

clinical trial updates

Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non–Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study

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abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically on the basis of the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

We present 5-year outcomes from the phase 3 KEYNOTE-189 study (ClinicalTrials.gov identifier: [NCT02578680](https://clinicaltrials.gov/ct2/show/study/NCT02578680)). Eligible patients with previously untreated metastatic nonsquamous non–small-cell lung cancer without *EGFR/ALK* alterations were randomly assigned 2:1 to pembrolizumab 200 mg or placebo once every 3 weeks for up to 35 cycles with pemetrexed and investigator's choice of carboplatin/cisplatin for four cycles, followed by maintenance pemetrexed until disease progression or unacceptable toxicity. Primary end points were overall survival (OS) and progression-free survival (PFS). Among 616 randomly assigned patients (n = 410, pembrolizumab plus pemetrexed-platinum; n = 206, placebo plus pemetrexed-platinum), median time from random assignment to data cutoff (March 8, 2022) was 64.6 (range, 60.1–72.4) months. Hazard ratio (95% CI) for OS was 0.60 (0.50 to 0.72) and PFS was 0.50 (0.42 to 0.60) for pembrolizumab plus platinum-pemetrexed versus placebo plus platinum-pemetrexed. 5-year OS rates were 19.4% versus 11.3%. Toxicity was manageable. Among 57 patients who completed 35 cycles of pembrolizumab, objective response rate was 86.0% and 3-year OS rate after completing 35 cycles (approximately 5 years after random assignment) was 71.9%. Pembrolizumab plus pemetrexed-platinum maintained OS and PFS benefits versus placebo plus pemetrexed-platinum, regardless of programmed cell death ligand-1 expression. These data continue to support pembrolizumab plus pemetrexed-platinum as a standard of care in previously untreated metastatic non–small-cell lung cancer without *EGFR/ALK* alterations.

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ASSOCIATED CONTENT

Appendix

Protocol

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

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INTRODUCTION

In the phase 3 KEYNOTE-189 study, pembrolizumab (an anti–programmed cell death protein-1 monoclonal antibody) plus pemetrexed and carboplatin/cisplatin significantly prolonged overall survival (OS; hazard ratio [HR], 0.49; 95% CI, 0.38 to 0.64; $P < .001$) and progression-free survival (PFS; 0.52; 0.43 to 0.64; $P < .001$) versus placebo plus pemetrexed-platinum in previously untreated metastatic nonsquamous non–small-cell lung cancer (NSCLC) without *EGFR/ALK* alterations.¹ In the protocol-specified final analysis, OS and PFS continued to improve with HRs (95% CI) of 0.56 (0.46 to 0.69) and 0.49 (0.41 to 0.59), respectively.² We present a 5-year exploratory analysis from KEYNOTE-189.

METHODS

Study Design and Patients

The study design for KEYNOTE-189 (ClinicalTrials.gov identifier: [NCT02578680](https://clinicaltrials.gov/ct2/show/study/NCT02578680)) has been previously described.¹⁻³ The Protocol (online only) and its amendments were approved by the appropriate institutional review boards and ethics committees. Patients provided written informed consent before enrollment.

Patients were randomly assigned 2:1 to pembrolizumab 200 mg or placebo once every 3 weeks for up to 35 cycles (approximately 2 years). Patients also received pemetrexed 500 mg/m² plus cisplatin 75 mg/m² or carboplatin area under the curve 5 mg/mL/min once every 3 weeks for four cycles followed by pemetrexed

CONTEXT

Key Objective

We examined whether patients with previously untreated metastatic nonsquamous non–small-cell lung cancer without *EGFR/ALK* alterations treated with pembrolizumab plus pemetrexed and platinum chemotherapy continue to experience improved survival outcomes versus placebo plus pemetrexed and platinum chemotherapy after 5 years of follow-up.

Knowledge Generated

After 5 years, pembrolizumab plus pemetrexed-platinum was associated with improved overall survival (OS) and progression-free survival compared with placebo plus pemetrexed-platinum in patients with metastatic nonsquamous non–small-cell lung cancer, regardless of programmed cell death ligand-1 expression. Five-year OS rates were 19.4% versus 11.3% in the intention-to-treat population.

Relevance (T.E. Stinchcombe)

The 5-year follow-up demonstrates durable benefit for the combination of platinum-pemetrexed and pembrolizumab and the benefit in the subsets of patients on the basis of tumor programmed cell death ligand-1 expression. In the future, the landmark analyses of progression-free survival or OS at 3 or 5 years may be used to assess the long-term benefit of novel immunotherapies.*

*Relevance section written by JCO Associate Editor Thomas E. Stinchcombe, MD.

maintenance therapy. Treatment continued until the maximum number of cycles or until radiographic progression, unacceptable toxicity, investigator's decision, or patient withdrawal. Patients in the placebo plus pemetrexed-platinum group could cross over to receive pembrolizumab monotherapy upon documented progressive disease (PD) per RECIST v1.1 by blinded independent central review (BICR) if eligibility criteria were met. Patients could receive a second course of pembrolizumab monotherapy for up to 17 cycles (approximately 1 year) upon PD after either completing 35 cycles of pembrolizumab with a best overall response of stable disease or better or having achieved confirmed investigator-assessed complete response (CR) after receiving ≥ 8 cycles of pembrolizumab and ≥ 2 cycles beyond the initial CR assessment.

End Points and Statistical Analysis

Primary end points were PFS per RECIST v1.1 by BICR and OS. Secondary end points were objective response rate (ORR) and duration of response (DOR) per RECIST v1.1 by BICR and safety. Exploratory end points included PFS2 (time from random assignment to second/subsequent PD on next-line treatment or death from any cause). No alpha was assigned to this analysis.

RESULTS

Patients

Overall, 616 patients were randomly assigned to pembrolizumab plus pemetrexed-platinum ($n = 410$) or placebo plus pemetrexed-platinum ($n = 206$; [Table 1](#)). At data cutoff (March 8, 2022), seven patients (all in the pembrolizumab plus pemetrexed-platinum group) were continuing to

receive pemetrexed. Among patients randomly assigned to pembrolizumab plus pemetrexed-platinum, 224 (54.6%) received subsequent anticancer therapy (103 received anti-PD-1 or anti-programmed cell death ligand 1 [PD-L1] therapy, including nine who began on-study second-course pembrolizumab; [Appendix Table A1](#), online only). In the placebo plus pemetrexed-platinum group, 84 patients crossed over to pembrolizumab monotherapy on-study; an additional 34 patients received subsequent anti-PD-(L)1 therapy outside the study for an effective crossover rate of 57.3%.

Efficacy Outcomes

Median time from random assignment to data cutoff was 64.6 (range, 60.1-72.4) months. In the intention-to-treat (ITT) population, HRs (95% CI) for pembrolizumab plus pemetrexed-platinum versus placebo plus pemetrexed-platinum were 0.60 (0.50 to 0.72) for OS and 0.50 (0.42 to 0.60) for PFS ([Figs 1A and 1E](#)). Five-year OS rates were 19.4% versus 11.3%, and 5-year PFS rates were 7.5% versus 0.6%. ORR (95% CI) was 48.3% (43.4 to 53.2) and 19.9% (14.7 to 26.0), respectively. Median (range) DOR was 12.7 (1.1+ to 68.3+) and 7.1 (2.4 to 31.5) months, respectively ([Fig 2A](#)). Similar trends were observed across the PD-L1 subgroups analyzed ([Figs 1B-1D, 1F-1H](#); [Appendix Table A2](#) [online only]; and [Appendix Fig A1](#) [online only]).

Median (95% CI) PFS2 was 17.0 (15.0 to 19.2) months in the pembrolizumab plus pemetrexed-platinum group versus 9.1 (7.6 to 10.8) months in the placebo plus pemetrexed-platinum group (HR, 0.54; 95% CI, 0.45 to 0.65). Five-year PFS2 rates (95% CI) were 16.7% (13.2 to 20.5) versus 7.8% (4.7 to 12.1).

TABLE 1. Patient Baseline Characteristics

Characteristic	Pembrolizumab Plus Chemotherapy (n = 410)	Placebo Plus Chemotherapy (n = 206)	Completed 35 Cycles of Pembrolizumab (n = 57)
Age, years, median (range)	65.0 (34-84)	63.5 (34-84)	66.0 (42-82)
Sex			
Male	254 (62.0)	109 (52.9)	34 (59.6)
Female	156 (38.0)	97 (47.1)	23 (40.4)
ECOG performance status			
0	185 (45.1)	79 (38.3)	35 (61.4)
1	221 (53.9)	126 (61.2)	22 (38.6)
2	1 (0.2)	0	0
Missing	3 (0.7)	1 (0.5)	0
Smoking status			
Former or current	362 (88.3)	181 (87.9)	52 (91.2)
Never	48 (11.7)	25 (12.1)	5 (8.8)
Histology			
Adenocarcinoma	394 (96.1)	199 (96.6)	57 (100.0)
NSCLC not otherwise specified	10 (2.4)	4 (1.9)	0
Other	6 (1.5)	3 (1.5)	0
Brain metastases	73 (17.8)	35 (17.0)	6 (10.5)
Liver metastases	66 (16.1)	50 (24.3)	8 (14.3)
PD-L1 TPS ^a			
< 1%	127 (31.0)	63 (30.6)	6 (10.5)
≥ 1%	260 (63.4)	128 (62.1)	48 (84.2)
1%-49%	128 (31.2)	58 (28.2)	17 (29.8)
≥ 50%	132 (32.2)	70 (34.0)	31 (54.4)
Could not be evaluated	23 (5.6)	15 (7.3)	3 (5.3)
Platinum chemotherapy			
Cisplatin	113 (27.6)	58 (28.2)	17 (29.8)
Carboplatin	297 (72.4)	148 (71.8)	40 (70.2)
Prior therapy			
Thoracic radiotherapy	29 (7.1)	19 (9.2)	5 (8.8)
Neoadjuvant therapy	5 (1.2)	6 (2.9)	0
Adjuvant therapy	25 (6.1)	14 (6.8)	5 (8.8)

NOTE. Data are No. (%) unless noted otherwise.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score.

^aPD-L1 expression was determined by PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA), as previously described.¹

Safety

Overall, 404 patients (99.8%) in the pembrolizumab plus pemetrexed-platinum group and 200 (99.0%) in the placebo plus pemetrexed-platinum group experienced adverse events (AEs). All fatal AEs were previously reported.^{2,3} Immune-mediated AEs and infusion reactions occurred in 113 (27.9%) and 27 (13.4%) patients, respectively (Appendix Table A3, online only).

Patients Who Completed 35 Cycles of Pembrolizumab

Of the patients randomly assigned to pembrolizumab plus pemetrexed-platinum, 57 (13.9%) completed 35 cycles of pembrolizumab (Table 1) and received a median of 35 (range, 2-98) cycles of pemetrexed. ORR was 86.0% (8 CRs, 41 partial responses) and eight patients had best response of stable disease (Fig 2B). Median DOR was 57.7 (range, 4.2 to 68.3+) months. Estimated OS rate 3 years

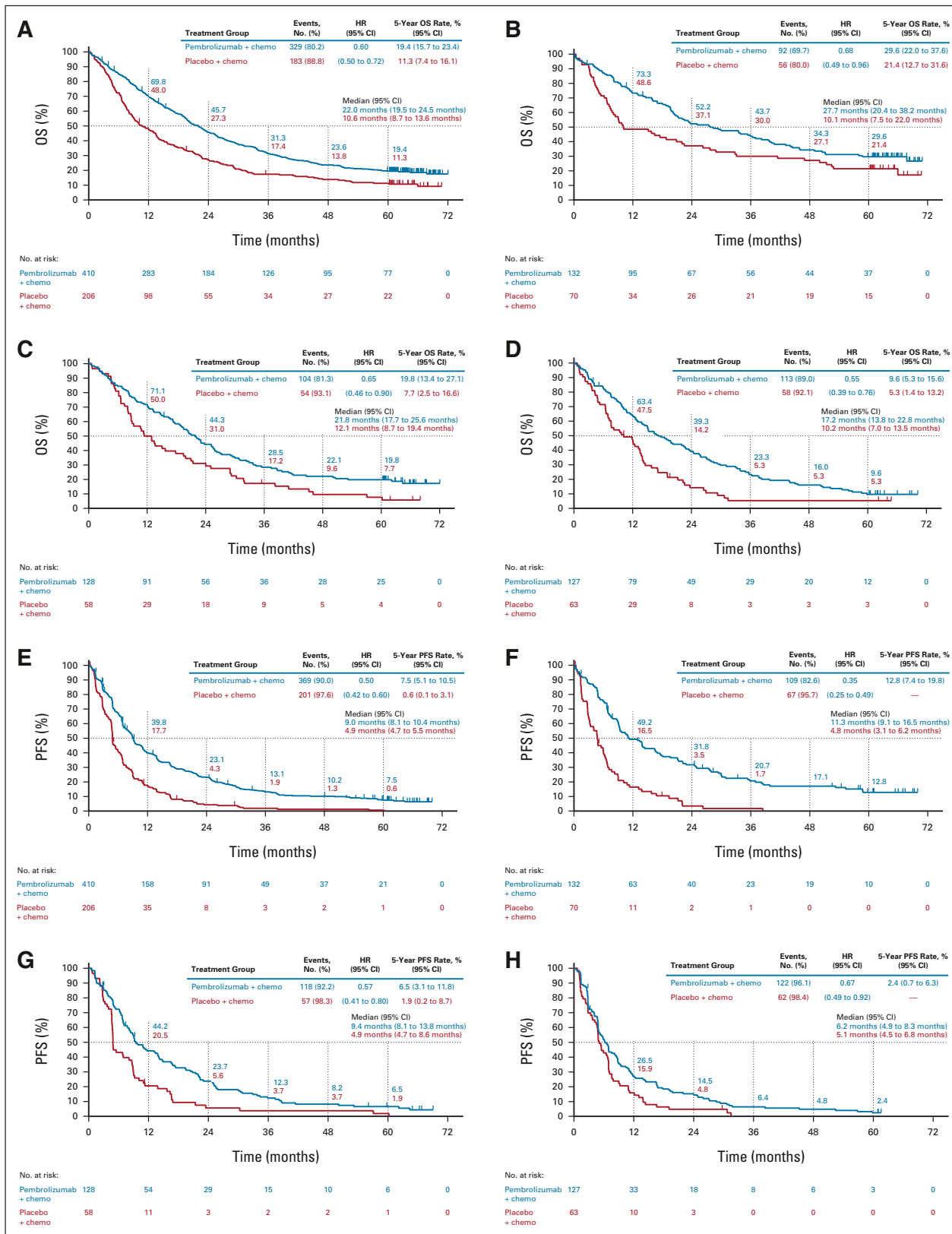


FIG 1. Kaplan-Meier estimates of OS in the (A) ITT, (B) PD-L1 TPS ≥ 50%, (C) PD-L1 TPS 1%-49%, and (D) PD-L1 TPS < 1% populations and PFS by RECIST version 1.1 by blinded independent central review in the (E) ITT, (F) PD-L1 TPS ≥ 50%, (G) PD-L1 TPS 1%-49%, and (H) PD-L1 TPS < 1% populations. Chemo, chemotherapy; ITT, intention-to-treat; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

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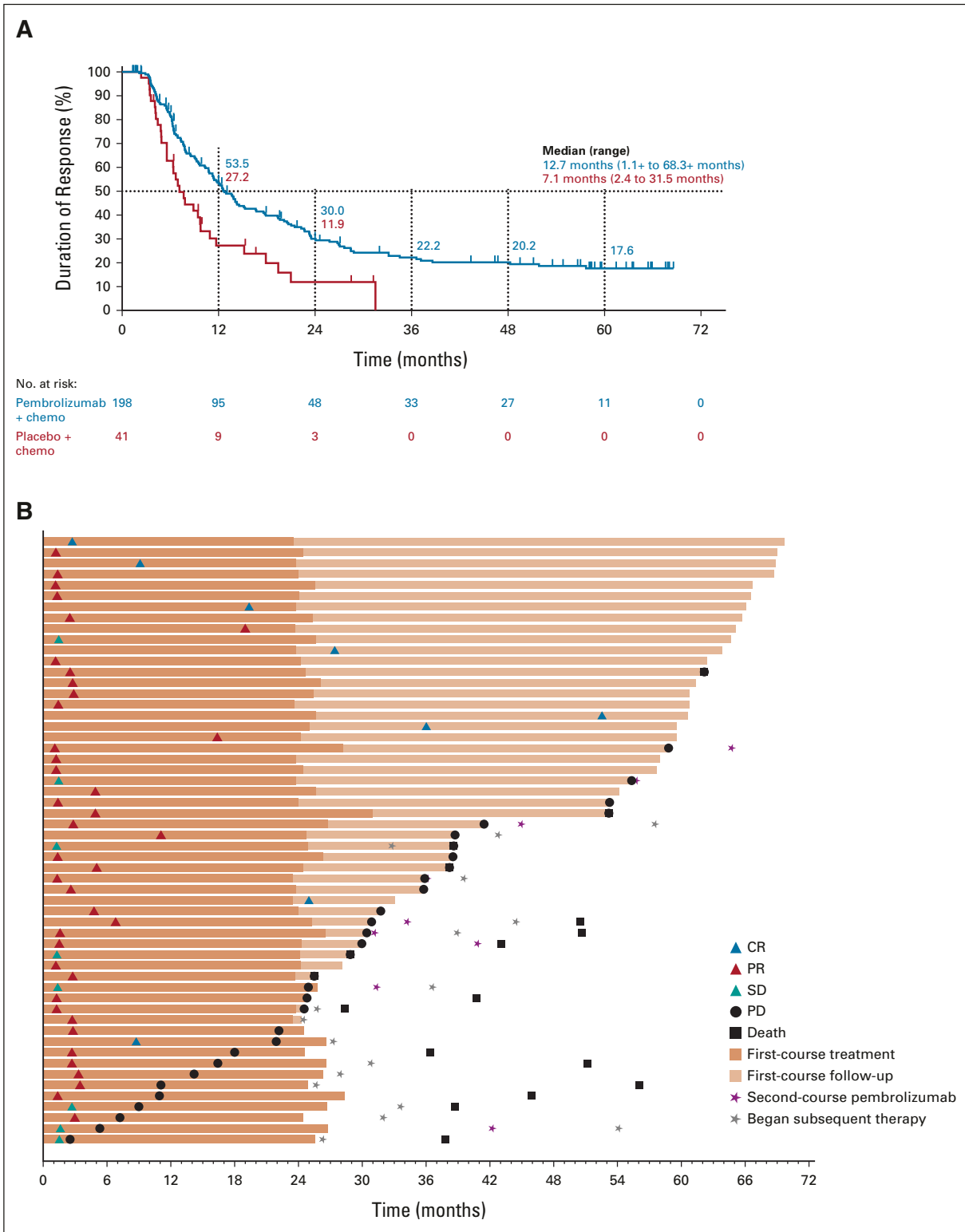


FIG 2. (A) Duration of response in the ITT population and (B) treatment duration and time to response in patients who completed 35 cycles of pembrolizumab. Response assessments are shown per RECIST version 1.1 by BICR. Median PFS was not reached (95% CI, 14.7 months to not reached). PFS rate 3 years after completion of 35 cycles was 56.2% (95% CI, 39.7 to 69.8). BICR, blinded independent central review; chemo, chemotherapy; CR, complete response; ITT, intention-to-treat; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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after completion of 35 cycles (ie, approximately 5 years from random assignment) was 71.9% (95% CI, 58.3 to 81.8). At data cutoff, 23 of 57 patients (40.4%) were alive without PD or subsequent therapy.

All patients experienced ≥ 1 AE (grade 3/4 AEs, 38 [66.7%]); none were grade 5. Immune-mediated AEs and infusion reactions occurred in 23 patients (40.4%; grade 3/4 in 7 [12.3%]).

DISCUSSION

In this 5-year update from KEYNOTE-189, pembrolizumab plus pemetrexed-platinum continued to prolong OS and PFS regardless of PD-L1 expression versus placebo plus pemetrexed-platinum with manageable toxicity (consistent with previous reports)^{2,3} in patients with previously untreated metastatic nonsquamous NSCLC without *EGFR/ALK* alterations. Five-year OS rate was approximately 20% with pembrolizumab plus pemetrexed-platinum in the ITT population (*v* 11% with placebo plus pemetrexed-platinum) and was higher in patients with higher PD-L1 tumor proportion score (TPS), especially in the TPS $\geq 50\%$ subgroup (29.6% *v* 21.4%; similar to the 5-year OS rates in the KEYNOTE-024 study of pembrolizumab monotherapy *v* chemotherapy [31.9% *v* 16.3%]¹⁴). However, there were a limited number of patients at risk at 5 years in some subgroups. Importantly, benefits were also observed in the PD-L1 TPS < 1% subgroup, for whom pembrolizumab monotherapy is not indicated.

Sustained improvements in OS were observed with pembrolizumab plus pemetrexed-platinum versus placebo plus pemetrexed-platinum despite an effective crossover rate of 57% from placebo plus pemetrexed-platinum to subsequent anti-PD-(L)1 therapy, which is reflected in the plateauing of the placebo plus pemetrexed-platinum Kaplan-Meier curve and was not

previously observed in studies of chemotherapy alone.⁵ These factors likely attenuated the differences in 5-year OS rates in the ITT population and in OS HR observed in later analyses compared with the first interim analysis.¹ The improvement in PFS2 with pembrolizumab plus pemetrexed-platinum versus placebo plus pemetrexed-platinum also suggests the benefit of pembrolizumab plus pemetrexed-platinum is maintained after initial disease progression, further supporting its use as first-line treatment.

Pembrolizumab demonstrated robust and durable antitumor activity in patients who completed 35 cycles of pembrolizumab, with a majority of patients (72%) alive 3 years after completion (approximately 5 years after random assignment). These data support the feasibility of a 2-year treatment duration with pembrolizumab plus pemetrexed-platinum and are consistent with the outcomes reported in patients who completed 35 cycles of pembrolizumab monotherapy^{6,7} and in the KEYNOTE-407 study of pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel versus placebo plus carboplatin and paclitaxel/nab-paclitaxel in previously untreated metastatic squamous NSCLC.⁸ Although this is the first report of 5-year outcomes for anti-PD-(L)1 therapy plus chemotherapy from a phase 3 study, improved survival outcomes at 5 years were reported with nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) versus chemotherapy in the CheckMate 227 study.⁹

In conclusion, pembrolizumab plus pemetrexed-platinum continued to demonstrate prolonged survival and durable antitumor activity versus placebo plus pemetrexed-platinum after 5 years of follow-up, with manageable toxicity,² in patients with previously untreated metastatic nonsquamous NSCLC without *EGFR/ALK* alterations. These results continue to support the combination of first-line pembrolizumab plus a platinum and pemetrexed as a standard of care for these patients.

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DATA SHARING STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ (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 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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Subsequent Anticancer Therapy

Subsequent Therapy	Pembrolizumab Plus Chemotherapy (n = 405 ^a)	Placebo Plus Chemotherapy (n = 202 ^a)
Any subsequent pharmacologic therapy	224 (55.3)	130 (64.4)
Any subsequent anti-PD-(L)1 therapy	103 (25.4) ^b	118 (58.4) ^b
First subsequent therapy	224 (55.3)	130 (64.4)
Pembrolizumab in-study crossover ^c	0	84 (41.2)
Pembrolizumab	24 (5.9)	7 (3.5)
Pembrolizumab + chemotherapy	2 (0.5)	0
Pembrolizumab + immunotherapy	1 (0.2)	0
Pembrolizumab + platinum doublet	3 (0.7)	0
Other anti-PD-(L)1 antibody	18 (4.4)	22 (10.9)
Other anti-PD-(L)1 antibody + chemotherapy	1 (0.2)	0
Other anti-PD-(L)1 antibody + immunotherapy	4 (1.0)	0
Other anti-PD-(L)1 antibody + targeted therapy	3 (0.7)	0
Other immunotherapy	2 (0.5)	0
Other immunotherapy + targeted therapy	2 (0.5)	1 (0.5)
Nonplatinum chemotherapy doublet	1 (0.2)	0
Nonplatinum chemotherapy + targeted therapy	26 (6.4)	2 (1.0)
Nonplatinum single-agent chemotherapy	70 (17.3)	7 (3.5)
Platinum doublet	24 (5.9)	2 (1.0)
Platinum doublet + targeted therapy	1 (0.2)	0
Platinum monotherapy	9 (2.2)	0
VEGF inhibitor	2 (0.5)	0
VEGF inhibitor + chemotherapy	14 (3.5)	1 (0.5)
VEGF inhibitor + platinum doublet	2 (0.5)	0
VEGF inhibitor + targeted therapy	1 (0.2)	0
Targeted therapy	14 (3.5)	4 (2.0)
Second subsequent therapy	115 (28.4)	52 (25.7)
Pembrolizumab	7 (1.7)	7 (3.5)
Pembrolizumab + chemotherapy	2 (0.5)	0
Pembrolizumab + platinum doublet	1 (0.2)	0
Other anti-PD-(L)1 antibody	15 (3.7)	2 (1.0)
Other anti-PD-(L)1 antibody + VEGF inhibitor	1 (0.2)	0
Other anti-PD-(L)1 antibody + targeted therapy	1 (0.2)	0
Nonplatinum chemotherapy doublet	1 (0.2)	0
Nonplatinum chemotherapy + targeted therapy	2 (0.5)	8 (4.0)
Nonplatinum single-agent chemotherapy	47 (11.6)	21 (10.4)
Platinum doublet	8 (2.0)	6 (3.0)
Platinum doublet + targeted therapy	1 (0.2)	0
Platinum monotherapy	0	1 (0.5)
VEGF inhibitor + chemotherapy	4 (1.0)	1 (0.5)
Targeted therapy	25 (6.2)	6 (3.0)

(continued on following page)

TABLE A1. Subsequent Anticancer Therapy (continued)

Subsequent Therapy	Pembrolizumab Plus Chemotherapy (n = 405^a)	Placebo Plus Chemotherapy (n = 202^a)
Third subsequent therapy	48 (11.9)	19 (9.4)
Pembrolizumab	3 (0.7)	0
Pembrolizumab + chemotherapy	1 (0.2)	0
Other anti-PD-(L)1 antibody	9 (2.2)	3 (1.5)
Other anti-PD-(L)1 antibody + VEGF inhibitor + platinum doublet	1 (0.2)	0
Nonplatinum chemotherapy + targeted therapy	1 (0.2)	0
Platinum doublet	6 (1.5)	2 (1.0)
Platinum monotherapy	1 (0.2)	0
Single-agent chemotherapy	15 (3.7)	8 (4.0)
VEGF inhibitor	1 (0.2)	0
VEGF inhibitor + chemotherapy	1 (0.2)	1 (0.5)
Targeted therapy	9 (2.2)	5 (2.5)
Fourth subsequent therapy	21 (5.2)	10 (5.0)
Pembrolizumab	0	0
Pembrolizumab + platinum doublet	1 (0.2)	1 (0.5)
Other anti-PD-(L)1 antibody	3 (0.7)	1 (0.5)
Nonplatinum chemotherapy doublet	0	1 (0.5)
Nonplatinum chemotherapy + targeted therapy	2 (0.5)	0
Nonplatinum single-agent chemotherapy	9 (2.2)	4 (2.0)
VEGF inhibitor + chemotherapy	1 (0.2)	0
Targeted therapy	5 (1.2)	3 (1.5)
Fifth subsequent therapy	8 (2.0)	3 (1.5)
Pembrolizumab	0	0
Other anti-PD-(L)1 antibody	1 (0.2)	0
Nonplatinum single-agent chemotherapy	3 (0.7)	3 (1.5)
Platinum doublet	1 (0.2)	0
Platinum monotherapy	1 (0.2)	0
VEGF inhibitor + chemotherapy	1 (0.2)	0
Targeted therapy	1 (0.2)	0
Sixth subsequent therapy	6 (1.5)	0
Pembrolizumab	0	0
Other anti-PD-(L)1 antibody	2 (0.5)	0
Other anti-PD-(L)1 antibody + VEGF inhibitor + platinum doublet	1 (0.2)	0
Nonplatinum chemotherapy doublet	1 (0.2)	0
VEGF inhibitor	1 (0.2)	0
Targeted therapy	1 (0.2)	0
Seventh subsequent therapy	3 (0.7)	0
Platinum doublet	2 (0.5)	0
Nonplatinum single-agent chemotherapy	1 (0.2)	0

NOTE. Data presented as No. (%).

Abbreviations: BICR, blinded independent central review; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor.

^aPercentages were calculated on the basis of the as-treated population.

^bIncluding patients who received on-study second-course pembrolizumab.

^cEligible patients in the placebo plus chemotherapy group with confirmed progressive disease per BICR were allowed to cross over to pembrolizumab monotherapy for up to 35 cycles.

TABLE A2. Tumor Response

Response	ITT Population (N = 616)		PD-L1 TPS ≥ 50% (n = 202 ^a)		PD-L1 TPS 1%-49% (n = 186 ^a)		PD-L1 TPS < 1% (n = 190 ^a)	
	Pembrolizumab Plus Chemotherapy (n = 410)	Placebo Plus Chemotherapy (n = 206)	Pembrolizumab Plus Chemotherapy (n = 132)	Placebo Plus Chemotherapy (n = 70)	Pembrolizumab Plus Chemotherapy (n = 128)	Placebo Plus Chemotherapy (n = 58)	Pembrolizumab Plus Chemotherapy (n = 127)	Placebo Plus Chemotherapy (n = 63)
ORR, ^b % (95% CI)	48.3 (43.4 to 53.2)	19.9 (14.7 to 26.0)	62.1 (53.3 to 70.4)	25.7 (16.0 to 37.6)	50.0 (41.0 to 59.0)	20.7 (11.2 to 33.4)	33.1 (25.0 to 42.0)	14.3 (6.7 to 25.4)
Best overall response, No. (%)								
CR	10 (2.4)	1 (0.5)	4 (3.0)	0	4 (3.1)	1 (1.7)	1 (0.8)	0
PR	188 (45.9)	40 (19.4)	78 (59.1)	18 (25.7)	60 (46.9)	11 (19.0)	41 (32.3)	9 (14.3)
SD ^c	149 (36.3)	104 (50.5)	33 (25.0)	28 (40.0)	46 (35.9)	33 (56.9)	58 (45.7)	36 (57.1)
PD	37 (9.0)	36 (17.5)	6 (4.5)	16 (22.9)	15 (11.7)	7 (12.1)	15 (11.8)	9 (14.3)
Not evaluable ^d	12 (2.9)	8 (3.9)	5 (3.8)	1 (1.4)	0	2 (3.4)	7 (5.5)	4 (6.3)
No assessment ^e	14 (3.4)	17 (8.3)	6 (4.5)	7 (10.0)	3 (2.3)	4 (6.9)	5 (3.9)	5 (7.9)
DOR, months, ^f median (range)	12.7 (1.1+ to 68.3+)	7.1 (2.4 to 31.5)	15.3 (1.2+ to 68.3+)	7.1 (3.4 to 31.5)	13.6 (2.1+ to 67.6+)	7.6 (2.4 to 31.0+)	10.8 (1.1+ to 59.4+)	7.8 (4.1 to 28.3+)
DOR ≥ 4 years, ^f No. (%)	27 (20.2)	NA ^g	16 (28.2)	NA ^g	6 (14.1)	NA ^g	3 (9.6) ^g	NA ^g
Time to response, months, median (range)	2.4 (1.1-19.3)	1.4 (1.2-13.6)	1.6 (1.1-19.1)	1.5 (1.2-13.6)	2.6 (1.1-19.3)	2.0 (1.2-11.1)	2.7 (1.2-19.2)	1.4 (1.2-4.8)

NOTE. +, no PD by the time of last disease assessment.

Abbreviations: CR, complete response; DOR, duration of response; ITT, intention-to-treat; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease; TPS, tumor proportion score.

^aExcludes 38 patients for whom PD-L1 expression could not be evaluated.

^bPer Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent central review.

^cStable disease includes both stable disease and non-CR/non-PD.

^dPostbaseline assessment(s) available but not evaluable or CR/PR/SD < 6 weeks from random assignment.

^eNo postbaseline assessment available for response evaluation.

^fOn the basis of Kaplan-Meier estimate.

^gFewer than four patients at risk after 24 months.

TABLE A3. Summary of AEs in Patients Who Received ≥ 1 Dose of Study Treatment

Event	Pembrolizumab Plus Chemotherapy (n = 405)		Placebo Plus Chemotherapy (n = 202)	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Any AE (all-cause)	404 (99.8)		200 (99.0)	
Grade 3-5	295 (72.8)		136 (67.3)	
Led to death ^a	29 (7.2)		14 (6.9)	
Led to discontinuation of any treatment component	145 (35.8)		35 (17.3)	
Treatment-related	377 (93.1)		183 (90.6)	
Grade 3-5	212 (52.3)		85 (42.1)	
Led to discontinuation of any treatment component ^b	111 (27.4)		20 (9.9)	
Led to discontinuation of pembrolizumab or placebo	71 (17.5)		11 (5.4)	
Led to discontinuation of pemetrexed	96 (23.7)		17 (8.4)	
AEs occurring in $\geq 15\%$ of patients in either treatment group	Any grade	Grade 3-5	Any grade	Grade 3-5
Nausea	235 (58.0)	14 (3.5)	108 (53.5)	8 (4.0)
Anemia	196 (48.4)	77 (19.0)	98 (48.5)	36 (17.8)
Fatigue	174 (43.0)	31 (7.7)	80 (39.6)	7 (3.5)
Constipation	144 (35.6)	4 (1.0)	67 (33.2)	1 (0.5)
Diarrhea	131 (32.3)	21 (5.2)	44 (21.8)	6 (3.0)
Decreased appetite	122 (30.1)	5 (1.2)	64 (31.7)	2 (1.0)
Neutropenia	114 (28.1)	68 (16.8)	50 (24.8)	24 (11.9)
Vomiting	109 (26.9)	16 (4.0)	48 (23.8)	6 (3.0)
Cough	104 (25.7)	0	62 (30.7)	0
Dyspnea	103 (25.4)	17 (4.2)	54 (26.7)	8 (4.0)
Peripheral edema	103 (25.4)	2 (0.5)	35 (17.3)	0
Asthenia	90 (22.2)	27 (6.7)	47 (23.3)	7 (3.5)
Pyrexia	89 (22.0)	1 (0.2)	34 (16.8)	1 (0.5)
Rash	89 (22.0)	8 (2.0)	27 (13.4)	3 (1.5)
Thrombocytopenia	77 (19.0)	35 (8.6)	30 (14.9)	15 (7.4)
Lacrimation increased	75 (18.5)	0	22 (10.9)	0
Arthralgia	71 (17.5)	5 (1.2)	28 (13.9)	1 (0.5)
Back pain	71 (17.5)	7 (1.7)	27 (13.4)	4 (2.0)
Dizziness	62 (15.3)	3 (0.7)	23 (11.4)	0
Immune-mediated AEs and infusion reactions	113 (27.9)	52 (12.8)	27 (13.4)	9 (4.5)
Hypothyroidism	32 (7.9)	2 (0.5)	5 (2.5)	0
Hyperthyroidism	20 (4.9)	0	7 (3.5)	0
Pneumonitis	20 (4.9)	12 (3.0)	6 (3.0)	4 (2.0)
Colitis	13 (3.2)	7 (1.7)	0	0
Infusion reactions	12 (3.0)	2 (0.5)	3 (1.5)	0
Severe skin reactions	10 (2.5)	10 (2.5)	5 (2.5)	4 (2.0)
Nephritis	8 (2.0)	6 (1.5)	0	0
Hepatitis	7 (1.7)	6 (1.5)	0	0
Hypophysitis	3 (0.7)	0	0	0

(continued on following page)

TABLE A3. Summary of AEs in Patients Who Received ≥ 1 Dose of Study Treatment (continued)

Event	Pembrolizumab Plus Chemotherapy (n = 405)		Placebo Plus Chemotherapy (n = 202)										
Myositis	3 (0.7)	0	0	0									
Pancreatitis	4 (1.0)	3 (0.7)	0	0									
Adrenal insufficiency	2 (0.5)	1 (0.2)	1 (0.5)	1 (0.5)									
Encephalitis	2 (0.5)	2 (0.5)	0	0									
Type 1 diabetes mellitus	2 (0.5)	2 (0.5)	0	0									
Vasculitis	2 (0.5)	1 (0.2)	0	0									
Cholangitis sclerosing	1 (0.2)	1 (0.2)	0	0									
Myocarditis	1 (0.2)	1 (0.2)	0 </tr <tr> <td>Thyroiditis</td> <td>1 (0.2)</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Guillain-Barré syndrome</td> <td>1 (0.2)</td> <td>1 (0.2)</td> <td>0</td> <td>0</td> </tr>	Thyroiditis	1 (0.2)	0	0	0	Guillain-Barré syndrome	1 (0.2)	1 (0.2)	0	0
Thyroiditis	1 (0.2)	0	0	0									
Guillain-Barré syndrome	1 (0.2)	1 (0.2)	0	0									

NOTE. Data presented as No. (%).

Abbreviation: AE, adverse event.

^aEight patients (2.0%) in the pembrolizumab plus chemotherapy group and two patients (1.0%) in the placebo plus chemotherapy group died from AEs attributed to study treatment by the investigator, all reported previously.²

^bForty-one patients (10.1%) in the pembrolizumab plus chemotherapy group and three (1.5%) in the placebo plus chemotherapy group discontinued any treatment component because of an immune-mediated AE or infusion reaction.

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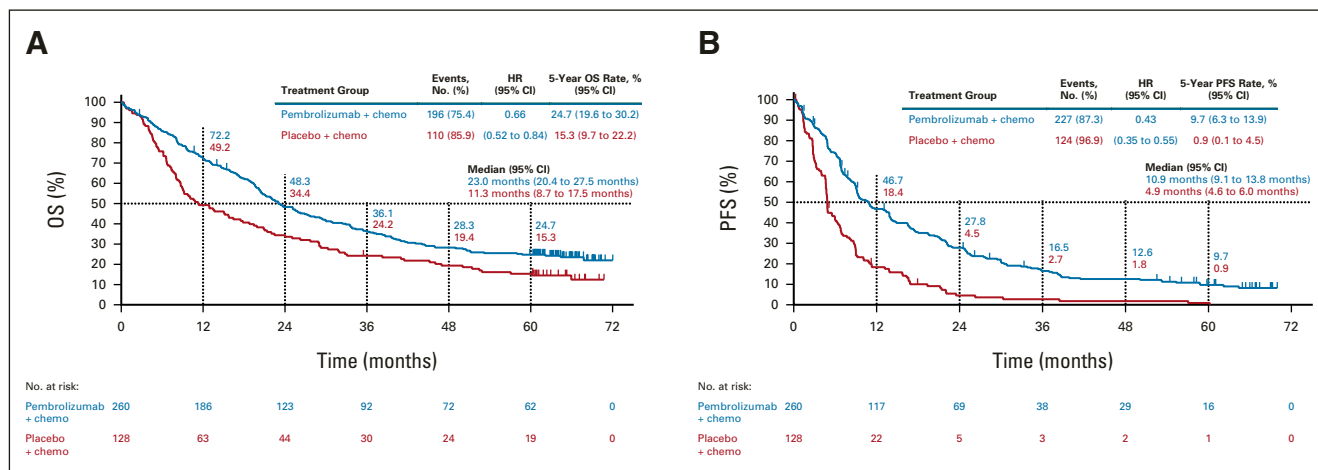


FIG A1. Kaplan-Meier estimates of (A) OS and (B) PFS per Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent central review in patients with PD-L1 TPS ≥ 1%. Chemo, chemotherapy; OS, overall survival; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; TPS, tumor proportion score.