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Updated analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater

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Abstract

PURPOSE In the randomized, open-label, phase III KEYNOTE-024 study, pembrolizumab significantly improved progression-free survival and overall survival (OS) compared with platinum-based chemotherapy in patients with previously untreated advanced non-small-cell lung cancer (NSCLC) with a programmed death ligand 1 tumor proportion score of 50% or greater and without EGFR/ALK aberrations. We report an updated OS and tolerability analysis, including analyses adjusting for potential bias introduced by crossover from chemotherapy to pembrolizumab.

PATIENTS AND METHODS Patients were randomly assigned to pembrolizumab 200 mg every 3 weeks (for up to 2 years) or investigator's choice of platinum-based chemotherapy (four to six cycles). Patients assigned to chemotherapy could cross over to pembrolizumab upon meeting eligibility criteria. The primary end point was progression-free survival; OS was an important key secondary end point. Crossover adjustment analysis was done using the following three methods: simplified two-stage method, rank-preserving structural failure time, and inverse probability of censoring weighting.

RESULTS Three hundred five patients were randomly assigned (pembrolizumab, n = 154; chemotherapy, n = 151). At data cutoff (July 10, 2017; median follow-up, 25.2 months), 73 patients in the pembrolizumab arm and 96 in the chemotherapy arm had died. Median OS was 30.0 months (95% CI, 18.3 months to not reached) with pembrolizumab and 14.2 months (95% CI, 9.8 to 19.0 months) with chemotherapy (hazard ratio, 0.63; 95% CI, 0.47 to 0.86). Eighty-two patients assigned to chemotherapy crossed over on study to receive pembrolizumab. When adjusted for crossover using the two-stage method, the hazard ratio for OS for pembrolizumab versus chemotherapy was 0.49 (95% CI, 0.34 to 0.69); results using rank-preserving structural failure time and inverse probability of censoring weighting were similar. Treatment-related grade 3 to 5 adverse events were less frequent with pembrolizumab compared with chemotherapy (31.2% v 53.3%, respectively).

CONCLUSION With prolonged follow-up, first-line pembrolizumab monotherapy continues to demonstrate an OS benefit over chemotherapy in patients with previously untreated, advanced NSCLC without EGFR/ALK aberrations, despite crossover from the control arm to pembrolizumab as subsequent therapy.

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Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater

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PURPOSE In the randomized, open-label, phase III KEYNOTE-024 study, pembrolizumab significantly improved progression-free survival and overall survival (OS) compared with platinum-based chemotherapy in patients with previously untreated advanced non–small-cell lung cancer (NSCLC) with a programmed death ligand 1 tumor proportion score of 50% or greater and without *EGFR/ALK* aberrations. We report an updated OS and tolerability analysis, including analyses adjusting for potential bias introduced by crossover from chemotherapy to pembrolizumab.

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CONCLUSION With prolonged follow-up, first-line pembrolizumab monotherapy continues to demonstrate an OS benefit over chemotherapy in patients with previously untreated, advanced NSCLC without *EGFR/ALK* aberrations, despite crossover from the control arm to pembrolizumab as subsequent therapy.

INTRODUCTION

KEYNOTE-024 (ClinicalTrials.gov identifier: NCT02142738) is an international, randomized, open-label, phase III study of pembrolizumab monotherapy versus platinum-based chemotherapy in patients with previously untreated advanced non–small-cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1) tumor proportion score (TPS) of 50% or greater and without *EGFR* mutation or *ALK* translocation.[1] At the

second preplanned interim analysis (median follow-up, 11.2 months), pembrolizumab was associated with significantly improved progression-free survival (PFS; hazard ratio [HR], 0.50; 95% CI, 0.37 to 0.68; one-sided $P < .001$) and overall survival (OS; HR, 0.60; 95% CI, 0.41 to 0.89; one-sided $P = .005$). Median OS was not reached (NR) in either arm. Importantly, pembrolizumab was generally well tolerated. On the basis of these results, the independent

data and safety monitoring committee recommended the trial be stopped early to allow for use of pembrolizumab in patients randomly assigned to chemotherapy. The improvement in OS occurred despite the study design allowing patients randomly assigned to chemotherapy to cross over to pembrolizumab. The observed treatment effect was potentially attenuated because many patients participated in this crossover.

We report an updated analysis of OS and other efficacy and safety outcomes after a median follow-up of 25.2 months. In addition, we describe outcomes among patients who crossed over from chemotherapy to pembrolizumab per protocol and analyses that adjusted for potential bias introduced by treatment crossover.

PATIENTS AND METHODS

Patients

As described previously,[1] adult patients eligible for enrollment had untreated stage IV NSCLC with PD-L1 TPS of 50% or greater, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 or lower, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,[2] and life expectancy of 3 months or longer. Patients were excluded if they had sensitizing *EGFR* mutations, *ALK* translocations, untreated brain metastases, or active autoimmune disease requiring systemic therapy or were receiving systemic glucocorticoids or other immunosuppressive therapy.

Patients provided written informed consent. The protocol (MK-3475-024-06) was approved by the institutional review boards or independent ethics committees of the participating institutions, and the trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Study Design

Eligible patients were randomly assigned (1:1; stratified by ECOG PS of 0 *v* 1, squamous *v* nonsquamous histology, East Asian *v* non–East Asian enrollment site) to receive intravenous pembrolizumab (200 mg every 3 weeks) for 35 cycles (2 years) or investigator's choice of platinum-based chemotherapy (carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel; pemetrexed-containing regimens were only permitted for patients with nonsquamous disease) for four to six cycles, in the absence of radiologic disease progression (per RECIST), treatment-related adverse events (AEs) of unacceptable severity, or patient withdrawal. Pemetrexed-containing chemotherapy regimens and subsequent use of pemetrexed as maintenance therapy were permitted for patients with nonsquamous tumors. Patients assigned to chemotherapy could cross over to pembrolizumab (starting 30 days or more after last chemotherapy dose) if safety eligibility criteria were met; before the second interim analysis that

revealed superiority, only patients with progressive disease confirmed by blinded, independent, central radiology review were eligible. The protocol did not include pre-planned crossover from pembrolizumab to chemotherapy or postprogression treatment guidelines for pembrolizumab recipients. Patients in either arm who were clinically stable and considered by the investigator to be deriving clinical benefit could continue therapy after disease progression.

The primary end point was PFS (time since random assignment to disease progression or death from any cause, whichever occurred first). OS (time since random assignment to death from any cause) was an important secondary end point; objective response rate (ORR; confirmed complete and partial responses) and safety were other secondary end points. Exploratory end points included duration of response (DOR), patient-reported outcomes,[3] and time since random assignment to objective tumor progression on next-line treatment or death from any cause, whichever occurred first.[4]

Assessments

As described previously,[1] PD-L1 expression was assessed in formalin-fixed tumor samples (from core-needle or excisional biopsy or tissue resected at time of diagnosis of metastatic disease) using the PD-L1 IHC 22C3 pharmDx assay (Agilent, Santa Clara, CA).[5,6] Imaging studies were performed every 9 weeks. Response was assessed per RECIST version 1.1 by blinded, independent, central radiology review (stopped after the second interim analysis [protocol amendment 6]) and by investigator assessment. Patients were contacted every 2 months during follow-up to evaluate OS. All AEs occurring from random assignment until 30 days after the last dose of study treatment (90 days for serious AEs) were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The sponsor reviewed all AEs and condensed several AE preferred terms that suggested an immune-mediated etiology for specific categories, regardless of investigator-assessed attribution of the event.

Statistical Analysis

The final protocol-specified OS analysis was to occur after approximately 170 patients had died, providing approximately 75% power to observe an HR of less than 1, assuming approximately 70% of the patients in the chemotherapy arm crossed over to pembrolizumab. Because OS benefit was confirmed at the second interim analysis (data cutoff, May 9, 2016; 108 of 305 patients had died), this final analysis was not subjected to multiplicity control. Efficacy was assessed in the intent-to-treat population (all randomly assigned patients), and safety was assessed in the as-treated population (patients who were randomly assigned and received one or more doses of study treatment, analyzed by treatment received). The Kaplan-Meier method was used to estimate OS, with censoring of data for patients alive or lost to follow-up at time of last contact.

Between-group difference in OS was assessed using a stratified log-rank test. HRs and associated 95% CIs were assessed using a stratified Cox proportional hazards model with Efron's method of handling ties. Randomization stratification factors were applied to the stratified log-rank and Cox models. After crossover to pembrolizumab, DOR was summarized using the Kaplan-Meier method for patients with confirmed complete or partial responses in this phase.

Additional analyses for OS, intended to complement the intent-to-treat analysis, were conducted to estimate the treatment difference between pembrolizumab and chemotherapy adjusted for crossover. The following three statistical methods were applied: the simplified two-stage, rank-preserving structural failure time (RPSFT), and inverse probability of censoring weighting (IPCW) methods. In stage 1 of the two-stage model (described by Latimer et al[7,8]), a log-normal parametric survival model accounting for important covariates was developed to estimate the effect of crossover in the chemotherapy arm (acceleration factor) that was then used to adjust survival times for patients who crossed over to pembrolizumab. Patients were eligible for inclusion in stage 1 if they met the following criteria consistent with the clinical criteria for crossover before the second interim analysis: centrally verified disease progression, no discontinuation of chemotherapy for any reason other than progressive disease, ECOG PS of 0 or 1 at progression, survival of 30 days or longer after cessation of chemotherapy, and initiation of pembrolizumab 30 days or more after last chemotherapy dose. In the second stage, observed survival times in the pembrolizumab arm were compared with adjusted survival times in the chemotherapy arm and analyzed with a stratified proportional hazards model. Bootstrapping was used to estimate the 95% CI of the acceleration factor and treatment effect HR.

In the RPSFT model,[9,10] survival times of patients in the chemotherapy arm who crossed over were adjusted multiplicatively by an acceleration factor determined by G-estimation to estimate the expected survival time if patients had not crossed over. Survival times of all patients randomly assigned to chemotherapy were recensored to maintain the assumption of noninformative censoring. Observed survival times in the pembrolizumab arm were compared with adjusted survival times in the chemotherapy arm using a Cox proportional hazards model. Bootstrapping was used to estimate the 95% CIs of the HR.

The IPCW method addressed treatment crossover by introducing artificial censoring at time of crossover for each patient. To adjust for potential confounding from artificial censoring, weights were calculated for observations before crossover according to patient baseline and time-varying demographic and disease-related characteristics (as described by Latimer et al[11]). These were then used in a weighted Cox proportional hazards model to estimate the

HR of pembrolizumab versus chemotherapy; the 95% CI was estimated by bootstrapping.

RESULTS

Patients and Treatment

KEYNOTE-024 included 305 randomly assigned patients (pembrolizumab, n = 154; chemotherapy, n = 151) from 142 sites in 16 countries; all except one patient in the chemotherapy arm received study treatment (Fig 1). At data cutoff (July 10, 2017), median follow-up was 25.2 months (range, 20.4 to 33.7 months); 235 treated patients across both arms had discontinued initially assigned study treatment. Median treatment duration was 7.9 months (range, 1 day to 28.8 months) in the pembrolizumab arm and 3.5 months (range, 1 day to 30.5 months) in the chemotherapy arm. In the chemotherapy arm, 82 patients had crossed over to pembrolizumab on study; 15 additional patients received anti–PD-1 treatment outside of the crossover (second line, n = 12; third or later line, n = 3), for a crossover rate of 64.2% (97 of 151 patients) in the intent-to-treat population and an effective crossover rate of 65.1% (97 of 149 patients) excluding patients remaining on therapy. Median treatment duration for patients receiving on-study pembrolizumab crossover was 3.9 months (range, 1 day to 23.7 months; Fig 1). In the pembrolizumab arm, 56 patients went on to receive one or more subsequent oncologic treatments, including surgery, radiation therapy, chemotherapy, and immunotherapy (pembrolizumab, n = 3; nivolumab, n = 5), after discontinuation. Patient demographic and baseline clinical characteristics were generally well balanced between the arms (Table 1).

Efficacy Outcomes

At data cutoff, 169 patients had died (pembrolizumab, n = 73; chemotherapy, n = 96). Median OS was 30.0 months (95% CI, 18.3 months to NR) in the pembrolizumab arm and 14.2 months (95% CI, 9.8 to 19.0 months) in the chemotherapy arm (HR, 0.63; 95% CI, 0.47 to 0.86; one-sided nominal P = .002). Kaplan-Meier estimates of OS at 12 months for pembrolizumab and chemotherapy were 70.3% (95% CI, 62.3% to 76.9%) and 54.8% (95% CI, 46.4% to 62.4%), respectively, with corresponding 24-month rates of 51.5% (95% CI, 43.0% to 59.3%) and 34.5% (95% CI, 26.7% to 42.4%; Fig 2A), respectively. An OS benefit for pembrolizumab compared with chemotherapy was observed in all subgroups evaluated (Fig 2B).

Efficacy Outcomes in the On-Study Crossover Phase

Baseline characteristics for the 82 patients who crossed over to on-study pembrolizumab were similar to those for the overall study population (Appendix Table A1, online only). Seventeen of 82 patients who crossed over had an objective response per investigator assessment (ORR, 20.7%; 95% CI, 12.6% to 31.1%). Nineteen patients (23.2%) had stable disease. Median time to response was
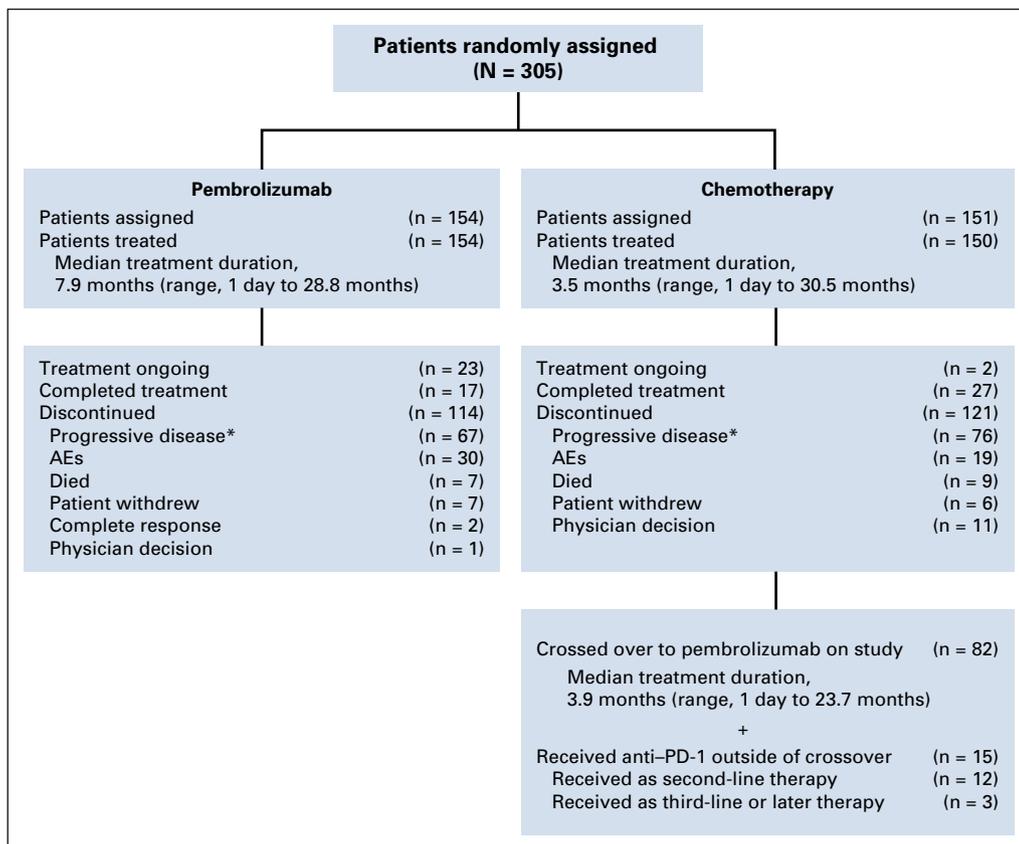
FIG 1. Disposition of patients in the study. (*) Includes patients with clinical progression or progressive disease. AEs, adverse events; PD-1, programmed death 1.

2.0 months (range, 1.1 to 8.4 months), and median DOR was NR (range, 2.1 [ongoing] to 22.9 [ongoing] months) after on-study crossover (Fig 3).

Crossover Adjustment

Seventy-seven patients randomly assigned to chemotherapy met the prespecified criteria for inclusion in stage 1 of the two-stage analysis (centrally verified progression, no discontinuation of chemotherapy other than for progressive disease, ECOG PS of 0 or 1 at time of progression, and survival of 30 days or more after cessation of chemotherapy). This is less than the number of patients who qualified for on-study crossover (n = 82), as described earlier, as a result of the requirement for disease progression. Sixty-three of these 77 patients crossed over to pembrolizumab on study; 14 of these patients did not, although four patients received anti–PD-1 treatment outside the study (pembrolizumab, n = 2; nivolumab, n = 2). The estimated acceleration factor was 4.00 (95% CI, 1.59 to 11.30), indicating the survival period after disease progression was reduced by 75% in the chemotherapy arm versus unadjusted outcomes, resulting in an adjusted median OS of 8.7 months (95% CI, 7.3 to 11.5 months). In stage 2, the adjusted HR for the adjusted OS in the chemotherapy arm versus the observed OS in the pembrolizumab arm was 0.49 (95% CI, 0.34 to 0.69; Fig 4). Similar results were obtained with the RPSFT and IPCW methods; RPSFT-adjusted median OS was 11.8 months (95% CI, 8.7 months to NR; adjusted HR, 0.52; 95% CI,

0.33 to 0.75) and IPCW-adjusted median OS was 11.8 months (95% CI, 8.7 to 21.3 months; adjusted HR, 0.52; 95% CI, 0.33 to 0.80).

Toxicity

During treatment with initially assigned therapy, treatment-related AEs occurred in 76.6% (grade 3 to 5, 31.2%) and 90.0% (grade 3 to 5, 53.3%) of patients in the pembrolizumab and chemotherapy arms, respectively (Table 2). Incidences of serious treatment-related AEs (22.7% and 20.7% in the pembrolizumab and chemotherapy arms, respectively) and treatment discontinuation as a result of treatment-related AEs (13.6% and 10.7% in the pembrolizumab and chemotherapy arms, respectively) were similar between the arms. There were five treatment-related fatal AEs (pembrolizumab, n = 2; chemotherapy, n = 3; four were previously reported[1] [pembrolizumab: sudden death of unknown cause; chemotherapy: pulmonary sepsis, pulmonary alveolar hemorrhage, and death of unknown cause]). With longer follow-up in this analysis, there was one additional death in the pembrolizumab arm (pneumonitis occurring on day 181 of pembrolizumab treatment with significant delay in start of immunosuppressive therapy).

The most frequent treatment-related AEs were diarrhea (16.2%) and fatigue (14.3%) in the pembrolizumab arm and anemia (44.0%) and nausea (43.3%) in the chemotherapy arm (Table 2). In the pembrolizumab arm, the most

TABLE 1. Patient Demographic and Baseline Disease Characteristics

Characteristic	Pembrolizumab (n = 154)	Chemotherapy (n = 151)
Median age, years (range)	64.5 (33-90)	66.0 (38-85)
Sex		
Male	92 (59.7)	95 (62.9)
Female	62 (40.3)	56 (37.1)
ECOG PS score		
0	54 (35.1)	53 (35.1)
1	99 (64.3)	98 (64.9)
2	1 (0.6)	0 (0)
Region of enrollment		
East Asia	21 (13.6)	19 (12.6)
Non–East Asia	133 (86.4)	132 (87.4)
Histology		
Squamous*	29 (18.8)	27 (17.9)
Nonsquamous†	125 (81.2)	124 (82.1)
Smoking status		
Current	34 (22.1)	31 (20.5)
Former	115 (74.7)	101 (66.9)
Never	5 (3.2)	19 (12.6)
Treated brain metastases	18 (11.7)	10 (6.6)
Prior neoadjuvant therapy	3 (1.9)	1 (0.7)
Prior adjuvant therapy	6 (3.9)	3 (2.0)

NOTE. Data presented as No (%), unless otherwise noted.

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

*Includes poorly differentiated squamous cell carcinoma (chemotherapy, n = 1).

†Includes adenosquamous (pembrolizumab, n = 2; chemotherapy, n = 2), sarcomatoid (pembrolizumab, n = 3; chemotherapy, n = 2), and poorly differentiated (pembrolizumab, n = 9; chemotherapy, n = 3) histologies.

common grade 3 to 5 treatment-related AEs were diarrhea (3.9%) and pneumonitis (3.2%). Immune-mediated AEs and infusion reactions, regardless of relationship to treatment, occurred in 33.8% (grade 3 to 5, 13.6%) and 5.3% (grade 3 to 5, 0.7%) of patients in the pembrolizumab and chemotherapy arms, respectively (Table 2).

During crossover, the rates of any grade, grade 3 to 5, and serious treatment-related AEs were 61.0%, 9.8%, and 8.5%, respectively (discontinuation rate due to treatment-related AEs, 6.1%). There were no grade 5 treatment-related AEs during on-study crossover. Among crossover patients, 16 (19.5%) developed an immune-mediated AE and/or infusion reaction (hypothyroidism, 9.8%; hyperthyroidism, 6.1%; pneumonitis, 4.9%; adrenal insufficiency, 1.2%; and infusion reaction, 1.2%).

DISCUSSION

In this updated analysis of KEYNOTE-024, pembrolizumab continues to show an OS benefit as first-line therapy for advanced NSCLC with PD-L1 TPS of 50% or greater compared with platinum-based chemotherapy (HR, 0.63; 95% CI, 0.47 to 0.86; nominal P = .002). The improvement in OS first reported at the second interim analysis[1] was maintained despite significant crossover to pembrolizumab in the chemotherapy arm, with a notable median OS of 30.0 months for patients randomly assigned to pembrolizumab compared with 14.2 months for patients in the chemotherapy arm. This efficacy outcome is more favorable than that described in trials evaluating platinum-based chemotherapy as first-line treatment of NSCLC.[12] To our knowledge, KEYNOTE-024 is the first study to show an OS benefit with anti–PD-1 monotherapy compared with platinum-based chemotherapy as first-line treatment in patients with advanced NSCLC and has changed the treatment paradigm of this disease.

With median exposure of 7.9 months in the pembrolizumab arm at the time of analysis (more than double that in the chemotherapy arm), pembrolizumab continues to demonstrate a favorable safety profile. The incidence, severity, and nature of AEs were consistent with those described previously,[1] with no evidence of cumulative toxicity with longer exposure and no new safety signals when comparing incidence of AEs during pembrolizumab treatment with those among patients who received chemotherapy (notwithstanding the longer treatment duration with initial therapy in the pembrolizumab arm). In the updated analysis, there was one additional fatal immune-mediated AE as a result of pneumonitis. Although median time to the first pneumonitis event was 100 days in the pembrolizumab arm, this AE developed at day 181. Initially confused with disease progression, immunosuppression was delayed until after the patient underwent two separate biopsies.

Whereas at the second interim analysis 66 patients had received pembrolizumab crossover therapy, at the time of this analysis 82 patients had crossed over and 15 additional patients had received subsequent anti–PD-1 therapy (crossover rate, 64.2% in the intent-to-treat population; effective crossover rate, 65.1% excluding patients remaining on therapy). Outcomes in the crossover population are indicative of treatment benefit for second-line pembrolizumab monotherapy (ORR, 20.7%; median DOR, NR) and are consistent with outcomes for patients with PD-L1 TPS of 50% or greater in the phase III KEYNOTE-010 (ClinicalTrials.gov identifier: NCT01905657) study of pembrolizumab versus docetaxel in patients with previously treated NSCLC.[13]

The high rate of crossover in this study (reflecting both the study design and decision of the data and safety monitoring committee to stop the trial analysis early) and apparent activity of pembrolizumab during the crossover period likely attenuated the observed OS effect. We used three statistical methods to adjust for the influence of crossover on OS, and all three supported an HR more strongly favoring the pembrolizumab arm. The two-stage model was preferred, as a result of evidence of deviation from the common
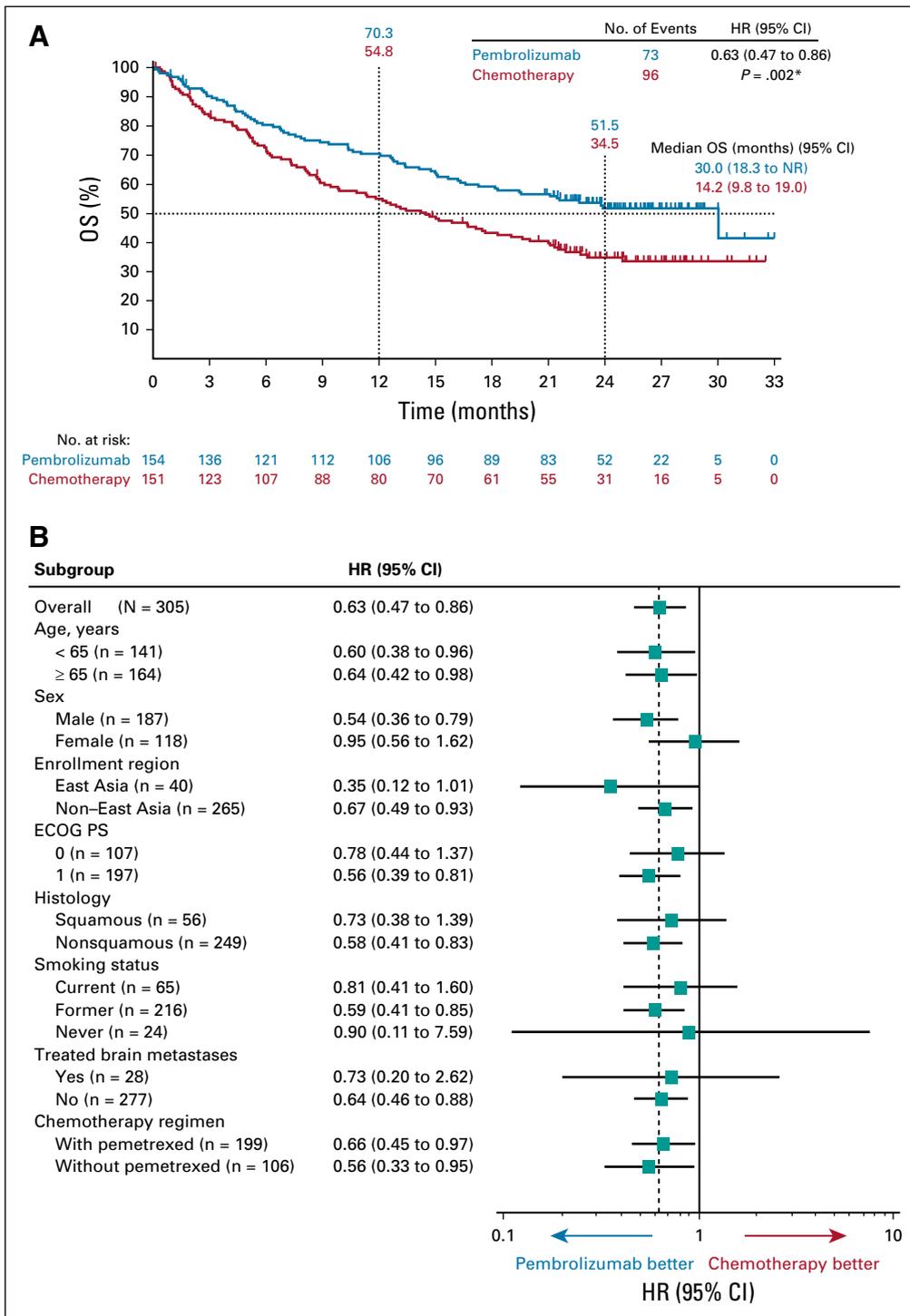
FIG 2. (A) Kaplan-Meier analysis and (B) subgroup analysis of overall survival (OS). Vertical dotted line in subgroup analysis represents hazard ratio (HR) in the overall population. (*) Nominal *P* value. ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reached; PD-1, programmed death 1.

treatment effect assumed in RPSFT and because the IPCW method is more prone to bias in the presence of relatively small sample sizes.[7,11] Overall, the crossover-adjusted analyses complement the primary efficacy analysis and reinforce the potential to improve outcomes with early use of pembrolizumab as first-line treatment.

Given the OS and PFS benefits observed in KEYNOTE-024, pembrolizumab remains the only checkpoint inhibitor approved in the first-line setting as monotherapy for patients with PD-L1 TPS of 50% or greater. Recently, results from the KEYNOTE-042 (ClinicalTrials.gov identifier: NCT02220894) study confirmed and extended those from KEYNOTE-024 by demonstrating significantly improved OS with pembrolizumab versus platinum-based chemotherapy not only in treatment-naive patients with PD-L1 TPS of 50% or greater (HR, 0.69; 95% CI, 0.56 to 0.85; *P* = .0003), but
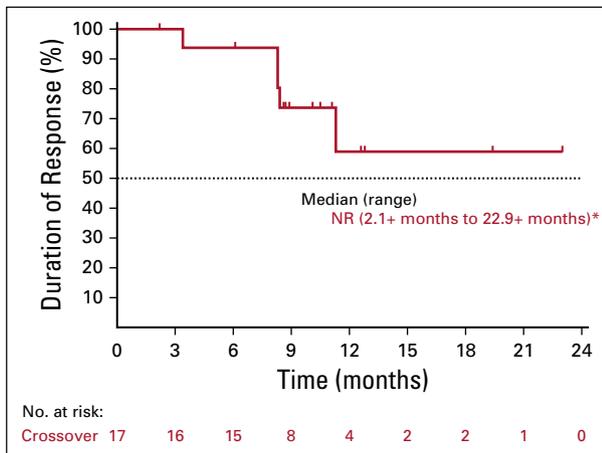
FIG 3. Kaplan-Meier analysis of duration of response per investigator assessment in patients who crossed over from chemotherapy to on-study pembrolizumab (ie, duration of response for responses occurring after day 1 of crossover treatment cycle 1). (*) Plus sign indicates that the response duration is censored. NR, not reached.

also in those with PD-L1 TPS of 20% or greater (HR, 0.77; 95% CI, 0.64 to 0.92; *P* = .002) and 1% or greater (HR, 0.81; 95% CI, 0.71 to 0.93; *P* = .0018).[14] In contrast, administration of nivolumab 3 mg/kg every 2 weeks in the CheckMate 026 (ClinicalTrials.gov identifier: NCT02041533) study did not improve PFS or OS among patients with previously untreated advanced NSCLC with PD-L1 expression of 5% or greater.[15] Although cross-trial comparisons should be approached with caution, different PD-L1 assays (with different anti–PD-L1 antibodies) and thresholds were used in CheckMate 026 relative to KEYNOTE-024 and KEYNOTE-042, which may, in part, explain the opposing outcomes.[16]

Pembrolizumab with platinum chemotherapy has been evaluated in several trials. In the randomized cohort G of the phase I/II KEYNOTE-021 (ClinicalTrials.gov identifier: NCT02039674) study, pembrolizumab plus carboplatin and pemetrexed in patients with newly diagnosed, advanced, nonsquamous NSCLC without *EGFR/ALK* alterations irrespective of PD-L1 TPS demonstrated improved ORR and PFS compared with carboplatin and pemetrexed alone,[17] leading to approval in the United States. The phase III KEYNOTE-189 (ClinicalTrials.gov identifier: NCT 02578680) study evaluated first-line pembrolizumab plus pemetrexed and platinum in patients with nonsquamous metastatic NSCLC irrespective of PD-L1 tumor expression and showed significant improvement in OS (HR, 0.49; 95% CI, 0.38 to 0.64; *P* < .001) and PFS (HR, 0.52; 95% CI, 0.43 to 0.64; *P* < .001) compared with placebo plus chemotherapy.[18] Pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel resulted in improved OS and PFS compared with placebo plus carboplatin and paclitaxel or nab-paclitaxel in patients with squamous histology regardless of PD-L1 expression (OS HR, 0.64; 95% CI, 0.49 to 0.85; *P* < .001; PFS HR, 0.56; 95% CI, 0.45 to 0.70; *P* < .001) in the phase III KEYNOTE-407 (ClinicalTrials.gov identifier: NCT02775435) study.[19] Together with our current analyses, these data show that for all patients with advanced NSCLC without *EGFR/ALK* alterations, a first-line treatment regimen containing pembrolizumab (either as monotherapy or in combination with platinum chemotherapy) is available that can improve OS compared with platinum doublet chemotherapy.

In addition, other anti–programmed death 1 or anti–PD-L1 antibodies have been evaluated in combination with chemotherapy or immunotherapy in patients with NSCLC. Atezolizumab with bevacizumab, carboplatin, and paclitaxel
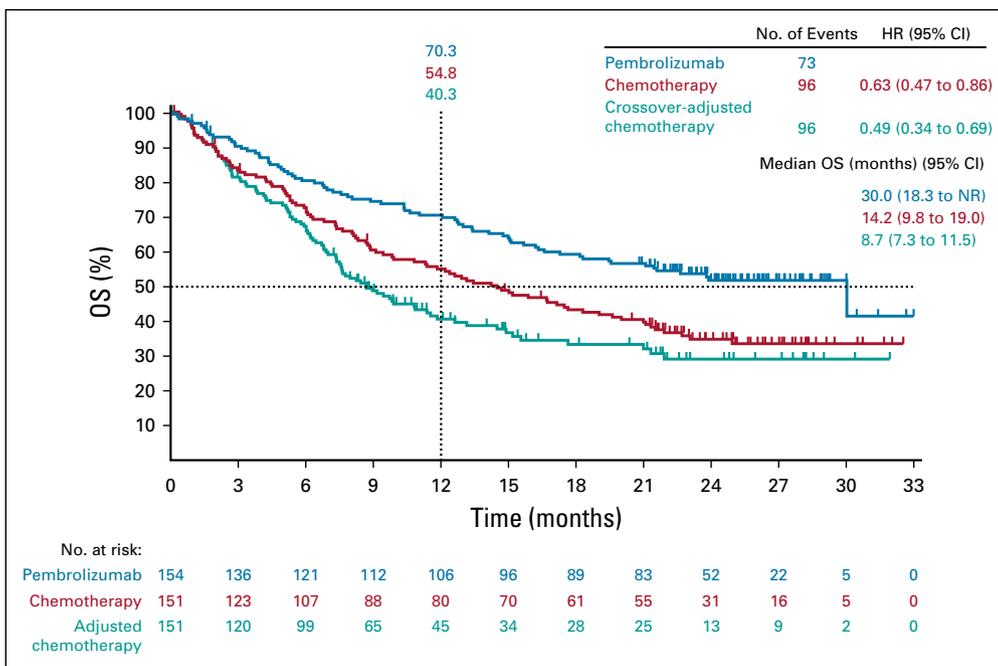

FIG 4. Kaplan-Meier analysis of overall survival (OS) adjusting for treatment crossover using two-stage analysis. HR, hazard ratio; NR, not reached.

TABLE 2. Adverse Events in the As-Treated Population

	No. of Patients (%)			
Adverse Event	**Pembrolizumab (n = 154)**		**Chemotherapy (n = 150)**	
Treatment-related AEs†				
Any grade	118 (76.6)		135 (90.0)	
Grade 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)	
Treatment-related AEs occurring in ≥ 10% of patients in either arm‡	Any Grade	Grade 3 or 4*	Any Grade	Grade 3 or 4*
Diarrhea	25 (16.2)	6 (3.9)	21 (14.0)	2 (1.3)
Fatigue	22 (14.3)	3 (1.9)	43 (28.7)	5 (3.3)
Pyrexia	18 (11.7)	0	9 (6.0)	0
Pruritus	18 (11.7)	0	3 (2.0)	0
Rash	16 (10.4)	2 (1.3)	3 (2.0)	0
Nausea	15 (9.7)	0	65 (43.3)	3 (2.0)
Decreased appetite	15 (9.7)	0	39 (26.0)	4 (2.7)
Anemia	8 (5.2)	2 (1.3)	66 (44.0)	29 (19.3)
Constipation	6 (3.9)	0	17 (11.3)	0
Blood creatinine increased	5 (3.2)	0	16 (10.7)	0
Vomiting	4 (2.6)	0	30 (20.0)	0
Stomatitis	4 (2.6)	0	18 (12.0)	2 (1.3)
Neutropenia	1 (0.6)	0	33 (22.0)	20 (13.3)
Neutrophil count decreased	1 (0.6)	0	21 (14.0)	7 (4.7)
WBC count decreased	1 (0.6)	0	17 (11.3)	4 (2.7)
Dysgeusia	1 (0.6)	0	16 (10.7)	0
Platelet count decreased	0	0	18 (12.0)	10 (6.7)
Thrombocytopenia	0	0	16 (10.7)	8 (5.3)
AEs with possible immune etiology occurring in ≥ 0% of patients	Any Grade	Grade 3 or 4§	Any Grade	Grade 3 or 4§
Any	52 (33.8)	20 (13.2)	8 (5.3)	1 (0.7)
Hypothyroidism	16 (10.4)	0	3 (2.0)	0
Pneumonitis	12 (7.8)	4 (2.6)	1 (0.7)	1 (0.7)
Hyperthyroidism	11 (7.1)	0	2 (1.3)	0
Infusion reactions	8 (5.2)	1 (0.6)	2 (1.3)	0
Severe skin reactions	8 (5.2)	8 (5.2)	0	0
Colitis	6 (3.9)	3 (1.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Myositis	3 (1.9)	0	0	0
Hepatitis	1 (0.6)	1 (0.6)	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0
(continued on following page)				

TABLE 2. Adverse Events in the As-Treated Population (continued)

Adverse Event	No. of Patients (%)			
	Pembrolizumab (n = 154)		Chemotherapy (n = 150)	
Pancreatitis	1 (0.6)	1 (0.6)	0	0
Type 1 diabetes	1 (0.6)	1 (0.6)	0	0
Uveitis	1 (0.6)	1 (0.6)	0	0

NOTE. The as-treated population included all patients who were randomly assigned and received one or more doses of a trial treatment. Adverse events that occurred during crossover from the chemotherapy arm to pembrolizumab are excluded.

Abbreviation: AEs, adverse events.

*Two grade 5 treatment-related adverse events occurred in the pembrolizumab arm (pneumonitis and sudden death) and three in the chemotherapy arm (death, pulmonary sepsis, and pulmonary alveolar hemorrhage).

†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.

§One grade 5 immune-mediated AE occurred in the pembrolizumab arm (pneumonitis).

improved OS (HR, 0.78; 95% CI, 0.64 to 0.96; P = .02) and PFS (HR, 0.62; 95% CI, 0.52 to 0.74; P < .001) compared with bevacizumab, carboplatin, and paclitaxel in patients with nonsquamous histology,[20] and atezolizumab with carboplatin and nab-paclitaxel improved median PFS (HR, 0.715; 95% CI, 0.603 to 0.848; P = .0001) but not OS (HR, 0.96; 95% CI, 0.78 to 1.18; P = .6931) compared with carboplatin plus nab-paclitaxel in patients with squamous NSCLC.[21] Nivolumab with chemotherapy improved PFS compared with chemotherapy alone in patients whose tumors did not express PD-L1 (HR, 0.74; 95% CI, 0.58 to 0.94).[22] Finally, nivolumab plus ipilimumab demonstrated longer PFS compared with chemotherapy (HR, 0.83; 95% CI, 0.72 to 0.96), particularly in patients with high tumor mutational burden (HR, 0.58; 97.5% CI, 0.41 to 0.81).[23] At present, tumor mutational burden does not have a role in guiding treatment decisions, because an OS benefit has not been shown.

In conclusion, in this updated analysis of KEYNOTE-024, pembrolizumab continued to provide improved OS relative to platinum-based chemotherapy, notwithstanding the high rate of crossover. There was no evidence of cumulative toxicity. These results support pembrolizumab monotherapy as a standard-of-care regimen for first-line treatment of advanced NSCLC with PD-L1 TPS of 50% or greater and without *EGFR/ALK* alterations.

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REFERENCES

1. 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 375: 1823-1833, 2016

2. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009

3. Brahmer JR, Rodríguez-Abreu D, Robinson AG, et al: Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): A multicentre, international, randomised, open-label phase 3 trial. Lancet Oncol 18:1600-1609, 2017

4. European Medicines Agency: Guideline on the evaluation of anticancer medicinal products in man. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/11/WC500238764.pdf

5. 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 24:392-397, 2016

6. Brahmer JR, Rodriguez-Abreu D, Robinson AG, et al: Progression after the next line of therapy (PFS2) and updated OS among patients (pts) with advanced NSCLC and PD-L1 tumor proportion score (TPS) ≥ 50% enrolled in KEYNOTE-024. J Clin Oncol 35, 2017 (suppl; abstr 9000)

7. Latimer NR, Abrams KR, Lambert PC, et al: Adjusting survival time estimates to account for treatment switching in randomized controlled trials: An economic evaluation context—Methods, limitations, and recommendations. Med Decis Making 34:387-402, 2014

8. Latimer NR, Abrams KR, Lambert PC, et al: Adjusting for treatment switching in randomised controlled trials: A simulation study and a simplified two-stage method. Stat Methods Med Res 26:724-751, 2017

9. Robins JM, Tsiatis AA: Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Commun Stat Theory Methods 20:2609-2631, 1991

10. Zhang J, Chen C: Correcting treatment effect for treatment switching in randomized oncology trials with a modified iterative parametric estimation method. Stat Med 35:3690-3703, 2016

11. Latimer NR, Bell H, Abrams KR, et al: Adjusting for treatment switching in the METRIC study shows further improved overall survival with trametinib compared with chemotherapy. Cancer Med 5:806-815, 2016

12. Pilkington G, Boland A, Brown T, et al: A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer. Thorax 70:359-367, 2015

13. 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 387:1540-1550, 2016

14. 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 36, 2018 (suppl; abstr LBA4)

15. 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 376:2415-2426, 2017

16. Garon EB: Cancer immunotherapy trials not immune from imprecise selection of patients. N Engl J Med 376:2483-2485, 2017

17. 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 17:1497-1508, 2016

18. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378:2078-2092, 2018

19. Paz-Ares L, Luft A, Vicente D, et al: Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 379:2040-2051, 2018

20. Socinski MA, Jotte RM, Cappuzzo F, et al: Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 378:2288-2301, 2018

21. 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 36, 2018 (suppl; abstr LBA9000)

22. Borghaei H, Hellman 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 36, 2018 (suppl; abstr 9001)

23. Hellmann MD, Ciuleanu TE, Pluzanski A, et al: Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 378:2093-2104, 2018

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater

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APPENDIX

TABLE A1. Demographic and Baseline Disease Characteristics Among Patients Who Crossed Over to On-Study Pembrolizumab

Characteristic	No. of Crossover Patients (n = 82)
Median age, years (range)	65.0 (40-83)
Sex	
Male	47 (57.3)
Female	35 (42.7)
ECOG PS score	
0	37 (45.1)
1	45 (54.9)
Region of enrollment	
East Asia	10 (12.2)
Non–East Asia	72 (87.8)
Histology	
Squamous	18 (22.0)
Nonsquamous*	64 (78.0)
Smoking status	
Current	15 (18.3)
Former	52 (63.4)
Never	15 (18.3)
Treated brain metastases	3 (3.7)
Prior neoadjuvant therapy	0
Prior adjuvant therapy	3 (3.7)

NOTE. Data presented as No (%), unless otherwise noted.

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

*Includes adenosquamous (n = 1), sarcomatoid (n = 2), and poorly differentiated (n = 1) histologies.