clinical trial updates

Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study

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abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on 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 report 5-year efficacy and safety outcomes from the phase III KEYNOTE-407 study (ClinicalTrials.gov identifier: NCT02775435). Eligible patients with previously untreated, metastatic squamous non–small-cell lung cancer (NSCLC) were randomly assigned 1:1 to pembrolizumab 200 mg or placebo plus carboplatin and paclitaxel/nab-paclitaxel once every 3 weeks for four cycles, followed by pembrolizumab or placebo for up to 35 cycles. Primary end points were overall survival (OS) and progression-free survival (PFS) per RECIST version 1.1 by blinded independent central review (BICR). Five hundred fifty-nine patients were randomly assigned in the intention-to-treat population (pembrolizumab plus chemotherapy, n = 278; placebo plus chemotherapy, n = 281). The median time from random assignment to data cutoff was 56.9 (range, 49.9-66.2) months. OS and PFS were improved with pembrolizumab plus chemotherapy versus placebo plus chemotherapy (hazard ratio [95% CI], 0.71 [0.59 to 0.85] and 0.62 [0.52 to 0.74]), with 5-year OS rates of 18.4% versus 9.7%, respectively. Toxicity was manageable. Among 55 patients who completed 35 cycles of pembrolizumab, the objective response rate was 90.9% and the 3-year OS rate after completion of 35 cycles (approximately 5 years after random assignment) was 69.5%. Pembrolizumab plus chemotherapy maintained an OS and PFS benefit versus placebo plus chemotherapy in previously untreated, metastatic squamous NSCLC and is a standard-of-care first-line treatment option for metastatic squamous NSCLC regardless of programmed death ligand 1 expression.

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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

The primary analysis of the global, randomized, phase III KEYNOTE-407 study demonstrated significantly improved overall survival (OS) and progression-free survival (PFS) with pembrolizumab, an anti–programmed death 1 (anti–PD-1) monoclonal antibody, in combination with carboplatin and paclitaxel or nab-paclitaxel chemotherapy versus placebo plus chemotherapy in patients with previously untreated, metastatic squamous non–small-cell lung cancer (NSCLC; OS hazard ratio [HR], 0.64 [95% CI, 0.49 to 0.85], $P < .001$; PFS HR, 0.56 [95% CI, 0.45 to 0.70], $P < .001$).[1] Pembrolizumab plus chemotherapy continued to show a clinically meaningful improvement in OS (HR, 0.71; 95% CI, 0.58 to 0.88) and PFS (HR, 0.57; 95% CI, 0.47 to 0.69) versus placebo plus chemotherapy in the protocol-specified final analysis.[2] We report efficacy outcomes and safety from KEYNOTE-407 with an approximately 5-year follow-up.

METHODS

Study Design and Patients

The design for this study has been previously described.[1,2] Patients provided written informed consent.

Eligible patients had previously untreated, histologically/cytologically confirmed stage IV

CONTEXT

Key Objective

This exploratory analysis of the phase III KEYNOTE-407 study evaluated whether patients with previously untreated, metastatic squamous non–small-cell lung cancer (NSCLC) treated with pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel chemotherapy had improved long-term survival outcomes versus patients treated with placebo plus chemotherapy after a 5-year follow-up.

Knowledge Generated

With an approximately 5-year follow-up, pembrolizumab plus chemotherapy continued to provide a clinically meaningful survival benefit compared with placebo plus chemotherapy with manageable safety in patients with metastatic squamous NSCLC. Five-year overall survival rates were 18.4% with pembrolizumab plus chemotherapy versus 9.7% with placebo plus chemotherapy in the intention-to-treat population.

Relevance *(T.E. Stinchcombe)*

The 5-year follow-up demonstrates durable benefit for the combination of carboplatin and paclitaxel or nab-paclitaxel and pembrolizumab and the benefit in the patient subsets based on tumor programmed death ligand 1 expression. In the future, the landmark analyses of progression-free survival or overall survival 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.

squamous NSCLC, measurable disease per RECIST version 1.1, and provided tumor tissue for determination of programmed death ligand 1 (PD-L1) status. Patients were randomly assigned 1:1 to pembrolizumab 200 mg or placebo once every 3 weeks plus carboplatin area under the curve 6 mg/mL/min plus paclitaxel 200 mg/m^2 or nab-paclitaxel 100 mg/m^2 on days 1, 8, and 15 once every 3 weeks for four cycles, followed by pembrolizumab 200 mg or placebo per initially assigned treatment until completion of 35 cycles, progressive disease (PD), unacceptable adverse event (AE), or patient withdrawal. Eligible patients in the placebo plus chemotherapy group with confirmed PD per blinded independent central review (BICR) could cross over to pembrolizumab monotherapy for up to 35 cycles. Patients were eligible to receive second-course pembrolizumab monotherapy for 17 cycles (approximately 1 year) on PD after either completing 35 cycles of pembrolizumab with a best overall response of stable disease (SD) or better or achieving a confirmed complete response (CR) per investigator assessment after receiving eight or more cycles of pembrolizumab and having received two or more cycles beyond the initial CR assessment.

End Points and Statistical Analysis

The dual primary end points were OS and PFS per RECIST version 1.1 by BICR. Secondary end points included objective response rate (ORR) and duration of response (DOR) per RECIST version 1.1 by BICR and safety. PFS2 (time from random assignment to subsequent PD after next line of treatment or death from any cause) was an exploratory end point. After documented PD or the start of new anticancer treatment, patients were followed up for survival once every 12 weeks. Statistical methods have been previously reported.[1,2] No alpha was assigned to this analysis.

RESULTS

Patients

There were 559 patients in the intention-to-treat (ITT) population (pembrolizumab plus chemotherapy, n = 278; placebo plus chemotherapy, n = 281). Baseline characteristics are summarized in Table 1. Subsequent anticancer therapy was received by 109 patients in the pembrolizumab plus chemotherapy group (33 received anti–PD-[L]1 therapy, including 12 who received on-study second-course pembrolizumab). In the placebo plus chemotherapy group, 172 patients received subsequent therapy. Of these, 117 patients crossed over to pembrolizumab monotherapy on-study and an additional 26 had received subsequent anti–PD-(L)1 therapy outside the study for an effective crossover rate of 50.9% (Appendix Table A1, online only). Fifty-five patients in the pembrolizumab plus chemotherapy group completed 35 cycles of pembrolizumab, and 12 began a second course of pembrolizumab.

Efficacy Outcomes

The median time from random assignment to database cutoff (February 23, 2022) was 56.9 (range, 49.9-66.2) months. OS was improved with pembrolizumab plus chemotherapy versus placebo plus chemotherapy (HR, 0.71; 95% CI, 0.59 to 0.85; Fig 1). Estimated 5-year OS rates were 18.4% versus 9.7%. PFS was improved with

TABLE 1. Patient Demographics and Disease Characteristics in the ITT Population

Characteristic	Pembrolizumab Plus Chemotherapy (n = 278)	Placebo Plus Chemotherapy (n = 281)	Completed 35 Cycles (2 years) of Pembrolizumab (n = 55)
Age, years, median (range)	65.0 (29-87)	65.0 (36-88)	64.0 (40-78)
< 65	127 (45.7)	127 (45.2)	29 (52.7)
Sex			
Male	220 (79.1)	235 (83.6)	43 (78.2)
Female	58 (20.9)	46 (16.4)	12 (21.8)
Region of enrollment			
East Asia	54 (19.4)	52 (18.5)	9 (16.4)
Rest of the world	224 (80.6)	229 (81.5)	46 (83.6)
ECOG performance status			
0	73 (26.3)	90 (32.0)	18 (32.7)
1	205 (73.7)	191 (68.0)	37 (67.3)
Smoking status			
Former or current	256 (92.1)	262 (93.2)	52 (94.5)
Never	22 (7.9)	19 (6.8)	3 (5.5)
Histology			
Squamous	271 (97.5)	274 (97.5)	53 (96.4)
Adenosquamous	6 (2.2)	7 (2.5)	2 (3.6)
Others	1 (0.4)	0	0
Brain metastases	20 (7.2)	23 (8.2)	2 (3.6)
PD-L1 TPS[a]			
< 1%	95 (34.2)	99 (35.2)	13 (23.6)
≥ 1%	176 (63.3)	177 (63.0)	41 (74.5)
1%-49%	103 (37.1)	104 (37.0)	25 (45.5)
≥ 50%	73 (26.3)	73 (26.0)	16 (29.1)
Could not be evaluated[b]	7 (2.5)	5 (1.8)	1 (1.8)
Taxane chemotherapy			
Paclitaxel	169 (60.8)	167 (59.4)	30 (54.5)
Nab-paclitaxel	109 (39.2)	114 (40.6)	25 (45.5)
Previous therapy			
Thoracic radiotherapy	17 (6.1)	22 (7.8)	3 (5.5)
Neoadjuvant or adjuvant therapy	5 (1.8)	8 (2.8)	1 (1.8)

NOTE. All values are No. (%) unless stated otherwise.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

[a]Baseline tumor PD-L1 expression was assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA) at a central laboratory and reported as TPS.

[b]Patients unevaluable for PD-L1 status were included in the PD-L1 TPS < 1% group.

pembrolizumab plus chemotherapy versus placebo plus chemotherapy (HR, 0.62; 95% CI, 0.52 to 0.74; Fig 1). Estimated 5-year PFS rates were 10.8% versus 3.5%. HRs for OS and PFS favored pembrolizumab plus chemotherapy across all PD-L1 tumor proportion score (TPS) subgroups (Fig 1; Appendix Fig A1, online only).

The ORR (95% CI) was 62.2% (56.2 to 68.0) and 38.8% (33.1 to 44.8) with pembrolizumab plus chemotherapy versus placebo plus chemotherapy, respectively (Appendix Table A2, online only). The median (range) DOR was 9.0 (1.3+ to 61.5+) months and 4.9 (1.3+ to 58.6+) months, respectively (Fig 2). A higher ORR and longer DOR were observed in the pembrolizumab plus chemotherapy group in all PD-L1 TPS subgroups (Appendix Table A2).

Median PFS2 was longer for pembrolizumab plus chemotherapy versus placebo plus chemotherapy (HR, 0.60; 95% CI, 0.50 to 0.72). Five-year PFS2 rates were 18.1% (95% CI, 13.6 to 23.1) versus 7.1% (95% CI, 4.4 to 10.7).

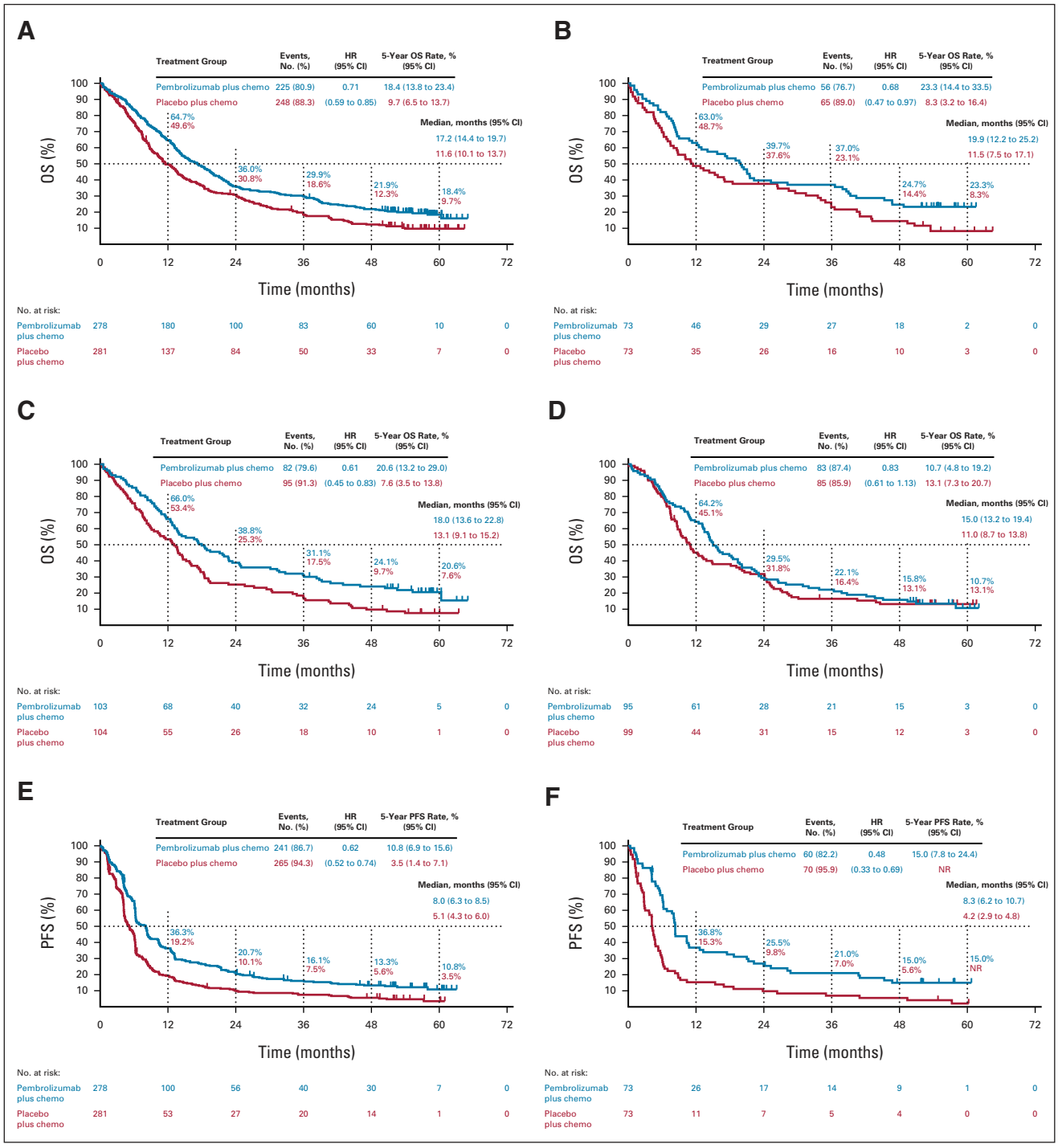

FIG 1. Kaplan-Meier estimates of OS and PFS in the (A and E) ITT population, (B and F) patients with PD-L1 TPS ≥ 50%, (C and G) patients with PD-L1 TPS 1%-49%, and (D and H) patients with PD-L1 TPS < 1%. chemo, chemotherapy; HR, hazard ratio; ITT, intention to treat; NR, not reached; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; TPS, tumor proportion score. (continued on following page)

Safety

In the as-treated population (pembrolizumab plus chemotherapy, n = 278; placebo plus chemotherapy, n = 280), 98.6% and 98.2% experienced an AE (grade 3-5, 74.8% *v* 70.0%). No new treatment-related deaths were reported since the protocol-specified final analysis.[2] Immune-mediated AEs and infusion reactions occurred in 35.6% (grade 3-5, 13.3%) and 9.3% (grade 3-5, 3.2%) of patients, respectively (Appendix Table A3, online only).

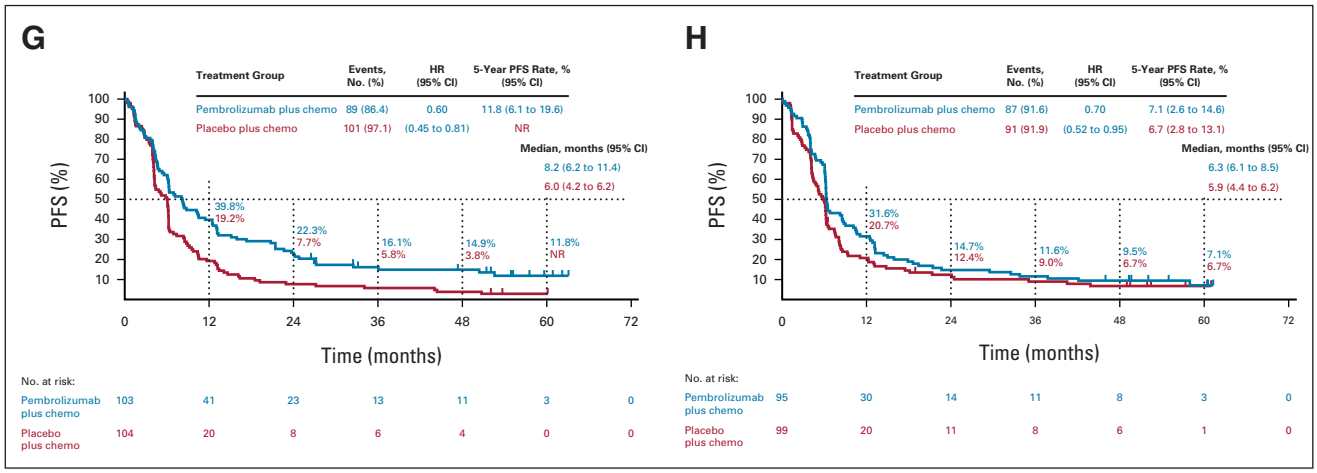

FIG 1. (Continued).

Patients Who Completed 35 Cycles of Pembrolizumab

Among patients randomly assigned to pembrolizumab plus chemotherapy, 55 (19.8%) completed 35 cycles of pembrolizumab. Baseline characteristics are provided in Table 1. The ORR was 90.9%; nine patients (16.4%) had CR, 41 (74.5%) had partial response (PR), and an additional five (9.1%) had SD. Median DOR was not reached (range, 7.1-61.5+ months). At data cutoff, 38 patients (69.1%) were alive and 24 (43.6%) were alive without PD or subsequent therapy (Fig 2). The 3-year OS rate after completion of 35 cycles of pembrolizumab (ie, approximately 5 years after random assignment) was 69.5% (95% CI, 54.8 to 80.2). All 55 patients had an AE (all treatment-related), and 35 (63.6%) had grade 3/4 AEs (no deaths). Immune-mediated AEs and infusion reactions occurred in 21 patients (38.2%; one grade 3 event).

DISCUSSION

In this 5-year analysis of KEYNOTE-407, first-line pembrolizumab plus chemotherapy provided clinically meaningful improvements in OS and PFS compared with placebo plus chemotherapy in patients with metastatic squamous NSCLC, regardless of PD-L1 TPS. Five-year OS rates were approximately doubled with pembrolizumab plus chemotherapy over placebo plus chemotherapy, although there were a limited number of patients at risk at 5 years. Toxicity was manageable and consistent with prior reports from KEYNOTE-407.[1,2] These findings are consistent with those reported for the phase III KEYNOTE-189 study of first-line pembrolizumab plus pemetrexed-platinum versus placebo plus pemetrexed-platinum in metastatic nonsquamous NSCLC.[3]

Sustained improvements in OS were observed despite an effective crossover rate of 50.9% of patients in the placebo plus chemotherapy group to subsequent anti–PD-(L)1 therapy. This high crossover rate likely provides an explanation for the flattening of the Kaplan-Meier curve observed with placebo plus chemotherapy, particularly among patients with PD-L1 TPS ≥ 1%, which was not observed in historical chemotherapy trials before the introduction of immunotherapy.[4] This crossover rate and plateauing of the Kaplan-Meier curve in the placebo plus chemotherapy group likely attenuated the differences in the OS HR between treatment groups observed in later analyses compared with the first reported analysis.[1] Improvement in PFS2 with pembrolizumab plus chemotherapy versus placebo plus chemotherapy indicated that the benefit of pembrolizumab plus chemotherapy was maintained after initial PD, further supporting first-line use. Notably, the HR for OS favored the pembrolizumab group across subgroups defined by baseline PD-L1 TPS, although the treatment effect was less pronounced among patients with PD-L1 TPS ≤ 1% and the 95% CI contained 1.

Among patients who completed 35 cycles of pembrolizumab, responses were durable, with the majority of patients (69.0%) alive at data cutoff (ie, approximately 5 years after random assignment). These findings provide evidence of long-term benefit in the first-line setting and support the duration of treatment for pembrolizumab (35 cycles [approximately 2 years]); similar benefit was observed among patients with PD-L1–positive disease receiving pembrolizumab monotherapy.[5,6]

In conclusion, pembrolizumab plus chemotherapy provided OS and PFS benefit versus placebo plus chemotherapy in patients with previously untreated, metastatic squamous NSCLC. As reported in the final analysis,[2] toxicity was manageable. These data support pembrolizumab plus chemotherapy as a standard-of-care first-line treatment option for metastatic squamous NSCLC, regardless of PD-L1 expression.

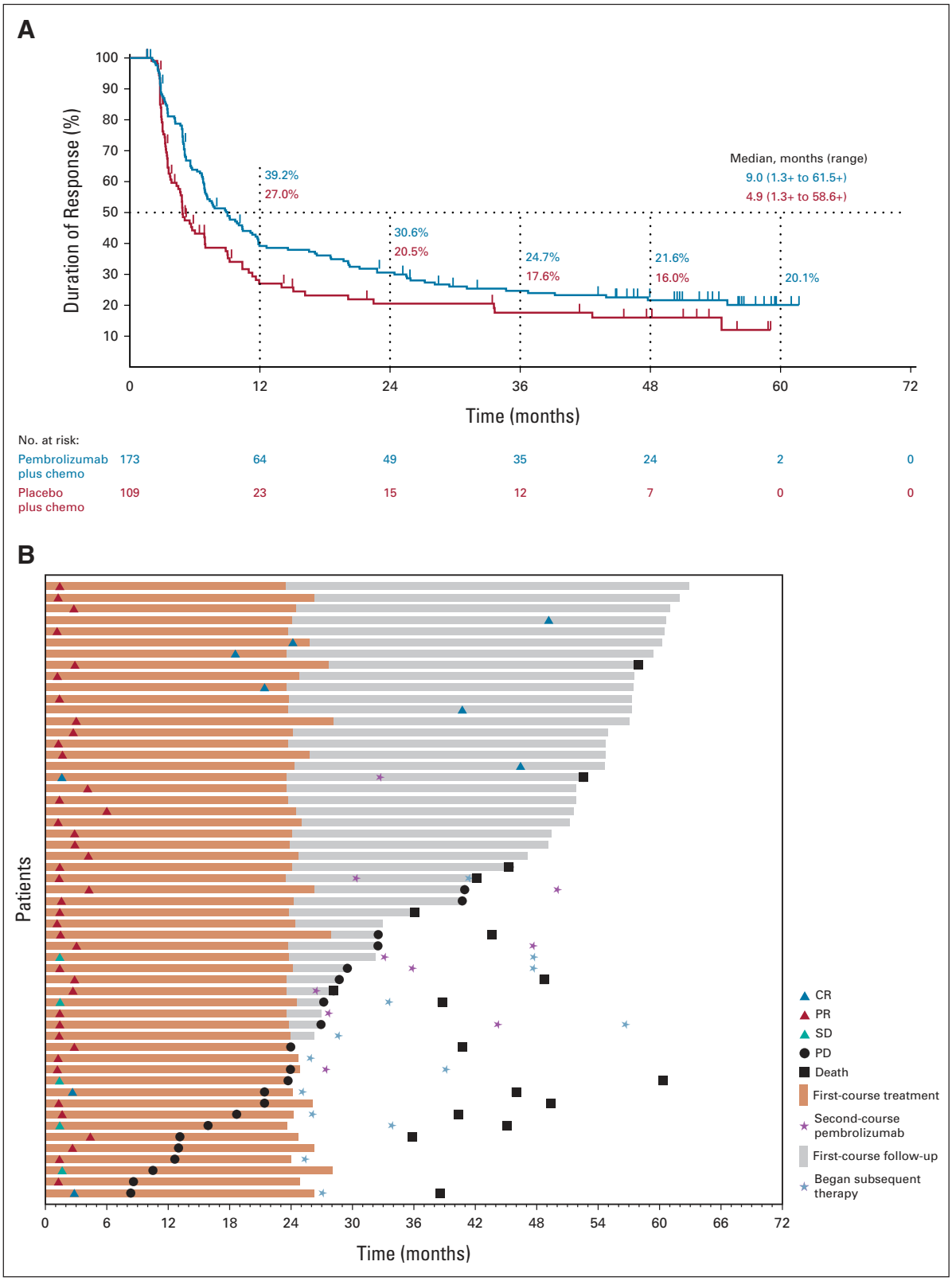

FIG 2. Patient response to pembrolizumab plus chemotherapy and placebo plus chemotherapy. (A) DOR in the ITT population and (B) time to response and DOR in patients who completed 35 cycles of pembrolizumab. Median PFS was NR (95% CI, 21.2 months to NR) among patients who completed 35 cycles. The PFS rate 3 years after completion of 35 cycles was 58.4% (95% CI, 39.8 to 73.0). chemo, chemotherapy; CR, complete response; DOR, duration of response; ITT, intention to treat; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study

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Leadership: Genomica, ALTUM Sequencing
Honoraria: Roche/Genentech, Lilly, Pfizer, Bristol Myers Squibb, MSD, AstraZeneca, Merck Serono, PharmaMar, Novartis, Amgen, Sanofi, Bayer, Takeda, Mirati Therapeutics, Daiichi Sankyo, Hutchmed, BeiGene, GlaxoSmithKline, Janssen, Medscape, Regeneron
Speakers' Bureau: MSD Oncology, BMS, Roche/Genentech, Pfizer, Lilly, AstraZeneca, Merck Serono
Research Funding: BMS (Inst), AstraZeneca (Inst), PharmaMar (Inst), Kura Oncology (Inst), MSD (Inst), Pfizer (Inst)
Other Relationship: Novartis, Ipsen, Pfizer, SERVIER, Sanofi, Roche, Amgen, Merck, Roche

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Subsequent Anticancer Therapy

Subsequent Therapy	Pembrolizumab Plus Chemotherapy (n = 278)[a]	Placebo Plus Chemotherapy (n = 280)[a]
Any subsequent pharmacologic therapy, No. (%)	109 (39.2)	172 (61.4)
Any subsequent anti–PD-(L)1 therapy	33 (11.9)[b]	143 (51.1)
First subsequent therapy, No. (%)	109 (39.2)	172 (61.4)
Pembrolizumab in study crossover[c]	0	117 (41.8)
Pembrolizumab	7 (2.5)	4 (1.4)
Other anti–PD-(L)1 antibodies with/without tyrosine kinase inhibitor	5 (1.8)	15 (5.4)
Platinum doublet with/without third agent	39 (14.0)	14 (5.0)
Platinum monotherapy	4 (1.4)	0
Nonplatinum single-agent chemotherapy	50 (18.0)	19 (6.8)
Nonplatinum chemotherapy plus VEGFR2 antagonist	4 (1.4)	2 (0.7)
Others	0	1 (0.4)
Second subsequent therapy, No. (%)	49 (17.6)	68 (24.3)
Pembrolizumab plus others	1 (0.4)	1 (0.4)
Pembrolizumab	1 (0.4)	3 (1.1)
Other anti–PD-(L)1 antibodies with/without tyrosine kinase inhibitor	7 (2.5)	6 (2.1)
Other immunotherapies	0	1 (0.4)
Other anti–PD-(L)1 antibodies with/without single-agent chemotherapy	1 (0.4)	0
Platinum doublet with/without third agent	8 (2.9)	19 (6.8)
Platinum monotherapy	0	2 (0.7)
Nonplatinum single-agent chemotherapy	27 (15.1)	31 (11.1)
Nonplatinum chemotherapy plus VEGFR2 antagonist	3 (1.1)	4 (1.4)
Tyrosine kinase inhibitor	1 (0.4)	0
Others	0	1 (0.4)
Third subsequent therapy, No. (%)	16 (5.8)	21 (7.5)
Pembrolizumab plus chemotherapy	0	1 (0.4)
Other anti–PD-(L)1 antibodies	4 (1.4)	2 (0.7)
Platinum doublet with/without third agent	2 (0.7)	4 (1.4)
Platinum monotherapy	1 (0.4)	0
Nonplatinum single-agent chemotherapy	6 (2.2)	13 (4.7)
Nonplatinum agent plus VEGF inhibitor	1 (0.4)	0
Tyrosine kinase inhibitor	2 (0.7)	1 (0.4)
Fourth subsequent therapy, No. (%)	8 (2.9)	7 (2.5)
Pembrolizumab	0	0
Other anti–PD-(L)1 antibodies	1 (0.4)	2 (0.7)
Platinum doublet with/without third agent	2 (0.7)	2 (0.7)
Nonplatinum single-agent chemotherapy	3 (1.1)	2 (0.7)
Nonplatinum chemotherapy plus VEGFR2 antagonist	0	1 (0.4)
Tyrosine kinase inhibitor	1 (0.4)	0
Others	1 (0.4)	0
Fifth subsequent therapy, No. (%)	5 (1.8)	2 (0.7)
Other anti–PD-(L)1 antibodies	0	0

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TABLE A1. Subsequent Anticancer Therapy (continued)

Subsequent Therapy	Pembrolizumab Plus Chemotherapy (n = 278)[a]	Placebo Plus Chemotherapy (n = 280)[a]
Nonplatinum single-agent chemotherapy	3 (1.1)	2 (0.7)
Nonplatinum chemotherapy plus VEGFR2 antagonist	1 (0.4)	0
Tyrosine kinase inhibitor	1 (0.4)	0
Sixth subsequent therapy, No. (%)	1 (0.4)	2 (0.7)
Other anti–PD-(L)1 antibodies	0	1 (0.4)
Nonplatinum single-agent chemotherapy	1 (0.4)	1 (0.4)

Abbreviations: BICR, blinded independent central review; PD, progressive disease; PD-L1, programmed death ligand 1; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

[a]Percentages were calculated on the basis of the as-treated population.

[b]Including patients who received on-study second-course pembrolizumab.

[c]Eligible patients in the placebo plus chemotherapy group with confirmed PD per BICR were allowed to cross over to pembrolizumab monotherapy for up to 35 cycles.

TABLE A2. Tumor Response and DOR in the ITT Population and According to PD-L1 Status

	ITT Population (n = 559)		PD-L1 TPS ≥ 50% (n = 146)		PD-L1 TPS 1%-49% (n = 207)		PD-L1 TPS < 1% (n = 194)	
Outcome	**Pembrolizumab Plus Chemotherapy (n = 278)**	**Placebo Plus Chemotherapy (n = 281)**	**Pembrolizumab Plus Chemotherapy (n = 73)**	**Placebo Plus Chemotherapy (n = 73)**	**Pembrolizumab Plus Chemotherapy (n = 103)**	**Placebo Plus Chemotherapy (n = 104)**	**Pembrolizumab Plus Chemotherapy (n = 95)**	**Placebo Plus Chemotherapy (n = 99)**
ORR (95% CI),[a] %	62.2 (56.2 to 68.0)	38.8 (33.1 to 44.8)	64.4 (52.3 to 75.3)	30.1 (19.9 to 42.0)	54.4 (44.3 to 64.2)	43.3 (33.6 to 53.3)	67.4 (57.0 to 76.6)	41.4 (31.6 to 51.8)
Best overall response, No. (%)								
CR	10 (3.6)	11 (3.9)	3 (4.1)	3 (4.1)	6 (5.8)	3 (2.9)	1 (1.1)	5 (5.1)
PR	163 (58.6)	98 (34.9)	44 (60.3)	19 (26.0)	50 (48.5)	42 (40.4)	63 (66.3)	36 (36.4)
SD[b]	66 (23.7)	102 (36.3)	14 (19.2)	26 (35.6)	30 (29.1)	40 (38.5)	21 (22.1)	34 (34.3)
PD	17 (6.1)	40 (14.2)	3 (4.1)	12 (16.4)	9 (8.7)	9 (8.7)	5 (5.3)	18 (18.2)
Not evaluable[c]	6 (2.2)	7 (2.5)	2 (2.7)	3 (4.1)	1 (1.0)	2 (1.9)	3 (3.2)	2 (2.0)
No assessment[d]	16 (5.8)	23 (8.2)	7 (9.6)	10 (13.7)	7 (6.8)	8 (7.7)	2 (2.1)	4 (4.0)
DOR, months, median (range)[e]	9.0 (1.3+ to 61.5+)	4.9 (1.3+ to 58.6+)	10.4 (2.7 to 59.4+)	4.6 (1.3+ to 58.6+)	11.1 (1.3+ to 61.5+)	4.8 (2.0 to 58.6+)	6.9 (1.4+ to 58.9+)	5.7 (1.4+ to 55.8+)
Response duration ≥ 4 years, No. (%)	24 (21.6)	7 (16.0)	8 (24.0)	3 (17.5)	8 (23.9)	2 (8.1)	6 (16.8)	2 (21.0)
Time to response, months, median (range)	1.4 (1.1-10.9)	1.4 (1.0-18.7)	1.5 (1.1-8.4)	1.4 (1.2-3.0)	1.4 (1.1-10.9)	1.4 (1.0-18.7)	1.4 (1.2-10.6)	1.4 (1.2-10.4)

NOTE. + indicates that there was no PD at the time of last assessment. Tumor imaging was performed at baseline; at weeks 6, 12, and 18 from the time of random assignment; then every 9 weeks for the first 45 weeks in the treatment period; and every 12 weeks thereafter in the first course.

Abbreviations: BICR, blinded independent central review; CR, complete response; DOR, duration of response; ITT, intention to treat; NR, not reached; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease; TPS, tumor proportion score.

[a]Per RECIST version 1.1 by BICR.

[b]Includes both SD and non-CR/non-PD.

[c]Postbaseline assessment(s) available but not evaluable (ie, all postbaseline assessments not evaluable or CR/PR/SD < 6 weeks from random assignment).

[d]No postbaseline assessment available for response assessment.

[e]Kaplan-Meier estimate.

TABLE A3. AEs in the As-Treated Population

AE	Pembrolizumab Plus Chemotherapy (n = 278)	Placebo Plus Chemotherapy (n = 280)
Any	274 (98.6)	275 (98.2)
Grade 3-5	208 (74.8)	196 (70.0)
Led to treatment discontinuation		
Any treatment	80 (28.8)	37 (13.2)
All treatments[a]	48 (17.3)	21 (7.5)
Led to death	32 (11.5)	20 (7.1)
Any treatment-related AE	266 (95.7)	252 (90.0)
Grade 3-5	159 (57.2)	156 (55.7)
Led to treatment discontinuation	58 (20.9)	21 (7.5)
Led to death	12 (4.3)[b]	5 (1.8)[c]

AEs Occurring in ≥ 15% of Patients	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Anemia	152 (54.7)	44 (15.8)	145 (51.8)	58 (20.7)
Alopecia	128 (46.0)	1 (0.4)	105 (37.5)	3 (1.1)
Neutropenia	105 (37.8)	64 (23.0)	91 (32.5)	69 (24.6)
Nausea	101 (36.3)	4 (1.4)	91 (32.5)	3 (1.1)
Diarrhea	93 (33.5)	12 (4.3)	71 (25.4)	7 (2.5)
Thrombocytopenia	86 (30.9)	23 (8.3)	65 (23.2)	19 (6.8)
Decreased appetite	77 (27.7)	7 (2.5)	82 (29.3)	4 (1.4)
Arthralgia	71 (25.5)	5 (1.8)	48 (17.1)	2 (0.7)
Constipation	70 (25.2)	2 (0.7)	62 (22.1)	3 (1.1)
Fatigue	68 (24.5)	13 (4.7)	74 (26.4)	12 (4.3)
Asthenia	63 (22.7)	6 (2.2)	63 (22.5)	12 (4.3)
Peripheral neuropathy	61 (21.9)	3 (1.1)	48 (17.1)	2 (0.7)
Rash	52 (18.7)	2 (0.7)	32 (11.4)	0
Pruritus	51 (18.3)	1 (0.4)	25 (8.9)	1 (0.4)
Vomiting	51 (18.3)	1 (0.4)	33 (11.8)	6 (2.1)
Cough	49 (17.6)	2 (0.7)	56 (20.0)	3 (1.1)
Pyrexia	42 (15.1)	2 (0.7)	38 (13.6)	5 (1.8)
Dyspnea	41 (14.7)	4 (1.4)	47 (16.8)	4 (1.4)

Immune-Mediated AEs and Infusion Reactions	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Any	99 (35.6)	37 (13.3)	26 (9.3)	9 (3.2)
Hypothyroidism	34 (12.2)	1 (0.4)	6 (2.1)	0
Pneumonitis	23 (8.3)	9 (3.3)	6 (2.1)	3 (1.1)
Hyperthyroidism	21 (7.6)	1 (0.4)	2 (0.7)	0
Infusion reactions	15 (5.4)	5 (1.8)	7 (2.5)	1 (0.4)
Colitis	9 (3.2)	7 (2.5)	4 (1.4)	3 (1.1)
Hepatitis	6 (2.2)	6 (2.2)	0	0
Severe skin reactions	6 (2.2)	4 (1.4)	1 (0.4)	1 (0.4)
Hypophysitis	4 (1.4)	2 (0.8)	0	0
Thyroiditis	3 (1.1)	1 (0.4)	0	0

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TABLE A3. AEs in the As-Treated Population (continued)

Immune-Mediated AEs and Infusion Reactions	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Nephritis	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)
Vasculitis	2 (0.7)	1 (0.4)	0	0
Adrenal insufficiency	1 (0.4)	0	0	0

NOTE. All values are No. (%). AEs were monitored from random assignment through 30 days (90 days for serious AEs) after treatment cessation and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Abbreviation: AE, adverse event.

[a]Includes patients who discontinued pembrolizumab or placebo, carboplatin, and taxane owing to an AE at any time and patients who discontinued pembrolizumab or placebo owing to an AE after completing four 3-week cycles of carboplatin and taxane.

[b]Including sepsis, n = 3; death (cause not specified), n = 2; cardiac arrest, cardiac failure, hepatic failure, necrotizing fasciitis, pneumonitis, pulmonary hemorrhage, and respiratory failure, n = 1 each.

[c]Including septic shock, n = 2; pneumonia, acute renal injury, and pulmonary hemorrhage, n = 1 each.

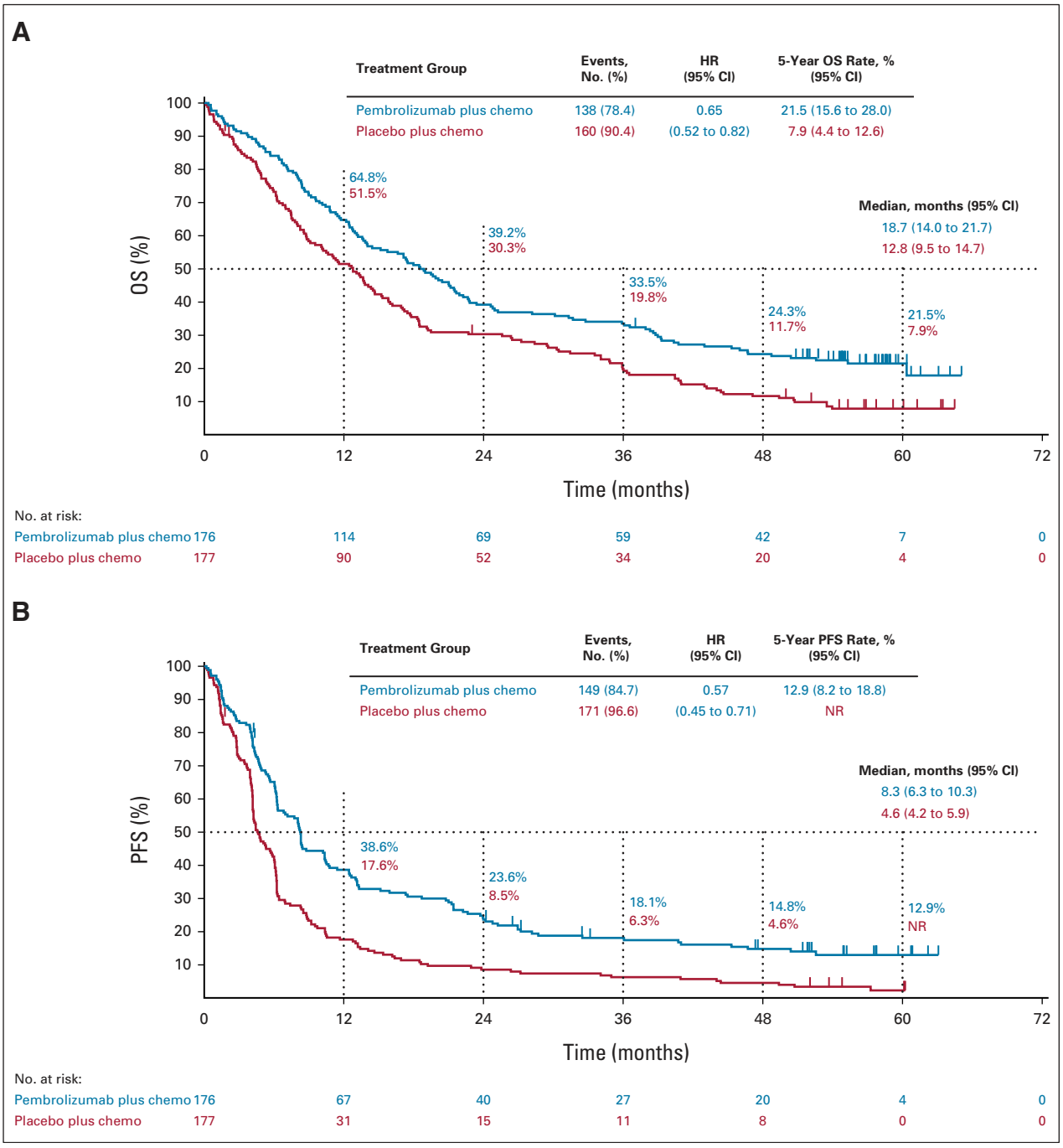

FIG A1. Kaplan-Meier estimates of (A) OS and (B) PFS in patients with PD-L1 TPS ≥ 1%. chemo, chemotherapy; HR, hazard ratio; NR, not reached; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; TPS, tumor proportion score.