ORIGINAL ARTICLE

Pembrolizumab With or Without Lenvatinib for First-Line Metastatic NSCLC With Programmed Cell Death-Ligand 1 Tumor Proportion Score of at least 1% (LEAP-007): A Randomized, Double-Blind, Phase 3 Trial

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ABSTRACT

Introduction: Lenvatinib plus pembrolizumab was found to have antitumor activity and acceptable safety in previously treated metastatic NSCLC. We evaluated first-line lenvatinib plus pembrolizumab versus placebo plus pembrolizumab in metastatic NSCLC in the LEAP-007 study (NCT03829332/NCT04676412).

Methods: Patients with previously untreated stage IV NSCLC with programmed cell death-ligand 1 tumor proportion score of at least 1% without targetable *EGFR/ROS1/ALK* aberrations were randomized 1:1 to lenvatinib 20 mg or placebo once daily; all patients received pembrolizumab 200 mg every 3 weeks for up to 35 cycles. Primary end

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points were progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 and overall survival (OS). We report results from a prespecified nonbinding futility analysis of OS performed at the fourth independent data and safety monitoring committee review (futility bound: one-sided $p < 0.4960$).

Results: A total of 623 patients were randomized. At median follow-up of 15.9 months, median (95% confidence interval [CI]) OS was 14.1 (11.4–19.0) months in the lenvatinib plus pembrolizumab group versus 16.4 (12.6–20.6) months in the placebo plus pembrolizumab group (hazard ratio = 1.10 [95% CI: 0.87–1.39], $p = 0.79744$ [futility criterion met]). Median (95% CI) PFS was 6.6 (6.1–8.2) months versus 4.2 (4.1–6.2) months, respectively (hazard ratio = 0.78 [95% CI: 0.64–0.95]). Grade 3 to 5 treatment-related adverse events occurred in 57.9% of patients (179 of 309) versus 24.4% (76 of 312). Per data and safety monitoring committee recommendation, the study was unblinded and lenvatinib and placebo were discontinued.

Conclusions: Lenvatinib plus pembrolizumab did not have a favorable benefit–risk profile versus placebo plus pembrolizumab. Pembrolizumab monotherapy remains an approved treatment option in many regions for first-line metastatic NSCLC with programmed cell death-ligand 1 tumor proportion score of at least 1% without *EGFR/ALK* alterations.

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Keywords: Pembrolizumab; Lenvatinib; Non–small cell lung cancer; Programmed cell death-ligand 1

Introduction

The anti–programmed cell death protein 1 (anti–PD-1) monoclonal antibody pembrolizumab is an established treatment for previously untreated advanced or metastatic NSCLC without *EGFR* or *ALK* genomic tumor alterations, as monotherapy in patients with programmed cell death-ligand 1 (PD-L1) tumor proportion score (TPS) of at least 1%, and in combination with chemotherapy irrespective of PD-L1 TPS.[1–8] Despite the considerable progress made with the introduction of checkpoint inhibitor-based immunotherapies, including pembrolizumab, most patients with metastatic NSCLC will still die of the disease. Therefore, there is substantial unmet medical need for novel therapies that can potentiate the clinical benefit of immunotherapies, extend the benefit to a broader population of patients, and further improve treatment response and survival in patients with metastatic NSCLC.

There is compelling rationale for combining pembrolizumab with the multiple receptor tyrosine kinase inhibitor lenvatinib as a treatment approach for NSCLC. Lenvatinib is an established treatment as monotherapy for thyroid, hepatocellular, and thymic carcinomas, and when combined with pembrolizumab, for endometrial and renal cell carcinomas.[9–11] It has also been found to have antitumor activity and manageable safety when combined with chemotherapy or best supportive care in advanced/metastatic NSCLC, including in heavily pretreated disease.[12,13] Lenvatinib has antiangiogenic and antiproliferative effects and, through inhibition of vascular endothelial growth factor (VEGF) receptor and fibroblast growth factor receptor signaling, may reduce the number of intratumoral regulatory T cells and survival and migration of tumor-associated macrophages into tumors.[14] Lenvatinib may also reactivate interferon gamma-signaling pathways, leading to up-regulation of PD-L1 and thereby enhancing the combined antitumor activity of lenvatinib with anti–PD-1 antibodies.[15] In a preclinical model, the combination of lenvatinib and anti–PD-1 therapy more potently inhibited tumor growth than either treatment alone.[16] Preliminary clinical evidence in NSCLC also suggests that these complementary effects of lenvatinib and pembrolizumab on the tumor microenvironment could further improve tumor responses.[17] Among 21 patients with metastatic NSCLC (52% of whom had received at least two prior therapies, including PD-[L]1 and VEGF inhibitors) in the phase 1b/2 study 111/KEYNOTE-146 trial,[18] lenvatinib plus pembrolizumab had an objective response rate (ORR) of 33% and an acceptable safety profile.

Here, we report results from the phase 3, randomized LEAP-007 study, which evaluated lenvatinib plus pembrolizumab versus placebo plus pembrolizumab in patients with previously untreated metastatic NSCLC with PD-L1 TPS of at least 1%.

Materials and Methods

Patients

Patients aged 18 years or older were eligible for enrollment in this study (ClinicalTrials.gov, NCT03829332) if they had histologically or cytologically confirmed stage IV NSCLC without targetable *EGFR*, *ALK*, or *ROS1* genetic alterations; no prior systemic treatment for metastatic disease; measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[19]; PD-L1 TPS of at least 1%; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; life expectancy of at least 3 months; adequately controlled blood pressure with or without antihypertensive

medication (defined as blood pressure ≤150/90 mmHg with no change in antihypertensive medication ≤1 wk before randomization); and adequate organ function on the basis of laboratory assessments. Patients were ineligible if they had clinically important hemoptysis (defined as ≥0.5 teaspoon of bright red blood) or tumor bleeding within 2 weeks before study treatment; either known central nervous system metastases or carcinomatous meningitis or both, unless previously treated and radiologically stable (i.e., no evidence of progression for ≥4 wk per repeat imaging performed during screening), clinically stable, and with no steroid treatment required within 14 days before study treatment; active autoimmune disease that required systemic treatment in the previous 2 years; history of noninfectious pneumonitis that required steroids or current pneumonitis/interstitial lung disease; diagnosis of immunodeficiency or immunosuppressive therapy within 7 days before study treatment; history of a gastrointestinal condition/procedure that could affect absorption of oral lenvatinib; or clinically relevant cardiovascular impairment (e.g., congestive heart failure classified as greater than New York Heart Association class II, unstable angina, myocardial infarction, cerebrovascular accident, or cardiac arrhythmia associated with hemodynamic instability) within 12 months before study treatment. Additional exclusion criteria included prior anti−PD-1/anti−PD-L1/anti−PD-L2 therapy or any treatment directed at another stimulatory or co-inhibitory T-cell receptor, prior lenvatinib treatment as monotherapy or in combination with anti−PD-1 agents, or any radiotherapy within 14 days or lung radiotherapy of more than 30 Gy within 6 months before study treatment.

The study protocol also specified that patients were ineligible if there was radiographic evidence of invasion or infiltration of a major blood vessel. Despite this, fatal bleeding events occurred during the study in a few patients who were retrospectively found to have major blood vessel encasement at enrollment, and thus the protocol was amended to specify exclusion of encasement of a major blood vessel or intratumoral cavitation and to further clarify major blood vessels in the chest.

After enrollment in the global LEAP-007 study was closed, the protocol was amended to extend the enrollment period in the People's Republic of China to allow for sufficient exposure and follow-up to assess the efficacy and safety of the study treatments in Chinese patients. The China extension study was identical in design to the global study (Supplementary Appendix 1).

The study was conducted in accordance with local and/or national regulations and ethical requirements outlined in the Declaration of Helsinki. The study protocol and amendments were approved by an investigational review board/ethics committee at each study site. All patients provided written informed consent before participation. An external independent data and safety monitoring committee (DMC) reviewed safety data every 6 months and efficacy data at prespecified interim analyses.

Study Design and Treatment

In this multicenter, double-blind, phase 3 study, patients were randomized 1:1 to receive oral lenvatinib 20 mg or placebo administered once daily; all patients received intravenous pembrolizumab 200 mg administered once every 3 weeks for up to 35 cycles (treatment with lenvatinib or placebo could continue beyond 35 cycles). Randomization was stratified by geographic region (East Asia versus non-East Asia), ECOG performance status (0 versus 1), and PD-L1 TPS (1%−49% versus ≥50%). Treatment continued for the specified number of cycles or until disease progression (PD), unacceptable toxicity, intercurrent illness precluding further study treatment, investigator decision, or patient withdrawal of consent.

Assessments

Archival tumor tissue samples or newly obtained core or excisional biopsy samples of a tumor lesion not previously irradiated were centrally evaluated for PD-L1 expression during screening using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA). Tumor imaging was performed every 9 weeks from randomization through week 54, then every 12 weeks until PD, initiation of new anticancer therapy, or completion of 35 cycles of pembrolizumab. Response was assessed using RECIST version 1.1 by blinded independent central review (BICR). Per iRECIST,[20] clinically stable patients (i.e., no signs/symptoms of clinically important PD, no decline in ECOG performance status, and no requirement for intensified care) with PD per investigator review could continue treatment until PD was confirmed on the basis of repeat imaging performed 4 to 8 weeks after the initial assessment of PD.

Adverse events (AEs) were monitored through 30 days after the end of treatment (90 d for serious AEs) using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 to grade severity.

End Points

The study had two primary end points: overall survival (OS), defined as time from randomization to death because of any cause, and progression-free survival (PFS), defined as time from randomization to the first documented assessment of PD (per RECIST version 1.1

by BICR) or death from any cause, whichever occurred first. Secondary end points were ORR, defined as a confirmed complete response (CR) or partial response (PR) per RECIST version 1.1 by BICR, and safety. Duration of response, defined as time from earliest documented response to the first of either PD or death because of any cause, was an exploratory end point.

Statistical Analysis

Efficacy analyses were performed in all randomized patients according to assigned treatment (intention-to-treat population). Safety analyses were performed in all randomized patients who received at least one dose of the study treatment according to treatment received (as-treated population). OS and PFS were estimated using the nonparametric Kaplan-Meier method. For the OS analysis, patients without documented death were censored at the last known contact before the data cutoff date. For the PFS analysis, patients without documented PD or death were censored at the time of the last disease assessment before the data cutoff date or at the start of new anticancer therapy, whichever was earlier. Between-group treatment differences in OS and PFS were assessed using the stratified log-rank test; all p values are one sided. The magnitude of the treatment difference was calculated using a stratified Cox proportional hazard model with Efron's method of tie handling. The difference in ORR between treatment groups and corresponding 95% confidence interval (CI) were calculated using the stratified Miettinen and Nurminen method, with strata weighting by sample size. Randomization stratification factors were used for all stratified analyses.

Planned enrollment for the global study was 620 patients. This sample size was determined to provide 90% power to detect a treatment difference in OS, with a hazard ratio (HR) of 0.71 and one-sided alpha of 1.95% (based on 388 OS events), and at least 86.5% power to detect a treatment difference in PFS, with an HR of 0.7 and one-sided alpha of 0.55% (based on 416 PFS events). In March 2021, the protocol was amended to allow a sufficient duration of follow-up for the evaluation of efficacy, and the alpha initially assigned to the secondary end point of ORR (one-sided alpha = 0.001), which was to be formally tested only at the first interim analysis (after approximately 420 patients had $\geq$9 mo of follow-up), was reallocated to the primary end points of PFS and OS, with analysis planned after approximately 416 PFS events had occurred and the last patient randomized had approximately 8.8 months of follow-up. For the fourth DMC safety review, a prespecified nonbinding futility analysis was performed at the request of the DMC. OS was evaluated first using a p value futility boundary of 0.4960. If the p value was less than 0.4960, the futility criterion for OS was not met and PFS was evaluated using a futility boundary of HR equal to 1.0. If the PFS HR was less than 1, representing no PFS harm, then the futility criterion was not met. If the PFS HR was 1 or greater, then the OS HR was to be re-evaluated, with a futility boundary of OS HR equal to 0.9. If the OS HR was less than 0.9, then the futility criterion was not met. If the OS HR was 0.9 or greater, then the DMC would evaluate the totality of the data to make the recommendation for futility. All data reported here for the global study are based on the data cutoff date of May 19, 2021, which coincided with the fourth DMC safety review and was before the first protocol prespecified interim analysis.

Results

Patients and Treatment

Between April 9, 2019, and January 28, 2021, a total of 623 patients were randomized in the LEAP-007 global study to lenvatinib plus pembrolizumab (n = 309) or placebo plus pembrolizumab (n = 314). All patients in the lenvatinib plus pembrolizumab group and 312 patients in the placebo plus pembrolizumab group received at least one dose of treatment (Supplementary Fig. 1). Baseline demographics and disease characteristics were generally balanced between the treatment groups (Table 1); 137 of 309 patients (44.3%) in the lenvatinib plus pembrolizumab group and 139 of 314 (44.3%) in the placebo plus pembrolizumab group had a PD-L1 TPS of at least 50%; 115 (37.2%) and 108 (34.4%), respectively, had tumors with squamous histology.

Median (range) duration of follow-up (i.e., time from randomization to data cutoff) was 15.9 (3.7–25.4) months. The median (range) duration of treatment was 6.2 (0.07–23.4) months in the lenvatinib plus pembrolizumab group and 5.5 (0.13–24.4) months in the placebo plus pembrolizumab group. The median (range) number of cycles of pembrolizumab was 9 (1–34) and 8 (1–35), respectively. At the time of data cutoff, 106 patients (34.3%) in the lenvatinib plus pembrolizumab group and 98 (31.4%) in the placebo plus pembrolizumab group remained on the treatment (Supplementary Fig. 1). Furthermore, 44 (14.2%) and 88 patients (28.0%), respectively, received subsequent anticancer therapy (Table 2).

Efficacy

In the intention-to-treat population, 286 patients (45.9%) had died by the time of data cutoff. After a median follow-up of 15.9 months, the median (95% CI) OS was 14.1 (11.4–19.0) months in the lenvatinib plus pembrolizumab group and 16.4 (12.6–20.6) months in the placebo plus pembrolizumab group (HR = 1.10 [95%

Table 1. Baseline Demographic and Disease Characteristics of the Global Study Population

Characteristics	Lenvatinib + Pembrolizumab n = 309	Placebo + Pembrolizumab n = 314
Age, median (range), y	66 (34-85)	66 (37-87)
Age ≥65 y	168 (54.4)	176 (56.1)
Male	230 (74.4)	224 (71.3)
Geographic region		
East Asia	103 (33.3)	104 (33.1)
Not East Asia	206 (66.7)	210 (66.9)
ECOG performance status		
0	110 (35.6)	108 (34.4)
1	199 (64.4)	206 (65.6)
Tumor histology		
Squamous	115 (37.2)	108 (34.4)
Nonsquamous	194 (62.8)	206 (65.6)
Smoking history		
Current or former	255 (82.5)	247 (78.7)
Never	54 (17.5)	67 (21.3)
PD-L1 TPS		
≥50%	137 (44.3)	139 (44.3)
1%–49%	172 (55.7)	175 (55.7)
Brain metastases	19 (6.1)	42 (13.4)
Liver metastases	43 (13.9)	54 (17.2)
Prior thoracic radiation	14 (4.5)	13 (4.1)
Prior adjuvant therapy	13 (4.2)	11 (3.5)
Prior neoadjuvant therapy	5 (1.6)	3 (1.0)

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

Table 2. Summary of Subsequent Anticancer Therapy in Each Treatment Group

Therapy[a]	Lenvatinib + Pembrolizumab n = 309	Placebo + Pembrolizumab n = 314
Any anticancer therapy	44 (14.2)	88 (28.0)
Carboplatin	28 (9.1)	69 (22.0)
Pemetrexed disodium	20 (6.5)	50 (15.9)
Paclitaxel	10 (3.2)	17 (5.4)
Cisplatin	7 (2.3)	15 (4.8)
Docetaxel	7 (2.3)	8 (2.5)
Gemcitabine	5 (1.6)	14 (4.5)
Pembrolizumab	5 (1.6)	11 (3.5)
Bevacizumab	3 (1.0)	8 (2.5)
Atezolizumab	2 (0.6)	0
Tegafur	2 (0.6)	0
Cyclophosphamide	1 (0.3)	0
Epirubicin	1 (0.3)	0
Etoposide	1 (0.3)	1 (0.3)
Nivolumab	1 (0.3)	2 (0.6)
Paclitaxel albumin	1 (0.3)	3 (1.0)
Ramucirumab	1 (0.3)	1 (0.3)
Trastuzumab	1 (0.3)	0
Vinorelbine tartrate	1 (0.3)	6 (1.9)
Ipilimumab	0	1 (0.3)
MK-5890	0	2 (0.6)
Monoclonal antibodies	0	1 (0.3)
Tislelizumab	0	1 (0.3)

Note: All data are n (%).
[a]Patients are counted a single time for each applicable specific subsequent therapy. A patient with multiple subsequent therapies within a medication category is counted a single time for that category.

CI: 0.87−1.39], $p = 0.79744$; Fig. 1*A*). The prespecified nonbinding futility criterion was met as the futility p value boundary for OS was 0.4960. The 6-month OS rate (95% CI) was 73.9% (68.6%−78.5%) for lenvatinib plus pembrolizumab and 75.6% (70.3%−80.0%) for placebo plus pembrolizumab. The OS HRs were generally similar across all subgroups analyzed, although some point estimates suggested worse outcomes with lenvatinib plus pembrolizumab versus placebo plus pembrolizumab (e.g., in the East Asia and squamous NSCLC subgroups; Fig. 1*B*).

In the intention-to-treat population, 419 patients (67.3%) experienced a PFS event. After median follow-up of 15.9 months, the median (95% CI) PFS was 6.6 (6.1−8.2) months in the lenvatinib plus pembrolizumab group and 4.2 (4.1−6.2) months in the placebo plus pembrolizumab group (HR = 0.78 [95% CI: 0.64−0.95], nominal $p = 0.00624$; Fig. 2*A*). The 6-month PFS rate (95% CI) was 57.2% (51.3%−62.7%) for lenvatinib plus pembrolizumab and 47.0% (41.2%−52.6%) for placebo plus pembrolizumab. The PFS HRs were similar across all subgroups analyzed (Fig. 2*B*).

Confirmed objective response was achieved in 125 of 309 patients (40.5% [95% CI: 34.9%−46.2%]; seven CRs, 118 PRs) in the lenvatinib plus pembrolizumab group and 87 of 314 (27.7% [95% CI: 22.8%−33.0%]; six CRs, 81 PRs) in the placebo plus pembrolizumab group, with an estimated between-group difference of 12.8% (95% CI: 5.4%−20.1%; nominal $p = 0.00037$). Median (range) duration of response was 13.0 (1.5 to 20.1+) months and 16.1 (0.0+ to 18.7+; + indicates no PD at last disease assessment) months, respectively. The best overall response was SD for 115 patients (37.2%) and PD for 32 (10.4%) in the lenvatinib plus pembrolizumab group versus 113 patients (36.0%) and 87 (27.7%) in the placebo plus pembrolizumab group.

Safety

In the as-treated population, treatment-related AEs occurred in 282 patients (91.3%) in the lenvatinib plus pembrolizumab group and 219 (70.2%) in the placebo plus pembrolizumab group (Table 3). Hypertension and

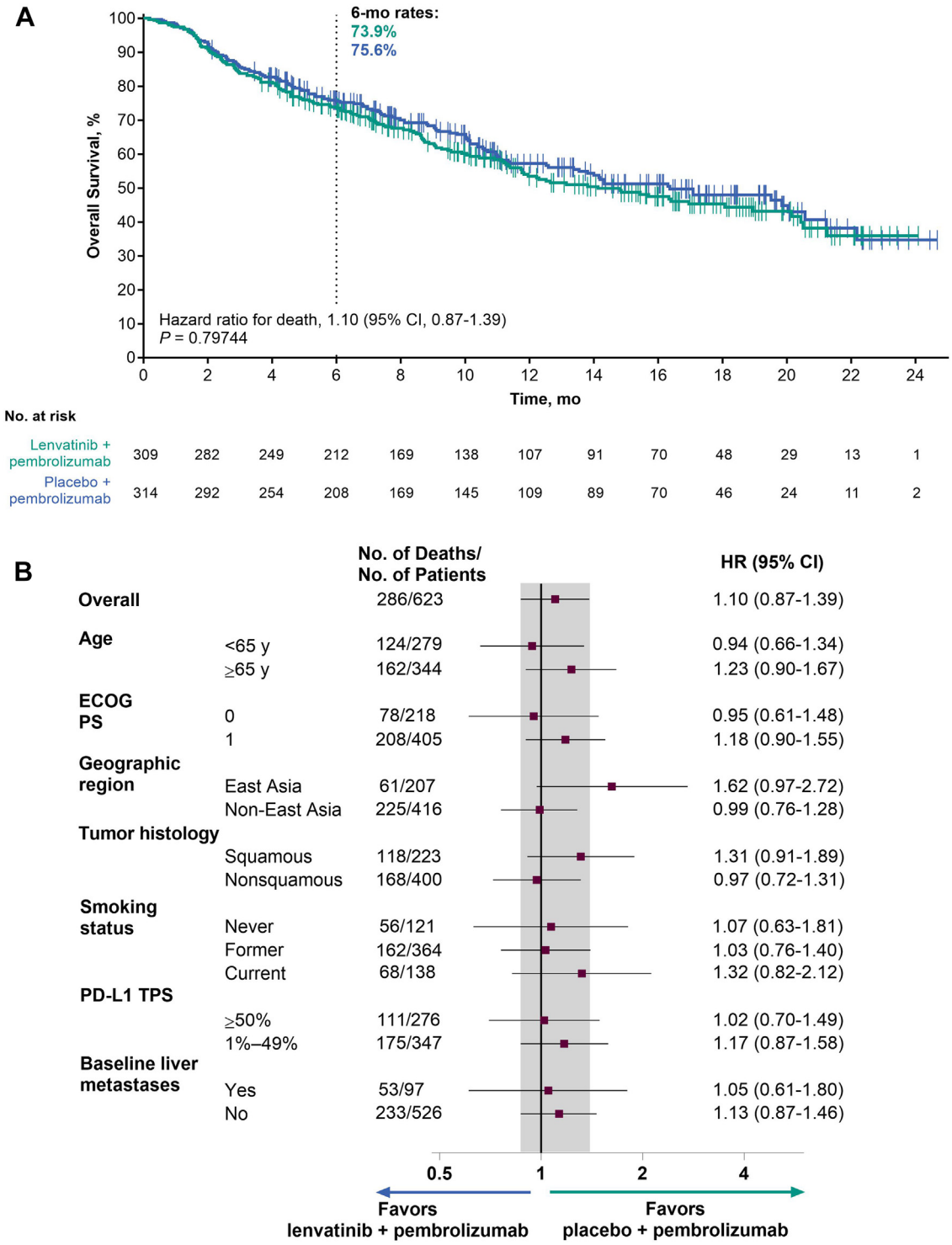

Figure 1. Kaplan-Meier estimates of overall survival in the intention-to-treat population of the global study (*A*) overall and (*B*) in subgroups defined by select baseline characteristics. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

hypothyroidism were the most common treatment-related AEs in both treatment groups. Treatment-related AEs of grade 3 or greater occurred in 179 (57.9%) and 76 patients (24.4%) in each group, respectively. Treatment-related AEs led to death in 16 (5.2%) and six patients (1.9%), respectively (Supplementary Table 1). The most common fatal treatment-related AEs in the lenvatinib plus pembrolizumab group were hemoptysis (n = 4; 1.3%), pneumonitis (n = 2; 0.6%), and pulmonary hemorrhage

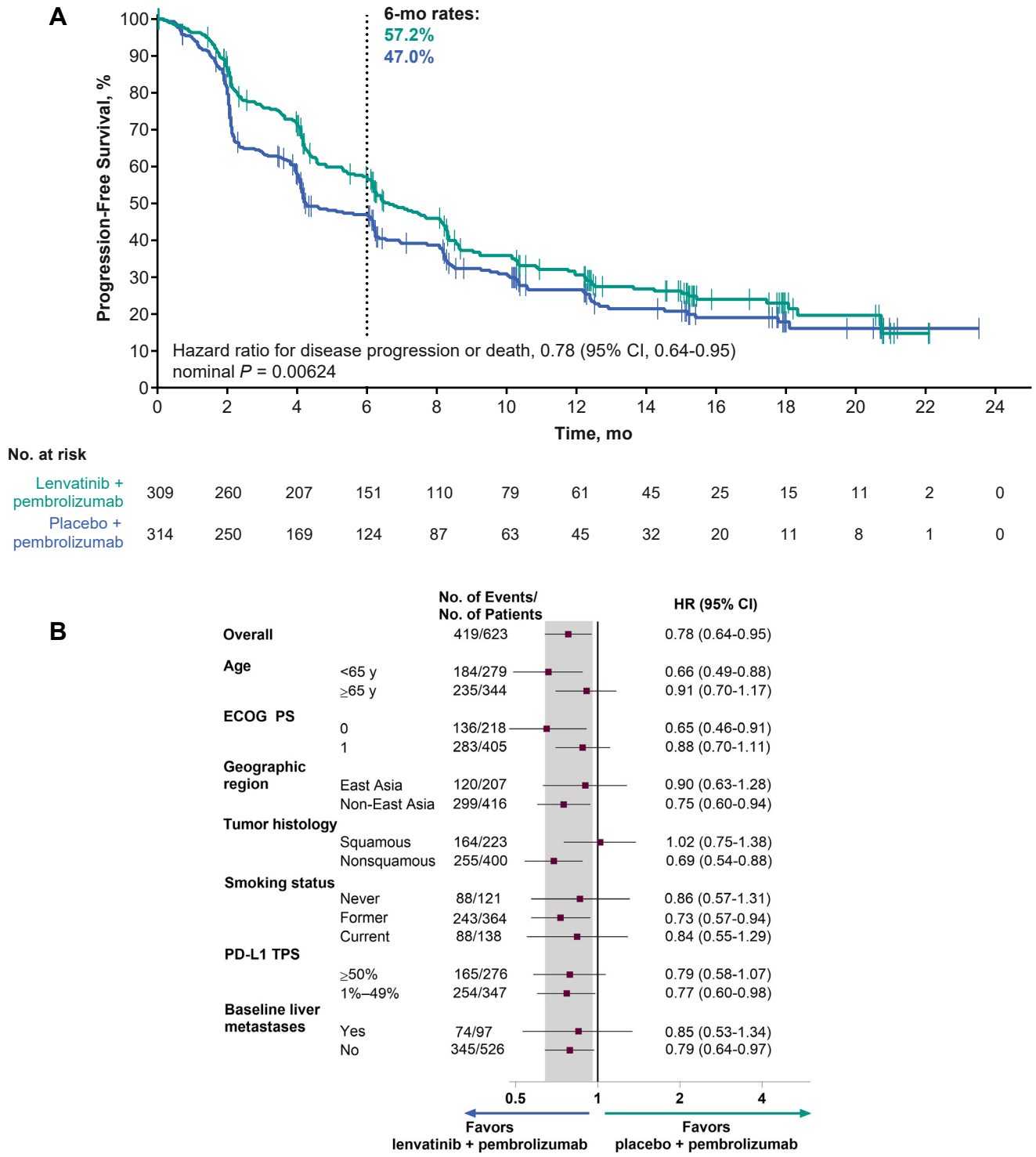

Figure 2. Kaplan-Meier estimates of progression-free survival in the intention-to-treat population of the global study (*A*) overall and (*B*) in subgroups defined by select baseline characteristics. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

(n = 2; 0.6%). Among seven patients with grade 5 pulmonary bleeding events, five had squamous tumor histology, one had adenosquamous tumor histology, and one had adenocarcinoma. Of note, five of the seven patients with grade 5 pulmonary bleeding events were found on retrospective review to have baseline major blood vessel encasement at enrollment. Treatment-related AEs that led to death in the placebo plus

Table 3. Incidence of Treatment-Related Adverse Events in the As-Treated Population

Adverse Event	Lenvatinib + Pembrolizumab n = 309	Placebo + Pembrolizumab n = 312
Any treatment-related adverse event	282 (91.3)	219 (70.2)
Grades 3–5	179 (57.9)	76 (24.4)
Led to death	16 (5.2)	6 (1.9)
Led to treatment interruption		
Lenvatinib or placebo	143 (46.3)	54 (17.3)
Pembrolizumab	123 (39.8)	53 (17.0)
Both drugs	70 (22.7)	35 (11.2)
Led to discontinuation of any treatment	90 (29.1)	35 (11.2)
Lenvatinib or placebo	85 (27.5)	28 (9.0)
Pembrolizumab	45 (14.6)	25 (8.0)
Both drugs	35 (11.3)	17 (5.4)

Treatment-related adverse events with incidence ≥10% in either treatment group	Any Grade	Grades 3–5	Any Grade	Grades 3–5
Hypertension	112 (36.2)	53 (17.2)	33 (10.6)	8 (2.6)
Hypothyroidism	112 (36.2)	0	30 (9.6)	0
Proteinuria	89 (28.8)	19 (6.1)	24 (7.7)	3 (1.0)
Diarrhea	86 (27.8)	10 (3.2)	27 (8.7)	2 (0.6)
Decreased appetite	54 (17.5)	6 (1.9)	25 (8.0)	1 (0.3)
Nausea	43 (13.9)	4 (1.3)	29 (9.3)	0
Increased ALT	43 (13.9)	8 (2.6)	20 (6.4)	7 (2.2)
Increased AST	43 (13.9)	6 (1.9)	20 (6.4)	5 (1.6)
Stomatitis	42 (13.6)	6 (1.9)	7 (2.2)	0
Fatigue	40 (12.9)	10 (3.2)	23 (7.4)	4 (1.3)
Asthenia	37 (12.0)	6 (1.9)	15 (4.8)	4 (1.3)
Rash	32 (10.4)	1 (0.3)	22 (7.1)	1 (0.3)
PPES	33 (10.7)	6 (1.9)	3 (1.0)	0
Decreased weight	32 (10.4)	6 (1.9)	10 (3.2)	1 (0.3)

Note: All data are n (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPES, palmar-plantar erythrodysesthesia syndrome.

pembrolizumab group included pneumonitis, cerebrovascular accident, death, prolonged electrocardiogram QT, immune-mediated lung disease, and respiratory distress in one patient each.

Treatment-related AEs led to interruption of both study treatments in 70 patients (22.7%) in the lenvatinib plus pembrolizumab group and 35 (11.2%) in the placebo plus pembrolizumab group, led to interruption of only lenvatinib or placebo in 143 (46.3%) and 54 patients (17.3%), respectively, and led to interruption of only pembrolizumab in 123 (39.8%) and 53 patients (17.0%) (Table 3). Treatment-related AEs led to discontinuation of any study treatment in 90 patients (29.1%) in the lenvatinib plus pembrolizumab group and 35 (11.2%) in the placebo plus pembrolizumab group, including 35 patients (11.3%) in the lenvatinib plus pembrolizumab group and 17 (5.4%) in the placebo plus pembrolizumab group who discontinued both study treatments.

AEs of special interest for pembrolizumab occurred in 164 patients (53.1%) in the lenvatinib plus pembrolizumab group versus 77 (24.7%) in the placebo plus pembrolizumab group and were grades 3 to 5 in severity in 34 (11.0%) versus 16 patients (5.1%), respectively (Table 4). The most frequently occurring AEs of special interest for pembrolizumab in the lenvatinib plus pembrolizumab versus placebo plus pembrolizumab groups were hypothyroidism, which occurred in 128 (41.4%) versus 31 patients (9.9%); hyperthyroidism, in 30 (9.7%) versus 21 (6.7%); and pneumonitis, in 24 (7.8%) versus 21 (6.7%). Clinically relevant AEs for lenvatinib occurred in 257 patients (83.2%) in the lenvatinib plus pembrolizumab group versus 165 (52.9%) in the placebo plus pembrolizumab group and were grades 3 to 5 in severity in 125 (40.5%) versus 46 patients (14.7%) (Table 4). The most frequently occurring AEs of clinical significance for lenvatinib in the lenvatinib plus pembrolizumab versus placebo plus pembrolizumab groups were hypothyroidism, which occurred in 128 (41.4%) versus 31 patients (9.9%); hypertension, in 126 (40.8%) versus 46 (14.7%); and proteinuria, in 99 (32.0%) versus 34 (10.9%).

LEAP-007 China Study

In total, 107 Chinese patients were randomized to lenvatinib plus pembrolizumab (n = 49) or placebo

Table 4. Incidence of Adverse Events of Special Interest for Pembrolizumab and Clinically Relevant Adverse Events for Lenvatinib in the As-Treated Population

	Lenvatinib + Pembrolizumab n = 309		Placebo + Pembrolizumab n = 312	
Adverse Event	Any Grade	Grades 3–5	Any Grade	Grades 3–5
Adverse events of special interest for pembrolizumab[a]	164 (53.1)	34 (11.0)	77 (24.7)	16 (5.1)
Hypothyroidism	128 (41.4)	0	31 (9.9)	0
Hyperthyroidism	30 (9.7)	2 (0.6)	21 (6.7)	0
Pneumonitis	24 (7.8)	12 (3.9)	21 (6.7)	8 (2.6)
Thyroiditis	13 (4.2)	1 (0.3)	2 (0.6)	0
Severe skin reactions	7 (2.3)	4 (1.3)	2 (0.6)	2 (0.6)
Adrenal insufficiency	6 (1.9)	2 (0.6)	4 (1.3)	2 (0.6)
Colitis	5 (1.6)	3 (1.0)	3 (1.0)	1 (0.3)
Hepatitis	5 (1.6)	4 (1.3)	4 (1.3)	3 (1.0)
Pancreatitis	5 (1.6)	3 (1.0)	0	0
Nephritis	4 (1.3)	1 (0.3)	1 (0.3)	1 (0.3)
Hypophysitis	3 (1.0)	1 (0.3)	1 (0.3)	0
Infusion reactions	2 (0.6)	0	3 (1.0)	0
Myocarditis	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)
Vasculitis	2 (0.6)	2 (0.6)	0	0
Encephalitis	1 (0.3)	0	0	0
Uveitis	1 (0.3)	0	0	0
Myositis	0	0	1 (0.3)	0
Clinically relevant adverse events for lenvatinib[a]	257 (83.2)	125 (40.5)	165 (52.9)	46 (14.7)
Hypothyroidism	128 (41.4)	0	31 (9.9)	0
Hypertension	126 (40.8)	59 (19.1)	46 (14.7)	12 (3.8)
Proteinuria	99 (32.0)	19 (6.1)	34 (10.9)	4 (1.3)
Hepatotoxicity	87 (28.2)	23 (7.4)	52 (16.7)	19 (6.1)
Hemorrhage	77 (24.9)	19 (6.1)	53 (17.0)	5 (1.6)
PPES	34 (11.0)	6 (1.9)	3 (1.0)	0
Hypocalcemia	21 (6.8)	3 (1.0)	9 (2.9)	1 (0.3)
Cardiac dysfunction	14 (4.5)	3 (1.0)	7 (2.2)	2 (0.6)
Renal events	12 (3.9)	5 (1.6)	8 (2.6)	3 (1.0)
Arterial thromboembolic event	11 (3.6)	6 (1.9)	11 (3.5)	5 (1.6)
QT prolongation	6 (1.9)	1 (0.3)	1 (0.3)	1 (0.3)
Fistula formation	5 (1.6)	4 (1.3)	0	0
Gastrointestinal perforation	4 (1.3)	0	1 (0.3)	1 (0.3)
PRES	3 (1.0)	1 (0.3)	0	0

Note: All data are n (%).
[a]Adverse events based on lists of terms specified by the sponsors and considered regardless of attribution by investigators. Related terms are included in the preferred terms listed.
PPES, palmar-plantar erythrodysesthesia syndrome; PRES, posterior reversible encephalopathy syndrome.

plus pembrolizumab (n = 58) in the global or China extension study (Supplementary Table 2; Supplementary Fig. 1). As of May 19, 2021, data cutoff and as detailed in Supplementary Appendix 1, median OS was 11.4 months (95% CI: 8.4 mo–not reached [NR]) in the lenvatinib plus pembrolizumab group and NR in the placebo plus pembrolizumab group (HR, 1.53 [95% CI: 0.61–3.87]); median (95% CI) PFS was 6.1 (4.2–8.7) versus 10.3 (5.6–NR) months (HR = 1.18 [95% CI: 0.61–2.25]) (Supplementary Fig. 2A and B). Safety results in the China study were similar to those in the global study. Additional data and details for the China study are included in Supplementary Appendix 1.

Discussion

On the basis of the prespecified nonbinding futility analysis of the LEAP-007 study, the DMC determined that the benefit–risk ratio for lenvatinib plus pembrolizumab was not favorable compared with placebo plus pembrolizumab in patients with previously untreated metastatic NSCLC with PD-L1 TPS of at least 1%. The nonbinding futility criterion was met when comparing OS between the two treatment groups. As a result, no further statistical testing was performed, although results for PFS and ORR suggested antitumor activity with the combination of lenvatinib plus pembrolizumab. Nevertheless, given that the incidence of treatment-related AEs was higher with the lenvatinib

plus pembrolizumab combination, without OS benefit, the benefit–risk ratio was not considered positive. At the recommendation of the DMC after a prespecified nonbinding futility analysis, treatment assignment was unblinded and lenvatinib and placebo were discontinued; the protocol was then amended to permit continuation of open-label pembrolizumab monotherapy for up to 35 cycles.

The reasons for the observed PFS benefit and higher ORR that did not translate to OS benefit with lenvatinib plus pembrolizumab are unclear. Although cross-study comparisons should be undertaken with caution and the treatment regimen and study design differed from the current study, a similar pattern of results was previously observed with the antiangiogenic agent bevacizumab.[21,22] Although bevacizumab plus paclitaxel and carboplatin had OS benefit (primary end point; $p = 0.003$) versus chemotherapy alone in the phase 3 E4599 study in patients with advanced nonsquamous NSCLC,[23] the combination of bevacizumab plus cisplatin and gemcitabine did not reveal OS benefit (secondary end point) in the phase 3 AVAiL study in patients with advanced or recurrent nonsquamous NSCLC despite significant ($p < 0.05$) improvement in PFS (primary end point) and ORR compared with placebo plus chemotherapy.[21,22] The authors attributed the lack of OS benefit in part to poststudy treatment based on an exploratory analysis that excluded patients who received subsequent therapies and revealed a separation in the Kaplan-Meier OS curves (HR = 0.84 [$p = 0.20$] for bevacizumab plus chemotherapy versus placebo plus chemotherapy).[22] Subsequent therapies could have similarly contributed to the lack of OS benefit observed in our study given that the proportion of patients who received subsequent therapy was lower in the lenvatinib plus pembrolizumab group versus the placebo plus pembrolizumab group (14.2% versus 28.0%). Other possible explanations for the lack of OS benefit despite the PFS and ORR benefits observed could relate to the higher incidence of treatment-related AEs, including those that led to interruption and discontinuation of the study treatment, the latter of which may or may not have precluded subsequent therapy in the lenvatinib plus pembrolizumab group, or differences in treatment practices after discontinuation of the study regimen in each of the treatment groups.

Results were generally similar across the subgroups analyzed, with no specific group revealing greater benefit than others. Similar to the global study, results from the China study suggested worse OS outcomes with lenvatinib plus pembrolizumab versus placebo plus pembrolizumab, although the CI was wide, likely owing to the smaller sample size and low proportion of events.

The safety profile of pembrolizumab in this double-blind, placebo-controlled study was generally similar to that observed with pembrolizumab monotherapy in other advanced NSCLC clinical trials.[3,4] Hypertension was the most common treatment-related AE in both treatment groups. Because hypertension is an AE of interest associated with antiangiogenic agents,[24–26] it is possible that investigators more vigilantly monitored for this potential toxicity. The incidence of treatment-related AEs of hypertension in the lenvatinib plus pembrolizumab group was similar to that previously observed in studies of lenvatinib plus pembrolizumab in patients with NSCLC and other advanced solid tumors.[18,27,28] In general, VEGF inhibitors have been associated with a higher risk for adverse bleeding events.[21,23,29,30] Several grade 5 bleeding events occurred with lenvatinib plus pembrolizumab, although it was retrospectively determined that most of these events occurred in patients who had major blood vessel encasement at baseline; this led to a protocol amendment to improve the clarity of the bleeding-related eligibility criterion.

Early unblinding and discontinuation of lenvatinib and placebo in the LEAP-007 study resulted in a modest median duration of study follow-up, with many patients being censored beyond 4 months, which limits interpretation of data after this time point. It should also be noted that because this study enrolled patients with NSCLC with PD-L1 TPS of at least 1%, it was not possible to evaluate PD-L1 TPS of at least 1% versus less than 1% as a potential biomarker for response to lenvatinib plus pembrolizumab.

Although lenvatinib plus pembrolizumab was associated with higher rates of treatment-related grade 3 to 5 AEs and AEs leading to discontinuation or death, as may be expected with combination versus single-agent therapy, the ORR observed with lenvatinib plus pembrolizumab in this study was encouraging and supported further evaluation of the combination of a VEGF inhibitor and pembrolizumab. At the time the DMC recommended stopping the LEAP-007 study for futility, they recommended continuing the phase 3 LEAP-006 and LEAP-008 studies evaluating lenvatinib plus pembrolizumab with and without chemotherapy in NSCLC as originally planned. Nevertheless, it was recently reported that at the final study analysis, both LEAP-006 and LEAP-008 did not meet their primary and secondary efficacy end points, including OS, PFS, and ORR. The full publication of data from these studies could provide insight into which patient population may have benefited the most from this treatment combination.

In conclusion, although there was evidence of clinical benefit based on PFS and ORR findings with lenvatinib plus pembrolizumab in this randomized, double-blind,

placebo-controlled study in patients with previously untreated metastatic NSCLC with PD-L1 TPS of at least 1%, the futility criterion for OS was met and the benefit–risk ratio for lenvatinib plus pembrolizumab was not considered favorable versus pembrolizumab alone. Further evaluation of lenvatinib continues in NSCLC and other tumor types. Pembrolizumab monotherapy remains a standard of care in many regions for first-line metastatic NSCLC with PD-L1 TPS of at least 1% and without targetable *EGFR* or *ALK* alterations.

CRediT Authorship Contribution Statement

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Data Sharing Statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. (MSD), Rahway, New Jersey, 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: 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 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 United States and European Union 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.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.12.023.

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