ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer

L. Paz-Ares, A. Luft, D. Vicente, A. Tafreshi, M. Gümüş, J. Mazières, B. Hermes, F. Çay Şenler, T. Csőszi, A. Fülöp, J. Rodríguez-Cid, J. Wilson, S. Sugawara, T. Kato, K.H. Lee, Y. Cheng, S. Novello, B. Halmos, X. Li, G.M. Lubiniecki, B. Piperdi, and D.M. Kowalski, for the KEYNOTE-407 Investigators*

ABSTRACT

BACKGROUND

Standard first-line therapy for metastatic, squamous non–small-cell lung cancer (NSCLC) is platinum-based chemotherapy or pembrolizumab (for patients with programmed death ligand 1 [PD-L1] expression on ≥50% of tumor cells). More recently, pembrolizumab plus chemotherapy was shown to significantly prolong overall survival among patients with nonsquamous NSCLC.

METHODS

In this double-blind, phase 3 trial, we randomly assigned, in a 1:1 ratio, 559 patients with untreated metastatic, squamous NSCLC to receive 200 mg of pembrolizumab or saline placebo for up to 35 cycles; all the patients also received carboplatin and either paclitaxel or nanoparticle albumin-bound [nab]–paclitaxel for the first 4 cycles. Primary end points were overall survival and progression-free survival.

RESULTS

After a median follow-up of 7.8 months, the median overall survival was 15.9 months (95% confidence interval [CI], 13.2 to not reached) in the pembrolizumab-combination group and 11.3 months (95% CI, 9.5 to 14.8) in the placebo-combination group (hazard ratio for death, 0.64; 95% CI, 0.49 to 0.85; P<0.001). The overall survival benefit was consistent regardless of the level of PD-L1 expression. The median progression-free survival was 6.4 months (95% CI, 6.2 to 8.3) in the pembrolizumab-combination group and 4.8 months (95% CI, 4.3 to 5.7) in the placebo-combination group (hazard ratio for disease progression or death, 0.56; 95% CI, 0.45 to 0.70; P<0.001). Adverse events of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab-combination group and in 68.2% of the patients in the placebo-combination group. Discontinuation of treatment because of adverse events was more frequent in the pembrolizumab-combination group than in the placebo-combination group (13.3% vs. 6.4%).

CONCLUSIONS

In patients with previously untreated metastatic, squamous NSCLC, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. (Funded by Merck Sharp & Dohme; KEYNOTE-407 ClinicalTrials.gov number, NCT02775435.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Paz-Ares at the Department of Medical Oncology, Hospital Universitario 12 de Octubre, Avenida de Córdoba, Madrid 28041, Spain, or at lpazaresr@seom.org.

*A complete list of investigators who participated in the KEYNOTE-407 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 25, 2018, at NEJM.org.

N Engl J Med 2018;379:2040-51.
DOI: 10.1056/NEJMoa1810865

Squamous non–small-cell lung cancer (NSCLC) accounts for approximately 20 to 30% of all lung cancers and is associated with shorter survival than is nonsquamous NSCLC.[1-4] Historically, the lack of targetable aberrations meant that treatment for squamous NSCLC was mostly limited to cytotoxic chemotherapy. The combination of the epidermal growth factor receptor inhibitor necitumumab and chemotherapy with gemcitabine and cisplatin in the first-line treatment of squamous NSCLC significantly prolonged overall survival, as compared with chemotherapy alone, but the magnitude of benefit was small.[5] Inhibitors of programmed death receptor 1 (PD-1) and its ligand PD-L1 are effective in the treatment of squamous and nonsquamous NSCLC.[6-11] To determine whether the addition of the PD-1 inhibitor pembrolizumab (Keytruda, Merck) to platinum-based chemotherapy improves outcomes in patients with squamous NSCLC of any level of PD-L1 expression, we conducted the global, double-blind, placebo-controlled, phase 3 KEYNOTE-407 trial, which compared pembrolizumab plus chemotherapy (carboplatin and either paclitaxel or nanoparticle albumin-bound [nab]–paclitaxel [Abraxane, Celgene]) with placebo plus chemotherapy (carboplatin and either paclitaxel or nab-paclitaxel).

Methods

Patients

Patients were eligible for enrollment if they were 18 years of age or older, had pathologically confirmed stage IV squamous NSCLC (as classified according to the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer[12]), 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; a score of 0 indicates no symptoms, and 1 mild symptoms),[13] had at least one measurable lesion according to version 1.1 of the Response Evaluation Criteria in Solid Tumors (RECIST),[14] and provided a tumor sample for the 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. Full eligibility criteria are listed in the trial protocol, available with the full text of this article at NEJM.org.

Trial Design and Treatments

In this double-blind trial, randomization was performed with the use of an interactive voice-response and integrated Web-response system. Randomization was stratified according to PD-L1 tumor proportion score (≥1% vs. <1%; tumor proportion score is the percentage of tumor cells with membranous PD-L1 staining, with <1% indicating PD-L1–negative), choice of taxane (paclitaxel vs. nab-paclitaxel), and geographic region of enrollment (East Asia vs. the rest of the world). Patients were randomly assigned, in a 1:1 ratio, to receive 200 mg of pembrolizumab or saline placebo on day 1 for up to 35 cycles. For the first 4 cycles, all the patients also received carboplatin (at a dose calculated to produce an area under the concentration–time curve of 6 mg per milliliter per minute) on day 1 and either paclitaxel (200 mg per square meter of body-surface area) on day 1 or nab-paclitaxel (100 mg per square meter) on days 1, 8, and 15. All treatments were administered intravenously in 3-week cycles. The patients who received paclitaxel also received premedication with a glucocorticoid, a type 1 antihistamine, and a type 2 antihistamine according to local guidelines; premedication with a glucocorticoid and antihistamines was not required for patients who received nab-paclitaxel.

The assigned treatment was continued until radiographic disease progression, the occurrence of unacceptable toxic effects, an investigator's decision to discontinue the treatment, or withdrawal of patient consent. If toxic effects were clearly attributed to one component of the treatment, that component alone could be discontinued. Patients who had radiographic disease progression but were clinically stable could continue to receive treatment at the discretion of an investigator until disease progression was confirmed by imaging performed at least 28 days after the imaging assessment that first showed disease progression. The trial-group assignment could be unblinded for a patient who had disease progression confirmed by blinded, independent review of radiologic im-

ages at a central laboratory; such patients in the placebo-combination group were eligible to cross over to receive pembrolizumab monotherapy if all protocol-specified criteria were met. Patients in the pembrolizumab-combination group who were deemed to have clinical benefit from treatment despite radiographically confirmed disease progression were permitted to continue open-label pembrolizumab monotherapy. Additional details regarding treatment decisions, management of adverse events, and eligibility criteria for crossover are available in the protocol.

ASSESSMENTS

The PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) was used to assess PD-L1 expression in formalin-fixed tumor samples obtained at the time metastatic disease was diagnosed. PD-L1 expression was assessed during screening at a central laboratory and was characterized according to the tumor proportion score.[15] Investigators and patients were unaware of the tumor proportion score. Adverse events and abnormal laboratory findings were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Tumor imaging was scheduled for weeks 6, 12, and 18 and then every 9 weeks through week 45 and every 12 weeks thereafter. Response was assessed according to RECIST, version 1.1.[14] Patients were contacted to assess survival every 12 weeks during follow-up.

TRIAL OVERSIGHT

The trial was designed by a panel of academic advisors and employees of Merck Sharp & Dohme, the sponsor of the trial. An external, independent 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 committee at each participating center. All patients provided written informed consent before enrollment.

The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The trial was conducted in accordance with the provisions of the International Conference on Harmonisation Good Clinical Practice guidelines. All the authors had access to the data. Assistance in the preparation of the manuscript was provided by a medical writer employed by the sponsor, and all the authors participated in writing or reviewing and editing the manuscript.

STATISTICAL ANALYSIS

The trial had dual primary end points of overall survival and progression-free survival, which was assessed by means of blinded, independent central review of radiologic images. The secondary end points were response rate and duration of response, which were assessed by means of blinded, independent central radiologic review, and safety. The effects of PD-L1 expression on overall survival, progression-free survival, and response rate were prespecified exploratory end points. 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 underwent randomization and received at least one dose of the assigned combination treatment.

The Kaplan–Meier method was used to estimate overall survival, progression-free survival, and duration of response. The stratified log-rank test was used to assess between-group differences in overall and progression-free survival. A stratified Cox proportional-hazards model and Efron's method of tie handling were used to assess the magnitude of the difference between the trial groups. There was no violation of the proportional-hazards model in the intention-to-treat population. In some subgroups, there was a delayed separation of the survival curves, suggesting a possible deviation from the proportional-hazards assumption. The stratified method of Miettinen and Nurminen was used to assess differences in response rate. The randomization stratification factors were applied to all stratified analyses.

The full statistical analysis plan is available with the protocol. The graphical method of Maurer and Bretz was used to control the family-wise type I error rate at a one-sided alpha level of 0.025 across all hypotheses and interim analyses (Fig. S1 in the Supplementary Appendix, available at NEJM.org). We determined that with a sample of 560 patients, the trial would have 90% power to show a hazard ratio for disease progression or death of 0.70 at a one-sided alpha level of 0.01 (as calculated on the basis of 415 events of disease progression or death) and 85% power to show a hazard ratio for death of 0.70 at a one-sided alpha level of 0.01 (as calculated on the basis of 361 deaths) for the comparison between the pembrolizumab-combination group and the placebo-combination group.

The original protocol specified the performance

of two interim analyses and a final analysis (Table S1 in the Supplementary Appendix). To improve the ability of the trial to identify long-term treatment effects, the protocol was amended to specify the performance of three interim analyses and a final analysis (Table S1 in the Supplementary Appendix). The second interim analysis was to be performed after enrollment was complete and approximately 332 events of disease progression or death had been observed; it was estimated that approximately 212 deaths would be observed at this time. As of April 3, 2018, there were 349 events of disease progression or death and 205 deaths, and the multiplicity-adjusted, one-sided alpha spent at this interim analysis (as determined on the basis of the Lan–DeMets O'Brien–Fleming spending function) was 0.008 for progression-free survival and 0.0029 for overall survival. The external monitoring committee reviewed the results of the second interim analysis on May 21, 2018. Because the committee reported that the efficacy boundaries for the primary hypotheses of overall survival and progression-free survival had been met, the decision was made to report the results of the second interim analysis. The trial is continuing in order to evaluate outcomes with additional follow-up.

RESULTS

PATIENTS AND TREATMENTS

A total of 779 patients from 137 sites in 17 countries were screened for randomization (Fig. S2 in the Supplementary Appendix). Of the 561 patients who met all eligibility criteria, 2 were excluded from randomization because of a physician's decision. Between August 19, 2016, and December 28, 2017, the remaining 559 patients from 125 sites underwent randomization; 278 patients were assigned to the pembrolizumab-combination group and 281 to the placebo-combination group. With respect to the stratification factors, a PD-L1 tumor proportion score of 1% or greater was observed for 63.1% of patients, paclitaxel was the choice of taxane for 60.1% of patients, and East Asia was the region of enrollment for 19.0% of patients. Baseline demographic and disease characteristics were as expected for a trial involving patients with metastatic, squamous NSCLC and were well balanced between groups (Table 1).

At least one dose of the assigned combination treatment was received by all 278 patients in the

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

Characteristic	Pembrolizumab Combination (N=278)	Placebo Combination (N=281)
Age		
Median (range) — yr	65 (29–87)	65 (36–88)
<65 yr — no. (%)	127 (45.7)	127 (45.2)
Male sex — no. (%)	220 (79.1)	235 (83.6)
Region of enrollment — no. (%)		
East Asia	54 (19.4)	52 (18.5)
Rest of the world	224 (80.6)	229 (81.5)
ECOG performance-status score — no. (%)†		
0	73 (26.3)	90 (32.0)
1	205 (73.7)	191 (68.0)
Smoking status — no. (%)		
Current or former	256 (92.1)	262 (93.2)
Never	22 (7.9)	19 (6.8)
Histologic features — no. (%)		
Squamous	272 (97.8)	274 (97.5)
Adenosquamous‡	6 (2.2)	7 (2.5)
Brain metastases — no. (%)	20 (7.2)	24 (8.5)
PD-L1 tumor proportion score — no. (%)§		
<1%	95 (34.2)	99 (35.2)
≥1%	176 (63.3)	177 (63.0)
1–49%	103 (37.1)	104 (37.0)
≥50%	73 (26.3)	73 (26.0)
Could not be evaluated¶	7 (2.5)	5 (1.8)
Previous therapy for nonmetastatic disease — no. (%)		
Thoracic radiotherapy	17 (6.1)	22 (7.8)
Neoadjuvant or adjuvant therapy	5 (1.8)	8 (2.8)

* Patients in the pembrolizumab-combination group received pembrolizumab, carboplatin, and either paclitaxel or nanoparticle albumin-bound (nab)–paclitaxel. Patients in the placebo-combination group received placebo, carboplatin, and either paclitaxel or nab-paclitaxel. There were no significant differences 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.[13]

‡ Patients whose tumors were of a mixed histologic subtype were eligible for enrollment if there was a squamous component in the specimen.

§ 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 of patients with a PD-L1 tumor proportion score of less than 1%; these patients were excluded from analyses of efficacy according to the PD-L1 tumor proportion score.

pembrolizumab-combination group and by 280 of 281 patients in the placebo-combination group. The median duration of follow-up (defined as the time from randomization to death or the date of data cutoff for those who were alive) was 7.8 months (range, 0.1 to 19.1). The mean (±SD) duration of treatment was 6.3±4.1 months in the pembrolizumab-combination group and 4.7±3.5 months in the placebo-combination group. Four doses of carboplatin were received by 78.8% of the patients in the pembrolizumab-combination group and by 73.2% of the patients in the placebo-combination group (Table S2 in the Supplementary Appendix). Among the patients who received paclitaxel, 78.7% in the pembrolizumab-combination group and 71.3% in the placebo-combination group received all 4 cycles; among the patients who received nab-paclitaxel, 22.9% in the pembrolizumab-combination group and 21.2% in the placebo-combination group received all 12 doses (66.1% and 64.6%, respectively, received 5 to 11 doses) (Table S2 in the Supplementary Appendix).

As of April 3, 2018, a total of 121 patients (43.5%) in the pembrolizumab-combination group and 72 patients (25.7%) in the placebo-combination group were still receiving their assigned treatment (Fig. S2 in the Supplementary Appendix). In the pembrolizumab-combination group, 12 patients received pembrolizumab monotherapy for a median of 3 cycles (range, 1 to 10) after disease progression was confirmed. In the placebo-combination group, 75 patients crossed over to receive pembrolizumab monotherapy in the trial after the occurrence of disease progression, and an additional 14 patients received a subsequent PD-1 or PD-L1 inhibitor outside the trial; thus, the effective crossover rates (i.e., the rates among the patients who crossed over in the trial and those who received the same treatment or class of treatment outside the in-trial crossover) were 31.7% among the 281 patients in the intention-to-treat population and 42.8% among the 208 patients who discontinued their assigned treatment for any reason.

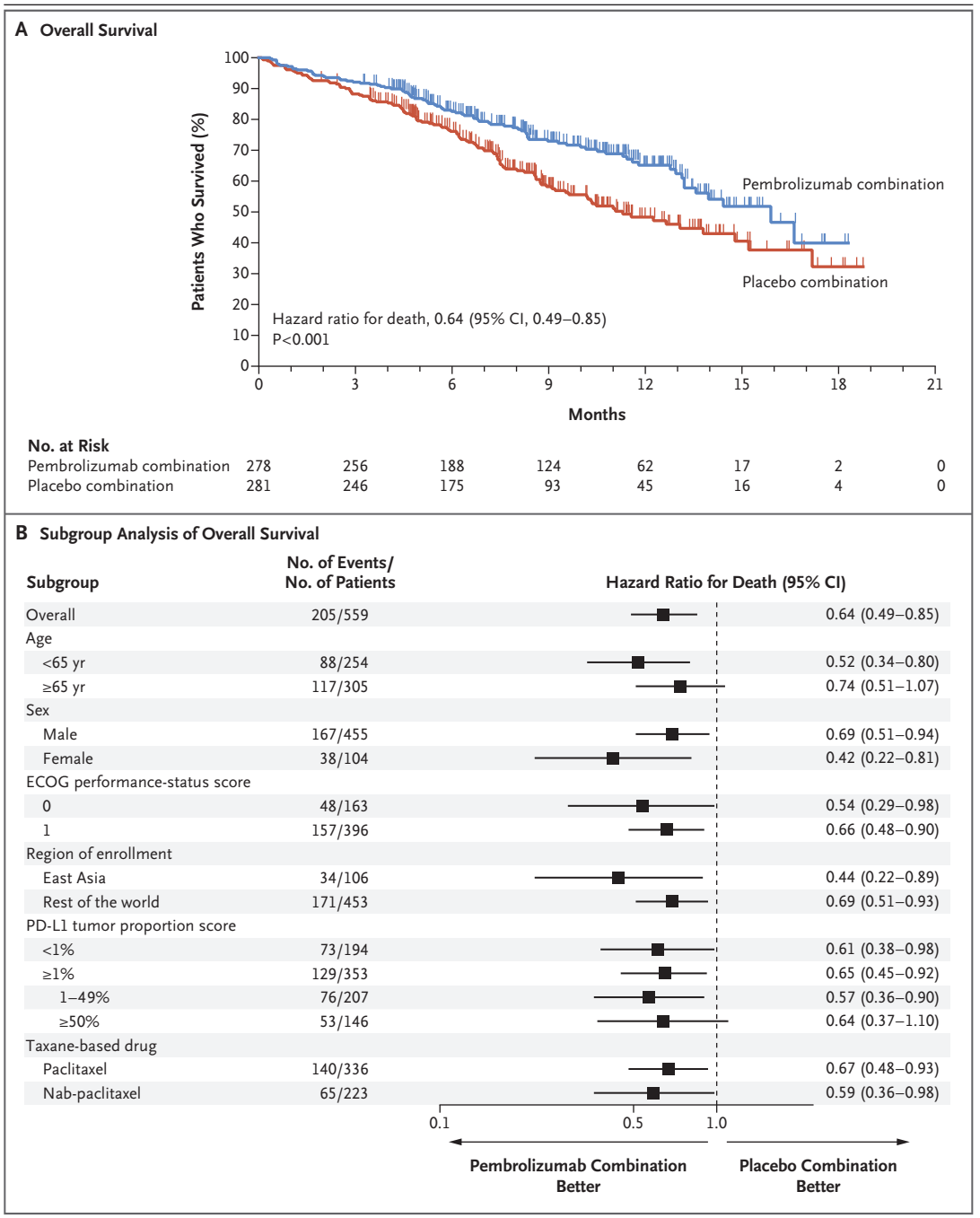
Figure 1 (facing page). Overall Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier estimates of overall survival in the two trial groups (Panel A) and an analysis of overall survival in key prespecified subgroups (Panel B). Patients in the pembrolizumab-combination group received pembrolizumab plus carboplatin and either paclitaxel or nanoparticle albumin-bound (nab)–paclitaxel. Patients in the placebo-combination group received placebo plus carboplatin and either paclitaxel or nab-paclitaxel. Tick marks in Panel A indicate censoring of data at the last time the patient was known to be alive. In Panel B, overall survival was analyzed in the overall population and in the subgroups defined according to the programmed death ligand 1 (PD-L1) tumor proportion score with the use of a Cox regression model that included trial group and the randomization stratification factors (PD-L1 tumor proportion score [≥1% vs. <1%], choice of taxane [paclitaxel vs. nab-paclitaxel], and geographic region of enrollment [East Asia vs. the rest of the world]) as covariates; overall survival was analyzed in all the other subgroups with the use of an unstratified Cox regression model that included trial group as a covariate. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.[13]

EFFICACY

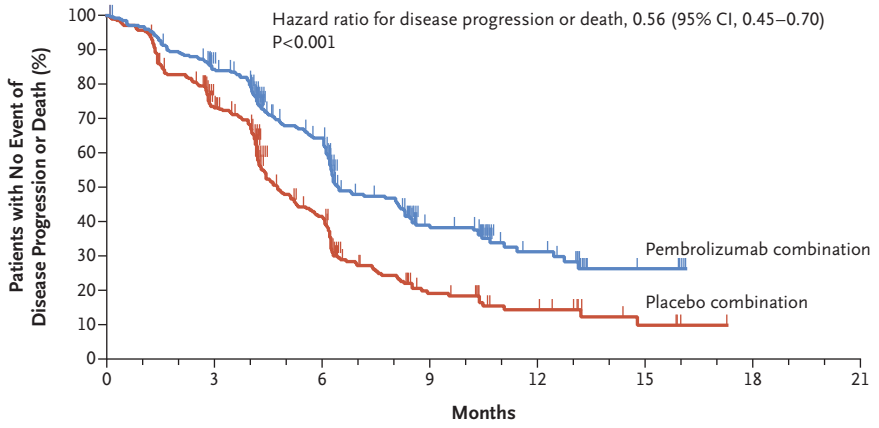
A total of 205 deaths occurred in the intention-to-treat population; the median overall survival was 15.9 months (95% confidence interval [CI], 13.2 to not reached) in the pembrolizumab-combination group and 11.3 months (95% CI, 9.5 to 14.8) in the placebo-combination group (hazard ratio for death, 0.64; 95% CI, 0.49 to 0.85; P<0.001) (Fig. 1A). Kaplan–Meier estimates of the rate of survival at 1 year were 65.2% in the pembrolizumab-combination group and 48.3% in the placebo-combination group. The benefit of adding pembrolizumab was observed in all prespecified subgroups (Fig. 1B), including in the subgroups defined according to PD-L1 tumor proportion score (estimated 1-year survival rate among patients with a PD-L1 tumor proportion score of <1% in the pembrolizumab-combination group vs. the placebo-combination group, 64.2% vs. 43.3% [hazard ratio for death, 0.61; 95% CI, 0.38 to 0.98]; among those with a score of 1 to 49%, 65.9% vs. 50.0% [hazard ratio, 0.57; 95% CI, 0.36 to 0.90]; and among those with a score of ≥50%, 63.4% vs. 51.0% [hazard ratio, 0.64; 95% CI, 0.37 to 1.10]) (Fig. S3 in the Supplementary Appendix).

A total of 349 events of disease progression or death occurred in the intention-to-treat population, as assessed by means of blinded, independent central radiologic review; the median progression-free survival was 6.4 months (95% CI, 6.2 to 8.3) in the pembrolizumab-combination group and 4.8 months (95% CI, 4.3 to 5.7) in the placebo-combination group (hazard ratio for dis-



ease progression or death, 0.56; 95% CI, 0.45 to 0.70; P<0.001) (Fig. 2A). The results were similar when progression-free survival was assessed by means of investigator review (Fig. S4 in the Supplementary Appendix). The progression-free survival benefit of the pembrolizumab combination was observed in all prespecified subgroups (Fig. 2B), with incremental improvements noted with increasing PD-L1 tumor proportion score (median progression-free survival among patients with a PD-L1 tumor proportion score of <1% in the pembrolizumab-combination group vs. the placebo-combination group, 6.3 months vs. 5.3 months [hazard ratio for progression or death, 0.68; 95% CI, 0.47 to 0.98]; among those with a score of 1 to 49%, 7.2 months vs. 5.2 months [haz-

A Progression-free Survival



No. at Risk

Pembrolizumab combination	278	223	142	57	23	5	0	0
Placebo combination	281	190	90	26	12	4	0	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	349/559	0.56 (0.45–0.70)
Age		
<65 yr	162/254	0.50 (0.37–0.69)
≥65 yr	187/305	0.63 (0.47–0.84)
Sex		
Male	284/455	0.58 (0.46–0.73)
Female	65/104	0.49 (0.30–0.81)
ECOG performance-status score		
0	96/163	0.45 (0.29–0.68)
1	253/396	0.61 (0.48–0.78)
Region of enrollment		
East Asia	61/106	0.49 (0.30–0.82)
Rest of the world	288/453	0.58 (0.46–0.73)
PD-L1 tumor proportion score		
<1%	122/194	0.68 (0.47–0.98)
≥1%	221/353	0.49 (0.38–0.65)
1–49%	127/207	0.56 (0.39–0.80)
≥50%	94/146	0.37 (0.24–0.58)
Taxane-based drug		
Paclitaxel	231/336	0.52 (0.40–0.68)
Nab-paclitaxel	118/223	0.65 (0.45–0.94)

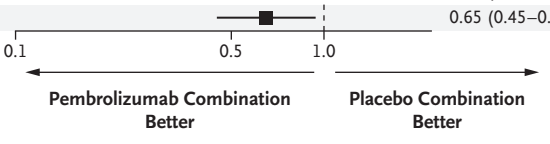


Figure 2. Progression-free Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier estimates of progression-free survival in the two trial groups (Panel A) and an analysis of progression-free survival in key prespecified subgroups (Panel B). Progression-free survival was assessed according to version 1.1 of the Response Evaluation Criteria in Solid Tumors by means of blinded, independent central radiologic review. Tick marks in Panel A indicate censoring of data at the last time the patient was known to be alive and without disease progression (i.e., at the time of the last imaging assessment). In Panel B, progression-free survival was analyzed in the overall population and in the subgroups defined according to the PD-L1 tumor proportion score with the use of a Cox regression model that included trial group and the randomization stratification factors as covariates; progression-free survival was analyzed in all the other subgroups with the use of an unstratified Cox regression model that included trial group as a covariate.

ard ratio, 0.56; 95% CI, 0.39 to 0.80]; and among those with a score of ≥50%, 8.0 months vs. 4.2 months [hazard ratio, 0.37; 95% CI, 0.24 to 0.58]) (Fig. S5 in the Supplementary Appendix).

The response rate, as assessed by means of blinded, independent central radiologic review, was 57.9% (95% CI, 51.9 to 63.8) in the pembrolizumab-combination group and 38.4% (95% CI, 32.7 to 44.4) in the placebo-combination group. The best overall response in each trial group is summarized in Table S3 in the Supplementary Appendix. The median time to response was 1.4 months in each group. The median duration of response was 7.7 months (range, 1.1+ to 14.7+ [the plus sign indicates ongoing response at the time of data cutoff]) in the pembrolizumab-combination group and 4.8 months (range, 1.3+ to 15.8+) in the placebo-combination group (Fig. S6 in the Supplementary Appendix). In the subgroups defined according to PD-L1 tumor proportion score, the response rates were higher among the patients who received the pembrolizumab combination than among those who received the placebo combination (response rate among patients with a PD-L1 tumor proportion score of <1% in the pembrolizumab-combination group vs. the placebo-combination group, 63.2% vs. 40.4%; among those with a score of 1 to 49%, 49.5% vs. 41.3%; and among those with a score of ≥50%, 60.3% vs. 32.9%). A summary of overall survival, progression-free survival, and response rate in the total population and in subgroups defined according to PD-L1 tumor proportion score is provided in Table S4 in the Supplementary Appendix.

SAFETY

Adverse events of any grade, regardless of attribution to a trial regimen by an investigator, occurred in 98.2% of the patients in the pembrolizumab-combination group and in 97.9% of the patients in the placebo-combination group (Table 2). Adverse events of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab-combination group and in 68.2% of the patients in the placebo-combination group; led to dose reduction of chemotherapy in 22.7% and 17.5%, respectively; led to the discontinuation of any treatment component in 23.4% and 11.8%; and led to the discontinuation of all treatment components in 13.3% and 6.4%. Adverse events led to death in 23 patients (8.3%) in the pembrolizumab-combination group and in 18 patients (6.4%) in the placebo-combination group. Summaries of adverse events that occurred in the patients who received paclitaxel and in those who received nab-paclitaxel are provided in Tables S5 and S6, respectively, in the Supplementary Appendix.

The most common adverse events in both trial groups were anemia, alopecia, and neutropenia (Table 2). Among the adverse events that were reported in at least 10% of patients, alopecia and pruritus occurred more frequently in the pembrolizumab-combination group than in the placebo-combination group, whereas back pain occurred more frequently in the placebo-combination group; after adjustment for exposure, rates of alopecia and pruritus were similar in the groups (Fig. S7A and Table S7 in the Supplementary Appendix). Adverse events of grade 3 or higher that occurred in at least 10% of patients were anemia and neutropenia (Table 2). Adverse events of grade 3 or higher that occurred more frequently in the pembrolizumab-combination group than in the placebo-combination group were pneumonitis and autoimmune hepatitis (Fig. S7B in the Supplementary Appendix). Immune-mediated adverse events and infusion reactions occurred in 28.8% of patients in the pembrolizumab-combination group and in 8.6% of patients in the placebo-combination group (Table 3); the events were of grade 3 or higher in 10.8% and 3.2%, respectively. One patient in each trial group died from an immune-mediated adverse event (pneumonitis in both).

DISCUSSION

The results of this phase 3 trial involving patients with untreated metastatic, squamous NSCLC showed that the addition of pembrolizumab to standard chemotherapy with carboplatin and either paclitaxel or nab-paclitaxel, as compared with chemotherapy alone, prolonged median overall survival by 4.6 months (15.9 months vs. 11.3 months) and median progression-free survival by 1.6 months (6.4 months vs. 4.8 months). The risk of death was 36% lower and the risk of disease progression or death was 44% lower in the pembrolizumab-combination group than in the placebo-combination group. The treatment effect was similar among the patients who received paclitaxel and those who received nab-paclitaxel. Prolongation of overall survival of a consistent magnitude was observed across the categories of

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

Event	Pembrolizumab Combination (N=278)		Placebo Combination (N=280)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	273 (98.2)	194 (69.8)	274 (97.9)	191 (68.2)
Event leading to discontinuation of all treatment components†	37 (13.3)	34 (12.2)	18 (6.4)	18 (6.4)
Event leading to discontinuation of any treatment component‡	65 (23.4)	54 (19.4)	33 (11.8)	29 (10.4)
Discontinuation of pembrolizumab or placebo	48 (17.3)	44 (15.8)	22 (7.9)	21 (7.5)
Discontinuation of carboplatin	31 (11.2)	28 (10.1)	21 (7.5)	19 (6.8)
Discontinuation of paclitaxel or nab-paclitaxel	44 (15.8)	33 (11.9)	28 (10.0)	24 (8.6)
Event leading to death§	23 (8.3)	23 (8.3)	18 (6.4)	18 (6.4)
Event leading to death that was attributed to a trial regimen by an investigator¶	10 (3.6)	10 (3.6)	6 (2.1)	6 (2.1)
Event occurring in ≥15% of patients in either group‖				
Anemia	148 (53.2)	43 (15.5)	145 (51.8)	57 (20.4)
Alopecia	128 (46.0)	1 (0.4)	102 (36.4)	3 (1.1)
Neutropenia	105 (37.8)	63 (22.7)	92 (32.9)	69 (24.6)
Nausea	99 (35.6)	3 (1.1)	90 (32.1)	4 (1.4)
Thrombocytopenia	85 (30.6)	19 (6.8)	65 (23.2)	18 (6.4)
Diarrhea	83 (29.9)	11 (4.0)	65 (23.2)	6 (2.1)
Decreased appetite	68 (24.5)	6 (2.2)	82 (29.3)	5 (1.8)
Constipation	64 (23.0)	2 (0.7)	61 (21.8)	3 (1.1)
Fatigue	63 (22.7)	9 (3.2)	72 (25.7)	11 (3.9)
Asthenia	60 (21.6)	6 (2.2)	59 (21.1)	10 (3.6)
Arthralgia	57 (20.5)	4 (1.4)	40 (14.3)	2 (0.7)
Peripheral neuropathy	57 (20.5)	3 (1.1)	45 (16.1)	2 (0.7)
Vomiting	45 (16.2)	1 (0.4)	33 (11.8)	6 (2.1)
Cough	37 (13.3)	2 (0.7)	47 (16.8)	3 (1.1)
Dyspnea	36 (12.9)	4 (1.4)	45 (16.1)	3 (1.1)

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

† This category includes patients who discontinued pembrolizumab or placebo, carboplatin, and paclitaxel or nab-paclitaxel because of an adverse event at any time and patients who discontinued pembrolizumab or placebo for an adverse event after completing four cycles of carboplatin and either paclitaxel or nab-paclitaxel.

‡ 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 respiratory failure and sepsis in 3 patients each, cardiac arrest and pulmonary hemorrhage in 2 patients each, and cardiac failure, circulatory collapse, hepatic failure, intestinal perforation, lung abscess, necrotizing fasciitis, pneumonia, pneumonitis, and pulmonary sepsis in 1 patient each; 4 of the deaths in this group had an unspecified cause. The adverse events leading to death in the placebo-combination group were septic shock in 3 patients, cardiorespiratory arrest in 2 patients, and acute kidney injury, cardiac arrest, hemothorax, multiple organ dysfunction syndrome, pleural effusion, pneumonia, pneumonitis, pulmonary hemorrhage, pulmonary mycosis, and sepsis in 1 patient each; 3 of the deaths in this group had an unspecified cause.

¶ In the pembrolizumab-combination group, the adverse events leading to death that were attributed to one or more components of the trial regimen by an investigator were sepsis in 3 patients and hepatic failure, necrotizing fasciitis, pneumonitis, pulmonary hemorrhage, and respiratory failure in 1 patient each; 2 of the deaths that were attributed to one or more components of the trial regimen in this group had an unspecified cause. The adverse events leading to death that were attributed to a component of the trial regimen in the placebo-combination group were septic shock in 2 patients and acute kidney injury, multiple organ dysfunction syndrome, pneumonia, and pulmonary hemorrhage in 1 patient each.

‖ Events are listed in descending order of frequency in the pembrolizumab-combination group. None of these events were of grade 5 severity.

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

Event	Pembrolizumab Combination (N=278)		Placebo Combination (N=280)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Any event	80 (28.8)	30 (10.8)	24 (8.6)	9 (3.2)
Hypothyroidism	22 (7.9)	1 (0.4)	5 (1.8)	0
Hyperthyroidism	20 (7.2)	1 (0.4)	2 (0.7)	0
Pneumonitis	18 (6.5)	7 (2.5)†	6 (2.1)	3 (1.1)†
Infusion reaction	8 (2.9)	4 (1.4)	6 (2.1)	1 (0.4)
Colitis	7 (2.5)	6 (2.2)	4 (1.4)	3 (1.1)
Hepatitis	5 (1.8)	5 (1.8)	0	0
Severe skin reaction	5 (1.8)	3 (1.1)	1 (0.4)	1 (0.4)
Hypophysitis	3 (1.1)	2 (0.7)	0	0
Thyroiditis	3 (1.1)	1 (0.4)	0	0
Nephritis	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)

* The adverse events of interest are infusion reactions and events with an immune-related cause; they are considered regardless of whether the investigator attributed the event to a trial regimen or considered the event to be immune-related. 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 patients who underwent randomization and received at least one dose of the assigned combination treatment.
† Data include 1 patient (0.4%) in each trial group who had grade 5 pneumonitis.

PD-L1 tumor proportion score (<1%, 1 to 49%, and ≥50%), although the upper limit of the 95% confidence interval for the subgroup with a score of 50% or greater exceeded 1. A higher response rate and longer duration of response were also observed.

In the phase 3 SQUIRE (Squamous NSCLC treatment with the Inhibitor of EGF Receptor) trial involving patients with untreated metastatic, squamous NSCLC, the median overall survival was 1.6 months longer (11.5 months vs. 9.9 months) and the risk of death 16% lower among patients who received necitumumab plus gemcitabine and cisplatin than among those who received gemcitabine and cisplatin alone.[5] The 11.3-month median overall survival observed in the placebo-combination group in the KEYNOTE-407 trial is similar to the 11.5-month median overall survival observed in the group that received necitumumab plus gemcitabine and cisplatin in the SQUIRE trial,[5] a finding that further validates the benefit of adding pembrolizumab to chemotherapy.

The results of the current trial and of three other phase 3 trials[8,10,11] suggest that pembrolizumab has a role in the first-line treatment of metastatic NSCLC, regardless of histologic subtype or PD-L1 tumor proportion score. In patients with PD-L1–negative tumors, pembrolizumab plus chemotherapy has shown a high level of activity as compared with chemotherapy alone. In patients with PD-L1–positive tumors, the currently available data do not permit the determination of whether pembrolizumab plus chemotherapy has greater efficacy than pembrolizumab alone. Therefore, the treatment decision should be made on an individual basis after a discussion of the relative risks and benefits and consideration of patient-specific factors.[16]

The findings with respect to other immune checkpoint inhibitors in the first-line treatment of metastatic NSCLC have been mixed. In a review of the literature, we found that, to date, pembrolizumab has been the only PD-1 or PD-L1 inhibitor to show a significant survival benefit over chemotherapy when given as monotherapy or as part of combination therapy for metastatic, squamous or nonsquamous NSCLC.[8,10,11,17-21] The addition of the cytotoxic T-lymphocyte–associated protein 4 inhibitor ipilimumab to chemotherapy with carboplatin and paclitaxel did not prolong overall survival, as compared with che-

motherapy alone, among patients with advanced squamous NSCLC.[18] Recently reported data from the phase 3 IMpower131 trial showed that the risk of disease progression or death among patients with untreated metastatic, squamous NSCLC was 29% lower with the addition of the PD-L1 inhibitor atezolizumab to carboplatin and nab-paclitaxel than with carboplatin and nab-paclitaxel alone; no effect on overall survival was observed in this interim analysis.[19]

The PD-L1 tumor proportion score is an established biomarker for selecting patients with metastatic NSCLC for first-line pembrolizumab monotherapy on the basis of the clear relationship between higher PD-L1 expression in tumors and increasing benefit of pembrolizumab.[8,10,22] Although there was a relationship between greater PD-L1 expression and longer progression-free survival in the KEYNOTE-407 trial and a relationship between greater PD-L1 expression and longer overall and progression-free survival in a phase 3 trial of pembrolizumab plus pemetrexed and a platinum-based drug for nonsquamous NSCLC,[11] the clinical usefulness of PD-L1 as a biomarker in patients receiving combination therapy may be less clear, given that the combination treatments improved outcomes over chemotherapy across all categories of PD-L1 tumor proportion scores. Other potential biomarkers for immune checkpoint inhibition have been evaluated, including tumor mutational burden, which appears to be complementary to and nonoverlapping with PD-L1 expression.[17,20,21] In the phase 3 CheckMate 227 trial, the risk of disease progression or death among patients with previously untreated squamous or nonsquamous NSCLC with a high tumor mutational burden was 42% lower with nivolumab plus ipilimumab than with chemotherapy.[20] An exploratory analysis of data from patients with PD-L1–negative tumors suggested that high tumor mutational burden may predict a progression-free survival benefit for nivolumab plus chemotherapy over chemotherapy alone.[21] Currently, the ability of tumor mutational burden to predict an overall survival benefit is uncertain.[17,20,21]

The adverse-event profile observed in the current trial was as expected on the basis of the known events associated with pembrolizumab, carboplatin, paclitaxel, and nab-paclitaxel, with no new safety signals identified. Although the rates of treatment discontinuation due to adverse events were generally low, more patients in the pembrolizumab-combination group than in the placebo-combination group discontinued the regimen because of adverse events, probably in part because of the longer duration of treatment in this group.

A limitation of this trial is the short duration of follow-up, which is a consequence of the second interim analysis being event-driven and not time-driven. Given the stringency of the protocol-specified criteria for declaring statistical significance at the time of the second interim analysis, the durability of the benefit of pembrolizumab, and results observed with long-term follow-up in other studies of pembrolizumab-based therapy in patients with metastatic NSCLC,[8,23-25] we expect that the benefit observed in the pembrolizumab-combination group will be maintained or even increase with longer follow-up. The short follow-up also precludes the identification of long-term toxic effects, although, on the basis of studies of pembrolizumab monotherapy, long-term toxic effects are not expected. This trial is being continued to evaluate long-term efficacy and safety. Another limitation is the low percentage of patients in the placebo-combination group who received a subsequent checkpoint inhibitor after treatment components were discontinued. Specific reasons for not receiving a subsequent checkpoint inhibitor were not collected and are not clear. Possible reasons include death soon after discontinuation or the decision to enter palliative care. It is likely that the percentage of patients who receive subsequent checkpoint inhibition will increase with additional follow-up.

In conclusion, the addition of pembrolizumab to standard chemotherapy with carboplatin and either paclitaxel or nab-paclitaxel in patients with previously untreated metastatic, squamous NSCLC resulted in significantly longer overall survival and progression-free survival, a higher response rate, and a longer duration of response than chemotherapy alone, regardless of the level of PD-L1 expression.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Supported by Merck Sharp & Dohme.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their families and caregivers for participating in this trial, the investigators and site personnel, and the following employees of Merck: Nicole Cecil and Nabeegha Shinwari for support in the trial conduct, Yue Shentu for assistance with statistical analysis, Saigovind Chenna and Vijetha Kode for assistance with statistical programming, Jonathan Cheng for critical review of an earlier version of the manuscript, and Melanie A. Leiby for medical writing and editorial assistance with an earlier version of the manuscript.

APPENDIX

The authors' full names and academic degrees are as follows: Luis Paz-Ares, M.D., Alexander Luft, M.D., David Vicente, M.D., Ali Tafreshi, M.D., Mahmut Gümüş, M.D., Julien Mazières, M.D., Ph.D., Barbara Hermes, M.D., Filiz Çay Şenler, M.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Jerónimo Rodríguez-Cid, M.D., Jonathan Wilson, M.D., Shunichi Sugawara, M.D., Ph.D., Terufumi Kato, M.D., Ki Hyeong Lee, M.D., Ying Cheng, M.D., Ph.D., Silvia Novello, M.D., Ph.D., Balazs Halmos, M.D., Xiaodong Li, Ph.D., Gregory M. Lubiniecki, M.D., Bilal Piperdi, M.D., and Dariusz M. Kowalski, M.D.

The authors' affiliations are as follows: Hospital Universitario 12 de Octubre, Spanish National Cancer Research Center, Universidad Complutense and Ciberonc, Madrid (L.P.-A.), and Hospital Universitario Virgen Macarena, Seville (D.V.) — both in Spain; Leningrad Regional Clinical Hospital, St. Petersburg, Russia (A.L.); Wollongong Oncology and Wollongong Private Hospital, Wollongong, NSW, Australia (A.T.); Istanbul Medeniyet University Hospital, Istanbul (M.G.), and Ankara University, Ankara (F.Ç.Ş.) — both in Turkey; Centre Hospitalier Universitaire de Toulouse, Université Paul Sabatier, Toulouse, France (J.M.); Universitätsklinikum Tübingen, Tübingen, Germany (B. Hermes); Jász-Nagykun-Szolnok County Hospital, Szolnok (T.C.), and Országos Korányi TBC és Pulmonológiai Intézet, Budapest (A.F.) — both in Hungary; Oncology Center, Medica Sur Hospital, Mexico City (J.R.-C.); Humber River Regional Hospital, Toronto (J.W.); Sendai Kousei Hospital, Sendai (S.S.), and the Kanagawa Cancer Center, Yokohama (T.K.) — both in Japan; Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheong-ju, South Korea (K.H.L.); Jilin Cancer Hospital, Changchun, China (Y.C.); University of Turin, Orbassano, Italy (S.N.); Montefiore Medical Center–Albert Einstein College of Medicine, New York (B. Halmos); Merck, Kenilworth, NJ (X.L., G.M.L., B.P.); and the Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland (D.M.K.).

REFERENCES

1. Lortet-Tieulent J, Soerjomataram I, Ferlay J, Rutherford M, Weiderpass E, Bray F. International trends in lung cancer incidence by histological subtype: adenocarcinoma stabilizing in men but still increasing in women. Lung Cancer 2014;84:13-22.
2. Cheng TY, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The international epidemiology of lung cancer: latest trends, disparities, and tumor characteristics. J Thorac Oncol 2016;11:1653-71.
3. Soldera SV, Leighl NB. Update on the treatment of metastatic squamous non-small cell lung cancer in new era of personalized medicine. Front Oncol 2017;7:50.
4. Socinski MA, Obasaju C, Gandara D, et al. Current and emergent therapy options for advanced squamous cell lung cancer. J Thorac Oncol 2018;13:165-83.
5. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol 2015;16:763-74.
6. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med 2015;373:123-35.
7. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
8. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016;375:1823-33.
9. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
10. Lopes G, Wu Y-L, Kudaba I, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥1%: open-label, phase 3 KEYNOTE-042 study. J Clin Oncol 2018;36:Suppl:LBA4. abstract.
11. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med 2018;378:2078-92.
12. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC cancer staging manual. 7th ed. New York: Springer, 2010.
13. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.
14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
15. Roach C, Zhang N, Corigliano E, et al. Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non–small-cell lung cancer. Appl Immunohistochem Mol Morphol 2016;24:392-7.
16. Cutica I, Vie GM, Pravettoni G. Personalised medicine: the cognitive side of patients. Eur J Intern Med 2014;25:685-8.
17. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415-26.
18. Govindan R, Szczesna A, Ahn MJ, et al. Phase III trial of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer. J Clin Oncol 2017;35:3449-57.
19. Jotte RM, Cappuzzo F, Vynnychenko I, et al. IMpower131: primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol 2018;36:Suppl:LBA9000. abstract.
20. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018;378:2093-104.
21. Borghaei H, Hellmann MD, Paz-Ares LG, et al. Nivolumab (nivo) + platinum-doublet chemotherapy (chemo) vs chemo as first-line (1L) treatment (Tx) for advanced non-small cell lung cancer (NSCLC) with <1% tumor PD-L1 expression: results from CheckMate 227. J Clin Oncol 2018;36:Suppl:9001. abstract.
22. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non–small-cell lung cancer. N Engl J Med 2015;372:2018-28.
23. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497-508.
24. Brahmer J, Rodriguez-Abreu D, Robinson A, et al. Updated analysis of KEYNOTE-024: pembrolizumab vs platinum-based chemotherapy for advanced NSCLC with PD-L1 TPS ≥50%. J Thorac Oncol 2017;12:Suppl 2:S1793. abstract.
25. Borghaei H, Langer CJ, Gadgeel S, et al. 24-Month overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced non-squamous non-small-cell lung cancer. J Thorac Oncol 2018 August 20 (Epub ahead of print).