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Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Pembrolizumab is a humanized monoclonal antibody against programmed death 1 (PD-1) that has antitumor activity in advanced non–small-cell lung cancer (NSCLC), with increased activity in tumors that express programmed death ligand 1 (PD-L1).

METHODS

In this open-label, phase 3 trial, we randomly assigned 305 patients who had previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and no sensitizing mutation of the epidermal growth factor receptor gene or translocation of the anaplastic lymphoma kinase gene to receive either pembrolizumab (at a fixed dose of 200 mg every 3 weeks) or the investigator's choice of platinum-based chemotherapy. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression. The primary end point, progression-free survival, was assessed by means of blinded, independent, central radiologic review. Secondary end points were overall survival, objective response rate, and safety.

RESULTS

Median progression-free survival was 10.3 months (95% confidence interval [CI], 6.7 to not reached) in the pembrolizumab group versus 6.0 months (95% CI, 4.2 to 6.2) in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; P<0.001). The estimated rate of overall survival at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P=0.005). The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%), the median duration of response was longer (not reached [range, 1.9+ to 14.5+ months] vs. 6.3 months [range, 2.1+ to 12.6+]), and treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse events (26.6% vs. 53.3%).

CONCLUSIONS

In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy. (Funded by Merck; KEYNOTE-024 ClinicalTrials.gov number, NCT02142738.)

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*A complete list of investigators in the KEYNOTE-024 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Approximately 23 to 28% of patients with advanced non–small-cell lung cancer (NSCLC) have a high level of programmed death ligand 1 (PD-L1) expression, which is defined as membranous PD-L1 expression on at least 50% of tumor cells, regardless of the staining intensity (i.e., a PD-L1 tumor proportion score of 50% or greater).[1,2] Data from the phase 1 KEYNOTE-001 and phase 3 KEYNOTE-010 studies indicated that patients with advanced NSCLC and a PD-L1 tumor proportion score of 50% or greater were more likely than those with lower tumor proportion scores to have a response to pembrolizumab, a highly selective, humanized monoclonal antibody against programmed death 1 (PD-1) that prevents PD-1 from engaging PD-L1 and PD-L2.[1-3]

Current first-line treatment decisions for advanced NSCLC are based on the presence of genetic aberrations, such as sensitizing mutations of epidermal growth factor receptor (*EGFR*) and translocations of anaplastic lymphoma kinase (*ALK*). However, most patients with NSCLC do not harbor these oncogenic drivers, and for these patients, treatment options are limited to cytotoxic chemotherapy. In patients enrolled in the KEYNOTE-001 trial who had previously untreated NSCLC and a PD-L1 tumor proportion score of 50% or greater, pembrolizumab (administered every 2 or 3 weeks at a dose of 10 mg per kilogram of body weight) was associated with a response rate of 58.3%, median progression-free survival of 12.5 months, and 24-month overall survival of 60.6%.[4]

In the international, randomized, open-label, phase 3 KEYNOTE-024 trial, we compared pembrolizumab (administered at a fixed dose of 200 mg every 3 weeks) with the investigator's choice of cytotoxic chemotherapy as first-line therapy for patients with advanced NSCLC and a PD-L1 tumor proportion score of 50% or greater.

METHODS

PATIENTS

Patients 18 years of age or older were eligible for enrollment if they had histologically or cytologically confirmed stage IV NSCLC with no sensitizing *EGFR* mutations or *ALK* translocations, had undergone no previous systemic therapy for metastatic disease, and had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with 0 indicating no symptoms and higher scores indicating increasing disability), at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[5] a life expectancy of at least 3 months, and a PD-L1 tumor proportion score of 50% or greater. Patients were ineligible if they were receiving systemic glucocorticoids (excluding daily glucocorticoid-replacement therapy for conditions such as adrenal or pituitary insufficiency) or other immunosuppressive treatment or if they had untreated brain metastases, active autoimmune disease for which they had received systemic treatment during the previous 2 years, active interstitial lung disease, or a history of pneumonitis for which they had received glucocorticoids.

TRIAL DESIGN AND TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive treatment with either pembrolizumab (administered intravenously at a dose of 200 mg every 3 weeks) for 35 cycles or the investigator's choice of one of the following five platinum-based chemotherapy regimens for 4 to 6 cycles: carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Chemotherapy regimens that included pemetrexed were permitted only for patients who had nonsquamous tumors; these patients could continue to receive pemetrexed as maintenance therapy after the completion of combination chemotherapy. The intended chemotherapy regimen, including the use of pemetrexed maintenance therapy, was chosen before the patient underwent randomization. Randomization was stratified by ECOG performance-status score (0 vs. 1), tumor histologic type (squamous vs. nonsquamous), and region of enrollment (East Asia vs. non–East Asia) and did not include any provisions regarding equal distribution of enrollment across participating sites or stratification by site. Treatment was continued for the specified number of cycles or until the patient had radiologic disease progression (defined according to RECIST; Table S2 in the Supplementary Appendix), had treatment-related adverse events of unacceptable severity, or withdrew consent or until the investigator decided to withdraw the patient, whichever occurred first. Patients in the chemotherapy group who had disease progression, which was verified

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by means of blinded, independent, central radiologic review, could cross over to receive pembrolizumab, if safety criteria were met. There was no preplanned crossover from the pembrolizumab group to the chemotherapy group, and there were no guidelines regarding therapy after disease progression for patients in the pembrolizumab group. Patients in either treatment group who were in clinically stable condition and were considered by the investigator to be deriving clinical benefit could continue therapy after disease progression. Full guidance on treatment decisions, including the management of adverse events, can be found in the trial protocol, available at NEJM.org.

TRIAL ASSESSMENTS

PD-L1 expression was assessed in formalin-fixed tumor samples at a central laboratory with the use of the commercially available PD-L1 IHC 22C3 pharmDx assay (Dako North America).[6,7] Tumor samples were obtained by core-needle or excisional biopsy or from tissue resected at the time the metastatic disease was diagnosed. Fine-needle aspirates or samples obtained from irradiated sites or before the administration of adjuvant or neoadjuvant therapy were not permitted to be used. Imaging studies of the tumors were obtained every 9 weeks, and the response to treatment was assessed according to RECIST by means of blinded, independent, central radiologic review. Adverse events were reviewed, a physical examination was performed, and vital signs, a complete blood count with a differential count, and a comprehensive blood panel were assessed every 3 weeks during treatment and at the time of treatment discontinuation; T3, free T4, and thyrotropin were assessed every 6 weeks. During the survival follow-up phase, patients were contacted every 2 months for an assessment of survival. The full assessment schedule is available in the trial protocol. All adverse events and abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

END POINTS

The primary end point was progression-free survival, which was defined as the time from randomization to disease progression or death from any cause. Secondary end points included overall survival, which was defined as the time from randomization to death from any cause; objective response rate, which was defined as the percentage of patients with a confirmed complete or partial response; and safety. An exploratory end point was duration of response, which was defined as the time from the first documentation of a complete or partial response to disease progression. A full list of end points is available in the protocol. Efficacy was assessed in the intention-to-treat population, which included all patients who underwent randomization. Safety was assessed in the as-treated population, which included all patients who received at least one dose of the assigned trial treatment.

TRIAL OVERSIGHT

The KEYNOTE-024 trial was designed by Merck representatives and academic advisors. Data were collected by investigators and associated site personnel, analyzed by statisticians employed by Merck, and interpreted by academic authors and Merck representatives. An external data and safety monitoring committee oversaw the trial and assessed the safety and efficacy at prespecified interim analyses. Committee members are listed in the Supplementary Appendix.

The trial protocol and all amendments were approved by the appropriate institutional review board or independent ethics committee at each trial center. The trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All the patients provided written informed consent before enrollment.

All the authors had full access to the data, vouch for the completeness and accuracy of the data, and attest that the trial was conducted in accordance with the protocol and all amendments. The first draft of the manuscript was written by the first and last authors with input from authors employed by Merck. All the authors participated in reviewing and editing the manuscript, and approved the submitted draft. As part of the site agreement signed before trial participation, investigators agreed to keep all aspects of the trial, including the resultant data, confidential.

STATISTICAL ANALYSIS

The Kaplan–Meier method was used to estimate progression-free and overall survival. For the analysis of progression-free survival, data for patients who were alive and had no disease progression or who were lost to follow-up were censored at the time of the last tumor assess-

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ment. For the analysis of overall survival, data for patients who were alive or who were lost to follow-up were censored at the time of the last contact. Between-group differences in progression-free and overall survival were assessed with the use of a stratified log-rank test. Hazard ratios and associated 95% confidence intervals were assessed with the use of a stratified Cox proportional-hazards model with Efron's method of handling ties. The same stratification factors used for randomization were applied to the stratified log-rank and Cox models. Differences in response rate were assessed with the use of the stratified method of Miettinen and Nurminen.

The overall type I error rate for this trial was strictly controlled at a one-sided alpha level of 2.5%. The full statistical analysis plan is available in the protocol. The protocol specified two interim analyses before the final analysis. The first interim analysis was to be performed after the first 191 patients who underwent randomization had a minimum of 6 months of follow-up; at this time, the objective response rate would be analyzed at an alpha level of 0.5%. The primary objective of the second interim analysis, which was to be performed after approximately 175 events of progression or death had been observed, was to evaluate the superiority of pembrolizumab over chemotherapy with respect to progression-free survival, at a one-sided alpha level of 2.0%. If pembrolizumab was superior with respect to progression-free survival, the superiority of pembrolizumab over chemotherapy with respect to overall survival would be assessed by means of a group-sequential test with two analyses, to be performed after approximately 110 and 170 deaths had been observed. We calculated that with approximately 175 events of progression or death, the trial would have 97% power to detect a hazard ratio for progression or death with pembrolizumab versus chemotherapy of 0.55. At the time of the second interim analysis, the trial had approximately 40% power to detect a hazard ratio for death with pembrolizumab versus chemotherapy of approximately 0.65 at a one-sided alpha level of 1.18%.

The second interim analysis was performed after 189 events of progression or death and 108 deaths had occurred and was based on a cutoff date of May 9, 2016. The data and safety monitoring committee reviewed the results on June 8, 2016, and June 14, 2016. Because pembrolizumab was superior to chemotherapy with respect to overall survival at the prespecified multiplicity-adjusted, one-sided alpha level of 1.18%, the external data and safety monitoring committee recommended that the trial be stopped early to give the patients who were receiving chemotherapy the opportunity to receive pembrolizumab. All data reported herein are based on the second interim analysis.

RESULTS

PATIENT CHARACTERISTICS AND TREATMENT

A total of 1934 patients at 142 sites in 16 countries were screened for enrollment, including 1729 who submitted samples for PD-L1 assessment (Fig. S1 in the Supplementary Appendix). Of the 1653 patients whose samples could be evaluated for PD-L1, 500 (30.2%) had a PD-L1 tumor proportion score of 50% or greater. Between September 19, 2014, and October 29, 2015, a total of 305 patients at 102 sites who met inclusion criteria were randomly assigned to either the pembrolizumab group (154 patients) or the chemotherapy group (151 patients). In the chemotherapy group, the most common regimen was carboplatin plus pemetrexed (in 67 patients). All the patients in the pembrolizumab group received the trial treatment. In the chemotherapy group, 1 patient withdrew consent before receiving the planned trial treatment, and 46 patients received pemetrexed maintenance therapy after completion of combination chemotherapy. The demographic characteristics of the patients and the disease characteristics at baseline were generally well balanced between treatment groups (Table 1), although more patients in the chemotherapy group than in the pembrolizumab group had never smoked (12.6% vs. 3.2%) and more patients in the pembrolizumab group than in the chemotherapy group had brain metastases (11.7% vs. 6.6%). These differences were not statistically significant.

As of May 9, 2016, the median duration of follow-up was 11.2 months (range, 6.3 to 19.7), and 48.1% of the patients in the pembrolizumab group and 10.0% of the patients in the chemotherapy group were still receiving the assigned treatment (Fig. S1 in the Supplementary Appendix). The median duration of treatment was 7.0 months (range, 1 day to 18.7 months) in the pembrolizumab group and 3.5 months (range, 1 day to

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Table 1. Baseline Demographic and Disease Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Pembrolizumab Group (N=154)	Chemotherapy Group (N=151)
Age — yr		
Median	64.5	66.0
Range	33–90	38–85
Male sex — no. (%)	92 (59.7)	95 (62.9)
Region of enrollment — no. (%)		
East Asia	21 (13.6)	19 (12.6)
Non–East Asia	133 (86.4)	132 (87.4)
ECOG performance-status score — no. (%)†		
0	54 (35.1)	53 (35.1)
1	99 (64.3)	98 (64.9)
Smoking status — no. (%)		
Current	34 (22.1)	31 (20.5)
Former	115 (74.7)	101 (66.9)
Never	5 (3.2)	19 (12.6)
Histology — no. (%)		
Squamous	29 (18.8)	27 (17.9)
Nonsquamous	125 (81.2)	124 (82.1)
Brain metastases — no. (%)	18 (11.7)	10 (6.6)
Previous systemic neoadjuvant therapy — no. (%)	3 (1.9)	1 (0.7)
Previous systemic adjuvant therapy — no. (%)	6 (3.9)	3 (2.0)

* The intention-to-treat population included all patients who underwent randomization. There were no significant differences between treatment groups.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. One patient (0.6%), who was in the pembrolizumab group, had an ECOG performance-status score of 2.

16.8 months) in the chemotherapy group. The median number of treatment cycles in the pembrolizumab group was 10.5 (range, 1 to 26); the median number in the chemotherapy group was 4 (range, 1 to 6), both for patients who had squamous tumors and for those who had nonsquamous tumors. In the chemotherapy group, 66 patients (43.7%) crossed over to receive pembrolizumab after disease progression. Of the patients who crossed over, 57.6% were still receiving pembrolizumab at the time of data cutoff.

PROGRESSION-FREE SURVIVAL

In the intention-to-treat population, on the basis of 189 total events of progression or death, median progression-free survival was 10.3 months (95% confidence interval [CI], 6.7 to not reached) in the pembrolizumab group and 6.0 months (95% CI, 4.2 to 6.2) in the chemotherapy group (Fig. 1A). The estimated percentage of patients who were alive and had no disease progression at 6 months was 62.1% (95% CI, 53.8 to 69.4) in the pembrolizumab group and 50.3% (95% CI, 41.9 to 58.2) in the chemotherapy group. Progression-free survival was significantly longer in the pembrolizumab group than in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; P<0.001). The benefit of pembrolizumab with respect to progression-free survival was evident in all subgroups examined (Fig. 1B).

OVERALL SURVIVAL

At the time of the second interim analysis, 108 deaths had occurred. The estimated percentage of patients who were alive at 6 months was 80.2% (95% CI, 72.9 to 85.7) in the pembrolizumab group and 72.4% (95% CI, 64.5 to 78.9) in the

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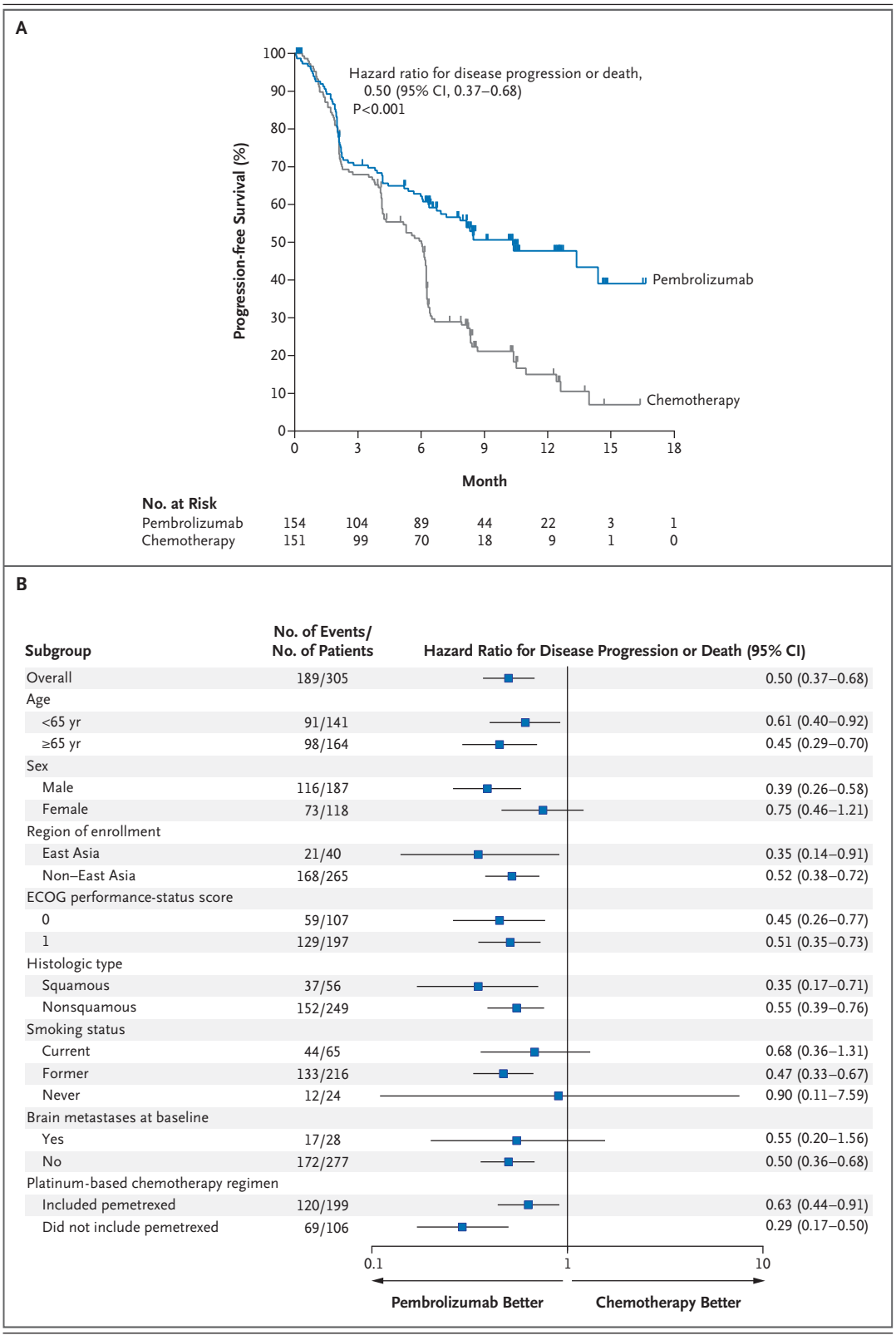

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Figure 1 (facing page). Progression-free Survival in the Intention-to-Treat Population.

Panel A shows Kaplan–Meier estimates of progression-free survival, according to treatment group. Tick marks represent data censored at the last time the patient was known to be alive and without disease progression. Panel B shows the analysis of progression-free survival in key subgroups. Progression-free survival was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by means of blinded, independent, central radiologic review. The intention-to-treat population included all patients who underwent randomization. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. The subgroups for the platinum-based chemotherapy regimen are based on the regimen chosen before the patient was randomly assigned to treatment with either pembrolizumab or platinum-based chemotherapy.

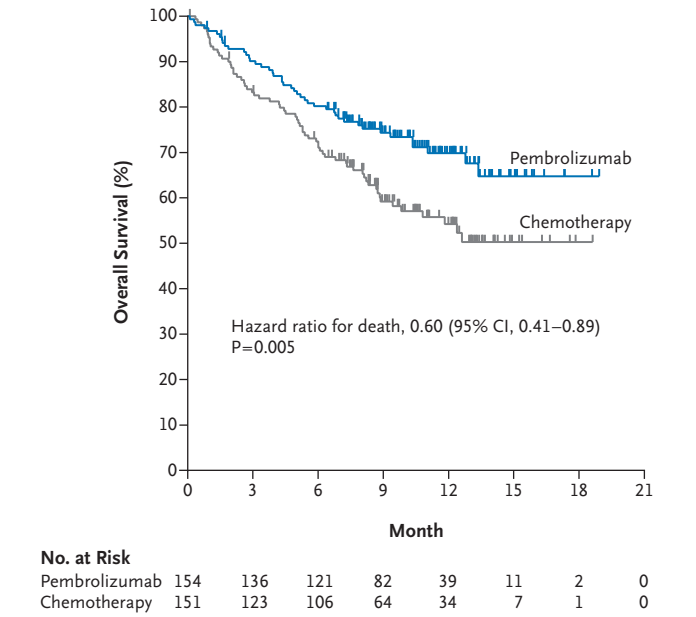

Figure 2. Overall Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier estimates of overall survival, according to treatment group. Tick marks represent data censored at the last time the patient was known to be alive. The intention-to-treat population included all patients who underwent randomization.

chemotherapy group (Fig. 2); median overall survival was not reached in either group. Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P=0.005).

OBJECTIVE RESPONSE RATE

The objective response rate, assessed according to RECIST, was 44.8% (95% CI, 36.8 to 53.0) in the pembrolizumab group and 27.8% (95% CI, 20.8 to 35.7) in the chemotherapy group (Table 2). The median time to response was 2.2 months in both groups. The median duration of response was not reached (range, 1.9+ to 14.5+ months) in the pembrolizumab group and was 6.3 months (range, 2.1+ to 12.6+) in the chemotherapy group. (Plus signs in the ranges indicate the response was ongoing at cutoff.)

ADVERSE EVENTS

During treatment with the initially assigned therapy, treatment-related adverse events occurred in 73.4% of the patients in the pembrolizumab group and in 90.0% of the patients in the chemotherapy group (Table 3). Grade 3, 4, or 5 treatment-related adverse events occurred in twice as many patients in the chemotherapy group as in the pembrolizumab group (53.3% vs. 26.6%). Serious treatment-related adverse events occurred in a similar percentage of patients in the pembrolizumab group and the chemotherapy group (21.4% and 20.7%, respectively). Discontinuation of treatment because of treatment-related adverse events occurred in 7.1% of patients in the pembrolizumab group and in 10.7% of patients in the chemotherapy group. Treatment-related adverse events that led to death occurred in one patient in the pembrolizumab group (sudden death of unknown cause on day 2) and three patients in the chemotherapy group (one death due to pulmonary sepsis on day 25, one death due to pulmonary alveolar hemorrhage on day 112, and one death of unknown cause on day 8).

The most common treatment-related adverse events were diarrhea (in 14.3% of the patients), fatigue (10.4%), and pyrexia (10.4%) in the pembrolizumab group and anemia (44.0%), nausea (43.3%), and fatigue (28.7%) in the chemotherapy group (Table 3). Grade 3, 4, or 5 treatment-related adverse events that occurred in four or more patients were diarrhea (in 3.9% of the patients) and pneumonitis (2.6%) in the pembrolizumab group and anemia (19.3%), neutropenia (13.3%), decreased platelet count (6.0%), thrombocytopenia (5.3%), decreased neutrophil count (4.0%),

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Table 2. Summary of Response in the Intention-to-Treat Population.*

Variable	Pembrolizumab Group (N=154)	Chemotherapy Group (N=151)
Objective response†		
No. of patients	69	42
% (95% CI)	44.8 (36.8 to 53.0)	27.8 (20.8 to 35.7)
Time to response — mo‡		
Median	2.2	2.2
Range	1.4 to 8.2	1.8 to 12.2
Duration of response — mo‡§		
Median	NR	6.3
Range	1.9+ to 14.5+	2.1+ to 12.6+

* The intention-to-treat population included all patients who underwent randomization. NR denotes not reached.

† Objective response was considered to be a confirmed complete or partial response, as assessed by means of blinded, independent, central radiologic review according to Response Evaluation Criteria in Solid Tumors, version 1.1. The estimated difference between the pembrolizumab group and the chemotherapy group, which was assessed with the use of the stratified method of Miettinen and Nurminen, was 16.6 percentage points (95% CI, 6.0 to 27.0).

‡ Time to response and duration of response were evaluated in the patients who had an objective response (69 patients in the pembrolizumab group and 42 in the chemotherapy group).

§ Duration of response was calculated with the use of the Kaplan–Meier method for censored data. Plus signs in the ranges indicate the response was ongoing at cutoff.

fatigue (3.3%), and decreased appetite (2.7%) in the chemotherapy group. Although decreased neutrophil count and neutropenia may reflect the same condition, they were listed by the investigators as two distinct events; this is also the case for decreased platelet count and thrombocytopenia.

Immune-mediated adverse events, both those that were and those that were not attributed by the investigator to treatment, occurred in 29.2% of patients in the pembrolizumab group and in 4.7% of patients in the chemotherapy group; grade 3 or 4 immune-mediated events occurred in 9.7% and 0.7% of patients, respectively (Table 3). The only grade 3 or 4 immune-mediated events that occurred in two or more patients occurred in the pembrolizumab group: severe skin reactions (in 3.9%), pneumonitis (2.6%), and colitis (1.3%). There were no grade 5 immune-mediated events.

DISCUSSION

The results of this randomized trial showed the superiority of anti–PD-1 therapy over platinum-based combination chemotherapy as first-line treatment for advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and with no sensitizing *EGFR* mutations or *ALK* translocations. First-line treatment with pembrolizumab resulted in significantly longer progression-free and overall survival than did standard chemotherapy, which included the use of pemetrexed maintenance therapy for patients with nonsquamous tumors. The magnitude of benefit observed in the chemotherapy group is consistent with that previously observed with platinum-based combination regimens and pemetrexed maintenance therapy.[8-10] The longer progression-free survival with pembrolizumab than with chemotherapy was observed across all subgroups analyzed and thus appeared to occur independently of patient age, sex, ECOG performance-status score, tumor histologic type, region of enrollment, presence or absence of brain metastases at baseline, chemotherapy regimen administered, and smoking status, although the low number of patients who had never smoked (24 patients) precludes accurate interpretation of the benefit in this population. The benefit of pembrolizumab observed in patients who had squamous tumors is notable, given the limited treatment options available for these patients. Pembrolizumab was also associated with a higher objective response rate, a longer duration of response, and a lower frequency of treatment-related adverse events than was chemotherapy.

Pembrolizumab was associated with significantly longer overall survival than was chemotherapy, despite the low number of deaths observed and the potentially confounding effect of crossover from the chemotherapy group to the pembrolizumab group. On the basis of data from the second interim analysis, the data and safety monitoring committee recommended that the trial be stopped and that patients remaining in the chemotherapy group be offered pembrolizumab. At the time of data cutoff, 35.4% of the enrolled patients had died and 43.7% of the patients in the chemotherapy group had crossed over to receive pembrolizumab. These data underscore the substantial benefit of pembrolizumab as initial therapy for advanced NSCLC with PD-L1 expression on at least 50% of tumor cells.

All the patients enrolled in this study had a PD-L1 tumor proportion score of 50% or greater. The 50% cutoff was established on the basis of data from the KEYNOTE-001 trial that showed

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

Adverse Event	Pembrolizumab Group (N=154)		Chemotherapy Group (N=150)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Treatment-related†				
Any	113 (73.4)	41 (26.6)	135 (90.0)	80 (53.3)
Serious	33 (21.4)	29 (18.8)	31 (20.7)	29 (19.3)
Led to discontinuation	11 (7.1)	8 (5.2)	16 (10.7)	9 (6.0)
Led to death	1 (0.6)	1 (0.6)	3 (2.0)	3 (2.0)
Occurred in ≥10% of patients in either group‡				
Nausea	15 (9.7)	0	65 (43.3)	3 (2.0)
Anemia	8 (5.2)	3 (1.9)	66 (44.0)	29 (19.3)
Fatigue	16 (10.4)	2 (1.3)	43 (28.7)	5 (3.3)
Decreased appetite	14 (9.1)	0	39 (26.0)	4 (2.7)
Diarrhea	22 (14.3)	6 (3.9)	20 (13.3)	2 (1.3)
Neutropenia	1 (0.6)	0	34 (22.7)	20 (13.3)
Vomiting	4 (2.6)	1 (0.6)	30 (20.0)	1 (0.7)
Pyrexia	16 (10.4)	0	8 (5.3)	0
Constipation	6 (3.9)	0	17 (11.3)	0
Stomatitis	4 (2.6)	0	18 (12.0)	2 (1.3)
Decreased neutrophil count	0	0	20 (13.3)	6 (4.0)
Increased blood creatinine level	3 (1.9)	0	15 (10.0)	1 (0.7)
Decreased platelet count	0	0	18 (12.0)	9 (6.0)
Thrombocytopenia	0	0	17 (11.3)	8 (5.3)
Decreased white-cell count	1 (0.6)	0	16 (10.7)	3 (2.0)
Dysgeusia	1 (0.6)	0	15 (10.0)	0
Immune-mediated§				
Any	45 (29.2)	15 (9.7)	7 (4.7)	1 (0.7)
Hypothyroidism	14 (9.1)	0	2 (1.3)	0
Hyperthyroidism	12 (7.8)	0	2 (1.3)	0
Pneumonitis	9 (5.8)	4 (2.6)	1 (0.7)	1 (0.7)
Infusion reaction	7 (4.5)	0	2 (1.3)	0
Severe skin reaction	6 (3.9)	6 (3.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Colitis	3 (1.9)	2 (1.3)	0	0
Myositis	3 (1.9)	0	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0
Pancreatitis	1 (0.6)	1 (0.6)	0	0
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)	0	0

* The as-treated population included all patients who received at least one dose of a trial treatment. For the patients in the chemotherapy group who crossed over to the pembrolizumab group after disease progression, only events that occurred during treatment with the assigned chemotherapy regimen are included.

† Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case-report form. Although decreased neutrophil count and neutropenia may reflect the same condition, they were listed by the investigators as two distinct events; this is also the case for decreased platelet count and thrombocytopenia.

‡ Events are listed in descending order of frequency in the total population.

§ The immune-mediated events, both those that were and those that were not attributed to study treatment by the investigator, are listed in descending order of frequency in the pembrolizumab group. In addition to specific preferred terms, related terms are also included.

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a significantly increased objective response rate in this population.[2] The prevalence of a tumor proportion score of 50% or greater in the KEYNOTE-024 screened population (30.2%) was consistent with the prevalence observed in the KEYNOTE-001 trial among previously untreated patients (24.9%) and in the KEYNOTE-010 trial among previously treated patients (28%).[1,2] Ongoing phase 3 studies, such as KEYNOTE-042 (ClinicalTrials.gov number, NCT02220894), will assess the benefit of pembrolizumab over chemotherapy in previously untreated patients who have a tumor proportion score of 1% or greater.

In the KEYNOTE-024 trial, pembrolizumab was administered at a fixed dose. Pharmacokinetic modeling suggested that a 200-mg fixed dose of pembrolizumab would provide exposure similar to the weight-based dosing regimens used in previous studies of pembrolizumab.[11] The progression-free survival, overall survival, objective response rate, and duration of response observed in the pembrolizumab group in this trial are consistent with those observed in patients enrolled in the KEYNOTE-001 trial who had previously untreated NSCLC with a PD-L1 tumor proportion score of 50% or greater and who were treated with pembrolizumab at a dose of 10 mg per kilogram[4]; these results suggest that 200 mg is an appropriate dose of pembrolizumab for this patient population.

The safety profile of pembrolizumab observed in this trial was consistent with that seen previously with pembrolizumab for the treatment of advanced NSCLC[1,2] and other tumor types.[12-16] The safety profile of chemotherapy was also as expected. Immune-mediated adverse events (including pneumonitis) occurred more frequently in the pembrolizumab group than in the chemotherapy group, whereas cytopenias occurred more frequently in the chemotherapy group than in the pembrolizumab group; these results are consistent with the mechanism of action for each therapy. Most immune-mediated events were of grade 1 or 2 severity, and none led to death. However, the overall safety profile appeared to be better with pembrolizumab than with chemotherapy.

In conclusion, the results of the KEYNOTE-024 trial showed that pembrolizumab was associated with longer progression-free and overall survival and fewer treatment-related adverse events than was platinum-based combination chemotherapy in patients with previously untreated advanced NSCLC and a PD-L1 tumor proportion score of 50% or greater.

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