ORIGINAL ARTICLE

Outcomes With Pembrolizumab Plus Platinum-Based Chemotherapy for Patients With NSCLC and Stable Brain Metastases: Pooled Analysis of KEYNOTE-021, -189, and -407

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ABSTRACT

Introduction: This exploratory analysis retrospectively evaluated outcomes in patients with advanced NSCLC to determine whether baseline brain metastases influenced the efficacy of first-line pembrolizumab plus chemotherapy versus chemotherapy alone.

Methods: We pooled data for patients with advanced NSCLC in KEYNOTE-021 cohort G (nonsquamous), KEYNOTE-189 (nonsquamous), and KEYNOTE-407 (squamous). Patients were assigned to platinum-doublet chemotherapy with or without the addition of 35 cycles of pembrolizumab 200 mg every 3 weeks. All studies permitted enrollment of patients with previously treated or untreated (KEYNOTE-189 and KEYNOTE-407 only) stable brain metastases. Patients with previously treated brain metastases were clinically stable for 2 or more weeks (≥4 wk in KEYNOTE-021 cohort G), had no evidence of new or enlarging brain metastases, and had no steroid use at least 3 days before dosing. Patients with known untreated asymptomatic brain metastases required regular imaging of the brain.

Results: A total of 1298 patients were included, 171 with and 1127 without baseline brain metastases. Median (range) durations of follow-up at data cutoff were 10.9 (0.1–35.1) and 11.0 (0.1–34.9) months, respectively. Hazard ratios (pembrolizumab + chemotherapy/chemotherapy) were similar for patients with and without brain metastases for overall survival (0.48 [95% confidence interval (CI): 0.32–0.70] and 0.63 [95% CI: 0.53–0.75], respectively) and progression-free survival (0.44 [95% CI: 0.31–0.62] and 0.55 [95% CI: 0.48–0.63], respectively). In patients with brain metastases, median overall survival was 18.8 months with pembrolizumab plus chemotherapy and 7.6 months with chemotherapy, and median progression-free survival was 6.9 months and 4.1 months, respectively. Objective response rates were higher and duration of response longer with pembrolizumab plus chemotherapy versus chemotherapy regardless of brain metastasis status. Incidences of treatment-related adverse events with pembrolizumab plus chemotherapy versus chemotherapy were 88.2% versus 82.8% among patients with brain metastases and 94.5% versus 90.6% in those without.

Conclusions: With or without brain metastasis, pembrolizumab plus platinum-based histology-specific chemotherapy improved clinical outcomes versus chemotherapy alone across all programmed death ligand 1 subgroups, including patients with programmed death ligand 1 tumor proportion score less than 1% and had a manageable safety profile in patients with advanced NSCLC. This regimen is a standard-of-care treatment option for treatment-naive patients with advanced NSCLC, including patients with stable brain metastases.

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Keywords: Pembrolizumab; Brain metastases; Chemotherapy; Non–small-cell lung cancer; PD-L1

Introduction

Approximately one-third of patients with advanced NSCLC develop brain metastases.[1] Outcomes for patients with NSCLC after diagnosis of brain metastases historically have been poor, with median overall survival (OS) estimated at 7.8 months, regardless of whether patients present with or subsequently develop brain metastases.[2] Although prognosis is poor for these patients, they are only infrequently enrolled in clinical trials, resulting in a paucity of efficacy and safety data for this group.[3–7] Treatment with systemic therapy has been reported to correlate with better outcomes in these patients,[1] and several clinical trials have explored the synergistic effects of checkpoint inhibitor immunotherapy combined with or administered before or after chemotherapy.[8–14]

First-line treatment with the anti–programmed death 1 monoclonal antibody pembrolizumab plus platinum-based chemotherapy was shown to improve efficacy compared with platinum-based chemotherapy alone and to have a manageable safety profile in both nonsquamous NSCLC (phase 2 KEYNOTE-021 [cohort G], phase 3 KEYNOTE-189)[8,9] and squamous NSCLC (phase 3 KEYNOTE-407).[10] In cohort G of KEYNOTE-021, the primary end point of objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 based on blinded, independent central review was 55% with pembrolizumab plus chemotherapy versus 29% with chemotherapy alone ($p = 0.0016$). The coprimary end points of OS and progression-free survival (PFS) in KEYNOTE-189 and KEYNOTE-407 were both significantly improved with combination therapy. In these two studies, the hazard ratios (HRs) for death were 0.49 (95% confidence interval [CI]: 0.38−0.64) and 0.64 (95% CI: 0.49−0.85), and the HRs for disease progression or death were 0.52 (95% CI: 0.43−0.64) and 0.56 (95% CI: 0.45−0.70), respectively (all $p < 0.001$).

KEYNOTE-021 cohort G, KEYNOTE-189, and KEYNOTE-407 each enrolled patients with chemotherapy-naive advanced NSCLC and allowed enrollment of patients with brain metastases provided the patients were clinically stable. This exploratory analysis was conducted to better characterize outcomes in this population with historically

poor prognosis. We pooled individual patient data across these three clinical trials to retrospectively evaluate the effects of pembrolizumab plus platinum-based chemotherapy versus chemotherapy alone in patients with or without stable brain metastases at baseline.

Materials and Methods

Patients

Patients from three studies, KEYNOTE-021 cohort G (NCT02039674),[8] KEYNOTE-189 (NCT02578680),[9] and KEYNOTE-407 (NCT02775435),[10] were included in this post hoc pooled analysis. Methods for each study have been described previously and are summarized here briefly. The study protocols were approved by institutional review boards/ethics committees, and the studies were conducted according to Good Clinical Practice guidelines. All patients provided written informed consent.

In all three studies, eligible patients were aged at least 18 years and had pathologically confirmed nonsquamous NSCLC without sensitizing *EGFR* or *ALK* alteration (KEYNOTE-021 cohort G and KEYNOTE-189) or squamous NSCLC (KEYNOTE-407), with at least one measurable lesion as defined by RECIST version 1.1 and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients in KEYNOTE-189 and KEYNOTE-407 had stage IV (i.e., metastatic) disease; patients in KEYNOTE-021 cohort G had stage IIIB or IV disease. All patients were required to provide a tumor sample for determination of programmed death ligand 1 (PD-L1) status and could not have previously received systemic therapy for advanced disease. In each study, baseline central nervous system (CNS) imaging was required for all patients. Those with previously treated brain metastases who had been clinically stable for at least 2 weeks ($\geq$4 wk in KEYNOTE-021 cohort G) and who had not received steroids for at least 3 days before the start of the study treatment were eligible for enrollment; patients with asymptomatic brain metastases (i.e., no neurologic symptoms, no requirement for corticosteroids, and lesions $\leq$1.5 cm) were eligible to participate in KEYNOTE-189 and KEYNOTE-407 but required regular imaging of the brain as a site of disease.

Study Design and Treatment

Patients in KEYNOTE-021 cohort G were randomized 1:1 to receive four cycles of pembrolizumab 200 mg plus pemetrexed 500 mg/m^2 and carboplatin area under the curve (AUC) 5 mg/mL/min every 3 weeks followed by pembrolizumab for 24 months or to four cycles of pemetrexed 500 mg/m^2 and carboplatin AUC 5 mg/mL/min. Optional indefinite pemetrexed maintenance therapy was permitted in each arm. In KEYNOTE-189, patients were randomized 2:1 to receive four cycles of pemetrexed 500 mg/m^2 and a platinum-based drug (cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min) plus either pembrolizumab 200 mg or placebo every 3 weeks followed by pembrolizumab or placebo for up to a total of 35 cycles plus indefinite pemetrexed maintenance therapy. Patients in KEYNOTE-407 were randomized 1:1 to receive 200 mg of pembrolizumab or placebo on day 1 for up to 35 three-week cycles; for the first four cycles, all patients received carboplatin (AUC 6 mg/mL/min) on day 1 and either paclitaxel (200 mg/m^2) on day 1 or nab-paclitaxel (100 mg/m^2) on days 1, 8, and 15. Randomization was stratified as described in the primary publications; in all studies, the presence versus absence of baseline brain metastases was not a stratification factor.

Assessments

In KEYNOTE-021 cohort G and KEYNOTE-407, radiographic imaging with computed tomography or magnetic resonance imaging was done at baseline, every 6 weeks for the first 18 weeks, then every 9 weeks to 45 weeks (KEYNOTE-407) or to the end of 1 year (KEYNOTE-021 cohort G), and every 12 weeks thereafter for response assessment. In KEYNOTE-189, imaging was performed at baseline, at weeks 6 and 12, then every 9 weeks to 48 weeks, and every 12 weeks thereafter. Baseline CNS imaging was required in all studies; subsequent CNS imaging was required with each response assessment for patients with asymptomatic brain metastases and was obtained at the investigator's discretion for patients with treated brain metastases. In the imaging charter, which was consistent across the KEYNOTE lung program, all brain lesions were to be categorized as nontarget lesions even if they were measurable. Tumor response was evaluated according to RECIST version 1.1 by blinded, independent central review.[15] Adverse events (AEs) were monitored during study treatment and for 30 days after treatment and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0 for KEYNOTE-021 cohort G and KEYNOTE-189; version 4.03 for KEYNOTE-407). Serious AEs were monitored for 90 days after treatment. PD-L1 expression status was determined by a central laboratory in formalin-fixed tumor samples collected at the time of metastatic disease diagnosis using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA).

End Points

End points evaluated in this pooled analysis were OS, PFS, ORR, duration of response (DOR), and the incidence of AEs. OS was defined as time from randomization to death from any cause. PFS was defined as the time from

randomization to disease progression, defined by RECIST version 1.1, or death from any cause. ORR was defined as the proportion of patients with radiologically confirmed complete or partial response. DOR, determined for patients with a complete or partial response, was defined as the time from first documented evidence of response until disease progression.

Statistical Analysis

Individual patient data from the intent-to-treat populations of the three studies were included in this pooled analysis. Efficacy was evaluated in the pooled intent-to-treat population; safety was evaluated in the pooled population of patients who received at least one dose of study treatment. All analyses were descriptive and not controlled for multiplicity.

The Kaplan-Meier method was used to estimate OS, PFS, and DOR. For OS and PFS, HRs and 95% CIs of the treatment differences were based on the Cox proportional hazards regression model with treatment as a covariate.

Results

Patient Disposition

A total of 1298 patients were included in this pooled analysis; 171 (13.2%) had brain metastases at baseline and 1127 (86.8%) did not. Of the patients with baseline brain metastases, 105 were assigned to receive pembrolizumab plus chemotherapy and 66 were assigned to receive chemotherapy alone. Of the patients without baseline brain metastases, 643 and 484 patients were assigned pembrolizumab plus chemotherapy or chemotherapy, respectively (Fig. 1). The data cutoff dates were December 1, 2017, for KEYNOTE-021 cohort G; September 21, 2018, for KEYNOTE-189; and April 3, 2018, for KEYNOTE-407. Median (range) durations of follow-up for patients with and without brain metastases were 10.9 (0.1–35.1) and 11.0 (0.1–34.9) months, respectively.

Baseline characteristics were generally similar between patients with and without baseline brain metastases (Table 1). The brain metastases group had a greater percentage of patients with nonsquamous histology (71.3% versus 51.8%), use of carboplatin (60.2% versus 41.3%), previous receipt of radiotherapy (50.3% versus 13.1%), and liver metastases (25.1% versus 16.9%). Among patients with brain metastases, 20 received radiotherapy to the brain previously (pembrolizumab + chemotherapy, n = 11; chemotherapy alone, n = 9). The percentages of patients in PD-L1 subgroups (<1%, 1%−49%, ≥50%) were similar between patients with and without brain metastases.

Overall Survival

At data cutoff, among patients with baseline brain metastases, 56 of 105 patients (53.3%) in the pembrolizumab plus chemotherapy group and 49 of 66 patients (74.2%) in the chemotherapy group had died. Among patients without baseline brain metastases, 264 of 643 (41.1%) in the pembrolizumab plus chemotherapy group and 250 of 484 (51.7%) in the chemotherapy group had died. As illustrated in Figure 2*A* and *B*, median OS was longer with pembrolizumab plus chemotherapy versus chemotherapy both in patients with brain metastases (18.8 [95% CI: 13.8−25.9] versus 7.6 mo [95% CI: 5.4−10.9]; HR for death = 0.48 [95% CI: 0.32−0.70]) and in those without brain metastases (22.5 [95% CI: 19.8−25.2] versus 13.5 mo [95% CI: 11.3−15.8]; HR for death = 0.63 [95% CI: 0.53−0.75]).

The benefit of pembrolizumab plus chemotherapy versus chemotherapy with respect to OS was found across all PD-L1 subgroups (Fig. 2*C*).

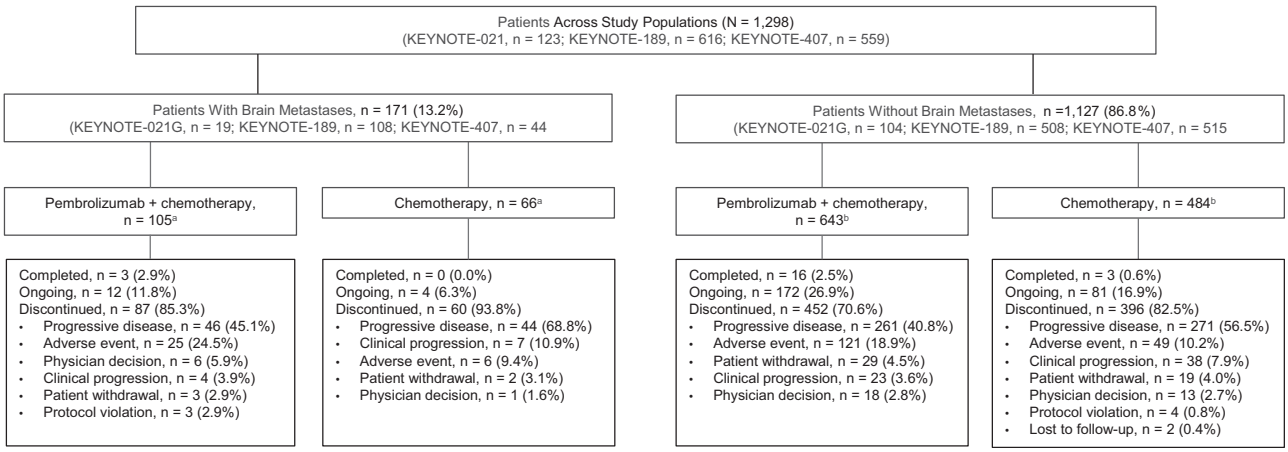

Figure 1. Patient disposition of pooled analysis. [a]Three patients allocated to pembrolizumab plus chemotherapy and two to chemotherapy did not receive the study treatment. [b]Three patients allocated to pembrolizumab plus chemotherapy and four to chemotherapy did not receive the study treatment.

Table 1. Baseline Characteristics in Patients With and Without Brain Metastases (Pooled Intent-To-Treat Population)

Characteristic	With Brain Metastases		Without Brain Metastases	
	Pembrolizumab + Chemotherapy (n = 105)	Chemotherapy (n = 66)	Pembrolizumab + Chemotherapy (n = 643)	Chemotherapy (n = 484)
Male	70 (66.7)	36 (54.5)	426 (66.3)	334 (69.0)
Age, median (range), y	63.0 (35-82)	63.5 (47-81)	65.0 (29-87)	65.0 (34-88)
ECOG				
0	41 (39.0)	17 (25.8)	242 (37.6)	182 (37.6)
1	64 (61.0)	49 (74.2)	396 (61.6)	301 (62.2)
2	0	0	2 (0.3)	0
Missing	0	0	3 (0.5)	1 (0.2)
Smoking history				
Current/former	98 (93.3)	62 (93.9)	565 (87.9)	435 (89.9)
Never	7 (6.7)	4 (6.1)	78 (12.1)	49 (10.1)
Histologic variant				
Nonsquamous	81 (77.1)	41 (62.1)	371 (57.7)	213 (44.0)
Squamous	20 (19.0)	24 (36.4)	258 (40.1)	257 (53.1)
Other	4 (3.8)	1 (1.5)	14 (2.2)	14 (2.9)
Liver metastases	22 (21.0)	21 (31.8)	105 (16.3)	85 (17.6)
Chemotherapy regimen selected				
Carboplatin	68 (64.8)	35 (53.0)	289 (44.9)	176 (36.4)
Cisplatin	17 (16.2)	7 (10.6)	96 (14.9)	51 (10.5)
Paclitaxel	13 (12.4)	11 (16.7)	156 (24.3)	156 (32.2)
Nab-paclitaxel	7 (6.7)	13 (19.7)	102 (15.9)	101 (20.9)
Prior therapy				
Neoadjuvant	3 (2.9)	1 (1.5)	5 (0.8)	9 (1.9)
Adjuvant	5 (4.8)	2 (3.0)	29 (4.5)	24 (5.0)
Radiotherapy	52 (49.5)	34 (51.5)	80 (12.4)	68 (14.0)
Radiotherapy to the brain	11 (10.5)	9 (13.6)	0	0
PD-L1 TPS, %				
<1	41 (39.0)	24 (36.4)	202 (31.4)	161 (33.3)
1-49	25 (23.8)	17 (25.8)	225 (35.0)	168 (34.7)
≥50	33 (31.4)	23 (34.8)	192 (29.9)	137 (28.3)

Note: Values are n (%) of patients unless otherwise indicated.
ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

Progression-Free Survival

At data cutoff, among patients with baseline brain metastases, 82 of 105 patients (78.1%) in the pembrolizumab plus chemotherapy group and 62 of 66 patients (93.9%) in the chemotherapy group had disease progression or died. Among patients without baseline brain metastases, 402 of 643 (62.5%) in the pembrolizumab plus chemotherapy group and 368 of 484 (76.0%) in the chemotherapy group had disease progression or died. As shown in Figure 3*A* and *B*, median PFS was longer with pembrolizumab plus chemotherapy versus chemotherapy both in patients with brain metastases (6.9 [95% CI: 5.7−8.9] versus 4.1 mo [95% CI: 2.3−4.6]; HR for PFS = 0.44 [95% CI: 0.31−0.62]) and in those without brain metastases (8.8 [95% CI: 8.1−9.5] versus 5.3 mo [95% CI: 4.8−6.1]; HR for PFS = 0.55 [95% CI: 0.48−0.63]).

The benefit of pembrolizumab plus chemotherapy versus chemotherapy with respect to PFS was found across all PD-L1 subgroups (Fig. 3*C*).

Objective Response Rate

Addition of pembrolizumab to chemotherapy improved ORR compared with chemotherapy alone in patients with or without baseline brain metastases (Table 2). Among patients with brain metastases, ORR was 39.0% with pembrolizumab plus chemotherapy and 19.7% with chemotherapy. Among patients without brain metastases, ORR was 54.6% with pembrolizumab plus chemotherapy and 31.8% with chemotherapy. Of note, these are systemic responses per RECIST version 1.1; CNS responses were not collected.

Among patients with brain metastases, median (range) DOR was 11.3 (1.1+ to 27.9+) and 6.8 (1.3+ to 9.4) months in the pembrolizumab plus chemotherapy and chemotherapy groups, respectively. Among patients without brain metastases, median (range) DOR was 12.2 (1.1+ to 29.3+) and 6.0 (1.4+ to 30.1+) months in the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.

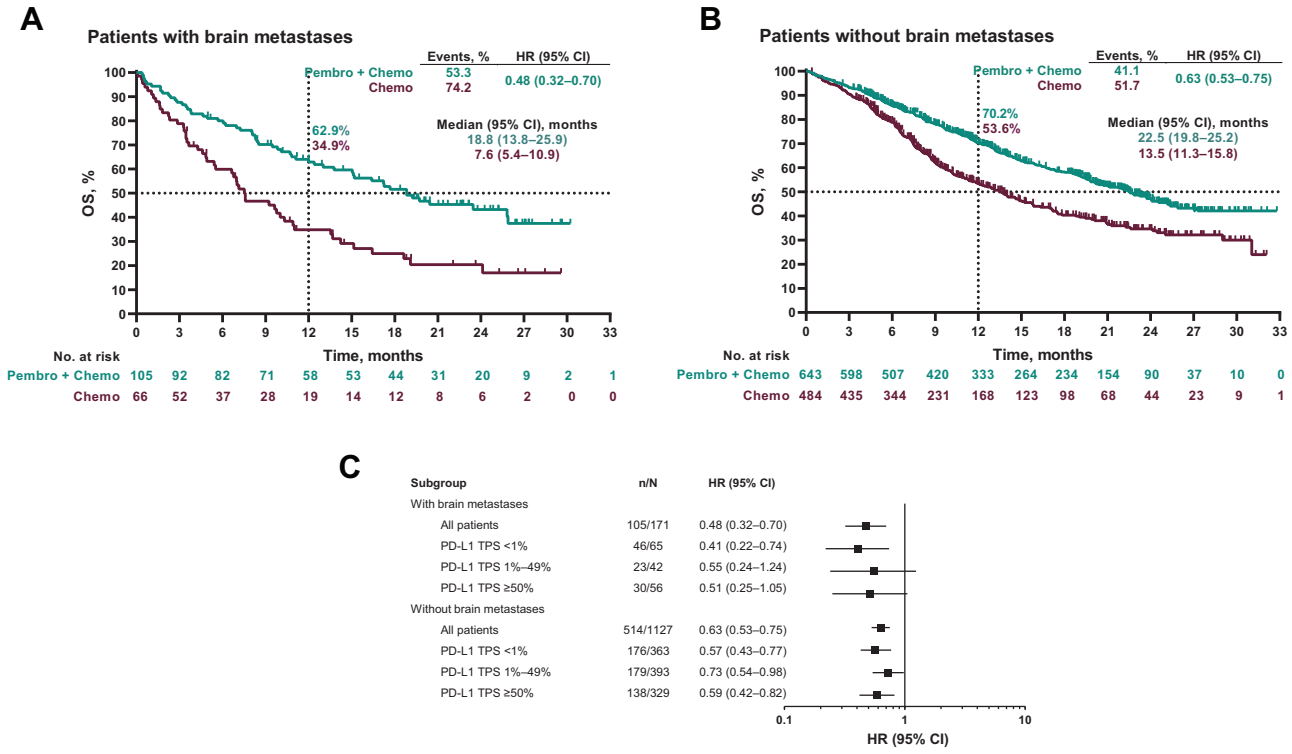

Figure 2. OS in patients (*A*) with and (*B*) without baseline brain metastases in the pooled intent-to-treat population and (*C*) OS stratified by PD-L1 TPS. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1; Pembro, pembrolizumab; TPS, tumor proportion score.

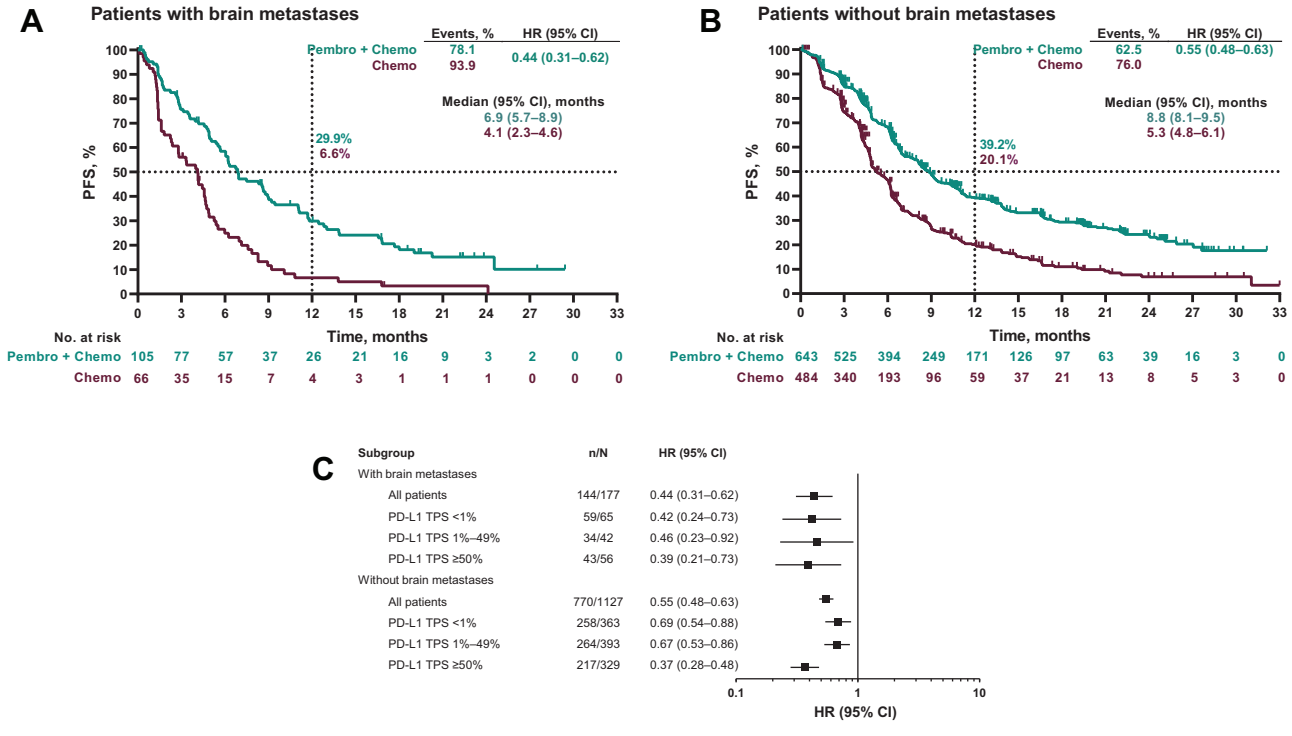

Figure 3. PFS in patients (*A*) with and (*B*) without baseline brain metastases in the pooled intent-to-treat population and (*C*) PFS stratified by PD-L1 TPS. Response was assessed per RECIST version 1.1 by blinded, independent central review. Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; PD-L1, programmed death ligand 1; Pembro, pembrolizumab; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score.

Table 2. Objective Response Rate in Patients With and Without Brain Metastases (Pooled Intent-To-Treat Population)

Outcome	With Brain Metastases		Without Brain Metastases	
	Pembrolizumab + Chemotherapy (n = 105)	Chemotherapy (n = 66)	Pembrolizumab + Chemotherapy (n = 643)	Chemotherapy (n = 484)
ORR, n (%) [95% CI]	41 (39.0) [29.7-49.1]	13 (19.7) [10.9-31.3]	351 (54.6) [50.6-58.5]	154 (31.8) [27.7-36.2]
Response, n (%)				
Complete response	0 (0.0)	0 (0.0)	10 (1.6)	8 (1.7)
Partial response	41 (39.0)	13 (19.7)	341 (53.0)	146 (30.2)
Stable disease	39 (37.1)	23 (34.8)	208 (32.3)	211 (43.6)
Progressive disease	9 (8.6)	16 (24.2)	47 (7.3)	70 (14.5)
Not evaluable	8 (7.6)	5 (7.6)	15 (2.3)	18 (3.7)
No assessment	8 (7.6)	9 (13.6)	22 (3.4)	31 (6.4)
Response duration, median (range), mo	11.3 (1.1+ to 27.9+)	6.8 (1.3+ to 9.4)	12.2 (1.1+ to 29.3+)	6.0 (1.4+ to 30.1+)

Note: Responses were based on blinded, independent central review assessment per RECIST version 1.1.
CI, confidence interval; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Safety

The median (range) treatment duration for patients with baseline brain metastases who received pembrolizumab plus chemotherapy or chemotherapy alone was 7.0 (0.03–29.1) and 4.2 (0.03–18.5) months, respectively. In this population, treatment-related AEs of any grade occurred in 90 of 102 patients (88.2%) in the combination therapy group and 53 of 64 patients (82.8%) in the chemotherapy group (Table 3). Grade 3 or higher treatment-related AEs occurred in 61 (59.8%) and 29 patients (45.3%), respectively. Treatment-related AEs resulted in the discontinuation of study treatment for 26 patients (25.5%) in the combination therapy group and seven patients (10.9%) in the chemotherapy group; 6 (5.9%) and one patients (1.6%), respectively, died owing to treatment-related AEs. A total of 33 patients (32.4%) had at least one treatment-related AE affecting the nervous system in the combination therapy group compared with 11 patients (17.2%) in the chemotherapy group; the most common AEs are shown in Table 3. Immune-mediated events, regardless of relationship to study treatment, occurred in 26 patients (25.5%) and six patients (9.4%) in the combination therapy and chemotherapy groups, respectively.

Table 3. Treatment-Related AEs in Patients With and Without Brain Metastases (Pooled Safety Population)

Treatment-Related AEs, n (%)	With Brain Metastases		Without Brain Metastases	
	Pembrolizumab + Chemotherapy (n = 102)	Chemotherapy (n = 64)	Pembrolizumab + Chemotherapy (n = 640)	Chemotherapy (n = 480)
Any	90 (88.2)	53 (82.8)	605 (94.5)	435 (90.6)
Grade ≥3	61 (59.8)	29 (45.3)	323 (50.5)	225 (46.9)
Led to discontinuation of study treatment	26 (25.5)	7 (10.9)	137 (21.4)	39 (8.1)
Led to death	6 (5.9)	1 (1.6)	13 (2.0)	9 (1.9)
Affected the nervous system	33 (32.4)	11 (17.2)	233 (36.4)	161 (33.5)
Most common (>2% in any group)				
Dysgeusia	15 (14.7)	2 (3.1)	60 (9.4)	26 (5.4)
Peripheral neuropathy	4 (3.9)	1 (1.6)	64 (10.0)	40 (8.3)
Peripheral sensory neuropathy	5 (4.9)	0	37 (5.8)	40 (8.3)
Dizziness	4 (3.9)	2 (3.1)	18 (2.8)	15 (3.1)
Paresthesia	2 (2.0)	2 (3.1)	28 (4.4)	20 (4.2)
Headache	0	0	22 (3.4)	13 (2.7)
Immune-mediated AEs and infusion reactions,[a] %	26 (25.5)	6 (9.4)	178 (27.8)	51 (10.6)
Grades 3–5	14 (13.7)	1 (1.6)	62 (9.7)	18 (3.8)

AE graded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
[a]Immune-mediated AEs were classified on the basis of a list of preferred terms identified by the sponsor as having an immune etiology.
AE, adverse event.

Safety results in patients without baseline brain metastases (Table 3) were consistent with the overall study population. Median (range) treatment duration for patients without baseline brain metastases who received pembrolizumab plus chemotherapy or chemotherapy was 6.9 (0.03–30.4) and 4.3 (0.03–30.7) months, respectively.

In the combination therapy arm, a greater percentage of patients with versus without brain metastases died owing to treatment-related AEs (n = 6 [5.9%] versus n = 13 [2.0%]); of these 19 deaths, only one was attributed to a neurologic event (encephalopathy in a patient with brain metastases).

Discussion

Outcomes in patients with NSCLC with brain metastases are typically poor, and these patients are often underrepresented in clinical trials.[3–7,16] Indeed, in this pooled analysis of patients from three randomized controlled trials, prognosis was poorer in patients with versus without treated or untreated, stable brain metastases at baseline, regardless of treatment group. Pembrolizumab plus platinum-based chemotherapy had substantial improvement in clinical outcomes versus chemotherapy alone in patients with advanced NSCLC, irrespective of the presence of baseline brain metastases. Among patients with brain metastases, pembrolizumab plus chemotherapy reduced the risk of death (HR for OS = 0.48) and progression or death (HR for PFS = 0.44). Median OS among patients with brain metastases who received pembrolizumab plus chemotherapy was meaningfully longer than that for patients who received chemotherapy, notwithstanding the poor prognosis in this group (18.8 versus 7.6 mo). The benefit of combination therapy in patients with baseline brain metastases was demonstrated for all end points analyzed (i.e., OS, PFS, ORR, DOR) and across all three PD-L1 TPS subgroups evaluated (<1%, 1%–49%, ≥50%). Pembrolizumab plus chemotherapy had a manageable safety profile in patients with and without baseline brain metastases.

Although radiotherapy has been a mainstay of treatment for patients with NSCLC with brain metastases, there is a growing body of evidence to suggest a clinical benefit for immunotherapy as a single agent.[7,17–19] A recent phase 2 study demonstrated that pembrolizumab monotherapy had activity in patients with NSCLC with untreated brain metastases and PD-L1 expression greater than or equal to 1%, with a brain metastasis response rate of 29.7% (95% CI: 15.9%–47.0%).[17] Limited data from clinical studies exist on the use of other checkpoint inhibitors in combination with platinum-based chemotherapy in patients with advanced NSCLC and brain metastases. We are unaware of any publications on the combination of other programmed death 1 or PD-L1 inhibitors with chemotherapy in this population, although an ongoing phase 2 study is evaluating atezolizumab plus carboplatin/pemetrexed in patients with NSCLC and untreated, asymptomatic brain metastases (NCT03526900). A recent phase 3 clinical trial of nivolumab plus ipilimumab versus chemotherapy alone in patients with advanced NSCLC found that OS favored combination therapy in patients with (n = 81) and without (n = 712) treated asymptomatic CNS metastases at baseline.[20] In addition, our results are consistent with those from a real-world study that evaluated pembrolizumab plus carboplatin and pemetrexed in patients with advanced nonsquamous NSCLC with and without brain metastases and showed activity with the combination in both groups.[21]

No new safety signals were identified in our pooled analysis. The safety profile of pembrolizumab plus chemotherapy was similar in patients with and without baseline brain metastases, and the presence of brain metastases did not increase the rate of treatment-related AEs affecting the nervous system. The incidence of treatment-related AEs, including those leading to discontinuation of the study treatment, was higher in the combination therapy group compared with the chemotherapy group. The longer treatment duration in the combination therapy group may have contributed to this finding.

Our results are comparable to and extend those of a separate analysis of pembrolizumab monotherapy versus chemotherapy in a similar patient population.[22] In that analysis, data were pooled across four clinical trials (KEYNOTE-001, -010, -024, and -042) to retrospectively evaluate outcomes in patients with PD-L1–positive NSCLC and previously treated stable brain metastases. Pembrolizumab monotherapy improved clinical outcomes and was well tolerated versus chemotherapy in this cohort while providing similar benefits in patients with and without brain metastases.

Our pooled analysis was exploratory, and no adjustments were made for multiplicity; thus, the results must be interpreted with caution. Nevertheless, pooling of patient data across three clinical trials, with a resultant increased number of patients included, allowed for a more robust evaluation of outcomes than could be achieved with analysis of outcomes in individual clinical trials. Another limitation was that our analysis was retrospective, although the protocols for two of the three included clinical trials (KEYNOTE-189 and KEYNOTE-407) specified that patients with brain metastases would be the subject of exploratory analyses. A small proportion of patients received brain radiotherapy previously, suggesting most patients had asymptomatic

small brain metastases. This limits translation of the results to the general population of patients with NSCLC. Unfortunately, it was not possible to evaluate intracranial responses in our pooled analysis, as brain lesions were considered nontarget lesions in these studies. Although some previous evidence suggests modest intracranial responses in patients with NSCLC treated with immune checkpoint inhibitors,[23] including pembrolizumab monotherapy in patients with PD-L1–expressiong tumors,[17] prospective studies would be needed to evaluate the influence of pembrolizumab plus chemotherapy on intracranial response and its association with systemic response and OS. Disruption of the blood-brain barrier and neovascularization may allow chemotherapy to penetrate the brain,[24] and in preclinical studies, chemotherapy agents have exhibited immunomodulatory properties that increase the immunogenicity of tumors.[25–27] The lack of data related to the sites of disease progression was another limitation.

In conclusion, pembrolizumab plus platinum-based chemotherapy improved survival outcomes and objective responses compared with those of chemotherapy alone and had a manageable tolerability profile regardless of the presence of baseline brain metastases. Combination therapy with pembrolizumab plus platinum-based chemotherapy is a standard-of-care treatment option for treatment-naive patients with advanced NSCLC, including patients with treated and untreated stable brain metastases.

CRediT Authorship Contribution Statement

Steven F. Powell: Investigation, Writing—original draft, Writing—review and editing, Visualization, Funding Acquisition.

Delvys Rodríguez-Abreu: Investigation, Formal Analysis, Writing—review and editing.

Corey J. Langer: Conceptualization, Methodology, Investigation, Writing—review and editing, Resources.

Ali Tafreshi, Luis Paz-Ares, Jeronimo Rodríguez-Cid, Ying Cheng, Mark M. Awad: Investigation, Writing—review and editing.

Hans-Georg Kopp, Takayasu Kurata, Marina C. Garassino: Investigation, Resources, Writing—review and editing.

Dariusz M. Kowalski: Investigation, Formal Analysis, Writing—review and editing.

Jinaxin Lin: Software, Validation, Formal Analysis, Data Curation, Writing—review and editing, Visualization, Funding Acquisition.

Bin Zhao, M. Catherine Pietanza: Writing—review and editing, Supervision, Funding Acquisition.

Bilal Piperdi: Conceptualization, Methodology, Formal Analysis, Data Curation, Writing—original draft, Writing—review and editing, Visualization, Supervision, Project Administration, Funding Acquisition.

Data Sharing Statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey (Merck Sharp & Dohme), 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. Merck Sharp & Dohme 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 Merck Sharp & Dohme 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 Merck Sharp & Dohme subject matter experts to evaluate 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 Merck Sharp & Dohme 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 Merck Sharp & Dohme 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 Merck Sharp & Dohme subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, Merck Sharp & Dohme will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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