ORIGINAL ARTICLE

Lenvatinib Plus Pembrolizumab, Pemetrexed, and a Platinum as First-Line Therapy for Metastatic Nonsquamous NSCLC: Phase 3 LEAP-006 Study

Roy S. Herbst, MD, PhD,[a,*] Byoung Chul Cho, MD, PhD,[b] Caicun Zhou, MD,[c] Mauricio Burotto, MD,[d] Manuel Cobo Dols, MD,[e] Mehmet A. N. Sendur, MD,[f] Vladimir Moiseyenko, MD,[g] Ignacio Casarini, MD,[h] Makoto Nishio, MD, PhD,[i] Rina Hui, M.B.B.S., PhD,[j] Elvire Pons-Tostivint, MD,[k] Julia Dudnik, MD,[l] Samreen Ahmed, MD,[m] Chinyere E. Okpara, PhD,[n] Corina Dutcus, MD,[o] Lina Yin, PhD,[p] Yiwen Luo, PhD,[p] Diana Chirovsky, PhD,[p] Niyati Bhagwati, MD,[p] Delvys Rodriguez Abreu, MD, PhD[q]

[a]*Yale School of Medicine, Yale Cancer Center, and Smilow Cancer Hospital, New Haven, Connecticut*
[b]*Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea*
[c]*Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China*
[d]*Centro de Investigación Clínica Bradford Hill, Santiago, Chile*
[e]*Medical Oncology, Málaga Regional University Hospital, IBIMA, Málaga, Spain*
[f]*Ankara Yıldırım Beyazıt University Faculty of Medicine and Ankara Bilkent City Hospital, Ankara, Turkey*
[g]*Saint-Petersburg Clinical Research Center of Specialized Types of Medical Care (Oncology) named after "N.P. Napalkov" (GBUZ "SPb CRPCstmc(o)" named after N.P. Napalkov), St. Petersburg, Russia*
[h]*Hospital Bernardo Houssay, Mar del Plata, Argentina*
[i]*Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto-Ku, Japan*
[j]*Westmead Hospital and the University of Sydney, Sydney, Australia; Current affiliation: Centre of Cancer Medicine, University of Hong Kong, Hong Kong*
[k]*Nantes University, Centre Hospitalier Universitaire Nantes, Nantes, France*
[l]*The Legacy Heritage Oncology Center & Dr. Larry Norton Institute, Soroka University Medical Center, Beer-Sheva, Israel*
[m]*University Hospitals of Leicester National Health Service Trust, Leicester, United Kingdom*
[n]*Eisai Ltd., Hatfield, United Kingdom*
[o]*Eisai Inc., Nutley, New Jersey*
[p]*Merck & Co., Inc., Rahway, New Jersey*
[q]*Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Gran Canaria, Spain*

Received 21 February 2025; revised 16 May 2025; accepted 19 May 2025
Available online - 24 May 2025

ABSTRACT

Introduction: We present the LEAP-006 (NCT03829319) phase 3 study evaluating the addition of lenvatinib to first-line pembrolizumab plus chemotherapy in metastatic nonsquamous NSCLC.

Methods: Adults with previously untreated stage IV nonsquamous NSCLC without targetable genetic alterations were randomized 1:1 to lenvatinib 8 mg/d or placebo once daily plus pembrolizumab 200 mg every 3 weeks with pemetrexed and carboplatin or cisplatin for 4 cycles, followed by pembrolizumab (≤35 total cycles) and pemetrexed until disease progression or intolerable toxicity. Primary end points were progression-free survival and overall survival (OS). Part 1 was an open-label safety run-in

*Corresponding author.

Previous presentations: A portion of these results was previously presented at the 2020 European Society for Medical Oncology Congress on September 19-21, 2020; Virtual congress; abstract 1313P and the 2023 European Society for Medical Oncology Immuno-Oncology Congress in Geneva, Switzerland on December 6-8, 2023; abstract 1200.

Address for correspondence: Roy S. Herbst, MD, PhD, Yale School of Medicine, Yale Cancer Center, and Smilow Cancer Hospital, New Haven, CT 06520. E-mail: roy.herbst@yale.edu

Cite this article as: Herbst RS, Cho BC, Zhou C, et al. Lenvatinib plus pembrolizumab, pemetrexed, and a platinum as first-line therapy for metastatic nonsquamous NSCLC: phase 3 LEAP-006 study. *J Thorac Oncol*. 2025;20:1302-1314.

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2025.05.016

of lenvatinib plus pembrolizumab and chemotherapy; part 2 was the randomized, double-blind study.

Results: Participants (n = 748) were randomized to the lenvatinib (n = 375) or placebo (n = 373) arms. Median follow-up at final analysis (August 11, 2023) for OS was 36.8 months. Median (95% confidence interval [CI]) progression-free survival was 12.1 (10.4–14.1) versus 9.5 (8.3–10.7) months in the lenvatinib and placebo arms, respectively (hazard ratio, 0.88 [95% CI, 0.74–1.05]; 1-sided $p = 0.07976$). Median (95% CI) OS was 21.8 (18.6–24.0) versus 22.1 (19.7–24.2) months (hazard ratio, 1.05 [95% CI, 0.88–1.26]; 1-sided $p = 0.70818$). Grade 3 or higher treatment-related adverse events occurred in 69.7% and 55.6% of participants, respectively (grade 5, 5.6% versus 2.7%).

Conclusions: Adding lenvatinib to first-line pembrolizumab plus chemotherapy did not improve efficacy versus pembrolizumab plus chemotherapy in stage IV nonsquamous NSCLC without targetable genetic alterations. There were no new safety signals. Pembrolizumab plus chemotherapy remains a standard of care for this population.

Trial registration: ClinicalTrials.gov (https://clinicaltrials.gov/), NCT03829319

Keywords: Lenvatinib; Pembrolizumab; First-line therapy; Metastatic nonsquamous non–small cell lung cancer; NSCLC

Introduction

Pembrolizumab, an anti–programmed cell death protein 1 (PD-1), plus pemetrexed with cisplatin or carboplatin is standard-of-care therapy for patients with previously untreated metastatic nonsquamous NSCLC without targetable *EGFR* or *ALK* alterations and regardless of programmed cell death-ligand 1 (PD-L1) expression.[1]

Lenvatinib, a small-molecule inhibitor of multiple tyrosine kinases including vascular endothelial growth factor receptors and fibroblast growth factor receptors,[2,3] has demonstrated antitumor activity and manageable safety in combination with pembrolizumab in select previously treated advanced solid tumors[4] and previously untreated advanced NSCLC.[5] In the phase 1b/2 study 111/KEYNOTE-146, lenvatinib plus pembrolizumab demonstrated an objective response rate (ORR) of 33% in 21 participants with metastatic NSCLC, 52% of whom had received at least 2 previous systemic therapies.[4] In the phase 2 KEYNOTE-495/KeyImPaCT study, lenvatinib plus pembrolizumab (n = 80) demonstrated an ORR of 35%, which met the prespecified efficacy threshold.[5] However, in the phase 3 LEAP-007 study, the futility criterion for overall survival (OS) was met, and the benefit:risk ratio for lenvatinib plus pembrolizumab was not favorable versus pembrolizumab alone in previously untreated metastatic NSCLC with a PD-L1 tumor proportion score (TPS) greater than or equal to 1%.[6]

We report results from the phase 3 LEAP-006 study, which evaluated pembrolizumab plus pemetrexed and platinum chemotherapy with or without lenvatinib as first-line therapy for metastatic nonsquamous NSCLC without actionable genetic alterations.

Materials and Methods

Study Design and Participants

LEAP-006 (NCT03829319) was a 2-part, phase 3, randomized, double-blind, active- and placebo-controlled study that evaluated first-line pembrolizumab plus pemetrexed plus platinum chemotherapy with or without lenvatinib in participants with metastatic nonsquamous NSCLC. The study included an open-label safety run-in of lenvatinib plus pembrolizumab and platinum-based chemotherapy (part 1) and a randomized, double-blind study of pembrolizumab plus pemetrexed and platinum-based chemotherapy with or without lenvatinib (part 2).

Full eligibility criteria are provided in the study protocol, which is available in the Data Supplement. Eligible adults (≥18 y old) had previously untreated, histologically or cytologically confirmed stage IV nonsquamous NSCLC (per American Joint Committee on Cancer, eighth edition) without targetable *EGFR*, *ALK*, or *ROS1* genetic alterations, measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, provided an archival tumor tissue sample or newly obtained core or excisional biopsy of an unirradiated tumor lesion for PD-L1 evaluation, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and adequately controlled blood pressure with or without antihypertensive medication.

Participants were excluded if they had untreated central nervous system metastases or carcinomatous meningitis; participants with previously treated brain metastases who were clinically and radiologically stable for at least 4 weeks per repeat imaging and had not required steroids for at least 14 days before study treatment could participate.

The 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 before enrolling. An external independent data and safety monitoring committee reviewed safety and efficacy data.

Treatment

In the open-label safety run-in (part 1), 13 participants received lenvatinib in combination with pembrolizumab plus pemetrexed and platinum-chemotherapy, ensuring at least six participants each received cisplatin or carboplatin.

In part 2 of the study, participants were randomized (1:1) to oral lenvatinib 8 mg or placebo once daily plus intravenous infusion of pembrolizumab 200 mg, carboplatin area under the concentration-time curve 5 mg/mL/min or cisplatin 75 mg/m^2, and pemetrexed 500 mg/m^2 on day 1 of each 21-day cycle for up to 4 cycles. Participants could then receive maintenance treatment with lenvatinib or placebo plus pembrolizumab plus pemetrexed. A maximum of 35 cycles of pembrolizumab was permitted; there was no limit on treatment duration for lenvatinib or pemetrexed. Treatment crossover was not allowed.

Random allocation in part 2 was conducted centrally through an interactive voice and web-response system and stratified by PD-L1 TPS (<50% versus ≥50%), geographic region (East Asia versus rest of world), and ECOG PS at screening (0 versus 1).

Assessments

In part 1, participants were followed for 21 days after the first dose of the study treatment for the occurrence of dose-limiting toxicities (DLTs; Supplementary Table 1). If less than three DLTs occurred among six participants in each platinum-containing arm, enrollment to part 2 was permitted. In part 2, tumor imaging was performed at weeks 6, 12, and 18 from randomization, then every 9 weeks through week 54, and then every 12 weeks until progressive disease (PD), initiation of new anticancer therapy, or the end of the study. Tumor response was assessed per RECIST version 1.1 by blinded independent central review for determination of study end points and per the modified RECIST version 1.1 for immune-based therapeutics (iRECIST).[7] Adverse events (AEs) were monitored throughout the study until 30 days after the last treatment (90 d for serious AEs), with severity graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. PD-L1 TPS was centrally evaluated using PD-L1 immunohistochemistry 22C3 pharmDx (Agilent Technologies, Carpinteria, CA). Patient-reported outcomes (PROs) were assessed in part 2 using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 (EORTC QLQ-C30), the EORTC QLQ—Lung Cancer Module 13 (LC13), and the European Quality of Life 5-Dimension, 5-Level (EQ-5D-5L) questionnaire. Details regarding collection of PRO data are available in the Data Supplement.

End Points

The primary end points of part 1 were to evaluate the DLTs, AEs, and treatment discontinuations due to AEs. The dual primary end points of part 2 were progression-free survival (PFS; time from randomization to first documentation of PD or death from any cause) and OS (time from randomization to death from any cause). Secondary end points included ORR (proportion of participants with confirmed complete response [CR] or partial response [PR]); duration of response (DOR; time from first documented CR or PR until first documentation of PD or death in participants with a confirmed CR or PR); safety; and PROs, including mean change from baseline to week 27 in global health status/quality of life (GHS/QoL), cough, chest pain, dyspnea, and physical functioning scores, time to true deterioration (TTD) in GHS/QoL, dyspnea, physical functioning, cough and chest pain scores, and TTD in the composite end point of cough, chest pain, or dyspnea. TTD was defined as the time from baseline to first onset of a deterioration of 10 or more points with a confirmed second, adjacent deterioration of 10 or more points from baseline in PRO scores.

Statistical Analyses

Efficacy was assessed in the intention-to-treat population (all randomized participants), safety (in parts 1 and 2) in all randomized participants who received at least 1 dose of the study drug, and PROs in all participants with a minimum of 1 PRO assessment available who received at least 1 dose of the study treatment.

OS, PFS, DOR, and TTD were estimated using the Kaplan–Meier method. Censoring rules are summarized in the Data Supplement (Supplementary Table 2). Between-group treatment differences in PFS, OS, and TTD were assessed using the stratified log-rank test with one-sided p values. Hazard ratios (HRs) with 95% CIs were estimated using a stratified Cox proportional model with Efron's method of tie handling. Treatment differences in ORR were estimated using the stratified Miettinen and Nurminen method. Changes in least squares mean from baseline to week 27 in PRO scores were estimated using a constrained longitudinal data analysis model, with the PRO score as the response variable and the treatment, time, treatment by time interaction, and stratification factors as covariates. Randomization stratification factors were used for all stratified analyses. Further details are available in the study protocol, which is available in the Data Supplement.

The overall type I error over the primary (PFS, OS) and secondary (ORR) hypotheses was strongly controlled at 2.5% (one-sided) across all hypotheses. The graphical method of Maurer and Bretz was used to

control the family-wise type I error rate of 0.025 for hypothesis testing of ORR, PFS, and OS, with preallocated α of 0.001, 0.005, and 0.019 (Supplementary Fig. 1).

The protocol specified three interim analyses (IAs) and a final analysis (FA). IA1 (final ORR analysis) was performed after approximately 420 participants were randomized, with approximately 9 months of follow-up. IA2 (interim PFS and OS analyses) was performed after approximately 420 PFS events and approximately 8 months after the last participant was randomized. IA3 (final PFS and OS analyses) was performed after approximately 480 PFS events and approximately 18 months after the last participant was randomized. The planned sample size for part 2 of approximately 714 participants provided approximately 90% power to detect a treatment difference in PFS at IA3 based on an estimated 480 PFS events, with an HR of 0.7 and one-sided α of 0.005. Similarly, this sample size provided approximately 90% power to detect a treatment difference in OS at the FA, with an estimated 445 events, with an HR of 0.725 and one-sided α of 1.9%. Superiority boundaries were derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds.

Results

Participants

In part 1 (safety run-in), 13 participants across eight global sites were enrolled and received at least 1 dose of the study treatment. At the FA (data cutoff; August 11, 2023), 12 participants had discontinued study treatment and one participant was ongoing. Median duration of treatment was 15.1 (range, 1.3–47.6) months, and median number of treatment cycles was 22.0 (range, 2.0–67.0). There were two DLTs (grade 3 hyponatremia) in participants who received lenvatinib plus pembrolizumab, pemetrexed, and cisplatin. Twelve participants (92.3%) had a treatment-related AE, of which 10 (76.9%) were grade 3 or higher. Two participants (15.4%) died and nine participants (69.2%) discontinued any study treatment due to a treatment-related AE. Based on reported DLTs and the overall safety profile observed in part 1, part 2 of the study was initiated and both cisplatin and carboplatin were permitted.

During part 2, 748 participants were randomized between September 30, 2019, and March 31, 2021, at 124 sites to lenvatinib plus pembrolizumab, pemetrexed and a platinum (lenvatinib arm; n = 375) or placebo plus pembrolizumab, pemetrexed, and a platinum (placebo arm; n = 373; Fig. 1). Demographics and baseline disease characteristics were generally balanced between treatment arms (Table 1). Median age was 63.0 (range, 18–87) years, 64.2% of participants had an ECOG PS of 1, and 72.3% had tumors that were PD-L1 TPS less than 50%. Median time from randomization to data cutoff at FA was 36.8 (range, 28.4–46.4) months. The median (range) duration of therapy was 10.8 (0.03–44.5) months in the lenvatinib arm and 9.3 (0.03–44.7) months in the placebo arm (Supplementary Table 3). The

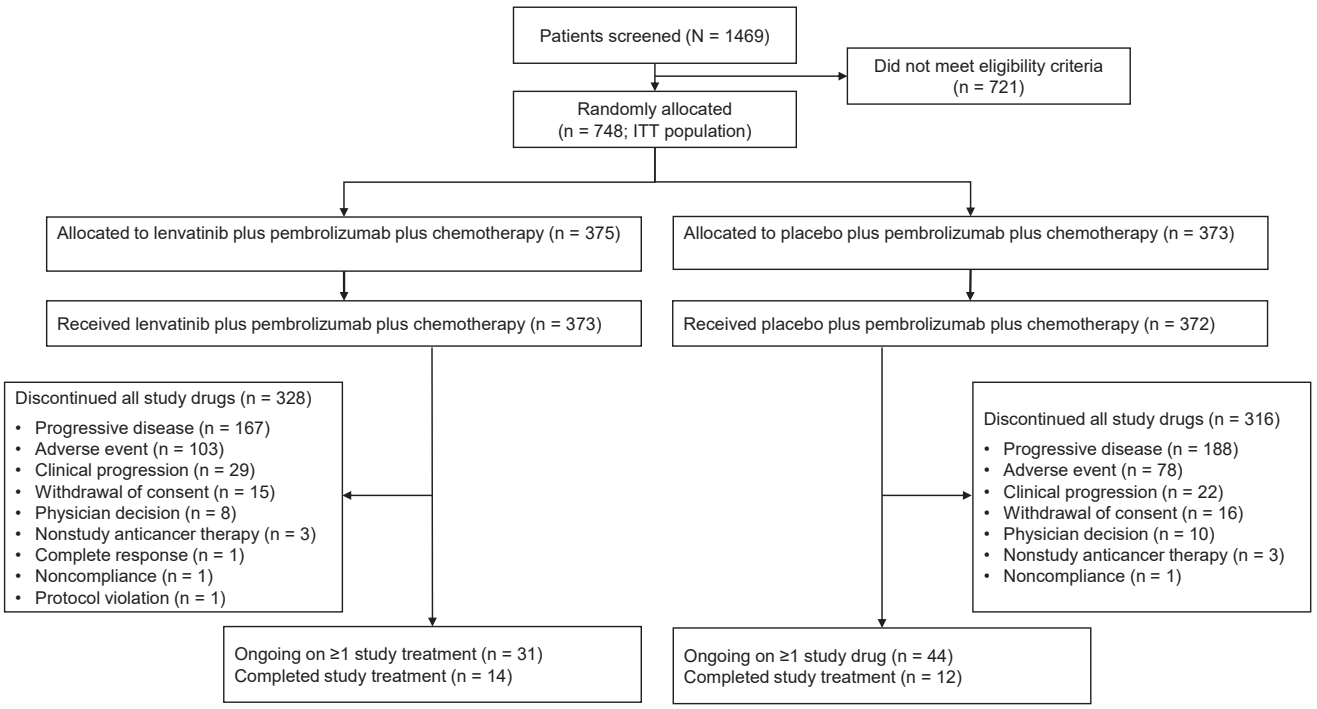


Figure 1. Participant disposition. ITT, intention to treat.

Table 1. Demographics and Baseline Disease Characteristics (ITT Population)

Characteristic	Lenvatinib Plus Pembrolizumab Plus Chemotherapy (n = 375)	Placebo Plus Pembrolizumab Plus Chemotherapy (n = 373)
Median age (range), y	63 (18–85)	64 (28–87)
Sex		
Male	254 (67.7)	247 (66.2)
Female	121 (32.3)	126 (33.8)
Geographic region		
East Asia	111 (29.6)	112 (30.0)
Rest of world	264 (70.4)	261 (70.0)
ECOG performance status		
0	135 (36.0)	133 (35.7)
1	240 (64.0)	240 (64.3)
Smoking status		
Current or former	320 (85.3)	302 (81.0)
Never	55 (14.7)	71 (19.0)
Brain metastases	50 (13.3)	37 (9.9)
Liver metastases	63 (16.8)	37 (9.9)
Previous therapy		
Neoadjuvant	5 (1.3)	5 (1.3)
Adjuvant	21 (5.6)	16 (4.3)
Radiotherapy	93 (24.8)	69 (18.5)
Thoracic radiotherapy	24 (6.4)	18 (4.8)
PD-L1 TPS		
≥50%	90 (24.0)	91 (24.4)
<50%	272 (72.5)	269 (72.1)
<1%	135 (36.0)	121 (32.4)
1%-49%	137 (36.5)	148 (39.7)
Not evaluable	13 (3.5)	13 (3.5)
Platinum chemotherapy		
Carboplatin	311 (82.9)	318 (85.3)
Cisplatin	62 (16.5)	54 (14.5)
None[a]	2 (0.5)	1 (0.3)

Note: Data are n (%) except where specified.
[a]Participants who were randomized but did not receive any study treatment.
ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

median (range) number of cycles in each arm was 15 (1–61) and 13 (1–65), respectively. A total of 131 participants (34.9%) in the lenvatinib arm and 150 (40.2%) in the placebo arm received any subsequent anticancer therapy (Supplementary Table 4).

Efficacy

At IA3 (protocol-specified final analysis for PFS), there were 244 (65.1%) and 251 (67.3%) events of death or PD in the lenvatinib and placebo arms, respectively. Median (95% CI) PFS was 12.1 (10.4−14.1) months in the lenvatinib arm and 9.5 (8.3−10.7) months in the placebo arm (HR, 0.88; 95% CI, 0.74–1.05; $p = 0.07976$ [superiority threshold, one-sided $p = 0.00409$]). At FA, 519 participants (69.4%) had an event of PD or death. Median (95% CI) PFS at FA was 12.2 (10.5–15.0) months in the lenvatinib arm and 9.2 (8.3–10.7) months in the placebo arm (HR, 0.88; 95% CI, 0.74–1.04; Fig. 2*A*). The 36-month PFS rates were 21.9% and 21.5% in the lenvatinib and placebo arms, respectively. PFS outcomes were similar between treatment arms across key participant subgroups (Fig. 2*B*).

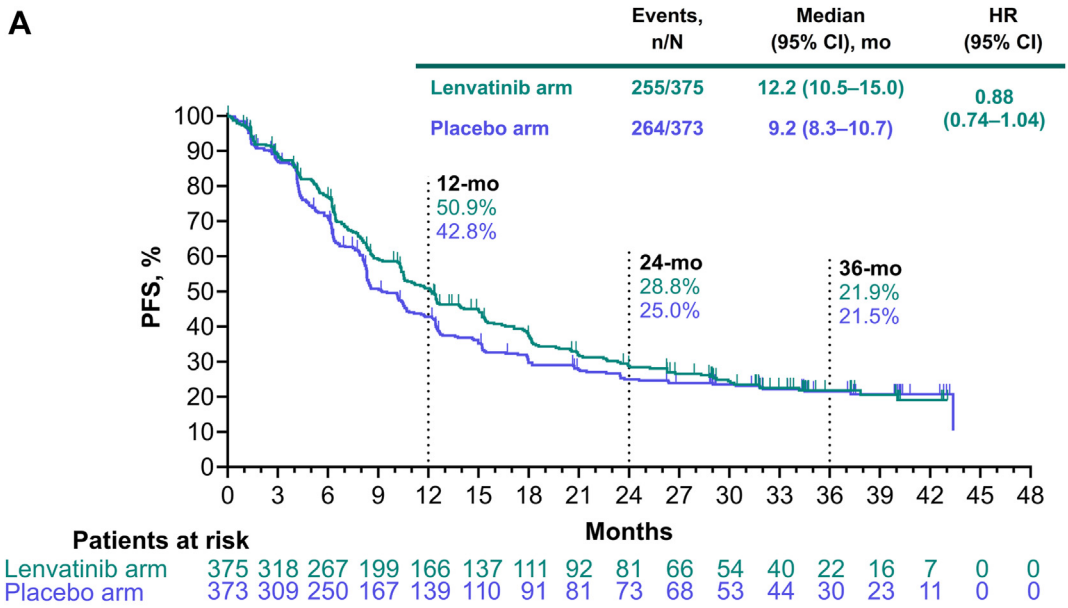
At the time of FA, 488 participants (65.2%) had died. Median (95% CI) OS was 21.8 (18.6–24.0) months in the lenvatinib arm and 22.1 (19.7–24.2) months in the placebo arm (HR, 1.05; 95% CI, 0.88–1.26; $p = 0.70818$ [superiority threshold, one-sided $p = 0.01618$]; Fig. 2*C*). The 36-month OS rates were 33.0% and 36.5% in the lenvatinib and placebo arms, respectively. OS was generally similar between treatment groups across key participant subgroups (Fig. 2*D*).

The ORRs were 60.0% (95% CI, 54.8%–65.0%) and 53.6% (95% CI, 48.4%–58.8%) in the lenvatinib and placebo arms, respectively (Table 2). At IA1, the protocol-specified final analysis for ORR, ORR in the lenvatinib arm was 57.1% (95% CI, 50.1%–63.8%) versus 50.7% (43.8%–57.6%) in the placebo arm. The difference was 6.3 (95% CI, −2.8 to 15.4); one-sided p is 0.086 (superiority threshold, one-sided $p = 0.001$). Median (range) DORs were 15.8 (1.6–41.7+) and 13.7 (1.2+–41.6+) months, respectively (Supplementary Fig. 2).

Safety

Treatment-related AEs occurred in 363 of 373 participants (97.3%) in the lenvatinib arm and 354 of 372 participants (95.2%) in the placebo arm (Table 3). Grade 3 to 5 treatment-related AEs occurred in 260 participants (69.7%) and 207 participants (55.6%), respectively. Treatment-related AEs led to discontinuation of any study treatment in 139 participants (37.3%) in the lenvatinib arm and 103 participants (27.7%) in the placebo arm and to death in 21 (5.6%) and 10 (2.7%) participants, respectively. Frequently occurring treatment-related AEs included decreased neutrophil count (47.7% and 40.3%), anemia (46.9% and 55.1%), and decreased platelet count (38.1% and 26.6%), respectively. The most commonly occurring grade 5 treatment-related AEs were pneumonitis (n = 5), febrile neutropenia, and pneumonia (n = 3 each) in the lenvatinib arm and death and pneumonitis (n = 2 each) in the placebo arm.

Adverse events of special interest for pembrolizumab occurred in 158 participants (42.4%) in the lenvatinib arm and 122 (32.8%) in the placebo arm and were of grades 3 to 5 in 50 (13.4%) and 34 (9.1%), respectively (Supplementary Table 5). Clinically significant AEs for



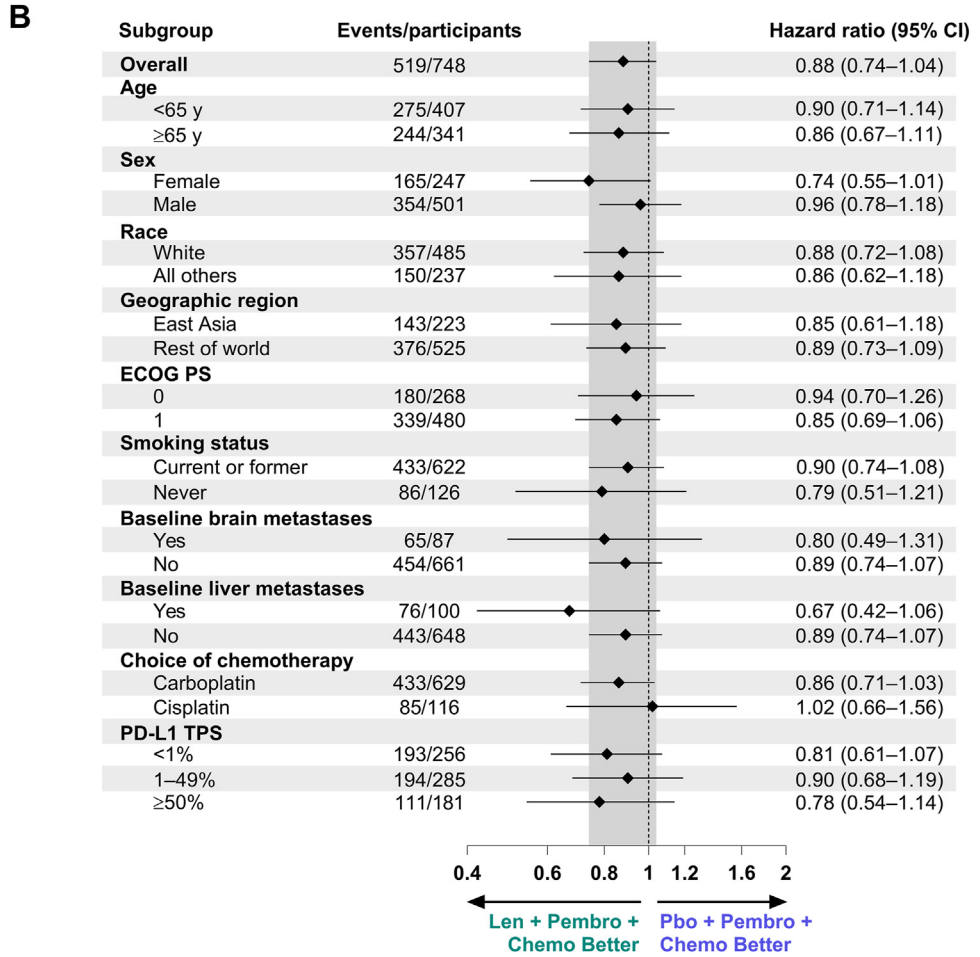


Figure 2. PFS and OS. (*A*) Kaplan-Meier estimates of PFS at FA per RECIST version 1.1 by BICR. (*B*) Analysis of PFS in key participant subgroups. (*C*) Kaplan-Meier estimates of OS at FA. (*D*) Analysis of OS in key participant subgroups. BICR, blinded independent central review; Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FA, final analysis; HR, hazard ratio; IA, interim analysis; ITT, intention to treat; Len, lenvatinib; OS, overall survival; PBO, placebo; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score.

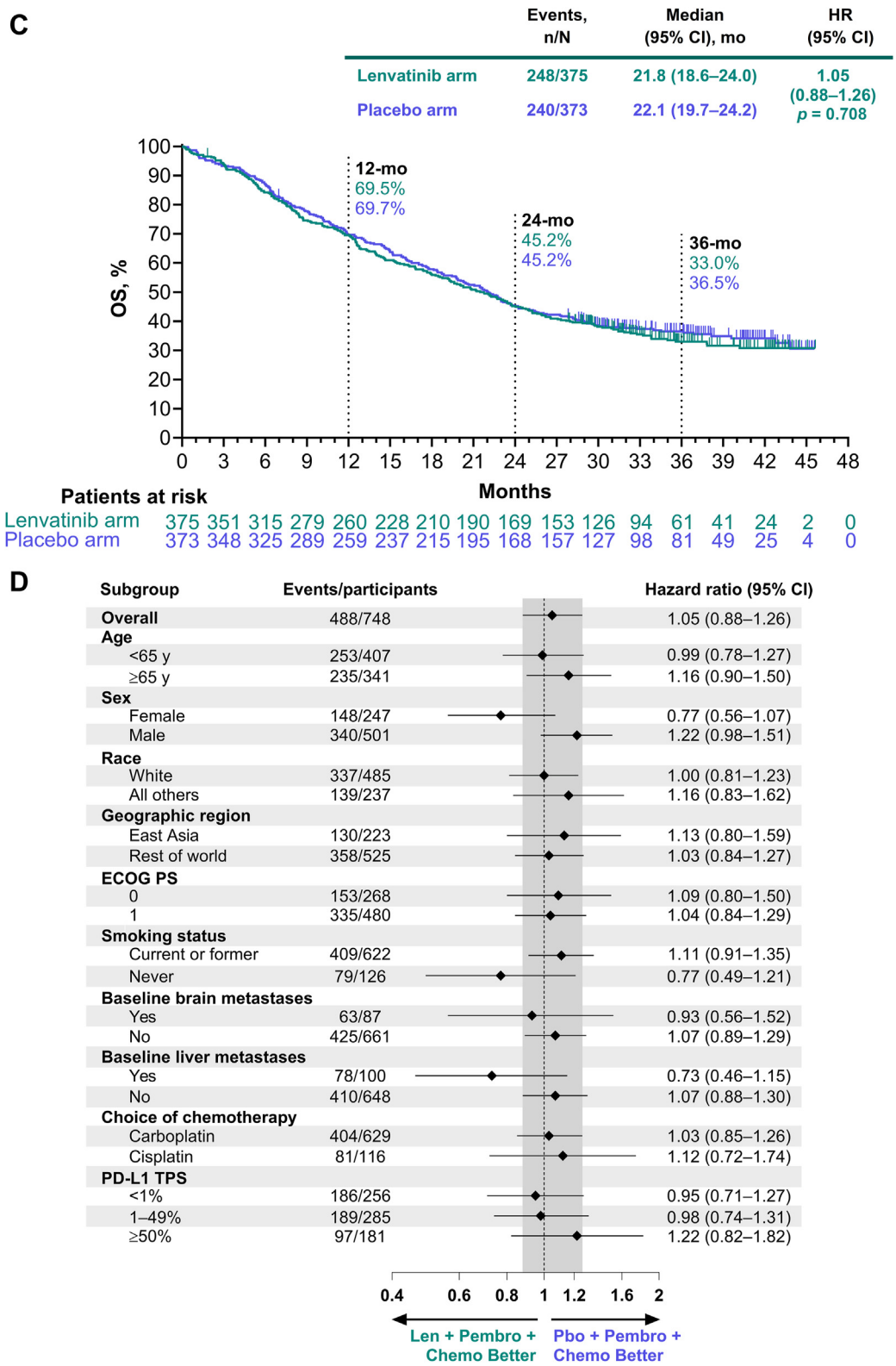


Figure 2. (*continued*).

lenvatinib occurred in 294 of 373 participants (78.8%) and 241 of 372 participants (64.8%), respectively (Supplementary Table 5).

Patient-Reported Outcomes

The PRO analysis population included 370 participants in the lenvatinib arm and 371 participants in the

Table 2. Summary of Tumor Response at FA (ITT Population)

Tumor Response	Lenvatinib Plus Pembrolizumab Plus Chemotherapy (n = 375)	Placebo Plus Pembrolizumab Plus Chemotherapy (n = 373)
ORR (95% CI),[a] %	60.0 (54.8–65.0)	53.6 (48.4–58.8)
Best overall response,[a] n (%)		
CR	24 (6.4)	33 (8.8)
PR	201 (53.6)	167 (44.8)
SD[b]	108 (28.8)	129 (34.6)
PD	21 (5.6)	18 (4.8)
Not evaluable[c]	3 (0.8)	6 (1.6)
No assessment[d]	18 (4.8)	20 (5.4)
Time to response, median (range), mo	1.6 (1.1–15.4)	1.6 (1.2–20.7)
DOR, median (range), mo	15.8 (1.6 to 41.7+)	13.7 (1.2+ to 41.6+)
DOR ≥24 mo,[e] n (%)	60 (36.2)	65 (39.7)

[a]Assessed by blinded independent central review per RECIST version 1.1.
[b]Stable disease includes stable disease, non-CR/non-PD, and no evidence of disease (no lesions identified at baseline or postbaseline assessments).
[c]Postbaseline assessment(s) available but not evaluable or CR/PR/SD <6 weeks from randomization.
[d]No postbaseline assessment available for response evaluation.
[e]Based on Kaplan-Meier method.
"+," no progressive disease at last assessment; CR, complete response; DOR, duration of response; FA, final analysis; ITT, intention to treat; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

placebo arm. The rates of completion and compliance with the EORTC QLQ-C30 and QLQ-LC13 instruments were more than 95.0% in both treatment arms at baseline and were more than 63.7% and more than 94.3%, respectively, at week 27 (Supplementary Table 6).

Mean change from baseline to week 27 in each of the EORTC QLQ-C30 GHS/QoL, dyspnea, and physical functioning, and EORTC QLQ-LC13 cough, and chest pain scores were stable in both the lenvatinib and placebo arms; no clinically meaningful between-group differences were observed (Supplementary Table 7).

The median (95% CI) TTD in the composite end point of cough, chest pain, or dyspnea was 8.3 (6.0–11.1) months in the lenvatinib arm and 9.3 (7.0–12.9) months in the placebo arm (HR, 1.04 [95% CI, 0.84–1.28]; Supplementary Table 8). TTD was generally similar between treatment arms in individual PRO scores (GHS/QoL, chest pain, dyspnea, cough, and physical functioning; Supplementary Table 8).

Discussion

The results of the phase 3 LEAP-006 study, which evaluated the addition of lenvatinib to first-line pembrolizumab plus platinum-containing chemotherapy in metastatic nonsquamous NSCLC, provide important insights into the potential role of multimodal therapy in this patient population. However, the study did not meet its primary end points of PFS and OS, with the addition of lenvatinib failing to demonstrate a significant improvement over the established pembrolizumab plus chemotherapy regimen.

Compared with results from the KEYNOTE-189 trial, which established pembrolizumab plus chemotherapy as a standard-of-care treatment for patients with previously untreated metastatic nonsquamous NSCLC without targetable genetic alterations, results from the placebo arm of LEAP-006 confirm the efficacy of this combination.[1] However, the LEAP-006 study also highlighted challenges of further enhancing outcomes in this population. The addition of lenvatinib to pembrolizumab plus chemotherapy resulted in a median PFS of 12.1 (95% CI, 10.4–14.1) months versus 9.5 (95% CI, 8.3–10.7) months in the placebo arm. Despite this numerical improvement, statistical significance was not achieved (HR, 0.88; 95% CI, 0.74–1.05; one-sided $p = 0.07976$). Similarly, median OS was 21.8 (95% CI, 18.6–24.0) and 22.1 (95% CI, 19.7–24.2) months in the lenvatinib and placebo arms, respectively, with no significant difference between the treatment arms (HR, 1.05; 95% CI, 0.88–1.26; one-sided $p = 0.70818$). Although these findings suggest moderate antitumor activity associated with lenvatinib, they did not translate into clinically meaningful survival benefits when combined with pembrolizumab and chemotherapy.

The efficacy data presented here are consistent with previously published phase 3 studies of lenvatinib plus pembrolizumab, including LEAP-007,[6] which evaluated lenvatinib plus pembrolizumab versus pembrolizumab monotherapy for previously untreated metastatic NSCLC with PD-L1 TPS greater than or equal to 1%, and LEAP-008,[8] which compared lenvatinib plus pembrolizumab versus docetaxel for metastatic NSCLC that progressed after treatment with immune checkpoint inhibitors plus chemotherapy. In both studies, lenvatinib plus pembrolizumab did not result in significant survival improvements versus the comparator. In addition, although conducted in a different participant population than that enrolled in the LEAP-006 study, results from the phase 3 SAPPHIRE study for sitravatinib, a multitargeted tyrosine kinase receptor inhibitor, plus nivolumab, a PD-1 blocking antibody, did not demonstrate statistically significant survival benefit versus chemotherapy in participants with previously treated metastatic nonsquamous NSCLC who initially benefited from, and subsequently progressed on, previous checkpoint inhibitor therapy with or after platinum-based chemotherapy as first- or second-line treatment.[9] Sitravatinib with nivolumab provided a numerical but not statistically significant improvement in OS (median, 12.2 versus 10.6 mo; HR, 0.86; 95% CI, 0.70–1.05; $p = 0.144$) versus docetaxel.

Table 3. Summary of Treatment-Related Adverse Events[a]

Adverse Event	Lenvatinib Plus Pembrolizumab Plus Chemotherapy (n = 373)		Placebo Plus Pembrolizumab Plus Chemotherapy (n = 372)	
Any	363 (97.3)		354 (95.2)	
Grades 3–5	260 (69.7)		207 (55.6)	
Serious	140 (37.5)		100 (26.9)	
Led to death	21 (5.6)[b]		10 (2.7)[c]	
Led to discontinuation of any treatment component	139 (37.3)		103 (27.7)	
Treatment-related AEs occurring in ≥15% of participants in either treatment group	Any Grade	Grades 3–5	Any Grade	Grades 3–5
Decreased neutrophil count	178 (47.7)	94 (25.2)	150 (40.3)	70 (18.8)
Anemia	175 (46.9)	49 (13.1)	205 (55.1)	63 (16.9)
Decreased platelet count	142 (38.1)	54 (14.5)	99 (26.6)	32 (8.6)
Nausea	132 (35.4)	6 (1.6)	126 (33.9)	4 (1.1)
Decreased white blood cell count	115 (30.8)	37 (9.9)	94 (25.3)	26 (7.0)
Increased alanine aminotransferase	109 (29.2)	19 (5.1)	106 (28.5)	13 (3.5)
Increased aspartate aminotransferase	103 (27.6)	13 (3.5)	97 (26.1)	8 (2.2)
Reduced appetite	103 (27.6)	4 (1.1)	93 (25.0)	2 (0.5)
Hypertension	98 (26.3)	33 (8.8)	35 (9.4)	11 (3.0)
Asthenia	92 (24.7)	16 (4.3)	91 (24.5)	8 (2.2)
Diarrhea	92 (24.7)	19 (5.1)	43 (11.6)	10 (2.7)
Fatigue	92 (24.7)	10 (2.7)	75 (20.2)	6 (1.6)
Hypothyroidism	71 (19.0)	0	37 (9.9)	1 (0.3)
Constipation	62 (16.6)	0	56 (15.1)	0

Note: All values are n (%).
[a]Included AEs considered by the investigator to be related to any or all study treatments.
[b]Pneumonitis (n = 5), febrile neutropenia and pneumonitis (each n = 3), myocardial infarction (n = 2), and cardiorespiratory arrest, cerebrovascular accident, enteritis, hepatic failure, interstitial lung disease, myocarditis, respiratory tract infection, and tracheal hemorrhage (each n = 1).
[c]Death and pneumonitis (each n = 2), and cerebral ischemia, ischemic cerebral infarction, pneumonia klebsiella, respiratory failure, sepsis, and upper gastrointestinal hemorrhage (each n = 1).
AE, adverse event.

PFS (median, 4.4 versus 5.4 mo; HR, 1.08; 95% CI, 0.89–1.32; $p = 0.452$) and ORR (15.6% versus 17.2%; $p = 0.597$) were also not improved with sitravatinib plus nivolumab compared with docetaxel.

At the time LEAP-006 was conducted, there were no randomized, controlled trials comparing the addition of an antiangiogenic agent to checkpoint inhibitor therapy with chemotherapy versus checkpoint inhibitor plus chemotherapy; all studies used anti-angiogenic agents in combination with chemotherapy as the control. For instance, in the phase 3 IMpower150 study, atezolizumab, an anti–PD-L1 antibody, plus bevacizumab, an anti-vascular endothelial growth factor antibody, plus chemotherapy was compared to bevacizumab plus chemotherapy in patients with previously untreated metastatic nonsquamous NSCLC.[10] In this trial, atezolizumab in combination with bevacizumab plus chemotherapy significantly improved PFS (median, 8.3 versus 6.8 mo; stratified HR, 0.62; 95% CI, 0.52–0.74; $p < 0.001$) and OS (median, 19.2 versus 14.7 mo; stratified HR, 0.78; 95% CI, 0.64–0.96; $p = 0.02$) compared with bevacizumab plus chemotherapy. In addition, the updated exploratory analysis after an additional approximately 20 months of follow-up revealed continued OS improvement (median, 19.5 versus 14.7 mo; HR, 0.80; 95% CI, 0.67–0.95) with atezolizumab plus bevacizumab plus chemotherapy versus bevacizumab plus chemotherapy.[11] The study also included atezolizumab plus chemotherapy as a treatment group, and at the final OS analysis, this combination demonstrated a numerical, but not statistically significant, improvement in OS (median, 19.0 versus 14.7 mo; HR, 0.84; 95% CI, 0.71–1.00; $p = 0.05$) versus bevacizumab plus chemotherapy. As noted, this study was not designed to formally compare atezolizumab plus bevacizumab plus chemotherapy versus atezolizumab plus chemotherapy; therefore, it is difficult to ascertain what proportion of treatment effects observed with atezolizumab plus bevacizumab plus chemotherapy was provided by the anti-vascular endothelial growth factor antibody bevacizumab.[10,11] In a separate phase 3 study, HARMONi-2, ivonescimab, a bispecific antibody targeting PD-1 and vascular endothelial growth factor, significantly improved PFS (median, 11.1 versus 5.8 mo; HR, 0.51; 95% CI, 0.38–0.69; one-sided $p < 0.0001$) versus pembrolizumab in Chinese patients with previously untreated PD-L1 positive (i.e., TPS $\geq$ 1) advanced NSCLC; however, the impact on OS is unknown as it was not mature at the time of the data

cutoff for PFS analysis.[12] Although positive outcomes have been observed with immune checkpoint inhibitors and anti-angiogenic agents, cross-trial comparisons should not be made because they are subject to bias, and interpretation of these studies is confounded by differences between studies, including the mechanisms of action of anti-angiogenic agents evaluated, study designs, and participant characteristics.

Another critical aspect to consider is the safety profile observed in this study. The rate of grade 3 or higher treatment-related AEs was higher with lenvatinib (69.7%) versus placebo (55.6%), along with a higher incidence of treatment-related grade 5 AEs (5.6% versus 2.7%, respectively). Although potentially unsurprising considering an additional anticancer agent, the added toxicity was not offset by significant survival improvements. The clinically relevant AEs for lenvatinib were consistent with the known toxicities of lenvatinib monotherapy,[13–15] particularly its association with hypertension and gastrointestinal side effects, which have been found previously to be dose limiting for lenvatinib.[16] In this study, two DLTs of grade 3 hyponatremia were reported during the safety run-in. Regardless of the safety findings, there were no significant differences in PROs between treatment arms, suggesting that the addition of lenvatinib did not contribute to a worsening in QoL. Improving clinical outcomes for this patient population remains a challenge, and, as such, future research should focus on biomarker-directed therapy, potentially selecting participants who might benefit from additional therapies. For example, the ongoing Lung Cancer Master Protocol (Lung-MAP) trial model compares standard of care with experimental therapies based on unique tumor profiles.[17] In addition, ongoing trials assessing novel agents or combinations targeting different aspects of the tumor microenvironment or immune landscape may offer new opportunities to improve outcomes.[18]

In conclusion, the LEAP-006 study explored an innovative approach by adding lenvatinib to the proven regimen of pembrolizumab plus chemotherapy. The lack of significant survival benefits observed with the addition of lenvatinib, along with a modest increase in toxicity, underscores the complexity of optimizing treatment for patients with metastatic NSCLC. However, the results presented here do reinforce the value of pembrolizumab plus chemotherapy as the cornerstone of first-line therapy in this setting.

CRediT Authorship Contribution Statement

Roy S. Herbst: Conceptualization, data curation, formal analysis, investigation, methodology, roles/writing – original draft, writing – review & editing.

Byoung Chul Cho: Conceptualization, data curation, investigation, writing – review & editing.

Caicun Zhou: Formal analysis, investigation, resources, writing – review & editing.

Mauricio Burotto: Data curation, investigation, writing – review & editing.

Manuel Cobo Dols: Data curation, investigation, resources, writing – review & editing.

Mehmet A. N. Sendur: Investigation, resources, writing – review & editing.

Vladimir Moiseyenko: Investigation, resources, writing – review & editing.

Ignacio Casarini: Formal analysis, investigation, writing – review & editing.

Makoto Nishio: Formal analysis, investigation, resources, writing – review & editing.

Rina Hui: Formal analysis, investigation, resources, writing – review & editing.

Elvire Pons-Tostivint: Investigation, writing – review & editing.

Julia Dudnik: Investigation, writing – review & editing.

Samreen Ahmed: Data curation, investigation, resources, writing – review & editing.

Chinyere E. Okpara: Formal analysis, investigation, writing – review & editing.

Corina Dutcus: Conceptualization, data curation, formal analysis, investigation, methodology, writing – review & editing.

Lina Yin: Conceptualization, data curation, formal analysis, investigation, writing – review & editing.

Yiwen Luo: Investigation, project administration, writing – review & editing.

Diana Chirovsky: Formal analysis, investigation, roles/writing – original draft, writing – review & editing.

Niyati Bhagwati: Data curation, formal analysis, investigation, writing – review & editing.

Delvys Rodriguez Abreu: Conceptualization, investigation, resources, writing – review & editing.

Data-Sharing 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 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.

Disclosure

Dr. Herbst reports having financial interests, personal, advisory board, and consulting for EGFR and angiogenesis for AstraZeneca, Bolt Biotherapeutics, Checkpoint Therapeutics, Cybrexa Therapeutics, I-Mab Biopharma, Immunocore, Ocean Biomedical, Inc.; having financial interests, personal, other, ad hoc consulting-oncology for Bristol Myers Squibb, DynamiCure Biotechnology, LLC, Eli Lilly and Company, Foundation Medicine, Inc., Genentech/Roche, Gilead, Johnson and Johnson, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Oncternal Therapeutics, Pfizer, Sanofi, NextCure; having financial interests, personal - research advisory board for Candel Therapeutics, Inc.; having financial interests, personal, other, clinical advisor for eFFECTOR Therapeutics, Inc.; serving on the data safety monitory committee of EMD Serono, Novartis; having ad hoc consulting-KRAS and angiogenesis for Mirati Therapeutics; serving on the advisory board (clinical) of Ribbon Therapeutics, Xencor, Inc.; Consultant: AbbVie Pharmaceuticals, Loxo Oncology, Oncology: Oncocyte, Regeneron, Seattle Genetics; serving on the advisory board, consultant of Revelar Biotherapeutics; serving as member of board of directors, board member (non-executive/independent) of Immunocore Holdings Limited, Junshi Pharmaceuticals; having stocks/shares, options from Bolt Biotherapeutics, Immunocore, Checkpoint Therapeutics, Normunity; having financial interests, institutional, coordinating PI, research support from AstraZeneca, Genentech/Roche, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; having research support from Eli Lilly and Company; having nonfinancial interests, personal, leadership role, board member/committee chair for American Association for Cancer Research, International Association for the Study of Lung Cancer; having nonfinancial interests, committee chair for Society for Immunotherapy of Cancer, and Southwest Oncology Group. Prof. Cho received royalties from Champions Oncology, Crown Bioscience, Imagen, and PearlRiver Bio GmbH; received grant/research support from GIInnovation, AstraZeneca, Champions Oncology, CJ Bioscience, Cyrus, Janssen, MSD, Dong-A ST, Yuhan, ImmuneOncia, Therapex, J INTS Bio, Vertical Bio AG; consultant for BeiGene, Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, CJ, Cyrus Therapeutics, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD, Gilead, Amgen, Daiichi Sankyo, Regeneron, Sanofi, AnHeart Therapeutics, Seagen, Harpoon Therapeutics, GSK, ArriVent; served on advisory boards for KANAPH Therapeutic Inc., Bridgebio Therapeutics, Cyrus Therapeutics, Guardant Health, Oscotec Inc., J INTS Bio, Therapex Co., Ltd.; was an invited speaker for American Society of Clinical Oncology (ASCO), AstraZeneca, Guardant, Roche, European Society of Medical Oncology (ESMO), International Association for the Study of Lung Cancer (IASLC), Korean Cancer Association, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, MSD, The Chinese Thoracic Oncology Society, Pfizer, Zailab; and holds stocks/shares of TheraCanVac Inc., Gencurix Inc., Bridgebio Therapeutics, KANAPH Therapeutic Inc., Cyrus Therapeutics, Interpark Bio Convergence Corp., and J INTS Bio; is the founder of DAAN Biotherapeutics; and is a member of the board of directors of J INTS Bio. Dr. Zhou reports receiving honoraria from Boehringer Ingelheim, Eli Lilly, Hengrui, MSD, Sanofi, Roche, and Qilu. Dr. Burotto reports receiving speaker fees from BMS, MSD, and Roche; serving on the advisory boards for BMS and MSD; and serving as a steering committee member for Roche. Dr. Dols reports receiving honoraria from Novartis, AstraZeneca, Boehringer Ingelheim, Roche, BMS, Lilly, MSD, Takeda, Kyowa, Pierre-Fabre, Novocure, Sanofi, Janssen; and has served on an advisory board and Data Safety Monitoring committee for Novartis, AstraZeneca, Boehringer Ingelheim, Roche, BMS, Lilly, MSD, Takeda, Pfizer, Kyowa, Sanofi, and Janssen. Dr. Sendur reports serving on the advisory board of Astellas, AstraZeneca, BMS, Gilead, Lilly, MSD, Novartis, Pfizer, and Takeda; serving as an invited speaker of Pfizer, Novartis, Astellas, BMS,

MSD, Lilly, Gilead, and Takeda. Dr. Moiseyenko reports receiving funding to the institution to support study conduct from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Dr. Casarini reports receiving financial interests through institutional support as local principal investigator of multiple clinical studies sponsored by MSD, Bristol Myers Squibb, AstraZeneca, Eli Lilly, Exelixis, Novartis, and Roche; and reports serving as an invited speaker for AstraZeneca. Dr. Nishio reports participating in the speakers' bureau for Ono Pharmaceuticals, Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly Japan K.K, AstraZeneca, MSD, AbbVie, Takeda, Pfizer Japan, Boehringer Ingelheim, Novartis Pharma, Nippon Kayaku, Merck Biopharma, and Janssen. Prof. Hui reports receiving funding to the institution to support study conduct from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; receiving research support or grants from Amgen, AstraZeneca, BMS, Corvus, Eisai, Eli Lilly, Janssen, MSD, Novartis, Oncosec, Olema, Roche, and Seagen; served as an advisor for Amgen, AstraZeneca, BMS, Eisai, Eli Lilly, Janssen, Merck Serono, MSD, Novartis, Olema, Oncosec, Pfizer, Roche, Seagen, Takeda, Zai Lab; and served as a speaker for Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Janssen, Johnson & Johnson, MSD, and Novartis. Dr. Pons-Tostivint reports serving on the advisory board for AstraZeneca, Takeda, BMS, and Sanofi; having financial interests, institutional, local PI from AstraZeneca, BMS, Daiichi Sankyo, Sanofi, PDC line, Takeda, and Amgen. Dr. Dudnik reports receiving funding to the institution to support study conduct from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Prof. Ahmed reports receiving travel grants, lecture fees, and consultancies from MSD, Merck Serono, AstraZeneca, Novartis, Eisai, Lilly, Roche, Pfizer, Daiichi, and Gilead. Dr. Okpara reports serving as an employee of Eisai Ltd., Hatfield, UK. Dr. Dutcus reports serving as an employee of Eisai Inc., Nutley, NJ, USA. Dr. Yin reports serving as an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. Dr. Luo reports serving as an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. Dr. Chirovsky reports serving as an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. Dr. Bhagwati reports serving as an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. Dr. Abreu reports receiving personal fees/honoraria for consultancy/having advisory role and lectures from Roche/Genentech, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, MSD, Merck Serono, Eli Lilly, Gilead, Sanofi, Regeneron, Incyte, Pfizer, Takeda, and Novartis; receiving travel expenses from Roche, Bristol-Myers Squibb, MSD, Sanofi, Regeneron, and Novartis; and receiving institutional grant support for studies from BMS.

Acknowledgments

Funding for this research was provided by Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. We thank the participants and their families and caregivers for participating in this study, along with all investigators and site personnel. Eli Lilly provided pemetrexed but had no additional role in trial conduct. Medical writing assistance was provided by Andrea Bothwell, BSc, of ICON plc (Blue Bell, PA, USA). This assistance was funded by Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. The list of trial investigators can be found in the Data Supplement.

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.2025.05.016.

References

1. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
2. Kimura T, Kato Y, Ozawa Y, et al. Immunomodulatory activity of lenvatinib contributes to antitumor activity in the Hepa1-6 hepatocellular carcinoma model. *Cancer Sci*. 2018;109:3993–4002.
3. Zhao Y, Zhang YN, Wang KT, Chen L. Lenvatinib for hepatocellular carcinoma: from preclinical mechanisms to anti-cancer therapy. *Biochim Biophys Acta Rev Cancer*. 2020;1874:188391.
4. Taylor MH, Lee CH, Makker V, et al. Phase IB/II trial of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma, endometrial cancer, and other selected advanced solid tumors. *J Clin Oncol*. 2020;38:1154–1163.
5. Gutierrez M, Lam WS, Hellmann MD, et al. Biomarker-directed, pembrolizumab-based combination therapy in non-small cell lung cancer: phase 2 KEYNOTE-495/KeyImPaCT trial interim results. *Nat Med*. 2023;29:1718–1727.
6. Yang JC, Han B, De La Mora Jiménez E, et al. 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. *J Thorac Oncol*. 2024;19:941–953.
7. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18:e143–e152.
8. Leighl N, Paz-Ares L, Abreu DR, et al. 65O Phase III LEAP-008 study of lenvatinib plus pembrolizumab versus docetaxel for metastatic non-small cell lung cancer (NSCLC) that progressed on a PD-(L)1 inhibitor and platinum-containing chemotherapy. *Immunooncol Technol*. 2023;20:100537.
9. Borghaei H, de Marinis F, Dumoulin D, et al. SAPPHIRE: phase III study of sitravatinib plus nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *Ann Oncol*. 2024;35:66–76.
10. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288–2301.
11. Socinski MA, Nishio M, Jotte RM, et al. IMpower150 final overall survival analyses for atezolizumab plus bevacizumab and chemotherapy in first-line metastatic nonsquamous NSCLC. *J Thorac Oncol*. 2021;16:1909–1924.
12. Xiong A, Wang L, Chen J, et al. Ivonescimab versus pembrolizumab for PD-L1-positive non-small cell lung cancer (HARMONi-2): a randomised, double-blind, phase 3 study in China. *Lancet*. 2025;405:839–849.
13. Schlumberger M, Jarzab B, Cabanillas ME, et al. A phase II trial of the multitargeted tyrosine kinase inhibitor lenvatinib (E7080) in advanced medullary thyroid cancer. *Clin Cancer Res*. 2016;22:44–53.
14. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372:621–630.
15. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol*. 2015;16:1473–1482.
16. Motzer RJ, Taylor MH, Evans TRJ, et al. Lenvatinib dose, efficacy, and safety in the treatment of multiple malignancies. *Expert Rev Anticancer Ther*. 2022;22:383–400.
17. Herbst RS, Blanke CD, Sigal EV. Novel approach to accelerate lung cancer research: Lung-MAP and the potential of public-private partnerships. *Clin Cancer Res*. 2024;30:29–32.
18. Li S, de Camargo Correia GS, Wang J, Manochakian R, Zhao Y, Lou Y. Emerging targeted therapies in advanced non-small-cell lung cancer. *Cancers (Basel)*. 2023;15:2899.