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Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer

Shirish Gadgeel, MB, BS[1]; Delvys Rodríguez-Abreu, MD[2]; Giovanna Speranza, MD, MSc[3]; Emilio Esteban, MD[4]; Enriqueta Felip, MD, PhD[5]; Manuel Dómine, MD, PhD[6]; Rina Hui, MB, BS, PhD[7]; Maximilian J. Hochmair, MD[8]; Philip Clingan, MB, BS[9]; Steven F. Powell, MD[10]; Susanna Yee-Shan Cheng, MD[11]; Helge G. Bischoff, MD[12]; Nir Peled, MD, PhD[13]; Francesco Grossi, MD[14]; Ross R. Jennens, MB, BS[15]; Martin Reck, MD[16]; Edward B. Garon, MD[17]; Silvia Novello, MD, PhD[18]; Belén Rubio-Viqueira, MD[19]; Michael Boyer, MB, BS, PhD[20]; Takayasu Kurata, MD, PhD[21]; Jhanelle E. Gray, MD[22]; Jing Yang, PhD[23]; Tuba Bas, PhD[23]; M. Catherine Pietanza, MD[23]; and Marina C. Garassino, MD[24]

abstract

PURPOSE In KEYNOTE-189, first-line pembrolizumab plus pemetrexed-platinum significantly improved overall survival (OS) and progression-free survival (PFS) compared with placebo plus pemetrexed-platinum in patients with metastatic nonsquamous non–small-cell lung cancer (NSCLC), irrespective of tumor programmed death-ligand 1 (PD-L1) expression. We report an updated analysis from KEYNOTE-189 (ClinicalTrials.gov: NCT02578680).

METHODS Patients were randomly assigned (2:1) to receive pemetrexed and platinum plus pembrolizumab (n = 410) or placebo (n = 206) every 3 weeks for 4 cycles, then pemetrexed maintenance plus pembrolizumab or placebo for up to a total of 35 cycles. Eligible patients with disease progression in the placebo-combination group could cross over to pembrolizumab monotherapy. Response was assessed per RECIST (version 1.1) by central review. No alpha was assigned to this updated analysis.

RESULTS As of September 21, 2018 (median follow-up, 23.1 months), the updated median (95% CI) OS was 22.0 (19.5 to 25.2) months in the pembrolizumab-combination group versus 10.7 (8.7 to 13.6) months in the placebo-combination group (hazard ratio [HR], 0.56; 95% CI, 0.45 to 0.70]). Median (95% CI) PFS was 9.0 (8.1 to 9.9) months and 4.9 (4.7 to 5.5) months, respectively (HR, 0.48; 95% CI, 0.40 to 0.58). Median (95% CI) time from randomization to objective tumor progression on next-line treatment or death from any cause, whichever occurred first (progression-free-survival-2; PFS-2) was 17.0 (15.1 to 19.4) months and 9.0 (7.6 to 10.4) months, respectively (HR, 0.49; 95% CI, 0.40 to 0.59). OS and PFS benefits with pembrolizumab were observed regardless of PD-L1 expression or presence of liver/brain metastases. Incidence of grade 3-5 adverse events was similar in the pembrolizumab-combination (71.9%) and placebo-combination (66.8%) groups.

CONCLUSION First-line pembrolizumab plus pemetrexed-platinum continued to demonstrate substantially improved OS and PFS in metastatic nonsquamous NSCLC, regardless of PD-L1 expression or liver/brain metastases, with manageable safety and tolerability.

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ASSOCIATED CONTENT

Data Supplement
Protocol

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

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INTRODUCTION

Until the advent of immunotherapy, first-line treatment of patients with advanced nonsquamous non–small-cell lung cancer (NSCLC) without an *EGFR*/*ALK* alteration was platinum-based chemotherapy, with addition of bevacizumab as an option in select patients.[1,2] The introduction of pembrolizumab, an anti–programmed death-1 (PD-1) monoclonal antibody, has altered the treatment paradigm for patients with NSCLC. Pembrolizumab has shown efficacy in first-line therapy of advanced/metastatic NSCLC both when administered as monotherapy in patients with programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) ≥ 50%[3] and ≥ 1%[4] and when administered in combination with platinum-based chemotherapy regardless of tumor PD-L1 expression.[5-7] In an analysis of the randomized, double-blind, phase III KEYNOTE-189 study conducted with a median follow-up of 10.5 months, pembrolizumab plus pemetrexed-platinum significantly improved overall survival (OS; hazard ratio [HR], 0.49; 95% CI, 0.38 to 0.64; $P < .001$), progression-free survival (PFS; HR, 0.52; 95% CI, 0.43 to 0.64; $P < .001$), and objective response rate (ORR; 47.6% *v* 18.9%; $P < .001$) compared with placebo plus pemetrexed-platinum in patients with

metastatic NSCLC without sensitizing *EGFR*/*ALK* alterations, regardless of PD-L1 TPS.[6] Toxicity with pembrolizumab plus pemetrexed-platinum was manageable.

In this updated analysis from KEYNOTE-189, we evaluated efficacy and safety with approximately 10 additional calendar months of follow-up from the first interim analysis data cutoff date. Extrapulmonary metastases to sites such as the liver and brain frequently occur in metastatic NSCLC and are associated with a poor prognosis[8,9]; whether such metastases alter the magnitude of benefit with immunotherapy has been uncertain.[10] Therefore, we assessed outcomes among patients with liver/brain metastases. Finally, to characterize the treatment effect of pembrolizumab on the next line of therapy, we conducted a protocol-specified exploratory analysis of progression-free survival-2 (PFS-2).[11]

METHODS

Patients and Study Design

The study design has been previously described.[6] Briefly, patients had previously untreated pathologically confirmed metastatic nonsquamous NSCLC without sensitizing *EGFR*/*ALK* alterations, Eastern Cooperative Oncology Group performance status of 0/1, and ≥ 1 measurable lesion, and provided a tumor sample for PD-L1 evaluation. Exclusion criteria included symptomatic CNS metastases, history of noninfectious pneumonitis requiring glucocorticoids, active autoimmune disease, or systemic immunosuppressive therapy. All patients provided written informed consent; study procedures were approved by an independent ethics committee at each site. Patients were randomly assigned (2:1) to receive either 200 mg pembrolizumab or saline placebo every 3 weeks for up to 35 cycles. Randomization was stratified by tumor PD-L1 TPS (≥ 1% *v* < 1%), choice of platinum (cisplatin *v* carboplatin), and smoking history (never *v* former/current). All patients received pemetrexed and investigators' choice of cisplatin or carboplatin every 3 weeks for 4 cycles followed by pemetrexed maintenance therapy every 3 weeks. Patients who received placebo could cross over to pembrolizumab monotherapy at the time of disease progression (as verified by a blinded, independent central radiologic review [BICR]) if they met eligibility criteria.

Assessments

Tumor tissue samples obtained by core-needle or excisional biopsy at the time of diagnosis were fixed in formalin and centrally assessed for PD-L1 expression using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA). PD-L1 expression was categorized by TPS (the percentage of tumor cells with membranous PD-L1 staining). Tumor imaging occurred at weeks 6 and 12, every 9 weeks through week 48, and every 12 weeks after week 48. Patients with brain metastases underwent imaging of the brain at the same intervals. Response was assessed per RECIST (version 1.1) by BICR. Survival was assessed every 12 weeks after discontinuation of study treatment. Adverse events (AEs), including AEs of special interest, through 30 days (90 days for serious AEs) after the last treatment dose or until start of new therapy were graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Events (version 4.0).

Endpoints

The dual primary endpoints were OS and PFS; secondary endpoints were ORR, duration of response (DOR), and safety. Efficacy analyses in patients with baseline liver or brain (prespecified) metastases were exploratory. PFS-2, which was defined as the time from randomization to objective tumor progression on next-line treatment (including subsequent anti–PD-[L]1 therapy) or death from any cause, whichever occurs first, was a protocol-specified exploratory endpoint. Events for PFS-2 analysis were characterized as time of investigator-assessed disease progression that led to cessation of second-line therapy, start of third-line therapy for patients who stopped second-line therapy without disease progression, and time of death for patients who either stopped second-line therapy without disease progression and did not initiate third-line therapy or did not receive second-line therapy. Patients were censored for PFS-2 at the time of last known survival if they were alive and either had not received second-line therapy or had stopped second-line therapy without disease progression and had not initiated third-line therapy.

Statistical Analyses

Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all randomly assigned patients; safety analyses were performed in the as-treated population, which included all randomly assigned patients who received ≥ 1 dose of therapy. The Kaplan-Meier method was used to estimate OS, PFS, and PFS-2. A stratified Cox proportional hazards model with Efron's method of tie handling was used to determine HRs and 95% CIs. Stratification factors used for randomization were applied. Analyses were not controlled for multiplicity; no alpha was assigned to this updated analysis.

RESULTS

Patients and Treatments

Overall, 616 patients were randomly assigned to pembrolizumab plus pemetrexed-platinum (n = 410) or placebo plus pemetrexed-platinum (n = 206). Patient demographics and baseline disease characteristics were generally similar between groups (Table 1). The proportions of patients in PD-L1 TPS subgroups (< 1%, 1%-49%, and ≥ 50%) were similar between treatment groups; approximately one third of patients had TPS < 1%. At baseline, 66 (16.1%) and 73 (17.8%) patients in the pembrolizumab-combination group had liver and brain metastases, respectively, versus 49 (23.8%) and 35 (17.0%), respectively, in the placebo-combination group.

TABLE 1. Patient Demographics and Baseline Disease Characteristics

Characteristic	Pembrolizumab Combination (n = 410)	Placebo Combination (n = 206)
Age, median (range), years	65.0 (34-84)	63.5 (34-84)
Male	254 (62.0)	109 (52.9)
ECOG performance status		
0	186 (45.4)	80 (38.8)
1	220 (53.7)	125 (60.7)
2	1 (0.2)	0
Smoking status		
Former or current	362 (88.3)	181 (87.9)
Never	48 (11.7)	25 (12.1)
Liver metastases	66 (16.1)	49 (23.8)
Brain metastases	73 (17.8)	35 (17.0)
Previously treated	43 (10)	23 (11)
PD-L1 TPS		
< 1%	127 (31.0)	63 (30.6)
1%-49%	128 (31.2)	58 (28.2)
≥ 50%	132 (32.2)	70 (34.0)
Could not be evaluated	23 (5.6)	15 (7.3)
Previous therapy		
Thoracic radiotherapy	29 (7.1)	19 (9.2)
Neoadjuvant therapy	5 (1.2)	6 (2.9)
Adjuvant therapy	25 (6.1)	14 (6.8)

NOTE. Data are No. (%) unless otherwise indicated.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; TPS, tumor proportion scale.

At data cutoff (September 21, 2018), median (range) study follow-up (time from randomization to database cutoff) was 23.1 (18.6 to 30.9) months, and median (range) time from randomization to death or database cutoff, whichever occurred first, was 18.7 (0.2 to 30.9) months. Mean (standard deviation) treatment duration was 9.8 (7.8) months in the pembrolizumab-combination group and 6.2 (5.7) months in the placebo-combination group (Data Supplement, online only). In the pembrolizumab-combination group, 58 patients (14.1%) remained on ≥ 1 component of study therapy compared with 7 patients (3.4%) in the placebo-combination group (Fig 1). An additional 58 patients (14.1%) in the pembrolizumab-combination group and 8 patients (3.9%) in the placebo-combination group had stopped all study treatment and were alive without subsequent treatment, including 36 (8.8%) and 4 (1.9%), respectively, who were without disease progression. Twenty-four patients in the pembrolizumab-combination group and 1 in the placebo-combination group completed 35 cycles of pembrolizumab or placebo, respectively; 12 patients remained on pemetrexed only (all in pembrolizumab-combination group). In the ITT population, 183/410 patients (44.6%) in the pembrolizumab-combination group and 122/206 (59.2%) in the placebo-combination group received ≥ 1 subsequent therapy; 84 patients (40.8%) in the placebo-combination group crossed over on-study to pembrolizumab monotherapy, and 111 received any subsequent anti–PD-(L)1-therapy (effective crossover rate, 53.9%; Data Supplement).

OS and PFS

At the time of data cutoff, 213 patients (52.0%) in the pembrolizumab-combination group and 144 patients (69.9%) in the placebo-combination group had died. Median (95% CI) OS was 22.0 (19.5 to 25.2) months in the pembrolizumab-combination group and 10.7 (8.7 to 13.6) months in the placebo-combination group (HR, 0.56; 95% CI, 0.45 to 0.70; Fig 2A); estimated 24-month OS rates were 45.5% and 29.9%, respectively. The addition of pembrolizumab provided survival benefit irrespective of PD-L1 expression (Figs 2B-2D); Data Supplement).

Median (95% CI) PFS was 9.0 (8.1 to 9.9) months and 4.9 (4.7 to 5.5) months in the pembrolizumab-combination and placebo-combination groups, respectively (HR, 0.48; 95% CI, 0.40 to 0.58; Fig 3A); estimated 24-month PFS rates were 20.5% and 1.5%. As with OS, PFS benefit with the addition of pembrolizumab was observed irrespective of PD-L1 expression (Figs 3B-3D); Data Supplement).

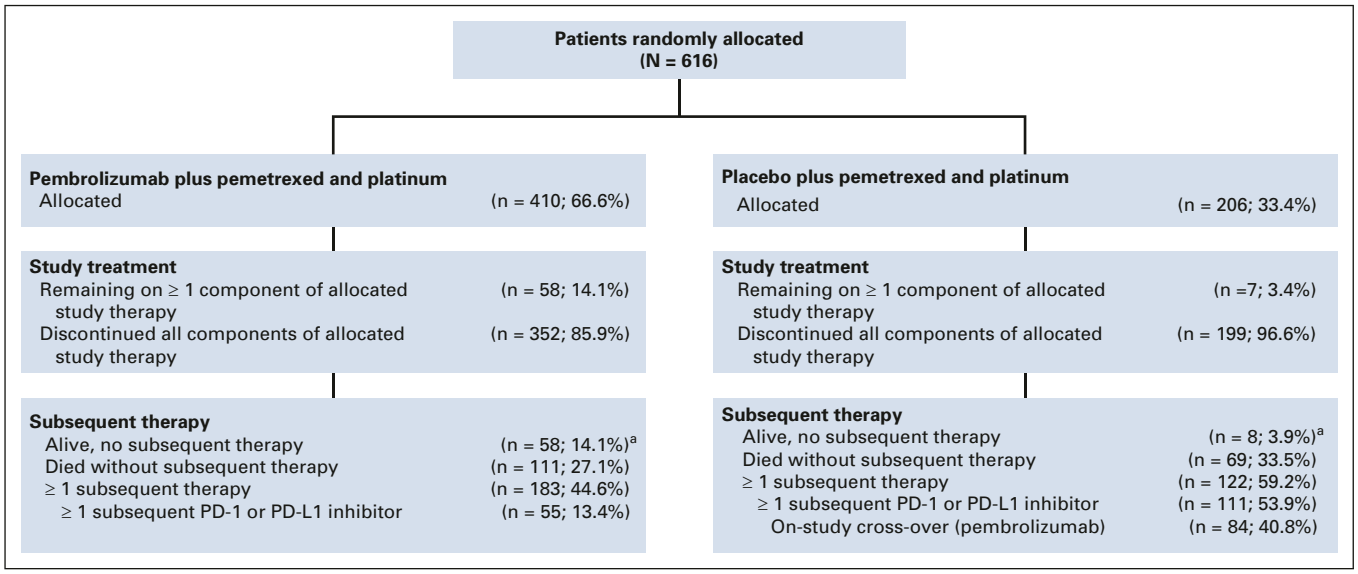

FIG 1. Disposition of patients in the study. PD-1, programmed death-1; PD-L1, programmed death-ligand 1; ([a]) Includes 36 patients (8.8%) in the pembrolizumab-combination arm and 4 patients (1.9%) in the placebo-combination arm who were alive without experiencing disease progression.

Objective Response

Confirmed objective response occurred in 197 (48.0%) patients in the pembrolizumab-combination group (complete response [CR], n = 4; partial response [PR], n = 193) and 40 patients (19.4%) in the placebo-combination group (CR, n = 1; PR, n = 39; Table 2). Median (range) DOR was 12.4 (1.1+ to 29.0+ months and 7.1 (2.4 to 22.0+) months in the pembrolizumab-combination and placebo-combination groups, respectively (+ indicates no progressive disease by the time of last disease assessment; Table 2). Ninety patients (52.3%) in the pembrolizumab-combination group and 8 (26.9%) in the placebo-combination group had estimated DOR ≥ 12 months. Response rate and DOR were higher in the pembrolizumab-combination group irrespective of PD-L1 expression (Table 2; Data Supplement).

Progression-Free Survival-2

Median (95% CI) PFS-2 was 17.0 (15.1 to 19.4) months in the pembrolizumab-combination group and 9.0 (7.6 to 10.4) months in the placebo-combination group (HR, 0.49; 95% CI, 0.40 to 0.59; Fig 4A). PFS-2 benefit associated with pembrolizumab was observed irrespective of PD-L1 expression (Figs 4B and 4C).

Outcomes in Patients With Baseline Liver or Brain Metastases

As in the overall population, an OS benefit was observed in the pembrolizumab-combination group versus the placebo-combination group in the subgroups of patients with liver (n = 115) or brain (n = 108) metastases (Figs 5A-5D). HRs for OS with pembrolizumab-combination versus placebo-combination were similar among patients with (0.62; 95% CI, 0.39 to 0.98) and without (0.58; 95% CI, 0.45 to 0.74) liver metastases (Figs 5A and 5B) and those with (0.41; 95% CI, 0.24 to 0.67) and without (0.59; 95% CI, 0.46 to 0.75) brain metastases (Figs 5C and 5D). PFS was also improved among patients with and without liver (Data Supplement) and brain metastases (Data Supplement).

Adverse Events

All-cause AEs occurred in 404 patients (99.8%) in the pembrolizumab-combination group and 200 (99.0%) in the placebo-combination group (Table 3). Grade 3-5 AEs occurred in 291 (71.9%) and 135 patients (66.8%), respectively. Compared with initial analysis, 2 additional patients in each group had all-cause AEs leading to death (pembrolizumab-combination: spinal fracture and general physical health deterioration, n = 1 each; total, n = 29 [7.2%]; placebo-combination: respiratory failure and bronchitis, n = 1 each; total, n = 14 [6.9%]; Data Supplement); 8 patients (2.0%) in the pembrolizumab-combination group died of AEs attributed to study treatment. AEs of acute kidney injury occurred in 25 patients (6.2%) in the pembrolizumab-combination group and occurred in 1 patient (0.5%) in the placebo-combination group. Since the prior analysis, no new patients who died as a result of the AE of acute kidney injury occurred in the pembrolizumab-combination group. The most frequently occurring AEs in both treatment groups were nausea, anemia, and fatigue (Table 3).

Immune-mediated AEs and infusion-related reactions (any grade) occurred in 107 patients (26.4%) and 26 patients (12.9%) in the pembrolizumab-combination and placebo-combination groups, respectively. Grade 3-5 immune-mediated AEs and infusion-related reactions occurred in 10.9% and 4.5%, respectively. The most frequently occurring immune-mediated AEs in the pembrolizumab-combination and placebo-combination groups were

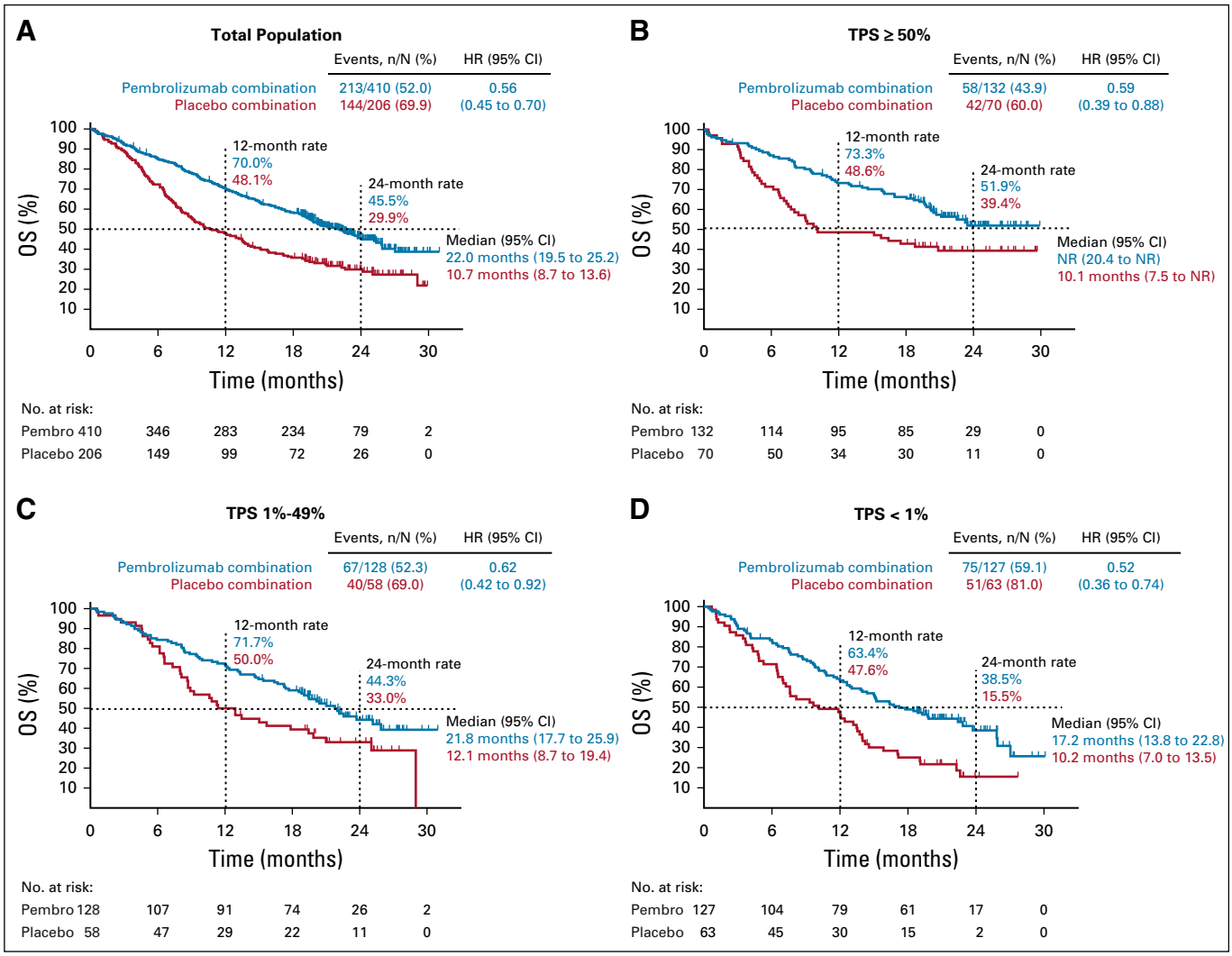

FIG 2. Kaplan-Meier analysis of overall survival (OS) in the (A) overall intention-to-treat population and in subsets of patients by tumor proportion score (TPS): (B) ≥ 50%, (C) 1%-49%, and (D) < 1%. HR, hazard ratio; NR, not reached; pembro, pembrolizumab.

hypothyroidism (7.9%), hyperthyroidism (4.9%), and pneumonitis (4.9%; Table 3). Eight patients (2.0%) in the pembrolizumab-combination group experienced nephritis, 6 of whom had grade 3-4 events; there were no additional grade 3-4 nephritis events since the prior analysis (when 6/7 patients with nephritis had grade 3-4 events). No patients in the placebo-combination group experienced nephritis.

In patients with and without liver metastases, AEs of grade ≥ 3 occurred in 69.2% and 72.4% of patients in the pembrolizumab-combination group, respectively, and 72.9% and 64.9% of patients in the placebo-combination group, respectively; in patients with and without brain metastases, AEs of grade ≥ 3 occurred in 80.0% and 70.1% of patients in the pembrolizumab-combination group, respectively, and 63.6% and 67.5% of patients in the placebo-combination group, respectively.

DISCUSSION

In this updated analysis from KEYNOTE-189, pembrolizumab plus pemetrexed-platinum continued to show substantial improvement in OS and PFS versus placebo plus pemetrexed-platinum when administered as first-line therapy for metastatic nonsquamous NSCLC without sensitizing *EGFR/ALK* alterations. Median OS and PFS were approximately doubled in the pembrolizumab-combination group, and this benefit was observed in patients with both PD-L1–positive and PD-L1–negative disease, as well as in patients with liver/brain metastases. PFS-2 was substantially improved in the pembrolizumab-combination group compared with the placebo-combination group. Safety outcomes were consistent with those from the previous interim analysis and showed that the combination of pembrolizumab and pemetrexed-platinum has a manageable toxicity profile. These data support use of pembrolizumab plus pemetrexed-platinum as first-line

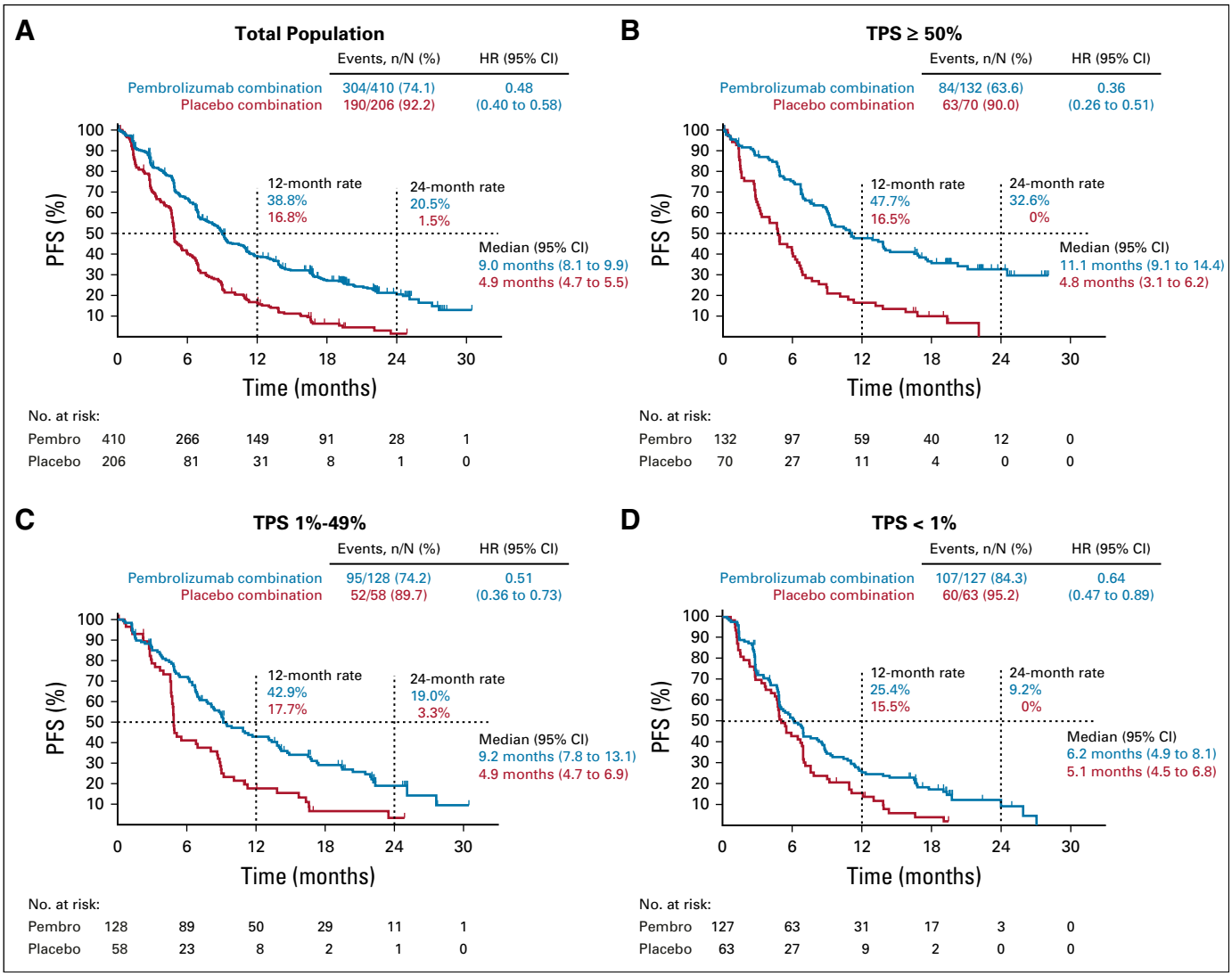

FIG 3. Kaplan-Meier analysis of progression-free survival in the (A) intention-to-treat population and in subsets of patients by programmed death-ligand 1 tumor proportion score (TPS): (B) ≥ 50%, (C) 1%-49%, and (D) < 1%. HR, hazard ratio; pembro, pembrolizumab.

treatment of patients with metastatic nonsquamous NSCLC.

Results from this updated analysis confirm and extend those from the first interim analysis of KEYNOTE-189 (median follow-up, 10.5 months),[6] in which the addition of pembrolizumab resulted in significantly longer OS than chemotherapy alone (HRs for OS, 0.56; 95% CI, 0.45 to 0.70 in this analysis *v* 0.49 in the prior analysis). We observed continued OS benefit, with an estimated 2-year OS rate of 46% in the pembrolizumab-combination group versus 30% in the placebo-combination group, despite 54% of patients in the chemotherapy arm crossing over to pembrolizumab monotherapy or other PD-1/PD-L1 inhibitors, underscoring the benefit of combining pembrolizumab with chemotherapy as first-line treatment in advanced NSCLC. Notably, the 30% 2-year OS rate we observed in the chemotherapy alone group was high compared with historical 2-year OS rates of 14%-19% with chemotherapy,[12,13] likely reflecting the effect of crossover to anti–PD-(L)1 agents. The ongoing improvement in OS was consistent with a long-term follow-up analysis from the phase II KEYNOTE-021 cohort G study[14] (pembrolizumab plus pemetrexed-carboplatin *v* pemetrexed-carboplatin), which showed long-term survival benefit with pembrolizumab (HR, 0.56; 95% CI, 0.32 to 0.95). Similar to OS results, this updated analysis with longer follow-up also confirmed the improved PFS and ORR observed with the addition of pembrolizumab compared with placebo in the first interim analysis of KEYNOTE-189.

Consistent with the initial analysis[6] and with other studies evaluating pembrolizumab monotherapy[4,15,16] and combination therapy[5] in patients with advanced/metastatic NSCLC, the magnitude of OS, PFS, and ORR benefit was greatest among the subgroup of patients with PD-L1

TABLE 2. Summary of Responses

	All Patients, N = 616		TPS ≥ 50%, n = 202[a]		TPS 1%-49%, n = 186[a]		TPS < 1%, n = 190[a]	
	Pembrolizumab Combination, n = 410	Placebo Combination, n = 206	Pembrolizumab Combination, n = 132	Placebo Combination, n = 70	Pembrolizumab Combination, n = 128	Placebo Combination, n = 58	Pembrolizumab Combination, n = 127	Placebo Combination, n = 63
Best overall response								
CR	4 (1.0)	1 (0.5)	1 (0.8)	0	3 (2.3)	1 (1.7)	0	0
PR	193 (47.1)	39 (18.9)	81 (61.4)	17 (24.3)	60 (46.9)	11 (19.0)	41 (32.3)	9 (14.3)
SD[b]	150 (36.6)	105 (51.0)	33 (25.0)	29 (41.4)	47 (36.7)	33 (56.9)	59 (46.5)	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	12 (2.9)	8 (3.9)	5 (3.8)	1 (1.4)	0	2 (3.4)	7 (5.5)	4 (6.3)
No assessment	14 (3.4)	17 (8.3)	6 (4.5)	7 (10.0)	3 (2.3)	4 (6.9)	5 (3.9)	5 (7.9)
ORR, % (95% CI)	48.0 (43.1 to 53.0)	19.4 (14.2 to 25.5)	62.1 (53.3 to 70.4)	24.3 (14.8 to 36.0)	49.2 (40.3 to 58.2)	20.7 (11.2 to 33.4)	32.3 (24.3 to 41.2)	14.3 (6.7 to 25.4)
Median DOR, months (range)[c]	12.4 (1.1+ to 29.0+)	7.1 (2.4 to 22.0+)	15.1 (1.2+ to 26.8+)	7.1 (3.4 to 19.4)	12.9 (2.1+ to 29.0+)	7.6 (2.4 to 22.0+)	10.8 (1.1+ to 22.6)	7.8 (4.1 to 18.1+)
DOR ≥ 12 months[c]	90 (52.3)	8 (26.9)	40 (56.5)	4 (30.1)	28 (52.2)	2 (31.3)	17 (45.9)	2 (26.7)

NOTE. Data are No. (%) unless otherwise indicated. + indicates no progressive disease by the time of last disease assessment.

Abbreviations: CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TPS, tumor proportion score.

[a]Excludes 38 patients for whom PD-L1 expression could not be evaluated.

[b]Stable disease includes both stable disease and noncomplete response/nonprogressive disease.

[c]Kaplan-Meier estimate.

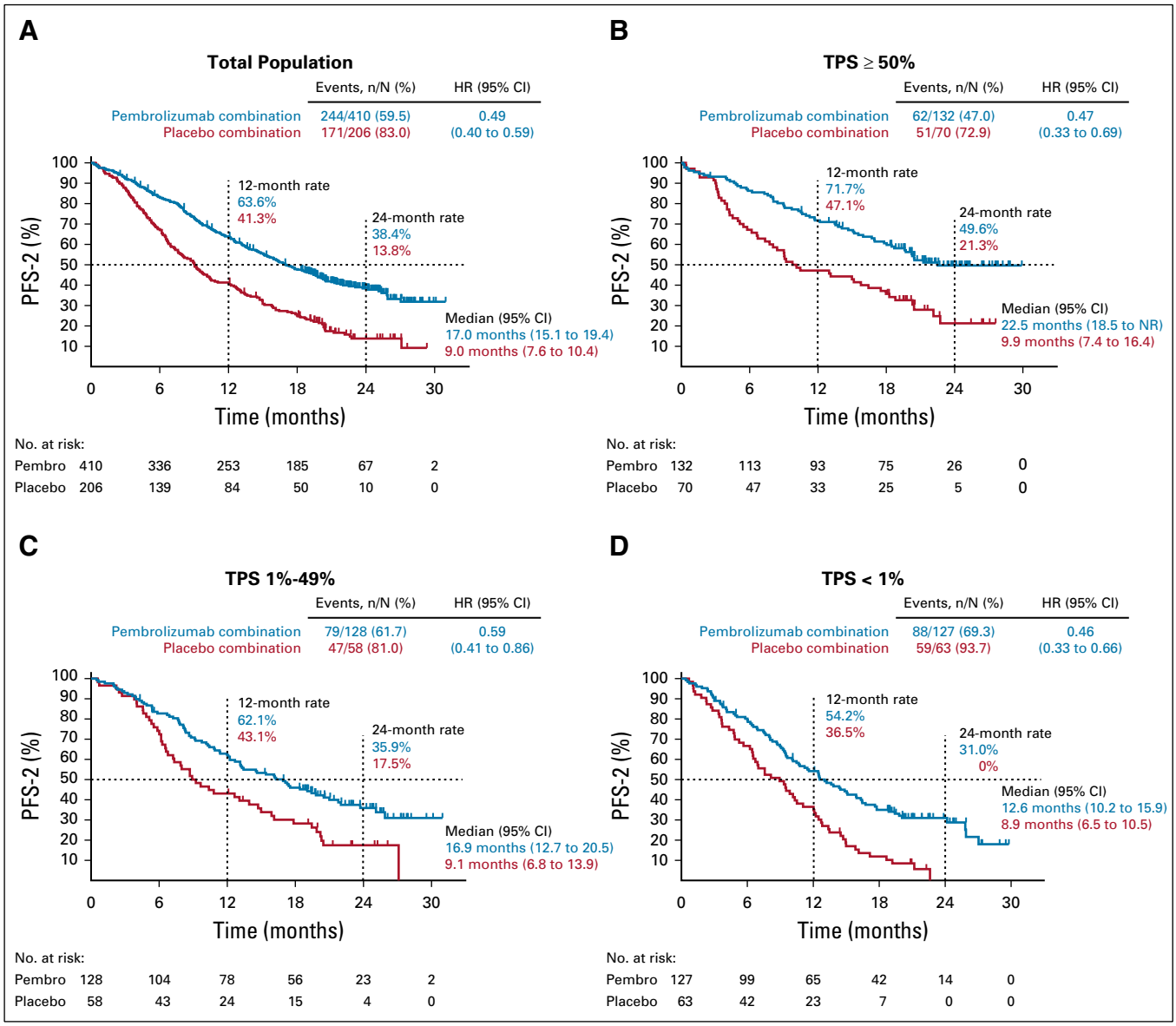

FIG 4. Kaplan-Meier analysis of progression-free survival-2 (PFS-2) in the (A) intention-to-treat population and in subsets of patients by programmed death-ligand 1 (PD-L1) tumor proportion score (TPS): (B) ≥ 50%, (C) 1%-49%, (D) < 1%. PFS-2 was defined as the time from randomization to objective tumor progression on next-line treatment (including subsequent anti–PD-[L]1 therapy) or death from any cause, whichever occurred first. HR, hazard ratio; pembro, pembrolizumab.

TPS ≥ 50%. We also continued to observe improved OS, PFS, and ORR among patients with PD-L1 TPS < 1%; importantly, with longer follow-up, the 95% CI for the PFS HR did not cross 1.0 in the current analysis. The magnitude of OS and PFS benefit in patients with PD-L1 TPS < 1% (HRs [95% CI] for OS and PFS, 0.52 [0.36 to 0.74] and 0.64 [0.47 to 0.89], respectively) was notable, particularly because patients with PD-L1 TPS < 1% have a lower chance of benefit with single-agent anti–PD-1 therapy.[1,3,15,16] In addition, survival was improved with the addition of pembrolizumab to chemotherapy in patients with PD-L1 TPS 1%-49%. Similar improvement in survival in this group of patients has not been observed with single-agent anti–PD-1 therapy compared with chemotherapy.[4] It has been suggested that improvements in outcome with regimens combining a checkpoint inhibitor with platinum may be due, at least in part, to induction of immunogenic cell death by platinum-based chemotherapy, which leads to recruitment of dendritic cells, downregulation of PD-L1 and PD-L2, and enhanced tumor-specific T-cell activation.[17] Additionally, preclinical data suggest that pemetrexed can enhance anticancer effects of immunotherapy.[18] Our results suggest that such mechanisms may contribute to improvements in patient outcomes.

The substantial PFS and OS benefit and 46% 2-year OS rate observed with pembrolizumab plus pemetrexed-platinum

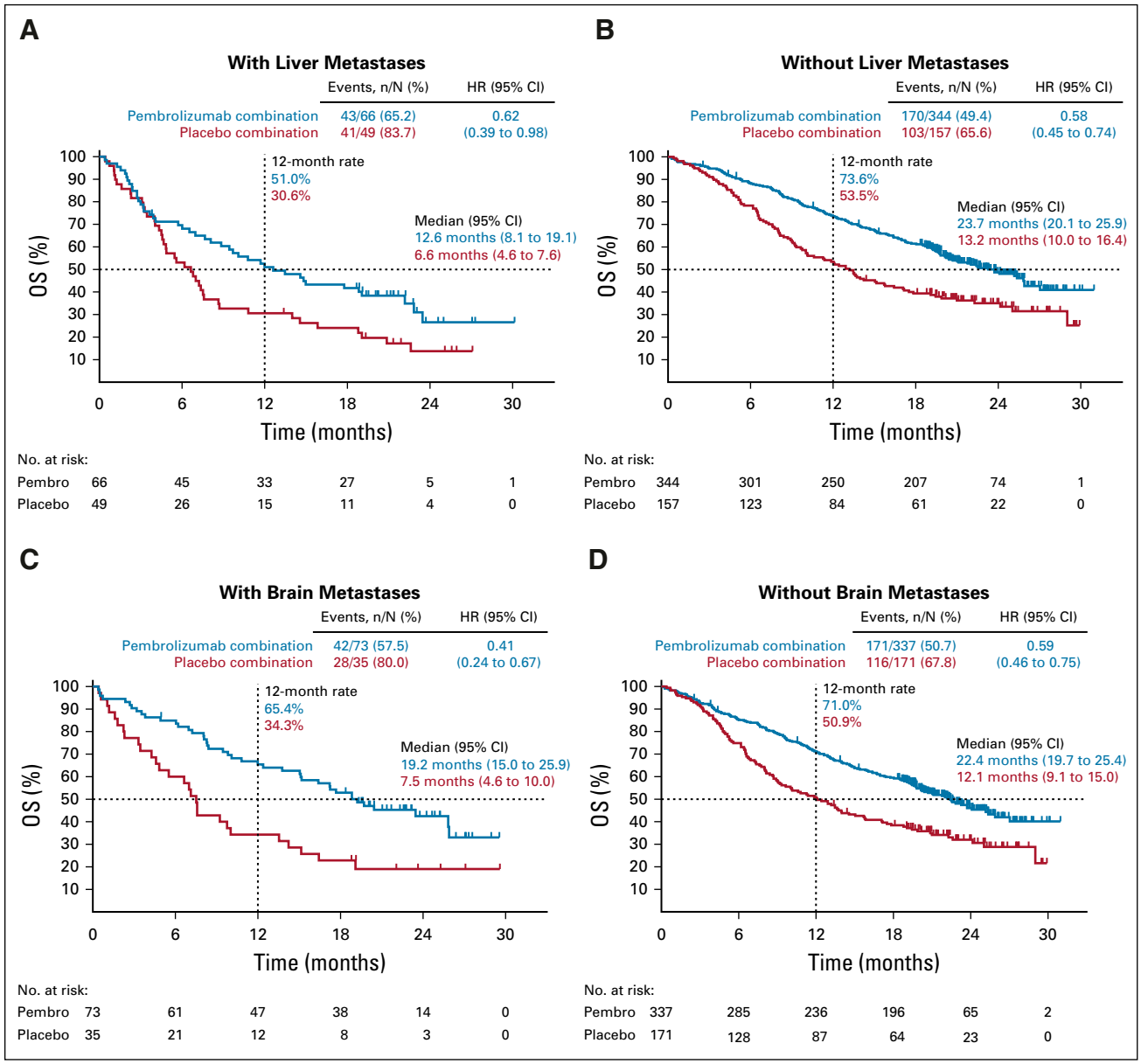

FIG 5. Kaplan-Meier analysis of overall survival (OS) in patients (A) with and (B) without liver metastases and (C) with and (D) without brain metastases. HR, hazard ratio; pembro, pembrolizumab.

in KEYNOTE-189 underscore that chemotherapy plus immunotherapy is an effective modality. Other phase III studies have evaluated immunotherapy-immunotherapy combination strategies for metastatic NSCLC. In CheckMate-227 part 1, the study coprimary endpoints were met with nivolumab plus ipilimumab versus chemotherapy (PFS in TMB-≥10mut/MB: HR, 0.58; 97.5% CI, 0.41 to 0.81; $P < .001$[19]; OS in PD-L1–positive population: HR, 0.79; 97.72% CI, 0.65 to 0.96; $P = .007$[20]). In MYSTIC, the primary OS and PFS endpoints with durvalumab with and without tremelimumab versus chemotherapy were not met (PD-L1-TC-expression-≥ 25% population: durvalumab *v* chemotherapy: OS HR, 0.76; 97.54% CI, 0.564 to 1.019; $P = .036$; durvalumab-plus-tremelimumab *v* chemotherapy: OS HR, 0.85; 98.77% CI, 0.611 to 1.173; $P = .202$; PFS HR, 1.05; 99.5% CI, 0.722 to 1.534; $P = .705$).[21]

The OS benefit observed with the addition of pembrolizumab occurred despite 54% (111/206) of patients in the placebo-combination group receiving subsequent anti–PD-(L)1 therapy, including 41% (84/206) who crossed over to pembrolizumab monotherapy on-study (of 122 patients who received subsequent therapy, 91% received anti–PD-[L]1 therapy). To assess the impact of pembrolizumab plus pemetrexed-platinum on subsequent therapy, we evaluated PFS-2, defined as the time from randomization to objective tumor progression on next-line

TABLE 3. Summary of All-Cause Adverse Events

	Pembrolizumab Combination (n = 405)		Placebo Combination (n = 202)	
Event	**Any Grade**	**Grade 3-5**	**Any Grade**	**Grade 3-5**
Experienced ≥ 1 adverse event	404 (99.8)	291 (71.9)	200 (99.0)	135 (66.8)
Led to discontinuation of any treatment component	136 (33.6)		33 (16.3)	
Led to death[a]	29 (7.2)		14 (6.9)	
Adverse events occurring in ≥ 15% of patients in either group				
Nausea	230 (56.8)	14 (3.5)	107 (53.0)	8 (4.0)
Anemia	192 (47.4)	74 (18.3)	98 (48.5)	32 (15.8)
Fatigue	172 (42.5)	28 (6.9)	78 (38.6)	7 (3.5)
Constipation	144 (35.6)	4 (1.0)	67 (33.2)	1 (0.5)
Diarrhea	128 (31.6)	21 (5.2)	44 (21.8)	6 (3.0)
Decreased appetite	120 (29.6)	5 (1.2)	64 (31.7)	2 (1.0)
Neutropenia	112 (27.7)	65 (16.0)	51 (25.2)	25 (12.4)
Vomiting	105 (25.9)	16 (4.0)	47 (23.3)	6 (3.0)
Cough	100 (24.7)	0	61 (30.2)	0
Dyspnea	98 (24.2)	17 (4.2)	54 (26.7)	10 (5.0)
Peripheral edema	88 (21.7)	2 (0.5)	29 (14.4)	0
Pyrexia	88 (21.7)	1 (0.2)	32 (15.8)	0
Asthenia	87 (21.5)	27 (6.7)	49 (24.3)	7 (3.5)
Rash	87 (21.5)	8 (2.0)	26 (12.9)	3 (1.5)
Thrombocytopenia	75 (18.5)	34 (8.4)	30 (14.9)	14 (6.9)
Lacrimation increased	74 (18.3)	0	22 (10.9)	0
Back pain	66 (16.3)	6 (1.5)	26 (12.9)	4 (2.0)
Immune-mediated adverse events[b]	107 (26.4)	44 (10.9)	26 (12.9)	9 (4.5)
Hypothyroidism	32 (7.9)	2 (0.5)	5 (2.5)	0
Hyperthyroidism	20 (4.9)	0	6 (3.0)	0
Pneumonitis	20 (4.9)	12 (3.0)	6 (3.0)	4 (2.0)
Colitis	12 (3.0)	6 (1.5)	0	0
Infusion reactions	11 (2.7)	1 (0.2)	3 (1.5)	0
Severe skin reactions	9 (2.2)	9 (2.2)	5 (2.5)	4 (2.0)
Nephritis	8 (2.0)	6 (1.5)	0	0
Hepatitis	5 (1.2)	4 (1.0)	0	0
Hypophysitis	3 (0.7)	0	0	0
Myositis	3 (0.7)	0	0	0
Pancreatitis	3 (0.7)	2 (0.5)	0	0
Encephalitis	2 (0.5)	2 (0.5)	0	0
Type I diabetes mellitus	2 (0.5)	2 (0.5)	0	0
Adrenal insufficiency	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)
Myocarditis	1 (0.2)	1 (0.2)	0	0
Thyroiditis	1 (0.2)	0	0	0

NOTE. Reported in all patients who received ≥ 1 dose of study treatment. Data are No. (%).

[a]Eight patients (2.0%) in the pembrolizumab-combination group and 2 patients in the placebo-combination group died of adverse events attributed by the investigator to study treatment.

[b]Events were based on a list from the sponsor and considered regardless of attribution to treatment or immune relatedness by the investigator.

treatment or death from any cause, whichever occurred first.[11] For the first time, we showed that first-line pembrolizumab plus pemetrexed-platinum improved PFS-2, which was approximately doubled for patients in the pembrolizumab-combination group. This PFS-2 outcome demonstrates that treatment effects observed in the first-line setting were maintained into the next line of therapy. Moreover, despite the high crossover rate, we observed improved survival outcomes in patients with metastatic nonsquamous NSCLC who initiated pembrolizumab as first-line treatment in combination with chemotherapy compared with those who initiated chemotherapy first and then received pembrolizumab (or another anti–PD-[L]1 agent) postprogression. These results are consistent with the PFS-2 analysis for pembrolizumab monotherapy in KEYNOTE-024[22] and support preferential use of pembrolizumab in the first-line setting.

Liver and brain metastases are poor prognostic factors in patients with NSCLC.[8,9] The efficacy of immunotherapy treatment effect in these patient populations has been uncertain, with results from one study suggesting reduced benefit in patients with liver metastases.[10] Consistent with poor prognosis among patients with brain or liver metastases, we observed shorter median OS times among these patients compared with patients without brain or liver metastases. However, this poorer prognosis did not diminish the treatment effect associated with the addition of pembrolizumab to pemetrexed-platinum: HRs for OS and PFS were similar among patients with and without brain metastases and among patients with and without liver metastases. Outcomes in patients with liver metastases were also evaluated in the IMpower130[23] and IMpower150[24,25] studies, which evaluated atezolizumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone and atezolizumab plus bevacizumab plus platinum-based chemotherapy versus atezolizumab plus platinum-based chemotherapy versus bevacizumab plus platinum-based chemotherapy, respectively, in patients with advanced nonsquamous NSCLC. In these 2 studies, OS benefit in patients with liver metastases was only observed among patients who received atezolizumab plus bevacizumab plus chemotherapy.

Addition of pembrolizumab to pemetrexed-platinum continued to show a manageable safety profile after a mean treatment duration of 9.8 months. Despite longer follow-up with this analysis, no new safety signals were identified, including no additional immune-mediated AEs beyond those previously observed with pembrolizumab monotherapy.[3,4] The proportion of patients experiencing grade 3-5 AEs was similar between the pembrolizumab-combination and placebo-combination groups, suggesting that addition of pembrolizumab to standard chemotherapy was associated with acceptable toxicity. Consistent with the primary analysis, a greater percentage of patients in the pembrolizumab-combination versus placebo-combination group experienced AEs of acute kidney injury and nephritis; however, despite longer treatment exposure, only 1 additional event of grade 2 nephritis occurred. AEs were generally similar between patients in the pembrolizumab-combination and placebo-combination groups across subgroups with or without liver/brain metastases.

In summary, after median follow-up of approximately 2 years, pembrolizumab plus pemetrexed-platinum resulted in substantially longer OS, PFS, and PFS-2 and a higher response compared with placebo plus pemetrexed-platinum in patients with metastatic nonsquamous NSCLC without sensitizing *EGFR*/*ALK* alterations. Survival benefit was observed across all PD-L1 TPS groups and in patients with liver/brain metastases. Safety and tolerability results were comparable with the first interim analysis (10.5 months median follow-up). These results support pembrolizumab plus pemetrexed-platinum as a standard-of-care first-line therapy among patients with metastatic nonsquamous NSCLC without sensitizing *EGFR*/*ALK* alterations, regardless of tumor PD-L1 expression.

AFFILIATIONS

[1]Karmanos Cancer Institute, Detroit, MI
[2]Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain
[3]Centre Integré de Cancérologie de la Montérégie, Hôpital Charles-Le Moyne, Greenfield Park, Quebec, Canada
[4]Hospital Universitario Central de Asturias, Oviedo, Spain
[5]Vall d'Hebron University, Vall d'Hebron Institute of Oncology, Barcelona, Spain
[6]Hospital Universitario Fundación Jiménez Díaz, IIS-FJD, Madrid, Spain
[7]Westmead Hospital and University of Sydney, Sydney, New South Wales, Australia
[8]Department of Respiratory and Critical Care Medicine, Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Vienna, Austria
[9]Southern Medical Day Care Centre, Wollongong, New South Wales, Australia
[10]Sanford Health, Sioux Falls, SD
[11]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[12]Thoraxklinik, Heidelberg, Germany
[13]Soroka Medical Center, Ben-Gurion University, Beer Sheva, Israel
[14]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
[15]Epworth Healthcare, Richmond, Victoria, Australia
[16]LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany
[17]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA
[18]Department of Oncology, University of Turin, Azienda Ospedaliero-Universitaria San Luigi, Orbassano, Italy
[19]Hospital Universitario Quirónsalud Madrid, Madrid, Spain
[20]Chris O'Brien Lifehouse, Camperdown, New South Wales, Australia
[21]Kansai Medical University Hospital, Osaka, Japan
[22]Moffitt Cancer Center, Tampa, FL
[23]Merck & Co, Kenilworth, NJ
[24]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale dei Tumori, Milan, Italy

CORRESPONDING AUTHOR

Shirish Gadgeel, MB, BS, Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, 1500 E Medical Center Dr, 7217CC, Ann Arbor, MI 48109; e-mail: sgadgeel@med.umich.edu.

PRIOR PRESENTATION

Results presented in part at the American Association for Cancer Research Annual Meeting 2019, Atlanta, GA, March 29-April 3, 2019; and at the American Society of Clinical Oncology Annual Meeting 2019, Chicago, IL, May 31-June 4, 2019.

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AUTHOR CONTRIBUTIONS

Conception and design: Helge G. Bischoff, M. Catherine Pietanza, Marina C. Garassino

Administrative support: Helge G. Bischoff

Provision of study materials or patients: Giovanna Speranza, Enriqueta Felip, Rina Hui, Philip Clingan, Francesco Grossi, Ross R. Jennens, Edward B. Garon, Silvia Novello, Michael Boyer, Takayasu Kurata, Jhanelle E. Gray

Collection and assembly of data: Shirish Gadgeel, Enriqueta Felip, Manuel Dómine, Rina Hui, Philip Clingan, Steven F. Powell, Susanna Yee-Shan Cheng, Helge G. Bischoff, Nir Peled, Ross R. Jennens, Martin Reck, Edward B. Garon, Belén Rubio-Viqueira, Michael Boyer, Takayasu Kurata, Jhanelle E. Gray, Tuba Bas, M. Catherine Pietanza, Marina C. Garassino

Data analysis and interpretation: Shirish Gadgeel, Delvys Rodríguez-Abreu, Giovanna Speranza, Emilio Esteban, Enriqueta Felip, Manuel Dómine, Rina Hui, Maximilian J. Hochmair, Steven F. Powell, Helge G. Bischoff, Nir Peled, Francesco Grossi, Martin Reck, Edward B. Garon, Silvia Novello, Michael Boyer, Jhanelle E. Gray, Jing Yang, Tuba Bas, M. Catherine Pietanza, Marina C. Garassino

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer

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Shirish Gadgeel
Honoraria: AstraZeneca, Merck, Genentech
Consulting or Advisory Role: Genentech, AstraZeneca, Bristol-Myers Squibb, Takeda, Xcovery, Boehringer Ingelheim, Novocure
Research Funding: Pfizer (Inst), Merck, Genentech (Inst), Merck (Inst), Blueprint Medicines (Inst), ARIAD/Takeda (Inst), Aeglea Biotherapeutics (Inst), Astellas Pharma (Inst), G1 Therapeutics (Inst), Lycera (Inst), Daiichi Sankyo (Inst)
Travel, Accommodations, Expenses: Genentech, Merck
Other Relationship: AstraZeneca

Delvys Rodríguez-Abreu
Consulting or Advisory Role: Roche, Bristol-Myers Squibb, MSD
Speakers' Bureau: Roche, Bristol-Myers Squibb, MSD
Travel, Accommodations, Expenses: Roche, Bristol-Myers Squibb, MSD

Emilio Esteban
Travel, Accommodations, Expenses: Pfizer/EMD Serono

Enriqueta Felip
Consulting or Advisory Role: Pfizer, Roche, Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, Guardant Health, Novartis, Takeda, AbbVie, Blue Print Medicines, Eli Lilly, Merck KGaA, Merck Sharp & Dohme, Janssen, Samsung
Speakers' Bureau: Pfizer, Roche, AstraZeneca, Bristol-Myers Squibb, Novartis, Takeda, Eli Lilly, Merck Sharp & Dohme, Medscape, Prime Oncology, Touchtime
Research Funding: Fundación Merck Salud, Oncology Innovation
Other Relationship: Grífols

Manuel Dómine
Consulting or Advisory Role: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, MSD Oncology, Pfizer, Roche
Travel, Accommodations, Expenses: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Pfizer, Roche

Rina Hui
Honoraria: Merck Sharp & Dohme, Novartis, Roche, AstraZeneca, Bristol-Myers Squibb, Eli Lilly
Consulting or Advisory Role: Merck Sharp & Dohme, AstraZeneca, Roche, Bristol-Myers Squibb, Novartis, Eli Lilly
Travel, Accommodations, Expenses: Roche, Novartis

Maximilian J. Hochmair
Honoraria: Boehringer Ingelheim, Takeda, MSD, BMS, AstraZeneca, Roche

Steven F. Powell
Consulting or Advisory Role: Bristol-Myers Squibb (Inst)
Research Funding: Merck Sharp & Dohme (Inst), Novartis (Inst), Genentech (Inst), Incyte (Inst), Bristol-Myers Squibb (Inst), Pfizer (Inst), Vyriad (Inst), Actuate Therapeutics (Inst), AstraZeneca/MedImmune (Inst)

Susanna Yee-Shan Cheng
Honoraria: Merck
Consulting or Advisory Role: Merck, AstraZeneca/MedImmune

Nir Peled
Honoraria: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Novartis, Pfizer, Roche, Takeda
Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, MSD, Novartis, Pfizer, Roche
Research Funding: MSD Oncology (Inst), Genentech (Inst), AstraZeneca (Inst), Takeda (Inst), Merck Serono (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: Genentech (Inst), MSD Oncology, AstraZeneca, Pfizer (Inst)

Francesco Grossi
Consulting or Advisory Role: MSD Oncology, Bristol-Myers Squibb, AstraZeneca, Roche, Pfizer, Bayer
Speakers' Bureau: MSD Oncology, Bristol-Myers Squibb, AstraZeneca, Roche, Pierre Fabre, Amgen, Celgene, Eli Lilly, Pfizer
Research Funding: Bristol-Myers Squibb
Travel, Accommodations, Expenses: Bristol-Myers Squibb, MSD, Roche, AstraZeneca, Pierre Fabre, Celgene, Amgen, Eli Lilly, Novartis

Martin Reck
Consulting or Advisory Role: Eli Lilly, MSD Oncology, Merck Serono, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, Celgene, Pfizer, Novartis, Genentech, AbbVie, Amgen
Speakers' Bureau: Genentech, Eli Lilly, MSD Oncology, Merck Serono, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Pfizer, Novartis, Amgen

Edward B. Garon
Consulting or Advisory Role: Dracen, EMD Serono, Novartis
Research Funding: Merck (Inst), Genentech (Inst), AstraZeneca (Inst), Novartis (Inst), Eli Lilly, Bristol-Myers Squibb (Inst), Mirati Therapeutics (Inst), Dynavax (Inst), Iovance Biotherapeutics (Inst), Neon Therapeutics (Inst), EMD Serono (Inst)

Silvia Novello
Speakers' Bureau: AstraZeneca, MSD, Bristol-Myers Squibb, Roche, Pfizer, Eli Lilly, Takeda, AbbVie, Boehringer Ingelheim, Bayer

Belén Rubio-Viqueira
Consulting or Advisory Role: Eli Lilly, MSD Oncology, Roche
Travel, Accommodations, Expenses: MSD Oncology, Roche

Michael Boyer
Honoraria: AstraZeneca, Merck Sharp & Dohme (Inst), Boehringer Ingelheim (Inst), Genentech (Inst)
Consulting or Advisory Role: Merck Sharp & Dohme (Inst), AstraZeneca (Inst), Bristol-Myers Squibb (Inst), Janssen (Inst)
Research Funding: Merck Sharp & Dohme (Inst), Pfizer (Inst), Boehringer Ingelheim (Inst), Eli Lilly (Inst), Genentech (Inst), AstraZeneca (Inst), Bristol-Myers Squibb (Inst), Amgen (Inst), BeiGene (Inst), Ascentage Pharma (Inst), Benitec (Inst), Novartis (Inst), Janssen (Inst)
Travel, Accommodations, Expenses: Merck Sharp & Dohme, Genentech

Takayasu Kurata
Honoraria: AstraZeneca, Ono Pharmaceutical, Bristol-Myers Squibb, Chugai Pharma, Eli Lilly, Boehringer Ingelheim, MSD Oncology
Research Funding: MSD Oncology (Inst), AstraZeneca (Inst), Eli Lilly (Inst), Ono Pharmaceutical (Inst)

Jhanelle E. Gray
Honoraria: Eli Lilly, AstraZeneca, Celgene, Takeda, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Genentech
Consulting or Advisory Role: Celgene, AstraZeneca, Takeda, Bristol-Myers Squibb
Research Funding: Array BioPharma (Inst), Merck (Inst), AstraZeneca (Inst), Bristol-Myers Squibb (Inst), Boehringer Ingelheim (Inst), Genentech (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: AstraZeneca/MedImmune, Takeda, Boehringer Ingelheim, Eli Lilly, Celgene, Bristol-Myers Squibb

Jing Yang
Employment: Merck

Tuba Bas
Employment: Merck Sharp & Dohme, Fiore Healthcare Advisors (I)
Stock and Other Ownership Interests: Merck Sharp & Dohme
Consulting or Advisory Role: Fiore Healthcare Advisors (I)
Travel, Accommodations, Expenses: Merck Sharp & Dohme, Fiore Healthcare Advisors (I)

M. Catherine Pietanza
Employment: Merck
Stock and Other Ownership Interests: Merck Sharp & Dohme

Marina C. Garassino
Honoraria: MSD Oncology, AstraZeneca/MedImmune, GlaxoSmithKline, Takeda, Roche, Bristol-Myers Squibb
Consulting or Advisory Role: Bristol-Myers Squibb, MSD, AstraZeneca, Novartis, Takeda, Roche, Tiziana Life Sciences, Sanofi-Aventis, Celgene, Daiiki Sankyo, Inivata, Incyte, Pfizer, Seattle Genetics, Eli Lilly
Speakers' Bureau: AstraZeneca, Takeda, MSD Oncology, Celgene, Incyte, Roche, Bristol-Myers Squibb, Otsuka, Eli Lilly
Research Funding: Bristol-Myers Squibb (Inst), MSD (Inst), Genentech (Inst), AstraZeneca/MedImmune (Inst), AstraZeneca (Inst), Pfizer (Inst), GlaxoSmithKline (Inst), Novartis (Inst), Merck (Inst), Incyte (Inst), Takeda (Inst), Spectrum Pharmaceuticals (Inst), Blueprint Medicines, Eli Lilly (Inst)
Travel, Accommodations, Expenses: Pfizer, Roche, AstraZeneca

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