

# Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score $\geq 50\%$

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**PURPOSE** We report the first 5-year follow-up of any first-line phase III immunotherapy trial for non–small-cell lung cancer (NSCLC). KEYNOTE-024 (ClinicalTrials.gov identifier: [NCT02142738](https://clinicaltrials.gov/ct2/show/study/NCT02142738)) is an open-label, randomized controlled trial of pembrolizumab compared with platinum-based chemotherapy in patients with previously untreated NSCLC with a programmed death ligand-1 (PD-L1) tumor proportion score of at least 50% and no sensitizing *EGFR* or *ALK* alterations. Previous analyses showed pembrolizumab significantly improved progression-free survival and overall survival (OS).

**METHODS** Eligible patients were randomly assigned (1:1) to pembrolizumab (200 mg once every 3 weeks for up to 35 cycles) or platinum-based chemotherapy. Patients in the chemotherapy group with progressive disease could cross over to pembrolizumab. The primary end point was progression-free survival; OS was a secondary end point.

**RESULTS** Three hundred five patients were randomly assigned: 154 to pembrolizumab and 151 to chemotherapy. Median (range) time from randomization to data cutoff (June 1, 2020) was 59.9 (55.1–68.4) months. Among patients initially assigned to chemotherapy, 99 received subsequent anti–PD-1 or PD-L1 therapy, representing a 66.0% effective crossover rate. Median OS was 26.3 months (95% CI, 18.3 to 40.4) for pembrolizumab and 13.4 months (9.4–18.3) for chemotherapy (hazard ratio, 0.62; 95% CI, 0.48 to 0.81). Kaplan-Meier estimates of the 5-year OS rate were 31.9% for the pembrolizumab group and 16.3% for the chemotherapy group. Thirty-nine patients received 35 cycles (ie, approximately 2 years) of pembrolizumab, 82.1% of whom were still alive at data cutoff (approximately 5 years). Toxicity did not increase with longer treatment exposure.

**CONCLUSION** Pembrolizumab provides a durable, clinically meaningful long-term OS benefit versus chemotherapy as first-line therapy for metastatic NSCLC with PD-L1 tumor proportion score of at least 50%.

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## INTRODUCTION

Historically, patients with advanced non–small-cell lung cancer (NSCLC) have poor prognosis despite use of platinum-based chemotherapy. For patients with distant metastases, the 5-year relative survival rate is low globally, being only 6.9% in the United States between 2010 and 2016.<sup>1,2</sup> Immunotherapy has altered the treatment approach for patients with NSCLC without oncogenic driver mutations.<sup>3</sup> Pembrolizumab, a monoclonal antibody against programmed death 1 (PD-1), has been shown in randomized controlled studies to improve overall survival (OS) versus platinum-based chemotherapy for patients with advanced or metastatic NSCLC without sensitizing *EGFR*

or *ALK* alterations when administered as monotherapy (in patients with programmed death ligand-1 [PD-L1]–positive NSCLC)<sup>4,5</sup> and when administered in combination with chemotherapy (regardless of tumor PD-L1 expression).<sup>6–9</sup>

KEYNOTE-024 is a randomized, open-label, phase III trial of pembrolizumab monotherapy versus platinum-based chemotherapy in patients with previously untreated NSCLC with PD-L1 tumor proportion score (TPS) of at least 50% and was, to our knowledge, the first phase III study to show superiority of immunotherapy over platinum-based chemotherapy in the first-line setting.<sup>10</sup> The study demonstrated significantly improved progression-free survival (PFS)

## ASSOCIATED CONTENT

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## Appendix Protocol

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

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## CONTEXT

### Key Objective

Patients with metastatic non–small-cell lung cancer (NSCLC) have a poor prognosis. We examined whether first-line treatment with pembrolizumab, an anti–programmed death 1 antibody, continued to provide improved long-term outcomes over platinum-based chemotherapy in patients with programmed death ligand-1 (PD-L1) tumor proportion score (TPS)  $\geq$  50%, without *EGFR* or *ALK* alterations.

### Knowledge Generated

Patients treated with pembrolizumab had improved 5-year overall survival rates compared with patients treated with platinum-based chemotherapy (31.9% v 16.3%).

### Relevance

Pembrolizumab continues to provide long-term improved patient outcomes over chemotherapy for patients with metastatic NSCLC with PD-L1 TPS  $\geq$  50% in the first-line treatment setting.

(hazard ratio [HR], 0.50; 95% CI, 0.37 to 0.68;  $P < .001$ ) and OS (HR, 0.60; 95% CI, 0.41 to 0.89;  $P = .005$ ) with pembrolizumab versus chemotherapy at the second interim analysis.<sup>10</sup> OS continued to be improved for pembrolizumab versus chemotherapy (HR, 0.63; 95% CI, 0.47 to 0.86) in subsequent analyses.<sup>4</sup>

Five-year survival is an important landmark in cancer treatment, but until recently there have been limited data with this length of follow-up in patients with metastatic NSCLC, in part because so few patients are alive at 5 years. In KEYNOTE-001, a single-arm phase Ib study that evaluated pembrolizumab monotherapy in patients with advanced NSCLC, the 5-year OS rate was 29.6% (95% CI, 7.7 to 56.1) among previously untreated patients with PD-L1 TPS of at least 50%.<sup>11</sup> We report 5-year efficacy and safety outcomes from KEYNOTE-024.

## METHODS

### Patients

As previously described,<sup>4,10</sup> eligible patients were  $\geq$  18 years with previously untreated stage IV NSCLC with PD-L1 TPS of at least 50%, measurable disease by RECIST v1.1, Eastern Cooperative Oncology Group performance status of 0 or 1, and life expectancy of at least 3 months.<sup>4,10</sup> Patients with sensitizing *EGFR* or *ALK* alterations, untreated brain metastases, or active autoimmune disease requiring systemic treatment or receiving systemic glucocorticoids or immunosuppressive therapy were excluded.

The Protocol (online only) was approved by institutional review boards or independent ethics committees at participating institutions. Patients provided written informed consent.

### Study Design

Patients were randomly assigned (1:1) to receive 200 mg of intravenous pembrolizumab once every 3 weeks for 35

cycles or investigator's choice of platinum chemotherapy (carboplatin/cisplatin) plus pemetrexed or gemcitabine, or carboplatin plus paclitaxel for 4 to 6 cycles.<sup>10</sup> Pemetrexed was permitted only for patients with non-squamous tumors and could be administered as maintenance therapy. Random assignment was stratified by Eastern Cooperative Oncology Group performance status (0 or 1), histology (squamous or nonsquamous), and region (East Asian or non–East Asian enrollment). Treatment continued for the specified number of cycles until progressive disease (PD; per RECIST v1.1), adverse events (AEs) of unacceptable severity, or patient withdrawal. Patients with PD were permitted to continue study treatment if the investigator determined the patient to be clinically stable and deriving benefit. Patients in the chemotherapy group could cross over to receive pembrolizumab 30 days after the last chemotherapy dose if safety eligibility criteria were met per the study Protocol: patients with PD confirmed by blinded, independent central review (BICR) were eligible to cross over before the second interim analysis; after the second interim analysis, investigator-assessed PD was required.<sup>10</sup>

Patients were eligible for a second course of pembrolizumab (up to 17 cycles) if PD occurred after completion of 35 cycles of pembrolizumab or after attaining confirmed complete response (CR) with at least 6 months of treatment and an additional two cycles of pembrolizumab after CR was achieved and anticancer therapy had not been administered since their last dose of pembrolizumab and Protocol-specified eligibility criteria were met (see the Protocol).

The primary end point was PFS (time from randomization to disease progression or death from any cause, whichever occurred first, per RECIST v1.1 by BICR). Secondary end points included evaluation of OS (time from randomization to death from any cause), objective response rate (ORR) per RECIST v1.1 by BICR, safety, and tolerability. Both PFS

and ORR are reported by investigator review because evaluation by BICR was discontinued after the second interim analysis (Protocol amendment 8). The exploratory end point PFS2, per RECIST v1.1 by investigator, was defined as time from randomization to subsequent disease progression after initiation of new anticancer therapy or death from any cause.

### Assessments

PD-L1 expression levels and AEs were assessed as previously described.<sup>10</sup> Imaging was performed every 9 weeks during the treatment phase (including during second-course treatment) and every 3 months during the follow-up phase, and patients were contacted every 2 months during survival follow-up.

### Statistical Analysis

Efficacy was assessed in the intention-to-treat population and safety in the as-treated population (patients who were randomly assigned and received at least one dose of study treatment, analyzed by treatment received). The study Protocol provided for one planned analysis of ORR and PFS and two planned analyses of OS. Exploratory analyses included outcomes in patients who completed 35 cycles of pembrolizumab and patients who received a second course of pembrolizumab. Superiority of pembrolizumab over chemotherapy for PFS and OS was determined during the second interim analysis.<sup>10</sup> The prespecified alpha was used at the second interim analysis. No alpha was assigned to the current analysis. The Kaplan-Meier method was used to estimate OS, PFS, and PFS2 as previously described.<sup>4,10</sup> A stratified Cox model with Efron's method of tie handling was used to determine HRs and 95% CIs; randomization stratification factors were applied to the Cox models.

## RESULTS

### Patient Characteristics and Treatment

A total of 305 patients were enrolled and randomly assigned to receive pembrolizumab monotherapy (n = 154) or chemotherapy (n = 151; Fig 1). All patients except one in the chemotherapy group received study treatment. Median time from randomization to data cutoff (June 1, 2020) was 59.9 months (range, 55.1-68.4 months). Median treatment durations were 7.9 months (range, 1 day-30.2 months) for the pembrolizumab group and 3.5 months (1 day-40.4 months) for the chemotherapy group. At data cutoff, no patients were continuing to receive their initially assigned study treatment. Among patients initially assigned to chemotherapy, 99 received anti-PD-1 or PD-L1 (PD-[L]1) therapy (83 crossed over to pembrolizumab on-study, and 16 additional patients received anti-PD-(L)1 therapy outside the study), representing a 66.0% effective crossover rate. In the pembrolizumab group, 80 of 154 (52.9%) received additional anticancer therapy, including 12 patients who received a second course of pembrolizumab on

study. Subsequent therapies for both treatment groups are summarized in Appendix Table A1 (online only). Patient demographics and baseline clinical characteristics are described in Table 1.

### Efficacy Outcomes in the Intention-to-Treat Population

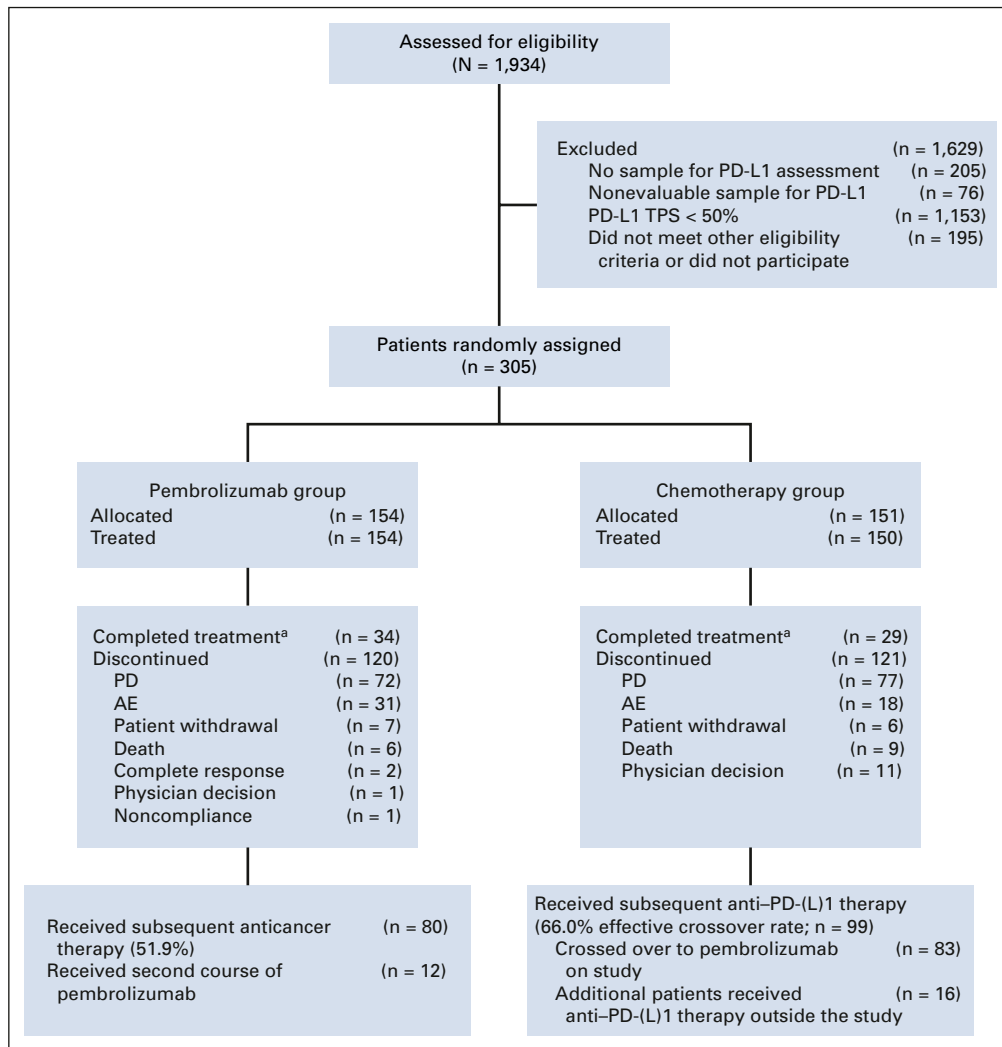
At data cutoff, 103 patients (66.9%) in the pembrolizumab group and 123 patients (81.5%) in the chemotherapy group had died. Median OS was 26.3 months (95% CI, 18.3 to 40.4 months) in the pembrolizumab group and 13.4 months (95% CI, 9.4 to 18.3 months) in the chemotherapy group (HR, 0.62; 95% CI, 0.48 to 0.81; Fig 2A). Kaplan-Meier estimates of OS at 5 years were 31.9% (95% CI, 24.5 to 39.5) in the pembrolizumab group and 16.3% (95% CI, 10.6 to 23.0) in the chemotherapy group.

In addition to patients who had CR or partial response (PR), patients who had stable disease (SD) also had OS benefit. In an exploratory analysis, median OS among patients with best response of SD was 21.1 months (95% CI, 14.1 to 34.5) for the pembrolizumab group and 14.5 months (95% CI, 8.9 to 21.1) for the chemotherapy group. In a further exploratory analysis, median OS for patients in the pembrolizumab group with treatment-related AEs leading to treatment discontinuation (n = 21) was 35.9 months (95% CI, 7.9 to NR) with a 5-year OS rate of 35.1% (95% CI, 15.7 to 55.3).

At data cutoff, 126 patients (81.8%) in the pembrolizumab group and 141 patients (93.4%) in the chemotherapy group had progressed per investigator assessment or died. Median PFS was 7.7 months (95% CI, 6.1 to 10.2 months) for patients in the pembrolizumab group versus 5.5 months (95% CI, 4.2 to 6.2 months) for patients in the chemotherapy group (HR, 0.50; 95% CI, 0.39 to 0.65; Fig 2B). Kaplan-Meier estimates of PFS at 3 and 5 years were 22.8% (95% CI, 16.3 to 29.9) and 12.8% (95% CI, 7.4 to 19.8), respectively, in the pembrolizumab group and 4.1% (95% CI, 1.3 to 9.4) and not reached (no evaluable patients) in the chemotherapy group.

The ORR by investigator review was 46.1% (71 of 154; 95% CI, 38.1 to 54.3) among patients in the pembrolizumab group versus 31.1% (47 of 151; 95% CI, 23.8 to 39.2) in the chemotherapy group (Table 2). Seven patients (4.5%) in the pembrolizumab group versus no patients in the chemotherapy group achieved a CR (Table 2). Median duration of response was 29.1 months (range, 2.2-60.8+ months) in the pembrolizumab group and 6.3 months (range, 3.1-52.4 months) in the chemotherapy group (+ indicates the response duration is censored).

Median PFS2 (time from randomization to subsequent disease progression after initiation of new anticancer therapy or death from any cause) was 24.1 months (95% CI, 15.0 to 31.4 months) in patients initially randomly assigned to pembrolizumab and 8.5 months (95% CI, 7.3 to 11.4 months) in patients initially randomly assigned to chemotherapy (HR, 0.51; 95% CI, 0.39 to 0.67). The



**FIG 1.** Disposition of patients. <sup>a</sup>Number of patients who completed treatment, as reported by investigator. AE, adverse event; PD, progressive disease; PD-L1, programmed death ligand-1; TPS, tumor proportion score.

PFS2 rate at 3 years was 39.5% (95% CI, 31.4 to 47.4) for pembrolizumab and 15.0% (95% CI, 9.4 to 21.8) for chemotherapy (Fig 3).

### Safety

No new safety signals were identified since prior analyses. Incidence of treatment-related AEs was 76.6% (grade 3-5, 31.2%) among patients who received pembrolizumab and 90.0% (grade 3-5, 53.3%) among patients who received chemotherapy (Table 3). Serious treatment-related AEs occurred in 22.7% and 20.7% of patients in the pembrolizumab and chemotherapy groups, respectively. There were two treatment-related deaths in the pembrolizumab group and three in the chemotherapy group (pembrolizumab: sudden death of unknown cause and pneumonitis; chemotherapy: pulmonary sepsis, pulmonary alveolar hemorrhage, and death of unknown cause; all previously reported).<sup>4,10</sup>

Immune-mediated AEs and infusion reactions (irrespective of attribution to study treatment by the investigator) occurred in 34.4% (grade 3-5, 13.6%) of patients who received pembrolizumab and 5.3% (grade 3-5, 0.7%) of those who received chemotherapy (Table 3).

There were no new safety signals identified with long-term follow-up. Exposure-adjusted AE rates in the total study population decreased over time in both treatment groups for treatment-related AEs and immune-mediated AEs and infusion reactions (Appendix Tables A2 and A3, online only).

### Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab

Among the patients initially assigned to pembrolizumab, 39 of 151 (25.8%) completed 35 cycles (ie, approximately 2 years) of treatment. Median (range) time from completion of 35 cycles to data cutoff was 34.7 months (31.2-44.1). Baseline characteristics of these patients were similar to the

**TABLE 1.** Patient Demographics and Baseline Clinical Characteristics

Characteristic	Pembrolizumab, n = 154	Chemotherapy, n = 151	35 Cycles of Pembrolizumab, n = 39 <sup>a</sup>	Second Course of Pembrolizumab, n = 12 <sup>b</sup>
Age, median (range), years	64.5 (33-90)	66.0 (38-85)	61.0 (43-80)	60.0 (43-77)
Sex				
Male	92 (59.7)	95 (62.9)	25 (64.1)	8 (66.7)
Female	62 (40.3)	56 (37.1)	14 (35.9)	4 (33.3)
ECOG performance status				
0	54 (35.1)	53 (35.1)	16 (41.0)	3 (25.0)
1	99 (64.3)	98 (64.9)	23 (59.0)	9 (75.0)
2	1 (0.6)	0 (0.0)	0	0 (0.0)
Region of enrollment				
East Asia	21 (13.6)	19 (12.6)	8 (20.5)	3 (25.0)
Non-East Asia	133 (86.4)	132 (87.4)	31 (79.5)	9 (75.0)
Histology				
Squamous	29 (18.8)	27 (17.9) <sup>c</sup>	2 (5.1)	1 (8.3)
Nonsquamous	125 (81.2)	124 (82.1)	37 (94.9)	11 (91.7)
Smoking status				
Current	34 (22.1)	31 (20.5)	8 (20.5)	2 (16.7)
Former	115 (74.7)	101 (66.9)	29 (74.4)	10 (83.3)
Never	5 (3.2)	19 (12.6)	2 (5.1)	0 (0.0)
Treated brain metastases	18 (11.7)	10 (6.6)	9 (23.1)	1 (8.3)
Prior neoadjuvant therapy	3 (1.9)	1 (0.7)	0	0
Prior adjuvant therapy	6 (3.9)	3 (2.0)	0	0

NOTE. Values are presented as No. (%) unless noted otherwise.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup>Includes only those patients initially allocated to pembrolizumab who received 35 cycles of pembrolizumab according to actual exposure assessment.

<sup>b</sup>Includes only those patients initially allocated to pembrolizumab who received a second course of pembrolizumab therapy according to actual exposure assessment.

<sup>c</sup>Includes patients with squamous cell carcinoma and poorly differentiated squamous cell carcinoma.

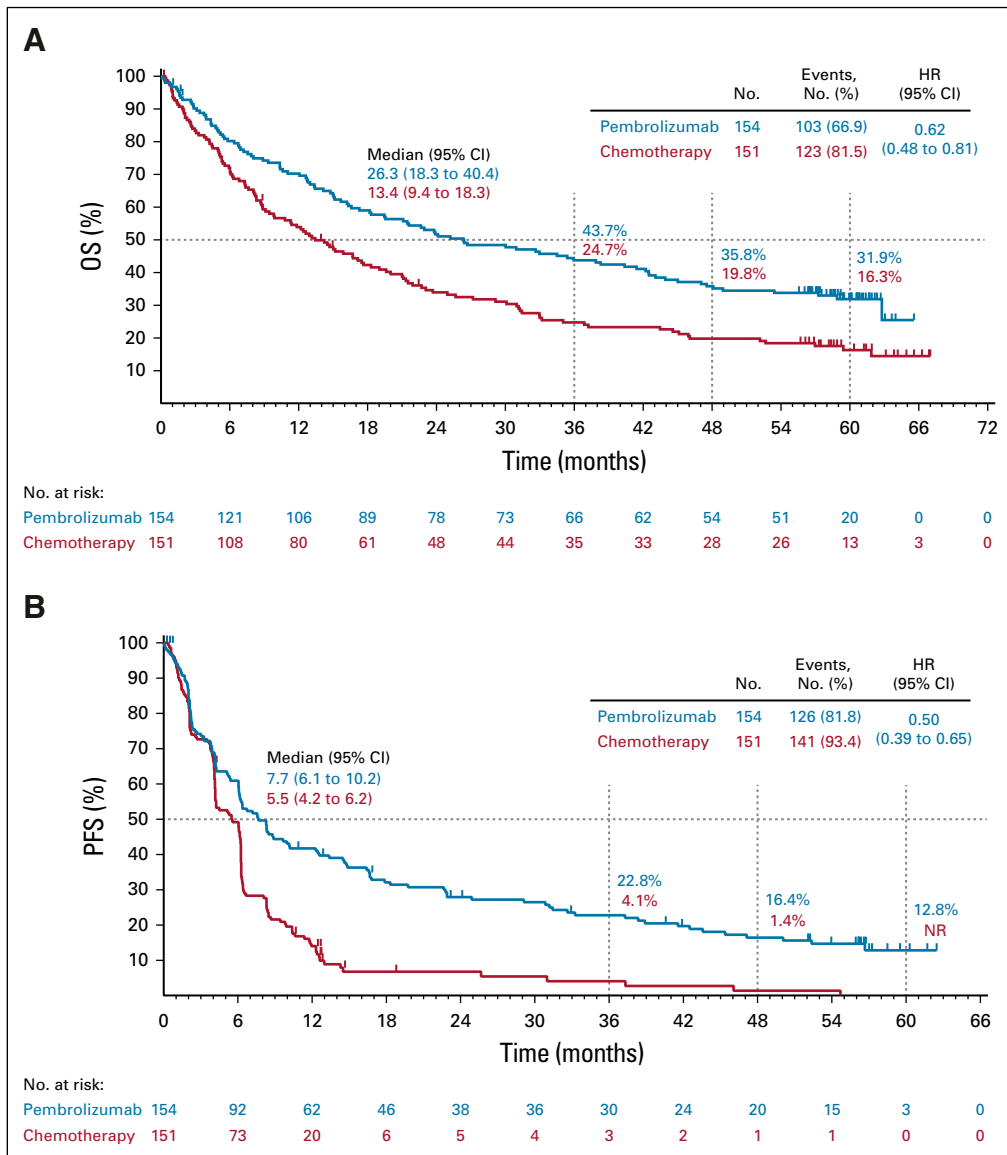
total study population (Table 1). Among these patients, 82.1% experienced a response, per RECIST v1.1 per investigator assessment (Fig 4A). Best response was CR in four patients (10.3%), PR in 28 (71.8%), SD in six (15.4%), and PD in one (2.6%). At data cutoff, 32 of 39 patients were alive and the OS rate at 36 months from completion of 35 cycles of pembrolizumab (ie, approximately 5 years) was 81.4% (95% CI, 64.7 to 90.7). Of 39 patients, 18 (46.2%) were alive without PD or subsequent therapy for NSCLC. One patient developed a second malignancy (gastric cancer) and was treated accordingly.

Among patients who completed 35 cycles, treatment-related AEs occurred in 87.2% (grade 3-4, 15.4%; no grade 5 events), which was consistent with the overall as-treated population. Treatment-related grade 3-4 AEs were diarrhea, autoimmune hepatitis, increased gamma-glutamyltransferase, hyperglycemia, type 2 diabetes mellitus, tubulointerstitial nephritis, and rash (all n = 1). Consistent with the all patients as-treated population, incidence of immune-mediated AEs and infusion reactions

was 30.8%, with grade 3-4 comprising 7.7% (one each of hepatitis, nephritis, and severe skin toxicity) and no grade 5 events.

#### Outcomes Among Patients Who Received a Second Course of Pembrolizumab

Twelve patients received a second course of pembrolizumab after an assessment of PD by the investigator. Median (range) time from last dose of second course to data cutoff was 15.2 months (0.4-29.6). Among these 12 patients, eight (66.7%) were alive at data cutoff. Four (33.3%) had an objective response after starting second-course pembrolizumab (all PRs) and six (50.0%) had SD as their best response per investigator assessment (Fig 4B). One patient experienced PD after receiving a second course of pembrolizumab, and one patient was not evaluable. At data cutoff, five patients (41.7%) were alive without PD and three (25.0%) had not received subsequent therapy. Five patients (41.7%) had treatment-related AEs during the second course; all were grade 1 or 2 and one



**FIG 2.** Kaplan-Meier estimates of (A) OS and (B) PFS in the pembrolizumab group and the chemotherapy group. For each treatment group, the Kaplan-Meier method was used to estimate OS and PFS, with censoring of data for patients alive or lost to follow-up at the time of last contact for OS or without disease progression or death at last disease assessment without documented disease progression prior to initiation of second-line therapy for PFS. Tick marks indicate censoring times. HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

event, grade 1 hypothyroidism, was an immune-mediated AE.

**DISCUSSION**

First-line pembrolizumab monotherapy produced clinically meaningful improvements in OS, PFS, ORR, and durable responses versus platinum-based chemotherapy among patients with metastatic NSCLC with PD-L1 TPS of at least 50% without sensitizing *EGFR* or *ALK* alterations. Notably, the 5-year OS rate in the pembrolizumab group (31.9%) was approximately double that in the chemotherapy group

(16.3%), and median OS was more than 1 year longer in the pembrolizumab group (26.3 months) than in the chemotherapy group (13.4 months; HR, 0.62; 95% CI, 0.48 to 0.81). In addition to those with an objective response, pembrolizumab also improved OS among patients with a best-response assessment of SD. These data confirm the 5-year OS outcomes in the single-arm KEYNOTE-001 study among previously untreated patients with PD-L1 TPS of at least 50% and represent a clinically meaningful improvement in survival for patients whose prognosis has historically been very poor.<sup>1,11</sup>

**TABLE 2.** Objective Response in the Intention-to-Treat Population<sup>a</sup>

Response	Pembrolizumab, n = 154	Chemotherapy, n = 151
Objective response, No. (%)	71 (46.1)	47 (31.1)
95% CI	38.1 to 54.3	23.8 to 39.2
Best objective response, No. (%)		
CR	7 (4.5)	0
PR	64 (41.6)	47 (31.1)
SD	37 (24.0)	60 (39.7)
PD	35 (22.7)	25 (16.6)
Not evaluable	0	1 (0.7)
No assessment	11 (7.1)	18 (11.9)
Time to response, median (range), months	2.1 (1.4-14.6)	2.1 (1.1-12.2)
DOR, median (range), months	29.1 (2.2-60.8+)	6.3 (3.1-52.4)

NOTE. + indicates response duration is censored.

Abbreviations: CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

<sup>a</sup>Per RECIST v1.1 by investigator review. Data cutoff: June 1, 2020.

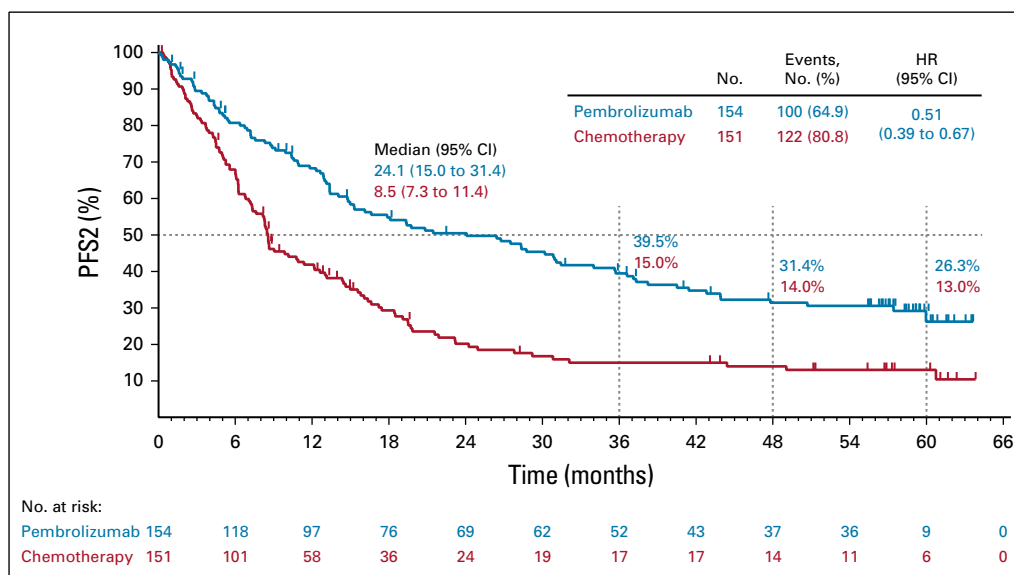
The magnitude of treatment effect for first-line pembrolizumab is notable given that the majority of patients (66.0%) in the chemotherapy group received subsequent anti-PD-(L)1 therapy. This high effective crossover rate may have reduced the observed treatment effect for pembrolizumab versus chemotherapy given that immunotherapy agents (including pembrolizumab) have demonstrated improved OS over chemotherapy in the second-line or later setting.<sup>12-16</sup> In a prior analysis, we showed that when OS for patients in the chemotherapy group of KEYNOTE-024 was adjusted for crossover using a

simplified 2-stage model, the HR for OS was 0.49 (95% CI, 0.34 to 0.69).<sup>4</sup> With a doubling of the median OS and the improvement in PFS2 among patients who received pembrolizumab, these data continue to support a first-line immunotherapy approach, which permits early inhibition of PD-1 signaling, in this patient population.

The long-term efficacy of pembrolizumab was further demonstrated by analysis of outcomes in the 39 patients who completed 35 cycles of pembrolizumab: 82.1% of patients were alive at data cutoff, and 46.2% were alive without PD or subsequent therapy. These data support duration of treatment of up to 2 years with pembrolizumab.

Analysis of outcomes for patients on a second course of pembrolizumab showed such treatment was not only feasible but also associated with antitumor activity. Of the 12 patients who subsequently progressed and received a second course of pembrolizumab, two-thirds were alive at data cutoff. Notably, five of 12 were alive without PD. These data support pembrolizumab re-treatment upon PD.

Pembrolizumab was well-tolerated and was associated with a lower incidence of treatment-related AEs (any-grade and grade 3-5 toxicities) than platinum-based chemotherapy in the as-treated population and patients who completed 35 cycles. We did not identify new safety signals with long-term follow-up, and there was no evidence of increasing toxicity during long-term follow-up. Additionally, analysis of patients who discontinued pembrolizumab treatment because of treatment-related AEs revealed a median OS of 35.9 months, demonstrating favorable outcomes could occur in patients with early discontinuation because of AEs. Among patients who completed 35 cycles of pembrolizumab, treatment-related AEs were similar to those



**FIG 3.** Kaplan-Meier estimates of PFS2 for each treatment group, with censoring of data at the time of last contact for patients alive without receiving second-line therapy, stopping second-line therapy without disease progression, and not initiating third-line therapy. Tick marks indicate censoring times. HR, hazard ratio; PFS, progression-free survival.

**TABLE 3.** Adverse Events<sup>a</sup>

<b>AE</b>	<b>Pembrolizumab, n = 154</b>		<b>Chemotherapy, n = 150</b>	
<b>Treatment-related AEs<sup>b</sup></b>				
Any grade	118 (76.6)		135 (90.0)	
Grades 3-5	48 (31.2)		80 (53.3)	
Serious	35 (22.7)		31 (20.7)	
Led to discontinuation	21 (13.6)		16 (10.7)	
Led to death	2 (1.3)		3 (2.0)	
<b>Treatment-related AEs occurring in ≥ 10% of patients in either group</b>	<b>Any grade</b>	<b>Grade 3 or 4<sup>c</sup></b>	<b>Any grade</b>	<b>Grade 3 or 4<sup>c</sup></b>
Nausea	15 (9.7)	0	65 (43.3)	3 (2.0)
Anemia	8 (5.2)	2 (1.3)	66 (44.0)	29 (19.3)
Fatigue	22 (14.3)	3 (1.9)	43 (28.7)	5 (3.3)
Decreased appetite	15 (9.7)	0	39 (26.0)	4 (2.7)
Diarrhea	25 (16.2)	6 (3.9)	21 (14.0)	2 (1.3)
Neutropenia	1 (0.6)	0	33 (22.0)	20 (13.3)
Vomiting	4 (2.6)	1 (0.6)	30 (20.0)	1 (0.7)
Pyrexia	18 (11.7)	0	9 (6.0)	0
Pruritus	20 (13.0)	0	4 (2.7)	0
Constipation	6 (3.9)	0	17 (11.3)	0
Neutrophil count decreased	1 (0.6)	0	21 (14.0)	7 (4.7)
Stomatitis	4 (2.6)	0	18 (12.0)	2 (1.3)
Blood creatinine increased	5 (3.2)	1 (0.6)	16 (10.7)	1 (0.7)
Rash	17 (11.0)	3 (1.9)	3 (2.0)	0
Platelet count decreased	0	0	18 (12.0)	10 (6.7)
WBC count decreased	1 (0.6)	0	17 (11.3)	4 (2.7)
Thrombocytopenia	0	0	16 (10.7)	8 (5.3)
<b>AEs with possible immune etiology occurring in &gt; 0% of patients</b>	<b>Any grade</b>	<b>Grade 3, 4, or 5<sup>d</sup></b>	<b>Any grade</b>	<b>Grade 3, 4, or 5<sup>d</sup></b>
Any	53 (34.4)	21 (13.6)	8 (5.3)	1 (0.7)
Colitis	6 (3.9)	3 (1.9)	0	0
Hepatitis	2 (1.3)	2 (1.3)	0	0
Hyperthyroidism	11 (7.1)	0	2 (1.3)	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Hypothyroidism	16 (10.4)	0	3 (2.0)	0
Infusion reactions	8 (5.2)	1 (0.6)	2 (1.3)	0
Myositis	3 (1.9)	0	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0
Pancreatitis	1 (0.6)	1 (0.6)	0	0
Pneumonitis	13 (8.4)	5 (3.2)	1 (0.7)	1 (0.7)
Severe skin toxicity	6 (3.9)	6 (3.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)	0	0
Uveitis	1 (0.6)	1 (0.6)	0	0

NOTE. All values are presented as No. (%).

Abbreviation: AE, adverse event.

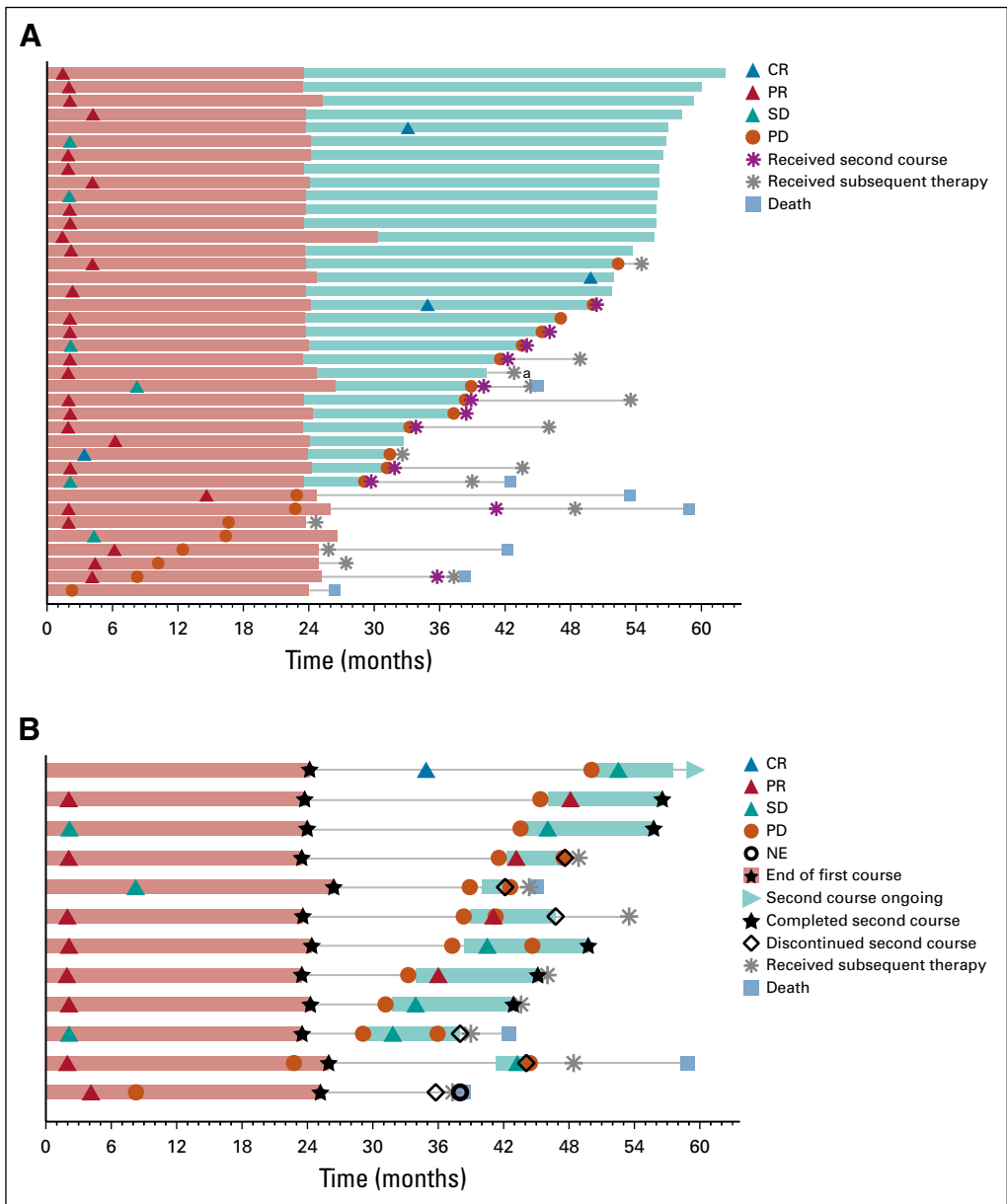
<sup>a</sup>AEs occurring from randomization to 30 days after final dose of initially assigned treatment (90 days for serious AEs).

<sup>b</sup>Relationship to treatment assessed by investigators.

<sup>c</sup>Two grade 5 treatment-related AEs occurred in the pembrolizumab group (pneumonitis and sudden death) and three in the chemotherapy group (pulmonary sepsis, death, and pulmonary alveolar hemorrhage).

<sup>d</sup>One grade 5 immune-mediated AE occurred in the pembrolizumab group (pneumonitis); there were no grade 5 immune-mediated AEs in the chemotherapy group.





**FIG 4.** Treatment duration and time to response in (A) patients completing 35 cycles of pembrolizumab treatment and (B) patients who received a second course of pembrolizumab treatment. Light red bars indicate the first course of pembrolizumab treatment duration. Light teal bars indicate the (A) first course follow-up duration or (B) second course of treatment duration. Follow-up was defined as the time to progression or last nonprogression assessment by investigator. Response was assessed by RECIST v1.1 per investigator review. The maximum treatment duration for the second course was 17 cycles. <sup>a</sup>Patient developed a secondary malignancy. CR, complete response; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

observed in the trial overall, with a similar incidence of grade 3 and 4 events and no deaths. Together with improvements in efficacy outcomes, the lower toxicity with pembrolizumab versus chemotherapy supports the improved or maintained patient-reported quality-of-life outcomes in the pembrolizumab group that have been previously reported.<sup>17</sup>

KEYNOTE-024 underscores the importance of pembrolizumab in first-line treatment of metastatic NSCLC. In an effort to extend the benefit of pembrolizumab to other patient populations, the KEYNOTE-042 study showed an OS benefit over chemotherapy in patients with advanced NSCLC and TPS > 1% without sensitizing *EGFR* or *ALK* alterations.<sup>5</sup> Furthermore, first-line pembrolizumab plus

chemotherapy also showed improved OS versus placebo plus chemotherapy for both nonsquamous (KEYNOTE-189) and squamous (KEYNOTE-407) metastatic NSCLC without *EGFR* or *ALK* alterations irrespective of tumor PD-L1 expression.<sup>8,9,18,19</sup> Studies evaluating other anti-PD-(L)1 therapies have also shown improvements in OS among patients with advanced or metastatic NSCLC (albeit with shorter follow-up than KEYNOTE-024), either as monotherapy or in combination with chemotherapy and/or antiangiogenic or anti-CTLA-4 agents.<sup>20-24</sup>

Epidemiologic data are beginning to show the effects of new therapies on the lung cancer disease state. Howlader et al recently described a substantial decrease in lung cancer mortality in the United States: incidence-based mortality from 2006 to 2013 decreased annually by 3.2% for men but improved more rapidly from 2013 to 2016, with an annual 6.3% decrease.<sup>25</sup> For women, incidence-based mortality decreased by 2.3% annually from 2006 to 2014 and then by 5.9% annually from 2014 to 2016. They

concluded that this decrease in mortality was likely because of the targeted agents that became available to treat patients with *EGFR* and *ALK* mutations (only a subset of patients with NSCLC are in this category). Five-year outcomes in KEYNOTE-024 suggest that availability of immunotherapy may result in further improvement in lung cancer survival at the population level and that pembrolizumab may be transforming metastatic NSCLC into a treatable chronic disease for patients who meet eligibility criteria.

In summary, these 5-year outcomes from the phase III KEYNOTE-024 study, which, to our knowledge, is the first randomized trial evaluating pembrolizumab in this setting, show the ability of this treatment to improve long-term outcomes for patients with NSCLC. Pembrolizumab provided a durable and clinically relevant long-term OS benefit versus chemotherapy as first-line therapy for metastatic NSCLC with PD-L1 TPS of at least 50% and is a standard-of-care therapy in this setting.

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## DATA SHARING STATEMENT

Merck Sharp & Dohme Corp (MSD), a subsidiary of Merck & Co, Inc, Kenilworth, NJ, is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data-sharing website (available at [http://engagezone.msd.com/ds\\_documentation.php](http://engagezone.msd.com/ds_documentation.php)) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and European Union or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or construct biomarker covariates and add them

to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score  $\geq$  50%**

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## APPENDIX

TABLE A1. Subsequent Therapies

Therapy	Pembrolizumab, n = 154	Chemotherapy, n = 151
With one or more subsequent oncologic treatment	77 (50.0) <sup>a</sup>	103 (68.2)
Alectinib	0	1 (0.7)
Antiangiogenic agent	3 (1.9)	2 (1.3)
Bevacizumab	2 (1.3)	1 (0.7)
Ramucirumab	1 (0.6)	1 (0.7)
Chemotherapy	2 (1.3)	2 (1.3)
Cyclophosphamide + epirubicin + vincristine	0	1 (0.7)
Fluorouracil + leucovorin calcium + oxaliplatin	1 (0.6)	0
Fluorouracil + folinic acid + oxaliplatin	1 (0.6)	0
Gemcitabine + vinorelbine tartrate	1 (0.6)	1 (0.7)
Immunotherapy	20 (13.0)	99 (65.6)
Anti-GITR monoclonal antibody (unspecified) + nivolumab	2 (1.3)	0
Atezolizumab	2 (1.3)	2 (1.3)
Avelumab	0	1 (0.7)
Avelumab + utomilumab	0	1 (0.7)
Durvalumab	1 (0.6)	0
Guadecitabine + pembrolizumab	1 (0.6)	0
Ipilimumab + nivolumab	0	1 (0.7)
Nivolumab	5 (3.2)	10 (6.6)
Pembrolizumab	11 (7.1)	12 (7.9)
Pembrolizumab (in study crossover)	0	83 (55.0)
Oncologic surgery	8 (5.2)	8 (5.3)
Platinum doublet chemotherapy with or without bevacizumab	57 (37.0)	8 (5.3)
Bevacizumab + carboplatin + paclitaxel	3 (1.9)	0
Bevacizumab + carboplatin + paclitaxel albumin	1 (0.6)	0
Bevacizumab + carboplatin + pemetrexed disodium	2 (1.3)	1 (0.7)
Bevacizumab + cisplatin + pemetrexed disodium	1 (0.6)	0
Carboplatin + docetaxel	0	1 (0.7)
Carboplatin + gemcitabine	13 (8.4)	2 (1.3)
Carboplatin + irinotecan hydrochloride	1 (0.6)	0
Carboplatin + paclitaxel	8 (5.2)	2 (1.3)
Carboplatin + paclitaxel albumin	2 (1.3)	1 (0.7)
Carboplatin + pemetrexed disodium	22 (14.3)	0
Carboplatin + vinorelbine tartrate	2 (1.3)	1 (0.7)
Cisplatin + etoposide	1 (0.6)	0
Cisplatin + gemcitabine	2 (1.3)	0
Cisplatin + paclitaxel	1 (0.6)	0
Cisplatin + pemetrexed disodium	7 (4.5)	0
Pemetrexed disodium + platinum	1 (0.6)	0

(continued on following page)

**TABLE A1.** Subsequent Therapies (continued)

Therapy	Pembrolizumab, n = 154	Chemotherapy, n = 151
Radiation therapy	14 (9.1)	6 (4.0)
Single-agent chemotherapy with or without antiangiogenic agent	31 (20.1)	43 (28.5)
Amrubicin hydrochloride	0	1 (0.7)
Bevacizumab + paclitaxel albumin	1 (0.6)	0
Bevacizumab + pemetrexed disodium	2 (1.3)	1 (0.7)
Cytarabine	1 (0.6)	0
Dexamethasone + docetaxel	0	1 (0.7)
Docetaxel	7 (4.5)	27 (17.9)
Docetaxel + ramucirumab	3 (1.9)	2 (1.3)
Gemcitabine	1 (0.6)	7 (4.6)
Gimeracil + oteracil potassium + tegafur	1 (0.6)	5 (3.3)
Irinotecan hydrochloride	0	2 (1.3)
Paclitaxel	3 (1.9)	2 (1.3)
Paclitaxel albumin	0	1 (0.7)
Paclitaxel disodium	18 (11.7)	5 (3.3)
Tegafur	1 (0.6)	0
Vinorelbine tartrate	2 (1.3)	7 (4.6)
Single-agent platinum	4 (2.6)	1 (0.7)
Carboplatin	4 (2.6)	0
Cisplatin	2 (1.3)	1 (0.7)
Targeted therapy with or without taxane	7 (4.5)	8 (5.3)
Cabozantinib	1 (0.6)	1 (0.7)
Capmatinib	0	1 (0.7)
Custirsen sodium + docetaxel	0	1 (0.7)
Dabrafenib mesylate + trametinib dimethyl sulfoxide	1 (0.6)	0
Dexamethasone + docetaxel + nintedanib	1 (0.6)	0
Docetaxel + nintedanib	1 (0.6)	2 (1.3)
Erlotinib hydrochloride	2 (1.3)	2 (1.3)
Luminespib mesylate	0	1 (0.7)
Osimertinib mesylate	1 (0.6)	0
Other	3 (1.9)	3 (2.0)
Cabazitaxel	1 (0.6)	0
Cytarabine + daunorubicin + prednisone + thioguanine	0	1 (0.7)
Dendritic cell vaccine (unspecified)	0	2 (1.3)
Investigational drug (unspecified)	0	1 (0.7)
Letrozole	1 (0.6)	0
Preladenant	1 (0.6)	0

<sup>a</sup>Three additional patients received a second course of pembrolizumab but no other subsequent therapy. Twelve patients received a second course of pembrolizumab.

**TABLE A2.** Exposure-Adjusted AE Rates for Most Common Treatment-Related AEs That Occurred in > 15% of Patients in Either Group

AE	Pembrolizumab				Chemotherapy			
	0-3	3-6	6-12	> 12	0-3	3-6	6-12	> 12
Diarrhea	25 (16.2)				21 (14.0)			
Fatigue	22 (14.3)				43 (28.7)			
Pruritus	20 (13.0)				4 (2.7)			
Nausea	15 (9.7)				65 (43.3)			
Decreased appetite	15 (9.7)				39 (26.0)			
Anemia	8 (5.2)				66 (44.0)			
Vomiting	4 (2.6)				30 (20.0)			
Neutropenia	1 (0.6)				33 (22.0)			
Observation period, months	0-3	3-6	6-12	> 12	0-3	3-6	6-12	> 12
Exposed at the start of interval, No.	154	115	96	66	150	101	40	15
Total exposure, person-months	412.1	318.6	472.9	663.6	387.6	209.0	140.7	65.5
Total events (rate per 100 person-months) <sup>a</sup>	317 (76.9)	114 (35.8)	97 (20.5)	77 (11.6)	827 (213.4)	143 (68.4)	96 (68.2)	7 (10.7)
Diarrhea	16 (3.9)	9 (2.8)	8 (1.7)	2 (0.3)	20 (5.2)	2 (1.0)	3 (2.1)	1 (1.5)
Fatigue	15 (3.6)	4 (1.3)	4 (0.8)	2 (0.3)	63 (16.3)	5 (2.4)	7 (5.0)	1 (1.5)
Pruritus	14 (3.4)	3 (0.9)	6 (1.3)	6 (0.9)	4 (1.0)	0	0	0
Nausea	14 (3.4)	5 (1.6)	2 (0.4)	0	90 (23.2)	16 (7.7)	14 (9.9)	1 (1.5)
Decreased appetite	11 (2.7)	3 (0.9)	1 (0.2)	0	47 (12.1)	4 (1.9)	3 (2.1)	0
Anemia	4 (1.0)	3 (0.9)	0	1 (0.2)	68 (17.5)	10 (4.8)	9 (6.4)	0
Vomiting	4 (1.0)	3 (0.9)	0	0	38 (9.8)	6 (2.9)	10 (7.1)	0
Neutropenia	1 (0.2)	1 (0.3)	1 (0.2)	0	44 (11.4)	11 (5.3)	8 (5.7)	0

NOTE. Values are presented as No. (%) unless noted otherwise.

Abbreviation: AE, adverse event.

<sup>a</sup>Data show AEs and include multiple occurrences of events. Data cutoff: June 1, 2020.

**TABLE A3.** Exposure-Adjusted AE Rates for Most Common Immune-Mediated AEs That Occurred in > 5% of Patients in Either Group

AE	Pembrolizumab				Chemotherapy			
	0-3	3-6	6-12	> 12	0-3	3-6	6-12	> 12
Hypothyroidism	16 (10.4)				3 (2.0)			
Pneumonitis	13 (8.4)				1 (0.7)			
Hyperthyroidism	11 (7.1)				2 (1.3)			
Observation period, months	0-3	3-6	6-12	> 12	0-3	3-6	6-12	> 12
Exposed at the start of interval, No.	154	115	96	66	150	101	40	15
Total exposure, person-months	412.1	318.6	472.9	663.6	387.6	209.0	140.7	65.5
Total events (rate per 100 person-months) <sup>a</sup>	42 (10.2)	13 (4.1)	12 (2.5)	10 (1.5)	8 (2.1)	1 (0.5)	1 (0.7)	0
Hypothyroidism	9 (2.2)	6 (1.9)	0	1 (0.2)	3 (0.8)	0	0	0
Pneumonitis	6 (1.5)	2 (0.6)	4 (0.8)	2 (0.3)	1 (0.3)	0	0	0
Hyperthyroidism	10 (2.4)	1 (0.3)	1 (0.2)	0	1 (0.3)	1 (0.5)	1 (0.7)	0

NOTE. Values are presented as No. (%) unless noted otherwise.

Abbreviation: AE, adverse event.

<sup>a</sup>Data show AEs and include multiple occurrences of events. Data cutoff: June 1, 2020.