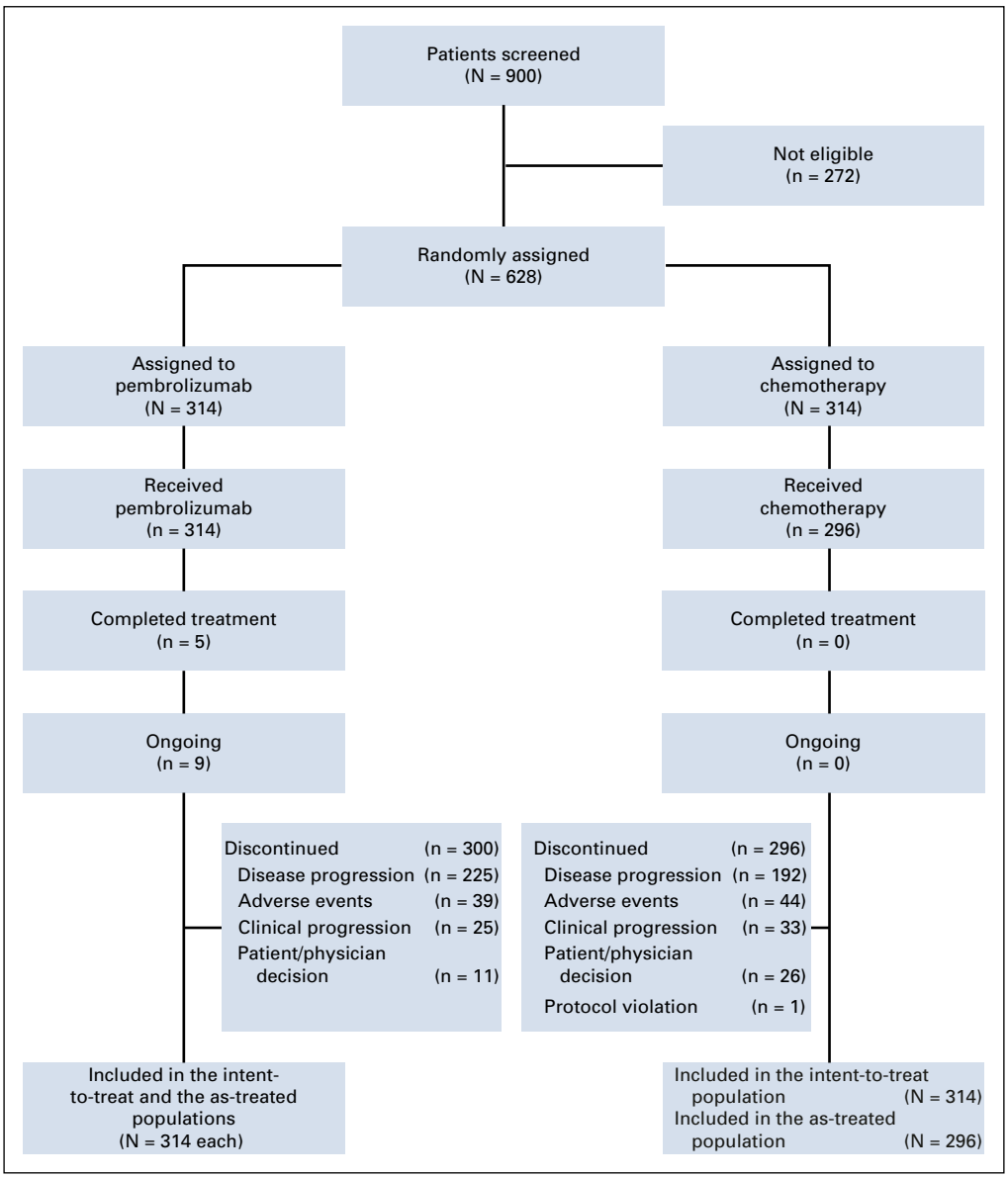


FIG 1. Study profile.

TABLE 1. Baseline Patient Demographic and Disease Characteristics

Characteristic	Pembrolizumab (N = 314)	Chemotherapy (N = 314)
Age, years, median (range)	63.0 (23-84)	62.0 (24-84)
≥ 65 years	139 (44.3)	133 (42.4)
Male	273 (86.9)	271 (86.3)
Geographic region		
Asia	121 (38.5)	122 (38.9)
Rest of world	193 (61.5)	192 (61.1)
ECOG performance status[a]		
0	126 (40.1)	116 (36.9)
1	187 (59.6)	197 (62.7)
2	1 (0.3)	1 (0.3)
Histology		
Squamous cell carcinoma[b]	198 (63.1)	203 (64.6)
Adenocarcinoma	116 (36.9)	111 (35.4)
PD-L1 combined positive score[c]		
≥ 10	107 (34.1)	115 (36.6)
< 10	201 (64.0)	196 (62.4)
Not evaluable[d]	6 (1.9)	3 (1.0)
Prior adjuvant or neoadjuvant therapy		
Yes	32 (10.2)	32 (10.2)
Disease stage		
Metastatic	290 (92.4)	286 (91.1)
Locally advanced	24 (7.6)	28 (8.9)
No. of prior therapies		
0	2 (0.6)	0 (0.0)
1	303 (96.5)	310 (98.7)
≥ 2	9 (2.9)	4 (1.3)

NOTE. Data are presented as No. (%) unless indicated otherwise. Patients in the chemotherapy group received investigator's choice of paclitaxel, docetaxel, or irinotecan. Percentages may not total 100 because of rounding. There were no significant differences between treatment groups at baseline. Data cutoff date was October 15, 2018.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand-1.

[a]ECOG performance status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.

[b]At the data cutoff date of February 13, 2019, the number of patients with squamous cell carcinoma increased to 199 (pembrolizumab) and 204 (chemotherapy).

[c]The PD-L1 combined positive score was defined as the number of PD-L1–positive cells (tumor cells, macrophages, and lymphocytes) divided by the total number of tumor cells.

[d]PD-L1 expression could not be evaluated because samples had an inadequate number of cells or no cells.

analysis (Data Supplement). Precision to the fifth decimal place of the nonparametric rank-based test used to assess survival is limited because survival time is collected in ≥ 24-hour intervals. The updated analysis and the 4-month follow-up analysis are post hoc and are not subject to the multiplicity model.

RESULTS

Patients and Treatment

Between December 8, 2015, and June 16, 2017, a total of 628 patients from 154 sites in 32 countries were randomly assigned to pembrolizumab (314 patients) or chemotherapy (314 patients; Fig 1). Baseline demographic and disease characteristics were as expected, with no significant differences between the groups (Table 1). Most patients (544 [86.6%]) were male, and 401 (63.9%) had squamous cell carcinoma. Expression of PD-L1 CPS ≥ 10 was well balanced between the groups, with 222 patients (35.4%) having PD-L1 CPS ≥ 10 (107 [34%] in the pembrolizumab group and 115 [37%] in the chemotherapy group). At the data cutoff date of October 15, 2018, the median follow-up duration from random assignment to data cutoff or death, whichever came first,

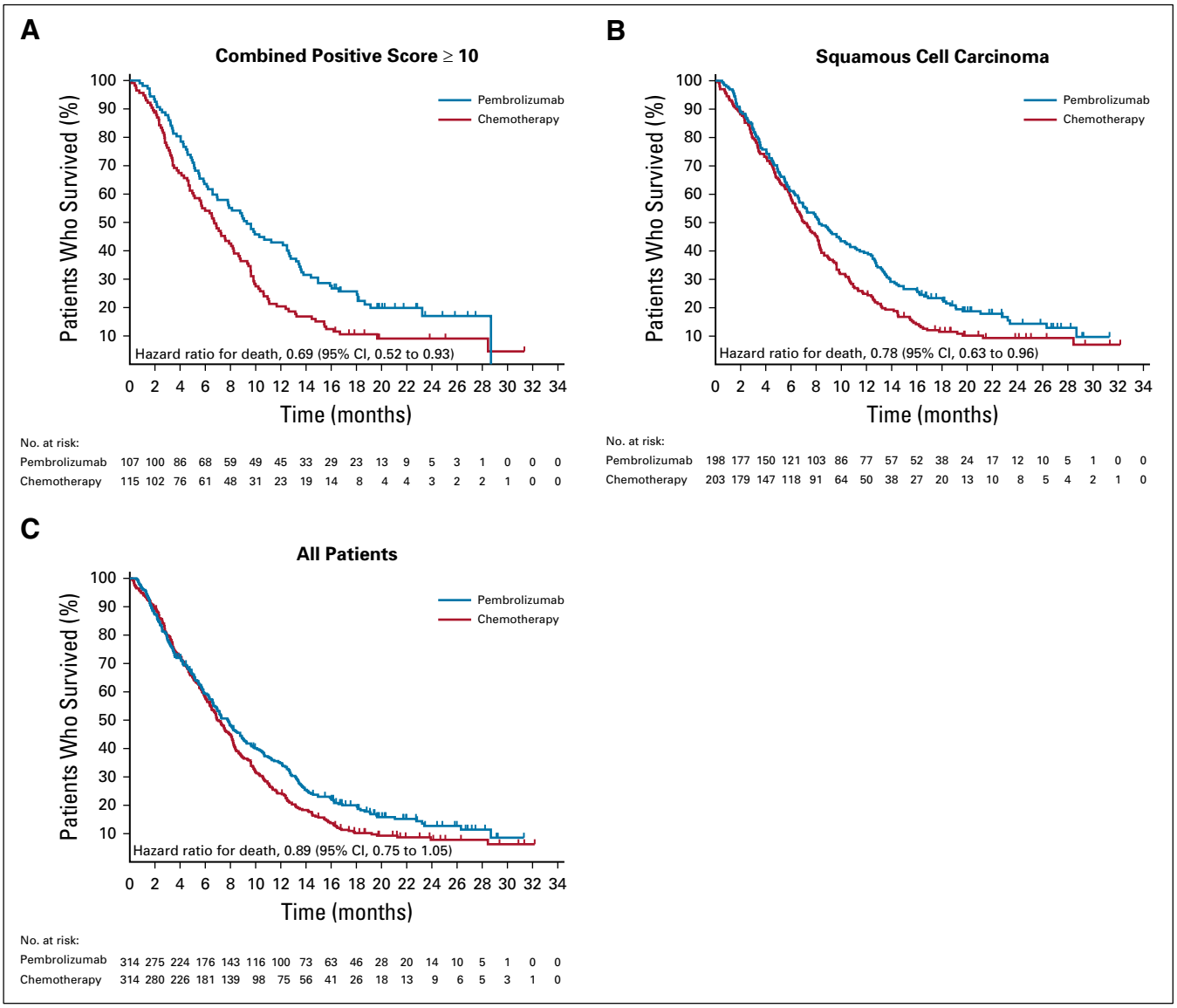


FIG 2. Overall survival in (A) patients with programmed death ligand 1 combined positive score ≥ 10, (B) patient with squamous cell carcinoma, and (C) the intent-to-treat population. The data cutoff date of the original final analysis of overall survival was October 15, 2018.

was 7.1 months (range, 0.5-31.3 months) for patients in the pembrolizumab group and 6.9 months (range, 0.2-32.2 months) in the chemotherapy group. A total of five patients (1.6%) completed 2 years of therapy (four with squamous cell carcinoma [PD-L1 CPS < 10] and one with adenocarcinoma [PD-L1 CPS ≥ 10]), and nine patients (2.9%) continued to receive therapy (five with squamous cell carcinoma [four PD-L1 CPS ≥ 10 and one PD-L1 CPS < 10] and four with adenocarcinoma [one PD-L1 CPS ≥ 10 and three PD-L1 CPS < 10]) in the pembrolizumab group; no patients continued to receive therapy in the chemotherapy group (Fig 1). A total of 31 patients (5%; one in the pembrolizumab group and 30 in the chemotherapy group) received treatment after progression with checkpoint inhibitor therapies.

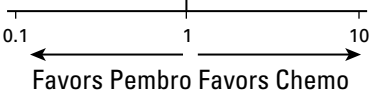
OS

At final analysis, a total of 190 patients with PD-L1 CPS ≥ 10 had died (87 [81.3%] in the pembrolizumab group and 103 [89.6%] in the chemotherapy group). Median OS was 9.3 months (95% CI, 6.6 to 12.5 months) and 6.7 months (95% CI, 5.1 to 8.2 months), respectively (Data Supplement). This difference met the prespecified boundary for showing superiority ($P < .00853$) of OS with pembrolizumab versus chemotherapy (HR, 0.69 [95% CI, 0.52 to 0.93]; $P = .0074$; Fig 2). The 12-month survival rate was 43.0% in the pembrolizumab group and 20.4% in the chemotherapy group (Data Supplement). The updated analysis showed that 191 patients with PD-L1 CPS ≥ 10 had died (88 [82.2%] in the pembrolizumab group and 103 [89.6%] in the chemotherapy group). The HR was 0.70

A

Combined Positive Score ≥ 10

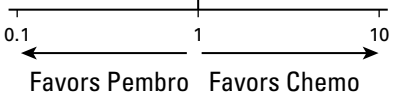
Subgroup	No. of deaths out of No. of patients	Hazard ratio (95% CI)
Overall	191 of 222	0.70 (0.52 to 0.94)
Age, years		
< 65	103 of 115	0.56 (0.38 to 0.84)
≥ 65	88 of 107	0.90 (0.57 to 1.42)
Sex		
Male	162 of 191	0.69 (0.50 to 0.96)
Female	29 of 31	0.77 (0.35 to 1.68)
ECOG PS		
0	68 of 81	0.73 (0.44 to 1.20)
1	123 of 141	0.74 (0.51 to 1.07)
Histology		
Squamous	140 of 167	0.64 (0.46 to 0.90)
Adenocarcinoma	51 of 55	0.93 (0.52 to 1.65)
Region		
Asia	93 of 115	0.59 (0.39 to 0.90)
Ex-Asia	98 of 107	0.83 (0.55 to 1.25)



B

Squamous Cell Carcinoma

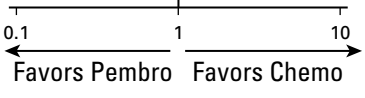
Subgroup	No. of deaths out of No. of patients	Hazard ratio (95% CI)
Overall	348 of 401	0.77 (0.63 to 0.96)
Age, years		
< 65	198 of 214	0.81 (0.61 to 1.07)
≥ 65	150 of 187	0.76 (0.55 to 1.06)
Sex		
Male	292 of 337	0.78 (0.62 to 0.98)
Female	56 of 64	0.80 (0.47 to 1.36)
ECOG PS		
0	125 of 152	0.64 (0.45 to 0.91)
1	222 of 248	0.89 (0.68 to 1.16)
PD-L1 CPS		
≥ 10	140 of 167	0.64 (0.46 to 0.90)
< 10	202 of 228	0.88 (0.66 to 1.16)
Region		
Asia	196 of 231	0.65 (0.49 to 0.87)
Ex-Asia	152 of 170	0.96 (0.70 to 1.32)



C

All Patients

Subgroup	No. of deaths out of No. of patients	Hazard ratio (95% CI)
Overall	555 of 628	0.89 (0.75 to 1.05)
Age, years		
< 65	329 of 356	0.88 (0.71 to 1.09)
≥ 65	226 of 272	0.93 (0.71 to 1.21)
Sex		
Male	480 of 544	0.89 (0.75 to 1.07)
Female	75 of 84	0.90 (0.57 to 1.43)
ECOG PS		
0	200 of 242	0.82 (0.62 to 1.08)
1	353 of 384	0.95 (0.77 to 1.77)
Histology		
Squamous	348 of 401	0.77 (0.63 to 0.96)
Adenocarcinoma	207 of 227	1.12 (0.85 to 1.47)
PD-L1 CPS		
≥ 10	191 of 222	0.70 (0.52 to 0.94)
< 10	355 of 397	1.00 (0.81 to 1.24)
Region		
Asia	207 of 243	0.66 (0.50 to 0.87)
Ex-Asia	348 of 385	1.06 (0.86 to 1.30)



(95% CI, 0.52 to 0.94) for pembrolizumab versus chemotherapy; this difference did not meet the prespecified boundary for showing superiority, $P < .00855$ (Data Supplement). With an additional 4 months of follow-up, the HR was 0.67 (95% CI, 0.50 to 0.89; Data Supplement). Survival outcomes were generally similar with pembrolizumab versus chemotherapy across key prespecified subgroups of patients with CPS ≥ 10, with the greatest survival benefit observed in patients with squamous cell carcinoma and in those from Asia (Fig 3).

The study did not meet the coprimary end point of OS in patients with squamous cell carcinoma. At final analysis, 346 deaths had occurred (165 [83.3%] in the pembrolizumab group and 181 [89.2%] in the chemotherapy group). Median OS was 8.2 months (95% CI, 6.7 to 10.3 months) and 7.1 months (95% CI, 6.1 to 8.2 months), respectively (Data Supplement); however, this difference did not reach the prespecified boundaries for significance (HR, 0.78 [95% CI, 0.63 to 0.96]; $P = .0095$; Fig 1B). The 12-month survival rate was 39.4% in the pembrolizumab group and 24.9% in the chemotherapy group (Data Supplement). The updated analysis showed that 348 deaths occurred (166 [83.8%] in the pembrolizumab group and 182 [89.7%] in the chemotherapy group). The HR was 0.77 (95% CI, 0.63 to 0.96; Data Supplement). With an additional 4 months of follow-up, the HR was 0.75 (95% CI, 0.61 to 0.93; Data Supplement). Among 401 patients with squamous cell carcinoma in the updated analysis, 167 (42%) had PD-L1 CPS ≥ 10 tumors (85 [51%] in the pembrolizumab group and 82 [49%] in the chemotherapy group). Median OS was 10.3 months (95%, CI, 7.0 to 13.5 months) and 6.7 months (95% CI, 4.8 to 8.6 months), respectively (HR 0.64 [95% CI, 0.46 to 0.90]; Data Supplement).

At final analysis, 553 of all patients had died (270 [86.0%] in the pembrolizumab group and 283 [90.1%] in the chemotherapy group). Median OS was 7.1 months in each group (95% CI, [6.2 to 8.1 months] and [95% CI, 6.3 to 8.0 months], respectively; Data Supplement; HR, 0.89 [95% CI, 0.75 to 1.05]; $P = .0560$; Fig 1C). The 12-month survival rate was 32.4% with pembrolizumab and 24.2% with chemotherapy (Data Supplement).

The updated analysis showed that a total of 555 patients had died (271 [86.3%] in the pembrolizumab group and 284 [90.4%] in the chemotherapy group), with no change in median OS between groups (Data Supplement). With an additional 4 months of follow-up, the HR was 0.85 (95% CI, 0.72 to 1.10; Data Supplement). Survival outcomes were generally similar with pembrolizumab versus chemotherapy across prespecified subgroups of patients with squamous cell carcinoma and in all patients (Fig 3).

PFS

In patients with PD-L1 CPS ≥ 10, median PFS was 2.6 months (95% CI, 2.1 to 4.1 months) in the pembrolizumab group and 3.0 months (95% CI, 2.1 to 3.7 months) in the chemotherapy group (Data Supplement; HR, 0.73 [95% CI, 0.54 to 0.97]; Fig 4A). The 12-month PFS rate was 20.8% in the pembrolizumab group and 6.7% in the chemotherapy group. Median PFS was 2.2 months (95% CI, 2.1 to 3.2 months) versus 3.1 months (95% CI, 2.2 to 3.9 months) in patients with squamous cell carcinoma (Data Supplement; HR 0.92 [95% CI, 0.75 to 1.13]; Fig 4B) and 2.1 months (95% CI, 2.1 to 2.2 months) versus 3.4 months (95% CI, 2.8 to 3.9 months) in all patients (Data Supplement; HR, 1.11 [95% CI, 0.94 to 1.31]; Fig 4C).

Tumor Response

In patients with PD-L1 CPS ≥ 10, 23 of 107 (21.5% [95% CI, 14.1% to 30.5%]) in the pembrolizumab group and seven of 115 (6.1% [95% CI, 2.5% to 12.1%]) in the chemotherapy group had an objective response. The median duration of response was 9.3 months (range, 2.1+ to 22.6+ months) in the pembrolizumab group and 7.7 months (4.3 to 16.8+) in the chemotherapy group (Data Supplement). Antitumor activity was more favorable with pembrolizumab versus chemotherapy in patients with PD-L1 CPS ≥ 10, regardless of histology (Data Supplement). In patients with squamous cell carcinoma, 33 of 198 (16.7% [95% CI, 11.8% to 22.6%]) in the pembrolizumab group and 15 of 203 (7.4% [95% CI, 4.2% to 11.9%]) in the chemotherapy group had an objective response (Data Supplement). In all patients, 41 of 314 (13.1% [95% CI, 9.5% to 17.3%]) in the pembrolizumab group and 21 of 314 (6.7% [95% CI, 4.2% to 10.0%]) in the chemotherapy group had an objective response (Data Supplement). Efficacy outcomes were not improved with pembrolizumab versus chemotherapy in patients with PD-L1 CPS < 10 metastatic esophageal cancer (Data Supplement).

AEs

Of 628 patients enrolled, 314 in the pembrolizumab group and 296 in the chemotherapy group received at least one dose of study treatment. The mean (standard deviation) time receiving treatment was 4.0 (5.0) months and 3.1 (2.9) months, respectively.

Patients in the chemotherapy group experienced significantly more AEs related to fatigue, diarrhea, and hematologic toxicities (Data Supplement). Treatment-related AEs occurred in 64% of patients in the pembrolizumab group and in 86% of patients in the chemotherapy group. Grade 3 or higher treatment-related AEs occurred in 18% of patients

FIG 3. Updated forest plot analysis of overall survival in subgroups of (A) patients with programmed death ligand 1 (PD-L1) combined positive score (CPS) ≥ 10, (B) patients with squamous cell carcinoma, and (C) all patients. This analysis includes two additional survival events not included in the data at final analysis. The data cutoff date was October 15, 2018. Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; Pembro, pembrolizumab.

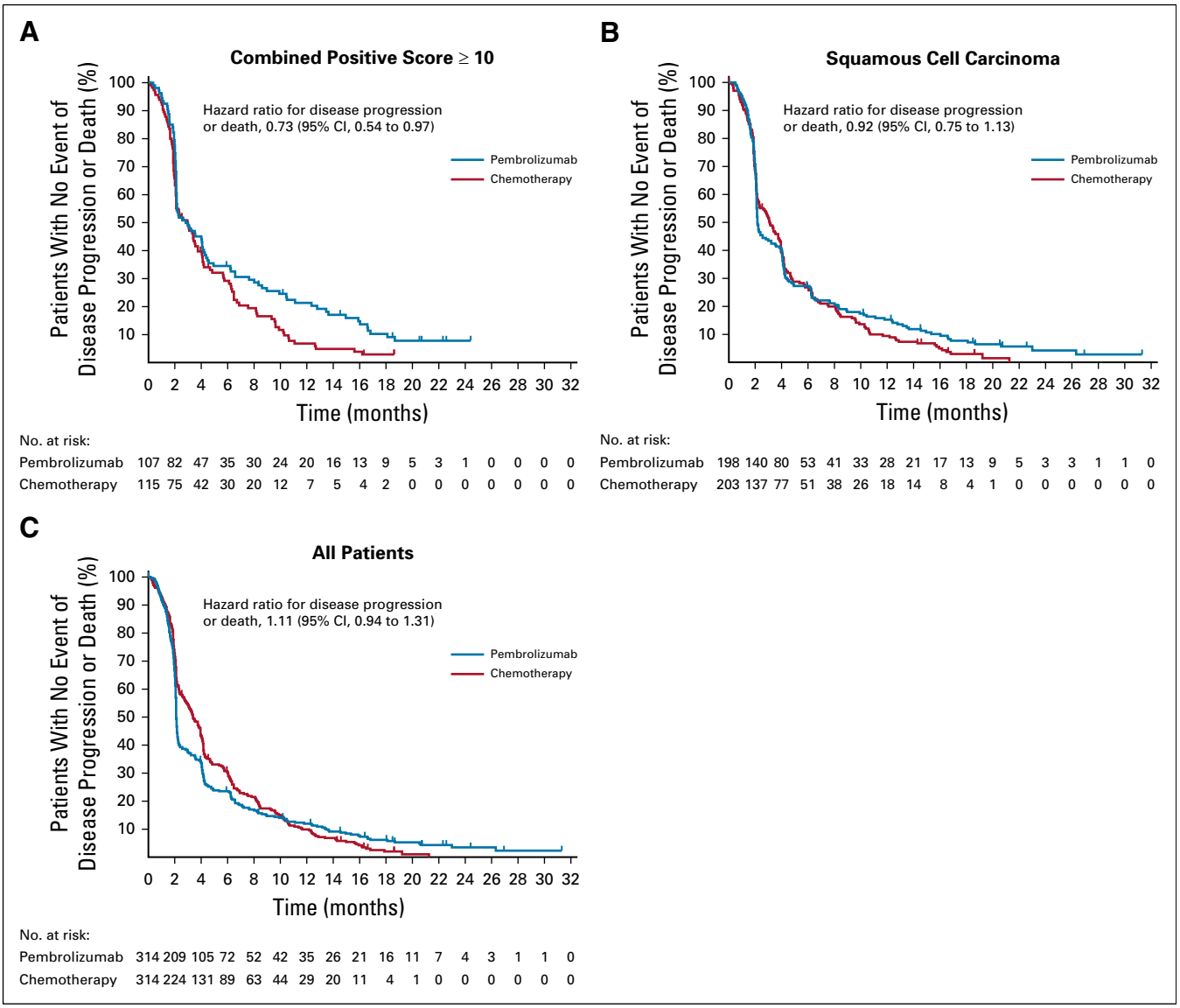


FIG 4. Progression-free survival in (A) patients with programmed death ligand 1 combined positive score ≥ 10, (B) patients with squamous cell carcinoma, and (C) the intent-to-treat population. The data cutoff date of the original final analysis of progression-free survival was October 15, 2018.

in the pembrolizumab group and in 40.9% of patients in the chemotherapy group. Treatment-related AEs led to discontinuation in approximately 6% of patients in each group and to death for five patients in each group (Tables 2 and 3). Immune-mediated AEs and infusion reactions occurred in 23.2% of patients in the pembrolizumab group and in 7.4% of patients in the chemotherapy group (Data Supplement).

DISCUSSION

Despite recent advances, patients with metastatic esophageal cancer who progress after first-line chemotherapy continue to have limited treatment options and poor prognosis. The international, randomized phase III KEYNOTE-181 study enrolled patients worldwide and showed that pembrolizumab provided a clinically meaningful OS benefit versus chemotherapy in a global population of patients with metastatic esophageal squamous cell carcinoma and with PD-L1 CPS ≥ 10 tumors that progressed after one prior therapy.

The survival benefit observed in patients with PD-L1 CPS ≥ 10 is highlighted by the more than twofold increase in the 12-month survival rate with pembrolizumab versus chemotherapy (43% *v* 20%) and by the consistent reduction in the risk of death. This consistent reduction was observed at final analysis (HR, 0.69 [95% CI, 0.52 to 0.93]; $P = .0074$), at the updated analysis (HR, 0.70 [95% CI, 0.52 to 0.94]), and with an additional 4 months of follow-up (HR, 0.67 [95% CI, 0.50 to 0.89]). A similar survival benefit was generally observed across key prespecified subgroups of

TABLE 2. Adverse Events in All Treated Patients

Adverse Event	Pembrolizumab (n = 314)	Chemotherapy (n = 296)
Any	300 (95.5)	288 (97.3)
Treatment related	202 (64.3)	255 (86.1)
Grade 3-5	57 (18.2)	121 (40.9)
Led to discontinuation	19 (6.1)	19 (6.4)
Led to death[a]	5 (1.6)	5 (1.7)

NOTE. Data are presented as No. (%). Data cutoff date was October 15, 2018.
[a]Grade 5 treatment-related adverse events were myocarditis, death, and decreased WBC count in one patient each and pneumonitis in two patients in the pembrolizumab group, and pneumonia, pneumonia aspiration, sepsis, decreased neutrophil count, and hemorrhagic shock in one patient each in the chemotherapy group.

patients with PD-L1 CPS ≥ 10, with the highest survival benefit observed in patients with squamous cell carcinoma with PD-L1 CPS ≥ 10 (HR, 0.64). In addition, Asian patients seemed to have an enhanced benefit with pembrolizumab versus chemotherapy. The reduction in the risk of death observed with pembrolizumab versus chemotherapy in the PD-L1 CPS ≥ 10 population is also supported by the clinically meaningful HR for PFS of 0.73 (95% CI, 0.54 to 0.97) and the greater than threefold increase in the 12-month PFS rate (20.8% *v* 6.7%). The updated analysis, which included two additional death events not in the original final analysis, missed the prespecified α level for significance (.00853) by .00002 (.00855). Together, these results show a durable benefit with pembrolizumab versus chemotherapy. Moreover, the approximately threefold increase in ORR with pembrolizumab versus chemotherapy (21.5% *v* 6.1%) suggests a favorable tumor response. More patients had durable responses with pembrolizumab versus chemotherapy, with 53.5% versus 38.1% of patients, respectively, estimated to have responses with durations of ≥ 9 months. These data are consistent with those from KEYNOTE-180 that showed enrichment of efficacy outcomes in patients with PD-L1 CPS ≥ 10 metastatic esophageal cancer,[11] reinforcing the use of PD-L1 expression for selecting patients to be treated with pembrolizumab.

TABLE 3. Treatment-Related Adverse Events in ≥ 10% of Patients in Either Group

	Pembrolizumab (n = 314)		Chemotherapy (n = 296)	
Adverse Event	All Grades	Grade 3-5	All Grades	Grade 3-5
Fatigue	37 (11.8)	2 (0.6)	61 (20.6)	1 (0.3)
Hypothyroidism	33 (10.5)	0 (0.0)	1 (0.3)	0 (0.0)
Decreased appetite	27 (8.6)	2 (0.6)	46 (15.5)	3 (1.0)
Asthenia	22 (7.0)	4 (1.3)	34 (11.5)	3 (1.0)
Nausea	22 (7.0)	0 (0.0)	64 (21.6)	7 (2.4)
Diarrhea	17 (5.4)	2 (0.6)	60 (20.3)	9 (3.0)
Vomiting	10 (3.2)	1 (0.3)	33 (11.1)	6 (2.0)
Anemia	8 (2.5)	4 (1.3)	66 (22.3)	23 (7.8)
Alopecia	2 (0.6)	0 (0.0)	86 (29.1)	1 (0.3)
Neutrophil count decreased	2 (0.6)	1 (0.3)	50 (16.9)	29 (9.8)
Peripheral sensory neuropathy	1 (0.3)	0 (0.0)	50 (16.9)	1 (0.3)
WBC count decreased	1 (0.3)	0 (0.0)	49 (16.6)	30 (10.1)
Neutropenia	0 (0.0)	0 (0.0)	34 (11.5)	21 (7.1)

NOTE. Data are presented as No. (%). Listed are treatment-related adverse events that occurred during the study period or within 30 days thereafter (within 90 days for serious events). Data cutoff date was October 15, 2018.

Although OS was longer with pembrolizumab versus chemotherapy in patients with squamous cell carcinoma (HR, 0.78 [95% CI, 0.63 to 0.96]; $P = .0095$), this difference did not meet the prespecified α level for significance (.0077). The survival rate at 12 months was also higher with pembrolizumab versus chemotherapy (39.4% *v* 24.9%). This survival benefit was generally observed across prespecified subgroups of patients with squamous cell carcinoma and was maintained at post hoc analysis and with additional follow-up, with the greatest benefit observed in patients with squamous cell carcinoma with PD-L1 CPS ≥ 10. As in patients with PD-L1 CPS ≥ 10, patients with squamous cell carcinoma experienced modest improvements in 12-month PFS rates and a more than twofold increase in ORR with pembrolizumab versus chemotherapy (16.7% *v* 7.4%). These responses were durable, with 49% of patients in the pembrolizumab group estimated to have responses with durations of at least 9 months. These data are consistent with those from the KEYNOTE-180 study that showed improved efficacy outcomes with pembrolizumab in patients with squamous cell carcinoma.[11] Moreover, these data are consistent with results of the phase III study of nivolumab versus chemotherapy in patients with advanced esophageal squamous cell carcinoma in the second-line setting, where a 23% reduction in the risk of death was observed with nivolumab versus chemotherapy (HR, 0.77 [95% CI, 0.62 to 0.96]; $P = .019$), with an ORR of (19% *v* 22%), and limited benefit in terms of risk of progression or death (HR, 1.08 [95% CI, 0.87 to 1.34]).[12]

Overall, fewer AEs were observed with pembrolizumab versus chemotherapy despite longer drug exposure (mean days receiving therapy of 112.4 *v* 94.8). A rainfall plot analysis showed that patients in the chemotherapy group experienced significantly more AEs related to fatigue, diarrhea, and hematologic toxicities. In addition, a lower incidence of drug-related and grade 3-5 drug-related AEs were reported with pembrolizumab versus chemotherapy. The incidence of immune-mediated AEs in the pembrolizumab group was similar to that observed previously in patients with metastatic esophageal cancer,[10-12] and no new safety signals were observed. The efficacy and safety outcomes observed with chemotherapy in this patient population were generally consistent with those in previous reports.[8]

A limitation of this study is the open-label nature of the study design that may have affected compliance. In addition, although OS was superior with pembrolizumab

compared with chemotherapy in patients with PD-L1 CPS ≥ 10, the study was not sufficiently powered to evaluate statistically significant differences between patients with PD-L1 CPS ≥ 10 squamous cell carcinoma or adenocarcinoma.

In conclusion, pembrolizumab provided a clinically meaningful survival benefit versus chemotherapy for patients with metastatic esophageal squamous cell carcinoma and PD-L1 CPS ≥ 10 tumors and also in patients with metastatic esophageal squamous cell carcinoma or PD-L1 CPS ≥ 10 tumors, in the second line, with reduced toxicity. These data contributed to the current US Food and Drug Administration approval of pembrolizumab for patients with metastatic or locally advanced, esophageal squamous cell carcinoma with PD-L1 CPS ≥ 10 in the second-line setting.

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Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer

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