

Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma

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PURPOSE The immunomodulatory effect of lenvatinib (a multikinase inhibitor) on tumor microenvironments may contribute to antitumor activity when combined with programmed death receptor-1 (PD-1) signaling inhibitors in hepatocellular carcinoma (HCC). We report results from a phase Ib study of lenvatinib plus pembrolizumab (an anti-PD-1 antibody) in unresectable HCC (uHCC).

PATIENTS AND METHODS In this open-label multicenter study, patients with uHCC received lenvatinib (body-weight \geq 60 kg, 12 mg; < 60 kg, 8 mg) orally daily and pembrolizumab 200 mg intravenously on day 1 of a 21-day cycle. The study included a dose-limiting toxicity (DLT) phase and an expansion phase (first-line patients). Primary objectives were safety/tolerability (DLT phase), and objective response rate (ORR) and duration of response (DOR) by modified RECIST (mRECIST) and RECIST version 1.1 (v1.1) per independent imaging review (IIR; expansion phase).

RESULTS A total of 104 patients were enrolled. No DLTs were reported ($n = 6$) in the DLT phase; 100 patients (expansion phase; included $n = 2$ from DLT phase) had received no prior systemic therapy and had Barcelona Clinic Liver Cancer stage B ($n = 29$) or C disease ($n = 71$). At data cutoff, 37% of patients remained on treatment. Median duration of follow-up was 10.6 months (95% CI, 9.2 to 11.5 months). Confirmed ORRs by IIR were 46.0% (95% CI, 36.0% to 56.3%) per mRECIST and 36.0% (95% CI, 26.6% to 46.2%) per RECIST v1.1. Median DORs by IIR were 8.6 months (95% CI, 6.9 months to not estimable [NE]) per mRECIST and 12.6 months (95% CI, 6.9 months to NE) per RECIST v1.1. Median progression-free survival by IIR was 9.3 months per mRECIST and 8.6 months per RECIST v1.1. Median overall survival was 22 months. Grade \geq 3 treatment-related adverse events occurred in 67% (grade 5, 3%) of patients. No new safety signals were identified.

CONCLUSION Lenvatinib plus pembrolizumab has promising antitumor activity in uHCC. Toxicities were manageable, with no unexpected safety signals.

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Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is estimated to be the sixth most prevalent cancer worldwide and the fourth leading cause of cancer-related death.¹ Despite advances in early detection, a majority of patients with HCC present with advanced disease.²

Patients with advanced HCC or tumor progression after locoregional treatment can benefit from systemic treatment.³ Sorafenib demonstrated a statistically significant survival benefit versus placebo in 2 randomized phase III studies in advanced HCC (SHARP

study⁴ and Asia-Pacific study⁵). Lenvatinib, a multi-kinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1 to 3, fibroblast growth factor (FGF) receptors 1 to 4, platelet-derived growth factor receptor- α (PDGFR α), RET, and KIT,⁶⁻⁹ was later approved for first-line treatment of unresectable HCC (uHCC) based on the phase III REFLECT study.¹⁰ In REFLECT, lenvatinib met its primary end point of overall survival (OS) by statistical confirmation of noninferiority to sorafenib (median OS, 13.6 months with lenvatinib v 12.3 months with sorafenib; hazard ratio [HR], 0.92; 95% CI, 0.79 to 1.06).¹⁰ Lenvatinib also resulted in

significant and clinically meaningful improvements versus sorafenib in objective response rate (ORR; including unconfirmed responses), progression-free survival (PFS), and time to progression (TTP).¹⁰ Specifically, ORR by blinded independent imaging review (IIR) was significantly higher with lenvatinib versus sorafenib per RECIST version 1.1 (RECIST v1.1; 18.8% v 6.5%; $P < .0001$) and modified RECIST¹¹ (mRECIST; 40.6% v 12.4%; $P < .0001$).¹⁰ PFS (by IIR per RECIST v1.1 and mRECIST) was also significantly longer with lenvatinib versus sorafenib (median PFS, 7.3 v 3.6 months; $P < .0001$ for both RECIST v1.1 and mRECIST).¹⁰

Immunotherapies, including immune checkpoint inhibitors, have had promising results in patients with advanced HCC, likely in part because of the contribution of both inflammation and suppressed immune microenvironments to the pathogenesis of HCC.^{12,13} The potential importance of programmed death receptor-1 (PD-1)/PD-1 ligand (PD-L1) blockade in HCC has been further underscored by the US Food and Drug Administration (FDA) decision to grant accelerated approvals of pembrolizumab and nivolumab (PD-1 monoclonal antibodies) for second-line HCC treatment after the results of phase II studies.¹⁴⁻¹⁷ The approvals of pembrolizumab and nivolumab were based on the therapeutic benefits of each drug (observed by ORR and duration of response [DOR]) in their respective phase II studies (CheckMate-040 for nivolumab; KEYNOTE-224 for pembrolizumab).¹⁴⁻¹⁷ In KEYNOTE-240, a phase III study evaluating pembrolizumab versus placebo as a second-line treatment option for HCC, pembrolizumab reduced the risk of death by 22% and improved PFS versus placebo; however, pembrolizumab did not reach its primary end points (ie, OS and PFS did not reach statistical significance per pre-specified criteria).¹⁸

Combination therapies involving PD-1 inhibitors are being studied for a variety of malignancies, including non-small-cell lung cancer, renal cell carcinoma, and endometrial cancer.^{19,20} In March 2020, the FDA granted ipilimumab plus nivolumab accelerated approval as a second-line treatment option for HCC.^{16,21} In addition, the combination of lenvatinib plus pembrolizumab was granted accelerated approval for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high or mismatch repair deficient, who have disease progression after systemic therapy, and who are not candidates for curative surgery or radiotherapy.^{15,22} The rationale for combining lenvatinib with pembrolizumab is based on the ability of lenvatinib to inhibit the proangiogenic and immunosuppressive effects of tumor microenvironments; such inhibition would improve the clinical benefit of PD-1 antibodies by boosting the antitumor immune response.^{23,24} Preclinical data have suggested that this combination may be effective in HCC; in a mouse model of HCC, lenvatinib combined with PD-1 signaling blockade resulted in promising antitumor activity compared with either monotherapy.²⁵ Specifically, in

a Hepa1-6 mouse HCC syngeneic tumor model, lenvatinib alone decreased proportions of monocytes and macrophages, and in combination with a PD-1 antibody, lenvatinib increased the percentage of early-activated CD8+ T cells.²⁵ These encouraging results led to the phase Ib study, which was conducted to assess the tolerability, safety, and efficacy profiles of lenvatinib plus pembrolizumab in uHCC, reported here.

PATIENTS AND METHODS

Study Design and Participants

Study 116 is an ongoing phase Ib multicenter open-label study of lenvatinib plus pembrolizumab in patients with uHCC. The study consists of 2 phases: a dose-limiting toxicity (DLT) phase and an expansion phase. Patients received lenvatinib 12 mg (if bodyweight \geq 60 kg) or 8 mg (if bodyweight $<$ 60 kg) orally once daily and pembrolizumab 200 mg intravenously on day 1 of a 21-day treatment cycle (for up to 2 years after cycle 1 day 1). If no DLTs were reported in the DLT phase, the expansion phase would be initiated using the recommended dose from the DLT phase. Treatment was continued until disease progression, development of unacceptable toxicity, or withdrawal of consent. Additional details regarding continued pembrolizumab treatment are provided in the Appendix (online only).

Key inclusion criteria comprised the following: histologically or cytologically confirmed HCC (excluding fibrolamellar, sarcomatoid, and mixed cholangio-HCC tumors) or clinically confirmed HCC according to the American Association for the Study of Liver Diseases criteria; stage B (not suitable for transarterial chemoembolization) or C categorization based on the Barcelona Clinic Liver Cancer (BCLC) staging system; at least 1 measurable target lesion according to mRECIST per investigator assessment; Child-Pugh class A (score, 5-6); and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Patients were excluded if they had clear invasion of the bile duct (classified clinically as a cholestatic type of HCC in which a patient's initial manifestation is obstructive jaundice resulting from tumor thrombosis/compression/diffuse infiltration into the biliary tract); portal vein invasion with Vp4²⁶; prior blood-enhancing treatment (including blood transfusion, blood products, or agents that stimulate blood cell production [eg, granulocyte colony-stimulating factor]) within 28 days before first dose of study drugs; prior treatment with lenvatinib or any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent; and imaging findings with HCC having \geq 50% liver occupation. Additionally, patients were excluded from the expansion phase if they had received prior systemic therapy for uHCC.

Written informed consent was provided by all patients before undergoing any study-specific procedures. The study protocol was approved by the relevant institutional

TABLE 1. Baseline Demographic and Clinical Characteristics of Patients Receiving Lenvatinib Plus Pembrolizumab (N = 100)

Characteristic	No. (%)
Age, years	
Median	66.5
Range	47-86
Age group, years	
< 65	38 (38)
≥ 65	62 (62)
Sex	
Male	81 (81)
Female	19 (19)
Race	
White	51 (51)
Asian	28 (28)
Black/African American	2 (2)
Other	5 (5)
Missing	14 (14)
Country	
Japan	18 (18)
United States	34 (34)
United Kingdom	4 (4)
France	17 (17)
Italy	4 (4)
Spain	6 (6)
Russian Federation	17 (17)
Bodyweight, kg	
< 60	19 (19)
≥ 60 kg	81 (81)
ECOG PS	
0	62 (62)
1	38 (38)
BCLC stage	
B	29 (29)
C	71 (71)
Serum AFP level, ng/mL ^a	
< 200	61 (61)
≥ 200	36 (36)
< 400	67 (67)
≥ 400	30 (30)
Child-Pugh score	
5	71 (71)
6	27 (27)
7	2 (2) ^b
Etiology ^{c,d}	
HBV	19 (19)

(continued in next column)

TABLE 1. Baseline Demographic and Clinical Characteristics of Patients Receiving Lenvatinib Plus Pembrolizumab (N = 100) (continued)

Characteristic	No. (%)
HCV	36 (36)
Alcohol	28 (28)
Other	22 (22)
Macroscopic vascular invasion	20 (20)
Macroscopic portal vein invasion	16 (16)
Extrahepatic sites	52 (52)
Macroscopic portal vein invasion, extrahepatic spread, or both	62 (62)
Radiographic evidence of cirrhosis ^e based on IIR	52 (52)
Involved disease sites	
Liver	93 (93)
Lung	18 (18)
Lymph nodes	30 (30)
Bone	10 (10)
Other	20 (20)
No. of involved disease sites per patient	
1	46 (46)
2	41 (41)
≥ 3	13 (13)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; IIR, independent imaging review.

^aData were missing for 3 patients.^bThese 2 patients had protocol deviations.^cPatients could be counted in multiple categories.^dBased on medical history.^eUnderlying liver cirrhosis of any etiology (eg, alcohol, nonalcoholic steatohepatitis, hepatitis).

review boards/independent ethics committees, and the study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

End Points and Clinical Assessments

Tolerability and safety of the combination regimen (the primary objectives of the DLT phase) were initially evaluated by assessing DLTs during the first treatment cycle using a 3 + 3 design. In the expansion phase, the primary end points were ORR and DOR by mRECIST and RECIST v1.1 per IIR. Tumor assessment scans were performed every 6 weeks until week 24 and then every 9 weeks; treatment decisions were based on mRECIST per investigator assessment. Additional information regarding tumor assessments is included in the Appendix. Secondary end points were ORR and DOR by investigator assessment per mRECIST. Additional secondary end points included

TABLE 2. Most Common Treatment-Related AEs in Those Receiving Lenvatinib Plus Pembrolizumab (N = 100)

Preferred AE Term	No. (%)			
	Any Grade ^{ab}	Grade 1	Grade 2	Grade 3
Hypertension	36 (36)	1 (1)	18 (18)	17 (17)
Diarrhea	35 (35)	19 (19)	11 (11)	5 (5)
Fatigue	30 (30)	12 (12)	14 (14)	4 (4)
Decreased appetite	28 (28)	12 (12)	16 (16)	0
Hypothyroidism	25 (25)	11 (11)	14 (14)	0
Palmar-plantar erythrodysesthesia syndrome	23 (23)	13 (13)	9 (9)	1 (1)
Weight decreased	22 (22)	8 (8)	11 (11)	3 (3)
Dysphonia	21 (21)	19 (19)	1 (1)	1 (1)
AST increased	20 (20)	4 (4)	5 (5)	11 (11)
Proteinuria	20 (20)	9 (9)	7 (7)	4 (4)
Asthenia	19 (19)	4 (4)	10 (10)	5 (5)
Nausea	17 (17)	10 (10)	6 (6)	1 (1)
Rash	15 (15)	11 (11)	3 (3)	1 (1)

NOTE. Any-grade treatment-related adverse events (AEs) occurring in $\geq 15\%$ of patients.

^aThere were 3 grade 5 treatment-related AEs, comprising acute respiratory failure/acute respiratory distress syndrome (n = 1), abnormal hepatic function (n = 1), and intestinal perforation (n = 1), all of which are well-described potential AEs for these drug classes.

^bNone of the most common treatment-related AEs (reported in this table) were grade ≥ 4 .

PFS, TTP, time to response (TTR), and OS. Safety assessments consisted of the monitoring and recording of adverse events (AEs) according to Common Terminology Criteria for Adverse Events version 4.03, laboratory evaluations, vital signs, electrocardiograms, and echocardiograms or multi-gated acquisition scans.

Statistical Analyses

The safety and efficacy analysis sets included all first-line patients from the DLT phase and the expansion phase who received at least 1 dose of study drug. A brief overview of the expansion of enrollment and sample size estimation can be found in the Appendix. ORR was calculated with 95% CI using the Clopper-Pearson method. DOR, PFS, TTP, and OS were estimated using the Kaplan-Meier method. DOR and TTR were analyzed for patients with confirmed complete response (CR) or partial response. Duration of follow-up was calculated by the reverse Kaplan-Meier estimate of OS.²⁷ All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients

Overall, 104 patients were enrolled in the study (DLT and expansion phases) between February 27, 2017, and April 11, 2019. The primary analysis set included 100 patients who were treated in the first-line setting (4 patients from the DLT phase were excluded because of prior sorafenib treatment). At the data cutoff date (October 31, 2019), all patients in the primary analysis set had an opportunity for a minimum follow-up period of ≥ 6 months; 37 patients

(37%) were still receiving treatment (both study drugs, n = 34; lenvatinib only, n = 3); 63 patients (63%) had discontinued treatment; and 26 of the 63 patients remained in survival follow-up (Appendix Table A1, online only). The primary reasons for treatment discontinuation are listed in Appendix Table A1. Data on subsequent anticancer medications during survival follow-up are summarized in Appendix Table A2 (online only).

Median patient age in the first-line setting was 66.5 years (range, 47-86 years), and most patients were White (51%) or Asian (28%). At baseline, 62% and 38% of patients had ECOG PS of 0 and 1, respectively. BCLC stage B was noted in 29% of patients and stage C in 71%. Child-Pugh scores of 5, 6, and 7 were reported for 71%, 27%, and 2% of patients, respectively. Proportions of patients with macroscopic portal vein invasion and extrahepatic spread at baseline were 16% and 52%, respectively. Etiology of HCC included hepatitis B (19%), hepatitis C (36%), and alcohol (28%); and 30% of patients had an alpha fetoprotein level ≥ 400 ng/mL (Table 1).

Study Drug Exposure

In the first-line setting, at the time of data cutoff, median duration of exposure was 7.9 months (range, 0.2-31.1 months) for lenvatinib plus pembrolizumab (lenvatinib: median, 7.6 months; range, 0.2-31.1 months; pembrolizumab: median, 7.4 months; range, 0.03-23.5 months). Median received dose as a percentage of the planned starting dose of lenvatinib was 69% (range, 23%-100%). Median number of pembrolizumab administrations was 11 (range, 1-33 administrations).

TABLE 3. Summary of Efficacy Outcomes in Those Receiving Lenvatinib Plus Pembrolizumab (N = 100)

Parameter	mRECIST		
	Investigator Review	IIR	RECIST Version 1.1 per IIR
ORR (confirmed responses only)	41 (41)	46 (46)	36 (36)
95% CI ^a	31.3 to 51.3	36.0 to 56.3	26.6 to 46.2
ORR (confirmed and unconfirmed responses)	46 (46)	53 (53)	44 (44)
95% CI ^a	36.0 to 56.3	42.8 to 63.1	34.1 to 54.3
Best overall response			
CR	5 (5)	11 (11)	1 (1)
PR	36 (36)	35 (35)	35 (35)
SD ^b	45 (45)	42 (42)	52 (52)
PD	7 (7)	7 (7)	7 (7)
Unknown/not evaluable	7 (7)	5 (5)	5 (5)
DOR ^c for confirmed responders, months			
Median	12.6	8.6	12.6
95% CI ^d	6.2 to 18.7	6.9 to NE	6.9 to NE
DOR ^c ≥ 6 months	22	24	17
Probability	0.75	0.83	0.73
95% CI ^e	0.57 to 0.86	0.68 to 0.92	0.52 to 0.86
TTR for confirmed responders, months			
Median	2.7	1.9	2.8
Range	1.2-11.8	1.2-5.5	1.2-7.7
DCR	86 (86)	88 (88)	88 (88)
95% CI ^a	77.6 to 92.1	80.0 to 93.6	80.0 to 93.6
PFS, months ^c			
Median	8.2	9.3	8.6
95% CI ^d	7.4 to 9.7	5.6 to 9.7	7.1 to 9.7
Patients with events	62 (62)	56 (56)	58 (58)
PD	47 (47)	42 (42)	43 (43)
Death	15 (15)	14 (14)	15 (15)
PFS rate, % ^c			
6 months	66.8	59.9	64.0
95% CI ^e	56.3 to 75.4	49.3 to 69.0	53.4 to 72.8
12 months	30.8	26.4	27.4
95% CI ^e	20.2 to 42.0	14.9 to 39.3	16.4 to 39.6
TTP, months ^c			
Median	9.7	9.7	9.7
95% CI ^d	7.7 to 13.9	7.9 to 11.8	7.7 to 13.9
OS, months ^c			
Median		22.0	
95% CI ^d		20.4 to NE	
Death		34 (34)	

(continued on following page)

TABLE 3. Summary of Efficacy Outcomes in Those Receiving Lenvatinib Plus Pembrolizumab (N = 100) (continued)

Parameter	mRECIST		
	Investigator Review	IIR	RECIST Version 1.1 per IIR
OS rate, % ^c			
6 months		81.0	
95% CI ^e		71.8 to 87.4	
12 months		67.5	
95% CI ^e		56.5 to 76.3	

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: CR, complete response; DCR, disease control rate; DOR, duration of response; IIR, independent imaging review; mRECIST, modified RECIST; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression; TTR, time to response.

^aCalculated using exact method of binomial distribution (Clopper-Pearson method).

^bIncludes unconfirmed PR, non-CR/non-PD, and durable SD.

^cKaplan-Meier method was used for estimating DOR, PFS, TTP, and OS.

^dBased on generalized Brookmeyer and Crowley method.

^eBased on Greenwood formula using log-log transformation.

Safety

No DLTs were reported in the 6 patients enrolled in the DLT phase of the study. In the first-line setting, most patients (99%) experienced an AE (the most common AEs are reported in Appendix Table A3, online only), and 95% of patients experienced ≥ 1 treatment-related AE. The most common any-grade treatment-related AEs (Table 2) were hypertension (36%), diarrhea (35%), fatigue (30%), decreased appetite (28%), and hypothyroidism (25%). Grade ≥ 3 treatment-related AEs occurred in 67% of patients (grade 3, 63% [n = 63]; grade 4, 1% [n = 1]; grade 5, 3% [n = 3]). The most common grade 3 treatment-related AE was hypertension (17%). Leukopenia/neutropenia was the only grade 4 treatment-related AE.

Serious AEs (SAEs) were reported in 65 patients (65%); treatment-related SAEs were reported in 36 patients (36%). During the study, 13 (13%) grade 5 AEs occurred: 10 deaths were considered unrelated to study treatment, and 3 deaths were considered treatment related (acute respiratory failure/acute respiratory distress syndrome [n = 1] on day 124; abnormal hepatic function [n = 1] on day 127; and intestinal perforation [n = 1] on day 60).

Treatment-related AEs led to treatment interruption, dose reduction, and treatment discontinuation of lenvatinib in 62 (62%), 52 (52%), and 14 patients (14%), respectively; treatment-related AEs led to treatment interruption and treatment discontinuation of pembrolizumab in 43 (43%) and 10 patients (10%), respectively. Discontinuation of both lenvatinib and pembrolizumab because of treatment-related AEs occurred in 6 patients (6%).

Efficacy

Efficacy data according to investigator assessment by mRECIST, IIR by mRECIST, and IIR by RECIST v1.1 are summarized in Table 3. The following results for tumor assessments (among patients treated in the first-line

setting) are based on IIR. Median duration of follow-up was 10.6 months (95% CI, 9.2 to 11.5 months). ORR (including confirmed responses only) was 46.0% (95% CI, 36.0% to 56.3%) by mRECIST and 36.0% (95% CI, 26.6% to 46.2%) by RECIST v1.1. CRs (as best overall response) were observed in 11 patients (11%) by mRECIST and 1 patient (1%) by RECIST v1.1. Median DOR for confirmed responders was 8.6 months (95% CI, 6.9 months to not estimable [NE]) by mRECIST and 12.6 months (95% CI, 6.9 months to NE) by RECIST v1.1 (Appendix Fig A1, online only). ORRs were consistent across various subgroups, including those with poor prognostic features, such as ECOG PS of 1, macroscopic portal vein invasion, high alpha fetoprotein level, and BCLC stage C (Appendix Table A4, online only). Median TTR for confirmed responders was 1.9 months by mRECIST and 2.8 months by RECIST v1.1 (Table 3). Median PFS was 9.3 months (95% CI, 5.6 to 9.7 months) by mRECIST (Table 3; Fig 1A) and 8.6 months by RECIST v1.1 (95% CI, 7.1 to 9.7 months; Table 3; Fig 1B). Median OS was 22.0 months (95% CI, 20.4 months to NE; Table 3; Fig 1C). Reductions in tumor size per IIR by mRECIST and RECIST v1.1 were reported in 89% (83 of 93) and 83% (78 of 94) of evaluable patients, respectively (Fig 2), and the reductions seemed to be durable (Fig 3; Appendix Fig A2, online only). Median TTP was 9.7 months (95% CI, 7.9 to 11.8 months) by mRECIST per IIR and 9.7 months (95% CI, 7.7 to 13.9 months) by RECIST v1.1 per IIR (Table 3; Appendix Fig A3, online only).

DISCUSSION

Treatment options for advanced HCC have rapidly evolved over the past several years. After a decade with sorafenib as the only available treatment in advanced disease, new options are now available to treat patients in various settings (eg, first and second lines).^{3,28} Although single-agent immune checkpoint inhibitors have demonstrated long-term disease control with manageable toxicity in a subset of

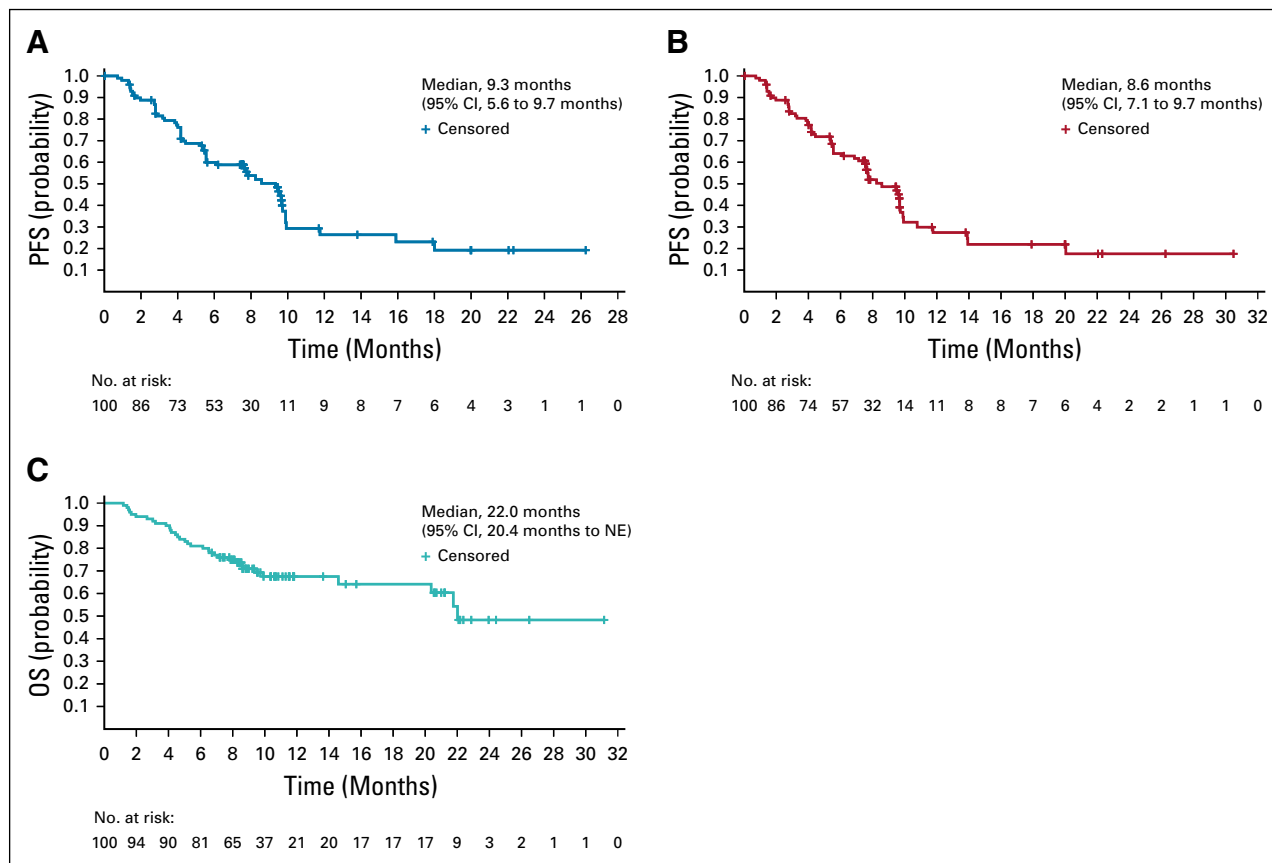


FIG 1. Kaplan-Meier estimates of (A) progression-free survival (PFS) by modified RECIST per independent imaging review (IIR), (B) PFS by RECIST version 1.1 per IIR, and (C) overall survival (OS; efficacy analysis set). NE, not estimable.

patients,^{12,13} phase III studies have failed to meet their primary end points in the first-line setting versus sorafenib²⁹ and second-line setting versus placebo.¹⁸

In this phase Ib single-arm study of 100 patients in the first-line setting, lenvatinib plus pembrolizumab yielded confirmed response rates (46% by mRECIST; 36% by RECIST v1.1) per IIR, median PFS of 9.3 months (by mRECIST; 8.6 months by RECIST v1.1) per IIR, and median OS of 22.0 months. Moreover, responses were durable (median DOR, 8.6 months by mRECIST and 12.6 months by RECIST v1.1) per IIR. Together, these numbers indicate that multikinase inhibition (ie, VEGF receptors 1-3, FGF receptors 1-4, PDGFR α , RET, and KIT)⁶⁻⁹ with lenvatinib plus PD-1 inhibition with pembrolizumab results in improved antitumor activity. Although the exact mechanism driving these higher response rates is still not well understood, preclinical data suggest that the immunomodulatory effect of lenvatinib complements pembrolizumab activity, thereby increasing sensitivity of tumors to this combination therapy.^{24,25} Similar observations have been described in other immune checkpoint inhibitor combination studies in advanced HCC. In the phase III IMbrave150 study,³⁰ atezolizumab (a PD-L1 antibody) plus bevacizumab (a VEGF inhibitor) treatment resulted in improved OS compared

with sorafenib (HR, 0.58; 95% CI, 0.42 to 0.79; $P = .0006$), as well as response rates (ORR and disease control rate [DCR]) $> 27\%$ per RECIST v1.1. This combination is now included in the National Comprehensive Cancer Network guidelines for hepatobiliary cancer.³² Moreover, ipilimumab (a CTLA-4 antibody) plus nivolumab (a PD-1 antibody) as second-line agents for HCC³³ had response rates (ORR and DCR) $> 30\%$ by RECIST v1.1. Similar to outcomes reported with lenvatinib plus pembrolizumab, these combinations yielded durable responses.

In this study, with patients who had uHCC but well-preserved liver function, there were no new or unexpected toxicities resulting from lenvatinib plus pembrolizumab combination therapy. Treatment-related AEs with the combination of lenvatinib and pembrolizumab were consistent with the known AEs of each individual agent,^{10,17,34} and there have been no reported cases of viral hepatitis flares with pembrolizumab to date.^{17,18} The most frequent any-grade treatment-related AEs were hypertension, diarrhea, fatigue, decreased appetite, and hypothyroidism; however, only grade 3 hypertension and elevated AST occurred in $> 10\%$ of patients, and the only grade 4 treatment-related AE was leukopenia/neutropenia (1%). There were 3 deaths (each occurred early during the study)

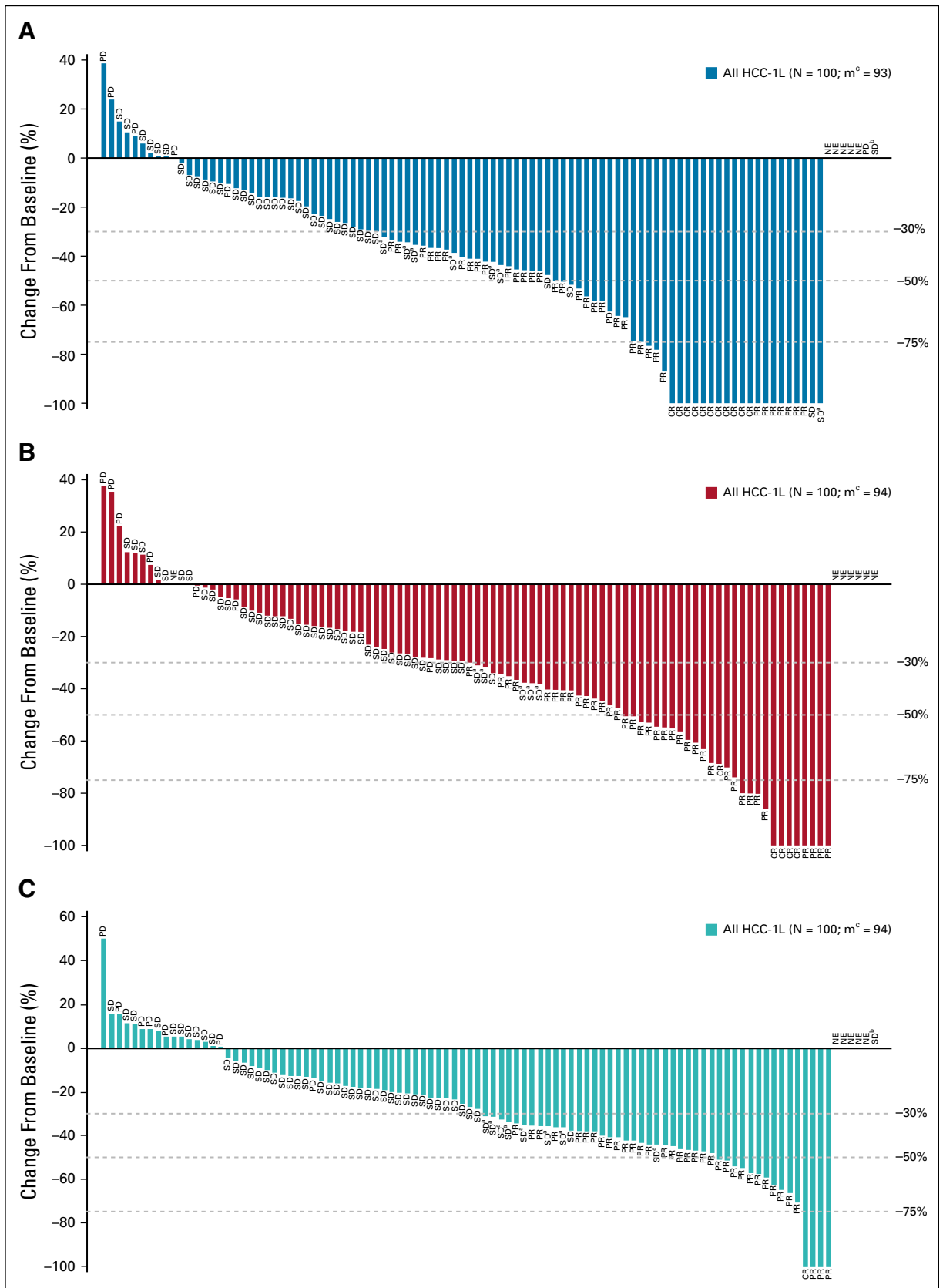


FIG 2. Percentage change from baseline in sums of diameters of target lesions by (A) modified RECIST (mRECIST) per independent imaging review (IIR), (B) mRECIST per investigator review, and (C) RECIST version 1.1 per IIR. CR, complete response; HCC-1L, hepatocellular carcinoma first line; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease. (a) Unconfirmed PR. (b) Non-CR/non-PD. (c) No. of patients with both baseline and postbaseline sums of diameters of target lesions.

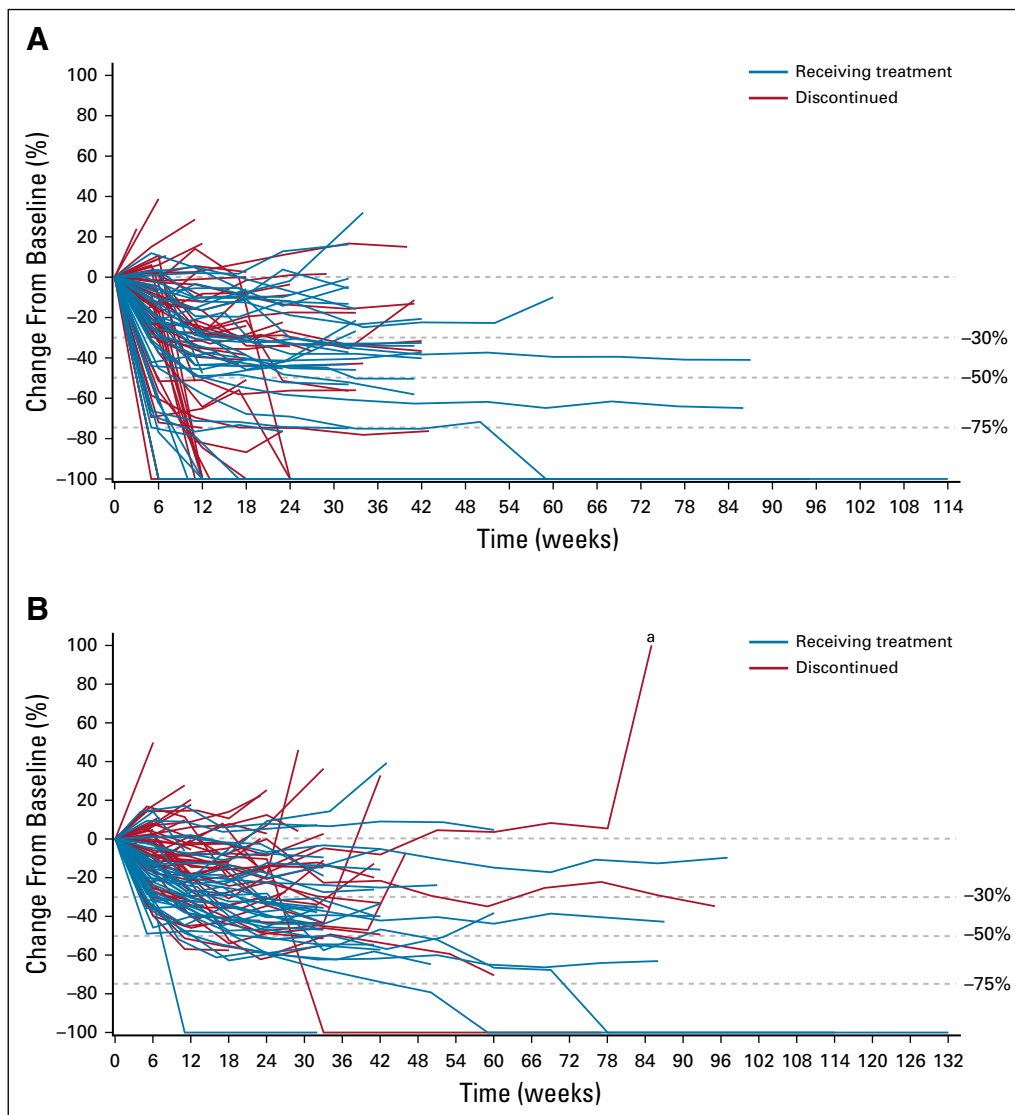


FIG 3. Percentage change from baseline in sums of diameters of target lesions by (A) modified RECIST per independent imaging review (IIR) and (B) RECIST version 1.1 per IIR. (a) Value (127.8%) beyond y-axis limit is truncated and not displayed.

considered to be treatment related by the investigator, attributed to acute respiratory failure/acute respiratory distress syndrome ($n = 1$), abnormal hepatic function ($n = 1$), and intestinal perforation ($n = 1$), all of which are well-described potential AEs for these drug classes. Overall, treatment-related AEs led to discontinuation of both lenvatinib and pembrolizumab in 6 patients (6%). These rates were comparable to those reported in monotherapy studies of each drug in patients with HCC, suggesting that the toxicity profile of this combination is manageable with appropriate monitoring, treatment interruption, and/or dose modification (this latter option applies to lenvatinib only).^{10,17,18,34}

Lenvatinib plus pembrolizumab resulted in a DCR of $> 85\%$ (irrespective of RECIST category) in this study, but further refinement of the population selection criteria to target those most likely to benefit from this combination therapy would be valuable. To date, serum and tissue biomarker analyses of patients with advanced HCC who were treated with either lenvatinib³⁵ or checkpoint

inhibitors^{17,18,36} have not clearly defined predictive markers of response or resistance. Importantly, in this current study, efforts were made to collect archival tumor tissue or a newly obtained biopsy before the first dose of study drug in the expansion phase, and these tissue samples will provide analytic material for future mechanism-based biomarker analyses.

Despite recent advances in treatment, advanced HCC is still associated with poor prognosis and median OS remains approximately 1 year.³ The competing risk of death from both underlying liver disease and malignancy adds significant complexity to the clinical management of these patients because AEs must be balanced with efficacy. Median OS and TTP for approved first-line treatments, such as sorafenib and lenvatinib, range from 11 to 14 and 4 to 9 months, respectively.^{3,4,10} Although most agents available to treat advanced HCC have improved survival, response rates remain low.²⁸ ORR rates after lenvatinib and sorafenib treatment have ranged from 19% to 41% and 7% to 12%,

respectively.¹⁰ In this study of lenvatinib plus pembrolizumab, improvements in both ORR and DCR were observed.

The current data are limited because of the nature of this study (ie, single arm and open label). However, the sample size, multicenter design, and AE profile of the study and its use of blinded IIR support the conclusion that lenvatinib plus pembrolizumab demonstrated promising antitumor activity with acceptable tolerability. Moreover, on the basis of interim

data from this study, the FDA granted lenvatinib plus pembrolizumab a breakthrough therapy designation for the first-line treatment of uHCC that is not amenable to locoregional therapy. An ongoing double-blind randomized controlled phase III study of lenvatinib plus pembrolizumab versus lenvatinib plus placebo as first-line treatment of uHCC (LEAP-002; ClinicalTrials.gov identifier: [NCT03713593](https://clinicaltrials.gov/ct2/show/study/NCT03713593)) should confirm the efficacy and safety of this combination in patients with uHCC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma**

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APPENDIX**Pembrolizumab Treatment**

Patients who stopped study treatment after receiving 35 administrations of pembrolizumab for reasons other than progressive disease or intolerance and patients who achieved a complete response and stopped study treatment were eligible to receive a second course of treatment of up to 17 additional administrations of pembrolizumab (approximately 1 year).

Tumor Responses

As of February 2018, all tumor assessment scans (including scans previously reviewed by investigators) were sent to an imaging core laboratory for independent imaging review by RECIST version 1.1 and modified RECIST. Tumor assessments of complete or partial response were confirmed ≥ 4 weeks after initial response.

Expansion of Enrollment and Sample Size Determination

A protocol amendment allowed for the expansion phase to be further expanded by approximately 94 evaluable patients. Interim analyses were planned to take place when 20 (6 patients for the DLT phase plus 14 patients for the expansion phase) and 56 patients (6 patients for the DLT phase plus 50 patients for the expansion phase) had sufficient follow-up to be evaluated for response. The decision to expand

enrollment was based on the results of these 2 interim analyses, which spent $\beta = 0.012$ and $\beta = 0.024$ at the first and second interim analyses, respectively.

On the basis of an assumption of H_0 : 25% objective response rate (ORR) and H_1 : 45% ORR, the 100-patient design with 2 futility analyses had approximately 96% statistical power at 2-sided $\alpha = 0.02$ (corresponding to 1-sided $\alpha = 0.01$). At the first interim analysis ($n = 20$), if there were > 5 responses, approximately 36 additional patients would be enrolled. At the second interim analysis ($n = 56$), if there were > 16 responses, approximately 44 additional patients would be enrolled. If there were ≤ 5 responses at the first interim analysis ($n = 20$) or ≤ 16 responses at the second interim analysis ($n = 56$), the sponsor would decide whether to expand enrollment based on clinical outcome (eg, duration of response). The 2 interim analyses were not formally conducted, because the numbers of responses required to enable expansion enrollment were reached before the planned interim analyses at $n = 20$ and $n = 56$, respectively.

Data-Sharing Statement

The data will not be available for sharing at this time, because the data are commercially confidential. However, Eisai will consider written requests to share the data on a case-by-case basis.

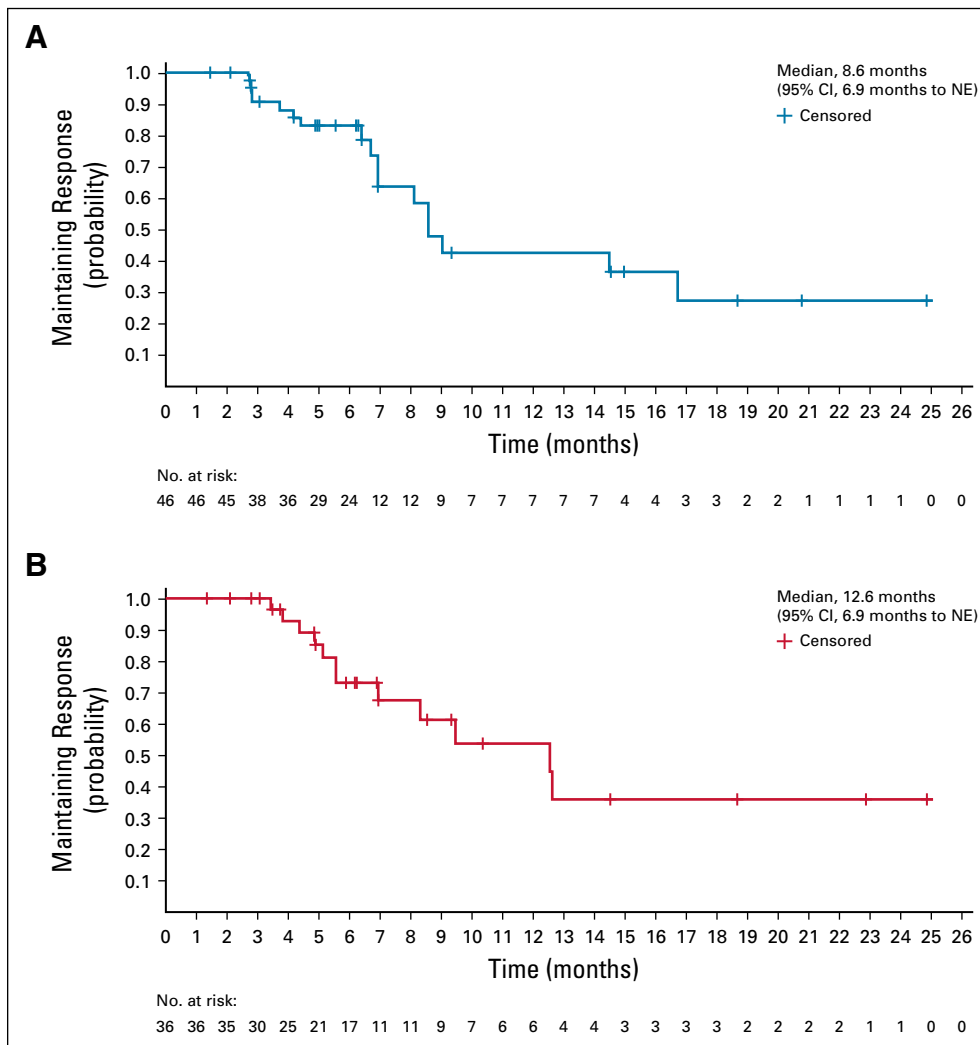


FIG A1. Kaplan-Meier estimate of duration of response by (A) modified RECIST and (B) RECIST version 1.1 per independent imaging review. NE, not estimable.

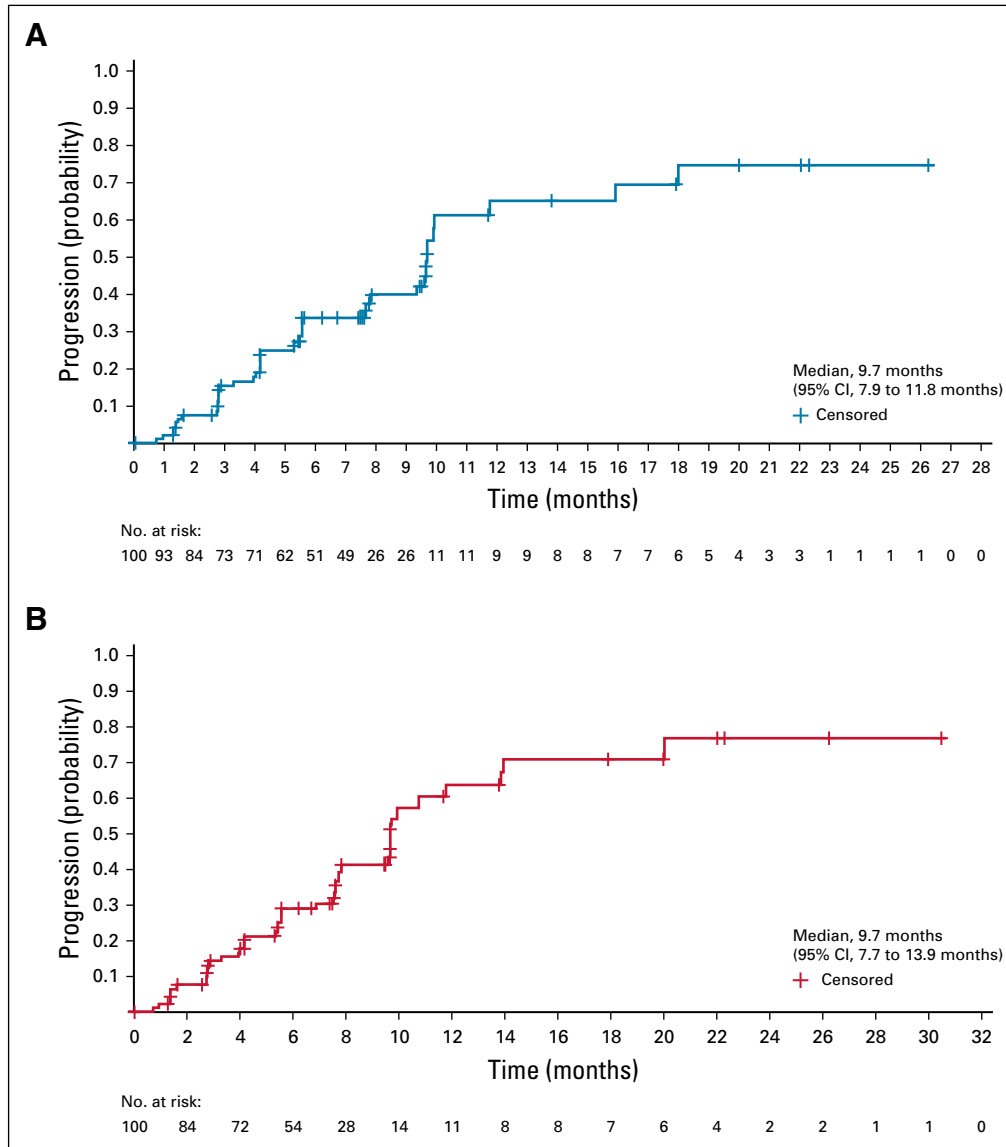


FIG A3. Kaplan-Meier estimate of time to progression (TTP) by (A) modified RECIST and (B) RECIST version 1.1 per independent imaging review.

TABLE A1. Patient Disposition and Reasons for Discontinuation From Treatment at Data Cutoff Date of October 31, 2019, Among Those Receiving Lenvatinib Plus Pembrolizumab (N = 100)

Parameter	No. (%)
Treatment ongoing	37 (37)
Both study drugs	34 (34)
Lenvatinib only	3 (3)
Pembrolizumab only	0
Discontinued treatment	63 (63)
Primary reason for discontinuation	
Radiologic disease progression	35 (35)
Clinical disease progression	7 (7)
Adverse event	18 (18)
Patient choice	1 (1)
Withdrawal of consent	1 (1)
Other ^a	1 (1)
Discontinued treatment but in survival follow-up	26 (26)

^aNoncompliance with protocol procedures.

TABLE A2. Anticancer Medications During Survival Follow-Up Among Those Receiving Lenvatinib Plus Pembrolizumab (N = 100)

Preferred Medication Term	No. (%)
≥ 1 Anticancer medication during survival follow-up	17 (17)
Antimetabolite	2 (2)
Fluorouracil	1 (1)
Gemcitabine	1 (1)
Other antineoplastic agent/regimen	16 (16)
Sorafenib	7 (7)
Regorafenib	3 (3)
Cisplatin	2 (2)
Ramucirumab	2 (2)
Cabozantinib	1 (1)
FOLFOX	1 (1)
Lenvatinib	1 (1)
Nivolumab	1 (1)
Ponatinib	1 (1)
Investigational drug	1 (1)

NOTE. Patients with ≥ 2 medications within a class level and drug name are counted only once within that class level and drug name.

Abbreviations: FOLFOX, leucovorin, fluorouracil, and oxaliplatin.

TABLE A3. Most Common Treatment-Emergent AEs Among Those Receiving Lenvatinib Plus Pembrolizumab (N = 100)

Preferred AE Term ^a	No. (%)				
	Any Grade ^b	Grade 1	Grade 2	Grade 3	Grade ≥ 4
Diarrhea	50 (50)	29 (29)	14 (14)	7 (7)	0
Hypertension	38 (38)	2 (2)	18 (18)	18 (18)	0
Decreased appetite	36 (36)	16 (16)	19 (19)	1 (1)	0
Fatigue	33 (33)	13 (13)	14 (14)	6 (6)	0
Hypothyroidism	31 (31)	15 (15)	16 (16)	0	0
AST level increased	30 (30)	8 (8)	8 (8)	14 (14)	0
Weight decreased	30 (30)	10 (10)	15 (15)	5 (5)	0
Proteinuria	25 (25)	9 (9)	11 (11)	5 (5)	0
Asthenia	24 (24)	6 (6)	12 (12)	6 (6)	0
Dysphonia	23 (23)	19 (19)	3 (3)	1 (1)	0
Nausea	23 (23)	13 (13)	7 (7)	3 (3)	0
Palmar-plantar erythrodysesthesia syndrome	23 (23)	13 (13)	9 (9)	1 (1)	0
Anemia	21 (21)	10 (10)	7 (7)	4 (4)	0
Abdominal pain	20 (20)	11 (11)	5 (5)	4 (4)	0
Blood bilirubin level increased	20 (20)	2 (2)	10 (10)	6 (6)	2 (2)
Lipase increased	20 (20)	5 (5)	4 (4)	11 (11)	0
ALT level increased	19 (19)	9 (9)	4 (4)	6 (6)	0
Vomiting	19 (19)	13 (13)	3 (3)	3 (3)	0
Pruritus	17 (17)	15 (15)	2 (2)	0	0
Rash	17 (17)	13 (13)	3 (3)	1 (1)	0
Arthralgia	16 (16)	12 (12)	4 (4)	0	0
Edema peripheral	16 (16)	11 (11)	5 (5)	0	0
Hypoalbuminemia	15 (15)	2 (2)	12 (12)	1 (1)	0
Stomatitis	15 (15)	7 (7)	4 (4)	4 (4)	0

NOTE. Any-grade treatment-emergent adverse events (AEs) occurring in ≥ 15% of patients.

^aPatient with ≥ 2 treatment-emergent AEs reported in the same preferred term is only counted once using the highest Common Terminology Criteria for Adverse Events grade.

^bPatients may have experienced multiple AEs per Common Terminology Criteria for Adverse Events grade. Grade 4 treatment-emergent AEs occurred in 10 patients and included thrombocytopenia (n = 1), neutropenia (n = 2), leukopenia (n = 1), pancytopenia (n = 1), general physical health deterioration (n = 1), hyperbilirubinemia (n = 1), sepsis (n = 1), biliary sepsis (n = 1), endocarditis (n = 1), WBC count decreased (n = 1), neutrophil count decreased (n = 1), blood bilirubin increased (n = 2), hyperkalemia (n = 1), hypertriglyceridemia (n = 1), acute lymphocytic leukemia (n = 1), pancreatic carcinoma (n = 1), and hepatic encephalopathy (n = 1). Grade 5 treatment-emergent AEs occurred in 13 patients and included abnormal hepatic function (n = 1), pneumonia (n = 1), death (n = 2), hepatic failure (n = 2), hepatic cirrhosis (n = 1), sepsis (n = 1), upper GI hemorrhage (n = 1), myocardial infarction (n = 1), intestinal perforation (n = 1), bacterial peritonitis (n = 1), acute respiratory distress syndrome (n = 1), and acute respiratory failure (n = 1).

TABLE A4. Summary of Tumor Response by Subgroup

Parameter	No. (%)								
	Overall (N = 100)	ECOG PS		MPVI		AFP Level (ng/mL)		BCLC Stage	
		0 (n = 62)	1 (n = 38)	Yes (n = 16)	No (n = 84)	< 200 (n = 61)	≥ 200 (n = 36)	B (n = 29)	C (n = 71)
ORR (IIR; RECIST v1.1)	36 (36.0)	23 (37.1)	13 (34.2)	6 (37.5)	30 (35.7)	21 (34.4)	15 (41.7)	12 (41.4)	24 (33.8)
95% CI	26.6 to 46.2	25.2 to 50.3	19.6 to 51.4	15.2 to 64.6	25.6 to 46.9	22.7 to 47.7	25.5 to 59.2	23.5 to 61.1	23.0 to 46.0
ORR (IIR; mRECIST)	46 (46.0)	30 (48.4)	16 (42.1)	5 (31.3)	41 (48.8)	27 (44.3)	17 (47.2)	15 (51.7)	31 (43.7)
95% CI	36.0 to 56.3	35.5 to 61.4	26.3 to 59.2	11.0 to 58.7	37.7 to 60.0	31.5 to 57.6	30.4 to 64.5	32.5 to 70.6	31.9 to 56.0

Abbreviations: AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IIR, independent imaging review; MPVI, macroscopic portal vein invasion; mRECIST, modified RECIST; ORR, objective response rate.