ORIGINAL ARTICLE

Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma

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ABSTRACT

BACKGROUND

The programmed death 1 (PD-1) inhibitor pembrolizumab has been found to prolong progression-free and overall survival among patients with advanced melanoma. We conducted a phase 3 double-blind trial to evaluate pembrolizumab as adjuvant therapy in patients with resected, high-risk stage III melanoma.

METHODS

Patients with completely resected stage III melanoma were randomly assigned (with stratification according to cancer stage and geographic region) to receive 200 mg of pembrolizumab (514 patients) or placebo (505 patients) intravenously every 3 weeks for a total of 18 doses (approximately 1 year) or until disease recurrence or unacceptable toxic effects occurred. Recurrence-free survival in the overall intention-to-treat population and in the subgroup of patients with cancer that was positive for the PD-1 ligand (PD-L1) were the primary end points. Safety was also evaluated.

RESULTS

At a median follow-up of 15 months, pembrolizumab was associated with significantly longer recurrence-free survival than placebo in the overall intention-to-treat population (1-year rate of recurrence-free survival, 75.4% [95% confidence interval {CI}, 71.3 to 78.9] vs. 61.0% [95% CI, 56.5 to 65.1]; hazard ratio for recurrence or death, 0.57; 98.4% CI, 0.43 to 0.74; P<0.001) and in the subgroup of 853 patients with PD-L1–positive tumors (1-year rate of recurrence-free survival, 77.1% [95% CI, 72.7 to 80.9] in the pembrolizumab group and 62.6% [95% CI, 57.7 to 67.0] in the placebo group; hazard ratio, 0.54; 95% CI, 0.42 to 0.69; P<0.001). Adverse events of grades 3 to 5 that were related to the trial regimen were reported in 14.7% of the patients in the pembrolizumab group and in 3.4% of patients in the placebo group. There was one treatment-related death due to myositis in the pembrolizumab group.

CONCLUSIONS

As adjuvant therapy for high-risk stage III melanoma, 200 mg of pembrolizumab administered every 3 weeks for up to 1 year resulted in significantly longer recurrence-free survival than placebo, with no new toxic effects identified. (Funded by Merck; ClinicalTrials.gov number, NCT02362594; EudraCT number, 2014-004944-37.)

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The development of effective adjuvant therapies for patients with high-risk melanoma has been preceded by the recent arrival of active agents to treat metastatic melanoma, including ipilimumab (an anti-CTLA4 antibody), pembrolizumab and nivolumab (both monoclonal antibodies against programmed death 1 [PD-1]), and combination BRAF and MEK inhibition for patients whose tumors harbor a *BRAF* mutation.[1-6] Pembrolizumab has been found to be associated with longer progression-free survival and overall survival in advanced melanoma than ipilimumab, regardless of PD-1 ligand (PD-L1) expression level and *BRAF* mutation status.[5] Phase 3 trials evaluating the efficacy of these drugs as adjuvant therapy for patients with resected high-risk melanoma have been undertaken. In 2015, ipilimumab was approved on the basis of a significant advantage over placebo with regard to recurrence-free survival in resected stage III melanoma, and a similar advantage for overall survival was shown in 2016.[7,8] In 2017, dabrafenib–trametinib and nivolumab were independently shown to have efficacy in resected *BRAF*-mutant melanoma of stage III and in resected *BRAF*-mutant and *BRAF*–wild-type melanoma of stage IIIB, IIIC, or IV, respectively.[9,10] The European Organization for Research and Treatment of Cancer (EORTC) 1325 (KEYNOTE-054) trial involved the same high-risk patient population with stage III melanoma as the EORTC 18071 trial of ipilimumab versus placebo, which limits its trial population to patients with stage IIIA disease who have a high risk of recurrence based on tumor load in the sentinel node (diameter, >1 mm, according to the Rotterdam Criteria).[11-13] In the randomized, double-blind, phase 3 EORTC 1325 trial, we compared pembrolizumab (200 mg every 3 weeks) with matching placebo as adjuvant therapy for patients with resected, high-risk stage III melanoma.

Methods

Patients

We enrolled patients who were 18 years of age or older and had histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes. The patients had to have either stage IIIA melanoma (patients with stage N1a melanoma had to have at least one micrometastasis measuring >1 mm in greatest diameter) or stage IIIB or IIIC disease with no in-transit metastases as defined by the American Joint Committee on Cancer 2009 classification, 7th edition.[14] A complete regional lymphadenectomy was required to have been performed within 13 weeks before the start of treatment. Exclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status score of more than 1 (scores range from 0 to 5, with higher numbers indicating greater disability), autoimmune disease, uncontrolled infections, use of systemic glucocorticoids, and previous systemic therapy for melanoma.

A tumor sample from melanoma-positive lymph nodes was required to be sent for central pathological evaluation of PD-L1 expression. Membranous expression of PD-L1 in tumor and tumor-associated immune cells was assessed by means of a clinical trial immunohistochemistry assay (22C3 antibody) and was scored on a scale of 0 to 5 that has been developed specifically for melanoma (with higher numbers reflecting a higher level of PD-L1 expression); a score of 2 or higher (i.e., staining on >1% of cells) was considered to indicate PD-L1 positivity.[15]

Trial Design

Registration was performed centrally at the EORTC headquarters. A central interactive voice-response system was used for randomization, which was based on a minimization technique. Randomization was stratified according to stage (stage IIIA, stage IIIB, stage IIIC with one to three positive nodes, or stage IIIC with four or more positive nodes) and geographic region (17 regions, each formed by 1 to 3 countries). Only the local pharmacists were aware of trial-group assignments, whereas the clinical investigators, patients, and those collecting or analyzing the data were not.

Patients were randomly assigned in a 1:1 ratio to receive either an intravenous infusion of 200 mg of pembrolizumab or placebo every 3 weeks for a total of 18 doses (approximately 1 year [part 1 of the trial]) or until disease recurrence, unacceptable toxic effects, a major protocol violation, or withdrawal of consent occurred (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The rules regarding the withholding of a dose of pembrolizumab or placebo and the management of immune-related adverse events are detailed in the protocol, available at NEJM.org. If a recurrence was

documented, patients were eligible for crossover or repeat treatment with pembrolizumab (part 2 of the trial).

The primary end point was recurrence-free survival in the overall intention-to-treat population and in the subgroup of patients with PD-L1–positive tumors. Secondary end points included distant metastasis-free survival, overall survival, safety measures, and measures of health-related quality of life.

ASSESSMENTS

Computed tomography, magnetic resonance imaging, or both were performed every 12 weeks for the first 2 years, every 6 months through year 5, then annually. Recurrence or metastatic lesions had to be histologically confirmed whenever possible. The first date when recurrence was observed was taken into account.

Recurrence-free survival was defined as the time from randomization until the date of first recurrence (local, regional, or distant metastasis) or death from any cause. For patients without any event, follow-up was censored at the latest disease evaluation performed according to the trial protocol.

Data on adverse events were collected for each treatment course with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Immune-related adverse events were programmatically determined from a predefined list of *Medical Dictionary for Regulatory Activities* (MedDRA) terms, which was updated in accordance with each new version of MedDRA.

TRIAL OVERSIGHT

The trial protocol was approved by the EORTC protocol review committee and independent ethics committees. The trial was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonisation. All patients provided written informed consent.

The trial was sponsored by Merck and was designed by the academic authors. Data were collected, computerized, and analyzed at the EORTC headquarters. All the authors participated in the revision and finalization of the manuscript and approved submission of the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

The EORTC independent data and safety monitoring committee assessed the safety data twice per year, without formal stopping rules. In December 2017, the independent data and safety monitoring committee also assessed the first analysis of recurrence-free survival, which was performed by an independent statistician. On-site source-data verification was provided by a clinical research organization.

STATISTICAL ANALYSIS

We planned for the trial to include 900 patients. We determined that a total of 409 events (recurrences or deaths without recurrences) would be required in order to provide 92% power to detect a hazard ratio for recurrence or death of 0.70, corresponding to a 1-year recurrence-free survival rate of 58.3% in the placebo group versus 68.5% in the pembrolizumab group and a 3-year recurrence-free survival rate of 35.3% in the placebo group versus 48.3% in the pembrolizumab group, at a one-sided alpha level of 1.4%. If the results in the overall intention-to-treat population were significant, the treatment comparison would be performed in the subgroup of patients with PD-L1–positive tumors at a one-sided alpha level of 2.5%.[16]

In July 2017, the positive results of the CheckMate 238 trial, in which the effect of adjuvant therapy in melanoma with nivolumab or ipilimumab was evaluated, were announced, and they were subsequently published in September 2017.[10] The estimated hazard ratio for disease recurrence or death in association with nivolumab versus ipilimumab was 0.65 (97.56% confidence interval [CI], 0.51 to 0.83), on the basis of an interim analysis. In August 2017, the EORTC 1325 protocol was amended to include an interim analysis of recurrence-free survival based on the 1019 patients who underwent randomization, conducted with the use a Lan–DeMets alpha spending function with an O'Brien–Fleming boundary.[17] At the clinical cutoff date (October 2, 2017), 351 events (recurrences or deaths) had been reported in the intention-to-treat population. The interim analysis was performed at a one-sided alpha level of 0.8% (two-sided alpha level, 1.6%). In December 2017, the independent data and safety monitoring committee reviewed

the unblinded results and recommended the reporting of the primary end points and safety. Because the results were positive in the intention-to-treat population, the interim analysis of recurrence-free survival became the final analysis. To preserve the alpha error, a hierarchical testing approach will be applied to the two remaining efficacy end points — distant metastasis–free survival first, and then overall survival (see the protocol).

The recurrence-free survival distribution was estimated with the Kaplan–Meier method, and the confidence intervals for the 12- and 18-month survival rates were obtained with the Greenwood variance formula. Comparisons between the trial groups were performed with the use of a log-rank test stratified according to disease stage at randomization, at a two-sided alpha level. A Cox proportional-hazards model stratified according to disease stage as provided at randomization was used to estimate the hazard ratio and its corresponding confidence interval, which was 98.4% (100 minus 1.6) for the total patient population and 95% (100 minus [2 times 2.5]) for the PD-L1–positive subgroup.

For exploratory purposes, we investigated the predictive importance of several factors with regard to the differences in recurrence-free survival. Forest plots were produced, and a test of interaction between each variable and the trial group in a Cox model was conducted. For these subgroup analyses, the hazard ratios were plotted along with their 99% confidence intervals.

The primary analysis of recurrence-free survival included all the patients who underwent randomization, according to the intention-to-treat principle. The safety profile was assessed in the group of patients who started their randomly assigned trial regimen. All analyses were performed with SAS software, version 9.4 (SAS Institute), and the power calculations were performed with East software, version 6.4 (Cytel).

RESULTS

PATIENTS AND TRIAL REGIMEN

From August 2015 through November 2016, a total of 1019 patients underwent randomization at 123 centers in 23 countries: 514 patients were assigned to the pembrolizumab group, and 505 were assigned to the placebo group. The characteristics of the patients at baseline were similar in the two groups (Table 1).

Eight patients did not start the regimen that had been randomly assigned (Fig. 1). The median number of doses received was 18 (interquartile range, 9 to 18) in the pembrolizumab group and 18 (interquartile range, 8 to 18) in the placebo group.

Of the 509 patients who started pembrolizumab, 70 (13.8%) discontinued the regimen owing to an adverse event; in 66 patients (13.0%), the event was considered by the investigators to be drug-related. Among the 502 patients who received placebo, 11 (2.2%) discontinued the regimen owing to an adverse event; in 8 patients (1.6%), the event was considered to be placebo-related. A total of 109 patients (21.4%) in the pembrolizumab group discontinued the regimen because of disease recurrence, as compared with 179 patients (35.7%) in the placebo group. A total of 282 patients (55.4%) in the pembrolizumab group and 294 (58.6%) in the placebo group completed the 1-year treatment period (Fig. 1). The overall median duration of follow-up was 15.1 months — 14.7 months in the pembrolizumab group and 15.4 months in the placebo group.

EFFICACY

Overall Intention-to-Treat Population

In the overall intention-to-treat population, the 12-month rate of recurrence-free survival was 75.4% (95% CI, 71.3 to 78.9) in the pembrolizumab group and 61.0% (95% CI, 56.5 to 65.1) in the placebo group (Fig. 2A). Recurrence-free survival was significantly longer in the pembrolizumab group than in the placebo group (hazard ratio for recurrence or death, 0.57; 98.4% CI, 0.43 to 0.74; P<0.001) (Fig. 2A). The results were similar in the per-protocol population (hazard ratio for recurrence or death, stratified according to stage, 0.56; 98.4% CI, 0.43 to 0.74; P<0.001). At 18 months, the rates of recurrence-free survival in the intention-to-treat population were 71.4% (95% CI, 66.8 to 75.4) in the pembrolizumab group and 53.2% (95% CI, 47.9 to 58.2) in the placebo group.

A total of 351 patients had a first recurrence of disease or died: 135 in the pembrolizumab group and 216 in the placebo group. There were 78 patients (15.2%) in the pembrolizumab group in whom distant metastases developed, alone or combined with locoregional recurrences, as compared with 138 patients (27.3%) in the placebo group (Fig. 2A). The 18-month cumulative incidence of distant metastasis being the first site of

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

Characteristic	Pembrolizumab (N=514)	Placebo (N=505)
Sex — no. (%)		
Male	324 (63.0)	304 (60.2)
Female	190 (37.0)	201 (39.8)
Age		
Median (range) — yr	54 (19–88)	54 (19–83)
<50 yr — no. (%)	193 (37.5)	186 (36.8)
50 to <65 yr — no. (%)	196 (38.1)	193 (38.2)
≥65 yr — no. (%)	125 (24.3)	126 (25.0)
Body-mass index — no./total no. (%)		
<25	155/501 (30.9)	184/501 (36.7)
25 to <30	224/501 (44.7)	194/501 (38.7)
≥30	122/501 (24.4)	123/501 (24.6)
Disease stage — no. (%)		
At randomization		
Stage IIIA	80 (15.6)	80 (15.8)
Stage IIIB	237 (46.1)	230 (45.5)
Stage IIIC with 1–3 positive lymph nodes	95 (18.5)	93 (18.4)
Stage IIIC with ≥4 positive lymph nodes	102 (19.8)	102 (20.2)
According to AJCC 2009 criteria†		
Stage IIIA	77 (15.0)	76 (15.0)
Stage IIIB	240 (46.7)	232 (45.9)
Stage IIIC with 1–3 positive lymph nodes‡	87 (16.9)	95 (18.8)
Stage IIIC with ≥4 positive lymph nodes§	110 (21.4)	102 (20.2)
Type of lymph node involvement — no. (%)†		
Microscopic	187 (36.4)	161 (31.9)
Macroscopic	327 (63.6)	344 (68.1)
No of positive lymph nodes on pathological testing — no. (%)†		
1	227 (44.2)	237 (46.9)
2 or 3‡	177 (34.4)	166 (32.9)
≥4§	110 (21.4)	102 (20.2)
Ulceration — no. (%)†		
Yes	208 (40.5)	197 (39.0)
No	230 (44.7)	251 (49.7)
Unknown	76 (14.8)	57 (11.3)
PD-L1 expression status — no. (%)¶		
Positive	428 (83.3)	425 (84.2)
Negative	59 (11.5)	57 (11.3)
Indeterminate	27 (5.3)	23 (4.6)
BRAF mutation status — no. (%)		
Wild type	233 (45.3)	214 (42.4)
V600E or V600K mutation	210 (40.9)	231 (45.7)
Other mutation	35 (6.8)	31 (6.1)
Unknown	36 (7.0)	29 (5.7)

* There were no significant between-group differences in the characteristics listed here. Percentages may not total 100 because of rounding. AJCC denotes American Joint Committee on Cancer 2009 classification, 7th edition.[14]

† Data were from electronic case-report forms.

‡ One patient with in-transit metastases or satellites and without metastatic nodes was included in this subgroup.

§ This subgroup also included 11 patients with matted nodes as well as 5 patients with in-transit metastases or satellites and at least one positive lymph node.

¶ Membranous expression of programmed death ligand 1 (PD-L1) in tumor and tumor-associated immune cells was assessed by means of a 22C3 antibody assay and was scored on a scale of 0 to 5 (with higher scores reflecting a higher level of expression); a score 2 or higher (i.e., staining on >1% of cells) was considered to indicate PD-L1 positivity.

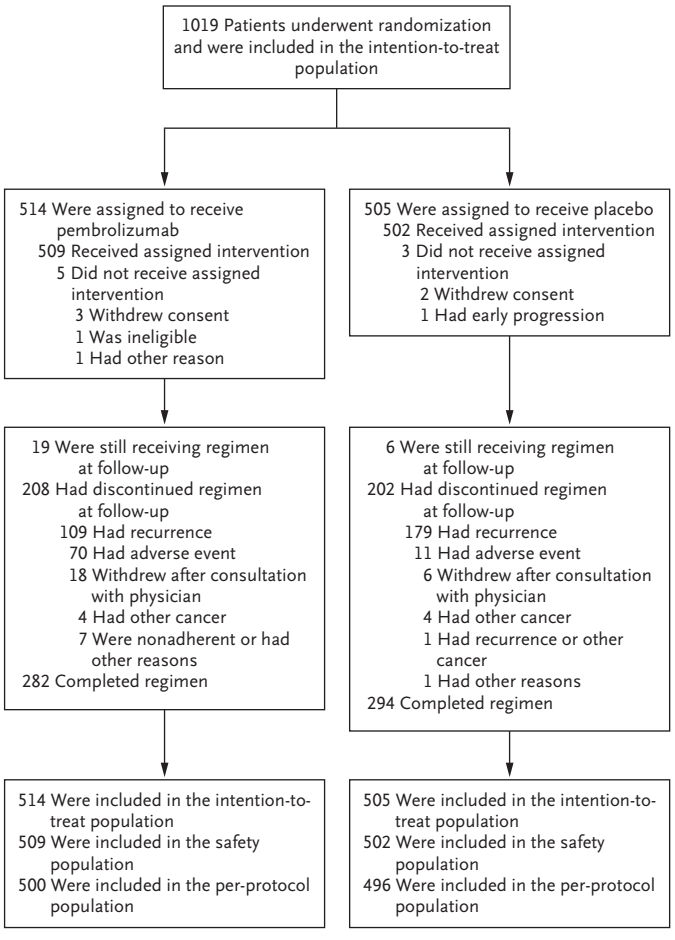


Figure 1. Enrollment, Randomization, and Follow-up.

The intention-to-treat population included all patients who underwent randomization. The safety population included all patients who started the trial regimen to which they had been randomly assigned. The per-protocol population included all eligible patients (i.e., those who did not have a major violation of eligibility criteria) who started the trial regimen to which they had been randomly assigned. In total, 10 patients in the pembrolizumab group (9 of whom started treatment) and 6 patients in the placebo group were found to have major eligibility violations.

Figure 2 (facing page). Kaplan–Meier Estimate of Recurrence-free Survival, as Assessed by Local Investigators, in the Overall Intention-to-Treat Population and According to Tumor Programmed Death Ligand 1 (PD-L1) Expression.

The log-rank test stratified according to disease stage at randomization was used to draw inferences. The estimate of the hazard ratio was based on a Cox model stratified according to disease stage at randomization. In the overall intention-to-treat population, there were 132 locoregional recurrences (55 in the pembrolizumab group and 77 in the placebo group), 183 distant metastases (69 in the pembrolizumab group and 114 in the placebo group), 33 concomitant locoregional and distant metastases (9 in the pembrolizumab group and 24 in the placebo group), and 3 deaths (2 in the pembrolizumab group and 1 in the placebo group). The 12-month rate of recurrence-free survival was 75.4% (95% confidence interval [CI], 71.3 to 78.9) in the pembrolizumab group and 61.0% (95% CI, 56.5 to 65.1) in the placebo group, and the 18-month rate of recurrence-free survival was 71.4% (95% CI, 66.8 to 75.4) in the pembrolizumab group and 53.2% (95% CI, 47.9 to 58.2) in the placebo group. Among patients with positive PD-L1 tumor expression (melanoma score, 2 to 5), the 12-month recurrence-free survival rate was 77.1% (95% CI, 72.7 to 80.9) in the pembrolizumab group and 62.6% (95% CI, 57.7 to 67.0) in the placebo group. Among patients with negative PD-L1 tumor expression (melanoma score, 0 or 1), the 12-month recurrence-free survival rate was 72.2% (95% CI, 58.6 to 82.0) in the pembrolizumab group and 52.2% (95% CI, 38.2 to 64.5) in the placebo group.

recurrence was 16.7% and 29.7% respectively (hazard ratio, 0.53; 99% CI, 0.37 to 0.76) (Fig. S2 in the Supplementary Appendix).

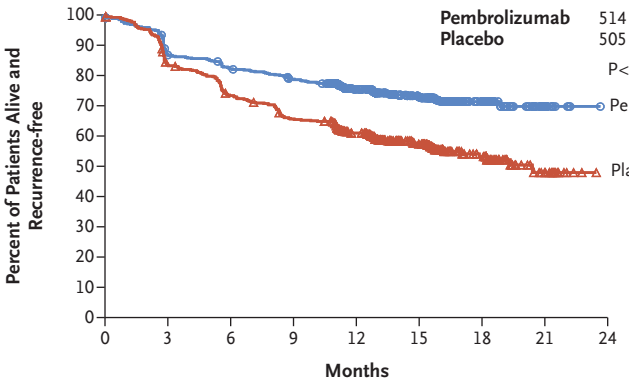
Recurrence-free Survival According to Tumor PD-L1 Expression

In the subgroup of 853 patients with PD-L1–positive tumors (melanoma score, ≥2), the 12-month recurrence-free survival rate was 77.1% (95% CI, 72.7 to 80.9) in the pembrolizumab group and 62.6% (95% CI, 57.7 to 67.0) in the placebo group (Fig. 2B). Recurrence-free survival was significantly longer in the pembrolizumab group than in the placebo group (hazard ratio for recurrence or death, 0.54; 95% CI, 0.42 to 0.69; P<0.001). Pembrolizumab was also consistently effective in patients with PD-L1–negative tumors (Figs. 2C and 3) and in those with undetermined tumor PD-L1 expression (Fig. S3 in the Supplementary Appendix).

Recurrence-free Survival According to Other Variables

The between-group difference in recurrence-free survival was consistently observed across subgroups that were based on baseline characteristics (Fig. 3). The benefit from pembrolizumab was similar in patients with stage IIIA, IIIB, or IIIC disease; the 12-month rate of recurrence-free survival among patients with stage IIIB or IIIC disease in the pembrolizumab group was 72.2% (95% CI, 67.6 to 76.2). The benefit from pembrolizumab was also similar in patients

A Overall Intention-to-Treat Population

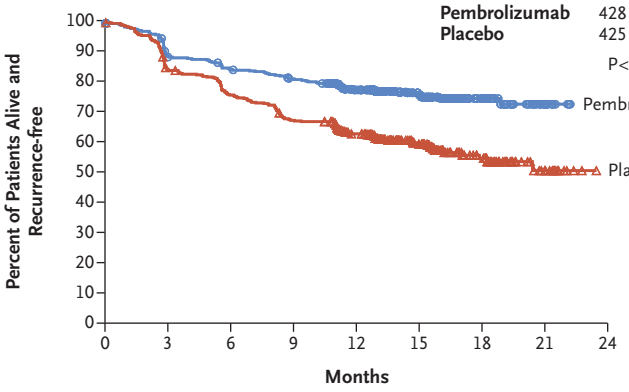


	Total No.	No. with Event	Hazard Ratio (98.4% CI)
Pembrolizumab	514	135	0.57 (0.43–0.74)
Placebo	505	216	1.00

P<0.001 by stratified log-rank test

No. at Risk									
Pembrolizumab	514	438	413	392	313	182	73	15	0
Placebo	505	415	363	323	264	157	60	15	0

B Patients with PD-L1–Positive Tumors

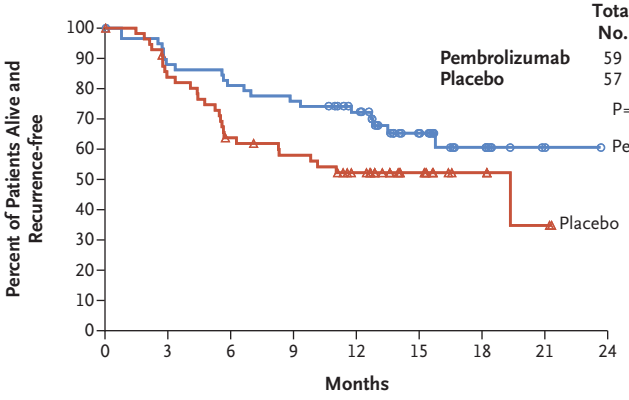


	Total No.	No. with Event	Hazard Ratio (95% CI)
Pembrolizumab	428	102	0.54 (0.42–0.69)
Placebo	425	176	1.00

P<0.001 by stratified log-rank test

No. at Risk									
Pembrolizumab	428	370	350	333	266	156	61	13	0
Placebo	425	353	317	281	233	141	55	13	0

C Patients with PD-L1–Negative Tumors



	Total No.	No. with Event	Hazard Ratio (95% CI)
Pembrolizumab	59	20	0.47 (0.26–0.85)
Placebo	57	27	1.00

P=0.01 by stratified log-rank test

No. at Risk									
Pembrolizumab	59	51	47	44	37	20	10	2	0
Placebo	57	46	34	30	23	12	5	2	0

Subgroup	Pembrolizumab	Placebo	Hazard Ratio (99% or 98.4% CI)	P Value for Interaction
	no. of events/total no.			
Tumor PD-L1 expression				0.60
Positive	102/428	176/425	0.54 (0.39–0.74)	
Negative	20/59	27/57	0.60 (0.28–1.28)	
Indeterminate	13/27	13/23	0.80 (0.29–2.19)	
Sex				0.49
Male	86/324	138/304	0.53 (0.37–0.76)	
Female	49/190	78/201	0.62 (0.39–1.00)	
Age				0.86
18 to <65 yr	96/389	154/379	0.57 (0.41–0.80)	
≥65 yr	39/125	62/126	0.55 (0.32–0.93)	
AJCC 2009 melanoma classification				0.69
Stage IIIA	6/77	15/76	0.38 (0.11–1.31)	
Stage IIIB	62/240	97/232	0.58 (0.38–0.88)	
Stage IIIC	67/197	104/197	0.58 (0.38–0.86)	
No. of positive lymph nodes				0.78
1	44/227	80/237	0.53 (0.33–0.86)	
2 or 3	46/177	76/166	0.52 (0.32–0.85)	
≥4	45/110	60/102	0.62 (0.37–1.03)	
Type of positive lymph nodes				0.86
Microscopic	35/187	50/161	0.56 (0.32–0.99)	
Macroscopic	100/327	166/344	0.59 (0.42–0.81)	
Ulceration				0.12
No	62/230	94/251	0.69 (0.45–1.05)	
Yes	64/208	101/197	0.52 (0.35–0.79)	
Not reported	9/76	21/57	0.30 (0.11–0.84)	
Lymph-node and ulceration status				0.35
Microscopic, ulceration	25/94	31/75	0.58 (0.29–1.15)	
Microscopic, no ulceration	10/89	19/85	0.48 (0.17–1.30)	
Macroscopic, ulceration	39/114	70/122	0.51 (0.31–0.86)	
Macroscopic, no ulceration	52/141	75/166	0.79 (0.50–1.26)	
BRAF mutation status				0.89
Wild type	69/233	97/214	0.61 (0.41–0.92)	
V600E mutation	54/186	94/209	0.59 (0.38–0.92)	
All Patients	135/514 (26.3%)	216/505 (42.8%)	0.57 (0.43–0.74)	

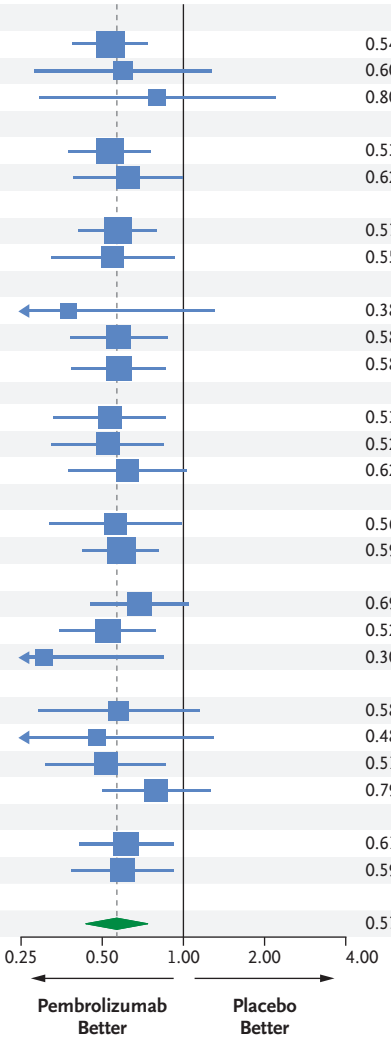


Figure 3. Forest Plot of Recurrence-free Survival According to Subgroup.

An unstratified univariate Cox model was used to estimate the hazard ratios for the risk of recurrence or death in the pembrolizumab group as compared with the placebo group among all the patients. An unstratified Cox model including the trial group, a covariate of interest (e.g., age 18 to <65 vs. ≥65 years) and the interaction term (e.g., age × treatment) was used to perform the interaction test and estimate the hazard ratios for the subgroups. P values were yielded by the test of the treatment difference in the overall intention-to-treat population or by the test of interaction; for each, the Wald test was used. The sizes of the blue boxes are nonlinearly proportional to the numbers of events. The green diamond is centered on the overall hazard ratio (dashed line) and covers its 98.4% confidence interval. In the subgroup analyses, 99% confidence intervals (blue lines) are presented. Data on lymph-node and ulceration status were not available for 133 patients; data on *BRAF* mutation status were not available for 65 patients, and the *BRAF* mutation present differed from V600E in 112 patients. P<0.001 in the unadjusted analysis of the overall effect of pembrolizumab versus placebo on recurrence-free survival. AJCC denotes American Joint Committee on Cancer 2009 classification, 7th edition.[14]

with microscopic or macroscopic nodal involvement; it was greater, but not significantly so, in patients with ulcerated melanomas (hazard ratio, 0.52) than in patients with nonulcerated melanomas (hazard ratio, 0.69). *BRAF* status, sex, and baseline body-mass index (the weight in kilograms divided by the square of the height in meters) did not significantly influence the dif-

ference in recurrence-free survival between the pembrolizumab and placebo groups (Fig. 3, and Figs. S4 and S5 in the Supplementary Appendix). For instance, the between-group difference was similar among men regardless of whether they were obese or had a normal body-mass index.

SAFETY

Adverse events of any grade that were considered to be related to the trial regimen occurred in 396 patients (77.8%) in the pembrolizumab group and in 332 patients (66.1%) in the placebo group (Table 2). The rates of fatigue or asthenia and of diarrhea were similar in the two trial groups. Adverse events of grade 3, 4, or 5 that were related to the trial regimen occurred in 14.7% of patients in the pembrolizumab group and in 3.4% in the placebo group. There was one pembrolizumab-related death due to myositis.

Immune-related adverse events of any grade occurred in 190 (37.3%) patients in the pembrolizumab group and in 45 (9.0%) patients in the placebo group. A higher incidence of endocrine disorders occurred in the pembrolizumab group than in the placebo group (23.4% in the pembrolizumab group and 5.0% in the placebo group); the most common endocrine disorders were hypothyroidism (14.3% and 2.8%) and hyperthyroidism (10.2% and 1.2%), and all cases were of grade 1 or 2 except one case of grade 3 hyperthyroidism. The incidence of sarcoidosis was low (1.4% and 0%), and all cases were of grade 1 or 2. The incidence of grade 3 or 4 immune-related adverse events was also low (7.1% and 0.6%); grade 3 or 4 immune-related adverse events included colitis (2.0% and 0.2%), hypophysitis or hypopituitarism (0.6% and 0%), and type 1 diabetes mellitus (1.0% and 0%). In the pembrolizumab group, a total of 43 grade 3 or 4 immune-related adverse events occurred in 36 patients (7.1%). Among these events, 34 resolved, including 21 within 2 months after the last dose of pembrolizumab.

DISCUSSION

In this randomized, phase 3 trial involving patients with resected, high-risk stage III melanoma, pembrolizumab was associated with a rate of recurrence-free survival at 1 year that was significantly higher than that with placebo. The risk of recurrence or death in the total population was 43% lower in the pembrolizumab group than in the placebo group; the risk was 46% lower in the pembrolizumab group than in the placebo group among patients with PD-L1–positive tumors, with similar results in the subgroup with PD-L1–negative tumors. In the overall intention-to-treat population, the estimated between-group difference in the 18-month rate of recurrence-free survival was 18.2 percentage points (71.4% for pembrolizumab vs. 53.2% for placebo). These data provide more evidence that drugs that are effective in advanced melanoma also have effectiveness as adjuvant therapy.[18]

The EORTC 1325 trial will continue to its secondary end points, distant metastasis-free survival and overall survival. We recently found that the effects of treatment on recurrence-free survival correlate very well with the effects on overall survival in trials of adjuvant therapy with interferon alfa and with ipilimumab in high-risk melanoma.[19] Therefore, one may reasonably expect that the benefit of pembrolizumab for relapse-free survival that we have found in our trial will translate into an overall survival benefit, unless effective post-relapse treatments compensate for the initial disadvantage; this is a question that may be answered by the crossover design of the trial.

Pembrolizumab as adjuvant therapy, which in this analysis had a rate of grade 3 or higher treatment-related adverse events of 14.7%, appears to be less toxic than ipilimumab (45.9%) and similar to nivolumab (14.4%). There was one pembrolizumab-related death (0.2%), as compared with none with nivolumab and five (1.1%) with ipilimumab in the respective trials of these agents as adjuvant therapy.[7,8,10] The immune-related adverse events that were relatively frequent in association with pembrolizumab were hypothyroidism (14.3%) and hyperthyroidism (10.2%), pneumonitis (3.3%), and sarcoidosis (1.4%), with the majority of events being of grade 1 or 2. The incidence of grade 3 or 4 immune-related adverse events was low (7.1%), and most events resolved within 2 months after the last dose of pembrolizumab, findings similar to those in advanced melanoma.[20,21]

Adjuvant therapy for high-risk melanoma has improved, with pembrolizumab and nivolumab now available as effective agents, along with the combination of dabrafenib and trametinib as an additional option for *BRAF*-mutant melanoma. In countries where access to these drugs can

Table 2. Adverse Events.*

Event	Pembrolizumab (N=509)		Placebo (N=502)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	475 (93.3)	161 (31.6)	453 (90.2)	93 (18.5)
Treatment-related adverse events†				
Any	396 (77.8)	75 (14.7)	332 (66.1)	17 (3.4)
Fatigue or asthenia	189 (37.1)	4 (0.8)	167 (33.3)	2 (0.4)
Skin reactions	144 (28.3)	1 (0.2)	92 (18.3)	0
Rash	82 (16.1)	1 (0.2)	54 (10.8)	0
Pruritus	90 (17.7)	0	51 (10.2)	0
Diarrhea	97 (19.1)	4 (0.8)	84 (16.7)	3 (0.6)
Arthralgia	61 (12.0)	3 (0.6)	55 (11.0)	0
Nausea	58 (11.4)	0	43 (8.6)	0
Dyspnea	30 (5.9)	1 (0.2)	15 (3.0)	0
Immune-related adverse events, regardless of investigator attribution				
Any	190 (37.3)	36 (7.1)	45 (9.0)	3 (0.6)
Endocrine disorders	119 (23.4)	9 (1.8)	25 (5.0)	0
Hypothyroidism	73 (14.3)	0	14 (2.8)	0
Hyperthyroidism	52 (10.2)	1 (0.2)	6 (1.2)	0
Thyroiditis	16 (3.1)	0	1 (0.2)	0
Hypophysitis, including hypopituitarism	11 (2.2)	3 (0.6)	1 (0.2)	0
Type 1 diabetes mellitus	5 (1.0)	5 (1.0)	0	0
Adrenal insufficiency	5 (1.0)	1 (0.2)	4 (0.8)	0
Respiratory, thoracic and mediastinal disorders	24 (4.7)	4 (0.8)	3 (0.6)	0
Pneumonitis or interstitial lung disease	17 (3.3)	4 (0.8)	3 (0.6)	0
Sarcoidosis	7 (1.4)	0	0	0
Vitiligo or severe skin reactions	27 (5.3)	3 (0.6)	8 (1.6)	0
Vitiligo	24 (4.7)	0	8 (1.6)	0
Severe skin reactions	3 (0.6)	3 (0.6)	0	0
Gastrointestinal conditions	20 (3.9)	10 (2.0)	4 (0.8)	2 (0.4)
Colitis	19 (3.7)	10 (2.0)	3 (0.6)	1 (0.2)
Pancreatitis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Hepatobiliary disorders	9 (1.8)	7 (1.4)	1 (0.2)	1 (0.2)
Hepatitis	9 (1.8)	7 (1.4)	1 (0.2)	1 (0.2)
Other immune-related adverse events	15 (2.9)	5 (1.0)	5 (1.0)	0
Nephritis	2 (0.4)	2 (0.4)	1 (0.2)	0
Uveitis	2 (0.4)	0	0	0
Myositis	1 (0.2)	1 (0.2)	1 (0.2)	0
Myocarditis	1 (0.2)	1 (0.2)	0	0

* The safety analysis included all patients who underwent randomization and received at least one dose of trial agent (1011 patients). Listed are the adverse events that were reported between the first dose and 30 days after the last dose; for all serious adverse events and serious immune-related adverse events, a time limit of 90 days after the last dose was used. All adverse events correspond to part 1 of the trial (the 1-year adjuvant-therapy period) and not to part 2 (in which patients with disease recurrence were eligible to cross over or receive repeat treatment with pembrolizumab). The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

† The investigators determined whether adverse events were related to a trial agent. Adverse events and immune-related adverse events that occurred in at least 10% of patients or those that were considered to be medically relevant are reported. Patients may have had more than one event.

take years, the use of interferon alfa may continue; however, on the basis of the EORTC 18952 and 18991 trials[22-26] and an individual-patient data meta-analysis comprising all trials in which interferon alfa was compared with observation only,[27] interferon alfa treatment would be limited to patients with stage IIB or III disease with ulcerated melanoma.

Although completion lymph-node dissection has been a mandatory component in all adjuvant phase 3 trials to date, in light of the results of the Multicenter Selective Lymphadenectomy Trial (MSLT-II) and the Dermatologic Cooperative Oncology Group (DeCOG) trial[18,28-30] it is no longer considered mandatory. Since the hazard ratios for recurrence or death among the sentinel node–positive patients in the nivolumab, pembrolizumab, and dabrafenib–trametinib trials are low, adjuvant therapy also seems reasonable in patients in this group who are not undergoing a completion lymph-node dissection; however, it must be acknowledged that data from these trials do not speak directly to this point.

In conclusion, pembrolizumab as adjuvant therapy for patients with resected, high-risk stage III melanoma was associated with a significantly longer recurrence-free survival than placebo and had a safety profile consistent with the toxicity spectrum that has already been defined for the drug.

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APPENDIX

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