

6 Lenvatinib Plus Pembrolizumab and Chemotherapy Versus Chemotherapy in Advanced Metastatic Gastroesophageal Adenocarcinoma: The Phase III, Randomized LEAP-015 Study

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ABSTRACT

PURPOSE The phase III randomized open-label LEAP-015 study (ClinicalTrials.gov identifier: [NCT04662710](https://clinicaltrials.gov/ct2/show/study?term=NCT04662710)) evaluated first-line lenvatinib plus pembrolizumab and chemotherapy versus chemotherapy for advanced metastatic gastroesophageal adenocarcinoma.

METHODS Eligible participants 18 years and older with untreated human epidermal growth factor receptor 2–negative locally advanced unresectable or metastatic gastroesophageal adenocarcinoma were randomly assigned 1:1 to induction with oral lenvatinib 8 mg once daily plus pembrolizumab 400 mg intravenously once every 6 weeks (×2) and investigators' choice of capecitabine and oxaliplatin once every 3 weeks (×4) or fluorouracil, leucovorin, and oxaliplatin once every 2 weeks (×6) and consolidation with lenvatinib plus pembrolizumab, or chemotherapy. Dual primary end points were progression-free survival (PFS) and overall survival (OS) in participants with PD-L1 combined positive score (CPS) ≥ 1 and all participants. Secondary end points included objective response rate (ORR) and duration of response.

RESULTS Of 880 participants randomly assigned, 443 received lenvatinib plus pembrolizumab and 437 received chemotherapy. The median follow-ups were 32.2 months (range, 19.0–41.7) in participants with PD-L1 CPS ≥ 1 and 31.8 months (19.0–41.7) in all participants. At interim analysis, PFS was statistically significant with lenvatinib plus pembrolizumab versus chemotherapy in participants with PD-L1 CPS ≥ 1 (median, 7.3 v 6.9 months; hazard ratio [HR], 0.75 [95% CI, 0.62 to 0.9]; $P = .0012$) and all participants (median, 7.2 v 7.0 months; HR, 0.78 [95% CI, 0.66 to 0.92]; $P = .0019$). The ORR was 59.5% versus 45.4% in participants with PD-L1 CPS ≥ 1 and 58.0% versus 43.9% in all participants, $P < .0001$ for both. At final analysis, OS was not statistically significant in participants with PD-L1 CPS ≥ 1 (median, 12.6 v 12.9 months; HR, 0.84 [95% CI, 0.71 to 1.00]; $P = .0244$; P value boundary = .0204). Grade ≥ 3 drug-related adverse event rates were 65% versus 49%.

CONCLUSION Lenvatinib plus pembrolizumab and chemotherapy versus chemotherapy provided a statistically significant improvement in PFS in advanced unresectable or metastatic gastroesophageal carcinoma at interim analysis although the clinical significance of this difference seems to be limited. No significant improvement occurred in OS in participants with PD-L1 CPS ≥ 1.

ACCOMPANYING CONTENT

 Listen to the podcast by Dr Li and Dr Ko at <https://ascopubs.org/doi/jco-asco-annual-meeting-lenvatinib-plus-pembrolizumab-and-chemotherapy-gastric-cancer>

 Appendix

 Data Sharing Statement

 Protocol

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INTRODUCTION

First-line treatment for advanced human epidermal growth factor receptor 2 (HER2)–negative gastric/gastroesophageal

junction (G/GEJ) adenocarcinoma has traditionally relied on platinum- and fluoropyrimidine-based chemotherapy. Recently, the combination of immune checkpoint inhibitors and chemotherapy has demonstrated an enhanced clinical

CONTEXT

Key Objective

To evaluate if the addition of lenvatinib and pembrolizumab to standard chemotherapy improves clinical outcomes in participants with previously untreated, human epidermal growth factor receptor 2 (HER2)–negative metastatic gastroesophageal adenocarcinoma.

Knowledge Generated

The LEAP-015 phase III study showed that the triplet regimen of lenvatinib, pembrolizumab, and chemotherapy resulted in a statistically significant improvement in progression-free survival compared with chemotherapy alone. However, the overall survival benefit did not meet the predefined threshold for statistical significance. The combination was associated with higher rates of treatment-related adverse events compared with the control arm.

Relevance (A.H. Ko)

While the mechanistic rationale for evaluating this combination was sound, adding lenvatinib and pembrolizumab to chemotherapy should not be routinely used in patients with HER2-negative metastatic gastroesophageal cancer.*

*Relevance section written by JCO Associate Editor Andrew H. Ko, MD, FASCO.

benefit, with enriched efficacy noted with increasing levels of PD-L1 expression in selected populations with PD-L1 combined positive score (CPS) 1 or more.¹⁻³ The addition of vascular endothelial growth factor (VEGF) receptor–targeted agents, such as ramucirumab, improved efficacy in the second-line treatment.⁴ However, the prognosis remains poor, with the median overall survival (OS) ranging from 12 to 14 months in global studies of untreated advanced gastric cancer.¹⁻³

Multiple studies have shown that targeting VEGF-mediated angiogenesis is associated with antitumor activity.⁵ Lenvatinib, an oral multikinase inhibitor, demonstrated preclinical synergy with PD-1 inhibitors in an in vivo model.⁶ In clinical studies, lenvatinib plus pembrolizumab has shown clinical activity across multiple malignancies, including endometrial cancer and renal cell carcinoma,^{7,8} with preliminary efficacy observed for G/GEJ adenocarcinoma.^{9,10} In the phase II EPOC1706 study of first- and second-line treatment in advanced gastric cancer, lenvatinib 20 mg once daily plus pembrolizumab provided an objective response rate (ORR) of 69%, with a median progression-free survival (PFS) of 7.1 months.⁹ This ORR suggested potential synergy of this combination for advanced gastric cancer as the expected response rate is approximately 15% for pembrolizumab monotherapy and <5% for lenvatinib.⁹ In addition, chemotherapy plus lenvatinib 8 mg once daily plus pembrolizumab had an acceptable safety profile with platinum-based chemotherapy in non–small cell lung cancer.¹¹

The randomized, open-label international phase III LEAP-015 study evaluated the efficacy and safety of first-line lenvatinib plus pembrolizumab and chemotherapy versus chemotherapy in advanced, HER2-negative, untreated G/GEJ adenocarcinoma. We report the results of the interim and final analyses of LEAP-015.

METHODS

Study Design and Participants

Eligible participants were 18 years and older with a histologically or cytologically confirmed HER2-negative unresectable or metastatic G/GEJ adenocarcinoma. Participants were required to have measurable disease per RECIST v1.1 per the investigator, have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, provide a tumor tissue sample for PD-L1 analysis, and have no previous systemic therapy for unresectable or metastatic disease and were not expected to require resection during treatment. Participants with a gastrointestinal condition that could affect study drug absorption; with previous treatment with PD-1/PD-L1 inhibitors, VEGF inhibitors, or lenvatinib; and who were eligible for radiotherapy or neoadjuvant therapy were excluded. The Protocol (online only) and all amendments were approved by the relevant institutional review board or the independent ethics committee at each study center. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided informed consent.

Trial Design and Treatment

In part 1 of LEAP-015 (Lead-in Phase), an initial cohort received induction with lenvatinib 8 mg orally once daily plus pembrolizumab 400 mg intravenously once every 6 weeks ($\times 2$) and investigator's choice chemotherapy of capecitabine and oxaliplatin (CAPOX) once every 3 weeks ($\times 4$), or modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) once every 2 weeks ($\times 6$). This was followed by consolidation with pembrolizumab 400 mg once every 6 weeks up to 16 doses plus lenvatinib, before advancing to part 2. Lenvatinib

8 mg once daily was escalated to 20 mg once daily if the initial 8 mg dose was tolerated with no more than a grade 1 lenvatinib-related adverse event or grade 2 hypothyroidism during induction. In part 1, dose-limiting toxicities (DLTs), defined as selected prespecified grade ≥ 3 adverse events or any-grade thromboembolic events, were evaluated for 21 days. If two or less DLTs were observed with either CAPOX or mFOLFOX6, enrollment in part 2 was initiated. In part 2 (randomized phase III phase), eligible participants were randomly assigned 1:1 to lenvatinib plus pembrolizumab with chemotherapy as in part 1 for four to six cycles or chemotherapy alone with CAPOX or mFOLFOX6 per investigator's choice in the control arm until progression or per local standards. As the study was planned in 2020, chemotherapy alone was selected as control as nivolumab had not been approved in many regions, and KEYNOTE-859 results were not yet available.

Random assignment was stratified by region (East Asia, North America, and Western Europe v rest of world), ECOG PS (0 v 1), and chemotherapy backbone (CAPOX v mFOLFOX6). Pembrolizumab was administered for up to 2 years, and participants who completed pembrolizumab without disease progression could continue lenvatinib monotherapy per investigator until disease progression, unacceptable toxicity, or withdrawal of consent. Treatment was continued until disease progression, unacceptable toxicity, pregnancy, intercurrent illness, or withdrawal of consent. Full protocol details are provided in the Protocol.

End Points

Dual primary end points were PFS (time from random assignment to disease progression or death from any cause, whichever occurred first) and OS (time from random assignment to death from any cause). Secondary end points included objective response (confirmed complete response [CR] or partial response [PR]), duration of response (DOR, time from first CR or PR to subsequent disease progression, or death from any cause, whichever occurred first), and safety and tolerability. Change from baseline to Week 18 in health-related quality of life as assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), EORTC Quality of Life Questionnaire-Stomach cancer module (QLQ-STO22) pain (Gastric), and the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaires was an exploratory end point.

Assessments

HER2-negative status was assessed locally by immunohistochemistry in situ hybridization or fluorescence in situ hybridization. HER2 status was assessed centrally if local standards were not sufficient as needed by country or site. Tumor response was assessed per RECIST v1.1 by blinded independent central review (BICR) with initial imaging performed at week 6 after random assignment and once every 6 weeks thereafter, until disease progression per

investigator verified by BICR. During follow-up, survival was assessed once every 12 weeks. The EORTC QLQ-C30, EORTC QLQ-STO22, and EQ-5D-5L questionnaires were administered once every 6 weeks on day 1 of each pembrolizumab cycle until the completion of 2 years of treatment or discontinuation of both lenvatinib and pembrolizumab, as well as at treatment discontinuation and during safety follow-up. Site staff recorded the reason for any missed completions.

Statistical Analysis

The Kaplan-Meier method was used to estimate OS, PFS, and DOR. Between-group differences in OS and PFS were assessed using a stratified log-rank test. Differences in ORR were assessed using the stratified Miettinen and Nurminen method. A stratified Cox proportional hazards model with Efron's method for tie handling was used to estimate the hazard ratios (HRs) and associated 95% CIs. The final analysis of OS was planned to occur after approximately 537 deaths in participants with PD-L1 CPS ≥ 1 and approximately 18 months after the last participant was randomly assigned. The overall type 1 error was strongly controlled at a one-sided α of .025 using the graphical method of Maurer and Bretz with 0.018 initially allocated to OS and 0.007 initially allocated to PFS in participants with PD-L1 CPS ≥ 1 (Appendix Fig A1, online only). Full details of the protocol and statistical analysis plan are provided in the Protocol (see also Appendix 1).

Trial Oversight

The study was designed by academic investigators and employees of the sponsor (Merck Sharp & Dohme, LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ). All the authors had access to the data, were involved in reviewing and editing the manuscript, and approved the submitted draft and vouch for the accuracy of the data reported. Assistance in the preparation of the manuscript was provided by a medical writer employed by the sponsor.

RESULTS

Participants and Treatment

In part 1, 15 participants enrolled between December 30, 2020, and January 27, 2021, to receive induction therapy. A total of two DLTs occurred (one DLT of grade 3 asthenia with CAPOX and one DLT of grade 4 neutropenia with mFOLFOX6). This met the criteria for enrollment in part 2. In part 2, between May 11, 2021, and March 31, 2023, 880 participants from 157 sites in 24 countries were randomly assigned to lenvatinib plus pembrolizumab and chemotherapy (443 participants [lenvatinib group]) or chemotherapy alone (437 participants [chemotherapy group]; Fig 1). Baseline participant characteristics and demographics were generally well balanced between groups. Participants had a median age of 61.0 years (range, 21-84), 689 (78%) had PD-L1 CPS ≥ 1 , 172 (20%) had PD-L1 CPS < 1 , and 662 (75%) had primary gastric adenocarcinoma (Table 1). At

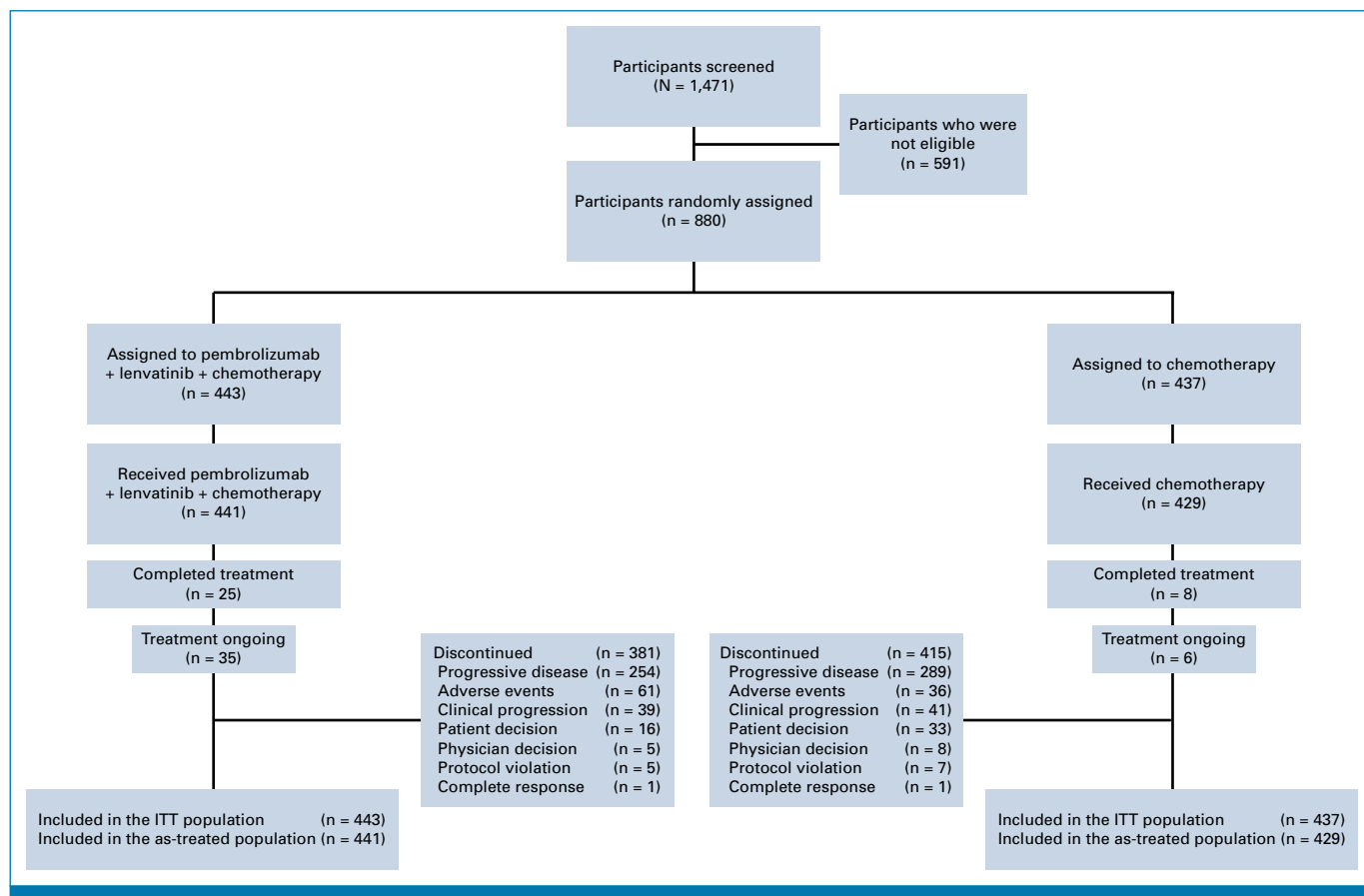


FIG 1. CONSORT diagram. ITT, intention-to-treat.

final analysis (data cutoff date October 29, 2024), the median time from random assignment was 32.2 months (range, 19.0–41.7) in participants with PD-L1 CPS ≥ 1 and 31.8 months (range, 19.0–41.7) in all participants. A total of 33 (4%) participants completed study treatment (25 [6%] in the lenvatinib group and eight [2%] in the chemotherapy group), and 41 (5%) remain on treatment (35 [8%] in the lenvatinib group and six [1%] in the chemotherapy group). A total of 796 (92%) participants discontinued treatment, 381 (86%) and 415 (97%) in the lenvatinib and chemotherapy groups, respectively. This was largely due to progressive disease ($n = 543$, 254 [58%] in the lenvatinib group and 289 [67%] in the chemotherapy group) and adverse events ($n = 97$, 61 [14%] in the lenvatinib group and 36 [8%] in the chemotherapy group).

PFS

At interim analysis (data cutoff date November 16, 2023), with the median follow-up of 20.8 months (range, 7.6–30.2) in participants with PD-L1 CPS ≥ 1 and 20.3 months (range, 7.6–30.2) in all participants, PFS per RECIST v.1 by BICR met the prespecified criteria for statistical significance with lenvatinib plus pembrolizumab versus chemotherapy in participants with PD-L1 CPS ≥ 1 (median, 7.3 v 6.9 months; HR, 0.75 [95% CI, 0.62 to 0.9]; $P = .0012$), with a 24-month

PFS rate of 20% versus 7%, and in all participants (median, 7.2 v 7.0 months; HR, 0.78 [95% CI, 0.66 to 0.92]; $P = .0019$), with a 24-month PFS rate of 21% versus 8%, respectively (Fig 2). PFS was generally consistent across the subgroups evaluated, including in participants with PD-L1 CPS ≥ 1 and PD-L1 CPS < 1 (Appendix Fig A2).

OS

At final analysis (data cutoff date October 29, 2024), OS in participants with PD-L1 CPS ≥ 1 was not statistically significant with lenvatinib plus pembrolizumab versus chemotherapy (median, 12.6 v 12.9 months; HR, 0.84 [95% CI, 0.71 to 1.00]; $P = .0244$), with a 24-month OS rate of 31% versus 23%. The P value boundary for significance was .0204 (Figs 3A and 3B). OS in all participants was not tested for significance per the multiplicity strategy (median, 13.1 v 13.0 months; HR, 0.87 [95% CI, 0.75 to 1.01]). OS was generally consistent across subgroups evaluated, including in participants with PD-L1 CPS ≥ 1 and PD-L1 CPS < 1 (Fig 3C). A total of 202 (46%) participants in the lenvatinib group versus 273 (63%) in the chemotherapy group received subsequent anticancer therapy. This included 196 (44%) versus 255 (58%) participants who received subsequent chemotherapy and 20 (5%) versus 83 (19%)

TABLE 1. Demographics and Participant Characteristics at Baseline in the Intention-to-Treat Population

Characteristic	Lenvatinib + Pembrolizumab + Chemotherapy (n = 443)	Chemotherapy (n = 437)
Age, years, median (range)	62 (21-84)	61 (24-84)
≥65 years, No. (%)	178 (40)	157 (36)
Male, No. (%)	292 (66)	306 (70)
Race, No. (%)		
American Indian/Alaska Native	11 (2)	15 (3)
Asian	164 (37)	161 (37)
African American/Black	1 (<1)	1 (<1)
White	235 (53)	223 (51)
Multiple/missing	32 (7)	37 (8)
Region, No. (%)		
East Asia	161 (36)	161 (37)
North America/Western Europe/Israel/Australia	125 (28)	122 (28)
Rest of world	157 (35)	155 (35)
ECOG performance status, No. (%)		
0	204 (46)	204 (47)
1	239 (54)	233 (53)
PD-L1 status, No. (%)		
PD-L1 CPS ≥1	334 (75)	355 (81)
PD-L1 CPS <1	101 (23)	71 (16)
Unknown	8 (2)	11 (3)
MSI-H status, No. (%)		
Non-MSI-H	346 (78)	316 (72)
MSI-H	14 (3)	8 (2)
Missing	83 (19)	113 (26)
Disease status, No. (%)		
Locally advanced	8 (2)	6 (1)
Metastatic	435 (98)	431 (99)
Primary location, No. (%)		
Gastric adenocarcinoma	340 (77)	322 (74)
Gastroesophageal junction adenocarcinoma	91 (21)	97 (22)
Esophagus adenocarcinoma	12 (3)	18 (4)
Histology subtype, No. (%)		
Diffuse	134 (30)	113 (26)
Indeterminate	157 (35)	166 (38)
Intestinal	152 (34)	158 (36)
Tumor burden, No. (%)		
≥Median	210 (47)	220 (50)
<Median	219 (49)	204 (47)
Previous gastrectomy/esophagectomy, No. (%)		
No	351 (79)	347 (79)
Yes	92 (21)	90 (21)
Chemotherapy, No. (%)		
CAPOX	232 (52)	225 (51)
mFOLFOX6	209 (47)	204 (47)
Missing	2 (<1)	8 (2)

Abbreviations: CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; mFOLFOX6, fluorouracil, leucovorin, and oxaliplatin; MSI-H, microsatellite instability-high.

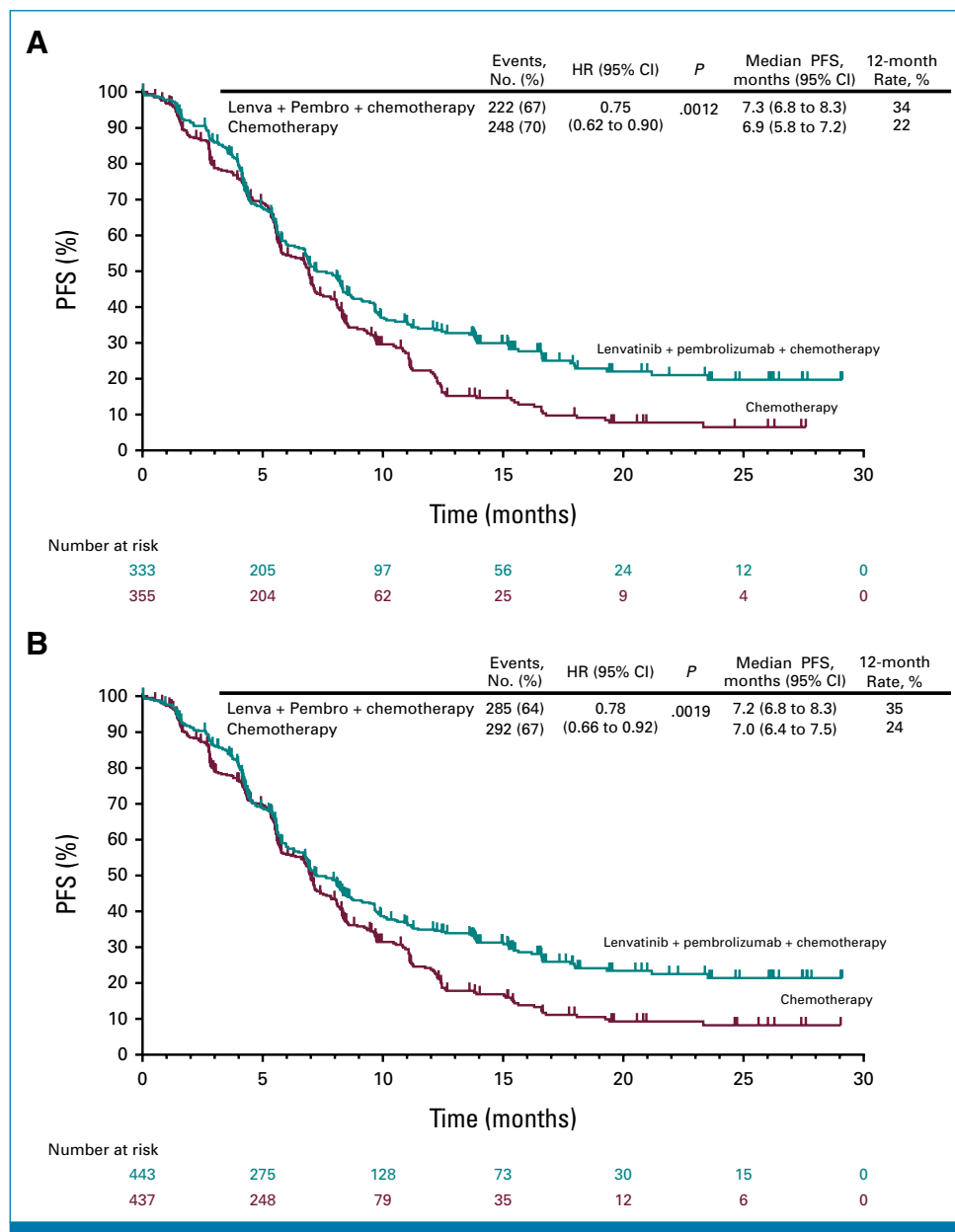


FIG 2. PFS in participants with advanced metastatic HER2-negative gastric and gastroesophageal junction adenocarcinoma. Kaplan-Meier estimate of PFS at interim analysis in (A) participants with PD-L1 CPS ≥ 1 (H2; *P* value boundary for significance = .007000) and (B) all participants (H4; *P* value boundary for significance = .005999). PFS was assessed per the RECIST version 1.1 by blinded, independent central review. Tick marks represent data censored at the time of last imaging assessment. CPS, combined positive score; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; Lenva, lenvatinib; Pembro, pembrolizumab; PFS, progression-free survival.

participants who received subsequent immunotherapy in the lenvatinib versus chemotherapy groups, respectively (Appendix Table A1).

Antitumor Response

At interim analysis, the ORR was 59.5% (198 of 333 [95% CI, 54.0 to 64.8]) in the lenvatinib group versus 45.4% (161 of

355 [95% CI, 40.1 to 50.7]) in the chemotherapy group in participants with PD-L1 CPS ≥ 1 and 58.0% (257 of 443 [95% CI, 53.3 to 62.7]) versus 43.9% (192 of 437 [95% CI, 39.2 to 48.7]), respectively, in all participants (*P* < .0001 for both). The median DOR was 8.5 months (range, 1.0+ to 27.7+) in the lenvatinib group versus 6.5 months (range, 1.0+ to 25.8+) in the chemotherapy group in participants with PD-L1 CPS ≥ 1 and 8.9 months (range, 1.0+ to 27.7+) and

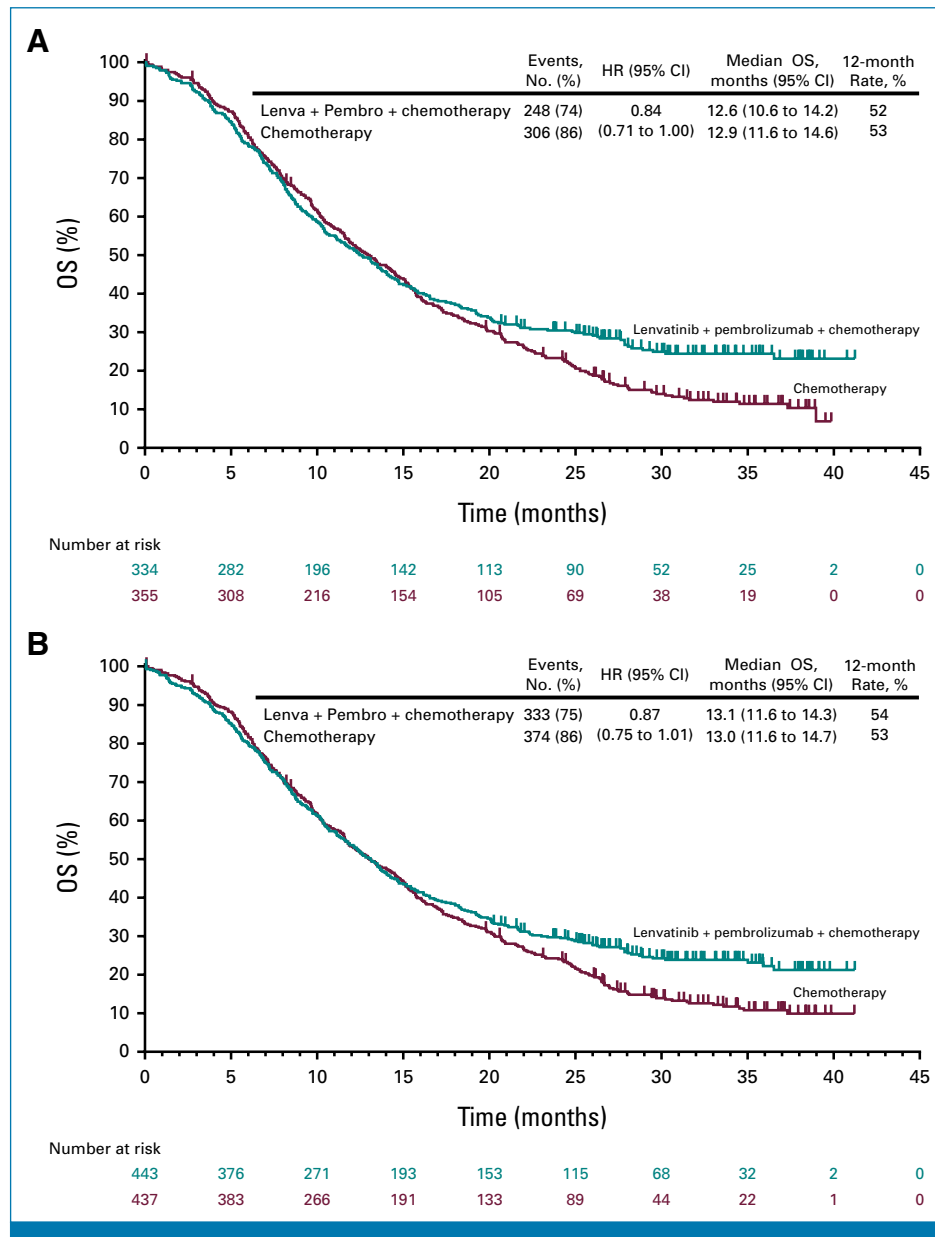


FIG 3. OS in participants with advanced metastatic HER2-negative gastric and gastroesophageal junction adenocarcinoma. Kaplan-Meier estimate of OS at final analysis in (A) participants with PD-L1 CPS ≥ 1 (H1) and (B) all participants (H3). Tick marks represent data censored at the time of last imaging assessment. (C) Forest plot of OS at final analysis in prespecified subgroups. The unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate was used to assess the magnitude of the treatment difference between arms. CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; Lenva, lenvatinib; mFOLFOX6, fluorouracil, leucovorin, oxaliplatin; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NA, North America; OS, overall survival; Pembro, pembrolizumab. (continued on following page)

6.8 months (range, 1.0+ to 25.8+), respectively, in all participants (Table 2; Appendix Fig A3).

Safety

A total of 870 participants received at least one dose of study treatment (441 in the lenvatinib group and 429 in the

chemotherapy group). The median (range) duration of treatment was 6.5 months (0–41) versus 5.6 (0–41), respectively. In the lenvatinib group, the median (range) duration of treatment was 6.0 months (0–41) for lenvatinib, 5.6 (0–30) for pembrolizumab, 2.6 (0–7) for CAPOX, and 2.4 (0–5) for mFOLFOX6. In the chemotherapy group, the median duration of treatment was 5.1 months (0–41) for

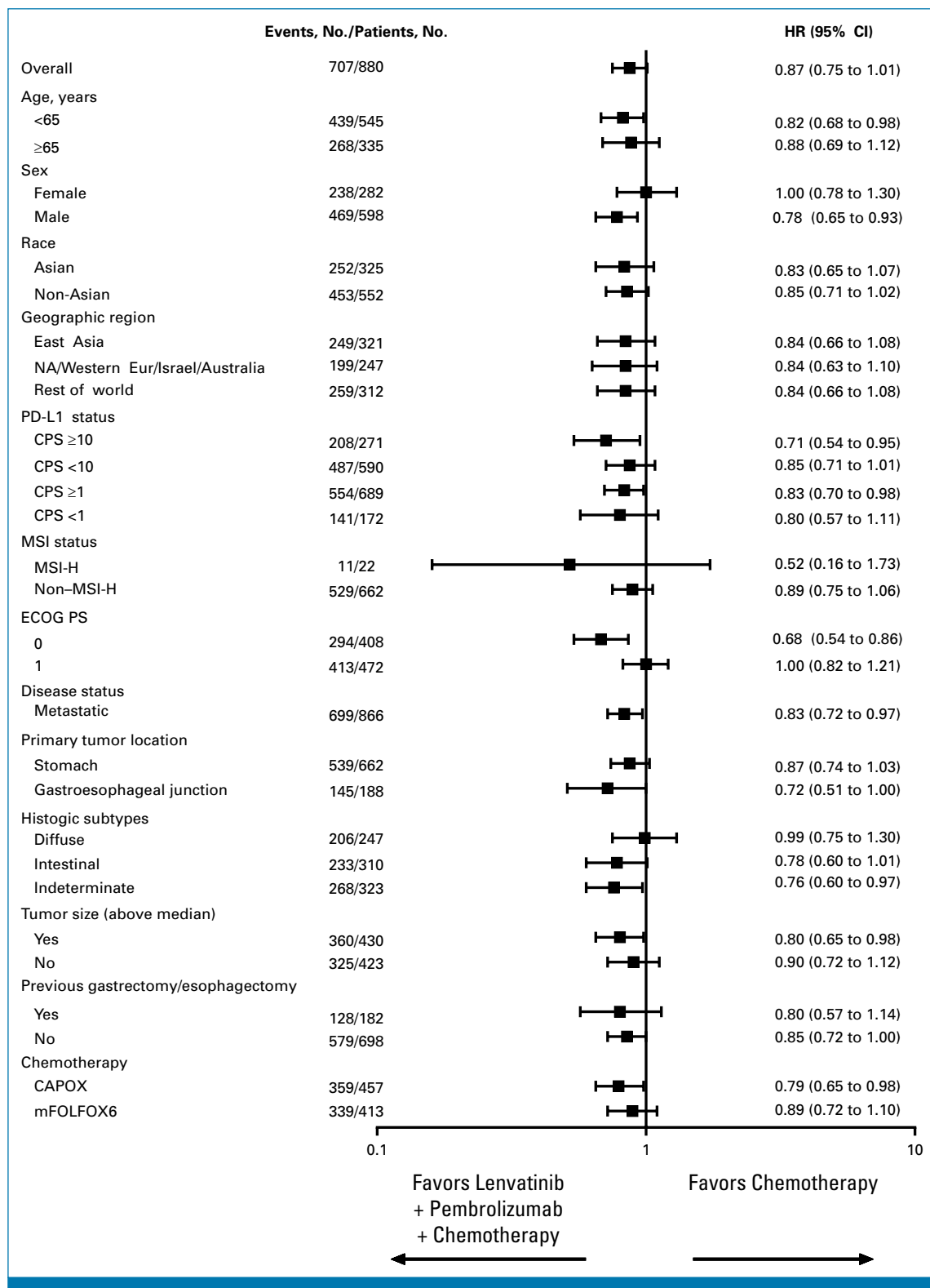


TABLE 2. Antitumor Activity in the Intention-to-Treat Population at Interim Analysis

Response	Lenvatinib + Pembrolizumab + Chemotherapy (n = 443)	Chemotherapy (n = 437)
Objective response rate, No. (%)	257 (58.0)	192 (43.9)
95% CI ^a	53.3 to 62.7	39.2 to 48.7
Difference, % (95% CI); <i>P</i>	14.2 (7.7 to 20.6); ^b <i>P</i> < .0001 ^c	
Best overall response, No. (%)		
Complete response	38 (8.6)	22 (5.0)
PR	219 (49.4)	170 (38.9)
Stable disease	140 (31.6)	168 (38.4)
Progressive disease	18 (4.1)	39 (8.9)
Not evaluable/no assessment	28 (6.3)	38 (8.7)
Response duration, months, median (range)	8.9 (1.0+ to 27.7+)	6.8 (1.0+ to 25.8+)
Response duration ≥24 months; ^d %	29.7	8.7

NOTE. + indicates no progressive disease by the time of last assessment.

Abbreviations: BICR, blinded independent central review; PR, partial response.

^aParticipants with confirmed complete response or PR by BICR per RECIST v1.1. Percentages were calculated using all randomly assigned participants.

^bBased on the Miettinen and Nurminen method stratified by region, performance status, and chemotherapy.

^cOne-sided *P* value for testing.

^dFrom the Kaplan-Meier method for censored data.

CAPOX and 6.1 (0–37) for mFOLFOX6. Of note, in the lenvatinib group, chemotherapy was restricted to four cycles for CAPOX and six cycles for mFOLFOX6 in the induction phase only, whereas in the control group, chemotherapy continued until progression or per local standards. Overall, participants received lenvatinib at a median dose intensity of 8 mg/d (range, 2–19), with 359 (81%) participants receiving lenvatinib at a median dose intensity of 7.9 mg/d (range, 2–10) during induction and 343 (78%) receiving lenvatinib at a median dose intensity of 11.5 mg/d (range, 2–20) during consolidation. In total, 200 of 441 (46%) treated participants in the lenvatinib group had lenvatinib dose escalated to 20 mg once daily during consolidation.

Adverse events of any cause occurred in 439 (99%) participants in the lenvatinib group and 414 (97%) in the chemotherapy group. Grade ≥3 events occurred in 350 (79%) versus 276 (64%) participants in the lenvatinib versus chemotherapy groups, with neutrophil count decreased (25% v 24%), hypertension (12% v 1%), anemia (8% v 10%), and diarrhea (5% v 3%) being most common. Serious adverse events occurred in 226 (51%) versus 137 (32%) participants in the lenvatinib versus chemotherapy groups, respectively, with discontinuation of any drug because of adverse events occurring in 146 (33%) versus 116 (27%) participants, respectively. In the lenvatinib group, 106 participants (24%) discontinued lenvatinib, 79 (18%) discontinued pembrolizumab, and 54 (12%) discontinued both drugs. Drug-related adverse events occurred in 430 (98%) versus 394 (92%) participants in the lenvatinib versus chemotherapy groups, respectively. Grade ≥3 drug-related events occurred in 288 (65%) versus 208 (48%) participants, respectively. Discontinuations because of a drug-related adverse event occurred in 119 (27%) versus 99 (23%) participants. Grade

5 drug-related adverse events occurred in 24 (5%) versus two (<1%) participants in the lenvatinib versus chemotherapy groups, respectively (Table 3). Immune-mediated adverse events of special interest occurred in 202 (46%) participants in the lenvatinib group and 51 (12%) participants in the chemotherapy group. Grade ≥3 events occurred in 44 (10%) versus six (1%) participants, respectively (Appendix Table A2).

Health-Related Quality of Life

A total of 850 participants were enrolled in the PRO population (430 lenvatinib plus pembrolizumab; 420 chemotherapy). At baseline, the observed completion rates were 97% for the QLQ-C30 and QLQ-STO22 questionnaires for both treatment groups and 94% and 93% for the EQ-5D-5L questionnaire in the lenvatinib and chemotherapy groups, respectively. At baseline, compliance rates were 100% for all questionnaires in both groups. At week 18, the observed completion rates were 70% and 57% for QLQ-C30 and QLQ-STO22 and 68% and 56% for the EQ-5D-5L questionnaire with lenvatinib plus pembrolizumab and chemotherapy, respectively. Compliance rates were 97% for all questionnaires with lenvatinib and pembrolizumab and ranged from 99% to 100% for chemotherapy. No meaningful differences in least square mean change from baseline to Week 18 were observed between groups for the prespecified QLQ-C30 Global Health Status/Quality of Life, QLQ-STO22, or EQ-5D-5L visual analog scale questionnaires (Appendix Table A3).

DISCUSSION

In this phase III study, lenvatinib plus pembrolizumab and chemotherapy demonstrated a statistically significant

TABLE 3. Treatment-Related Adverse Events Occurring in $\geq 5\%$ of All the Treated Participants

Adverse Event	Lenvatinib + Pembrolizumab + Chemotherapy (n = 441), No. (%)		Chemotherapy (n = 429), No. (%)	
	Any	Grade ≥ 3	Any	Grade ≥ 3
Treatment-related events ^a	430 (97)	288 (65)	394 (92)	208 (48)
Neutrophil count decreased	203 (46)	105 (24)	194 (45)	97 (23)
Nausea	171 (39)	10 (2)	173 (40)	5 (1)
Diarrhea	169 (38)	20 (5)	109 (25)	9 (2)
Hypertension	140 (32)	49 (11)	0	0
Decreased appetite	130 (29)	11 (2)	79 (18)	4 (1)
Hypothyroidism	121 (27)	2 (<1)	0	0
Platelet count decreased	117 (27)	21 (5)	172 (40)	35 (8)
Fatigue	103 (23)	14 (3)	61 (14)	6 (1)
WBC count decreased	102 (23)	15 (3)	89 (21)	14 (3)
Anemia	101 (23)	17 (4)	109 (25)	25 (6)
PPES	95 (22)	14 (3)	59 (14)	7 (2)
Proteinuria	92 (21)	9 (2)	1 (<1)	0
AST increased	81 (18)	11 (2)	75 (17)	5 (1)
Vomiting	79 (18)	10 (2)	92 (21)	8 (2)
ALT increased	70 (16)	16 (4)	57 (13)	5 (1)
Weight decreased	70 (16)	9 (2)	43 (10)	6 (1)
Peripheral neuropathy	69 (16)	1 (<1)	100 (23)	13 (3)
Stomatitis	64 (15)	7 (2)	40 (9)	2 (<1)
Peripheral sensory neuropathy	54 (12)	2 (<1)	81 (19)	6 (1)
Asthenia	51 (12)	6 (1)	54 (13)	1 (<1)
Mucosal inflammation	51 (12)	9 (2)	26 (6)	2 (<1)
Lipase increased	46 (10)	12 (3)	27 (6)	8 (2)
Rash	44 (10)	1 (<1)	10 (2)	0
Pruritus	42 (10)	1 (<1)	6 (1)	0
Constipation	41 (9)	0	40 (9)	0
Amylase increased	40 (9)	6 (1)	19 (4)	1 (<1)
Blood thyroid-stimulating hormone increased	37 (8)	0	2 (<1)	0
Blood bilirubin increased	35 (8)	6 (1)	32 (7)	6 (1)
Abdominal pain	32 (7)	3 (1)	19 (4)	3 (1)
Hyperthyroidism	30 (7)	1 (<1)	4 (1)	0
Hypokalemia	27 (6)	6 (1)	16 (4)	3 (1)
Paraesthesia	26 (6)	1 (<1)	36 (8)	3 (1)
Dysgeusia	25 (6)	0	38 (9)	0
Blood alkaline phosphatase increased	24 (5)	4 (1)	28 (7)	3 (1)
Dry mouth	24 (5)	0	5 (1)	0
Arthralgia	23 (5)	3 (1)	4 (1)	0
Dysphonia	22 (5)	0	3 (1)	0

Abbreviation: PPES, palmar-plantar erythrodysesthesia syndrome.

^aTreatment-related events with incidence $\geq 5\%$ in any group. Treatment-related grade 5 events included autoimmune hemolytic anemia, cardiac arrest, myocarditis, gastric hemorrhage (n = 2), gastric perforation (n = 3), gastric ulcer perforation, gastrointestinal hemorrhage, immune-mediated enterocolitis, intestinal ischemia, acute pancreatitis, upper gastrointestinal hemorrhage (n = 3), death, aseptic meningitis, sepsis, urosepsis, pulmonary embolism, intracranial hemorrhage, and malignant neoplasm progression and encephalitis in the lenvatinib plus pembrolizumab and chemotherapy group in one participant each unless otherwise indicated and gastrointestinal hemorrhage and hepatic failure in one participant each in the chemotherapy group.

improvement in PFS and ORR versus chemotherapy as first-line treatment for advanced, unresectable, or metastatic HER2-negative G/GEJ adenocarcinoma. The study did not

meet the prespecified threshold for OS significance in participants with PD-L1 CPS ≥ 1 , and OS in the overall population was not tested per the multiplicity strategy. The safety

profile in both arms was consistent with the known adverse events of the therapeutic agents although higher rates of treatment-related adverse events were observed with the combination. Despite the limitations inherent in analysis of self-reported patient outcomes, there were no meaningful differences in quality-of-life measures between arms, potentially reflecting both treatment-related toxicity and tumor-related symptom improvement from disease control.

In LEAP-015, chemotherapy induction was designed to reduce potential for early disease progression as observed in previous global studies of first-line treatment in advanced G/GEJ cancer.^{12,13} The 12-week duration of induction chemotherapy in the LEAP-015 study was similar to that in the JAVELIN-100 study of induction chemotherapy and maintenance avelumab in urothelial carcinoma and selected for maximizing initial response with chemotherapy.¹⁴ Of note, the control arm of chemotherapy alone was selected as the standard of care at study initiation preceding approval of nivolumab and pembrolizumab in many countries and publication of CheckMate-649 and KEYNOTE-859 results, respectively.² The study design was based on preliminary results from the EPOC1706 phase II study, which demonstrated the activity of lenvatinib plus pembrolizumab in G/GEJ adenocarcinoma in a Japanese population.⁹ Moreover, data from the LEAP-015 safety lead-in phase showed a low incidence of DLT, no drug-related deaths, and a preliminary ORR of 73% in 11 of 15 participants who received at least one dose of study therapy, suggesting the feasibility of this combination.¹⁵

In part 2 of LEAP-015, lenvatinib plus pembrolizumab and chemotherapy versus chemotherapy provided a significant improvement in PFS (median, 7.2 v 7.0 months) in all participants and in participants with PD-L1 CPS ≥ 1 (median, 7.3 v 6.9 months) although the magnitude of this difference is minimal, suggesting a limited clinical value. This benefit in PFS is supported by the extended tail observed in the PFS Kaplan-Meier curves. However, the lack of early separation until approximately 4 months suggests limited early benefit of lenvatinib plus pembrolizumab. Despite these results, the OS benefit in LEAP-015 in participants with PD-L1 CPS ≥ 1 (HR, 0.84 [95% CI, 0.71 to 1.00]) was not statistically significant. A similar lack of OS benefit with VEGF inhibition plus first-line fluoropyrimidines and platinum-based chemotherapy was previously reported in the RAINFALL¹⁶ and AVAGAST¹⁷ phase III, randomized studies, despite the positive OS benefit reported in the second line in the RAINBOW study.⁴ These outcomes suggest a potential lack of synergy with VEGF inhibition and platinum-based chemotherapy in this indication.

By contrast, a statistically significant OS benefit was observed in KEYNOTE-859 in all participants (HR, 0.78) and in participants with PD-L1 CPS ≥ 1 (HR, 0.74) and PD-L1 CPS ≥ 10 (HR, 0.65). Potential factors that may account for this difference in OS outcomes between the LEAP-015 and KEYNOTE-859 studies include the potential impact of

chemotherapy discontinuation after 3 months in the experimental versus control group of LEAP-015 as studies have suggested that immunotherapy alone does not prolong OS compared with chemotherapy maintenance with or without immunotherapy.^{14,18} Another factor may be the higher rate of drug-related grade ≥ 3 events (65% v 49%) and serious events (51% v 32%) in the lenvatinib versus chemotherapy groups, respectively. In addition, treatment discontinuation because of adverse events associated with lenvatinib dose escalation might have influenced long-term outcomes, possibly reducing treatment exposure. A lower lenvatinib dose escalation may offer a better balance between efficacy and tolerability.

The performance of the control group in LEAP-015 exceeded expectations, with median OS and PFS comparable with that of pembrolizumab plus chemotherapy in KEYNOTE-859. The lower rate of subsequent anticancer therapy in the experimental versus control group in LEAP-015 (46% v 63%), with 44% versus 58% receiving subsequent chemotherapy and 5% versus 19% receiving subsequent immunotherapy, might have influenced survival outcomes in the LEAP-015 control arm. By contrast, subsequent anticancer therapy was more balanced between the pembrolizumab and placebo groups (45% v 47%) in KEYNOTE-859. Notably, in KEYNOTE-859, the OS benefit was enriched at higher PD-L1 CPS levels, with an OS HR of 0.65 and a median OS of 15.7 versus 11.8 months for PD-L1 CPS ≥ 10 tumors.² A consistent outcome was observed in LEAP-015 for participants with PD-L1 CPS ≥ 10 for OS (HR, 0.71; median OS, 14.7 v 13.9 months) and PFS (HR, 0.56; median PFS, 8.5 v 6.7 months) although these differences were likely not clinically significant.

Beyond efficacy, the feasibility of multikinase inhibitors in combination with pembrolizumab and chemotherapy requires further exploration. While this regimen has demonstrated clinical activity across multiple tumor types, recent studies^{11,19-22} have failed to show an OS benefit with similar combination strategies. The various on-target and off-target toxicities of multikinase inhibitors remain an important consideration as higher rates of adverse events and treatment discontinuation in the experimental group might have compromised treatment compliance. Of note, the rate of treatment-related grade 5 adverse events in the experimental versus control arm of LEAP-015 (5% v 1%) was higher than that in the CheckMate 649 (2% v 1%) and KEYNOTE-859 (1% v 2%) studies.^{1,2} Alternative strategies that offer improved tolerability while maintaining efficacy should be considered.

In conclusion, in LEAP-015, lenvatinib plus pembrolizumab and chemotherapy versus chemotherapy provided a significant improvement in PFS and ORR, but not OS in participants with PD-L1 CPS ≥ 1 . These findings could not confirm the role of anti-VEGF and anti-PD-1 combination therapies while raising critical questions regarding sequencing, chemotherapy maintenance, and toxicity management.

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A data sharing statement provided by the authors is available with this article at DOI <https://doi.org/10.1200/JCO-25-00748>. Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ (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 study participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical study 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 EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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Lenvatinib Plus Pembrolizumab and Chemotherapy Versus Chemotherapy in Advanced Metastatic Gastroesophageal Adenocarcinoma: The Phase III, Randomized LEAP-015 Study

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APPENDIX 1. METHODS

Assessments

PD-L1 expression was centrally assessed during screening using the PD-L1 immunohistochemistry 22C3 assay (Agilent Technologies, Carpinteria, CA). PD-L1 combined positive score (CPS) was calculated as the number of PD-L1–staining cells (tumor cells, macrophages, and lymphocytes) divided by the total number of viable tumor cells, multiplied by 100. A prespecified validated cutoff of PD-L1 CPS of 1 or higher was used in the study. Microsatellite instability status was assessed in tumor tissue at a central laboratory by polymerase chain reaction (Almac Diagnostics, Armagh, United Kingdom). Adverse events were evaluated throughout the study and at 30 days (90 days for serious adverse events and events of interest to pembrolizumab) after treatment discontinuation and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical Analysis

Efficacy was assessed in the intention-to-treat population of all randomly assigned participants. Safety was assessed in the as-treated population of all randomly

assigned participants who received at least one dose of study treatment. Participant-reported outcomes (PROs) were assessed in the PRO full analysis set (FAS) population of all randomly assigned participants with at least one PRO assessment available for the specific end point and who had received at least one dose of study treatment.

Completion and compliance rates of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, Quality of Life Questionnaire-Stomach cancer module, and EuroQoL 5-dimension, 5-level questionnaire by visit and by treatment are described. Completion rate is defined as the number of treated participants who complete at least one item/number of participants in the PRO FAS population. Compliance rate is defined as the number of treated participants who complete at least one item/the number of eligible participants who are expected to complete. The protocol specified four primary and two secondary hypotheses. One interim analysis and a final analysis were planned. The interim analysis (final analysis of objective response rate and progression-free survival (PFS) and interim analysis of overall survival in participants with PD-L1 CPS ≥ 1 and all participants) were planned to occur after approximately 494 PFS events were observed in participants with PD-L1 CPS ≥ 1 and approximately 8 months after the last participant was randomly assigned.

APPENDIX 2

TABLE A1. Postdiscontinuation Anticancer and Immunotherapy in All Treated Participants

Therapy	Lenvatinib + Pembrolizumab + Chemotherapy (n = 443), No. (%)	Chemotherapy (n = 437), No. (%)
Received any subsequent systemic anticancer therapy	202 (46)	273 (62)
Subsequent systemic therapy by type		
Chemotherapy	196 (44)	255 (58)
Any PD-1/PD-L1	20 (5)	83 (19)
Any VEGF	85 (19)	126 (29)
Other	93 (21)	108 (25)
Other immunotherapy	2 (1)	8 (2)

Abbreviation: VEGF, vascular endothelial growth factor.

TABLE A2. Potentially Immune-Mediated Adverse Events in All Treated Participants

Adverse Event	Lenvatinib + Pembrolizumab + Chemotherapy (n = 441), No. (%)		Chemotherapy (n = 429), No. (%)	
	Any	Grade ≥ 3	Any	Grade ≥ 3
Any	202 (46)	44 (10)	51 (12)	6 (1)
Adrenal insufficiency	13 (3)	4 (1)	1 (<1)	0
Arthritis	1 (<1)	0	0	0
Cholangitis sclerosing	1 (<1)	0	0	0
Colitis	11 (2)	6 (1)	1 (<1)	1 (<1)
Encephalitis	1 (<1)	1 (<1)	0	0
Exocrine pancreatic insufficiency	0	0	1 (<1)	0
Gastritis	9 (2)	1 (<1)	4 (1)	1 (<1)
Hemolytic anemia	1 (<1)	1 (<1)	0	0
Hepatitis	8 (2)	5 (1)	1 (<1)	0
Hyperthyroidism	33 (7)	1 (<1)	7 (2)	0
Hypophysitis	5 (1)	1 (<1)	0	0
Hypothyroidism	128 (29)	3 (1)	5 (1)	0
Infusion reactions	24 (5)	5 (1)	34 (8)	3 (1)
Myelitis	0	0	1 (<1)	0
Myositis	1 (<1)	1 (<1)	0	0
Myocarditis	2 (<1)	1 (<1)	0	0
Nephritis	5 (1)	2 (<1)	0	0
Pancreatitis	6 (1)	3 (1)	1 (<1)	0
Pneumonitis	15 (3)	1 (<1)	2 (<1)	1 (<1)
Severe skin reactions	15 (3)	12 (3)	0	0
Thyroiditis	2 (<1)	0	0	0
Type 1 diabetes mellitus	2 (<1)	2 (<1)	0	0
Vasculitis	3 (1)	1 (<1)	1 (<1)	0

TABLE A3. Change From Baseline to Week 18 in EORTC QLQ-C30 GHS/QoL, QLQ-STO22 Pain, and EQ-5D-5L Scores in the Total PRO FAS Population

Questionnaire	Lenvatinib + Pembrolizumab + Chemotherapy, LSM (95% CI)	Chemotherapy, LSM (95% CI)	Difference in LSM Change ^a (95% CI)
QLQ-C30 GHS/QoL	n = 430 -1.72 (-3.95 to 0.50)	n = 420 2.42 (-0.01 to 4.86)	-4.15 (-7.18 to -1.12)
QLQ-STO22 pain scale	n = 429 -5.55 (-7.73 to -3.38)	n = 418 -8.62 (-10.97 to -6.27)	3.07 (0.21 to 5.93)
EQ-5D-5L VAS	n = 427 -0.80 (-2.76 to 1.15)	n = 416 -0.02 (-2.14 to 2.10)	-0.78 (-3.43 to 1.86)

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-STO22, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach cancer module; EQ-5D-5L VAS, EuroQoL 5-dimension, 5-level visual analog scale; GHS/QoL, Global Health Status/Quality of Life; FAS, full analysis set; LSM, least squares mean; PRO, participant-reported outcome.

^aFor EORTC QLQ-C30 GHS/QoL and EQ-5D-5L VAS, a higher score indicates better HR QoL; for EORTC-QLQ STO22 pain scale, a higher score indicates worsened symptoms.

TABLE A4. LEAP-015 Investigators

Country	Investigator
Argentina	Ezequiel Heman Slutsky
	Juan Cundom
	Andrea Gabriela Soria
	Marcela Alejandro Carballido
	Juan Manuel O'Connor
	Julieta Grasseli
Australia	Matthew Burge
	Daniel Paul Brungs
	Muhammad Adnan Khattak
Belgium	Karen Paula Jozefa Geboes
	Eric Van Cutsem/Jeroen Dekervel
	Lionel D. Hondt
Canada	Frederic Lemay
	Rosalyn Anne Juergens
Chile	Felipe Reyes
	Gonzalo Pizarro Brito
	Maria Alejandra Ojeda
	Herman Adolfo Araya
	Patricio Eduardo Yanez
China	Jianwei Yang
	Xi Chen
	Yuxian Bai
	Hongming Pan
	Nong Xu
	Yueyin Pan
	Qinghong Guo
	Baorui Liu
	Feng Ye
	Xin Wang
	Qi Li
	Yong Tang
	Huiting Xu
	Haichuan Su
	Ying Cheng
	Xianli Yin
	Qun Zhao
	Ning Li
	Jun You
	Yi Ba
	Jinsheng We
	Lin Shen
	Jin Li
	Wangjun Liao
	Zhen Li
	Lei Yang

(continued in next column)

TABLE A4. LEAP-015 Investigators (continued)

Country	Investigator
Colombia	Yovany Eduardo Rodriguez Pena
	Ivan Jose Bustillo
	Carlos Jose Narvaez
	Manuel Enrique Gonzalez Fernandez
	Raimundo Manneh
	Andres Fernando Arenas Arias
Costa Rica	Luis Corrales
	Andres Wiernik Rodriguez
France	Thomas Aparicio
	Yuan Touchefeu
	Helene BouSSION-Desloges
	Laurent Mineur
	Christophe Tournigand
	Francois Ghiringhelli
	Marie Pierre Galais
	Eric Terrebonne
Germany	Thomas Walter
	Mathieu Baconnier
	Sylvie Lorenzen
	Eray Goekkurt
	Annika Kurreck
	Arne Kandulski
Guatemala	Thorsten Goetze
	Florian Lordick
	Mynor Aguilar
	Karla Alejandra Lopez
	Rixci Augusto Lenin Ramirez Fallas
	Pier Anyelo Ramos Elias
Hong Kong	Juan Pablo Moreira
	Wing Lok Wendy Chan
	Ashely Cheng
Ireland	Winnie Yeo
	Maeve Lowery
Israel	Adrian Murphy
	Sharon Pelles Avraham
	Ayala Hubert
	Irit Ben-Aharon
	Valeriya Semenisty
	Gali Perl
Italy	Wael Hozaeel
	Armando Santoro
	Elena Aurelia Mazza
	Ferdinando de Vita
	Guisepppe Aprile
	Giovanni Gerardo Cardellino
	Filippo Pietrantonio
	Pierfrancesco Tassone

(continued on following page)

TABLE A4. LEAP-015 Investigators (continued)

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	Yukiya Narita
	Hiroki Hara
	Kensei Yamaguchi
	Naotoshi Sugimoto
	Nozomu Machida
	Tomohiro Nishina
	Akihito Tsuji
	Yasuhiro Choda
	Kenji Amagai
	Masahiro Tsuda
Poland	Shogen Boku
	Boguslawa Karaszewska
	Kamil Stanislaw Kuc
	Jacek Mackiewicz
	Lucjan Stanislaw Wyrwicz
Russia	Lukasz Hajac
	Alexy Alexandrovich Tryakin
	Dmitry Aleksandrovich Nosov
	Rashida Orlova
	Alexey Mikhailovich Karachun
	Michael Osipov
	Mikhail Valerievich Kopp
	Natalia Vladimirovna Fadeeva
South Korea	Nikolay Viktorovich Kislov
	Sun Young Rha
	Seung Tae Kim
	Min-Hee Ryu
	Do-Youn Oh
	Keun-Wook Lee
	Hei-Cheul Jeung
	Jonggwon Choi
Spain	Sang Cheul Oh
	Paula Jimenez Fonseca
	Fernando Rivera Herrero
	Pilar Aitana Calvo Ferrandiz
Taiwan	Daniel Acosta Eyzaguirre
	Kun-Huei Yeh
	Jen-Shi Chen
	Li-Yuan Bai
Turkey	Chia-Jui Yen
	Bulent Erdogan
	Pinar Gursoy
	Mustafa Ozguroglu
	Suayib Yalcin
	Umut Demirci
	Mehmet Bilici
	Ilhan Hacibekiroglu
(continued in next column)	

TABLE A4. LEAP-015 Investigators (continued)

Country	Investigator
United Kingdom	Hugo Ford
	Kai-Keen Shiu
	Martin Scott-Brown
	Russell Petty
	Wasat Mansoor
United States	Zev A. Wainberg
	Marcus Noel
	Peter Enzinger
	Sreenivasa Chandana
	Geoffrey Ku
	Dierdre Cohen
Vincent Lam	

NOTE. Investigators with at least one participant randomly assigned and enrolled.

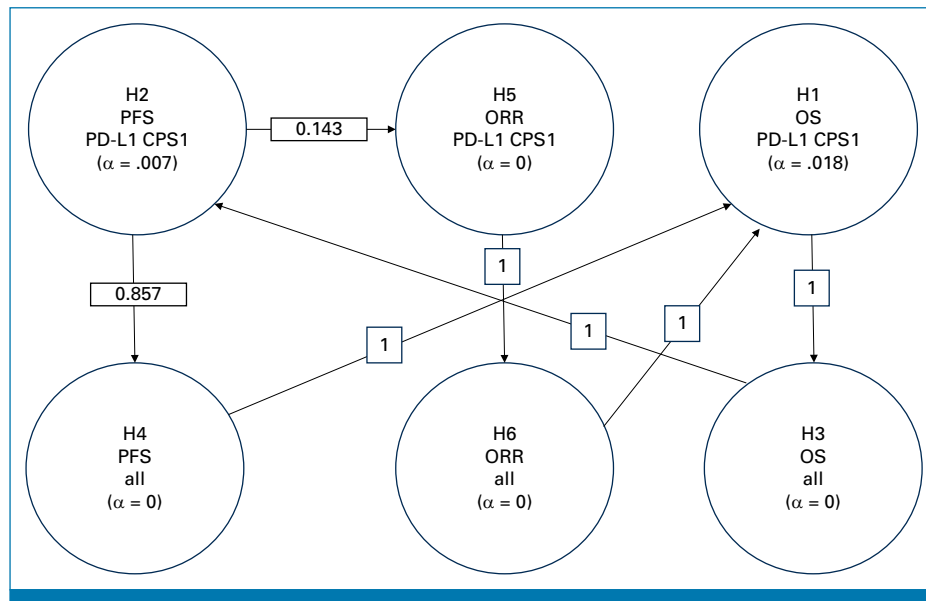


FIG A1. Multiplicity strategy for α reallocation. Hypotheses (H) are indicated in order of α reallocation. CPS, combined positive score; PFS, progression-free survival; ORR, objective response rate; OS, overall survival.

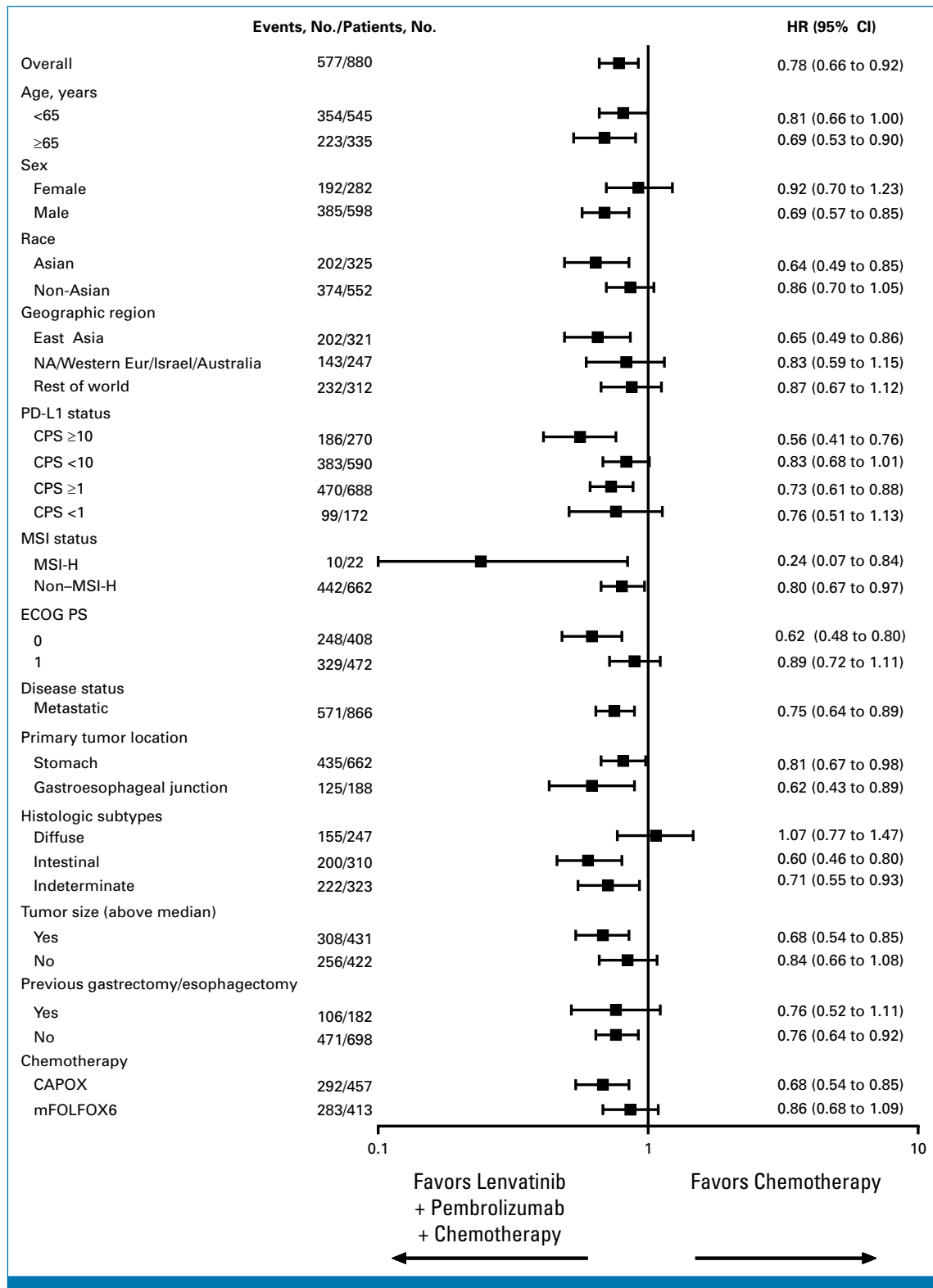


FIG A2. Forest plot of progression-free survival at interim analysis in participants with advanced metastatic HER2-negative gastric and gastroesophageal junction adenocarcinoma. The unstratified Cox regression model with Efron's method of tie handling with treatment as a covariate was used to assess the magnitude of the treatment difference between arms. CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mFOLFOX6, fluorouracil, leucovorin, and oxaliplatin; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NA, North America.

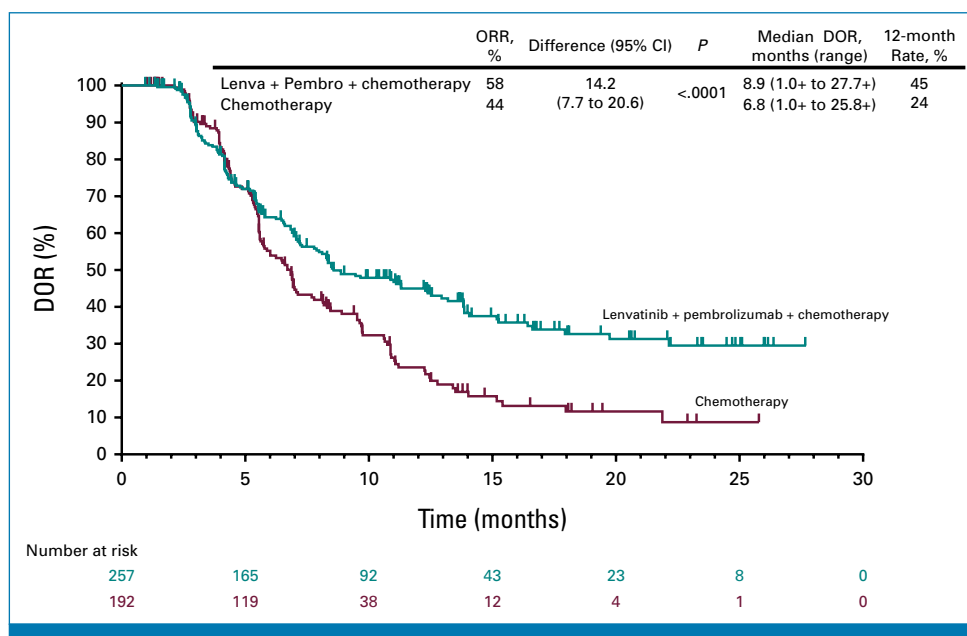


FIG A3. DOR in participants with advanced metastatic HER2-negative gastric and gastroesophageal junction adenocarcinoma. Kaplan-Meier estimate of DOR at interim analysis. Tick marks represent data censored at the time of last imaging assessment. DOR, duration of response; HER2, human epidermal growth factor receptor 2; Lenva, lenvatinib; Pembro, pembrolizumab; ORR, objective response rate.