ORIGINAL ARTICLE

Pembrolizumab Plus Chemotherapy for Metastatic NSCLC With Programmed Cell Death Ligand 1 Tumor Proportion Score Less Than 1%: Pooled Analysis of Outcomes After Five Years of Follow-Up

Shirish M. Gadgeel, MD,[a,*] Delvys Rodríguez-Abreu, MD, PhD,[b] Balazs Halmos, MD,[c] Marina C. Garassino, MD,[d,e] Takayasu Kurata, MD, PhD,[f] Ying Cheng, MD,[g] Erin Jensen, MS,[h] Mark Shamoun, MD,[h] Kumar Rajagopalan, MD,[h] Luis Paz-Ares, MD, PhD[i]

[a]*Karmanos Cancer Institute, Detroit, Michigan*
[b]*Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain*
[c]*Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York*
[d]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[e]*Current Affiliation: Thoracic Oncology Program, The University of Chicago Medicine & Biological Sciences, Chicago, Illinois*
[f]*Department of Thoracic Oncology, Kansai Medical University Hospital, Osaka, Japan*
[g]*Department of Oncology, Jilin Cancer Hospital, Changchun, People's Republic of China*
[h]*Merck & Co., Inc., Rahway, New Jersey*
[i]*Medical Oncology Department, Hospital Universitario 12 de Octubre, Universidad Complutense and Ciberonc, Madrid, Spain*

Received 26 February 2024; revised 11 April 2024; accepted 14 April 2024
Available online - XXX

ABSTRACT

Background: We report long-term outcomes from a pooled analysis of patients with previously untreated metastatic NSCLC with programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) less than 1% enrolled in phase III studies of pembrolizumab plus chemotherapy versus placebo plus chemotherapy.

Methods: This exploratory pooled analysis included individual patient data from the KEYNOTE-189 global (NCT02578680) and Japan extension (NCT03950674) studies of metastatic nonsquamous NSCLC without *EGFR* or *ALK* alterations and the KEYNOTE-407 global (NCT02775435) and People's Republic of China extension (NCT03875092) studies of metastatic squamous NSCLC. Patients received pembrolizumab or placebo plus pemetrexed and cisplatin or carboplatin in KEYNOTE-189 and pembrolizumab or placebo plus carboplatin and paclitaxel or nab-paclitaxel in KEYNOTE-407. PD-L1 TPS was centrally assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA).

Results: Overall, 442 patients were included in this analysis (pembrolizumab plus chemotherapy, n = 255; chemotherapy, n = 187). The median follow-up was 60.7 (range, 49.9–72.0) months. Pembrolizumab plus chemotherapy improved overall survival (hazard ratio, 0.64; 95% confidence interval [CI]: 0.51–0.79) and progression-free survival (hazard ratio, 0.66; 95% CI: 0.54–0.81) versus chemotherapy. The 5-year overall survival rates (95% CI) were 12.5% (8.6%–17.3%) versus 9.3% (5.6%–14.1%). Grades 3 to 5 treatment-related adverse events occurred in 59.1% of patients for pembrolizumab plus chemotherapy and 61.3% for chemotherapy.

Conclusion: With approximately 5 years of follow-up, pembrolizumab plus chemotherapy provided clinically

*Corresponding author.

Previous presentation: A portion of these results were previously presented at the IASLC 2023 World Conference on Lung Cancer, September 9-12, 2023; Singapore; abstract OA14.05.

Address for correspondence: Shirish M. Gadgeel, MD, Division of Hematology and Oncology, Department of Internal Medicine, Henry Ford Cancer Institute/Henry Ford Health, 2800 West Grand Boulevard, E3011, Detroit, MI 48202, USA. E-mail: sgadgee1@hfhs.org

Cite this article as: Gadgeel SM, Rodríguez-Abreu, D, Halmos B, et al. Pembrolizumab plus chemotherapy for metastatic NSCLC with programmed cell death ligand 1 tumor proportion score less than 1%: pooled analysis of outcomes after five years of follow-up. *J Thorac Oncol* XXXX;X:XXXXXX

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2024.04.011

meaningful and durable improvements in survival outcomes versus chemotherapy alone in patients with previously untreated metastatic NSCLC with PD-L1 TPS less than 1%. These results continue to support pembrolizumab plus chemotherapy as a standard of care in this patient population. ClinicalTrials.gov, NCT02578680 (KEYNOTE-189 global), NCT03950674 (KEYNOTE-189 Japan extension), NCT02775435 (KEYNOTE-407 global), NCT03875092 (KEYNOTE-407 People's Republic of China extension).

Keywords: Pembrolizumab; Non–small-cell lung cancer; Pooled analysis; PD-L1–negative

Introduction

Pembrolizumab in combination with chemotherapy was found to significantly improve overall survival (OS) and progression-free survival (PFS) compared with placebo plus chemotherapy in patients with previously untreated metastatic NSCLC without *EGFR* or *ALK* alterations, irrespective of programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS), in the KEYNOTE-189 (nonsquamous NSCLC) and KEYNOTE-407 (squamous NSCLC) studies.[1,2] On the basis of these data, pembrolizumab plus chemotherapy is a standard of care first-line therapy for patients with metastatic squamous and nonsquamous NSCLC regardless of PD-L1 TPS, including patients with PD-L1 TPS less than 1%.[3–7] Pembrolizumab is also approved as monotherapy in patients with previously untreated locally advanced or metastatic NSCLC with PD-L1 TPS greater than or equal to 1% and without *EGFR* or *ALK* gene alterations.[3,4]

As such, determination of PD-L1 TPS is routine clinical practice for guiding treatment decisions in patients with previously untreated squamous or nonsquamous metastatic NSCLC.[3] Results from real-world studies have revealed that up to 48% of patients with advanced or metastatic NSCLC have PD-L1 TPS less than 1%.[8–10] To better understand treatment outcomes in a larger population of patients with PD-L1 TPS less than 1%, a previous analysis pooled a set of patients with previously untreated advanced or metastatic NSCLC with PD-L1 TPS less than 1% enrolled in the KEYNOTE-189, KEYNOTE-407, and KEYNOTE-021 cohort G randomized controlled studies of pembrolizumab plus chemotherapy versus chemotherapy alone.[11] Among 444 patients with PD-L1 TPS less than 1% included in this pooled analysis, pembrolizumab plus chemotherapy improved OS (hazard ratio [HR], 0.63; 95% confidence interval [CI]: 0.50–0.79), PFS (HR, 0.68; 95% CI: 0.56–0.83), and objective response rate (ORR; 50.0% versus 29.8%) versus chemotherapy alone.[11] Despite these data, a real-world evidence survey of oncologists and pulmonologists and their patients across five European countries found that 62.4% of patients with *EGFR*-wildtype and *ALK*-wildtype metastatic NSCLC with PD-L1 expression less than 1% received chemotherapy only as first-line treatment, compared with 26.5% who received immunotherapy plus chemotherapy.[9] The remaining patients received immunotherapy alone (2.6%), chemotherapy combination (6.8%), targeted therapy (1.3%), and other treatments (0.4%).[9] Similarly, in a retrospective study using patient-level data across the United States from the Flatiron Health oncology database, among 979 patients with stage IV NSCLC with tumor PD-L1 expression less than 1%, a similar proportion of patients received chemotherapy alone versus immunotherapy plus chemotherapy as first-line treatment (32% versus 28%).[10] Both of these studies indicate that a substantial proportion of patients with previously untreated advanced or metastatic NSCLC with PD-L1 expression less than 1% continue to receive chemotherapy alone and, therefore, may not be receiving optimum treatment per current evidence and treatment guidelines.

Given these findings, we evaluated long-term outcomes on the basis of a pooled analysis of pembrolizumab plus chemotherapy versus placebo plus chemotherapy in patients with previously untreated metastatic NSCLC with PD-L1 TPS less than 1% enrolled in the KEYNOTE-189 and KEYNOTE-407 studies to better understand treatment outcomes in this population of patients.

Methods

Patients

In this exploratory posthoc analysis, individual patient data were pooled for patients with previously untreated metastatic NSCLC with tumor PD-L1 TPS less than 1% enrolled in the following randomized, double-blind, phase III studies: KEYNOTE-189 global (NCT02578680; nonsquamous)[1] and Japan extension (NCT03950674; nonsquamous)[12] studies and the KEYNOTE-407 global (NCT02775435; squamous)[2] and People's Republic of China extension (NCT03875092; squamous)[13] studies.

Detailed eligibility criteria for the KEYNOTE-189 and KEYNOTE-407 studies have been previously published.[1,2,12,13] Briefly, the patients included were at least 18 years old and with histologically or cytologically confirmed stage IV NSCLC and without previous systemic treatment for advanced or metastatic NSCLC. In addition, in KEYNOTE-189, eligible patients were without sensitizing *EGFR* or *ALK* alterations. Eligible patients also had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST)

version 1.1, an Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of at least 3 months, and adequate organ function. All patients were required to provide a tumor tissue sample for evaluation of PD-L1 TPS. The protocol and all its amendments were approved by an institutional review board or ethics committee at each study site. All patients provided written informed consent before enrollment.

Study Design and Treatment

The study designs of the KEYNOTE-189 Japan extension and KEYNOTE-407 People's Republic of China extension studies were identical to the respective global studies, with the exception that they only included patients enrolled in Japan and People's Republic of China, respectively. In KEYNOTE-189, patients were randomized 2:1 to receive either pembrolizumab 200 mg intravenously or saline placebo every 3 weeks for up to 35 cycles (approximately 2 years). All patients also received pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin area under the curve 5 mg/mL/min every 3 weeks for four cycles followed by pemetrexed maintenance therapy. In KEYNOTE-407, patients were randomized 1:1 to receive pembrolizumab 200 mg or saline placebo every 3 weeks for up to 35 cycles (approximately 2 years). Patients also received carboplatin area under the curve 6 mg/mL/min plus paclitaxel 200 mg/m^2 every 3 weeks or nab-paclitaxel 100 mg/m^2 (on days 1, 8, and 15) every 3 weeks for four cycles. In all studies, treatment continued until completion of 35 cycles of pembrolizumab or placebo, confirmed complete response (CR) by central review, confirmed radiographic disease progression (PD), intercurrent illness, unacceptable adverse events (AEs), investigator decision, or patient withdrawal of consent. In all studies, patients in the placebo plus chemotherapy group with PD confirmed by blinded independent central review per RECIST version 1.1 could have crossed over to receive open-label pembrolizumab 200 mg every 3 weeks for up to 35 cycles if eligibility criteria were met. Patients randomized to the pembrolizumab-containing arms or those who crossed over from the placebo plus chemotherapy group to open-label pembrolizumab with subsequent PD may have received a second course of pembrolizumab for up to 17 cycles (approximately 1 year) if they had stopped treatment after attaining a confirmed CR by central review after receipt of at least 8 cycles of pembrolizumab and at least 2 cycles of pembrolizumab after the initial CR was identified, or had a response of stable disease or better after completion of 35 cycles for reasons other than PD or intolerability and met all other eligibility criteria.

Randomization was stratified according to PD-L1 TPS ($\geq$1% versus <1%) in all studies. Additional stratification factors in KEYNOTE-189 were platinum chemotherapy (cisplatin versus carboplatin) and smoking status (never versus current/former) and in KEYNOTE-407 were taxane therapy (paclitaxel versus nab-paclitaxel) and region of enrollment (East Asia versus not East Asia).

Assessments

In all studies, PD-L1 TPS was assessed during screening at a central laboratory using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA) from a formalin-fixed tumor sample collected at diagnosis. Investigators and patients were blinded to PD-L1 TPS; sponsor personnel were blinded to PD-L1 TPS in KEYNOTE-189 but not in KEYNOTE-407. In KEYNOTE-189, tumor imaging was performed at baseline, at weeks 6 and 12 from randomization, then every 9 weeks to week 48 and every 12 weeks thereafter. In KEYNOTE-407, imaging was performed at baseline; at weeks 6, 12, and 18 from randomization; then every 9 weeks to week 45 and every 12 weeks thereafter. Tumor response was assessed per RECIST version 1.1 by blinded independent central review, with the exception of PFS2, which was assessed per RECIST version 1.1 by investigator review. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

End Points

In all studies, the dual primary end points were OS (time from randomization to death because of any cause) and PFS (time from randomization to first documented PD or death because of any cause). Secondary end points included ORR (proportion of patients who had CR or partial response [PR]), duration of response (DOR; time from first documented CR or PR until PD or death in patients with confirmed CR or PR), and safety. PFS2 (defined as the time from randomization to second or subsequent tumor progression on next line of treatment or death) was a protocol-specified exploratory end point in all studies.

Statistical Analysis

Patients from the KEYNOTE-189 global and Japan extension studies and the KEYNOTE-407 global and People's Republic of China extension studies with known PD-L1 TPS less than 1% were included in this analysis. Efficacy outcomes were assessed in the pooled intention-to-treat population and safety outcomes in the pooled as-treated population. OS, PFS, DOR, and PFS2 curves were estimated using the Kaplan-Meier method. HRs and corresponding 95% CIs for OS, PFS, and PFS2 were calculated using a stratified (by chemotherapy regimen) Cox regression model with the Efron method of tie handling

and treatment as a covariate. Analyses were performed posthoc, with no alpha assigned. The database cutoff dates were March 8, 2022, for the global KEYNOTE-189 study; February 7, 2023, for the KEYNOTE-189 Japan extension; February 23, 2022, for the global KEYNOTE-407 study; and February 10, 2023, for the KEYNOTE-407 People's Republic of China extension.

Results

Patients and Study Disposition

Of the 1315 total patients across the KEYNOTE-189 global and Japan extension (n = 646) and KEYNOTE-407 global and People's Republic of China extension studies (n = 669), 442 patients (33.6%) with PD-L1 TPS less than 1% were included in this pooled analysis. This comprised 254 patients who received treatment in the pembrolizumab plus chemotherapy group and 186 patients in the placebo plus chemotherapy group. At the time of data cutoff, all patients in both treatment groups had discontinued or completed treatment with the exception of one who was continuing pemetrexed treatment in the pembrolizumab plus chemotherapy group. In the pembrolizumab plus chemotherapy group, four patients had started a second course of pembrolizumab and 36 had received subsequent anti–PD-(L)1 therapy outside the study. In the placebo plus chemotherapy group, 76 patients had crossed over to pembrolizumab monotherapy on-study and 24 had received anti–PD-(L)1 therapy outside the study for an effective crossover rate of 53.5% (Fig. 1). Details on subsequent anticancer therapy are provided in the Supplementary Materials.

Demographics and baseline disease characteristics were generally similar between the treatment groups. Overall, 74.4% of patients were men, 65.2% had an Eastern Cooperative Oncology Group performance status of 1, and 14.9% had brain metastasis at baseline. There was a higher proportion of patients with nonsquamous NSCLC in the pembrolizumab plus chemotherapy group (52.5%) compared with the chemotherapy alone group (34.2%) owing to the 2:1 randomization ratio in KEYNOTE-189. In addition, there was a lower proportion of patients with liver metastases at baseline in the pembrolizumab plus chemotherapy group compared with the chemotherapy alone group (13.7% versus 21.4%) (Table 1). The median time from randomization to database cutoff was 60.7 (range, 49.9–72.0) months.

Efficacy

At the time of data cutoff, 218 patients (85.5%) in the pembrolizumab plus chemotherapy group and 167 (89.3%) in the placebo plus chemotherapy group had died. The median OS was 18.3 (95% CI: 15.2–20.9) months and 11.4 (95% CI: 9.4–13.2) months, respectively, and HR for OS was 0.64 (95% CI: 0.51–0.79). The estimated 5-year OS rates were 12.5% (95% CI: 8.6%–17.3%) and 9.3% (95% CI: 5.6%–14.1%), respectively (Fig. 2*A*). The HR for OS in key patient subgroups is provided in Figure 2*B*.

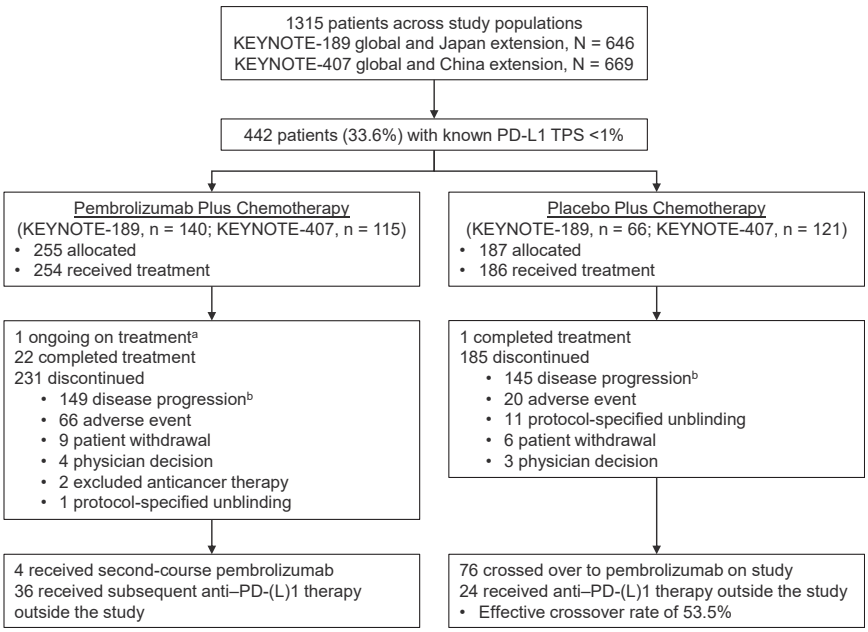

Figure 1. Patient disposition in the pooled analysis population of patients with metastatic NSCLC with known PD-L1 TPS less than 1%. [a]Ongoing pemetrexed treatment at data cutoff. [b]Includes patients with clinical progression or progressive disease. PD-L1, programmed cell death ligand 1; TPS, tumor proportion score.

Table 1. Demographics and Baseline Disease Characteristics

Characteristic	Pembrolizumab Plus Chemotherapy, n = 255	Placebo Plus Chemotherapy, n = 187	Completed 35 Cycles of Pembrolizumab, n = 27
Age, median (range), y	65.0 (31–87)	64.0 (43–82)	63.0 (31–74)
Sex			
Male	181 (71.0)	148 (79.1)	24 (88.9)
Female	74 (29.0)	39 (20.9)	3 (11.1)
ECOG performance status			
0	89 (34.9)	64 (34.2)	10 (37.0)
1	165 (64.7)	123 (65.8)	17 (63.0)
2	1 (0.4)	0	0
Histology			
Nonsquamous	134 (52.5)	64 (34.2)	8 (29.6)
Squamous	111 (43.5)	119 (63.6)	18 (66.7)
Other	10 (4.0)	4 (2.1)	1 (3.7)
Smoking status			
Former or current	225 (88.2)	175 (93.6)	26 (96.3)
Never	30 (11.8)	12 (6.4)	1 (3.7)
Brain metastases	40 (15.7)	26 (13.9)	2 (7.4)
Liver metastases	35 (13.7)	40 (21.4)	3 (11.1)
Prior therapy			
Radiation	47 (18.4)	34 (18.2)	1 (3.7)
Thoracic radiation	15 (5.9)	13 (7.0)	0
Neoadjuvant therapy	4 (1.6)	4 (2.1)	0
Adjuvant therapy	14 (5.5)	8 (4.3)	1 (3.7)
Region of enrollment			
East Asia	55 (21.6)	50 (26.7)	10 (37.0)
Europe	124 (48.6)	76 (40.6)	15 (55.6)
United States	31 (12.2)	20 (10.7)	0
Other	45 (17.6)	41 (21.9)	2 (7.4)

Values are n (%) unless noted otherwise.
ECOG, Eastern Cooperative Oncology Group.

At data cutoff, 238 patients (93.3%) in the pembrolizumab plus chemotherapy group and 178 (95.2%) in the placebo plus chemotherapy group had experienced PD or death. The median PFS was 6.5 (95% CI: 6.2–8.4) months and 5.5 (95% CI: 4.7–6.2) months, respectively, and the HR for PFS was 0.66 (95% CI: 0.54–0.81; Fig. 2*C*). The HR for PFS in key patient subgroups is provided in Figure 2*D*.

The median PFS2 was 14.4 (95% CI: 12.9–15.9) months in the pembrolizumab plus chemotherapy group and 9.2 (95% CI: 7.6–10.2) months in the placebo plus chemotherapy group, and the HR was 0.55 (95% CI: 0.44–0.68; Fig. 2*E*).

The ORR was 50.6% (95% CI: 44.3%–56.9%) in the pembrolizumab plus chemotherapy group and 33.2% (95% CI: 26.5%–40.4%) in the placebo plus chemotherapy group. The median DOR was 7.6 (range, 1.1+ to 59.4+) months and 5.5 (range, 1.4+ to 55.8+) months, respectively (Table 2; Figure 3).

Safety

In the pooled as-treated population, 252 of 254 patients (99.2%) in the pembrolizumab plus chemotherapy group and 185 of 186 patients (99.5%) in the placebo plus chemotherapy group experienced AEs of any cause. The most frequently reported grade 3 to 5 AEs were anemia, neutropenia, and decreased neutrophil count in both treatment groups (Table 3). Treatment-related AEs were reported in 245 patients (96.5%) and 175 patients (94.1%), respectively; grade 3 to 5 treatment-related AEs occurred in 150 patients (59.1%) and 114 patients (61.3%), respectively. Overall, 72 patients (28.3%) in the pembrolizumab plus chemotherapy group and 17 (9.1%) in the placebo plus chemotherapy group had discontinued any treatment because of treatment-related AEs. There were 14 patients (5.5%) in the pembrolizumab plus chemotherapy group and 1 (0.5%) in the placebo plus chemotherapy group who died because of a treatment-related AE (Table 3).

Immune-mediated AEs and infusion reactions occurred in 78 patients (30.7%) in the pembrolizumab group and 20 patients (10.8%) in the placebo plus chemotherapy group. These were grade 3 to 5 in 32 patients (12.6%) and six patients (3.2%), respectively. The most typically reported events were

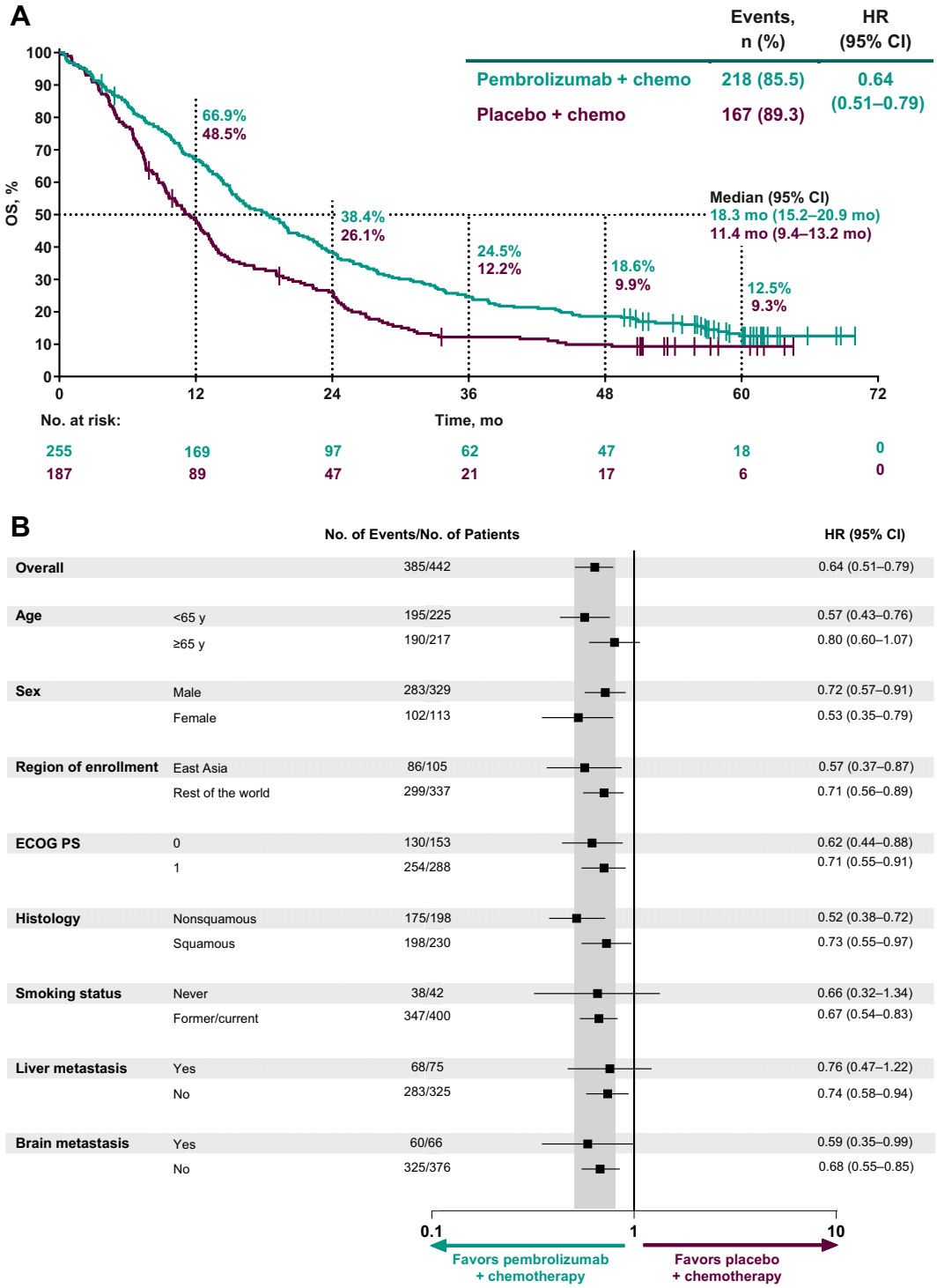

Figure 2. (*A*) Kaplan-Meier estimate of OS; (*B*) forest plot for OS in key patient subgroups; (*C*) Kaplan-Meier estimate of PFS; (*D*) forest plot for PFS in key patient subgroups; and (*E*) Kaplan-Meier estimate of PFS2 in patients with previously untreated metastatic NSCLC with PD-L1 TPS less than 1%. HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PFS2, progression-free survival 2; TPS, tumor proportion score.

hypothyroidism, hyperthyroidism, and pneumonitis across both treatment groups. Two patients (0.8%) in the pembrolizumab plus chemotherapy group had grade 5 pneumonitis; no patient in the placebo plus chemotherapy group experienced a grade 5 immune-mediated AE or infusion reaction (Table 3).

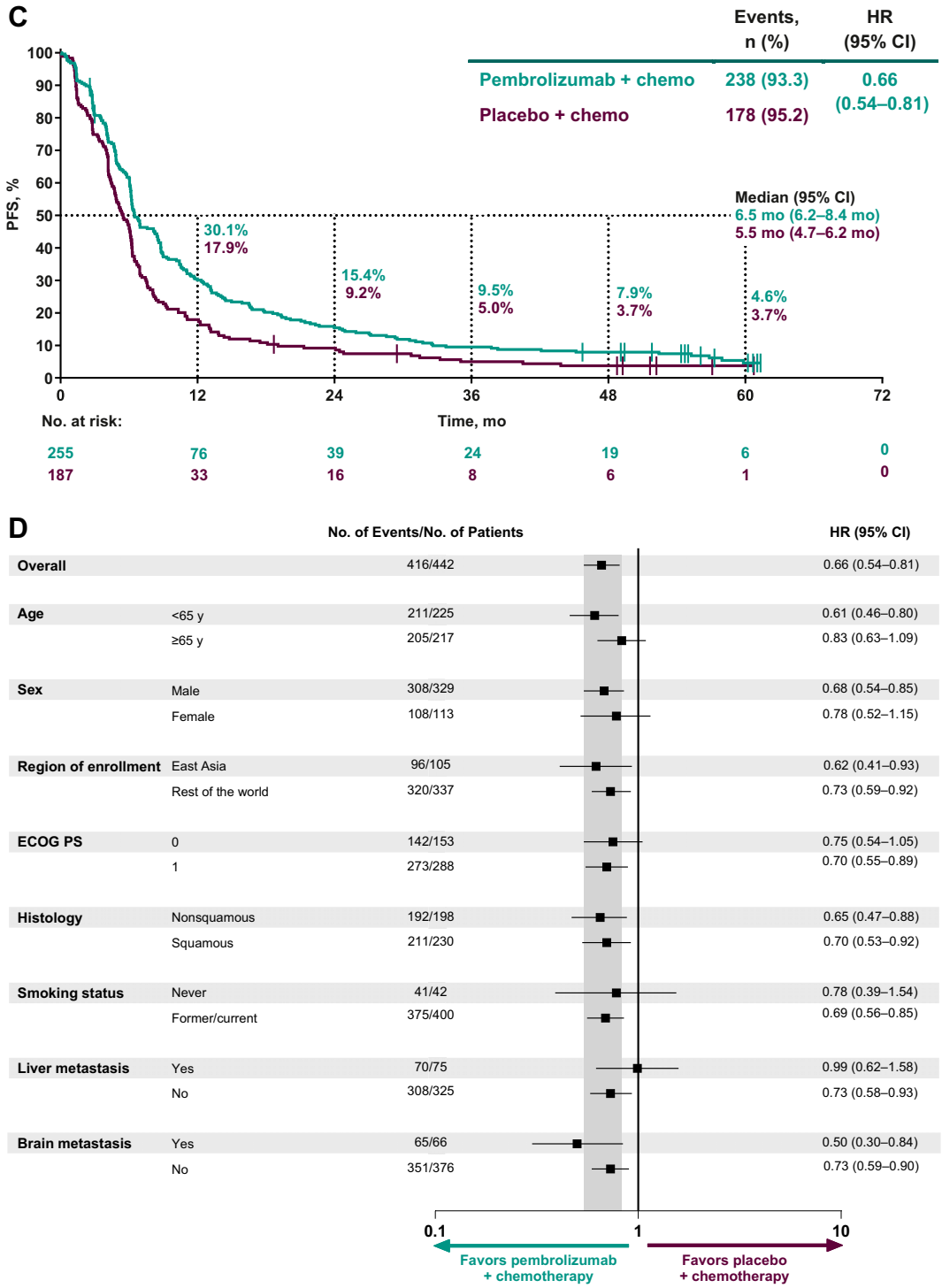

Figure 2. Continued.

Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab

Among patients randomized to the pembrolizumab plus chemotherapy group, 27 patients (10.6%) completed 35 cycles of pembrolizumab (Table 1). The ORR was 92.6% (95% CI: 75.7%–99.1%); three patients (11.1%) had CR, 22 (81.5%) had PR, and an additional 2 (7.4%) had stable disease. The median DOR was 55.1 (range, 7.4–59.3+) months. At the time of data cutoff, 17 patients were alive, of whom 12 had not received subsequent therapy or experienced PD. The 3-year OS rate after completion of 35 cycles of pembrolizumab (i.e., approximately 5 years from randomization) was 56.7% (95% CI: 33.4%–74.6%).

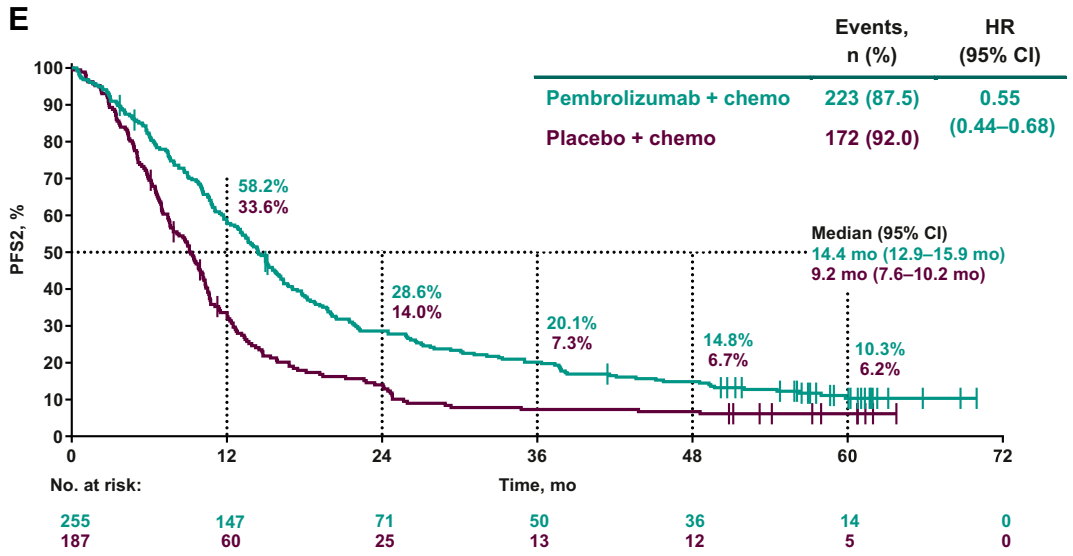

Figure 2. Continued.

All 27 patients reported at least one treatment-related AE. Grade 3 or 4 treatment-related AEs were reported in 15 patients (55.6%); no patient died because of a treatment-related AE. Immune-mediated AEs and infusion reactions occurred in eight patients (29.6%); one patient (3.7%) experienced a grade 3 immune-mediated AE (type 1 diabetes mellitus). No patient experienced grade 4 or 5 immune-mediated AEs or infusion reactions.

Discussion

Pembrolizumab plus chemotherapy is one of the recommended first-line treatment options in patients with metastatic NSCLC with PD-L1 TPS less than 1%.[3–7] Despite evidence from the KEYNOTE-189[1,12] and KEYNOTE-407 studies[2,13] reporting substantial OS and PFS benefits with pembrolizumab plus chemotherapy versus chemotherapy alone, real-world studies[9,10] have found that patients with metastatic NSCLC with PD-L1 TPS less than 1% more often received chemotherapy alone compared with immunotherapy plus chemotherapy. Because PD-L1 TPS was a stratification factor in both the KEYNOTE-189 and KEYNOTE-407 studies, we were able to pool patient-level data for those with metastatic NSCLC with PD-L1 TPS less than 1% enrolled in the KEYNOTE-189 global and Japan extension studies and KEYNOTE-407 global and People's Republic of China extension studies to allow for a larger sample size than the individual studies. In addition, PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA), approved by the U.S. Food and Drug Administration as a companion diagnostic assay for pembrolizumab, was used in all of the studies in the current pooled analysis to assess PD-L1 TPS, which minimizes assay-related variations.[14] Our pooled analysis found that after a minimum follow-up of 4 years (median, 5 years), pembrolizumab plus chemotherapy continued to provide clinically meaningful and durable improvements in OS, PFS, ORR, and PFS2 compared with placebo plus chemotherapy with a manageable safety profile in patients with previously untreated metastatic NSCLC with PD-L1 TPS less than 1%.

Our data indicate a 36% reduction in risk of death and an almost two-fold higher proportion of patients alive at 4 years after randomization in the pembrolizumab plus chemotherapy group versus chemotherapy alone. This result was observed despite the plateauing at the end of the chemotherapy Kaplan-Meier curve and is likely attributable to the high crossover rate to pembrolizumab monotherapy, as observed in each of these studies previously.[15,16] Similarly, there was a 34% reduction in risk of death or PD with pembrolizumab plus chemotherapy compared with chemotherapy alone. Pembrolizumab plus chemotherapy was also associated with improvement in PFS2 compared with chemotherapy alone, and, similar to the OS and PFS Kaplan-Meier curves, there was an early separation of the curves. The PFS2 data together with the high crossover rate from placebo plus chemotherapy to subsequent anti–PD-(L)1 therapy (including pembrolizumab) provide further support for treatment with pembrolizumab plus chemotherapy in the first-line setting in these patients, for whom pembrolizumab monotherapy is not an approved treatment option. Furthermore, pembrolizumab plus chemotherapy had durable antitumor activity among the 27 patients who completed 35 cycles of pembrolizumab, with more than half of the patients alive 3 years after completing the first course of pembrolizumab (i.e., approximately 5 years from

Table 2. Tumor Response per RECIST Version 1.1 by BICR

Response Parameter	Pembrolizumab Plus Chemotherapy, n = 255	Placebo Plus Chemotherapy, n = 187
ORR (95% CI), %	50.6 (44.3-56.9)	33.2 (26.5-40.4)
Best overall response, n (%)		
CR	4 (1.6)	5 (2.7)
PR	125 (49.0)	57 (30.5)
Stable disease	88 (34.5)	79 (42.2)
PD	20 (7.8)	31 (16.6)
Not evaluable[a]	11 (4.3)	6 (3.2)
Not assessed[b]	7 (2.7)	9 (4.8)
DOR,[c] median (range), mo	7.6 (1.1+ to 59.4+)	5.5 (1.4+ to 55.8+)
DOR ≥ 4 y,[c] no. at risk (%)	14 (16.3)	2 (14.2)
Time to response, median (range), mo	1.5 (1.2–19.2)	1.4 (0.8–10.4)

"+" indicates no PD at the time of last disease assessment.
[a]Postbaseline assessment(s) available but not evaluable or CR/PR/stable disease less than 6 weeks from randomization.
[b]No postbaseline assessment available for response evaluation.
[c]Based on Kaplan-Meier estimate.
BICR, blinded independent central review; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

randomization). Altogether, these data provide further evidence of the long-term efficacy of pembrolizumab in patients with PD-L1 TPS less than 1%.

At the time of data cutoff, all patients had completed first-course pembrolizumab, and there were no new safety signals identified. Overall, AEs were manageable with pembrolizumab plus chemotherapy with a similar proportion of patients reporting grade 3 to 5 treatment-related AEs versus chemotherapy alone (59.1% versus 61.3%). Although a higher proportion of patients in the

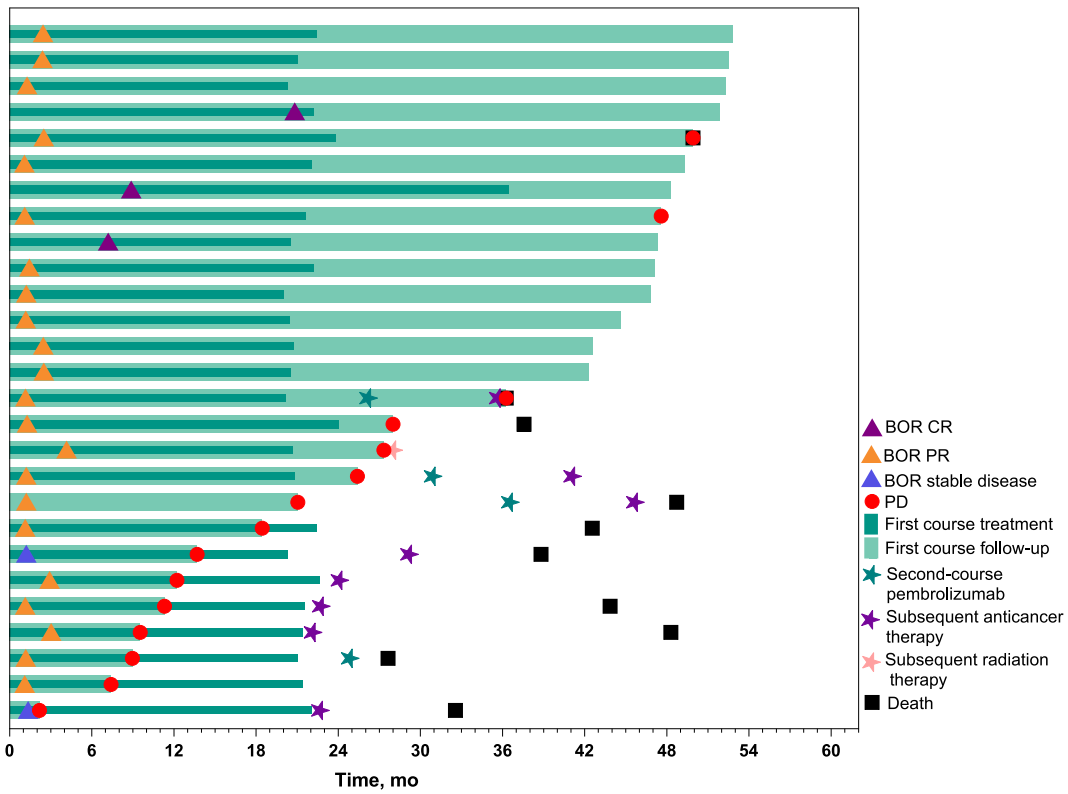

Figure 3. Patient response to pembrolizumab plus chemotherapy and placebo plus chemotherapy in patients with previously untreated metastatic NSCLC with PD-L1 TPS less than 1% who completed 35 cycles of pembrolizumab. BOR, best overall response; CR, complete response; PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; TPS, tumor proportion score.

Table 3. AE Summary in the Pooled Safety Population

Event, n (%)	Pembrolizumab Plus Chemotherapy, n = 254		Placebo Plus Chemotherapy, n = 186	
Any AE (all-cause)	252 (99.2)		185 (99.5)	
Grade 3–5	187 (73.6)		142 (76.3)	
Led to discontinuation of any treatment component	88 (34.6)		30 (16.1)	
Led to death	28 (11.0)		11 (5.9)	
Treatment-related	245 (96.5)		175 (94.1)	
Grade 3–5	150 (59.1)		114 (61.3)	
Led to discontinuation of any treatment component	72 (28.3)		17 (9.1)	
Led to death[a]	14 (5.5)		1 (0.5)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5
AEs occurring in ≥ 15% of patients in either treatment group				
Anemia	139 (54.7)	39 (15.4)	109 (58.6)	39 (21.0)
Nausea	121 (47.6)	5 (2.0)	79 (42.5)	5 (2.7)
Decreased appetite	86 (33.9)	2 (0.8)	59 (31.7)	0
Fatigue	83 (32.7)	15 (5.9)	47 (25.3)	6 (3.2)
Diarrhea	83 (32.7)	9 (3.5)	45 (24.2)	5 (2.7)
Constipation	74 (29.1)	1 (0.4)	59 (31.7)	3 (1.6)
Neutropenia	72 (28.3)	39 (15.4)	52 (28.0)	38 (20.4)
Alopecia	66 (26.0)	1 (0.4)	58 (31.2)	1 (0.5)
Thrombocytopenia	63 (24.8)	21 (8.3)	44 (23.7)	15 (8.1)
Asthenia	56 (22.0)	11 (4.3)	39 (21.0)	9 (4.8)
Vomiting	55 (21.7)	6 (2.4)	31 (16.7)	4 (2.2)
Cough	51 (20.1)	1 (0.4)	43 (23.1)	0
Arthralgia	52 (20.5)	2 (0.8)	34 (18.3)	1 (0.5)
Rash	48 (18.9)	1 (0.4)	21 (11.3)	2 (1.1)
Pyrexia	47 (18.5)	0	35 (18.8)	4 (2.2)
Decreased white blood cell count	43 (16.9)	16 (6.3)	35 (18.8)	16 (8.6)
Decreased neutrophil count	36 (14.2)	26 (10.2)	30 (16.1)	24 (12.9)
Dyspnea	32 (12.6)	2 (0.8)	36 (19.4)	2 (1.1)
Immune-mediated AEs and infusion reactions[b]	78 (30.7)	32 (12.6)	20 (10.8)	6 (3.2)
Hypothyroidism	22 (8.7)	1 (0.4)	4 (2.2)	0
Hyperthyroidism	16 (6.3)	0	4 (2.2)	0
Pneumonitis	16 (6.3)	10 (3.9)[c]	5 (2.7)	2 (1.1)
Infusion reactions	12 (4.7)	3 (1.2)	3 (1.6)	0
Colitis	5 (2.0)	3 (1.2)	1 (0.5)	1 (0.5)
Hepatitis	5 (2.0)	4 (1.6)	0	0
Nephritis	5 (2.0)	4 (1.6)	1 (0.5)	1 (0.5)
Severe skin reactions	4 (1.6)	2 (0.8)	3 (1.6)	3 (1.6)
Hypophysitis	3 (1.2)	1 (0.4)	0	0
Adrenal insufficiency	2 (0.8)	0	0	0
Pancreatitis	2 (0.8)	2 (0.8)	0	0
Thyroiditis	2 (0.8)	0	0	0
Encephalitis	1 (0.4)	1 (0.4)	0	0
Guillain-Barré syndrome	1 (0.4)	1 (0.4)	0	0
Myositis	1 (0.4)	0	0	0
Type 1 diabetes mellitus	1 (0.4)	1 (0.4)	0	0
Vasculitis	1 (0.4)	0	0	0

[a]Treatment-related AEs that led to death were: death, pneumonia, and pneumonitis (each n = 2); acute kidney injury, cardiac arrest, cardiac failure, encephalopathy, hepatic failure, neutropenic sepsis, pulmonary hemorrhage, respiratory failure, and septic shock (each n = 1) in the pembrolizumab plus chemotherapy group; and septic shock (n = 1) in the placebo plus chemotherapy group.
[b]Immune-mediated adverse events and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator.
[c]2 patients experienced grade 5 pneumonitis.
AE, adverse event.

pembrolizumab plus chemotherapy group than in the chemotherapy alone group discontinued any treatment because of treatment-related AEs (72 [28.3%] versus 17 [9.1%]) and had fatal treatment-related AEs (14 [5.5%] versus 1 [0.5%]), the safety profiles in both treatment groups were consistent with those observed in the individual studies included in this analysis[15,16] and the established safety profile of pembrolizumab.

The results from the current pooled analysis build on a previous pooled analysis of randomized controlled studies of pembrolizumab plus chemotherapy versus chemotherapy alone in patients with previously untreated NSCLC with PD-L1 TPS less than 1% after a median follow-up of 28.0 (range, 14.7–55.4) months.[11] Our results in a larger number of patients are consistent with the individual KEYNOTE-189 and KEYNOTE-407 studies included in this pooled analysis, which reported HRs for OS (for pembrolizumab plus chemotherapy versus chemotherapy alone) of 0.55 and 0.83, respectively, and HRs for PFS of 0.67 and 0.70, respectively, in the global studies after a median follow-up of 5 years.[15,16] The 5-year follow-up outcomes were not available in the respective Japan and People's Republic of China extension studies at the time of this analysis. However, long-term outcomes have been reported in a pooled analysis of 107 patients with advanced or metastatic NSCLC with PD-L1 TPS less than 1% enrolled in East Asian countries in randomized controlled trials of pembrolizumab plus chemotherapy versus chemotherapy alone, including patients enrolled in all four studies included in the current pooled analysis.[17] In the pooled analysis of East Asian patients, pembrolizumab plus chemotherapy was associated with improved OS (HR, 0.55; 2-year OS rate, 46% versus 28%) and PFS (HR, 0.64; 2-year PFS rate, 17% versus 10%) versus chemotherapy alone after a median follow-up of 33.4 (range, 25.3–49.2) months, consistent with the trends observed in our pooled analysis.

Although several studies have reported efficacy of other anti–PD-(L)1–based therapies versus chemotherapy alone in subgroups of patients with advanced or metastatic NSCLC with PD-L1 TPS less than 1%,[18–21] limited long-term efficacy and safety data are available in a large patient population in this setting. For context, 5-year outcomes from part 1 of the CheckMate 227 study reported an HR for OS of 0.80 (95% CI: 0.64–1.00) for nivolumab plus chemotherapy versus chemotherapy alone in patients with tumor PD-L1 expression less than 1%, which is higher than the HR observed in our pooled analysis for pembrolizumab plus chemotherapy and includes 1 in the CI.[18] The same study also evaluated the combination of nivolumab plus ipilimumab versus chemotherapy alone and reported an HR for OS of 0.65 (95% CI: 0.52–0.81), which is similar to the HR observed in our pooled analysis.[18] The safety profile of nivolumab plus chemotherapy was similar to that observed with pembrolizumab plus chemotherapy. Of note, neither nivolumab plus chemotherapy nor the nivolumab plus ipilimumab regimen is approved for the treatment of patients with previously untreated advanced or metastatic NSCLC with PD-L1 TPS less than 1%. In addition, recent findings from the CheckMate 9LA study of first-line nivolumab plus ipilimumab and chemotherapy versus chemotherapy alone reported an HR for OS of 0.66 (95% CI: 0.50–0.86) in a subgroup of patients with PD-L1 expression less than 1% (n = 264),[22] similar to the findings in the present study. Conversely, results from part 2 of the EMPOWER-Lung 3 study of cemiplimab (anti–PD-1) plus chemotherapy versus chemotherapy alone reported an HR for OS of 1.01 (95% CI: 0.63–1.60) in patients with tumor PD-L1 less than 1% (n = 139).[23] Although pembrolizumab plus chemotherapy is an effective standard of care in this setting, there is a need for additional treatment options for the subset of patients who achieve limited benefit from it.

The current pooled analysis had certain limitations. This was an exploratory posthoc analysis and therefore was not powered for statistical significance testing, which limits interpretation of the results. Our analysis also did not adjust for the relatively high rate of patients who crossed over from placebo plus chemotherapy to pembrolizumab, which potentially attenuated the treatment effect of pembrolizumab. Of note, pembrolizumab monotherapy is not approved as second-line therapy in patients with metastatic NSCLC with PD-L1 TPS less than 1%.[3]

In conclusion, pembrolizumab plus chemotherapy continued to exhibit clinically meaningful and durable improvements in survival outcomes and antitumor activity compared with placebo plus chemotherapy with manageable toxicity in patients with metastatic NSCLC with PD-L1 TPS less than 1% after a median follow-up of 5 years. These results continue to support pembrolizumab plus chemotherapy as a standard of care first-line therapy for metastatic NSCLC with PD-L1 TPS less than 1%.

Data Availability Statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA (MSD) 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) 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 US and EU 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 will 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.

CRediT Authorship Contribution Statement

Shirish M. Gadgeel: Formal analysis, Investigation, Resources, Writing - review & editing.

Delvys Rodríguez-Abreu: Formal analysis, Investigation, Resources, Writing - review & editing.

Balazs Halmos: Formal analysis, Investigation, Writing - review & editing.

Marina C. Garassino: Formal analysis, Resources, Writing - review & editing.

Takayasu Kurata: Investigation, Resources, Writing - review & editing.

Ying Cheng: Formal analysis, Investigation, Resources, Writing - review & editing.

Erin Jensen: Formal analysis, Writing - review & editing.

Mark Shamoun: Formal analysis, Writing - review & editing.

Kumar Rajagopalan: Formal analysis, Roles/Writing - original draft, Writing - review & editing.

Luis Paz-Ares: Conceptualization, Formal analysis, Investigation, Writing - review & editing.

Disclosure

Dr. Gadgeel receives consulting fees from AstraZeneca, Genentech/Roche, Takeda/Ariad, Bristol-Myers Squibb, AbbVie, Gilead, Bayer, Daiichi, Mirati, Janssen, Pfizer, Jazz Pharmaceuticals, Blueprint, Lilly, and Regeneron; is the Division Head for Hematology/Oncology and the Associate Director for Patient Experience and Clinical Care, Henry Ford Cancer Institute/Henry Ford Health, Detroit, Michigan; received study funding to the institution from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and participated in a Data Safety Monitoring Board or Advisory Board for AstraZeneca and Boehringer Ingelheim. Dr. Rodríguez-Abreu has received personal fees or honoraria for consultancy and lectures from Roche, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Eli Lilly, Pfizer, Gilead, Incyte, Sanofi, Regeneron, Takeda, and Novartis; received funding for travel expenses from Roche, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and Novartis; received study funding to the institution from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and participated in a Data Safety Monitoring Board or Advisory Board for Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Regeneron, BMS, GlaxoSmithKline, and Lilly. Dr. Halmos reports receiving grants from Boehringer Ingelheim, AstraZeneca, MSD, BMS, Advaxis, Amgen, AbbVie, Daiichi, Pfizer, GlaxoSmithKline, Beigene, and Janssen; consulting fees from AstraZeneca, Boehringer Ingelheim, Apollomics, Janssen, Takeda, MSD, BMS, Genentech, Pfizer, Eli Lilly, Arcus, Merus, and Daiichi; and participated in a Data Safety Monitoring Board or Advisory Board for BMS, TPT, and Apollomics. Dr. Garassino has personal financial interests in AstraZeneca, Abion, MSD International GmbH, Bayer, BMS, Boehringer Ingelheim Italia S.p.A, Celgene, Eli Lilly, Incyte, Novartis, Pfizer, Roche, Takeda, Seattle Genetics, Mirati, Daiichi-Sankyo, Regeneron, Merck & Co., Inc., Rahway, New Jersey, Blueprint, Janssen, Sanofi, AbbVie, BeiGenius, Oncohost, Medscape, Gilead, and Io Biotech; has institutional financial interests in Eli Lilly, MSD, Pfizer (MISP), AstraZeneca, MSD International GmbH, BMS, Boehringer Ingelheim Italia S.p.A, Celgene, Eli Lilly, Ignyta, Incyte, MedImmune, Novartis, Pfizer, Roche, Takeda, Tiziana, Foundation Medicine, GlaxoSmithKline, and Spectrum Pharmaceuticals; receives other assistance from AIRC, AIFA, Italian Moh, and TRANSCAN; research fundings from Horizon 2020; study funding to the institution from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Bristol-Myers Squibb, Roche/Genentech, AstraZeneca/MedImmune, AstraZeneca, Pfizer, GlaxoSmithKline, Novartis, Incyte, Takeda, Spectrum Pharmaceuticals, Blueprint Medicines, Eli Lilly, Ipsen, Janssen, Exelixis, Sanofi, Pfizer, and Amgen; has consulting or advisory role with Bristol-Myers Squibb, MSD, AstraZeneca, Novartis, Takeda, Roche, Sanofi-

Aventis, Celgene, Daiichi-Sankyo, Pfizer, Seattle Genetics, Eli Lilly, GlaxoSmithKline, Bayer Healthcare Pharmaceuticals, Blueprint Medicines, Janssen, Regeneron, Bayer, AbbVie, Mirati, Boehringer Ingelheim, and Abion; receives honoraria from MSD Oncology, AstraZeneca, GlaxoSmithKline, Takeda, Roche, Bristol-Myers Squibb, Daiichi-Sankyo, Regeneron, Pfizer, Blueprint Medicines, Novartis, Sanofi-Aventis, and Medscape; participated in the Speakers' bureau for AstraZeneca, MSD Oncology, Mirati, and Daiichi-Sankyo/AstraZeneca; and received funding for travel and accommodation from Pfizer, Roche, and AstraZeneca. Dr. Kurata receives honoraria from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Ono Pharmaceutical; Bristol-Myers Squibb; AstraZeneca; Chugai; Eli Lilly; Pfizer; and Nipponkayaku; and received research funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, AstraZeneca, Takeda, Bristol-Myers Squibb, Janssen Pharmaceutical, and Daiichi-Sankyo. Ms. Jensen, Dr. Shamoun, and Dr. Rajagopalan are employees and owns stock in Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Dr. Paz-Ares received grants to institution from AstraZeneca, BMS, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and Pfizer; received consulting fees from Lilly, MSD, Roche, Pharmamar, Merck Serono, AstraZeneca, Novartis, Servier, Amgen, Pfizer, Sanofi, Bayer, BMS, Mirati, GSK, Janssen, Takeda, and Daichii Sankyo; and honoraria from AstraZeneca, Janssen, Merck Serono, and Mirati.

Acknowledgments

Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA. We thank the patients and their families and caregivers for participating in this study, along with all investigators and site personnel. Medical writing assistance was provided by Christabel Wilson, MSc, of ICON plc (Blue Bell, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA.

This work was supported by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the Journal of Thoracic Oncology at www.jto.org and at https://doi.org/10.1016/j.jtho.2024.04.011.

References

1. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
2. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051.
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Small Cell Lung Cancer. Version 3.2023. https://www.nccn.org/. Accessed August 24, 2023.
4. National Health Commission Of The People's Republic Of China. National guidelines for diagnosis and treatment of lung cancer 2022 in China (English version). *Chin J Cancer Res*. 2022;34:176–206.
5. Akamatsu H, Ninomiya K, Kenmotsu H, et al. The Japanese Lung Cancer Society guideline for non-small cell lung cancer, stage IV. *Int J Clin Oncol*. 2019;24:731–770.
6. Wu YL, Planchard D, Lu S, et al. Pan-Asian adapted clinical practice guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. *Ann Oncol*. 2019;30:171–210.
7. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:358–376.
8. Dietel M, Savelov N, Salanova R, et al. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non-small-cell lung cancer: the global, multicenter Express study. *Lung Cancer*. 2019;134:174–179.
9. Bailey H, Lee A, Eccles L, et al. Treatment patterns and outcomes of patients with metastatic non-small cell lung cancer in five European countries: a real-world evidence survey. *BMC Cancer*. 2023;23:603.
10. Stenehjem D, Lubinga S, Betts KA, et al. Treatment patterns in patients with metastatic non-small-cell lung cancer in the era of immunotherapy. *Future Oncol*. 2021;17:2940–2949.
11. Borghaei H, Langer CJ, Paz-Ares L, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone in patients with advanced non-small cell lung cancer without tumor PD-L1 expression: a pooled analysis of 3 randomized controlled trials. *Cancer*. 2020;126:4867–4877.
12. Horinouchi H, Nogami N, Saka H, et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189 Japan Study. *Cancer Sci*. 2021;112:3255–3265.
13. Cheng Y, Zhang L, Hu J, et al. Pembrolizumab plus chemotherapy for Chinese patients with metastatic squamous NSCLC in KEYNOTE-407. *JTO Clin Res Rep*. 2021;2:100225.
14. Keytruda (pembrolizumab). Full Prescribing Information, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. 2024.
15. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. *J Clin Oncol*. 2023;41:1992–1998.
16. Novello S, Kowalski DM, Luft A, et al. Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer: 5-year update of the phase III KEYNOTE-407 study. *J Clin Oncol*. 2023;41:1999–2006.

17. Cheng Y, Yang JC, Okamoto I, et al. Pembrolizumab plus chemotherapy for advanced non-small-cell lung cancer without tumor PD-L1 expression in Asia. *Immunotherapy*. 2023;15:1029–1044.
18. Brahmer JR, Lee JS, Ciuleanu TE, et al. Five-year survival outcomes with nivolumab plus ipilimumab versus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer in CheckMate 227. *J Clin Oncol*. 2023;41:1200–1212.
19. Nishio M, Barlesi F, West H, et al. Atezolizumab plus chemotherapy for first-line treatment of nonsquamous NSCLC: results from the randomized phase 3 IMpower132 trial. *J Thorac Oncol*. 2021;16:653–664.
20. Paz-Ares LG, Ramalingam SS, Ciuleanu TE, et al. First-line nivolumab plus ipilimumab in advanced NSCLC: 4-year outcomes from the randomized, open-label, Phase 3 CheckMate 227 Part 1 Trial. *J Thorac Oncol*. 2022;17:289–308.
21. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924–937.
22. Carbone DP, Ciuleanu TE, Schenker M, et al. Four-year clinical update and treatment switching-adjusted outcomes with first-line nivolumab plus ipilimumab with chemotherapy for metastatic non-small cell lung cancer in the CheckMate 9LA randomized trial. *J Immunother Cancer*. 2024;12:e008189.
23. Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. *Nat Med*. 2022;28:2374–2380.