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ORIGINAL ARTICLE

Cemiplimab monotherapy as first-line treatment of patients with brain metastases from advanced non–small cell lung cancer with programmed cell death-ligand 1 ≥50%

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Abstract

Background: In the phase 3 EMPOWER-Lung 1 study, first-line cemiplimab monotherapy provided significant survival benefit versus chemotherapy in patients with advanced non–small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) ≥50%. This exploratory subgroup analysis investigated the clinical outcomes of cemiplimab treatment in patients with advanced NSCLC with brain metastases.

Methods: Patients with advanced NSCLC were randomized (1:1) to cemiplimab 350 mg every 3 weeks or four cycles of platinum doublet chemotherapy (NCT03088540).

The clinical trial registration is NCT03088540.

Patients with symptomatic radiotherapy-treated brain metastases were eligible to enroll. Of the 565 patients with confirmed PD-L1 expression ≥50%, 69 (12%) had brain metastases at baseline.

Results: Patients with brain metastases who received cemiplimab had a median overall survival (OS) of 52.4 months compared with 20.7 months for those who received chemotherapy (hazard ratio [HR], 0.40; $p = .0031$) and a median progression-free survival (PFS) of 12.5 versus 5.3 months (HR, 0.33; $p = .0002$), respectively. Patients without brain metastases had a median OS of 24.3 months with cemiplimab versus 12.5 months with chemotherapy (HR, 0.63; $p < .0001$); their median PFS was 6.5 months versus 5.2 months (HR, 0.55; $p < .0001$), respectively. Cemiplimab was associated with a significant improvement in global health status/quality of life in all patients, including those with brain metastases. The cemiplimab safety profile was generally similar in all patients.

Conclusions: In patients with advanced NSCLC with PD-L1 ≥50%, first-line cemiplimab monotherapy improved survival and patient-reported outcomes over chemotherapy for those who received prior radiotherapy for symptomatic brain metastases.

KEYWORDS
advanced NSCLC, brain metastases, cemiplimab, immunotherapy, PD-L1

INTRODUCTION

Brain metastases (BM) are detected in approximately 10% of patients with non–small cell lung cancer (NSCLC) and 26% with stage IV NSCLC at initial diagnosis.[1] In the absence of effective systemic therapies, patients with driver mutation-negative NSCLC have poor outcomes, regardless of whether BM are present at initial diagnosis or develop later, with a median overall survival (OS) of 4.8 and 3.7 months, respectively.[2]

Historically, radiotherapy represented the only treatment option for patients with BM and no driver mutations in NSCLC.[3] When combined with chemotherapy, whole-brain radiation demonstrated an intracranial objective response rate (ORR) of 27%–39%, a median OS of 6.0–9.9 months, and an overall progression-free survival (PFS) of 3.0–4.4 months.[4,5] Localized therapy such as stereotactic radiosurgery for one to ≥11 lesions, in combination with chemotherapy, led to an improvement in intracranial PFS (median, 9.4 months).[6]

Programmed cell death-1 (PD-1) pathway inhibitors have emerged as a state-of-the-art treatment for patients with advanced NSCLC.[7] PD-1/programmed cell death-ligand 1 (PD-L1) inhibitors may also exhibit clinical activity for BM from NSCLC. Although monoclonal antibodies targeting PD-1/PD-L1 theoretically have low penetration of the blood–brain barrier, the mechanism of action for these immune checkpoint inhibitors does not solely rely on close contact with all tumor cell foci.[8] PD-1/PD-L1 blockade activates tumor surveillance and enables efficient trafficking of T cells to brain lesions, resulting in antitumor immune responses.[9]

There is limited prospective clinical evidence on the activity of PD-1/PD-L1 inhibitor therapy in patients with NSCLC with BM.[10–13] Historically, these patients were excluded or under-represented in trials with PD-1/PD-L1 inhibitors.[14–17] Published literature is limited, often reflecting retrospective analyses or data from mixed patient populations with a wide array of diseases or therapies.[18,19]

Cemiplimab is a highly potent, fully human, immunoglobulin G4 mAb directed against PD-1, derived using VelocImmune technology.[20–22] In the EMPOWER-Lung 1 phase 3 study (NCT03088540), cemiplimab monotherapy was shown to significantly increase OS at 5 years compared with the investigator's choice of platinum-doublet chemotherapy (26.1 [95% confidence interval (CI), 22.1–31.9] vs. 13.3 months [95% CI, 10.5–16.2]; hazard ratio [HR], 0.59 [95% CI, 0.48–0.72]) for the first-line treatment of patients with advanced NSCLC expressing PD-L1 in ≥50% of tumor cells.[23]

EMPOWER-Lung 1 included a notable proportion of patients with BM at baseline.[24] Here, we present an exploratory subgroup analysis from EMPOWER-Lung 1, investigating clinical benefit and patient-reported outcomes (PROs) with cemiplimab in patients with symptomatic radiotherapy-treated BM at baseline. Given the limited amount of data from randomized phase 3 trials looking at this subpopulation and the unmet medical need, this analysis seeks to gain a better understanding of the clinical activity of PD-1 inhibitors in patients with advanced NSCLC and BM.

MATERIALS AND METHODS

Patients

EMPOWER-Lung 1 enrolled adult patients with histologically or cytologically confirmed squamous or nonsquamous stage IIIB/IIIC

NSCLC who were not candidates for treatment with concurrent chemoradiation, or patients with untreated stage IV disease (Figure S1). The methods and eligibility criteria for EMPOWER-Lung 1 have been reported previously.[24] This exploratory subgroup analysis was conducted in the PD-L1 ≥50% intention-to-treat population, determined using the 22C3 assay (per instructions for use), and evaluated first-line cemiplimab monotherapy versus the investigator's choice of platinum-doublet chemotherapy for the treatment of patients with and without BM at randomization.[24,25] For patients with treated symptomatic BM that had neurologically returned to baseline (except for residual signs/symptoms related to central nervous system treatment) for ≥2 weeks before randomization, radiologic confirmation of response or stability of BM post treatment was not required for inclusion in the study.

Study design

Patients were randomized (1:1) to receive cemiplimab 350 mg intravenously every 3 weeks for up to 108 weeks, or the investigator's choice of platinum-doublet chemotherapy for four to six cycles. Crossover from chemotherapy to cemiplimab was allowed following disease progression verified by the blinded independent review committee (IRC). Randomization was stratified according to histology (squamous or nonsquamous) and location (Europe, Asia, or the rest of the world). The blinded IRC assessed tumor response to therapy according to Response Evaluation Criteria in Solid Tumors version 1.1.[26] Radiographic tumor assessments were obtained every three cycles, at week 9, and every 9 weeks thereafter until disease progression.

In patients with a known history of treated BM at baseline, computed tomography or magnetic resonance imaging of the brain with contrast (unless contraindicated) was performed at screening, except if performed within 60 days before screening. Additional sites of known disease, including the central nervous system, were also imaged at screening. For these patients, during the treatment and follow-up period, surveillance imaging of the brain was performed at a minimum of every 18 weeks during year 1 and every 24 weeks during year 2, or sooner if clinically indicated. Routine screening for BM was not performed at the time of diagnosis.

Health-related quality of life assessments were measured before performing procedures at study visits using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30) and Lung Cancer Module (QLQ-LC13) questionnaires.[27,28] PROs were assessed at baseline and day 1 of each treatment cycle for the first six cycles, at day 1 of every third cycle, and at the end of treatment.

Outcomes

Primary end points were OS, defined as the time from randomization to death from any cause, and PFS, defined as the time from randomization to the date of the first documented disease progression, per IRC, or death from any cause. PROs and safety were secondary end points.

Statistical analysis

OS, PFS, and BM-specific-PFS (defined as the time from randomization to the date of the first evidence of central nervous system disease progression) were analyzed by stratified log-rank test using tumor histology as a stratification factor. Median OS, PFS, and BM PFS were estimated using the Kaplan–Meier method. HRs and associated 95% CIs were estimated by a stratified Cox regression model, using the treatment as a covariate and tumor histology as a stratification factor. The ORR and the associated odds ratio (OR) were analyzed using the Cochran-Mantel-Haenszel test, stratified by tumor histology. The ORR and its associated 95% CIs were calculated using the Clopper-Pearson method for each treatment. All p values were two-sided.

For PRO assessments, the mean change from baseline score to each post-baseline visit was summarized descriptively. Item scores for Likert scales were transformed to a 0–100 scale using a standard algorithm[27]; high scores on functional domains and low scores on symptoms reflect better outcomes. A change in score of ≥10 points in the transformed score is considered to be clinically meaningful.[29] Mixed-effects for repeated measures analyses were performed to compare overall change from baseline scores between the two treatment arms, controlling for treatment, time point, treatment*time point, baseline, histology, geographical region, baseline*time, and treatment*time. An unstructured covariance matrix was used; however, in the event of nonconvergence it was replaced first by a heterogeneous Toeplitz, then by an autoregressive (1) structure.

Clinical efficacy and safety data reported used a cutoff date of January 16, 2024. PROs are reported using a cutoff date of March 1, 2020.

RESULTS

Patients and treatments

The PD-L1 ≥50% intention-to-treat population comprised 565 patients (cemiplimab [n = 284]; chemotherapy [n = 281]). At the time of randomization, 69 of these patients (12.2%) had previously treated symptomatic BM (Figure S2). Patients with BM at baseline were evenly distributed between the cemiplimab (n = 34) and chemotherapy (n = 35) arms. Baseline characteristics were generally comparable between patients with and without BM (Table 1). However, a larger proportion of patients with BM had nonsquamous histology (n = 55 [79.7%]) than those without BM (n = 265 [53.4%]).

Among patients with BM, the median duration of follow-up from randomization to the data cutoff was 55.7 months (range, 46.9–72.7) for cemiplimab and 55.7 months (range, 46.5–66.0) for

TABLE 1 Patient demographics and baseline characteristics.

Characteristic	With BM at baseline		Without BM at baseline	
	Cemiplimab (n = 34)	Chemotherapy (n = 35)	Cemiplimab (n = 250)	Chemotherapy (n = 246)
Age, median (range), years	60.0 (45.0–76.0)	62.0 (48.0–77.0)	64.0 (31.0–79.0)	64.0 (40.0–84.0)
≥65 years, No. (%)	9 (26.5)	12 (34.3)	118 (47.2)	121 (49.2)
Male, No. (%)	33 (97.1)	29 (82.9)	216 (86.4)	202 (82.1)
ECOG PS, No. (%)				
0	10 (29.4)	6 (17.1)	67 (26.8)	70 (28.5)
1	24 (70.6)	29 (82.9)	183 (73.2)	176 (71.5)
Smoking status, No. (%)				
Current smoker	7 (20.6)	12 (34.3)	99 (39.6)	80 (32.5)
Past smoker	27 (79.4)	23 (65.7)	151 (60.4)	166 (67.5)
Histology, No. (%)				
Nonsquamous	29 (85.3)	26 (74.3)	132 (52.8)	133 (54.1)
Squamous	5 (14.7)	9 (25.7)	118 (47.2)	113 (45.9)
Metastatic sites, No. (%)				
Lung	18 (52.9)	26 (74.3)	172 (68.8)	165 (67.1)
Liver	4 (11.8)	5 (14.3)	46 (18.4)	40 (16.3)
Bone	4 (11.8)	7 (20.0)	60 (24.0)	66 (26.8)
Adrenal	9 (26.5)	6 (17.1)	49 (19.6)	47 (19.1)
Lymph nodes, intrathoracic	24 (70.6)	28 (80.0)	175 (70.0)	166 (67.5)
Lymph nodes, other	6 (17.6)	4 (11.4)	58 (23.2)	54 (22.0)
Duration of treatment exposure, median (range), weeks	55.5 (5.4–132.7)	17.9 (3.0–82.7)	36.0 (0.3–136.0)	18.0 (0.6–141.1)
Duration of follow-up, median (range), months	55.7 (46.9–72.7)	55.7 (46.5–66.0)	57.8 (46.5–78.4)	57.8 (46.7–76.1)

Abbreviations: BM, brain metastases; ECOG PS, Eastern Cooperative Oncology Group performance status.

chemotherapy. Twenty-six (37.7%) patients completed planned treatment (cemiplimab, n = 13; chemotherapy, n = 13), and 43 (62.3%) patients discontinued treatment (cemiplimab, n = 21; chemotherapy, n = 22) (Figure S2) by the data cutoff. The primary reason for discontinuation in both treatment arms was disease progression (cemiplimab, n = 17 [50.0%]; chemotherapy, n = 13 [37.1%]). Of 17 patients in the cemiplimab arm who discontinued due to disease progression, four (23.5%) had intracranial disease progression (due to new BM [n = 3, 17.6%]; progression of existing BM [n = 4, 23.5%]). Of 13 patients in the chemotherapy arm who discontinued due to disease progression, five (38.5%) had intracranial disease progression (due to new BM [n = 4, 30.8%]; progression of existing BM [n = 2, 5.7%]) (Table S1). In total, 21 (60.0%) patients with BM who were randomized to chemotherapy received cemiplimab as crossover treatment.

Among patients without BM, the median duration of follow-up was 57.8 months (range, 46.5–78.4) for cemiplimab and 57.8 months (range, 46.7–76.1) for chemotherapy. A total of 168 (33.9%) patients completed planned treatment (cemiplimab, n = 51 [20.4%]; chemotherapy, n = 117 [47.6%]) and 319 (64.3%) patients discontinued treatment (cemiplimab, n = 198 [79.2%]; chemotherapy, n = 121 [49.2%]) (Figure S2). The primary reason for discontinuation in both treatment arms was disease progression (cemiplimab, n = 136 [54.4%]; chemotherapy, n = 69 [28.0%]). Of 136 patients in the cemiplimab arm who discontinued due to disease progression, eight (5.9%) had intracranial disease progression due to new BM; of 69 patients in the chemotherapy arm who discontinued due to disease progression, one (1.4%) had intracranial disease progression due to new BM (Table S1).

Among patients with BM, five (14.7%) and seven (20.0%) patients in the cemiplimab and chemotherapy arms, respectively, experienced intracranial disease progression. In the cemiplimab arm, all five patients had progression of an existing lesion, and three (8.8%) also had progression due to a new lesion. In the chemotherapy arm, three (8.6%) had progression of an existing lesion, and five (14.3%) had progression due to a new lesion (Table S1).

Among patients without BM, eight (3.2%) and three (1.2%) patients in the cemiplimab and chemotherapy arms, respectively, experienced intracranial disease progression due to new BM (Table S1).

OS

A survival advantage over chemotherapy was observed with cemiplimab in patients with and without BM at baseline. In patients with BM, median OS was 52.4 months (95% CI, 20.6–not evaluable [NE]) with cemiplimab versus 20.7 months (95% CI, 9.1–29.5) with chemotherapy (HR, 0.40; 95% CI, 0.21–0.75; $p = .0031$) (Figure 1A). The estimated probability of OS at 12 months was 84.7% (95% CI, 67.1–93.3) with cemiplimab versus 59.6% (95% CI, 41.5–73.8) with chemotherapy.

In patients without BM, median OS was 24.3 (95% CI, 21.1–30.6) with cemiplimab versus 12.5 months (95% CI, 10.1–14.8) with chemotherapy (HR, 0.63; 95% CI, 0.50–0.78; $p < .0001$) (Figure 1B). The estimated probability of OS at 12 months was 68.3% (95% CI, 62.0–73.9) with cemiplimab versus 51.4% (95% CI, 44.5–57.8) with chemotherapy.

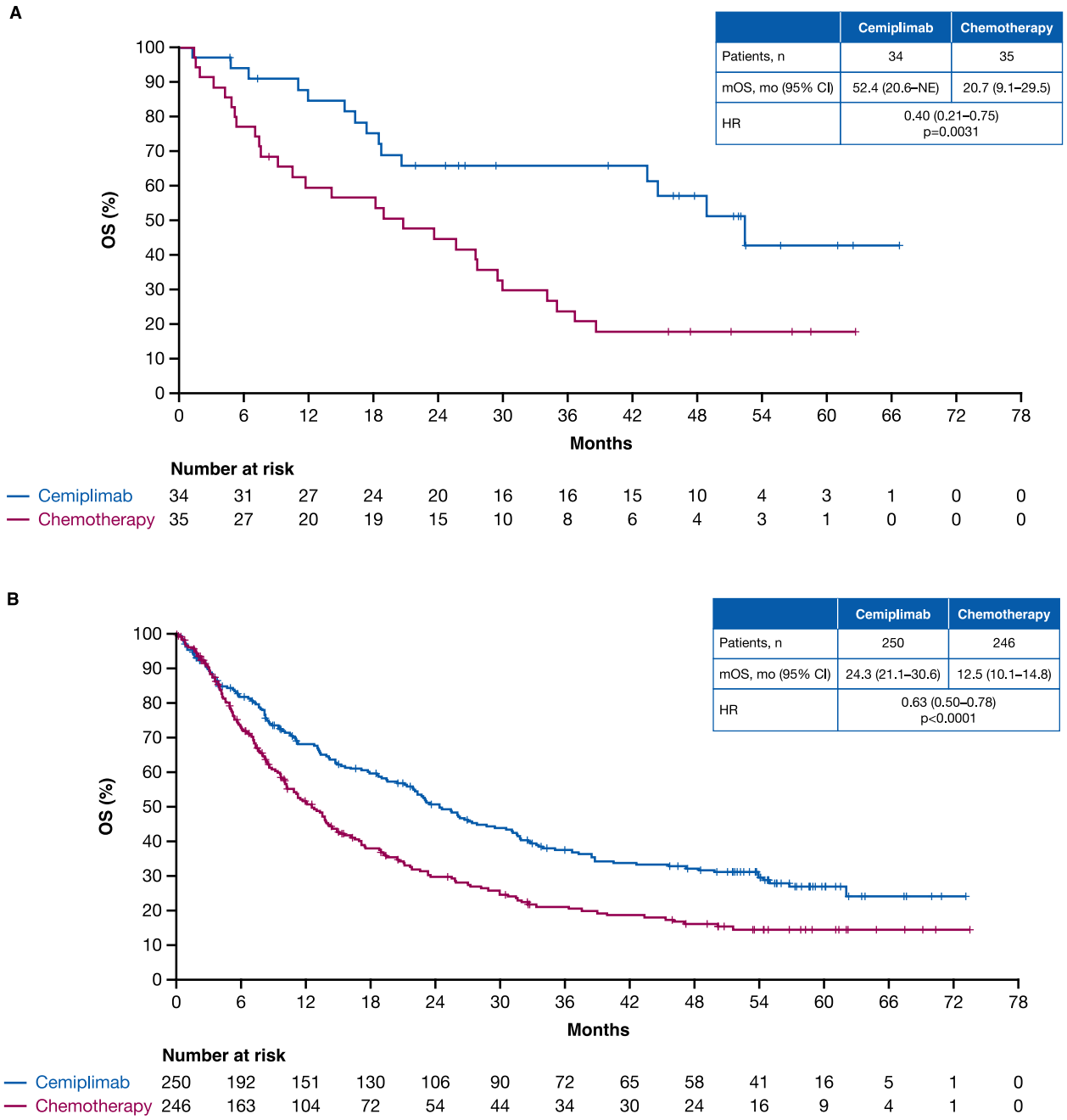


FIGURE 1 Kaplan–Meier curves showing OS by the independent review committee in patients (A) with and (B) without brain metastases at baseline. Patients were stratified by tumor histology, with HR based on a stratified Cox regression model using the treatment as a covariate and tumor histology as a stratification factor. *p* values are two-sided. CI indicates confidence interval; HR, hazard ratio; mOS, median overall survival; NE, not evaluable; OS, overall survival.

PFS

In patients with BM, median PFS with cemiplimab was 12.5 months (95% CI, 6.1–33.5) versus 5.3 months (95% CI, 2.2–6.5) with chemotherapy (HR, 0.33; 95% CI, 0.18–0.61; $p = .0002$) (Figure 2A). The estimated probability of PFS at 12 months was 55.1% (95% CI, 36.8–70.0) with cemiplimab versus 6.4% (95% CI, 1.2–18.5) with chemotherapy.

The magnitude of the PFS improvement observed with cemiplimab was less accentuated in patients without BM: median PFS was 6.5 months (95% CI, 5.2–8.5) with cemiplimab versus 5.2 months (95% CI, 4.3–6.1) with chemotherapy (HR, 0.55; 95% CI, 0.44–0.67; $p < .0001$) (Figure 2B). The estimated probability of PFS at 12 months was 39.8% (95% CI, 33.6–45.9) with cemiplimab versus 7.3% (95% CI, 4.2–11.6) with chemotherapy.

In patients with BM, median BM PFS was superior at 20.6 months (95% CI, 16.3–NE) with cemiplimab versus 9.1 months (95% CI, 5.1–20.7) with chemotherapy (HR, 0.35; 95% CI, 0.18–0.66; $p = .0008$) (Figure S3A). Likewise, in patients without BM, median BM PFS was superior at 22.7 months (95% CI, 17.7–26.2) with

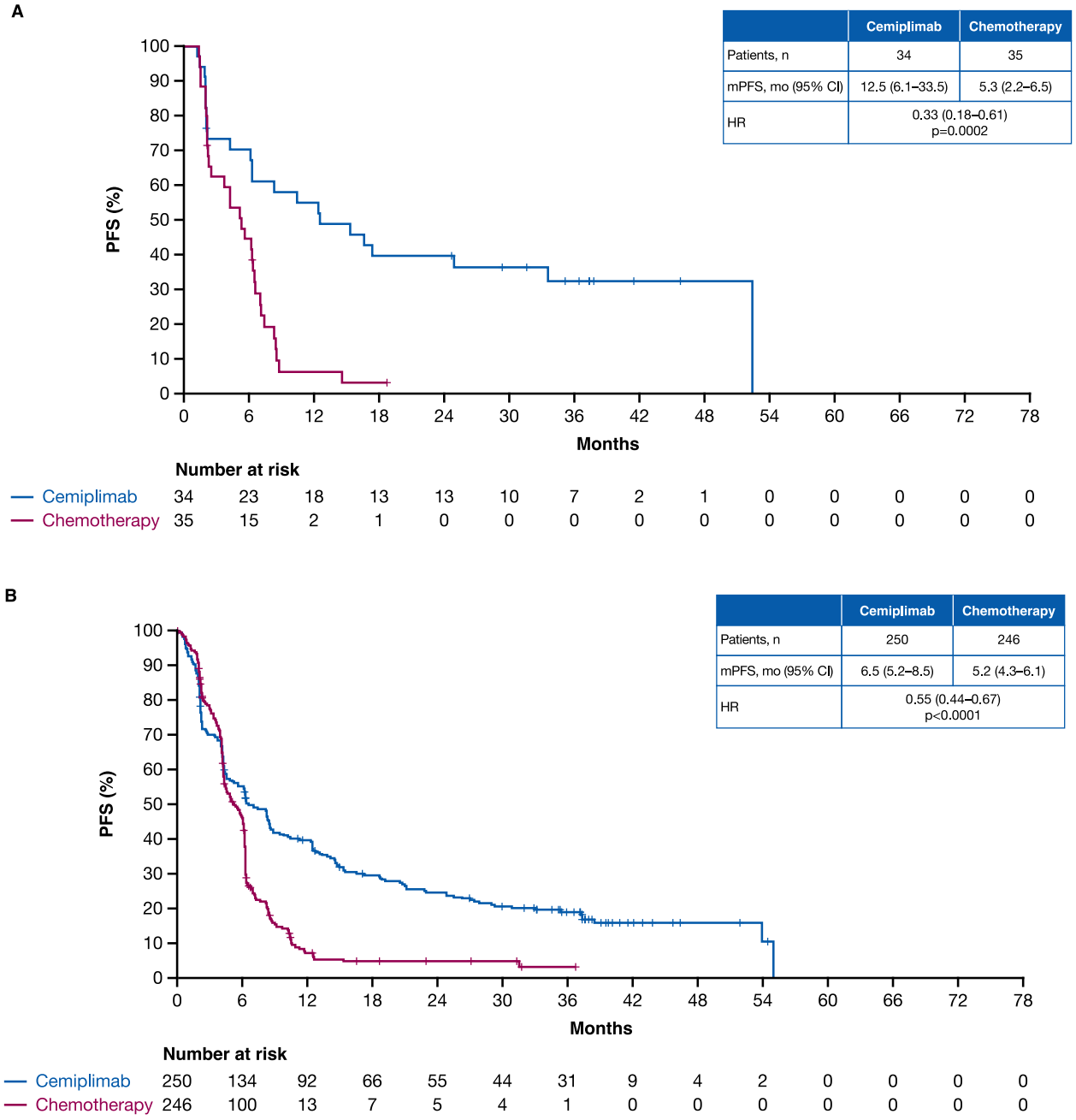


FIGURE 2 Kaplan–Meier curves showing PFS by the independent review committee in patients (A) with and (B) without brain metastases at baseline. Patients were stratified by tumor histology, with HR based on a stratified Cox regression model using the treatment as a covariate and tumor histology as a stratification factor. *p* values are two-sided. CI indicates confidence interval; HR, hazard ratio; NE, not evaluable; mPFS, median progression-free survival; PFS, progression-free survival.

cemiplimab versus 10.3 months (8.8–12.5) with chemotherapy (HR, 0.50; 95% CI, 0.40–0.62; $p < .0001$) (Figure S3B).

Tumor response

In patients with BM, the IRC-assessed ORR for cemiplimab was 55.9% (95% CI, 37.9–72.8) versus 11.4% (95% CI, 3.2–26.7) for chemotherapy (OR, 9.3; 95% CI, 2.6–32.7; $p = .0002$) (Table 2). For patients with confirmed complete or partial responses, median time to response was 2.1 months (range, 1.4–4.5) with cemiplimab and 4.1 months (range, 2.1–4.2) with chemotherapy; the estimated median duration of response (DOR) for cemiplimab was 50.3 months (95% CI, 14.7–NE) versus 12.5 months (95% CI, 4.4–NE) with chemotherapy.

In patients without BM, the ORR was 45.2% (95% CI, 38.9–51.6) with cemiplimab versus 22.0% (95% CI, 16.9–27.7) with chemotherapy (OR, 2.9; 95% CI, 2.0–4.3; $p < .0001$) (Table 2). The median time to response was 2.1 months (range, 1.4–12.7) with cemiplimab versus 2.1 months (range, 1.4–6.3) with chemotherapy; the estimated median DOR for cemiplimab was 22.8 months (95% CI, 16.6–33.0) versus 5.1 months (95% CI, 4.3–6.4) with chemotherapy.

Patient-reported outcomes

Among patients with BM, a statistically significant difference in overall change from baseline between the two treatment arms was observed in the global health status (GHS)/quality of life (QoL) scale of QLQ-C30, favoring cemiplimab over chemotherapy (9.35; 95% CI, 2.24–16.45; $p = .0110$) (Figure 3A). Moreover, cemiplimab resulted in a statistically significant favorable difference in overall change from baseline in the role functioning (8.59; 95% CI, 0.16–17.01; $p = .0459$) and emotional functioning (7.27; 95% CI, 1.86–12.69; $p = .0095$) scales of the QLQ-C30. No statistically significant overall between-arm differences were observed for the physical functioning (6.01; 95% CI, −0.37 to 12.39; $p = .0643$), cognitive functioning (1.62; 95% CI, −4.58 to 7.81; $p = .6029$), and social functioning (4.22; 95% CI, −2.74 to 11.19, $p = .2273$) scales of the QLQ-C30. Similarly, among patients without BM, a statistically significant difference favoring cemiplimab over chemotherapy was observed in GHS/QoL and all functional scales of the QLQ-C30 (Figure S4A).

Among patients with BM, statistically significant between-arm differences from baseline were observed favoring cemiplimab over chemotherapy for the QLQ-C30 cancer-specific symptom scales of fatigue (−8.19; 95% CI, −15.40 to −0.98; $p = .0268$) and appetite loss (−7.43; 95% CI, −14.48 to −0.38; $p = .0393$) (Figure 3B). No statistically significant overall between-arm differences were observed for the QLQ-C30 cancer-specific symptoms of nausea/vomiting (−0.76; 95% CI, −6.90 to 5.38; $p = .8052$), pain (5.88; 95% CI, −0.50 to 12.26; $p = .0698$), dyspnea (0.32; 95% CI, −7.91 to 8.54; $p = .9387$), insomnia (5.88; 95% CI, −2.31 to 14.07; $p = .1559$), constipation (0.75; 95% CI, −6.77 to 8.27; $p = .8426$), or diarrhea (2.08; 95% CI, −1.58 to 5.73; $p = .2597$). Among patients without BM, statistically significant between-arm differences from baseline were observed favoring cemiplimab over chemotherapy for the QLQ-C30 cancer-specific symptoms of fatigue, nausea/vomiting, pain, appetite loss, and constipation (Figure S4B).

TABLE 2 Summary of tumor response per RECIST v1.1 according to the independent review committee.

	With BM at baseline[a]		Without BM at baseline	
Variable	**Cemiplimab ($n = 34$)**	**Chemotherapy ($n = 35$)**	**Cemiplimab ($n = 250$)**	**Chemotherapy ($n = 246$)**
ORR, % (95% CI)	55.9 (37.9–72.8)	11.4 (3.2–26.7)	45.2 (38.9–51.6)	22.0 (16.9–27.7)
OR (95% CI)[b]	9.3 (2.6–32.7); $p = .0002$		2.9 (2.0–4.3); $p < .0001$	
Best overall tumor response, No. (%)				
Complete response	4 (11.8)	0	20 (8.0)	4 (1.6)
Partial response	15 (44.1)	4 (11.4)	93 (37.2)	50 (20.3)
Stable disease	6 (17.6)	18 (51.4)	59 (23.6)	124 (50.4)
Noncomplete response/nonpartial disease	—	—	2 (0.8)	2 (0.8)
Progressive disease	8 (23.5)	11 (31.4)	52 (20.8)	34 (13.8)
Not evaluable	1 (2.9)	2 (5.7)	24 (9.6)	32 (13.0)
Kaplan–Meier estimated duration of response, median (95% CI), months[c]	50.3 (14.7–NE)	12.5 (4.4–NE)	22.8 (16.6–33.0)	5.1 (4.3–6.4)
Observed time to response, median (range), months	2.1 (1.4–6.3)	4.1 (2.1–4.2)	2.1 (1.4–12.7)	2.1 (1.4–6.3)

Abbreviations: BM, brain metastases; CI, confidence interval; NE, not evaluable; OR, odds ratio; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

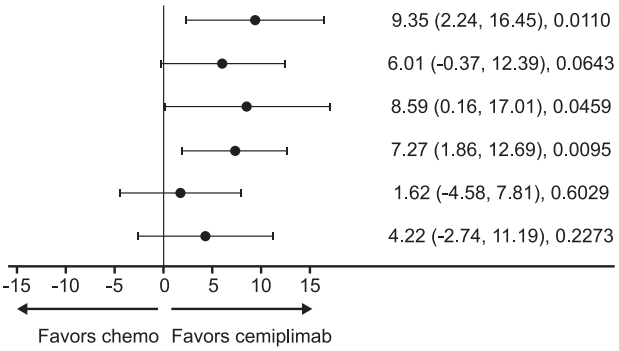
[a]In patients with BM at baseline, the brain was a nontarget lesion.

[b]Per two-sided p value and OR using a stratified Cochran-Mantel-Haenszel test; values relate to the comparison between treatment groups.

[c]The data are from patients who had a confirmed complete or partial response.

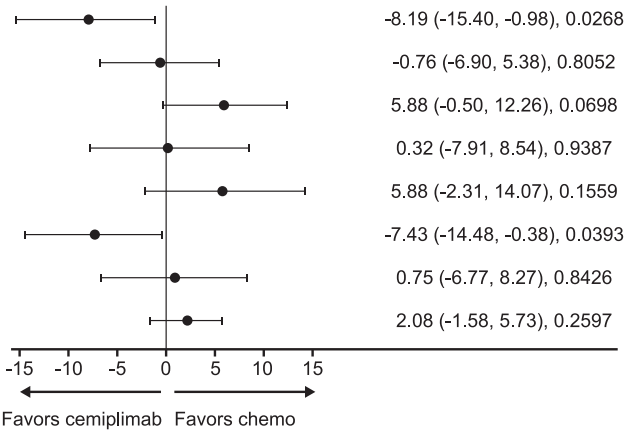
A

Domain	LS mean (SE) overall Cemiplimab	Chemo	Difference in LS means (95% CI), *P* value
Global health status/QoL	11.40 (3.25)	2.05 (3.35)	9.35 (2.24, 16.45), 0.0110
Physical functioning	4.42 (2.77)	-1.59 (2.83)	6.01 (-0.37, 12.39), 0.0643
Role functioning	7.51 (3.99)	-1.08 (4.09)	8.59 (0.16, 17.01), 0.0459
Emotional functioning	3.72 (2.54)	-3.55 (2.66)	7.27 (1.86, 12.69), 0.0095
Cognitive functioning	1.31 (2.77)	-0.31 (2.85)	1.62 (-4.58, 7.81), 0.6029
Social functioning	3.37 (3.11)	-0.86 (3.23)	4.22 (-2.74, 11.19), 0.2273



B

Domain	LS mean (SE) overall Cemiplimab	Chemo	Difference in LS means (95% CI), *P* value
Fatigue	-6.83 (3.39)	1.37 (3.48)	-8.19 (-15.40, -0.98), 0.0268
Nausea/vomiting	0.54 (2.94)	1.30 (3.00)	-0.76 (-6.90, 5.38), 0.8052
Pain	-5.13 (3.00)	-11.02 (3.04)	5.88 (-0.50, 12.26), 0.0698
Dyspnea	-0.47 (3.78)	-0.78 (3.81)	0.32 (-7.91, 8.54), 0.9387
Insomnia	-3.26 (3.78)	-9.13 (3.95)	5.88 (-2.31, 14.07), 0.1559
Appetite loss	-4.21 (3.31)	3.22 (3.46)	-7.43 (-14.48, -0.38), 0.0393
Constipation	1.52 (3.48)	0.77 (3.60)	0.75 (-6.77, 8.27), 0.8426
Diarhea	1.82 (1.48)	-0.25 (1.55)	2.08 (-1.58, 5.73), 0.2597



C

Domain	LS mean (SE) overall Cemiplimab	Chemo	Difference in LS means (95% CI), *P* value
LC - Dyspnea	-5.12 (3.22)	-2.69 (3.26)	-2.44 (-9.70, 4.83), 0.5045
LC - Coughing	-1.02 (3.33)	-7.50 (3.51)	6.49 (-1.12, 14.09), 0.0930
LC - Hemoptysis	1.19 (1.51)	-1.26 (1.64)	2.45 (-1.22, 6.13), 0.1857
LC - Sore mouth	-0.03 (1.22)	-0.40 (1.31)	0.37 (-3.00, 3.74), 0.8270
LC - Dysphagia	-3.43 (2.42)	-1.77 (2.48)	-1.66 (-6.85, 3.53), 0.5255
LC - Peripheral neuropathy	3.43 (3.67)	0.92 (3.74)	2.51 (-5.66, 10.68), 0.5409
LC - Alopecia	-3.23 (4.76)	2.59 (4.89)	-5.82 (-16.52, 4.88), 0.2801
LC - Pain in arm or shoulder	3.46 (3.47)	0.36 (3.57)	3.10 (-4.70, 10.89), 0.4292
LC - Pain in chest	-2.87 (2.69)	-4.58 (2.80)	1.71 (-4.42, 7.84), 0.5787
LC - Pain in other parts	-3.68 (3.69)	-6.25 (3.78)	2.57 (-5.76, 10.91), 0.5355

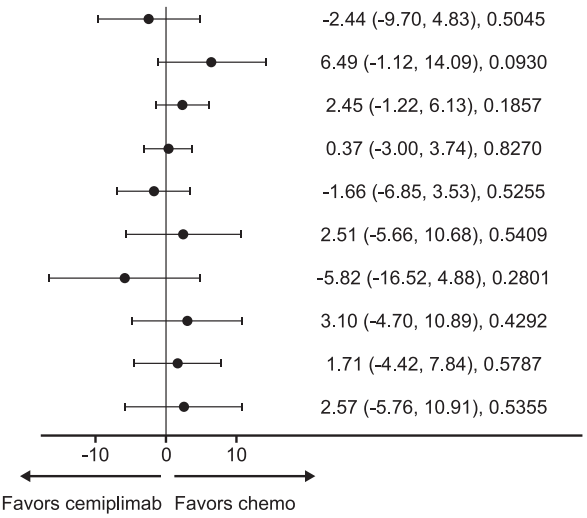


FIGURE 3 Forest plot model of estimated between-treatment differences (cemiplimab vs. chemotherapy) in overall change from baseline (MMRM model) in patients with brain metastases at baseline per (A) EORTC QLQ-C30 GHS/QoL and functional scales, (B) EORTC QLQ-C30 symptom scales, and (C) EORTC QLQ-LC13 symptom scales. CI indicates confidence interval; EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; LC, lung cancer; LS, least-squares; MMRM, mixed-model with repeated measures; QLQ-C30, Quality of Life-Core 30; QLQ-LC13, Quality of Life-Lung Cancer Module; QoL, quality of life; SE, standard error.

Analysis of QLQ-LC13 lung cancer-specific symptoms showed there was no significant overall between-arm difference from baseline in patients with BM (Figure 3C). Among patients without BM, statistically significant between-arm differences from baseline were observed favoring cemiplimab for the QLQ-LC13 lung cancer-specific symptoms of dyspnea, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and pain in parts of the body other than the arm/shoulder and chest (Figure S4C).

Safety

In patients with BM, treatment-emergent adverse events (TEAEs) of any grade, regardless of attribution, occurred in 33 (97.1%) and 34 (97.1%) patients treated with cemiplimab and chemotherapy, respectively (Table 3). Grade ≥3 TEAEs occurred in 12 (35.3%) and 21 (60.0%) patients treated with cemiplimab and chemotherapy, respectively. The most common grade ≥3 TEAEs in the cemiplimab arm were anemia (n = 2 [5.9%]), hypertension (n = 2 [5.9%]), and pulmonary embolism (n = 2 [5.9%]), and in the chemotherapy arm were anemia (n = 6 [17.1%]), decreased neutrophil count (n = 5 [14.3%]), and pneumonia (n = 5 [14.3%]). TEAEs of any grade leading to discontinuation of cemiplimab in three (8.8%) patients were dermatomyositis (n = 1) and pneumonitis (n = 2). In the chemotherapy arm, one (2.9%) patient discontinued treatment due to a TEAE of decreased platelet cell count. There were no TEAEs leading to death in the cemiplimab arm; in the chemotherapy arm, three (8.6%) patients experienced TEAEs leading to death.

In patients without BM, TEAEs of any grade, regardless of attribution, occurred in 229 (92.0%) and 227 (95.4%) patients treated with cemiplimab and chemotherapy, respectively (Table 3). Grade ≥3 TEAEs occurred in 117 (47.0%) and 113 (47.5%) patients treated with cemiplimab and chemotherapy, respectively, with the most common being pneumonia (n = 15 [6.0%]) in the cemiplimab arm and anemia (n = 42 [17.6%]) in the chemotherapy arm. TEAEs of any grade that led to treatment discontinuation occurred in 21 (8.4%) patients in the cemiplimab arm and six patients (2.5%) in the chemotherapy arm. TEAEs leading to death occurred in 21 (8.4%) and 23 (9.7%) patients treated with cemiplimab and chemotherapy, respectively (Table 3).

DISCUSSION

EMPOWER-Lung 1 was the first phase 3 immunotherapy trial that allowed the inclusion of patients with symptomatic, radiotherapy treated BM without the need for confirmational radiological scans before enrollment. To our knowledge, this exploratory subgroup analysis is unique to EMPOWER-Lung 1 and comprised the largest number of patients with advanced NSCLC with PD-L1 ≥50% and symptomatic, treated BM of all phase 3 studies evaluating anti–PD-1 monotherapy.[7, 14, 15, 17, 30, 31]

With a median follow-up of 55.7 months, the estimated OS probability at 48 months in patients with symptomatic radiotherapy-treated BM at initial presentation was 57.1% with cemiplimab versus 17.9% with chemotherapy. The substantially longer median OS achieved with cemiplimab in patients with BM was associated with a reduction in the relative risk of death of 58%. Cemiplimab also resulted in a substantially longer median PFS (12.5 months vs. 5.3 months) and higher ORR (55.9% vs. 11.4%) versus chemotherapy. Furthermore, the durability of responses achieved with cemiplimab was substantially longer, with a median DOR of 31.7 months versus 12.5 months with chemotherapy. The magnitude of clinical benefit observed with cemiplimab in patients with BM compares favorably with the overall PD-L1 ≥50% population of EMPOWER-Lung 1.[32]

Uniquely, this study included an evaluation of PROs separately in patients with and without BM at baseline. In patients with BM, statistically significant differences favoring cemiplimab over chemotherapy were observed in GHS/QoL, and in several functioning and symptom scales. Favorable PROs were also observed in patients without BM. Importantly, no analyses yielded statistically significant PRO results favoring chemotherapy over cemiplimab for any of the EORTC QLQ-C30 or EORTC QLQ-LC13 scales in patients with or without BM. The safety profile of cemiplimab was generally similar among patients with and without BM at baseline, and was consistent with the safety results previously reported for the overall EMPOWER-Lung 1 population.[24, 32] In individuals with BM at baseline treated with cemiplimab, brain progression occurred in five patients (14.7%), with four (11.8%) of these being associated with existing lesions. Limited prospective data are available for patients treated with PD-1/PD-L1 inhibitors for advanced NSCLC and BM; most published analyses use retrospective or pooled data. In a phase 2, single-center study of 18 patients with NSCLC and untreated BM treated with pembrolizumab, the ORR was 33% (95% CI, 14–59)[11]; patients who had previously been treated with radiotherapy demonstrated no response. In a pooled post hoc analysis of 293 patients treated with pembrolizumab monotherapy versus chemotherapy with PD-L1–positive NSCLC with stable BM at baseline from four studies (KEYNOTE-001, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042), HRs for OS and PFS were 0.83 (95% CI, 0.62–1.10) and 0.96 (95% CI, 0.73–1.25), respectively.[33] For both treatments, ORRs were similar between the treatment groups; DOR was longer with pembrolizumab.

In previous phase 3 randomized studies of pembrolizumab (KEYNOTE-024 and KEYNOTE-042) or atezolizumab (OAK, IMpower110), patients with treated BM could enroll if they had two brain imaging scans post radiotherapy (at least 4 weeks apart) showing no evidence of progression.[7, 30, 34, 35] Consequently, the patients included in these studies were not reflective of real-world clinical practice. In EMPOWER-Lung 1, patients with symptomatic radiotherapy-treated BM could participate without a requirement for repeated brain imaging to confirm response to radiotherapy. Therefore, our results represent a patient population more reflective of

TABLE 3 Treatment-emergent adverse events regardless of attribution.

	With BM at baseline				Without BM at baseline			
	Cemiplimab (n = 34)		Chemotherapy (n = 35)		Cemiplimab (n = 249)		Chemotherapy (n = 238)	
Event, no. of patients (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	33 (97.1)	12 (35.3)	34 (97.1)	21 (60.0)	229 (92.0)	117 (47.0)	227 (95.4)	113 (47.5)
Serious	9 (26.5)	3 (8.8)	13 (37.1)	12 (34.3)	88 (35.3)	71 (28.5)	62 (26.1)	57 (23.9)
Led to discontinuation	3 (8.8)	0	1 (2.9)	0	21 (8.4)	18 (7.2)	6 (2.5)	4 (1.7)
Led to death	0	0	3 (8.6)	3 (8.6)	21 (8.4)	21 (8.4)	23 (9.7)	23 (9.7)
Occurred in ≥5% in the cemiplimab or chemotherapy arms of either group[a]								
Anemia	9 (26.5)	2 (5.9)	19 (54.3)	6 (17.1)	50 (20.1)	9 (3.6)	128 (53.8)	42 (17.6)
Fatigue	7 (20.6)	1 (2.9)	5 (14.3)	1 (2.9)	32 (12.9)	4 (1.6)	45 (18.9)	1 (0.4)
Back pain	6 (17.6)	0	1 (2.9)	0	30 (12.0)	0	18 (7.6)	2 (0.8)
Decreased appetite	6 (17.6)	0	8 (22.9)	0	37 (14.9)	1 (0.4)	50 (21.0)	1 (0.4)
Hyperthyroidism	6 (17.6)	0	0	0	11 (4.4)	0	5 (2.1)	0
Pruritus	6 (17.6)	0	1 (2.9)	0	25 (10.0)	0	8 (3.4)	0
Nausea	5 (14.7)	0	9 (25.7)	0	19 (7.6)	0	69 (29.0)	1 (0.4)
Arthralgia	4 (11.8)	0	3 (8.6)	0	32 (12.9)	1 (0.4)	24 (10.1)	1 (0.4)
Dyspnea	4 (11.8)	0	1 (2.9)	0	29 (11.6)	6 (2.4)	21 (8.8)	8 (3.4)
Constipation	3 (8.8)	0	5 (14.3)	0	20 (8.0)	0	41 (17.2)	0
Diarrhea	3 (8.8)	0	3 (8.6)	0	25 (10.0)	0	24 (10.1)	5 (2.1)
Dizziness	3 (8.8)	0	3 (8.6)	0	7 (2.8)	0	6 (2.5)	0
Hyperglycemia	3 (8.8)	0	2 (5.7)	0	16 (6.4)	3 (1.2)	12 (5.0)	0
Hypertension	3 (8.8)	2 (5.9)	1 (2.9)	0	13 (5.2)	1 (0.4)	7 (2.9)	2 (0.8)
Hypothyroidism	3 (8.8)	0	0	0	25 (10.0)	0	1 (0.4)	0
Increased alanine aminotransferase	3 (8.8)	0	2 (5.7)	0	26 (10.4)	6 (2.4)	15 (6.3)	1 (0.4)
Pain in extremity	3 (8.8)	0	2 (5.7)	0	14 (5.6)	1 (0.4)	16 (6.7)	1 (0.4)
Pneumonia	3 (8.8)	1 (2.9)	6 (17.1)	5 (14.3)	31 (12.4)	15 (6.0)	27 (11.3)	11 (4.6)
Pneumonitis	3 (8.8)	0	0	0	8 (3.2)	2 (0.8)	2 (0.8)	0
Pyrexia	3 (8.8)	0	2 (5.7)	0	20 (8.0)	0	9 (3.8)	1 (0.4)
Decreased lymphocyte count	2 (5.9)	0	1 (2.9)	0	6 (2.4)	1 (0.4)	7 (2.9)	3 (1.3)
Decreased weight	2 (5.9)	0	1 (2.9)	0	15 (6.0)	2 (0.8)	18 (7.6)	1 (0.4)
Dermatitis	2 (5.9)	0	0	0	11 (4.4)	1 (0.4)	1 (0.4)	0
Erythematous rash	2 (5.9)	0	0	0	1 (0.4)	0	1 (0.4)	0
Gastroenteritis	2 (5.9)	0	0	0	2 (0.8)	0	1 (0.4)	1 (0.4)
Headache	2 (5.9)	1 (2.9)	2 (5.7)	0	20 (8.0)	0	5 (2.1)	0
Hemoptysis	2 (5.9)	0	0	0	18 (7.2)	2 (0.8)	15 (6.3)	0
Hypoalbuminemia	2 (5.9)	0	3 (8.6)	1 (2.9)	25 (10.0)	3 (1.2)	19 (8.0)	2 (0.8)
Increased aspartate aminotransferase	2 (5.9)	0	1 (2.9)	0	24 (9.6)	8 (3.2)	11 (4.6)	1 (0.4)
Maculopapular rash	2 (5.9)	0	0	0	4 (1.6)	0	0	0
Neutropenia[b]	2 (5.9)	0	3 (8.6)	2 (5.7)	8 (3.2)	3 (1.2)	47 (19.7)	24 (10.1)
Noncardiac chest pain	2 (5.9)	0	2 (5.7)	1 (2.9)	12 (4.8)	1 (0.4)	7 (2.9)	2 (0.8)
Pain	2 (5.9)	0	1 (2.9)	0	4 (1.6)	1 (0.4)	3 (1.3)	0
Pulmonary embolism	2 (5.9)	2 (5.9)	1 (2.9)	0	7 (2.8)	6 (2.4)	2 (0.8)	1 (0.4)

TABLE 3 (Continued)

	With BM at baseline				Without BM at baseline			
	Cemiplimab (n = 34)		Chemotherapy (n = 35)		Cemiplimab (n = 249)		Chemotherapy (n = 238)	
Event, no. of patients (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Thrombocytopenia[b]	2 (5.9)	0	6 (17.1)	3 (8.6)	3 (1.2)	1 (0.4)	39 (16.4)	18 (7.6)
Urticaria	2 (5.9)	0	0	0	2 (0.8)	0	0	0
Vomiting	2 (5.9)	0	7 (20.0)	0	12 (4.8)	0	32 (13.4)	1 (0.4)
Alopecia	1 (2.9)	0	5 (14.3)	0	2 (0.8)	0	63 (26.5)	2 (0.8)
Cough	1 (2.9)	0	3 (8.6)	0	26 (10.4)	0	21 (8.8)	1 (0.4)
Decreased neutrophil count[b]	1 (2.9)	0	10 (28.6)	5 (14.3)	1 (0.4)	1 (0.4)	29 (12.2)	11 (4.6)
Decreased platelet count[b]	1 (2.9)	0	7 (20.0)	1 (2.9)	5 (2.0)	0	27 (11.3)	10 (4.2)
Decreased white blood cell count	1 (2.9)	0	5 (14.3)	2 (5.7)	3 (1.2)	0	24 (10.1)	10 (4.2)
Hyponatremia	1 (2.9)	1 (2.9)	3 (8.6)	1 (2.9)	13 (5.2)	8 (3.2)	14 (5.9)	8 (3.4)
Increased amylase	1 (2.9)	0	1 (2.9)	1 (2.9)	14 (5.6)	2 (0.8)	2 (0.8)	0
Increased blood alkaline phosphatase	1 (2.9)	0	0	0	23 (9.2)	4 (1.6)	9 (3.8)	1 (0.4)
Leukopenia	1 (2.9)	0	4 (11.4)	1 (2.9)	4 (1.6)	1 (0.4)	24 (10.1)	8 (3.4)
Myalgia	1 (2.9)	0	2 (5.7)	0	5 (2.0)	1 (0.4)	8 (3.4)	0
Paresthesia	1 (2.9)	0	1 (2.9)	0	2 (0.8)	0	6 (2.5)	0
Peripheral neuropathy	1 (2.9)	0	0	0	2 (0.8)	1 (0.4)	28 (11.8)	2 (0.8)
Rash	1 (2.9)	0	1 (2.9)	0	23 (9.2)	3 (1.2)	10 (4.2)	0
Asthenia	0	0	4 (11.4)	0	16 (6.4)	0	20 (8.4)	2 (0.8)
Epistaxis	0	0	2 (5.7)	0	0	0	3 (1.3)	0
Hiccups	0	0	2 (5.7)	0	2 (0.8)	0	3 (1.3)	0
Hypersensitivity	0	0	2 (5.7)	0	1 (0.4)	0	1 (0.4)	0
Hypomagnesaemia	0	0	2 (5.7)	0	8 (3.2)	1 (0.4)	24 (10.1)	2 (0.8)
Increased blood creatinine	0	0	3 (8.6)	0	23 (9.2)	1 (0.4)	17 (7.1)	1 (0.4)
Insomnia	0	0	1 (2.9)	0	18 (7.2)	0	14 (5.9)	0
Lethargy	0	0	2 (5.7)	0	0	0	2 (0.8)	0
Peripheral sensory neuropathy	0	0	2 (5.7)	0	4 (1.6)	0	7 (2.9)	1 (0.4)
Peripheral edema	0	0	0	0	13 (5.2)	0	6 (2.5)	0

Abbreviation: BM, brain metastases.

[a]The events are listed in descending order of frequency in the cemiplimab arm in the population with BM at baseline. The events were coded according to the Preferred Terms of the Medical Dictionary for Regulatory Activities, version 22.1. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

[b]Although each pair of neutropenia and decreased neutrophil count and thrombocytopenia and decreased platelet count might reflect the same condition, they were listed as distinct events for the safety report of the study.

real-world clinical practice. Interestingly, patients in the cemiplimab group had similar outcomes independent of the presence of BM. Conversely, in the chemotherapy group, patients with BM had a worse outcome than those without.

Limitations of this subgroup analysis include the limited sample size and that it only evaluated patients with treated BM with neurologically stable disease, therefore we were not able to objectively evaluate intracranial response to cemiplimab. Consequently, the findings should be considered exploratory and interpreted with caution. Prospective studies of patients with untreated BM would be useful to demonstrate the benefit of first-line cemiplimab.

In conclusion, this study showed that first-line cemiplimab monotherapy improved clinical outcomes, including DOR and PROs, versus chemotherapy in patients with advanced NSCLC with PD-L1 ≥50% and symptomatic radiotherapy-treated BM at baseline. Thus, first-line cemiplimab monotherapy represents a suitable treatment option for this subgroup of patients.

AUTHOR CONTRIBUTIONS

Saadettin Kilickap: Investigation, writing–review and editing, and data curation. **Mustafa Özgüroğlu:** Investigation, writing–review and editing, and data curation. **Ahmet Sezer:** Investigation, writing–review and editing, and data curation. **Mahmut Gümüş:** Investigation, writing–review and editing, and data curation. **Igor Bondarenko:** Investigation, writing–review and editing, and data curation. **Miranda Gogishvili:** Investigation, writing–review and editing, and data curation. **Haci M. Turk:** Investigation, writing–review and editing, and data curation. **Irfan Cicin:** Investigation, writing–review and editing, and data curation. **Dmitry Bentsion:** Investigation, writing–review and editing, and data curation. **Oleg Gladkov:** Investigation, writing–review and editing, and data curation. **Virote Sriuranpong:** Investigation, writing–review and editing, and data curation. **Ruben G. W. Quek:** Conceptualization, writing–review and editing, and data curation. **Debra A. G. McIntyre:** Methodology, formal analysis, and writing–review and editing. **Xuanyao He:** Methodology, formal analysis, and writing–review and editing. **Jennifer McGinniss:** Methodology, formal analysis, and writing–review and editing. **Frank Seebach:** Conceptualization, writing–review and editing, and data curation. **Giuseppe Gullo:** Conceptualization, writing–review and editing, and data curation. **Petra Rietschel:** Conceptualization, writing–review and editing, and data curation. **Jean-Francois Pouliot:** Conceptualization, writing–review and editing, and data curation. All authors had full access to the data and contributed to the data analysis and interpretation, as well as critical review for important intellectual content, revision, and approval of the final report.

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CONFLICT OF INTEREST STATEMENT

Virote Sriuranpong reports fees for professional activities from Amgen, AstraZeneca, Daiichi Sankyo Company Ltd, Eisai, F. Hofmann-La Roche, Merck Sharp & Dohme, Novartis, and Pfizer. Haci M. Turk reports fees for professional activities from Regeneron Pharmaceuticals. Saadettin Kilickap reports travels funding from Regeneron Pharmaceuticals. Mustafa Özgüroğlu reports honoraria from Novartis, Roche, Janssen, Sanofi, and Astellas; advisory board fees from Janssen, Sanofi, and Astellas; travel support from Bristol-Myers Squibb, Janssen, AstraZeneca, and Regeneron Pharmaceuticals, Inc.; and speaker support from AstraZeneca. Ahmet Sezer reports institutional research support from Roche, Merck Sharp & Dohme, Merck Serono, AstraZeneca, Lilly, Novartis, Johnson & Johnson, Regeneron Pharmaceuticals, Inc., and Sanofi outside the submitted work. Mahmut Gümüş reports honoraria to institution for lectures from Roche, Merck Sharp & Dohme, Gen İlaç, and Novartis outside the submitted work. Irfan Cicin reports personal fees (paid to institution) from Pfizer, Merck Sharp & Dohme Oncology, Roche, Novartis-Ipsen, Eli Lilly, Bristol-Myers Squibb, Servier, Abdi Ibrahim, Nobelpharma, AbbVie, Teva, and Janssen Oncology; and speaker's bureau fees (paid to institution) from Novartis, Roche, Bristol-Myers Squibb, Pfizer, and Abdi Ibrahim. Ruben G. W. Quek is a shareholder of Regeneron Pharmaceuticals, Inc. Jennifer McGinniss is a shareholder of Regeneron Pharmaceuticals, Inc. Jean-Francois Pouliot is a shareholder of Regeneron Pharmaceuticals, Inc. Frank Seebach is a shareholder of Regeneron Pharmaceuticals, Inc. Giuseppe Gullo is a shareholder of Regeneron Pharmaceuticals, Inc. Debra A. G. McIntyre is a shareholder of Regeneron Pharmaceuticals, Inc. Xuanyao He is a shareholder of Regeneron Pharmaceuticals, Inc. Petra Rietschel is a shareholder of Regeneron Pharmaceuticals, Inc. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing 1) once the product and indication has been approved by major health authorities (e.g., Food and Drug Administration, European Medicines Agency, Pharmaceuticals and Medical Devices Agency, etc.) or development of the product has been discontinued globally for all indications on or after April 2020 and there are no plans for future development, 2) if there is legal authority to share the data, and 3) there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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