ORIGINAL ARTICLE

# LEAP-008: Lenvatinib Plus Pembrolizumab for Metastatic NSCLC That Has Progressed After an Anti–Programmed Cell Death Protein 1 or Anti–Programmed Cell Death Ligand 1 Plus Platinum Chemotherapy

Natasha B. Leighl, MD, MMSc,[a,*] Luis Paz-Ares, MD,[b] Delvys Rodriguez Abreu, MD, PhD,[c] Rina Hui, MBBS, PhD,[d,e] Sofia Baka, MD, MSc, PhD,[f] Frédéric Bigot, MD,[g] Makoto Nishio, MD, PhD,[h] Alexey Smolin, MD,[i] Samreen Ahmed, MD,[j] Adam J. Schoenfeld, MD,[k] Sameh Daher, MD,[l] Diego L. Cortinovis, MD,[m] Vincenzo Di Noia, MD,[n] Helena Linardou, MD,[o] Justin F. Gainor, MD,[p] Corina Dutcus, MD,[q] Chinyere E. Okpara, PhD,[r] Xuan Deng, PhD,[s] Debra Kush, MBA, BSN,[s,†] Ashwini Arunachalam, MD,[s] Andrew Song, MD,[s] Byoung Chul Cho, MD, PhD[t]

[a]*Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada*
[b]*Hospital Universitario 12 de Octubre, Spanish National Cancer Research Center (CNIO), and Universidad Complutense, Madrid, Spain*
[c]*Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain*
[d]*Westmead Hospital and the University of Sydney, Sydney, New South Wales, Australia*
[e]*Current affiliation: Centre of Cancer Medicine, University of Hong Kong, Hong Kong*
[f]*Interbalkan European Medical Center, Thessaloniki, Greece*
[g]*Institut de Cancérologie de l'Ouest, Angers, France*
[h]*Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto-Ku, Japan*
[i]*Burdenko Main Military Hospital, Moscow, Russia*
[j]*University Hospitals of Leicester National Health Service (NHS) Trust, Leicester, United Kingdom*
[k]*Memorial Sloan Kettering Cancer Center, New York, New York*
[l]*Rambam Cancer Division, Rambam Health Care Campus, Haifa, Israel*
[m]*Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Gerardo dei Tintori Monza, University Milano-Bicocca, Milano, Italy*
[n]*IRCCS Regina Elena National Cancer Institute, Rome, Italy*
[o]*Fourth Oncology Department and Comprehensive Clinical Trials Center, Metropolitan Hospital, Athens, Greece*
[p]*Massachusetts General Hospital Cancer Center, Boston, Massachusetts*
[q]*Eisai Inc., Nutley, New Jersey*
[r]*Eisai Ltd., Hatfield, United Kingdom*
[s]*Merck & Co., Inc., Rahway, NJ, USA*
[t]*Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea*

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*Corresponding author.

[†]Affiliation at the time of the analysis

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Address for correspondence: Natasha B. Leighl, MD, MMSc, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, 7-913 700 University Avenue, Toronto, ON M5G 1Z5, Canada. E-mail: Natasha.Leighl@uhn.ca

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**ABSTRACT**

**Background:** LEAP-008 (NCT03976375) was an open-label, randomized, phase 3 study of lenvatinib plus pembrolizumab versus docetaxel for metastatic NSCLC that progressed on anti–programmed cell death protein 1 or anti–programmed cell death ligand 1 therapy and platinum-containing chemotherapy.

**Methods:** Participants were randomized 4:4:1 to once-daily lenvatinib 20 mg plus pembrolizumab 200 mg every 3 weeks (maximum 35 cycles), docetaxel 75 mg/m$^2$ every 3 weeks, or once-daily lenvatinib 24 mg. Primary end points were overall survival (OS) and progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 by central review. The superiority of lenvatinib plus pembrolizumab versus docetaxel was assessed at interim analysis 2 for PFS and final analysis for OS.

**Results:** Participants (N = 422) were randomized to lenvatinib plus pembrolizumab (n = 185), docetaxel (n = 189), or lenvatinib monotherapy (n = 48). The median (95% confidence interval [CI]) PFS was 5.6 (4.2–6.5) months with lenvatinib plus pembrolizumab and 4.2 (3.2–5.2) months with docetaxel (hazard ratio, 0.89 [95% CI: 0.70–1.12]; $p = 0.164$). The median (95% CI) OS was 11.3 (9.4–13.2) versus 12.0 (9.6–13.7) months (hazard ratio, 0.98 [95% CI: 0.78–1.23]; $p = 0.434$). Rates of treatment-related adverse events were 91.7%, 91.0%, and 89.4% with lenvatinib plus pembrolizumab, docetaxel, and lenvatinib, respectively; the rates of grade 3 to 5 treatment-related adverse events were 59.7%, 48.6%, and 57.4%. Health-related quality of life scores were similar between treatment arms.

**Conclusion:** Lenvatinib plus pembrolizumab did not improve efficacy versus docetaxel in participants with stage IV NSCLC that progressed on anti–programmed cell death protein 1 or anti–programmed cell death ligand 1 therapy and platinum-containing chemotherapy. There were no unexpected safety signals. More effective therapies are needed for this patient population.



*Keywords:* Docetaxel; Phase 3 clinical trial; Lenvatinib; Non–small-cell lung cancer; NSCLC; Pembrolizumab

## Introduction

Anti–programmed cell death protein 1 (PD-1) and anti–programmed cell death ligand 1 (PD-L1) monoclonal antibodies and platinum-based chemotherapy are an integral part of NSCLC treatment.[1] However, there is an unmet medical need for therapies that improve outcomes after progression on anti–PD-1 or anti–PD-L1 therapies and chemotherapy. Treatment options are limited for these patients, with docetaxel as the current standard of care.[1,2] Data suggest limited incremental benefit from the addition of VEGF inhibitors ramucirumab[3] and nintedanib[4] to docetaxel, and the use of TROP2-targeting datopotamab deruxtecan, which may be a potential alternative to docetaxel.[5]

Pembrolizumab is an approved anti–PD-1 monoclonal antibody with demonstrated efficacy in patients with metastatic NSCLC with a PD-L1 tumor proportion score (TPS) greater than or equal to 1% who have progressed after previous platinum-based chemotherapy, on the basis of results from the phase 3 KEYNOTE-010 randomized trial.[6,7]

Lenvatinib, a multiple tyrosine kinase inhibitor of the VEGF receptor (VEGFR), FGFR, PDGFR, RET, and cKIT, has been found in preclinical studies to shift the tumor microenvironment to an immune-stimulatory state.[8–10] Preclinical data demonstrated antitumor activity with lenvatinib monotherapy in a broad range of human tumor xenograft models, including a lung model.[11] Data from clinical studies suggested antitumor activity with first-line lenvatinib plus carboplatin and paclitaxel in stage IIIB or IV NSCLC,[12] combined with supportive care as third- or later-line therapy for advanced NSCLC,[13] and as first- or subsequent-line monotherapy for RET-positive lung adenocarcinoma.[14] Antitumor activity has been demonstrated with the combination of first-line lenvatinib plus pembrolizumab for advanced NSCLC.[15] Furthermore, treatment with lenvatinib plus pembrolizumab as second- or subsequent-line therapy in advanced melanoma with progression after anti–PD-1 or anti–PD-L1 treatment or NSCLC after progression with an anticancer agent resulted in objective response rates (ORRs) of 21.4% and 33%, respectively. Of those with NSCLC, two experienced a response after previous anti–PD-1 treatment (1 partial response [PR], 1 complete response [CR]).[16,17]

Here, we report results from the phase 3 LEAP-008 study, which evaluated lenvatinib plus pembrolizumab versus docetaxel monotherapy in participants with metastatic NSCLC that progressed after one previous anti–PD-1 or anti–PD-L1 therapy and platinum-based chemotherapy given sequentially or in combination. We also sought to determine the contribution of lenvatinib to the overall treatment effect of lenvatinib plus pembrolizumab by adding a lenvatinib monotherapy arm for the purpose of comparison with the lenvatinib plus pembrolizumab arm.

## Materials and Methods

### *Study Design and Participants*

LEAP-008 (NCT03976375) was a phase 3, multicenter, randomized, open-label trial that compared the

efficacy and safety of lenvatinib in combination with pembrolizumab versus docetaxel monotherapy in participants with metastatic NSCLC and progressive disease (PD) after immunotherapy and platinum-doublet chemotherapy. Participants were also randomized to a treatment arm of lenvatinib monotherapy for the purpose of comparison with the lenvatinib plus pembrolizumab arm to assess the degree to which lenvatinib contributed to the combination.

Full eligibility criteria are provided in the study protocol which is available in the Data Supplement. Eligible participants (aged ≥18 years) had histologically or cytologically confirmed metastatic squamous or nonsquamous NSCLC (stage IV per American Joint Committee on Cancer staging manual, eighth edition) for which *EGFR*-, *ALK*-, or *ROS1*-directed therapy was not indicated, and investigator-confirmed PD (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) after treatment with one prior anti–PD-1 or anti–PD-L1 monoclonal antibody (≥2 doses as monotherapy or in combination with other checkpoint inhibitors or therapies) and during or after platinum-doublet chemotherapy (sequentially or concomitantly with previous anti–PD-1 or anti–PD-L1 therapy). Receipt of a platinum-containing doublet as (neo)adjuvant therapy or chemoradiation treatment for stage I to III disease within the previous 1 year or less satisfied the previous platinum-doublet chemotherapy requirement. Participants also had measurable disease per RECIST version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of at least 3 months, and available archival (i.e., obtained any time from the initial diagnosis to before receiving immunotherapy) tumor tissue sample for PD-L1 evaluation and new tumor (i.e., from after completion of previous immunotherapy, unirradiated, to before randomization) tissue sample. Participants were excluded if they had any of the following: (1) clinically significant hemoptysis or tumor bleeding 2 weeks or less before study treatment; (2) intratumoral cavitation, encasement, or invasion of a major blood vessel; (3) significant cardiovascular impairment 12 months or less before study treatment; (4) previously experienced a gastrointestinal condition or procedure that might affect drug absorption; (5) a preexisting grade 3 or higher fistula; (6) immunodeficiency or received long-term systemic steroids or immunosuppressive therapy 7 days or less before study treatment; (7) any other known malignancy, active central nervous system metastasis, carcinomatous meningitis, or active autoimmune disease requiring systemic treatment within 2 years or less; (8) an active infection requiring systemic therapy, or a history of human immunodeficiency virus or hepatitis B or C infection; (9) a history of noninfectious pneumonitis requiring systemic steroids or current pneumonitis or interstitial lung disease; or (10) any other condition that might affect the study results.

The study was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. The protocol and all amendments were approved by all relevant independent ethics committees, institutional review boards, or both. All participants provided written informed consent before enrolling.

## Treatment

Participants were randomized 4:4:1 by means of an interactive response technology system to receive oral lenvatinib 20 mg once daily plus intravenous pembrolizumab 200 mg every 3 weeks for 35 cycles or less (lenvatinib plus pembrolizumab arm), intravenous docetaxel 75 mg/m$^2$ every 3 weeks (docetaxel arm), or oral lenvatinib 24 mg monotherapy once daily. Randomization was stratified by previous anti–PD-1 or anti–PD-L1 therapy (immediately before versus not immediately before the study), PD-L1 TPS (<50% versus ≥50%), and ECOG performance status (0 versus 1). Treatment with lenvatinib or docetaxel continued until PD, participant or investigator withdrawal, loss to follow-up, or study end. Dose reductions and interruptions were permitted for lenvatinib and docetaxel; dose reductions were not permitted for pembrolizumab, but the dose was interrupted if needed because of toxicity. Treatment crossover was not permitted.

## End Points

The dual primary end points were OS (time from randomization to death from any cause) and PFS (time from randomization to first documented PD or death from any cause) per RECIST version 1.1 by blinded independent central review (BICR) with lenvatinib plus pembrolizumab versus docetaxel. Secondary end points included ORR and duration of response (DOR) per RECIST version 1.1 by BICR; adverse events (AEs); discontinuations because of AEs; mean changes from baseline in health-related quality of life scores (HRQoL), including global health status (GHS)/QoL, dyspnea, and physical functioning scores (assessed using the European Organization for Research and Treatment of Cancer [EORTC] Quality-of-Life Questionnaire–Core 30 [QLQ-C30]), and cough and chest pain scores (assessed using the EORTC Quality-of-Life Questionnaire–13-item Lung Cancer Module [QLQ-LC13]); and time to true deterioration (TTD) in GHS/QoL, dyspnea, physical functioning, cough, chest pain, and the composite symptom end point of dyspnea, cough, and chest pain. ORR was defined as a confirmed CR or PR, and DOR was defined as the time from first documented

evidence of CR or PR until PD or death because of any cause. TTD was defined as the time from baseline to first onset of a 10-point or higher decrease in each of the aforementioned HRQoL scales and items, with confirmation of at least a 10-point deterioration at the subsequent visit. Subgroup analyses of PFS per RECIST version 1.1 by BICR and OS were conducted in both prespecified and exploratory post hoc groups. The exploratory post hoc group assessed participants on the basis of the best response to immediate previous anti–PD-1 or anti–PD-L1 therapy.

### Assessments

Tumor PD-L1 expression was assessed centrally during screening using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA) using a formalin-fixed tumor sample collected at diagnosis. Tumor imaging was performed using computed tomography or magnetic resonance imaging at screening, every 6 weeks after randomization until week 36, every 9 weeks until week 54, and then every 12 weeks until the final study follow-up. Tumor response was centrally assessed as per RECIST version 1.1 modified to follow 10 or fewer target lesions, with 5 or fewer target lesions per organ.

AEs were monitored throughout the study until 30 days (90 days for serious AEs) after the last dose of the study drug, with severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Immune-mediated AEs and infusion reactions (i.e., AEs of special interest for pembrolizumab) and clinically significant AEs for lenvatinib were identified on the basis of a list of preferred terms intended to capture known risks of pembrolizumab or lenvatinib and were considered regardless of attribution to study treatment by the investigator.

EORTC QLQ-C30 and QLQ-LC13 questionnaires for assessment of HRQoL scores were completed electronically before any study procedure including dosing at every cycle up to cycle 17, at every other cycle through cycle 35, and then at the end-of-treatment and 30-day safety follow-up visits.

### Statistical Analyses

OS, PFS, ORR, and DOR were assessed in the intention-to-treat (ITT) population, including all randomized participants. Safety was assessed in all randomized participants who received at least one dose of the study drug. HRQoL was assessed in the patient-reported outcomes (PRO) population, including all randomized participants who had at least one PRO assessment and received one or more doses of the study drug.

The study's multiple testing strategy included hypotheses for analyses of OS, PFS, and ORR for lenvatinib plus pembrolizumab versus docetaxel and of ORR for lenvatinib plus pembrolizumab versus lenvatinib alone. Multiplicity was controlled using the graphical method of Maurer and Bretz with an overall one-sided 2.5% type I error rate for hypothesis testing of PFS, OS, and ORR for lenvatinib plus pembrolizumab versus docetaxel, with preallocated $\alpha$ at 0.0029, 0.019, and 0.003, respectively, and of ORR for lenvatinib plus pembrolizumab versus lenvatinib with preallocated $\alpha$ at 0 (Supplementary Fig. 1). The protocol specified a single-arm futility analysis, two interim analyses, and a final analysis. The single-arm futility analysis occurred after the first 18 participants in the lenvatinib plus pembrolizumab group had been treated and followed up for 20 weeks. Nonbinding passing criteria for passing futility were at least three objective responses or disease control rates of greater than 50% at 12 weeks and at least one objective response. The final analysis of ORR for lenvatinib plus pembrolizumab versus docetaxel occurred at the first interim analysis, the final analysis of PFS and interim analysis of OS for lenvatinib plus pembrolizumab versus docetaxel and ORR analysis for lenvatinib plus pembrolizumab versus lenvatinib occurred at the second interim analysis (IA2), and the final analysis of OS for lenvatinib plus pembrolizumab versus docetaxel occurred at the study's final analysis. The Lan-DeMets O'Brien-Fleming group sequential method was used to allocate an $\alpha$ of 0.019 among the interim and final analyses for OS. If the observed number of OS events at the interim and final analyses differs from those prespecified, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly, with spending time determined by the minimum of the actual information fraction and the expected information fraction.

The planned sample size was 405 participants, including 45 participants in the lenvatinib arm. The IA2 was planned for after approximately 279 PFS events had occurred in the lenvatinib plus pembrolizumab and docetaxel arms and 6 months or longer after the last participant was randomized. The final OS analysis was planned for after approximately 299 participants in the lenvatinib plus pembrolizumab and docetaxel arms had died and at least 12 months after the last participant was randomized. The planned sample size provided approximately 93.6% power to detect a treatment difference in PFS at the IA2 with a hazard ratio (HR) of 0.6 (on the basis of ~279 events in 360 participants and an assumed median PFS of 4.1 months in the docetaxel arm) at an overall $\alpha$ level of 0.29% (one-sided) and 93.3% power to detect a treatment difference in OS at the study's final analysis with an HR of 0.66 (on the basis of ~299 events in 360 participants and an assumed median OS of 8.6 months in the docetaxel arm) at an overall $\alpha$ level of 1.9% (one-sided).

For the primary analyses of OS and PFS, between-group differences for the lenvatinib plus pembrolizumab

versus docetaxel arm were estimated using a stratified log-rank test. HRs were estimated using a stratified Cox regression model with the Efron tie-handling method, and PFS and OS event rates over time were estimated using the Kaplan-Meier method. ORRs were estimated using the stratified Miettinen and Nurminen method with stratification (lenvatinib plus pembrolizumab versus docetaxel) and without stratification (lenvatinib plus pembrolizumab versus lenvatinib). DOR was analyzed using summary statistics and the Kaplan-Meier method.

Between-group differences in the least-squares (LS) mean changes from baseline in HRQoL scores and their accompanying 95% confidence intervals (CIs) were estimated using a constrained longitudinal data analysis model, with an unstructured covariance matrix of treatment, time (i.e., study visit), treatment by time interaction, and randomization stratification factors as covariates. Model-based LS means with 95% CIs were provided by treatment group for HRQoL scores at baseline and week 12. TTD was evaluated using the same statistical analyses as those used for the primary end points.

## Results

### *Participants*

Between June 26, 2019, and February 17, 2022, 422 participants were randomized at 143 global sites to receive lenvatinib plus pembrolizumab (n = 185), docetaxel (n = 189), or lenvatinib (n = 48) (Fig. 1). Overall, the median age was 65.0 (range, 30–82) years, 276 participants (65.4%) were of male sex, 271 (64.2%) had an ECOG performance status of 1, 309 (73.2%) had PD-L1 TPS less than 50%, and 333 (78.9%) had received anti–PD-1 or anti–PD-L1 therapy as immediate previous therapy (Table 1).

The median time from randomization to data cutoff at the study's final analysis (August 11, 2023) was 31.8 (range, 16.5–48.7) months. At the final analysis, the median duration of treatment was 6.1 months in the lenvatinib plus pembrolizumab arm, 3.4 months in the docetaxel arm, and 4.4 months in the lenvatinib arm (Supplementary Table 1), and the median number of treatment cycles was 8 and 5 in the lenvatinib plus pembrolizumab and docetaxel arms, respectively. A total of 188 participants received at least one subsequent systemic therapy (lenvatinib plus pembrolizumab, n = 74 [40.0%]; docetaxel, n = 99 [52.4%]; lenvatinib, n = 15 [31.3%]) (Supplementary Table 2).

### *Efficacy*

In the ITT population at IA2 (protocol-specified final analysis for PFS), 148 participants (80.0%) in the lenvatinib plus pembrolizumab arm and 139 participants (73.5%) in the docetaxel arm had experienced a PFS event; the median (95% CI) PFS was 5.6 (4.2–6.5) months and 4.2 (3.2–5.2) months, respectively (HR, 0.89 [95% CI: 0.70–1.12]; $p = 0.164$ [superiority threshold,

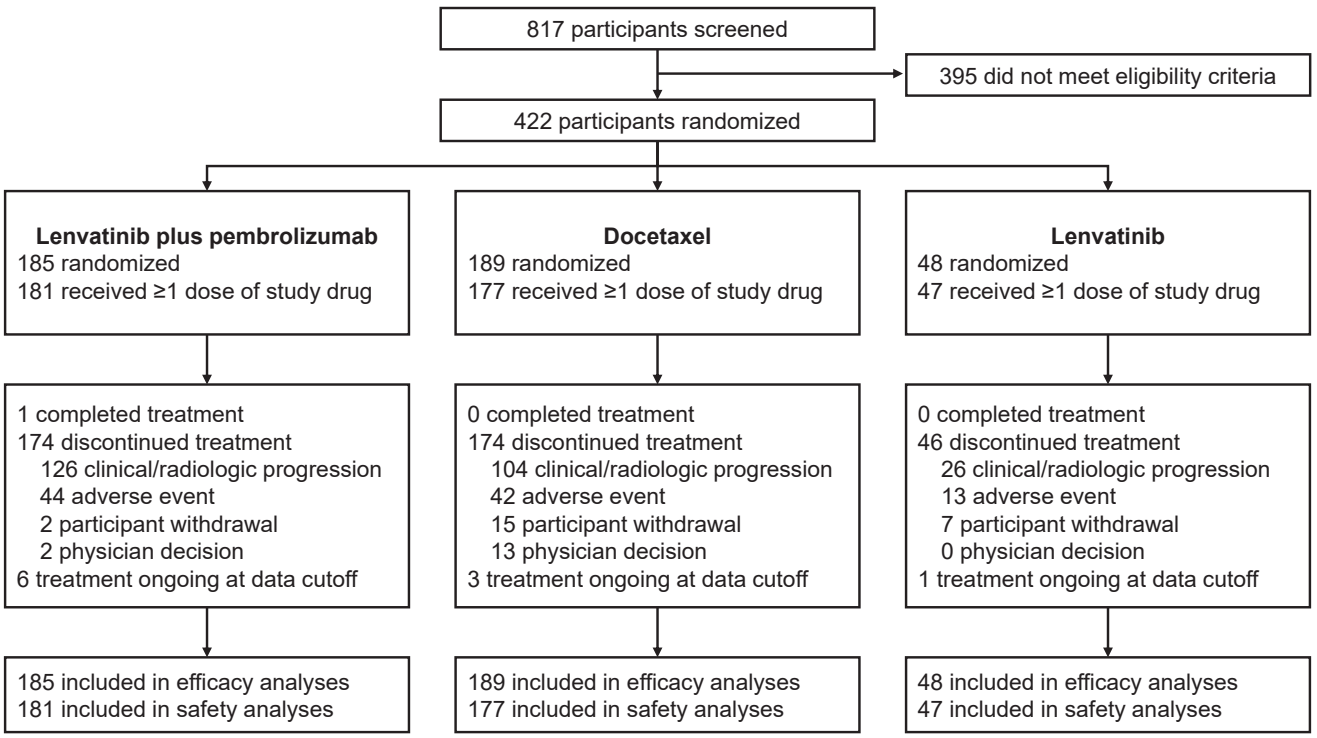


**Figure 1.** Participant disposition.

**Table 1.** Demographics and Baseline Disease Characteristics

| Characteristic | Lenvatinib Plus Pembrolizumab (n = 185) | Docetaxel (n = 189) | Lenvatinib (n = 48) |
|---|---|---|---|
| Age | | | |
| Median (range), y | 65.0 (41-81) | 65.0 (30-82) | 64.0 (47-77) |
| <65 | 91 (49.2) | 89 (47.1) | 25 (52.1) |
| ≥65 | 94 (50.8) | 100 (52.9) | 23 (47.9) |
| Sex | | | |
| Female | 67 (36.2) | 60 (31.7) | 19 (39.6) |
| Male | 118 (63.8) | 129 (68.3) | 29 (60.4) |
| PD-L1 TPS | | | |
| <1% | 90 (48.6) | 93 (49.2) | 24 (50.0) |
| 1%-49% | 45 (24.3) | 47 (24.9) | 10 (20.8) |
| ≥50% | 34 (18.4) | 33 (17.5) | 10 (20.8) |
| Unknown | 16 (8.6) | 16 (8.5) | 4 (8.3) |
| ECOG performance status | | | |
| 0 | 67 (36.2) | 67 (35.4) | 17 (35.4) |
| 1 | 118 (63.8) | 122 (64.6) | 31 (64.6) |
| Histology | | | |
| Squamous | 50 (27.0) | 58 (30.7) | 6 (12.5) |
| Nonsquamous | 135 (73.0) | 131 (69.3) | 42 (87.5) |
| Brain metastasis at baseline | 35 (18.9) | 33 (17.5) | 10 (20.8) |
| Previous neoadjuvant or adjuvant therapy | 22 (11.9) | 19 (10.1) | 5 (10.4) |
| Sequence of previous anti-PD-1 or anti-PD-L1 | | | |
| Immediate previous therapy | 145 (78.4) | 150 (79.4) | 38 (79.2) |
| Not immediate previous therapy | 40 (21.6) | 39 (20.6) | 10 (20.8) |
| Sequence of previous anti-PD-1 or anti-PD-L1 with chemotherapy | | | |
| Concomitant | 93 (50.3) | 106 (56.1) | 34 (70.8) |
| Sequential | 91 (49.2) | 83 (43.9) | 14 (29.2) |
| Missing | 1 (0.5) | 0 | 0 |
| Number of previous lines of therapy for recurrent or metastatic disease | | | |
| 1 | 82 (44.3) | 97 (51.3) | 28 (58.3) |
| 2 | 83 (44.9) | 78 (41.3) | 17 (35.4) |
| 3 | 13 (7.0) | 10 (5.3) | 2 (4.2) |
| ≥4 | 6 (3.2) | 4 (2.1) | 1 (2.1) |
| Not applicable | 1 (0.5) | 0 | 0 |
| Previous anti-PD-1 or anti-PD-L1 | | | |
| Pembrolizumab | 110 (59.5) | 105 (55.6) | 35 (72.9) |
| Other | 71 (38.4) | 82 (43.4) | 13 (27.1) |
| >1 anti-PD-1 or anti-PD-L1 | 4 (2.2) | 2 (1.1) | 0 |

Note: Except where indicated, data are n (%).
ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score.

one-sided $p = 0.0029$]). The HR (95% CI) did not change by the study's final analysis (Fig. 2*A*). Outcomes were similar in most subgroups defined by demographics and baseline clinical characteristics (Fig. 2*B*). For participants who had not received anti–PD-1 or anti–PD-L1 as immediate previous therapy, greater PFS benefit was observed with lenvatinib plus pembrolizumab versus docetaxel (HR, 0.56 [95% CI: 0.33–0.95]) compared with those who had received anti–PD-1 or anti–PD-L1 as immediate previous therapy (HR, 0.96 [95% CI: 0.74–1.24]) (Fig. 2*B*).

In the ITT population at the final analysis, 150 participants (81.1%) in the lenvatinib plus pembrolizumab arm and 154 participants (81.5%) in the docetaxel arm had died. The median (95% CI) OS was 11.3 (9.4–13.2) months in the lenvatinib plus pembrolizumab arm and 12.0 (9.6–13.7) months in the docetaxel arm (HR, 0.98 [95% CI: 0.78–1.23]; $p = 0.434$ [superiority threshold, one-sided $p = 0.0166$]) (Fig. 3*A*). Outcomes were generally similar in subgroups defined by demographics and baseline clinical characteristics (Fig. 3*B*). There was a trend toward improved OS with lenvatinib plus pembrolizumab versus docetaxel in participants who had not received anti–PD-1 or anti–PD-L1 as immediate previous therapy (HR, 0.73 [95% CI: 0.44–1.20]) compared with those who had received anti–PD-1 or anti–PD-L1 as

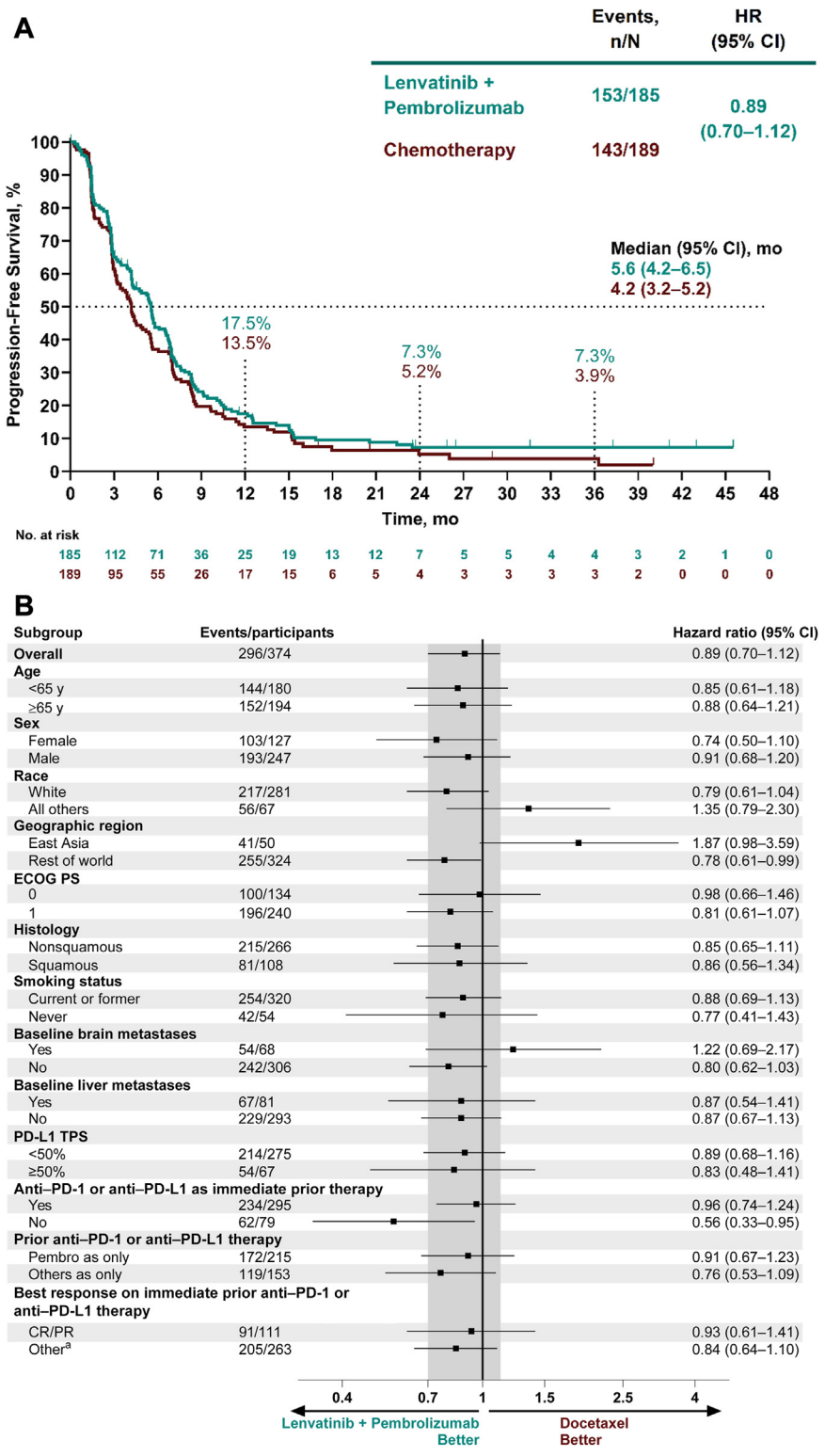


**Figure 2.** PFS in the lenvatinib plus pembrolizumab and docetaxel arms at the final analysis (data cutoff date: August 11, 2023). (*A*) Kaplan-Meier curves and (*B*) forest plot of analyses by participant subgroup. [a]Includes participants with best response of indeterminate response, stable disease, progressive disease, or not evaluable. CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intention-to-treat; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PR, partial response; TPS, tumor proportion score.

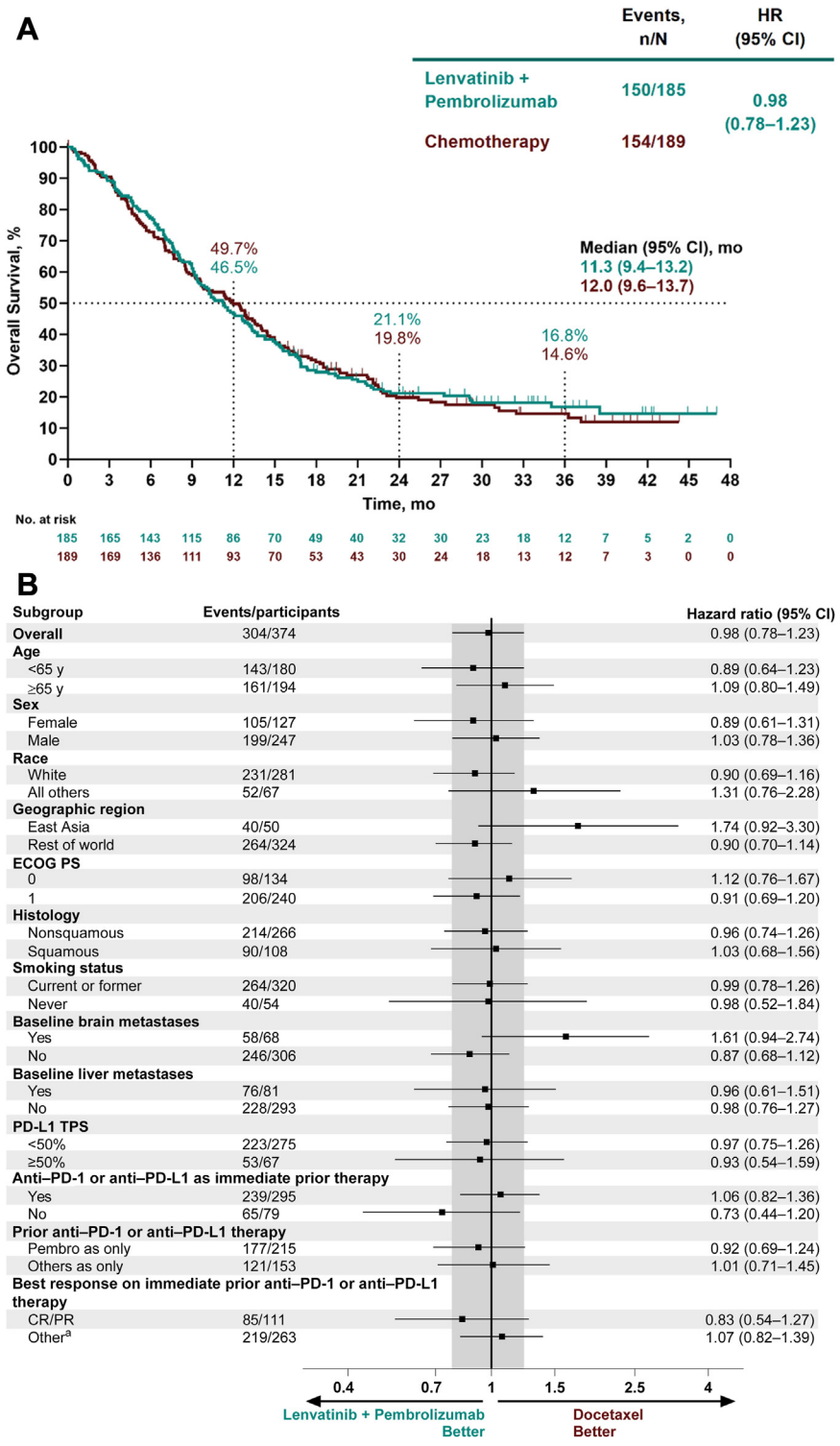


**Figure 3.** OS in the lenvatinib plus pembrolizumab and docetaxel arms at the final analysis (data cutoff date: August 11, 2023). (*A*) Kaplan-Meier curves and (*B*) forest plot of analyses by participant subgroup. [a]Includes participants with a best response of indeterminate response, stable disease, progressive disease, or not evaluable. CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PR, partial response; TPS, tumor proportion score.

immediate previous therapy (HR, 1.06 [95% CI: 0.82–1.36]) (Fig. 3*B*).

At the first interim analysis (protocol-specified final analysis of ORR for lenvatinib plus pembrolizumab versus docetaxel), ORR was not significantly different between the study arms, with 25.0% (95% CI: 16.9%–34.7%; n = 25/100 participants) for lenvatinib plus pembrolizumab versus 17.0% (10.2%–25.8%; n = 17/100) for docetaxel, with a difference of 8.1 percentage points (95% CI: −3.4 to 19.5; $p = 0.082$ [superiority threshold, one-sided $p = 0.003$]). At IA2 (protocol-specified final analysis of ORR for lenvatinib plus pembrolizumab versus lenvatinib), ORR (95% CI) was 21.6% (15.9%–28.3%; n = 40/185) versus 10.4% (3.5%–22.7%; n = 5/48), respectively; no statistical significance testing was performed per the prespecified multiplicity strategy. At the final analysis, 42 of 185 participants treated with lenvatinib plus pembrolizumab, 27 of 189 participants treated with docetaxel, and 6 of 48 participants treated with lenvatinib had a response, representing ORRs (95% CIs) of 22.7% (16.9%–29.4%), 14.3% (9.6%–20.1%), and 12.5% (4.7%–25.2%), respectively. At final analysis, the median (range) DOR was 6.9 (2.3–42.8+; + indicates no PD at last disease assessment) months with lenvatinib plus pembrolizumab, 6.8 (2.5+ to 33.0+) months with docetaxel, and 9.4 (2.6–16.6) months with lenvatinib monotherapy (Fig. 4).

## *Safety*

The safety analysis population included 405 participants (lenvatinib plus pembrolizumab, n = 181; docetaxel, n = 177; lenvatinib, n = 47). Treatment-related AEs occurred in 166 participants (91.7%) in the lenvatinib plus pembrolizumab arm, 161 (91.0%) in the docetaxel arm, and 42 (89.4%) in the lenvatinib arm (Table 2). Grade 3 or 4 treatment-related AEs occurred in 101 of 181 participants (55.8%) with lenvatinib plus pembrolizumab, 84 of 177 participants (47.5 %) with docetaxel, and 24 of 47 participants (51.1%) with lenvatinib monotherapy. Grade 5 treatment-related AEs occurred in 12 participants, including 7 (3.9%) in the lenvatinib plus pembrolizumab arm (cardiorespiratory arrest, n = 2; hemoptysis, n = 2; death, n = 1; pneumonitis, n = 1; pulmonary embolism, n = 1), 2 (1.1%) in the docetaxel arm (pneumonitis and pneumonia, n = 1 each), and 3 (6.4%) in the lenvatinib arm (cardiac arrest, aggravated condition, and pulmonary hemorrhage, n = 1 each). Treatment-related AEs led to treatment discontinuation in 50 participants (27.6%) in the lenvatinib plus pembrolizumab arm, 26 (14.7%) in the docetaxel arm, and 6 (12.8%) in the lenvatinib arm.

Immune-mediated AEs and infusion reactions occurred in 83 participants (45.9%) in the lenvatinib plus pembrolizumab arm and 18 (10.2%) in the docetaxel arm (Supplementary Table 3). The most common immune-mediated AEs in the lenvatinib plus pembrolizumab arm were hypothyroidism (35.4%), hyperthyroidism (4.4%),

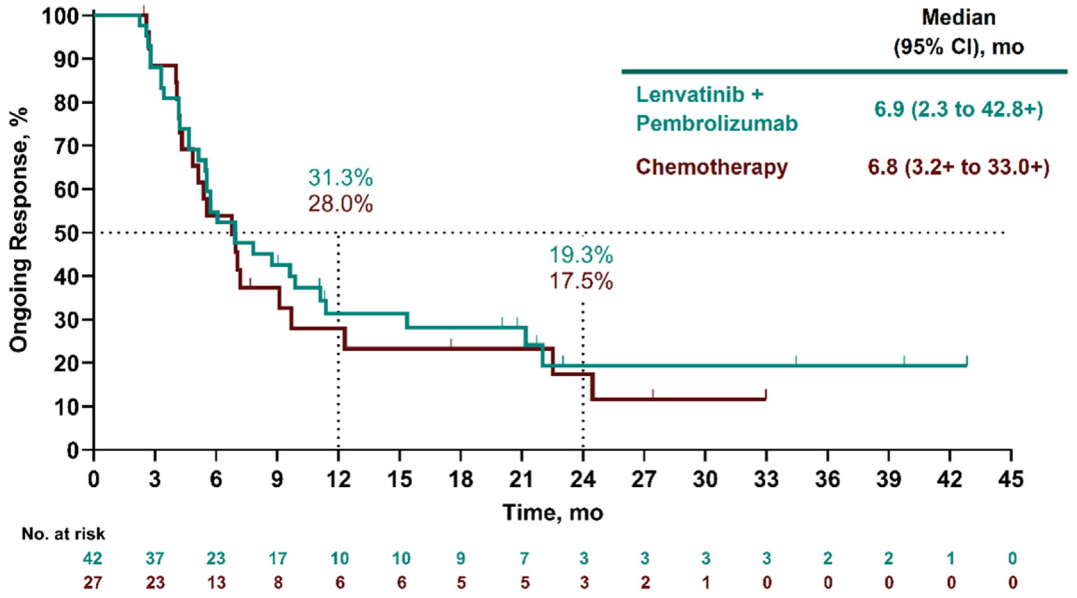


**Figure 4.** Kaplan-Meier estimates of duration of response with lenvatinib plus pembrolizumab or docetaxel (in the ITT population at the final analysis). + indicates there was no progressive disease by the time of the last disease assessment. ITT, intention-to-treat.

**Table 2.** Summary of Treatment-Related AEs

| Adverse Event | Lenvatinib Plus Pembrolizumab (n = 181) | | Docetaxel (n = 177) | | Lenvatinib (n = 47) | |
|---|---|---|---|---|---|---|
| Any AE | 179 (98.9) | | 174 (98.3) | | 47 (100) | |
| Led to dose reduction of lenvatinib | 83 (45.9) | | - | | 21 (44.7) | |
| Led to dose interruption of lenvatinib | 107 (59.1) | | - | | 37 (78.7) | |
| Treatment-related AEs | 166 (91.7) | | 161 (91.0) | | 42 (89.4) | |
| Grade 3–5 | 108 (59.7) | | 86 (48.6) | | 27 (57.4) | |
| Serious | 54 (29.8) | | 27 (15.3) | | 12 (25.5) | |
| Led to treatment discontinuation | 50 (27.6) | | 26 (14.7) | | 6 (12.8) | |
| Led to death | 7 (3.9)[a] | | 2 (1.1)[b] | | 3 (6.4)[c] | |
| Most common treatment-related AEs[d] | **Any Grade** | **Grade 3–5** | **Any Grade** | **Grade 3–5** | **Any Grade** | **Grade 3–5** |
| Hypertension | 65 (35.9) | 34 (18.8) | 0 | 0 | 17 (36.2) | 7 (14.9) |
| Hypothyroidism | 59 (32.6) | 0 | 0 | 0 | 13 (27.7) | 0 |
| Diarrhea | 57 (31.5) | 11 (6.1) | 29 (16.4) | 7 (4.0) | 16 (34.0) | 3 (6.4) |
| Asthenia | 37 (20.4) | 7 (3.9) | 33 (18.6) | 5 (2.8) | 9 (19.1) | 1 (2.1) |
| Decreased appetite | 36 (19.9) | 1 (0.6) | 24 (13.6) | 1 (0.6) | 7 (14.9) | 0 |
| Proteinuria | 31 (17.1) | 0 | 0 | 0 | 6 (12.8) | 2 (4.3) |
| Stomatitis | 31 (17.1) | 1 (0.6) | 19 (10.7) | 2 (1.1) | 10 (21.3) | 0 |
| Fatigue | 27 (14.9) | 2 (1.1) | 32 (18.1) | 4 (2.3) | 11 (23.4) | 2 (4.3) |
| Nausea | 26 (14.4) | 0 | 28 (15.8) | 3 (1.7) | 11 (23.4) | 1 (2.1) |
| Decreased platelet count | 22 (12.2) | 4 (2.2) | 4 (2.3) | 0 | 5 (10.6) | 2 (4.3) |
| Decreased weight | 20 (11.0) | 2 (1.1) | 4 (2.3) | 1 (0.6) | 6 (12.8) | 1 (2.1) |
| Pruritus | 19 (10.5) | 0 | 6 (3.4) | 0 | 1 (2.1) | 0 |
| Alopecia | 2 (1.1) | 0 | 45 (25.4) | 1 (0.6) | 0 | 0 |
| Anemia | 4 (2.2) | 1 (0.6) | 44 (24.9) | 7 (4.0) | 0 | 0 |
| Decreased neutrophil count | 6 (3.3) | 1 (0.6) | 35 (19.8) | 32 (18.1) | 3 (6.4) | 0 |
| Vomiting | 17 (9.4) | 3 (1.7) | 17 (9.6) | 2 (1.1) | 7 (14.9) | 1 (2.1) |
| Abdominal pain | 16 (8.8) | 2 (1.1) | 2 (1.1) | 0 | 6 (12.8) | 0 |
| Dysphonia | 14 (7.7) | 0 | 2 (1.1) | 0 | 5 (10.6) | 0 |
| Headache | 11 (6.1) | 0 | 4 (2.3) | 0 | 5 (10.6) | 0 |
| Constipation | 9 (5.0) | 0 | 7 (4.0) | 0 | 5 (10.6) | 0 |
| Myalgia | 11 (6.1) | 1 (0.6) | 18 (10.2) | 0 | 0 | 0 |
| Peripheral edema | 6 (3.3) | 0 | 18 (10.2) | 1 (0.6) | 0 | 0 |

Note: Data are n (%).
[a]Included cardiorespiratory arrest (n = 2), hemoptysis (n = 2), death (n = 1), pneumonitis (n = 1), and pulmonary embolism (n = 1).
[b]Included pneumonitis (n = 1) and pneumonia (n = 1).
[c]Included cardiac arrest (n = 1), aggravated condition (n = 1), and pulmonary hemorrhage (n = 1).
[d]Defined as those occurring in at least 10% of participants in any treatment arm.
AE, adverse event.

and colitis (3.3%). Immune-mediated AEs and infusion reactions were mostly grade 1 or 2; grade 3 events occurred in 12 participants (6.6%) in the lenvatinib plus pembrolizumab arm. One grade 5 immune-mediated AE occurred in the lenvatinib plus pembrolizumab arm (pneumonitis).

Clinically significant AEs for lenvatinib, on the basis of a prespecified list of terms and considered regardless of attribution to study treatment by investigators, occurred in 141 participants (77.9%) in the lenvatinib plus pembrolizumab arm, 46 (26.0%) in the docetaxel arm, and 36 (76.6%) in the lenvatinib arm (Supplementary Table 4). The most common clinically significant AEs in the lenvatinib plus pembrolizumab arm were hypertension (43.1%), hypothyroidism (35.4%), hemorrhage (22.7%), proteinuria (19.9%), and hepatotoxicity (18.8%); common clinically significant AEs in the lenvatinib arm included hypertension (53.2%), hypothyroidism (36.2%), and hemorrhage (21.3%). Grade 3 or 4 clinically significant AEs for lenvatinib occurred in 62 participants (34.3%) receiving lenvatinib plus pembrolizumab and in 17 participants (36.2%) receiving lenvatinib alone. Two participants in the lenvatinib plus pembrolizumab group (hemoptysis, n = 2) and one participant in the lenvatinib group (pulmonary hemorrhage) had grade 5 clinically significant AEs for lenvatinib.

## *Health-Related Quality of Life*

The PRO full analysis populations included 357 and 356 participants for the EORTC QLQ-C30 and QLQ-LC13 questionnaires, respectively (lenvatinib plus pembrolizumab, n = 181 each; docetaxel, n = 176 and n = 175, respectively). Completion and compliance rates for both the EORTC

QLQ-C30 and QLQ-LC13 instruments were similar between treatment arms, with >93.7% for both rates in both treatment arms at baseline and >64.8% and >91.9%, respectively, at week 12 (Supplementary Table 5).

Mean changes from baseline to week 12 in GHS/QoL, cough, chest pain, and physical functioning scales were similar, with no differences between the lenvatinib plus pembrolizumab and docetaxel arms (Supplementary Table 6). The mean dyspnea score worsened (decreased) from baseline to week 12 with lenvatinib plus pembrolizumab, and improved (score increased) with docetaxel (LS mean score, −2.92 versus 5.12; between-group difference, −8.04 [95% CI: −13.73 to −2.35]). There were no clinically meaningful differences in median TTD in GHS/QoL and physical functioning scores between treatment groups (Supplementary Fig. 2). The median TTD for the composite end point of dyspnea, cough, and chest pain was numerically longer with lenvatinib plus pembrolizumab versus docetaxel (HR, 0.84 [95% CI: 0.60−1.16]). HRs (95% CIs) for TTD in dyspnea (0.75 [0.49−1.16]) and cough (0.61 [0.38−0.98]) favored pembrolizumab plus lenvatinib.

## Discussion

In this phase 3 study of participants with metastatic NSCLC and PD after sequential or concomitant anti–PD-1 or anti–PD-L1 therapy and platinum-containing chemotherapy, the combination of lenvatinib plus pembrolizumab did not improve the primary end points of OS and PFS versus docetaxel. The safety profile of lenvatinib plus pembrolizumab was as expected on the basis of previous studies with the combination,[15,16] without any new safety signals identified. PROs were similar between treatment arms.

Lenvatinib plus pembrolizumab did not significantly improve PFS or OS versus docetaxel alone in this study. Although preclinical data reveal immune-modulating effects of lenvatinib on the tumor microenvironment,[8–10] comparing outcomes in the lenvatinib plus pembrolizumab arm with those in the lenvatinib monotherapy arm of this study demonstrated that the hypothesized additive effect of combination therapy with lenvatinib and pembrolizumab was not achieved in this patient population. Results from the lenvatinib arm provided evidence of moderate antitumor activity with lenvatinib monotherapy, with an ORR of 12.5% at the final analysis, suggesting a modest contribution of lenvatinib to the effects reported with lenvatinib plus pembrolizumab (ORR of 22.7% at final analysis). Two other phase 3 randomized trials evaluated regimens containing lenvatinib and pembrolizumab in advanced NSCLC. In the phase 3 LEAP-006 study, the addition of lenvatinib to pembrolizumab plus pemetrexed-platinum did not improve PFS or OS in participants with previously untreated nonsquamous NSCLC.[18] Similarly, in the phase 3 LEAP-007 study, lenvatinib plus pembrolizumab did not improve PFS or OS versus pembrolizumab alone in participants with previously untreated metastatic NSCLC and PD-L1 TPS of 1% or higher without targetable *EGFR* or *ALK* alterations.[19]

In this study, lenvatinib plus pembrolizumab exhibited improved PFS and a positive trend in OS versus docetaxel alone in participants who had not received anti–PD-1 or anti–PD-L1 as immediate previous therapy. In contrast, HRs for PFS and OS favored docetaxel in participants from East Asia compared with participants from the rest of the world, where the CIs for PFS in particular were almost nonoverlapping. Notably, greater efficacy has been reported previously with docetaxel in Asian patients compared with non-Asian patients with lung cancer.[20] HRs for PFS and OS also favored docetaxel in participants with baseline brain metastases; however, the sample size of participants with brain metastases is small and the CIs for HRs were wide and contained 1. Regardless, these results should be interpreted with caution without drawing definitive conclusions because the study was not powered to detect differences in treatment effects within participant subgroups. Immune checkpoint inhibitors in combination with antiangiogenic agents or multitargeted tyrosine kinase inhibitors after progression during immune checkpoint inhibitor therapy may overcome immunotherapy resistance by modulating the tumor immune microenvironment and providing broader anti-immunosuppression effects.[21] However, two additional phase 3 studies have failed to improve outcomes for immunotherapy plus multiple tyrosine kinase inhibitors versus chemotherapy in previously treated stage IV NSCLC.[22,23] The CONTACT-01 trial evaluated atezolizumab plus cabozantinib versus docetaxel in metastatic NSCLC previously treated with immune checkpoint inhibitors and chemotherapy.[22] No significant difference was found between treatments for OS (median, 10.7 versus 10.5 mo), PFS (median, 4.6 versus 4.0 mo), or ORR (11.8% versus 13.3%). Notably, the HR for OS favored docetaxel in participants who had not received anti–PD-1 or anti–PD-L1 as immediate previous therapy, although the CIs were wide and the number of participants in this subgroup was very small.[22] In the SAPPHIRE trial, no significant benefit was observed with nivolumab plus sitravatinib versus docetaxel in OS (12.2 versus 10.6 mo; HR, 0.86 [95% CI: 0.70−1.05]; $p = 0.144$), PFS (4.4 versus 5.4 mo; HR, 1.08 [95% CI: 0.89−1.32]; $p = 0.452$), or ORR (15.6% versus 17.2%; $p = 0.597$).[23] These findings align with the results from LEAP-008 and, together, suggest that an anti–PD-1 or anti–PD-L1 inhibitor plus a VEGF-targeting tyrosine kinase inhibitor does not improve outcomes for participants with previously treated metastatic NSCLC.

Another approach under investigation in a phase 3 trial (Pragmatica Lung; NCT05633602) is the combination of pembrolizumab and the anti-VEGFR2 antibody ramucirumab in participants with stage IV or recurrent NSCLC who have received at least one line of chemotherapy plus anti–PD-1 or anti–PD-L1 therapy, after promising results in a phase 2, randomized trial in which OS was significantly improved with pembrolizumab plus ramucirumab versus chemotherapy (OS HR, 0.69 [95% CI: 0.51–0.92]) in previously treated NSCLC.[24]

The safety profile for lenvatinib plus pembrolizumab was as anticipated on the basis of previous studies in previously untreated participants with advanced NSCLC or solid tumors including previously untreated NSCLC,[15,17] with hypertension, hypothyroidism, and diarrhea typically reported as any-grade treatment-related AEs with lenvatinib plus pembrolizumab in this analysis and previous studies of the combination.[15,17] In addition, rates of grade 3 or higher treatment-related AEs reported in the present analysis for lenvatinib plus pembrolizumab (59.7%) were generally similar to those reported in the phase 2 KEYNOTE-495/KeyImPaCT study in participants with previously untreated advanced NSCLC (68.8%) and a phase IB/II study in patients with advanced solid tumors, including previously untreated NSCLC (67%).[15,17] Among participants treated with lenvatinib plus pembrolizumab, rates of all-grade and grade 3 or higher AEs of special interest for pembrolizumab (45.9% and 7.2%, respectively) and clinically significant AEs for lenvatinib (77.9% and 35.4%, respectively) were consistent with rates observed with pembrolizumab[7,25] and lenvatinib monotherapy.[26–28] In addition, rates of any-grade and grade 3 or higher clinically significant AEs for lenvatinib reported in the lenvatinib arm (76.6% and 38.3%, respectively) were similar to those reported previously.[26–28]

HRQoL scores remained generally stable and similar relative to the baseline between treatment arms. Exceptions were changes from baseline in dyspnea symptoms, for which the between-group difference was −8.04 points (representing a slight improvement for docetaxel over lenvatinib plus pembrolizumab), and TTD in cough (HR, 0.61) and dyspnea (HR, 0.75), which favored the lenvatinib plus pembrolizumab arm.

Improving therapeutic outcomes for patients with metastatic NSCLC who progressed on anti–PD-1 or anti–PD-L1 therapies and chemotherapy remains a challenge, as does identifying predictive biomarkers to select for those most likely to benefit from anti–PD-1 or anti–PD-L1 plus anti-VEGF(R) combinations. The phase 2 KEYNOTE-495 study of advanced NSCLC evaluated first-line lenvatinib plus pembrolizumab therapy and categorized participants into prespecified subgroups on the basis of T-cell–inflamed gene expression ($Tcell_{inf}GEP$) profile and tumor mutational burden.[15] The data demonstrated a greater response to lenvatinib plus pembrolizumab in those with non-low $Tcell_{inf}GEP$ (indicating inflamed tumors) and non-high tumor mutational burden. Although this finding was not prospectively validated here, results from KEYNOTE-495 suggest that some patients may not derive benefit from treatment with an anti–PD-1 or anti–PD-L1 plus anti-VEGF(R) combination, particularly those with uninflamed tumors. In contrast, although not fully characterized, it has been proposed that participants who received at least 3 months of anti–PD-1 or anti–PD-L1 therapy before PD or those who progressed after an immunotherapy-free interval responded better to immunotherapy rechallenge,[29] and ongoing studies will be useful to determine if this is a feasible approach in certain populations of patients.[21,29] The LEAP-008 study enrolled a heterogeneous population with differing numbers of previous lines of therapy, sequences of anticancer therapy, and time to progression. Several studies are ongoing to evaluate novel approaches to treat patients with NSCLC and PD after previous therapy with or without immunotherapy, including targeted therapies such as antibody-drug conjugates plus immunotherapy and inhibitors of specific oncogenes.[30,31] There is a potential opportunity for findings from these studies to help identify the optimal management strategy in this heterogeneous, difficult-to-treat patient population.

In conclusion, lenvatinib plus pembrolizumab did not improve efficacy compared with docetaxel in participants with stage IV NSCLC that progressed after anti–PD-1 or anti–PD-L1 therapy and platinum-based chemotherapy given sequentially or concomitantly. The safety profile of lenvatinib plus pembrolizumab was as expected on the basis of previous studies. These findings align with those of previous studies evaluating PD-1 or PD-L1 inhibitors in combination with tyrosine kinase inhibitors in similar populations. An unmet need remains for therapies that improve survival outcomes for patients with metastatic NSCLC who have progressed on previous systemic treatment, including immune checkpoint inhibitors, and chemotherapy.

## CRediT Authorship Contribution Statement

**Natasha B. Leighl:** Conceptualization; data curation; formal analysis; investigation; methodology; roles/writing - original draft; and writing - review & editing.

**Luis Paz-Ares:** Data curation; formal analysis; investigation; roles/writing - original draft; and writing - review & editing.

**Delvys Rodriguez Abreu:** Conceptualization; investigation; methodology; and writing - review & editing.

**Rina Hui:** Data curation; investigation; and writing - review & editing.

**Sofia Baka:** Data curation and Writing - review & editing.

**Frédéric Bigot:** Data curation, Investigation, and Writing - review & editing.

**Makoto Nishio:** Conceptualization, Data curation, Methodology, and Writing - review & editing.

**Alexey Smolin:** Data curation, Investigation, and Roles/writing - original draft.

**Samreen Ahmed:** Data curation, Formal analysis, Investigation, and Writing - review & editing.

**Adam J. Schoenfeld:** Data curation, Formal analysis, Investigation, Roles/writing - original draft, and Writing - review & editing.

**Sameh Daher:** Data curation and Writing - review & editing.

**Diego L. Cortinovis:** Investigation and Writing - review & editing.

**Vincenzo Di Noia:** Data curation, Investigation, and Writing - review & editing.

**Helena Linardou:** Conceptualization, Data curation, Investigation, Methodology, and Writing - review & editing.

**Justin F. Gainor:** Data curation, Formal analysis, Investigation, and Writing - review & editing.

**Corina Dutcus:** Conceptualization, Investigation, Methodology, and Writing - review & editing.

**Chinyere E. Okpara:** Investigation and Writing - review & editing.

**Xuan Deng:** Conceptualization, Formal analysis, Investigation, Methodology, and Writing - review & editing.

**Debra Kush:** Conceptualization, Data curation, Investigation, Methodology, and Writing - review & editing.

**Ashwini Arunachalam:** Conceptualization, Investigation, Methodology, and Writing - review & editing.

**Andrew Song:** Data curation, Formal analysis, Investigation, Writing - original draft, and Writing - review & editing.

**Byoung Chul Cho:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, and Writing - review & editing.

## Disclosure

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## 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 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.

## 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 https://doi.org/10.1016/j.jtho.2025.05.020.

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