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ORIGINAL ARTICLE

Lenvatinib plus pembrolizumab for patients with previously treated select solid tumors: Results from the phase 2 LEAP-005 study recurrent glioblastoma cohort

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Abstract

Background: Patients with recurrent glioblastoma (GBM) have a poor prognosis and limited treatment options. The authors report the efficacy and safety of lenvatinib plus pembrolizumab in participants with recurrent GBM enrolled in the phase 2, multicohort LEAP-005 study (NCT03797326).

Methods: Eligible participants had histologically confirmed GBM (World Health Organization grade IV) with disease progression since previous treatment, and one or more prior lines of therapy. Participants were enrolled regardless of tumor programmed cell death ligand 1 (PD-L1) status and received oral lenvatinib 20 mg per day plus intravenous pembrolizumab 200 mg every 3 weeks. The dual primary end points were objective response rate (ORR; per Response Assessment in Neuro-Oncology by blinded independent central review) and safety.

Results: A total of 101 participants were enrolled, with median (range) follow-up of 23.7 (16.4–46.6) months. The median (range) duration of treatment with lenvatinib plus pembrolizumab was 3.4 (0.3–32.2) months. The ORR (95% confidence interval [CI]) was 20% (13%–29%), with 20 participants achieving a partial response, and the median (range) duration of response was 3.7 (1.4+ to 27.6) months. Median (95% CI) progression-free survival was 3.0 (2.7–4.0) months and median (95% CI) overall survival was 8.6 (7.4–10.8) months. Responses were observed regardless of PD-L1 status. Treatment-related adverse events occurred in 93 participants (92%; grade

3–5, $n = 41$ [41%]). Two participants died due to treatment-related adverse events (intestinal perforation and pneumonitis).

Conclusions: The combination of lenvatinib plus pembrolizumab demonstrated antitumor activity in a small subpopulation of participants with recurrent GBM as second-line or later treatment. The safety profile was manageable.

KEYWORDS
lenvatinib, pembrolizumab, phase 2, programmed cell death ligand 1, recurrent glioblastoma

INTRODUCTION

Glioblastoma (GBM) is an aggressive malignant central nervous system (CNS) tumor, accounting for approximately 15% of all CNS tumors and 48% of malignant CNS tumors.[1] Standard-of-care treatments for newly diagnosed GBM include surgical resection, when feasible, followed by radiotherapy with concurrent adjuvant systemic therapy, such as temozolomide[2] with or without tumor-treating fields.[2,3] Disease progression (PD) is usually rapid with radiotherapy plus temozolomide, with median overall survival (OS) of 14.6 months versus 12.1 months with radiotherapy alone.[4] Patients with GBM have low 5-year survival rates (7%–10%),[1,5] with poor survival outcomes following disease recurrence.[6,7] Because of high unmet need for effective treatments, guidelines recommend clinical trial enrollment for recurrent GBM.[2]

Tumor biopsies from patients with GBM have shown that 61% of patients have tumors with ≥1% programmed cell death ligand 1 (PD-L1)–positive cells, 5% of whom have tumors with ≥50% PD-L1–positive cells.[8] PD-L1–positive status is negatively correlated with OS outcomes in patients with GBM.[8] Prior phase 3 studies evaluating the anti–programmed cell death protein 1 (PD-1) antibody nivolumab as monotherapy in patients with first recurrence of GBM[6] and with radiotherapy in newly diagnosed GBM[9,10] have not demonstrated improvement over current standard-of-care therapies,[6,9,10] however, indicated potential antitumor activity. For example, median OS was comparable for nivolumab monotherapy versus bevacizumab monotherapy (9.8 vs 10.0 months, respectively) in recurrent GBM.[6] The anti–PD-1 inhibitor pembrolizumab showed promising antitumor activity in PD-L1–positive recurrent GBM in the phase 1b KEYNOTE-028 study, with two of 26 participants (8%) having a partial response (PR), one with a response duration of 22.8 months.[11]

Because of the lack of tumor-infiltrating lymphocytes (TILs), GBM is classified as a "cold" tumor, presenting challenges for immune checkpoint inhibitor monotherapy efficacy.[12] Strategies that increase the amount of TILs and normalize the vasculature have been investigated to support immunotherapy.[12] The anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab has shown efficacy as monotherapy in recurrent GBM.[2,13,14] Bevacizumab has also been investigated in combination with various systemic therapies, including temozolomide, lomustine, and irinotecan, in newly diagnosed GBM or recurrent GBM with mixed results.[7,13,15,16] Additionally, studies across several tumor types suggest that combining an anti–PD-(L)1 antibody with an agent targeting the VEGF pathway may improve antitumor activity.[17] In a phase 2 study in recurrent GBM, pembrolizumab showed modest efficacy as monotherapy (OS, 10.3 months [$n = 30$]) or in combination with bevacizumab (OS, 8.8 months [$n = 50$]).[18]

The small-molecule multiple receptor tyrosine kinase inhibitor lenvatinib inhibits VEGF receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, KIT, and RET.[19] Lenvatinib has shown promise in animal models of advanced GBM[20] and modest antitumor activity as monotherapy in patients with recurrent GBM.[21] Combining pembrolizumab plus lenvatinib may lead to synergistic immunomodulatory effects, enhancing antitumor activity.[22] Combination lenvatinib and anti–PD-1 therapy significantly suppressed tumor growth beyond that seen with either treatment alone in a preclinical model,[23] indicating potential for this combination to improve outcomes in cancers such as GBM.

The multicohort, multicenter, open-label, phase 2 LEAP-005 (ClinicalTrials.gov, NCT03797326) study evaluated antitumor activity and safety of lenvatinib plus pembrolizumab in previously treated selected solid tumors. We report findings from the recurrent GBM cohort (cohort E).

MATERIAL AND METHODS

Study design and participants

The LEAP-005 study was a phase 2, multicenter, open-label study including multiple tumor type-specific cohorts. Adults with histologically confirmed World Health Organization (WHO) grade IV GBM (per the 2016 classification criteria[24]) with treatment failure on standard first-line systemic therapy, which included at least standard dose CNS radiotherapy with/without concurrent and/or sequential temozolomide were eligible for the GBM cohort (cohort E). Participants were required to have a period of ≥3 weeks from prior surgical resection, ≥1 week from stereotactic biopsy, ≥6 months from prior radiotherapy (≤6 months from prior radiotherapy permitted if new area of enhancement was outside 80% of the original radiation field), ≥6 weeks from prior antibody treatment, ≥2 weeks from Optune TTFields treatment, and ≥4 weeks from any investigational agents, cytotoxic therapies, daily administered chemotherapeutics, or any

other antitumor therapies. Additional requirements included measurable disease per Response Assessment in Neuro-Oncology (RANO; per local investigator/radiology, confirmed by blinded independent central review [BICR]), a PD-L1–evaluable tumor tissue sample, stable neurologically (no neurologic symptom progression or escalation of systemic steroids needed ≤2 weeks before enrollment) and clinically, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, adequate hematologic, renal, hepatic, and coagulation function, and adequately controlled blood pressure with or without antihypertensive medications.

Exclusion criteria included leptomeningeal dissemination, a recurrent tumor >6 cm in maximum diameter or primarily localized to the brainstem or spinal cord, presence of multifocal tumor or extracranial disease, or evidence of intratumoral or peritumoral hemorrhage on baseline magnetic resonance imaging (MRI) scan (excluding grade ≤1 and postoperative/stable on ≥2 consecutive scans). Additional exclusion criteria included radiographic evidence of major blood vessel invasion or infiltration, clinically significant hemoptysis or tumor bleeding ≤2 weeks before the first dose of study drug, significant cardiovascular impairment or history of arterial thromboembolism ≤12 months before starting study drug, preexisting grade ≥3 gastrointestinal or nongastrointestinal fistula, QTc prolongation >480 ms or left ventricular ejection fraction <55%, active autoimmune disease that required systemic treatment ≤2 years before study entry, diagnosis of immunodeficiency or immunosuppressive therapy ≤7 days before the first dose of study drug, prior or current noninfectious pneumonitis requiring steroids, active infection requiring systemic therapy, or prior therapy with lenvatinib, an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent, or any agent directed to another stimulatory or coinhibitory T-cell receptor. Systemic steroid therapy was permitted if dexamethasone oral dose (or steroid equipotent dosing equivalent) was ≤2 mg daily and stable for ≤5 days before enrollment. Prior therapy with bevacizumab was not exclusionary.

This study was conducted in accordance with principles of Good Clinical Practice and approved by the appropriate institutional review boards and regulatory agencies. All participants provided written informed consent.

Study treatment

Participants received oral lenvatinib 20 mg per day plus intravenous pembrolizumab 200 mg every 3 weeks. Pembrolizumab treatment continued for up to 35 cycles or until PD per RANO, unacceptable toxicity, withdrawal of consent, or intercurrent illness that prevented further treatment. Treatment with lenvatinib could continue beyond 2 years in participants experiencing clinical benefit, at the discretion of the investigator in consultation with the sponsor. Participants who discontinued treatment due to adverse events (AEs) could discontinue one or both study drugs depending on which drug or drugs were deemed to be related to the AE per investigator assessment.

Assessments

Tumor PD-L1 status was assessed centrally in formalin-fixed, paraffin-embedded tumor tissue samples or newly obtained biopsies from blocks or slides collected at screening, using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, California). PD-L1 combined positive score (CPS) was calculated as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. CPS raw scores were determined prospectively based on evaluation of samples at the testing laboratory, and PD-L1 status of CPS ≥1 versus <1 was applied retrospectively based on these raw scores.[25] Isocitrate dehydrogenase (*IDH*) mutation status and tumor O^6-methylguanine DNA methyltransferase (*MGMT*) methylation status were not prospectively assessed in this multicohort study; however, where available, results were reported per local testing but were not centrally verified.

CNS tumor imaging was performed at baseline to determine eligibility using contrast-enhanced MRI to determine tumor size for five or fewer target lesions assessed via BICR per RANO. Imaging was performed at baseline, 6 weeks from treatment initiation, then every 6 weeks until week 18 and every 9 weeks thereafter unless additional scans were clinically indicated; from weeks 54 to 102, participants who remained on treatment had tumor imaging performed every 12 weeks, and after week 102, imaging was performed every 24 weeks unless clinically indicated.

Participants were monitored at all study visits and for 30 days after the last dose of study drug for AEs (90 days for serious AEs). AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

End points

Dual primary end points were objective response rate (ORR; proportion of participants who had the best overall response of either complete response [CR] or PR) per RANO by BICR and safety (treatment-emergent AEs, serious AEs, and discontinuations due to AEs). Key secondary end points included disease control rate (DCR; best overall response of CR, PR, or stable disease per RANO), duration of response (DOR; time from first documented evidence of CR or PR until the first documented sign of PD or death in the subset of participants with a CR or PR), progression-free survival (PFS; time from treatment initiation to first documented PD per RANO or death), and OS (time from treatment initiation to death).

Statistical analysis

The protocol specified an initial enrollment of 30 participants with recurrent GBM, with potential cohort expansion of ≤100 participants. Efficacy and safety analyses included all participants who received one or more doses of lenvatinib plus pembrolizumab. ORR

and DCR were estimated using point estimates and 95% exact Clopper-Pearson CIs. The Kaplan–Meier method was used for analyses of DOR, PFS, and OS. Prespecified exploratory analyses were performed in subgroups defined by PD-L1 status. Retrospective analyses were performed in subgroups defined by *IDH* mutation status and *MGMT* methylation status using historical local testing results. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Participants and treatment

In total, 101 participants with recurrent GBM were enrolled and treated in cohort E at 29 sites between March 8, 2019, and September 3, 2021. Participants had a median (range) age of 56 (19–77) years, 64 (63%) were male, 63 (62%) had an ECOG performance status of 1, and 57 (56%) had tumors with PD-L1 CPS <1 (Table 1). The median (range) time from first dose to data cutoff (February 6, 2023) was 23.7 (16.4–46.6) months. Among participants for whom local testing results for *MGMT* methylation (n = 56) and/or *IDH* status (n = 73) were available, 22 of 56 participants (39%) had methylated *MGMT*, 12 of 73 participants (16%) had *IDH1* mutations, and two of 73 participants (3%) had *IDH2* mutations. At data cutoff, treatment was ongoing for four participants (4%) and 97 (96%) had discontinued study treatment; 85 (84%) had discontinued because of PD, eight (8%) due to AEs, three (3%) due to participant withdrawal, and one (1%) due to physician withdrawal.

Antitumor activity

Among all 101 participants in the cohort, the ORR (95% CI) was 20% (13%–29%) with 20 participants achieving a PR. ORR (95% CI) was 24% (12%–40%) in the 41 participants with PD-L1 CPS ≥1 and 16% (8%–28%) in the 57 participants with PD-L1 CPS <1 (Table 2). DCR (95% CI) was 57% (47%–67%) in all participants, and 63% (47%–78%) and 54% (41%–68%) in the PD-L1 CPS ≥1 and PD-L1 CPS <1 groups, respectively. Among responders, median (range) time to response was 1.4 (1.1–4.2) months (Figure 1) and median (range) DOR was 3.7 (1.4+ to 27.6) months (Figure 3A). Of 94 participants with one or more postbaseline imaging assessment, 62 (66%) had a reduction in tumor size as the best percentage change from baseline in target lesions per BICR (Figure 2). Although several participants achieved a ≥50% reduction in target lesion size as best percentage change from baseline, not all achieved a PR per RANO criteria, potentially due to development of new lesions or subsequent assessments not meeting the threshold for PR per RANO. Median (range) time to response was 1.5 (1.2–4.2) months in participants with PD-L1 CPS ≥1 and 1.4 (1.1–4.0) months in participants with PD-L1 CPS <1, and median (range) DOR was 6.8 (2.5–27.6) months and 3.2 (1.4+ to 5.1) months, respectively (Figure 3B). Responses according to *IDH* mutation status and *MGMT* methylation status are summarized in Table 2.

At data cutoff, 76 participants (75%) had a PFS event. Median (95% CI) PFS was 3.0 (2.7–4.0) months, with PFS rates of 22% at 6

TABLE 1 Demographics and baseline disease characteristics.

	All participants, N = 101
Age, median (range), years	56 (19–77)
Male	64 (63)
Race	
White	72 (71)
Asian	17 (17)
American Indian or Alaska Native White	1 (1)
Native Hawaiian or other Pacific Islander	1 (1)
Missing	10 (10)
Ethnicity	
Not Hispanic or Latino	73 (72)
Hispanic or Latino	13 (13)
Not reported	15 (15)
Geographic region	
Non-US	98 (97)
US	3 (3)
ECOG performance status	
0	38 (38)
1	63 (62)
Sum of diameters of target lesions, median (range), mm^2	902 (110–4002)
No. of prior lines of systemic therapy	
1	94 (93)
2	7 (7)
Prior bevacizumab use	1 (1)
Concomitant steroid use at baseline	81 (80)
PD-L1 status	
CPS ≥1	41 (41)
CPS <1	57 (56)
Missing	3 (3)
IDH1 (n = 73)[a]	
Mutation detected	12 (16)
Mutation not detected	61 (84)
IDH2 (n = 73)[a]	
Mutation detected	2 (3)
Mutation not detected	71 (97)

TABLE 1 (Continued)

	All participants, N = 101
MGMT promoter (*n* = 56)[b]	
Methylated	22 (39)
Not methylated	34 (61)

Note: Unless specified otherwise, data are no. (%).

Abbreviations: CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; *IDH*, isocitrate dehydrogenase; *MGMT*, O^6-methylguanine DNA methyltransferase; PD-L1, programmed cell death ligand 1.

[a]Percentages are calculated based on the total number of participants for whom local *IDH1/IDH2* testing results were available (*n* = 73); these results were not centrally verified.

[b]Percentages are calculated based on the total number of participants for whom local *MGMT* promoter testing results were available (*n* = 56); these results were not centrally verified.

months and 2% at 12 months (Figure 3C). In participants with PD-L1 CPS ≥1 and with PD-L1 CPS <1, median (95% CI) PFS was 3.9 (1.9–4.4) months and 2.8 (2.6–4.0) months, respectively (Figure 3D). In participants with versus without *IDH* mutations, median (95% CI) PFS was 4.0 (1.1–not reached) versus 2.9 (2.0–4.1) months; and was 4.3 (2.8–5.3) versus 2.6 (1.5–3.2) months in participants with *MGMT* methylated versus nonmethylated status, respectively.

Eighty-eight participants (87%) had died at data cutoff. Median (95% CI) OS was 8.6 (7.4–10.8) months, with OS rates at 6 and 12 months of 72% and 33%, respectively (Figure 3E). In participants with PD-L1 CPS ≥1 and with PD-L1 CPS <1, median (95% CI) OS was 8.6 (6.8–12.6) months and 7.7 (6.4–10.6) months, respectively (Figure 3F). In participants with versus without *IDH* mutations, median (95% CI) OS was 12.6 (3.6–not reached) versus 8.1 (6.4–10.3) months and was 12.6 (7.5–14.3) versus 7.1 (4.1–9.2) months in participants with *MGMT* methylated versus nonmethylated status, respectively.

Safety

The median (range) duration of treatment was 2.7 (0.0–23.5) months for pembrolizumab and 3.4 (0.3–32.2) months for lenvatinib, median (range) number of cycles was five (1–35) for pembrolizumab, and median (range) number of lenvatinib doses was 99 (8–979). Overall, 93 participants (92%) experienced treatment-related AEs (TRAEs) of any grade (Table 3), most commonly hypertension (47%), hypothyroidism (27%), asthenia (22%), increased blood alanine aminotransferase (19%), diarrhea (17%), and fatigue (17%). Grade 3–5 TRAEs occurred in 41 participants (41%), including two (2%) who died due to intestinal perforation and pneumonitis (*n* = 1 each). The most common grade 3–5 TRAEs were hypertension (24%), increased alanine aminotransferase (8%), increased aspartate aminotransferase (3%), and proteinuria (3%). TRAEs led to treatment discontinuation in 10 participants (10%). Total exposure to study treatment (i.e., time between first dose date plus 1 day and the earlier of either last dose date plus 30 days or data cutoff date) among all 101 participants was 574.0 person-months. AE rates after adjusting for treatment exposure were 191.1 events/100 person-months of exposure for all-cause AEs and 22.8 events/100 person-months for AEs resulting in dose modification (i.e., dose reduction, interruption, or treatment discontinuation). Treatment exposure-adjusted rates were 94.1 events/100 person-months for TRAEs and 1.7 events/100 person-months for TRAEs leading to discontinuation.

Immune-mediated AEs and infusion reactions of any grade occurred in 38 participants (38%; grade 3–5, *n* = 5 [5%]), most commonly hypothyroidism (28%), hyperthyroidism (6%), and infusion reactions (3%). Clinically significant treatment-emergent AEs of any grade for lenvatinib occurred in 81 participants (80%; grade 3–5, *n* = 32 [32%]), most commonly hypertension (50%), hepatotoxicity (35%), hypothyroidism (28%), hemorrhage (14%), and proteinuria (12%).

DISCUSSION

Among the 101 participants with advanced GBM enrolled in the phase 2 LEAP-005 study, combination lenvatinib plus pembrolizumab demonstrated antitumor activity (ORR, 20%) with an expected safety profile as second- or later-line treatment. Responses were observed regardless of PD-L1 status, with modestly higher ORR in the PD-L1 CPS ≥1 versus PD-L1 CPS <1 group (ORR [95% CI]: 24% [12%–40%] vs. 16% [8%–28%]), although 95% CIs overlapped. Only 20 of 101 participants experienced a PR per RANO. Among 94 participants with one or more postbaseline imaging assessment, 66% had a reduction in target lesion size relative to baseline. Additionally, although the median DOR was 3.7 months, the range of 1.4+ to 27.6 months indicates that some participants experienced a sustained DOR, the longest being maintained for >2 years.

These results are in line with previous studies evaluating pembrolizumab in patients with GBM. In the phase 1b KEYNOTE-028 study GBM cohort, pembrolizumab monotherapy was evaluated in participants with recurrent PD-L1–positive GBM for whom prior standard therapy had failed or no standard therapy existed, and demonstrated an ORR per Response Evaluation Criteria in Solid Tumors version 1.1 by investigator of 8%, including two PRs and no CRs.[11] In KEYNOTE-028, median OS was 13.1 months,[11] whereas in the present study, median OS was 8.6 months with lenvatinib plus pembrolizumab. Median PFS with pembrolizumab monotherapy was 2.8 months[11] in KEYNOTE-028 compared with 3.0 months among all participants treated with lenvatinib plus pembrolizumab in the present study, and 6-month PFS rates were 38% with pembrolizumab[11] versus 22% with lenvatinib plus pembrolizumab. In addition to the overall higher ORR and median PFS for combination therapy in the present study, ORR and median PFS were also higher when comparing the PD-L1 CPS ≥1 group in the present study with the PD-L1–positive GBM population in KEYNOTE-028, where ORR was 24% and median PFS was 3.9 months with lenvatinib plus pembrolizumab in the present study compared with an ORR of 8% and median PFS of 2.8 months with pembrolizumab monotherapy in KEYNOTE-028.[11]

TABLE 2 Antitumor activity per RANO by central radiology assessment.

	All participants, $N = 101$	PD-L1 CPS ≥1, $n = 41$	PD-L1 CPS <1, $n = 57$	*IDH* mutation detected, $n = 12$	*IDH* mutation not detected, $n = 61$	*MGMT* methylated, $n = 22$	*MGMT* not methylated, $n = 34$
ORR (95% CI), %	20 (13–29)	24 (12–40)	16 (8–28)	8 (<1–39)	25 (15–37)	41 (21–64)	12 (3–28)
Best overall response, No. (%)							
CR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PR	20 (20)	10 (24)	9 (16)	1 (8)	15 (25)	9 (41)	4 (12)
SD	38 (38)	16 (39)	22 (39)	6 (50)	23 (38)	8 (36)	13 (38)
PD	34 (34)	14 (34)	18 (32)	3 (25)	21 (34)	4 (18)	15 (44)
Not evaluable[a]	4 (4)	0	4 (7)	0 (0)	2 (3)	0 (0)	1 (3)
No assessment[b]	5 (5)	1 (2)	4 (7)	2 (17)	0 (0)	1 (5)	1 (3)
Disease control rate (CR + PR + SD), No. (%)	58 (57)	26 (63)	31 (54)	7 (58)	38 (62)	17 (77)	17 (50)
Median time to response (range), months	1.4 (1.1–4.2)	1.5 (1.2–4.2)	1.4 (1.1–4.0)	2.7 (2.7–2.7)	1.4 (1.1–4.2)	1.5 (1.2–4.2)	1.4 (1.3–1.4)
Median duration of response[c] (range), months	3.7 (1.4^{+}–27.6)	6.8 (2.5–27.6)	3.2 (1.4^{+}–5.1)	3.5 (3.5–3.5)	4.6 (2.5–27.6)	3.2 (1.4^{+}–27.6)	5.1 (2.8^{+}–5.1)

Abbreviations: CI, confidence interval; CPS, combined positive score; CR, complete response; *IDH*, isocitrate dehydrogenase; *MGMT*, O^6-methylguanine DNA methyltransferase; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease.

[a]"Not evaluable" includes participants with postbaseline imaging and the best overall response was determined to be not evaluable per RANO.

[b]"No assessment" includes one participant who had no postbaseline imaging.

[c]Estimated by Kaplan–Meier method for censored data.

[+]There was no PD by the time of the last disease assessment.

Although this study demonstrated modest antitumor activity, combination lenvatinib plus pembrolizumab did not appear to provide better outcomes than the current standard-of-care therapy. The phase 3 CheckMate-143 study investigating nivolumab or bevacizumab monotherapy in recurrent GBM following first recurrence found median OS of 9.8 and 10.0 months, ORR of 8% and 23%, and median PFS of 1.5 and 3.5 months, respectively.[6] Comparably, the median OS of 8.6 months, ORR of 20%, and median PFS of 3.0 months observed in our study indicate that combination therapy may improve outcomes in patients with recurrent GBM who have rapid PD and limited treatment options. The median DOR of 3.7 months may suggest transient anti-angiogenic effects which have been reported for anti-VEGF therapy.[26,27] Identification of biomarkers associated with DOR would be valuable to investigate. It is important to note the challenges of cross-trial comparisons when comparing outcomes between studies, particularly with respect to differences in baseline characteristics (such as disease stage) that may influence outcomes.

In 2021, 2 years after enrollment for this study began, WHO updated their GBM classification guidelines to no longer include patients who have tumors with *IDH* mutations.[28] This study was designed before these updates, explaining why so few participants were tested for *IDH* mutational status, which is now an important consideration for diagnosis of GBM. In our study, among 73 participants with known *IDH* mutational status, ORR was numerically higher

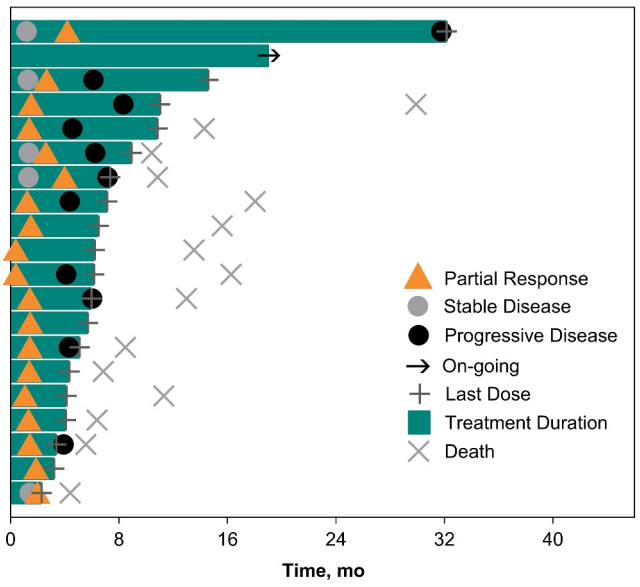

FIGURE 1 Time on study treatment and response evaluation per RANO by central radiology assessment among participants with a confirmed objective response (i.e., confirmed CR or PR). One participant with confirmed best overall response of partial response is shown without symbol indicating partial response (second bar from top) because response assessment time point was missing as of data cutoff for this analysis. CR, complete response; PR, partial response; RANO, Response Assessment in Neuro-Oncology.

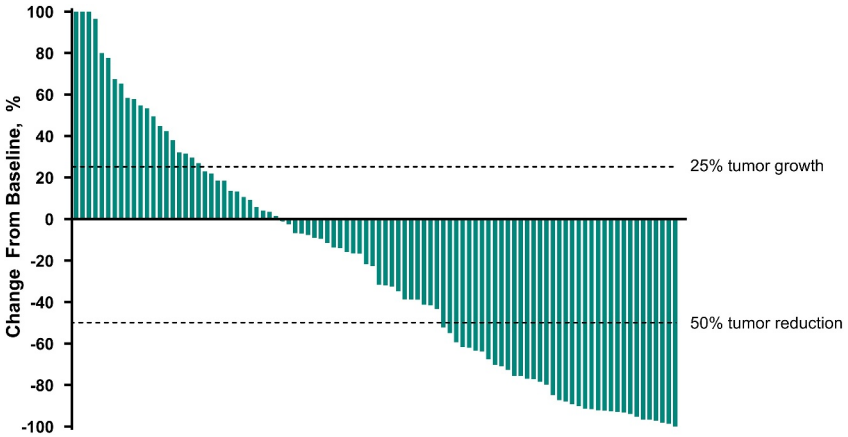

FIGURE 2 Best percentage change from baseline in target lesion size per RANO by central radiology assessment for target lesions in participants with GBM with one or more postbaseline imaging assessments (n = 94). Participants with percentage changes from baseline >100% (n = 3) are presented as 100%. GBM, glioblastoma; RANO, Response Assessment in Neuro-Oncology.

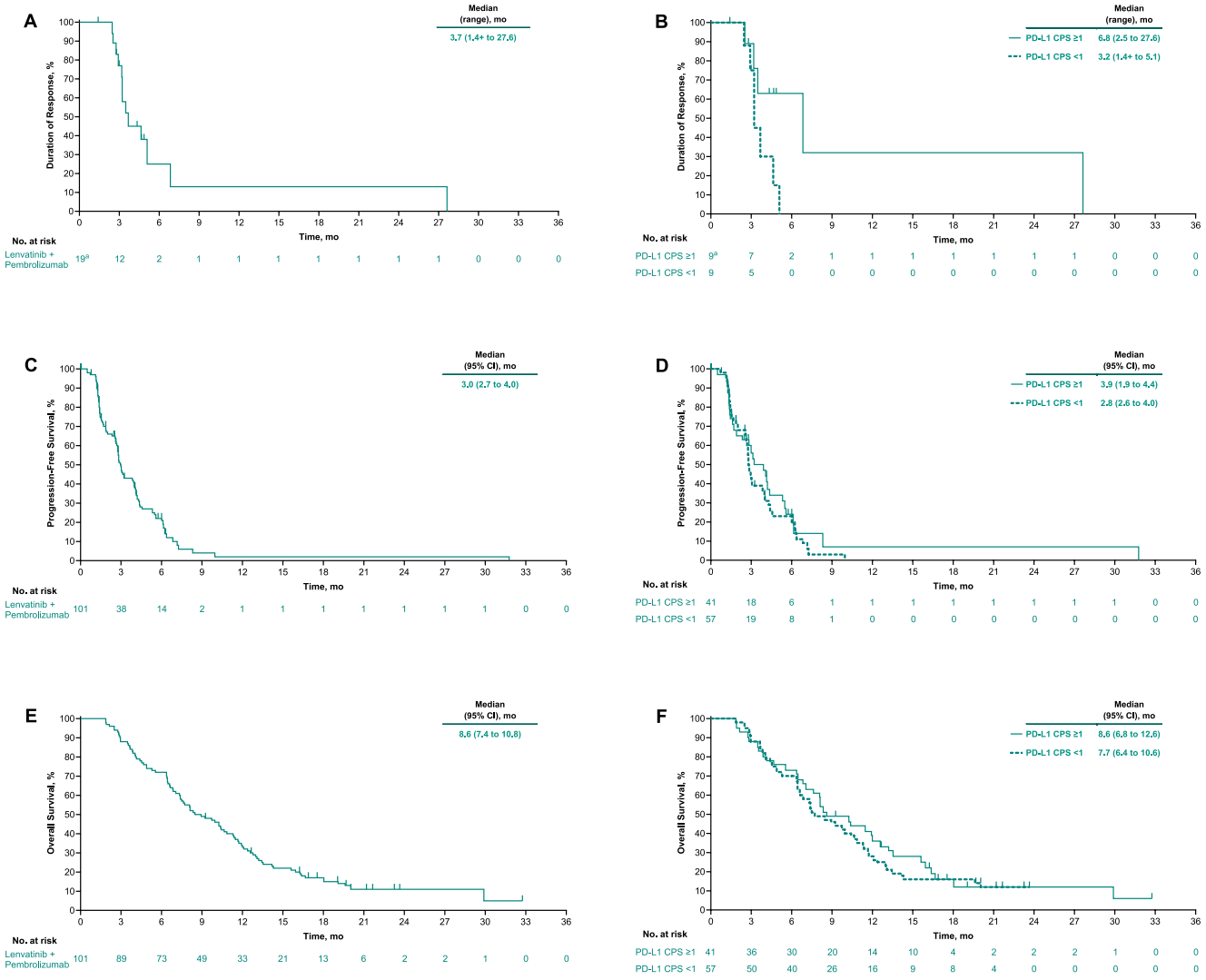

FIGURE 3 Response duration per RANO by central radiology assessment for target lesions in participants with GBM (A) among all participants and (B) by PD-L1 status. Progression-free survival per RANO by central radiology assessment for target lesions in participants with GBM (C) among all participants and (D) by PD-L1 status. Overall survival in participants with GBM in the lenvatinib plus pembrolizumab group (E) among all participants and (F) by PD-L1 status. [a]One participant with a confirmed best overall response of partial response was excluded from analysis due to missing data for response assessment time point as of data cutoff for this analysis. CPS, combined positive score; GBM, glioblastoma; PD-L1, programmed cell death ligand 1; RANO, Response Assessment in Neuro-Oncology.

TABLE 3 AEs among all participants treated.

	All participants, $N = 101$	
Participants with any treatment-related[a] AE	93 (92)	
Grade 3	36 (36)	
Grade 4	3 (3)	
Grade 5	2 (2)	
Serious	14 (14)	
Led to discontinuation of treatment	10 (10)	
Resulted in death[b]	2 (2)	
	Any grade	**Grade ≥3**
Treatment-related AEs occurring at any grade in >5% of participants		
Hypertension	47 (47)	24 (24)
Hypothyroidism	27 (27)	1 (1)
Asthenia	22 (22)	0
Increased ALT	19 (19)	8 (8)
Diarrhea	17 (17)	0
Fatigue	17 (17)	1 (1)
Increased AST	15 (15)	3 (3)
Nausea	13 (13)	0
Decreased appetite	12 (12)	0
Proteinuria	12 (12)	3 (3)
Palmar-plantar erythrodysesthesia syndrome	11 (11)	1 (1)
Rash	11 (11)	1 (1)
Mucosal inflammation	10 (10)	1 (1)
Dysphonia	9 (9)	0
Abdominal pain	8 (8)	0
Vomiting	8 (8)	0
Thrombocytopenia	7 (7)	0
Stomatitis	6 (6)	1 (1)
Increased TSH	6 (6)	0
Arthralgia	6 (6)	0
Hyperthyroidism	5 (5)	0
Increased lipase	5 (5)	0
Musculoskeletal pain	5 (5)	0
Myalgia	5 (5)	0
Participants with any immune-mediated AEs or infusion reactions[c]	38 (38)	5 (5)
Hypothyroidism	28 (28)	1 (1)
Hyperthyroidism	6 (6)	0
Infusion reactions	3 (3)	1 (1)
Pneumonitis	2 (2)	1 (1)
Hepatitis	2 (2)	0
Colitis	1 (1)	1 (1)
Severe skin reactions	1 (1)	1 (1)
Participants with any clinically significant treatment-emergent AEs for lenvatinib[d]	81 (80)	32 (32)
Hypertension	51 (50)	25 (25)
Hepatotoxicity	35 (35)	8 (8)
Hypothyroidism	28 (28)	1 (1)
Hemorrhage	14 (14)	1 (1)
Proteinuria	12 (12)	3 (3)
Palmar-plantar erythrodysesthesia syndrome	11 (11)	1 (1)
Hypocalcemia	4 (4)	0
Arterial thromboembolic events	3 (3)	1 (1)
Renal events	2 (2)	1 (1)
Gastrointestinal perforation	1 (1)	1 (1)

Note: All data are No. (%).

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TSH, thyroid-stimulating hormone.

[a]Determined by the investigator to be related to study drug.

[b]Two participants experienced grade 5 treatment-related AEs of intestinal perforation and pneumonitis ($n = 1$ each), which resulted in death.

[c]Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator.

[d]AEs are based on a list of terms specified by the sponsor and considered regardless of attribution by investigators.

among participants without *IDH* mutations (i.e., consistent with current classification of GBM), compared with those who had *IDH* mutations. However, this did not appear to translate to a survival benefit in participants without *IDH* mutations because median PFS (4.3 vs. 2.6 months with vs. without *IDH* mutations, respectively) and median OS (12.6 vs. 8.1 months, respectively) were numerically shorter in this group. Additionally, retrospective analysis according to *MGMT* methylation status, which was available for 56 participants from historical local testing, demonstrated a similar trend, with numerically higher ORR and numerically longer PFS and OS in participants with methylated *MGMT* compared with those who had non-methylated status and the overall cohort. Notably, *MGMT* methylation status has been shown to be a prognostic factor associated with improved overall survival in patients with GBM,[29,30] therefore, future clinical trials of novel therapies should prospectively assess the impact of *MGMT* status on treatment outcomes.

Although the GBM cohort of this study presents a robust sample size for a single-arm study ($N = 101$), the absence of a comparator arm warrants cautious interpretation of this analysis. Direct

comparisons of similar trials are confounded by differences in study designs and the patient populations enrolled; in particular, the present study included participants with *IDH* mutant tumors per local testing, which limits comparisons between this and other GBM studies. Although achieving an objective response is associated with prolonged survival among patients with GBM, importantly, ORR as an end point can be difficult to assess in GBM, as these tumors are highly vascular and anticancer therapies can alter tumor vascular permeability.[31,32] Thus, potential treatment effects may obscure interpretation of MRI scans increasing the possibility that changes in contrast enhancement are mistakenly assessed as PD ("pseudoprogression") or tumor response ("pseudoresponse"), depending on the potential vascular effects of a given treatment.[31–34] Notably, because bevacizumab has been associated with pseudoresponse,[31,32,34] and only one participant in the GBM cohort had a prior history of such treatment, there may have been a higher likelihood of observing a new pseudoresponse in our study. The severity and duration of disease can significantly impact the end points in GBM studies due to rapid PD, so direct comparisons between studies including participants experiencing a new diagnosis of GBM compared with recurrent GBM, as in the current study, should consider how these population differences can impact the study outcomes. Tumor-specific eligibility criteria that may impact efficacy outcomes, such as tumor size, are additional considerations when comparing GBM trials. For example, this phase 2 study excluded participants with tumors >6 cm, whereas the phase 3 CheckMate 143 trial, which specifically enrolled participants with GBM and was published after the present study was initiated, included participants with larger tumors[6]; thus comparisons between these trials should be made cautiously. Future studies should also consider assessing other factors that may impact treatment outcomes, including tumor mutational burden and microsatellite instability status, as these factors may provide further insight into this population.

The AEs observed in the GBM cohort of LEAP-005 were consistent with the known safety profiles of lenvatinib and pembrolizumab as monotherapy and in combination. Hypertension was the most commonly reported TRAE and the most common clinically significant AE. One participant died due to a TRAE of intestinal perforation, which is a known AE that has been associated with lenvatinib treatment. Overall, among this population of participants with recurrent GBM, lenvatinib plus pembrolizumab had a manageable safety profile that was generally consistent with other cohorts from the LEAP-005 study.

In summary, our findings suggest that lenvatinib plus pembrolizumab may have antitumor activity in a small subpopulation of participants with previously treated recurrent GBM. Additionally, the safety profile of this combination therapy approach was manageable. Further research is needed to define a potential role for such combinations in patients with GBM and to determine disease characteristics that could identify patients who are most likely to respond to such therapy.

AUTHOR CONTRIBUTIONS

Sun Young Rha: Data curation, formal analysis, investigation, and writing–review and editing. **Eduardo Castanon:** Formal analysis, investigation, writing–original draft, writing–review and editing, and resources. **Sanjeev Gill:** Data curation and writing–review and editing. **Helene Senellart:** Data curation and writing–review and editing. **Juanita Lopez:** Conceptualization, data curation, formal analysis, investigation, writing–original draft, writing–review and editing, and resources. **Iván Márquez-Rodas:** Data curation, investigation, writing–review and editing, and resources. **Iván Victoria:** Investigation and writing–review and editing. **Tae Min Kim:** Data curation, investigation, writing–review and editing, and resources. **Zarnie Lwin:** Data curation, formal analysis, investigation, writing–review and editing, and resources. **Michael C. Burger:** Data curation, writing–review and editing, and resources. **Matteo Simonelli:** Formal analysis, investigation, and writing–review and editing. **Philippe A. Cassier:** Data curation, investigation, writing–review and editing, and resources. **Andrew E. Hendifar:** Data curation, formal analysis, writing–review and editing, and resources. **Paolo A. Ascierto:** Investigation and writing–review and editing. **Corina Dutcus:** Conceptualization, formal analysis, investigation, and writing–review and editing. **Chinyere E. Okpara:** Conceptualization, investigation, and writing–review and editing. **Razi Ghori:** Conceptualization, formal analysis, investigation, and writing–review and editing. **Fan Jin:** Formal analysis, investigation, and writing–review and editing. **Roman Groisberg:** Data curation, formal analysis, investigation, writing–original draft, and writing–review and editing. **Luis Villanueva:** Investigation and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

Sun Young Rha reports research funding to institution for the present work from MSD; grant and/or contract funding to institution for clinical trials outside the present work from AstraZeneca, Ono Pharmaceutical, Eisai, Ipsen, MSD, Merck KGaA, Pfizer, BeiGene, Astellas Pharma, AMGEN, ALX Oncology, Zymeworks, Macrogenics, Seagen, Bold Therapeutics, MedPacto, ABLBIO, Daiichi Sankyo, Taiho Pharmaceutical, Leap Therapeutics, and Arcus Biosciences; consulting fees from LG Biochem and Indivumed; honoraria from MSD, Lilly, Daiichi-Sankyo, Eisai, Ipsen, Amgen, Astellas, and Sanofi; and fees for participation on a data safety monitoring board or advisory board for Amgen, Toray, and Arcus. Eduardo Castanon reports consulting fees from Glaxo Smith Kline, Bristol-Myers Squibb, Pfizer, and MSD; honoraria from Glaxo Smith Kline, Bristol-Myers Squibb, and Pfizer; and fees for participation on an advisory board for MSD. 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DATA AVAILABILITY STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting

legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: https://externaldatasharing-msd.com/) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD 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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