ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

First-line therapy for advanced non–small-cell lung cancer (NSCLC) that lacks targetable mutations is platinum-based chemotherapy. Among patients with a tumor proportion score for programmed death ligand 1 (PD-L1) of 50% or greater, pembrolizumab has replaced cytotoxic chemotherapy as the first-line treatment of choice. The addition of pembrolizumab to chemotherapy resulted in significantly higher rates of response and longer progression-free survival than chemotherapy alone in a phase 2 trial.

METHODS

In this double-blind, phase 3 trial, we randomly assigned (in a 2:1 ratio) 616 patients with metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* mutations who had received no previous treatment for metastatic disease to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy. Crossover to pembrolizumab monotherapy was permitted among the patients in the placebo-combination group who had verified disease progression. The primary end points were overall survival and progression-free survival, as assessed by blinded, independent central radiologic review.

RESULTS

After a median follow-up of 10.5 months, the estimated rate of overall survival at 12 months was 69.2% (95% confidence interval [CI], 64.1 to 73.8) in the pembrolizumab-combination group versus 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group (hazard ratio for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001). Improvement in overall survival was seen across all PD-L1 categories that were evaluated. Median progression-free survival was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (hazard ratio for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001). Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group.

CONCLUSIONS

In patients with previously untreated metastatic nonsquamous NSCLC without *EGFR* or *ALK* mutations, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. (Funded by Merck; KEYNOTE-189 ClinicalTrials.gov number, NCT02578680.)

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*A complete list of investigators in the KEYNOTE-189 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Inhibitors of programmed death 1 (PD-1) and its ligand PD-L1 are effective therapies for metastatic non–small-cell lung cancer (NSCLC) lacking sensitizing *EGFR* or *ALK* mutations. Pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol-Myers Squibb), and atezolizumab (Tecentriq, Genentech) are approved as second-line therapy. Among patients in whom the percentage of tumor cells with membranous PD-L1 staining (tumor proportion score) is 50% or greater, pembrolizumab has replaced cytotoxic chemotherapy as the first-line treatment of choice. However, patients with a tumor proportion score of 50% or greater represent a minority of those with NSCLC. Because patients with advanced NSCLC can undergo rapid clinical deterioration during disease progression, less than one half of patients with advanced NSCLC ever receive second-line therapy.[1,2] First-line combination regimens that include a PD-1 or PD-L1 inhibitor may maximize the chance of response and lead to prolonged survival. Modulation of the immune response through PD-1 inhibition may be enhanced by the potential immunogenic effects of cytotoxic chemotherapy, such as increasing the potential for antigen cross-presentation by dendritic cells after the destruction of tumor cells,[3] inhibiting myeloid-derived suppressor cells,[4] increasing the ratio of cytotoxic lymphocytes to regulatory T cells,[5] and blocking the STAT6 pathway to enhance dendritic-cell activity.[6]

A randomized, phase 2 trial of carboplatin plus pemetrexed (Alimta, Eli Lilly) with or without pembrolizumab showed significantly better rates of response and longer progression-free survival with the addition of pembrolizumab than with chemotherapy alone.[7] In the global, double-blind, placebo-controlled, phase 3 KEYNOTE-189 trial, we compared the combination of pemetrexed and a platinum-based drug plus either pembrolizumab or placebo in patients with nonsquamous NSCLC with any level of PD-L1 expression.

Methods

Patients

Patients who were at least 18 years of age were eligible for enrollment if they had pathologically confirmed metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* mutations; had received no previous systemic therapy for metastatic disease; had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating increasing disability)[8]; had at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[9]; and had provided a tumor sample for determination of PD-L1 status. Patients were excluded if they had symptomatic central nervous system metastases, had a history of noninfectious pneumonitis that required the use of glucocorticoids, had active autoimmune disease, or were receiving systemic immunosuppressive treatment. Because of an increased risk of pneumonitis,[10] patients were also excluded if they had received more than 30 Gy of radiotherapy to the lung in the previous 6 months. Full eligibility criteria are listed in the trial protocol, available with the full text of this article at NEJM.org.

Trial Design and Treatment

In this double-blind trial, patients were randomly assigned, in a 2:1 ratio, to receive either 200 mg of pembrolizumab or saline placebo, both administered intravenously every 3 weeks for up to 35 cycles. Randomization was performed by means of an integrated interactive voice-response and Web-response system (i.e., treatment assignments could be provided by following a series of prompts on a touch-tone phone or by following the same prompts in a Web-based portal). Randomization was stratified according to PD-L1 expression (tumor proportion score, ≥1% vs. <1%), choice of platinum-based drug (cisplatin vs. carboplatin), and smoking history (never vs. former or current).

All the patients received four cycles of the investigator's choice of intravenously administered cisplatin (75 mg per square meter of body-surface area) or carboplatin (area under the concentration–time curve, 5 mg per milliliter per minute) plus pemetrexed (500 mg per square meter), all administered intravenously every 3 weeks, followed by pemetrexed (500 mg per square meter) every 3 weeks. All the patients received premedication with folic acid, vitamin B_{12}, and glucocorticoids administered according to local guidelines for pemetrexed use.

Treatment was continued until radiographic progression, unacceptable toxic effects, investigator decision, or patient withdrawal of consent. If toxicity was clearly attributed to one agent, that drug alone could be discontinued. Patients in the placebo-combination group in whom disease progression was verified by blinded, independent

central radiologic review were eligible to cross over to receive pembrolizumab monotherapy. Additional details regarding treatment decisions, including the management of adverse events, are provided in the protocol.

ASSESSMENTS

PD-L1 expression was assessed during screening at a central laboratory by means of the PD-L1 IHC 22C3 pharmDx assay (Agilent) in formalin-fixed tumor samples obtained by core-needle or excisional biopsy from tissue resected at the time that metastatic disease was diagnosed. Expression was categorized according to the tumor proportion score (i.e., the percentage of tumor cells with membranous PD-L1 staining).[11] Investigators, patients, and representatives of the sponsor were unaware of the patients' tumor proportion scores. Adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Tumor imaging was scheduled for weeks 6 and 12, then every 9 weeks through week 48 and every 12 weeks thereafter. Response was assessed according to RECIST, version 1.1.[9] Patients were contacted every 12 weeks to assess survival during follow-up.

END POINTS

The two primary end points were overall survival (time from randomization to death from any cause) and progression-free survival (time from randomization to disease progression, as assessed by blinded, independent central radiologic review, or death from any cause, whichever occurred first). The secondary end points were the response rate (the percentage of patients with a confirmed complete or partial response), the duration of response (time from first documented complete or partial response to disease progression or death), and safety. Both the response rate and the duration of response were assessed by blinded, independent central radiologic review. Exploratory end points included the effect of PD-L1 expression on efficacy and patient-reported outcomes. The full list of end points and the statistical analysis plan are available in the protocol.

TRIAL OVERSIGHT

The trial was designed by a panel of academic advisors and employees of Merck (in Kenilworth, New Jersey), the trial sponsor. An external monitoring committee oversaw the trial and assessed efficacy and safety at prespecified interim analyses. The trial protocol and all amendments were approved by the appropriate ethics panel at each center. All the patients provided written informed consent before enrollment. Eli Lilly provided the pemetrexed but otherwise had no role in the trial.

All the authors attest that the trial was conducted in accordance with the protocol and all its amendments and with Good Clinical Practice standards. All the authors had access to the data and participated in the writing or reviewing and editing of the manuscript. The first draft of the manuscript was written by the first author with input from authors employed by the sponsor. Assistance in the preparation of the manuscript was provided by a medical writer employed by the sponsor. The investigators agreed to keep all aspects of the trial confidential. All the authors vouch for the accuracy and completeness of the data and analyses.

STATISTICAL ANALYSIS

Efficacy was assessed in the intention-to-treat population, which included all the patients who had undergone randomization. Safety was assessed in the as-treated population, which included all patients who had undergone randomization and received at least one dose of the assigned combination therapy. The Kaplan–Meier method was used to estimate overall and progression-free survival. Data for patients who were alive or lost to follow-up were censored for overall survival at the time they were last known to be alive; data for patients who crossed over were not censored at the time of crossover. Data for patients who were alive and did not have disease progression or who were lost to follow-up were censored for the analysis of progression-free survival at the time of the last imaging assessment. The stratified log-rank test was used to assess between-group differences in overall and progression-free survival. Hazard ratios and associated 95% confidence intervals were calculated with the use of a stratified Cox proportional-hazards model and Efron's method for handling tied events to assess the magnitude of the treatment difference. Differences in response rate were assessed with the stratified method of Miettinen and Nurminen. The randomization stratification factors were applied to all stratified efficacy analyses.

The full statistical analysis plan specified the

performance of two interim analyses and a final analysis. The family-wise type I error rate was strictly controlled at a one-sided alpha level of 0.025 with the use of the graphical method of Maurer and Bretz (Fig. S1 in the Supplementary Appendix, available at NEJM.org). If a significant benefit with regard to one of the primary end points was found in the pembrolizumab-combination group, the corresponding alpha level would be rolled over for testing of the other primary end point. The Lan–DeMets O'Brien–Fleming spending function was used to control the type I error in the interim and final analyses.

We determined that the trial would have a power of 90% to show a hazard ratio for disease progression or death of 0.70 at a one-sided alpha level of 0.0095 (based on 468 events) and a hazard ratio of 0.70 for death at a one-sided alpha level of 0.0155 (based on 416 deaths) for the comparison between the pembrolizumab-combination group and the placebo-combination group. The planned enrollment was 570 patients.

The first interim analysis was to be performed after enrollment was complete and approximately 370 events of progression or death had occurred; it was estimated that approximately 242 deaths would have occurred at this time. As of November 8, 2017, there were 410 events of disease progression or death and 235 deaths. On the basis of the observed number of events, the multiplicity-adjusted, one-sided alpha levels at the first interim analysis were 0.00559 for progression-free survival and 0.00128 for overall survival. Results were reviewed by the external monitoring committee on January 10, 2018. The monitoring committee reported that the efficacy boundaries for overall survival and progression-free survival had been met. The trial is continuing in order to evaluate outcomes with additional follow-up. All data reported here are based on the first interim analysis.

RESULTS

PATIENTS AND TREATMENT

A total of 965 patients were screened for enrollment at 126 sites in 16 countries (Fig. S2 in the Supplementary Appendix). Between February 26, 2016, and March 6, 2017, a total of 616 patients from 118 sites who had met all the eligibility criteria were randomly assigned to the pembrolizumab-combination group (410 patients) or the placebo-combination group (206 patients). The baseline demographic and disease characteristics were generally well balanced between the groups, although the percentage of men was higher in the pembrolizumab-combination group than in the placebo-combination group (62.0% vs. 52.9%, P=0.04) (Table 1). A PD-L1 tumor proportion score of 1% or greater was reported in 63.0% of the patients, carboplatin was the chosen platinum-based drug in 72.2% of the patients, and 88.1% of the patients were current or former smokers.

Of the 616 patients who were enrolled, 405 in the pembrolizumab-combination group and 202 in the placebo-combination group received at least one dose of the assigned combination therapy. With a median follow-up of 10.5 months (range, 0.2 to 20.4), the mean (±SD) duration of treatment was 7.4±4.7 months in the pembrolizumab-combination group and 5.4±4.3 months in the placebo-combination group. All four planned doses of cisplatin or carboplatin were received by 82.5% of the patients in the pembrolizumab-combination group and by 74.3% of those in the placebo-combination group; 76.5% and 66.8%, respectively, received five or more doses of pemetrexed. (Table S1 in the Supplementary Appendix shows the exposure to treatment in patients who received carboplatin and in those who received cisplatin.)

At the time of the data cutoff in the as-treated population, 137 of 405 patients (33.8%) in the pembrolizumab-combination group and 36 of 202 patients (17.8%) in the placebo-combination group were still receiving the assigned treatment (Fig. S2 in the Supplementary Appendix). In the intention-to-treat population, 125 of 410 patients (30.5%) in the pembrolizumab-combination group and 96 of 206 patients (46.6%) in the placebo-combination group had received at least one subsequent therapy either while continuing to participate in the trial or outside the trial (Table S2 in the Supplementary Appendix). In the placebo-combination group, 67 of 206 patients (32.5%) had crossed over during the trial to receive pembrolizumab monotherapy after disease progression. An additional 18 patients (8.7%) had received immunotherapy outside the trial, which resulted in an effective crossover rate of 41.3% in the intention-to-treat population and 50.0% in the 170 patients who had discontinued all trial drugs. The effective crossover rate in the intention-to-treat population was similar across the subgroups of PD-L1 tumor proportion score.

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

Characteristic	Pembrolizumab Combination (N=410)	Placebo Combination (N=206)
Age		
Median (range) — yr	65.0 (34.0–84.0)	63.5 (34.0–84.0)
<65 yr — no. (%)	197 (48.0)	115 (55.8)
Male sex — no. (%)†	254 (62.0)	109 (52.9)
Region of enrollment — no. (%)		
Europe	243 (59.3)	131 (63.6)
North America	111 (27.1)	46 (22.3)
East Asia	4 (1.0)	6 (2.9)
Other region	52 (12.7)	23 (11.2)
ECOG performance-status score — no. (%)‡		
0	186 (45.4)	80 (38.8)
1	221 (53.9)	125 (60.7)
2	1 (0.2)	0
Smoking status — no. (%)		
Current or former	362 (88.3)	181 (87.9)
Never	48 (11.7)	25 (12.1)
Histologic features — no. (%)		
Adenocarcinoma	394 (96.1)	198 (96.1)
NSCLC not otherwise specified	10 (2.4)	4 (1.9)
Other§	6 (1.5)	4 (1.9)
Brain metastases — no. (%)	73 (17.8)	35 (17.0)
PD-L1 tumor proportion score — no. (%)¶		
<1%	127 (31.0)	63 (30.6)
≥1%	260 (63.4)	128 (62.1)
1–49%	128 (31.2)	58 (28.2)
≥50%	132 (32.2)	70 (34.0)
Could not be evaluated‖	23 (5.6)	15 (7.3)
Previous therapy for nonmetastatic disease		
Thoracic radiotherapy	28 (6.8)	20 (9.7)
Neoadjuvant therapy	5 (1.2)	6 (2.9)
Adjuvant therapy	25 (6.1)	14 (6.8)

* Patients in the pembrolizumab-combination group received pemetrexed, a platinum-based drug, and pembrolizumab; those in the placebo-combination group received pemetrexed, a platinum-based drug, and placebo. Percentages may not total 100 because of rounding.

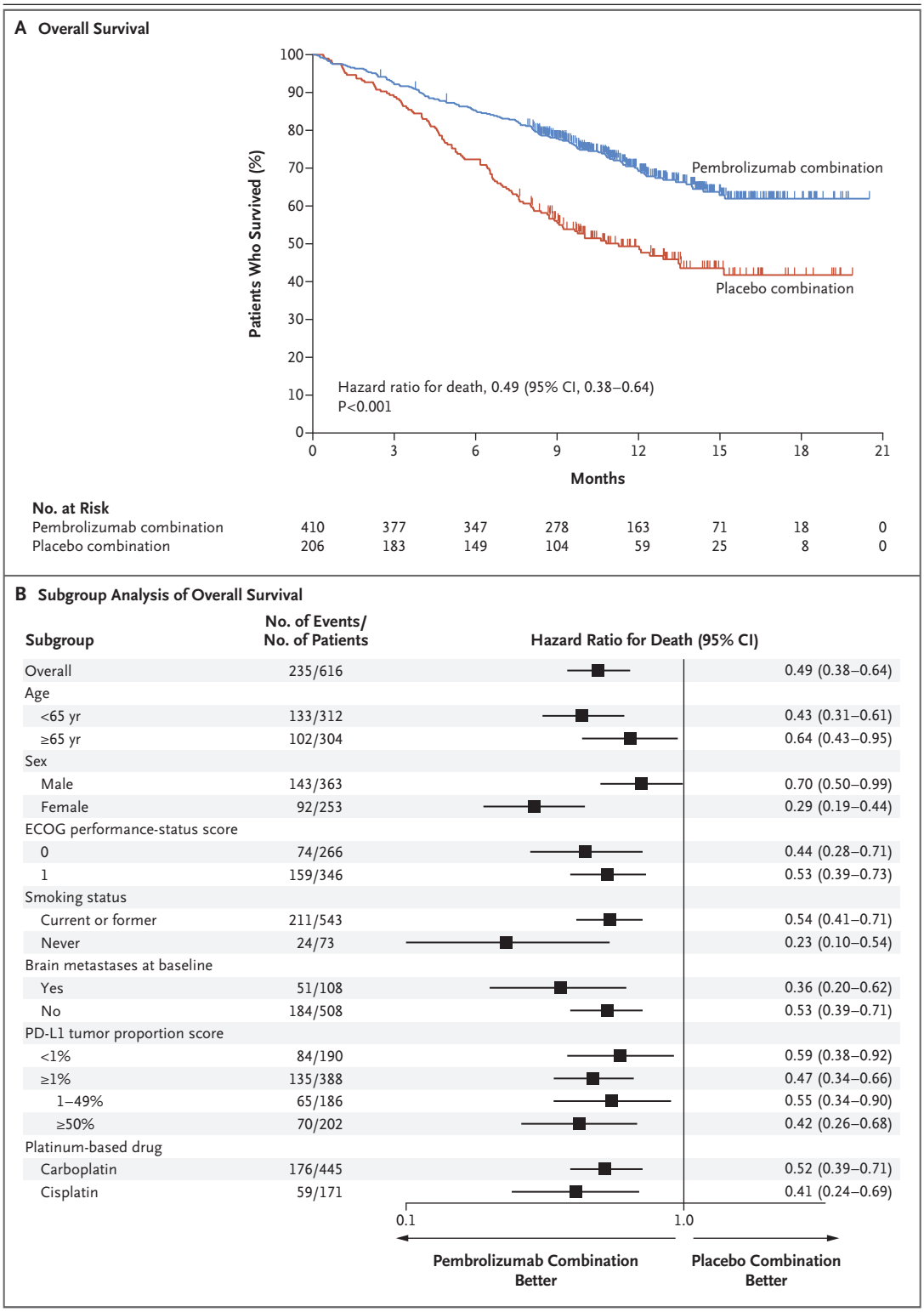
† There was a significant between-group difference in the proportion of men (P=0.04). There were no significant differences in any other baseline characteristics between groups at a two-sided alpha level of 0.05.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.[8] Data regarding the ECOG status were missing for 2 patients (0.5%) in the pembrolizumab-combination group and 1 patient (0.5%) in the placebo-combination group.

§ Other histologic features include large-cell carcinoma (5 patients in the pembrolizumab-combination group and 2 in the placebo-combination group), adenosquamous tumors (2 patients in the placebo-combination group), and other nonsquamous tumor (1 patient in the pembrolizumab-combination group).

¶ The programmed death ligand 1 (PD-L1) tumor proportion score was defined as the percentage of tumor cells with membranous PD-L1 expression.

‖ PD-L1 expression could not be evaluated because specimens had an inadequate number of tumor cells or no tumor cells. For stratification purposes, patients with PD-L1 expression that could not be evaluated were included in the subgroup with a tumor proportion score of less than 1%; these patients were excluded from analyses of efficacy according to the PD-L1 tumor proportion score.



OVERALL SURVIVAL

With 235 deaths in the intention-to-treat population, the estimated proportion of patients who were alive at 12 months was 69.2% (95% confidence interval [CI], 64.1 to 73.8) in the pembrolizumab-combination group and 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group. The median overall survival was not reached in

Figure 1 (facing page). Overall Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier estimates of overall survival (the first of the two primary end points) in the two trial groups (Panel A) and an analysis of overall survival in key subgroups (Panel B). Patients in the pembrolizumab-combination group received pemetrexed, a platinum-based drug, and pembrolizumab; those in the placebo-combination group received pemetrexed, a platinum-based drug, and placebo. Tick marks in Panel A indicate censoring of data at the last time the patient was known to be alive. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. PD-L1 denotes programmed death ligand 1.

the pembrolizumab-combination group and was 11.3 months (95% CI, 8.7 to 15.1) in the placebo-combination group (hazard ratio for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001) (Fig. 1A). The benefit of the pembrolizumab combination was observed in all subgroups that were analyzed (Fig. 1B), including those with a PD-L1 tumor proportion score of less than 1% (12-month overall survival rate, 61.7% vs. 52.2%; hazard ratio for death, 0.59; 95% CI, 0.38 to 0.92), a score of 1 to 49% (12-month overall survival rate, 71.5% vs. 50.9%; hazard ratio, 0.55; 95% CI, 0.34 to 0.90), and a score of 50% or greater (12-month overall survival rate, 73.0% vs. 48.1%; hazard ratio, 0.42; 95% CI, 0.26 to 0.68) (Fig. 2).

PROGRESSION-FREE SURVIVAL

With 410 events of progression or death, the median progression-free survival was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (hazard ratio for progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001) (Fig. 3A). The estimated proportion of patients who were alive and progression-free at 12 months was 34.1% (95% CI, 28.8 to 39.5) in the pembrolizumab-combination group and 17.3% (95% CI, 12.0 to 23.5) in the placebo-combination group. The results were similar when progression was assessed according to investigator review (Fig. S3 in the Supplementary Appendix). The hazard ratio for progression-free survival was less than 1.00 across all subgroups that were analyzed (Fig. 3B) and across all subgroups of PD-L1 tumor proportion score (Fig. 4), although the upper boundaries of the 95% confidence intervals crossed 1.00 for patients who were 65 years or older (median, 9.0 months vs. 6.7 months; hazard ratio, 0.75; 95% CI, 0.55 to 1.02) and those with a PD-L1 tumor proportion score of less than 1% (median, 6.1 months vs. 5.1 months; hazard ratio, 0.75; 95% CI, 0.53 to 1.05).

TUMOR RESPONSE

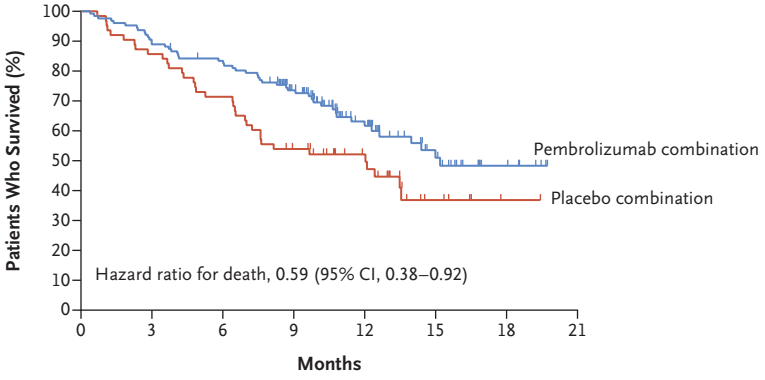
The response rate as assessed by blinded, independent central radiologic review was 47.6% (95% CI, 42.6 to 52.5) in the pembrolizumab-combination group and 18.9% (95% CI, 13.8 to 25.0) in the placebo-combination group (P<0.001). The results were similar when the response was assessed by investigator review (Table S3 in the Supplementary Appendix). The disease control rate (the proportion of patients with a confirmed complete or partial response or stable disease) was 84.6% in the pembrolizumab-combination group and 70.4% in the placebo-combination group. The change from baseline in the sum of the longest diameters of target lesions is shown in Figure S4 in the Supplementary Appendix.

The median duration of response was 11.2 months (range, 1.1+ to 18.0+) in the pembrolizumab-combination group and 7.8 months (range, 2.1+ to 16.4+) in the placebo-combination group. (Plus signs in the ranges indicate that there was no progressive disease at the time of the last disease assessment.) The response rate was higher in the pembrolizumab-combination group than in the placebo-combination group across all categories of PD-L1 tumor proportion score, with the greatest between-group difference in patients with a tumor proportion score of 50% or greater (61.4% vs. 22.9%) (Fig. S5 in the Supplementary Appendix).

ADVERSE EVENTS

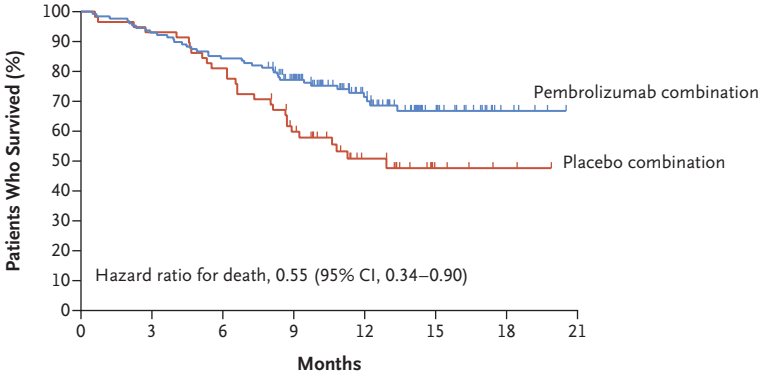
Adverse events of any cause and regardless of attribution to treatment by the investigator occurred in 99.8% of the patients in the pembrolizumab-combination group and in 99.0% of those in the placebo-combination group (Table 2). These events were of grade 3 or higher in 67.2% and 65.8% of the patients, respectively. Discontinuation of all trial drugs because of adverse events occurred in 13.8% of the patients in the pembrolizumab-combination group and in 7.9% of those in the placebo-combination group; discontinuation rates of pembrolizumab and placebo were 20.2% and 10.4%, respectively (Table 2). The rates of adverse events were similar in patients who received carboplatin and cisplatin (Tables S4 and S5 in the Supplementary Appendix). Adverse events led to

A Tumor Proportion Score of <1%



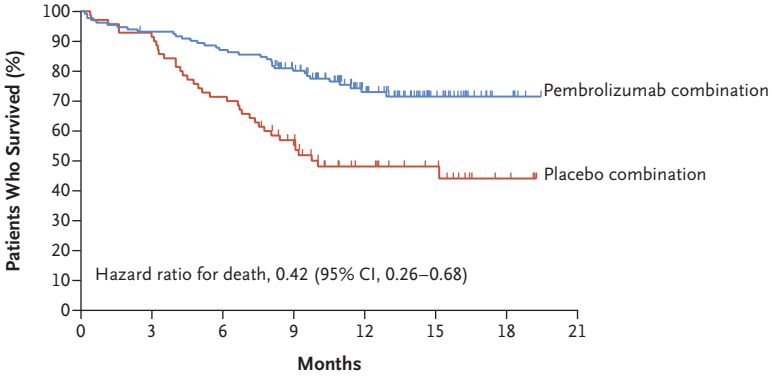
No. at Risk								
Pembrolizumab combination	127	113	104	79	42	20	6	0
Placebo combination	63	54	45	32	21	6	1	0

B Tumor Proportion Score of 1 to 49%



No. at Risk								
Pembrolizumab combination	128	119	108	84	52	21	5	0
Placebo combination	58	54	47	32	17	5	2	0

C Tumor Proportion Score of ≥50%



No. at Risk								
Pembrolizumab combination	132	122	114	96	56	25	6	0
Placebo combination	70	64	50	35	19	13	4	0

Figure 2 (facing page). Overall Survival, According to PD-L1 Tumor Proportion Score.

Shown are Kaplan–Meier estimates of overall survival in patients with a tumor proportion score of less than 1% (Panel A), a score of 1 to 49% (Panel B), or a score of 50% or greater (Panel C). The greatest relative benefit was observed in the subgroup with a PD-L1 tumor proportion score of 50% or greater, a finding that was consistent with the results of previous studies. Tick marks indicate censoring of data at the last time the patient was known to be alive.

death in 27 of 405 patients (6.7%) in the pembrolizumab-combination group and in 12 of 202 patients (5.9%) in the placebo-combination group.

In the two groups, the most common adverse events were nausea, anemia, and fatigue (Table 2; exposure-adjusted rates are provided in Table S6 in the Supplementary Appendix). The only adverse events that were reported in at least 10% of the patients that were more frequent in the pembrolizumab-combination group were diarrhea and rash (Fig. S6A in the Supplementary Appendix). Adverse events of grade 3 or higher that were reported in at least 10% of the patients in the pembrolizumab-combination group or the placebo-combination group were anemia (16.3% and 15.3%) and neutropenia (15.8% and 11.9%) (Table 2). The only adverse event of grade 3 or higher that was more frequent in the pembrolizumab-combination group was febrile neutropenia (Fig. S6B in the Supplementary Appendix). Acute kidney injury occurred more frequently in the pembrolizumab-combination group than in the placebo-combination group (5.2% vs. 0.5%). In the pembrolizumab-combination group, acute kidney injury was of grade 3 or higher in 8 patients (2.0%) and led to the discontinuation of all trial therapy in 8 patients (2.0%); at the time of this analysis, acute kidney injury of grade 3 or lower had resolved or was resolving in 9 of 19 patients.

Immune-mediated adverse events, which were defined on the basis of a list of terms specified by the sponsor and were included in the analysis regardless of whether they were attributed to treatment by the investigator, occurred in 92 of 405 patients (22.7%) in the pembrolizumab-combination group and in 24 of 202 patients (11.9%) in the placebo-combination group (Table 3). These events were of grade 3 or higher in 36 of 405 patients (8.9%) and 9 of 202 patients (4.5%), respectively. Three immune-mediated adverse events (all pneumonitis) led to death in the pembrolizumab-combination group.

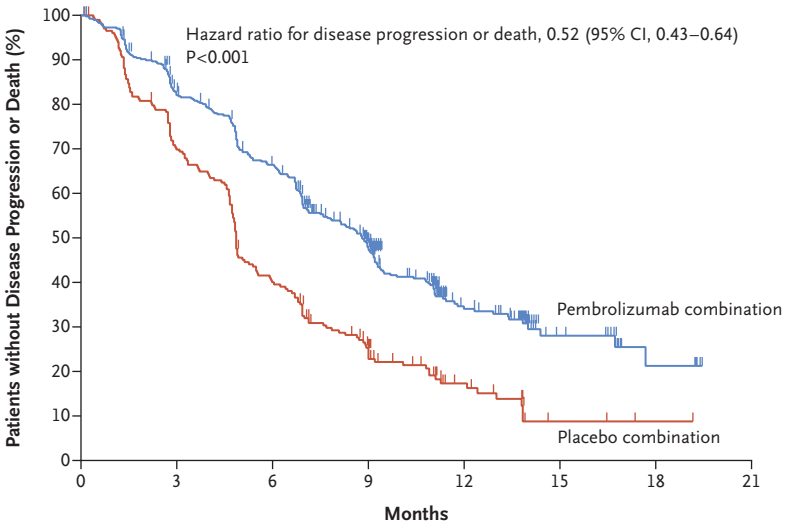
DISCUSSION

In this phase 3 trial, we found that adding pembrolizumab to standard chemotherapy with pemetrexed and a platinum-based drug resulted in a risk of the two primary end points that was approximately 50% lower than the risks with standard chemotherapy alone in patients with untreated, metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* mutations. Together with the results from KEYNOTE-024,[12,13] the data from KEYNOTE-189 suggest that introducing immunotherapy as a first-line therapy may have a favorable long-term effect on outcomes.

The survival benefit associated with the pembrolizumab combination was observed in all subgroups of PD-L1 tumor proportion scores, including patients with a score of less than 1%, a population for which single-agent PD-1 and PD-L1 inhibition have a small chance of benefit.[12,14-19] The greatest relative benefit was observed in the subgroup with a PD-L1 tumor proportion score of 50% or greater, a finding that was consistent with the results of previous studies of PD-1 pathway inhibition in advanced NSCLC.[14,15,20,21] An important question for further study is whether the addition of pembrolizumab to pemetrexed and a platinum-based drug has greater efficacy than pembrolizumab monotherapy in these patients. Without direct comparisons, physicians and patients will need to have an individualized discussion of benefit.[22]

Although the outcomes in the placebo-combination group appeared to be poorer than those in patients who had received pemetrexed and a platinum-based drug in some historical studies,[23-25] the rates of disease control and progression-free survival were consistent with those in many landmark studies.[12,26-29] The median overall survival in our trial may change with longer follow-up because there was substantial censoring of the Kaplan–Meier curves around the time that the medians

A Progression-free Survival



No. at Risk

Pembrolizumab combination	410	322	256	149	60	17	5	0
Placebo combination	206	141	80	40	16	3	1	0

B Subgroup Analysis of Progression-free Survival

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	410/616	0.52 (0.43–0.64)
Age		
<65 yr	224/312	0.43 (0.32–0.56)
≥65 yr	186/304	0.75 (0.55–1.02)
Sex		
Male	236/363	0.66 (0.50–0.87)
Female	174/253	0.40 (0.29–0.54)
ECOG performance-status score		
0	158/266	0.49 (0.35–0.68)
1	250/346	0.56 (0.43–0.72)
Smoking status		
Current or former	365/543	0.54 (0.43–0.66)
Never	45/73	0.43 (0.23–0.81)
Brain metastases at baseline		
Yes	81/108	0.42 (0.26–0.68)
No	329/508	0.53 (0.43–0.67)
PD-L1 tumor proportion score		
<1%	146/190	0.75 (0.53–1.05)
≥1%	238/388	0.44 (0.34–0.57)
1–49%	114/186	0.55 (0.37–0.81)
≥50%	124/202	0.36 (0.25–0.52)
Platinum-based drug		
Carboplatin	299/445	0.55 (0.44–0.70)
Cisplatin	111/171	0.44 (0.30–0.65)

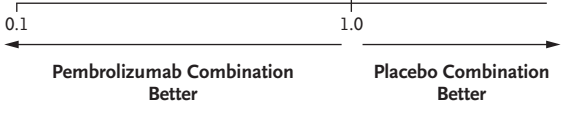


Figure 3. Progression-free Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier estimates of progression-free survival (the second of the two primary end points) in the two trial groups (Panel A) and an analysis of progression-free survival in key subgroups (Panel B). Tick marks in Panel A indicate censoring of data.

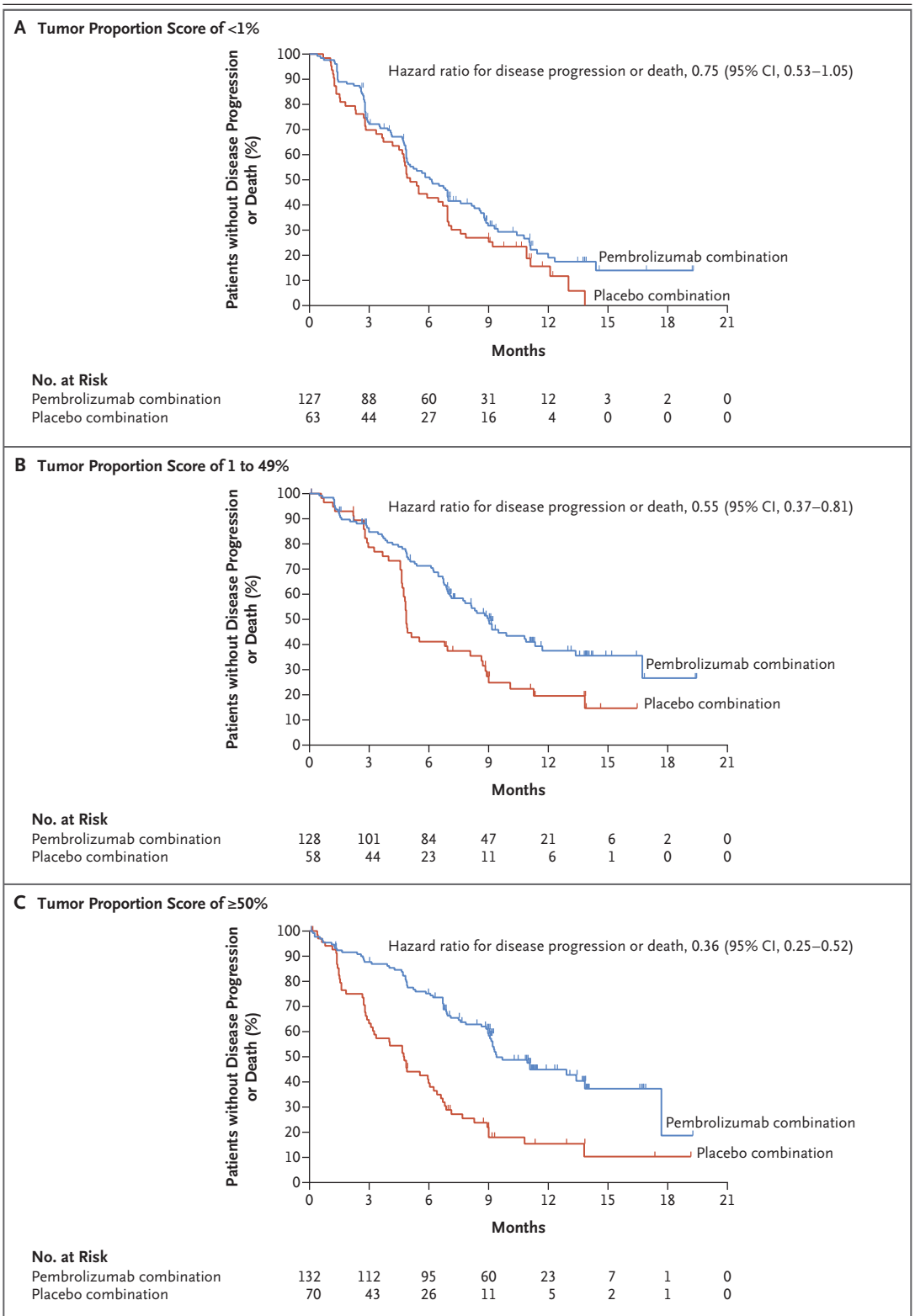


Figure 4. Progression-free Survival, According to PD-L1 Tumor Proportion Score.

Shown are Kaplan–Meier estimates of progression-free survival in patients with a tumor proportion score of less than 1% (Panel A), a score of 1 to 49% (Panel B), or a score of 50% or greater (Panel C). Tick marks indicate censoring of data.

Table 2. Adverse Events of Any Cause in the As-Treated Population.*

Event	Pembrolizumab Combination (N=405)		Placebo Combination (N=202)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	404 (99.8)	272 (67.2)	200 (99.0)	133 (65.8)
Event leading to discontinuation of all treatment†	56 (13.8)	48 (11.9)	16 (7.9)	14 (6.9)
Event leading to discontinuation of any treatment component‡	112 (27.7)	81 (20.0)	30 (14.9)	22 (10.9)
Discontinuation of pembrolizumab or placebo	82 (20.2)	64 (15.8)	21 (10.4)	17 (8.4)
Discontinuation of pemetrexed	93 (23.0)	69 (17.0)	23 (11.4)	17 (8.4)
Discontinuation of platinum-based drug	31 (7.7)	27 (6.7)	12 (5.9)	10 (5.0)
Event leading to death§	27 (6.7)	27 (6.7)	12 (5.9)	12 (5.9)
Event occurring in ≥15% of patients in either group¶				
Nausea	225 (55.6)	14 (3.5)	105 (52.0)	7 (3.5)
Anemia	187 (46.2)	66 (16.3)	94 (46.5)	31 (15.3)
Fatigue	165 (40.7)	23 (5.7)	77 (38.1)	5 (2.5)
Constipation	141 (34.8)	4 (1.0)	64 (31.7)	1 (0.5)
Diarrhea	125 (30.9)	21 (5.2)	43 (21.3)	6 (3.0)
Decreased appetite	114 (28.1)	6 (1.5)	61 (30.2)	1 (0.5)
Neutropenia	110 (27.2)	64 (15.8)	49 (24.3)	24 (11.9)
Vomiting	98 (24.2)	15 (3.7)	47 (23.3)	6 (3.0)
Cough	87 (21.5)	0	57 (28.2)	0
Dyspnea	86 (21.2)	15 (3.7)	52 (25.7)	11 (5.4)
Asthenia	83 (20.5)	25 (6.2)	49 (24.3)	7 (3.5)
Rash	82 (20.2)	7 (1.7)	23 (11.4)	3 (1.5)
Pyrexia	79 (19.5)	1 (0.2)	30 (14.9)	0
Peripheral edema	78 (19.3)	1 (0.2)	26 (12.9)	0
Thrombocytopenia	73 (18.0)	32 (7.9)	29 (14.4)	14 (6.9)
Increased lacrimation	69 (17.0)	0	22 (10.9)	0

* Listed are all adverse events that occurred during the trial period or within 30 days thereafter (within 90 days for serious events), regardless of attribution to any trial treatment by the investigator. Adverse events that occurred during crossover from the placebo-combination group to pembrolizumab monotherapy are excluded. The as-treated population included all the patients who had undergone randomization and received at least one dose of the assigned combination therapy.

† This category includes patients who discontinued pemetrexed, a platinum-based drug, and pembrolizumab or placebo because of an adverse event at any time and patients who discontinued pemetrexed and pembrolizumab or placebo for an adverse event after completing four cycles of a platinum-based drug.

‡ Patients could have discontinued one, two, or all agents for a given adverse event.

§ The adverse events leading to death in the pembrolizumab-combination group were pneumonitis in 3 patients; intestinal ischemia in 2 patients; and acute kidney injury, acute kidney injury plus neutropenic sepsis, cardiac arrest, cardiac arrest plus respiratory failure, cardiac failure, cardiopulmonary failure, cerebral infarction, chronic obstructive pulmonary disease, encephalopathy, hemoptysis, ischemic stroke, lung infection, mesenteric-artery embolism, myocardial infarction, neutropenic sepsis, peritonitis, *Pneumocystis jirovecii* pneumonia, pneumonia, and septic shock in 1 patient each; 3 of the deaths in this group had an unspecified cause. The adverse events leading to death in the placebo-combination group were cerebral hemorrhage, disseminated intravascular coagulation, hemoptysis, intracranial hemorrhage, hypokalemia plus supraventricular tachycardia, multiple organ dysfunction syndrome, pneumonia, pneumonia plus respiratory failure, renal failure, respiratory failure, and septic shock in 1 patient each; 1 of the deaths in this group had an unspecified cause.

¶ The events are listed in descending order of frequency in the pembrolizumab-combination group.

Table 3. Adverse Events of Interest in the As-Treated Population.*

Event	Pembrolizumab Combination (N = 405)		Placebo Combination (N = 202)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any	92 (22.7)	36 (8.9)	24 (11.9)	9 (4.5)
Hypothyroidism	27 (6.7)	2 (0.5)	5 (2.5)	0
Pneumonitis	18 (4.4)	11 (2.7)	5 (2.5)	4 (2.0)
Hyperthyroidism	16 (4.0)	0	6 (3.0)	0
Infusion reaction	10 (2.5)	1 (0.2)	2 (1.0)	0
Colitis	9 (2.2)	3 (0.7)	0	0
Severe skin reaction	8 (2.0)	8 (2.0)	5 (2.5)	4 (2.0)
Nephritis	7 (1.7)	6 (1.5)	0	0
Hepatitis	5 (1.2)	4 (1.0)	0	0
Hypophysitis	3 (0.7)	0	0	0
Pancreatitis	3 (0.7)	2 (0.5)	0	0
Adrenal insufficiency	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)
Myositis	1 (0.2)	0	0	0
Thyroiditis	1 (0.2)	0	0	0
Type 1 diabetes mellitus	1 (0.2)	1 (0.2)	0	0

* The events of interest are those with an immune-related cause and are considered regardless of attribution to a trial drug by the investigator. The events are listed in descending order of frequency in the pembrolizumab-combination group. In addition to the specific preferred terms that are listed, related terms were also included. The as-treated population included all the patients who had undergone randomization and received at least one dose of the assigned combination therapy.

were reached in this analysis. As expected in the era of immunotherapy, the survival curves in the two groups seemed to be reaching a plateau at the time of this analysis.

The addition of pembrolizumab did not appear to increase the frequency of adverse events that are commonly associated with chemotherapy regimens involving pemetrexed and a platinum-based drug. Similarly, the incidence of most immune-mediated adverse events was not higher with pembrolizumab-combination therapy than that previously observed with pembrolizumab monotherapy.[12,14,20] The exception may be nephritis and acute kidney injury, both of which are also associated with pemetrexed[30] and platinum-based drugs[31] and occurred with a greater frequency in this trial than in earlier trials of pembrolizumab monotherapy.[12,14,20] The frequency of deaths attributed to pneumonitis in this trial was consistent with the frequency previously observed with pembrolizumab monotherapy in advanced NSCLC.[12,14,20]

In conclusion, in patients with metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* mutations, the addition of pembrolizumab to induction therapy with pemetrexed and a platinum-based drug and to pemetrexed maintenance therapy resulted in significantly longer overall survival and progression-free survival and a higher response rate than the addition of placebo at a cost of a low incidence of renal dysfunction at the first interim analysis. The survival benefit for pembrolizumab-combination therapy was observed across all categories of PD-L1 expression.

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APPENDIX

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