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ORIGINAL RESEARCH

Survival Benefit of Lenvatinib Plus PD-1 Inhibitor with or Without HAIC in Advanced Hepatocellular Carcinoma Beyond Oligometastasis: a Multicenter Cohort Study

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Purpose: The outcome between Lenvatinib plus programmed cell death protein-1 (PD-1) inhibitor and Lenvatinib in HCC beyond oligometastasis was unclear. In this multicenter, we compared the prognosis of Lenvatinib plus PD-1 inhibitor with Lenvatinib in HCC beyond oligometastasis.

Patients and Methods: A total of 296 patients from six institutions were included. The patients were divided into two groups: (a) concurrent Lenvatinib plus PD-1 inhibitor treatment (Len+PD-1 group) and (b) Lenvatinib monotherapy (Len group). The primary endpoint was overall survival (OS), the second endpoint was progression-free survival (PFS) and efficacy.

Results: The median OS was 20.1 ± 1.2 (17.7–22.5) months and 15.7 ± 1.5 (12.8–18.6) months in the Len+PD-1 and Len groups, respectively. The 12-, 24-, and 36-month OS rates were 79.1%, 39.4%, and 10.7% in the Len+PD-1 group, and 76.3%, 29.7%, and 0% in the Len group, respectively. The OS and PFS rates of the Len+PD-1 group were significantly longer compared with the Len group (hazard ratio [HR], 0.88; 95% confidence index [CI], 0.49–0.94; $P = 0.021$) and (HR, 0.66; 95% CI, 0.50–0.87; $P = 0.003$). A subgroup analysis revealed that OS (HR, 0.57; 95% CI, 0.36–0.90; $P = 0.016$) was improved between the Len+PD-1 and Len groups with hepatic artery infusion chemotherapy (HAIC) treatment, whereas OS (HR, 1.11; 95% CI, 0.68–1.80; $P = 0.689$) was similar between the Len and Len+PD-1 groups without HAIC.

Conclusion: Lenvatinib combined with PD-1 inhibitor significantly improves the survival of HCC beyond oligometastasis. For patients with HAIC, there was obviously significance between Len and Len+PD-1 groups.

Plain Language Summary: Lenvatinib as one of system therapy, is recommended treatment for HCC with multimetastases. The LEAP-002 trial, which evaluated Lenvatinib combined with Pembrolizumab exhibited improved progression-free survival (PFS) and overall survival (OS) compared with Lenvatinib alone. However, the combination efficacy on HCC beyond oligometastasis is unknown. In this multicenter study, we found that Lenvatinib combined with PD-1 inhibitor significantly improved both the OS and PFS and this combination could be recommended for HCC beyond oligometastases. OS and PFS were improved in the Len+PD-1 versus the Len group with hepatic artery infusion chemotherapy (HAIC) treatment, whereas the OS and PFS were similar between the Len and Len+PD-1 groups without HAIC. We provided clinical value that HAIC could be recommended as an effective local therapy to improve the prognosis for advanced HCC.

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Introduction

Hepatocellular carcinoma (HCC) ranks fourth in cancer incidence and the second leading cause of cancer-related deaths in China.[1] For early HCC limited to the liver, resection or ablative surgery is the standard treatment.[2] Unfortunately, many patients have developed distant metastases at the time of diagnosis or recurrence, which is often considered as advanced HCC.[3] The standard treatment for HCC with more than five metastases which considered beyond oligometastasis (> 5 metastases), is system therapy.[4] Studies reported HCC beyond metastasis were few and most cases were included in advanced HCC for analysis.[5] However, as the severe stage of HCC, this subtype HCC usually presented with high invasiveness and deem prognosis.[6] The prognosis of HCC beyond oligometastasis is still dissatisfactory and required further study.[3,5] The recommended treatment for HCC beyond oligometastasis is system therapy.

Although the LEAP-002 trial did not meet the expected endpoint, it was important to note that this treatment regimen exhibited improved progression-free survival (PFS) and overall survival (OS) compared with Lenvatinib alone.[7] Some studies have shown that Lenvatinib plus PD-1 inhibitor had longer progression-free survival (PFS) and overall survival (OS) than Lenvatinib alone for advanced HCC especially combined with local therapy.[8,9] In China, Lenvatinib plus PD-1 inhibitor are usually recommended as common system therapy for HCC beyond oligometastasis.[10] Hepatic artery infusion chemotherapy (HAIC), as an effective local therapy for HCC, combined Lenvatinib and PD-1 inhibitor showed better survival than Lenvatinib plus PD-1 inhibitor for HCC with extrahepatic metastasis.[11]

However, there were no large studies that evaluated the combination of Lenvatinib and PD-1 inhibitor in HCC beyond oligometastasis. There was also no study evaluated the effect of HAIC in this subtype HCC. In this multicenter retrospective study, we compared the efficacy of the concurrent application of Lenvatinib and PD-1 inhibitor with Lenvatinib on advanced HCC beyond oligometastasis, and we also evaluated the HAIC value in HCC beyond metastasis.

Materials and Methods

Patients and Study Design

This study was conducted on patients with advanced HCC beyond oligometastasis, who were treated at Chinese PLA General Hospital, The First Affiliated Hospital of Sun Yat-Sen University, Cancer Center of Sun Yat-sen University, Hunan Provincial People's Hospital, and The Second Affiliated Hospital of Guangzhou Medical University, The First Affiliated Hospital of Jinzhou Medical University from January 2018 to December 2022. This study was conducted according to the guidelines of the Declaration of Helsinki.[12] The Ethics Committee Board of the Chinese PLA General Hospital approved this retrospective study and waived the requirement due to this retrospective study.

Enrolled patients had to meet the following inclusion criteria: (1) primary and recurrent HCC; (2) advanced stage with beyond oligometastasis; (3) patients treated with Lenvatinib plus PD-1 inhibitor or Lenvatinib as first-line systemic therapy; (4) patients who received hepatic arterial infusion chemotherapy (HAIC) were also included; (5) Child–Pugh grade A or B; (6) performance 0 or 1 based on the Eastern Collaborative Oncology Organization Performance Status Score (ECOG PS); (7) no history of other malignancies; and (8) no tumor thrombus in the atrium or superior mesenteric vein. The exclusion criteria were as follows: (1) under 18 years or over 75 years of age; (2) advanced HCC within oligometastasis (≤ 5); (3) incomplete clinical data; (4) lost to follow-up within 3 months after inclusion; and (5) patients who received non-Lenvatinib as first-line systemic treatment. The flow chart for patient selection was presented in Figure 1.

Treatment and Assessment of Response

All patients underwent contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) within two weeks before Lenvatinib or Lenvatinib plus PD-1 inhibitor. The patients were divided into two groups: (a) concurrent treatment with Lenvatinib and PD-1 inhibitor, or patients who received PD-1 inhibitor within one week following Lenvatinib administration were also included (Len+PD-1 group); and (b) treatment with Lenvatinib as monotherapy (Len group).

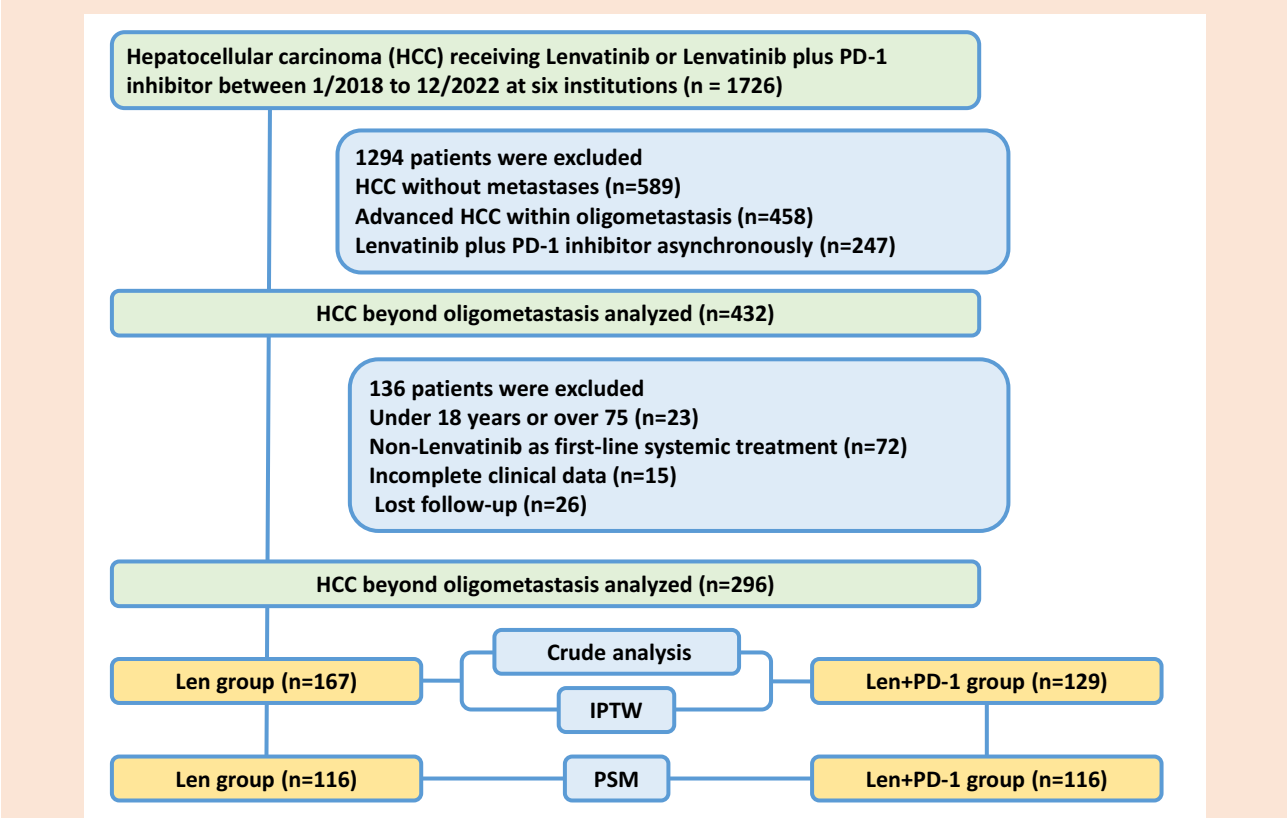

Figure 1 The flowchart of the study.

Information on adverse events (AEs) during treatment initiation and completion was systematically collected. Lenvatinib was administered at doses of 12 mg (weighing ≥ 60 kg) or 8 mg (weighing < 60 kg) orally once daily. Patients presenting with grade ≥3 severe AEs or any unacceptable grade 2 drug-related AEs underwent dose reduction or discontinued treatment based on the Lenvatinib dosing guidelines as well as other treatments recommended after tumor progression. PD-1 inhibitor (including Sintilimab, Tislelizumab, Toripalimab, Camrelizumab) was administered based on the drug manufacturer's instruction. The evaluation of tumor response was done every 6 weeks until radiological progression. Patients without disease progression continued to be evaluated.

Outcomes and Definitions

The primary endpoint of this study was overall survival (OS). The secondary endpoints included progression-free survival (PFS), efficacy, and safety. OS was defined as the time from the date of receiving Lenvatinib or Lenvatinib plus PD-1 inhibitor to patient death or final follow-up. PFS was defined as the time from receiving Lenvatinib or Lenvatinib plus PD-1 inhibitor to tumor progression or final follow-up. Tumor response was assessed by contrast-enhanced CT or MRI or PET/CT. Liver function was measured by albumin – bilirubin (ALBI) grade.[13] Portal vein tumor thrombus (PVTT) was classified by Cheng's criteria as follows: type I, tumor thrombus involving segmental branches of the portal vein or higher; type II, tumor thrombus involving the right/left portal vein; type III, tumor thrombus involving the main portal vein.[14] HAIC and drug-related complications were recorded.

Follow-Up

The follow-up period for this study ended on June 30, 2023. Patients were evaluated every six weeks following treatment. Imaging and laboratory tests, including alfa-fetoprotein (AFP), liver function, and blood tests were required at each follow-up visit. Targeted tumor evaluation required a maximum of two lesions per organ for a total of less than five lesions. Tumor response by imaging was evaluated according to Response Evaluation Criteria version 1.1 (RECIST

v 1.1).[15] The disappearance of arteriosclerosis in tumors was defined as complete response (CR), and tumor diameter reduction of ≥ 30% was designated partial response (PR). Progressive disease (PD) was defined as 20% increase in the diameter of the targeted tumors or the appearance of a new lesion. Stable disease (SD) was defined as neither CR, PR, or PD. An objective response rate (ORR) was considered the sum of CR and PR, whereas the disease control rate (DCR) was the sum of CR, PR, and SD.

Statistical Analysis

All patients who met the baseline eligibility criteria were included in the analysis. Propensity score matching (PSM) analysis was done to reduce selection bias and potential confounding effects between the two groups. Propensity variables included the following: type of HCC, tumor size in liver, tumor number in liver, HAIC, AFP, PVTT type, hepatic vein tumor thrombus (HVTT), albumin-bilirubin (ALBI) grade, organs involved, hepatitis, HBV-DNA, cirrhosis, and portal hypertension. PSM was done using the nearest neighbor 1:1 matching scheme with a calibration of 0.05.[16] A standardized mean difference (SMD) < 0.10 indicated adequate balance. To address the potential bias of the baseline characteristics and the influence of confounding variables, we conducted an inverse probability of treatment weighting (IPTW).[17] The balance of the characteristics was examined by the SMD.

Chi-square and Fisher tests were used for categorical variable analysis. The Kaplan–Meier method was used to generate cumulative PFS and OS curves and the Log rank test was used for comparison. A Cox proportional hazards regression model was used to gradually select variables for multivariate analysis. Statistical analysis was performed using SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA) and R software (version 3.6.4; http://www.r-project.org). $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 1726 patients with advanced HCC were screened, and 296 patients were included for analysis (Figure 1). Of these, 167 patients (56.4%) received Lenvatinib treatment (Len group), and 129 (43.6%) received Lenvatinib plus PD-1 inhibitor synchronously (Len+PD-1 group). For the entire cohort, patients had a higher proportion of primary HCC (83.7% vs 71.9%; $P = 0.016$) in the Len+PD-1 group compared with the Len group. The PSM analysis yielded 116 pairs of patients. The characteristics of the two groups were balanced with standardized mean difference (SMD) < 10% for all baseline variables (Figure S1). Clinicopathological data for all, PSM, and IPTW cohorts are summarized in Table 1 and Table S1.

Effect of Treatment on OS

For the entire cohort, 127 (76.0%) patients in the Len group and 72 (55.8%) patients in the Len+PD-1 group died. The median OS was 20.1±1.2 (17.7–22.4) months and 14.8±0.5 (13.9–15.8) months in the Len+PD-1 and Len groups, respectively. The 12-, 24-, and 36-month OS rates were 76.7%, 39.8%, and 8.7% in the Len+PD-1 group, and 69.3%, 23.7%, and 0% in the Len group, respectively (Table S2). In the PSM cohort, the median OS was 20.1 ± 1.2 (17.7–22.5) months and 15.7 ± 1.5 (12.8–18.6) months for the Len+PD-1 and Len groups, respectively. The 12-, 24-, and 36-month OS rates were 79.1%, 39.4%, and 10.7% in the Len+PD-1 group, and 76.3%, 29.7%, and 0% in the Len group, respectively (Table S2). The OS rates of the Len+PD-1 group were significantly higher compared with that of the Len group for the entire cohort (HR, 0.62; 95% CI, 0.46–0.82; $P < 0.001$) (Figure 2A), the PSM cohort (HR, 0.88; 95% CI, 0.49–0.94; $P = 0.021$) (Figure 2B), and the IPTW cohort (HR, 0.61; 95% CI, 0.45–0.80; $P < 0.001$) (Figure 2C).

Univariable and multivariable analyses of OS in the PSM cohort are shown in Table 2. The results indicated that Len treatment (HR, 1.45; 95% CI, 1.08–2.02; $P = 0.040$), absence of HAIC (HR, 2.10; 95% CI, 1.45–2.05; $P < 0.001$), ALBI grade III (HR, 1.04; 95% CI, 1.04–3.51; $P = 0.037$), and multiple organs involved (HR, 1.66; 95% CI, 1.16–2.39; $P = 0.006$) were correlated with poor OS.

Table 1 Baseline Characteristics of Patients in Entire and PSM Cohort

	Entire cohort				PSM cohort			
	Len (n=167)	Len+PD-1 (n=129)	*P* value	SMD	Len (n=116)	Len+PD-1 (n=116)	*P* value	SMD
Age			0.426	0.094			0.301	0.136
≤60	120 (71.9)	98 (76.0)			81 (69.8)	88 (75.9)		
>60	47 (28.1)	31 (24.0)			35 (30.2)	28 (24.1)		
Sex			0.965	0.005			1.000	<0.001
Male	146 (87.4)	113 (87.6)			101 (87.1)	101 (87.1)		
Female	21 (12.6)	16 (12.4)			15 (12.9)	15 (12.9)		
ALT, U/L			0.325	0.115			0.681	0.034
≤40	109 (65.3)	77 (59.7)			76 (65.5)	73 (49.1)		
>40	58 (34.7)	52 (40.3)			40 (34.5)	43 (50.9)		
AST, U/L			0.265	0.131			0.358	0.105
≤40	86 (51.5)	58 (45.0)			62 (40.5)	55 (45.7)		
>40	81 (48.5)	71 (65.0)			54 (59.5)	61 (54.3)		
Type of HCC			0.016	0.288			0.260	0.148
Primary	120 (71.9)	108 (83.7)			88 (75.9)	95 (81.9)		
Recurrent	47 (28.1)	21 (16.3)			28 (24.1)	21 (18.1)		
Tumor size in liver, cm			0.064	0.277			0.114	0.276
≤5	70 (41.9)	39 (30.2)			50 (43.1)	37 (31.9)		
>5, ≤10	56 (33.5)	59 (45.7)			41 (35.3)	56 (48.3)		
>10	41 (24.6)	31 (24.0)			25 (21.6)	23 (19.8)		
Tumor number in liver			0.971	0.004			1.000	<0.001
≤3	56 (33.5)	43 (33.3)			39 (33.6)	39 (33.6)		
>3	111 (66.5)	86 (66.7)			77 (66.4)	77 (66.4)		
HAIC			0.180	0.158			0.186	0.174
Absence	83 (49.7)	54 (41.9)			56 (48.3)	46 (39.7)		
Presence	84 (50.3)	75 (58.1)			60 (51.7)	70 (60.3)		
AFP, ng/mL			0.190	0.154			0.429	0.104
≤ 400	83 (49.7)	74 (57.4)			60 (51.7)	66 (56.9)		
> 400	84 (50.3)	55 (42.6)			56 (48.3)	50 (43.1)		
PVTT type			0.206	0.152			0.652	0.168
No	98 (58.7)	70 (54.3)			83 (71.6)	74 (63.8)		
I	15 (8.9)	10 (7.8)			5 (4.3)	6 (5.2)		
II	32 (19.2)	31 (24.0)			15 (12.9)	20 (17.2)		
III	22 (13.2)	18 (13.9)			13 (11.2)	16 (13.8)		
HVTT			0.086	0.199			1.000	<0.001
No	154 (92.2)	111 (86.0)			103 (88.8)	103 (88.8)		
Yes	13 (7.8)	18 (14.0)			13 (11.2)	13 (11.2)		
Child-Pugh			0.204					0.583
Grade A	95 (56.9)	82 (64.3)			73 (62.9)	77 (66.4)		
Grade B	72 (43.1)	47 (35.7)			43 (37.1)	39 (33.6)		
ALBI grade			0.111	0.248			0.104	0.282
Grade 1	72 (43.1)	45 (34.9)			47 (40.5)	38 (32.8)		
Grade 2	80 (47.9)	77 (59.7)			56 (48.3)	71 (61.2)		
Grade 3	15 (9.0)	7 (5.4)			13 (11.2)	7 (6.0)		
Organs involved			0.877	0.018			0.693	0.052
Single	93 (55.7)	73 (56.6)			61 (52.6)	64 (55.2)		
Multiple	74 (44.3)	56 (43.4)			55 (47.4)	52 (44.8)		

(*Continued*)

Table 1 (Continued).

	Entire cohort				PSM cohort			
	Len (n=167)	**Len+PD-1 (n=129)**	***P* value**	**SMD**	**Len (n=116)**	**Len+PD-1 (n=116)**	***P* value**	**SMD**
Hepatitis			0.054	0.224			0.858	0.024
No	20 (12.0)	26 (20.2)			18 (15.5)	19 (16.4)		
Yes	147 (88.0)	103 (79.8)			98 (84.5)	97 (83.6)		
HBV DNA			0.145	0.173			1.000	<0.001
Negative	43 (25.7)	24 (18.6)			92 (79.3)	92 (79.3)		
Positive	124 (74.3)	105 (81.4)			24 (20.7)	24 (20.7)		
Anti-virus			0.190	0.153			0.651	0.059
No	38 (22.8)	38 (29.5)			28 (24.1)	31 (26.7)		
Yes	129 (77.2)	91 (70.5)			88 (75.9)	85 (73.3)		
Cirrhosis			0.925	0.011			0.426	0.105
No	91 (54.5)	71 (55.0)			69 (59.5)	63 (54.3)		
Yes	76 (45.5)	58 (45.0)			47 (40.5)	53 (45.7)		
Portal hypertension			0.674	0.049			0.517	0.085
No	134 (80.2)	106 (82.2)			90 (77.6)	94 (81.0)		
Yes	33 (19.8)	23 (17.8)			26 (22.4)	22 (19.0)		

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV DNA, hepatitis B virus deoxyribonucleic acid; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; PD-1, programmed cell death protein-1; PSM, propensity score-matching; PVTT, portal vein tumor thrombus.

Effect of Treatment on Progression-Free Survival

For the entire cohort, the median PFS was 7.4 ± 0.2 (7.0–7.9) months and 6.1±0.2 (5.6–6.5) months in the Len+PD-1 and Len groups, respectively. The estimated 6-, 12-, and 18-month PFS rates were 65.1%, 27.2%, and 8.3% in the Len+PD-1 group and 51.5%, 15.5%, and 0% in the Len group, respectively (Table S3). For the PSM cohort, the median PFS was 7.4 ± 0.2 (7.0–7.8) months and 6.1 ± 0.3 (5.4–6.7) months in the Len+PD-1 and Len groups, respectively. The estimated 6-, 12-, and 18-month PFS rates were 63.8%, 26.4%, and 7.8% in the Len+PD-1 group and 50.9%, 15.7%, and 0% in the Len group, respectively (Table S3). PFS was significantly higher in the Len+PD-1 group compared with that in the Len group for the entire cohort (HR, 0.66; 95% CI, 0.52–0.85; $P < 0.001$) (Figure 2D), the PSM cohort (HR, 0.66; 95% CI, 0.50–0.87; $P = 0.003$) (Figure 2E), and the IPTW cohort (HR, 0.65; 95% CI, 0.51–0.86; $P < 0.001$) (Figure 2F).

The results of univariable and multivariable analysis of PFS are listed in Table S4. After multivariate Cox regression analysis in PSM cohort, the results indicated that Len treatment (HR, 1.47; 95% CI, 1.11–1.95; $P = 0.007$), ALT > 40 U/L (HR, 1.37; 95% CI, 1.03–1.84; $P = 0.032$), tumor number in liver > 3 (HR, 1.66; 95% CI, 1.23–2.25; $P = 0.001$), absence of HAIC (HR, 1.82; 95% CI, 1.35–2.44; $P < 0.001$), and multiple organs involved (HR, 1.46; 95% CI, 1.10–1.95; $P = 0.009$) were correlated with poor PFS (Table S4).

Efficacy Evaluation

The efficacy data were evaluated according to RECIST v 1.1, and the results are listed in Table 3. For the PSM cohort during 3-month evaluation, the ORR of the Len group and Len+PD-1 group were 20.7% and 43.9%, and the DCR was 81.0% and 87.1%, respectively. There were significant differences in the proportion of PR, SD, and PD between the two groups ($P = 0.002$). For the 6-month evaluation, two patients in the Len+PD-1 group achieved CR. The ORR of the Len group and Len+PD-1 group were 20.7% and 37.1%, and the DCR was 40.5% and 55.2%. There were also significant differences in the proportion of CR, PR, SD, and PD between the two groups ($P = 0.030$) (Table 3).

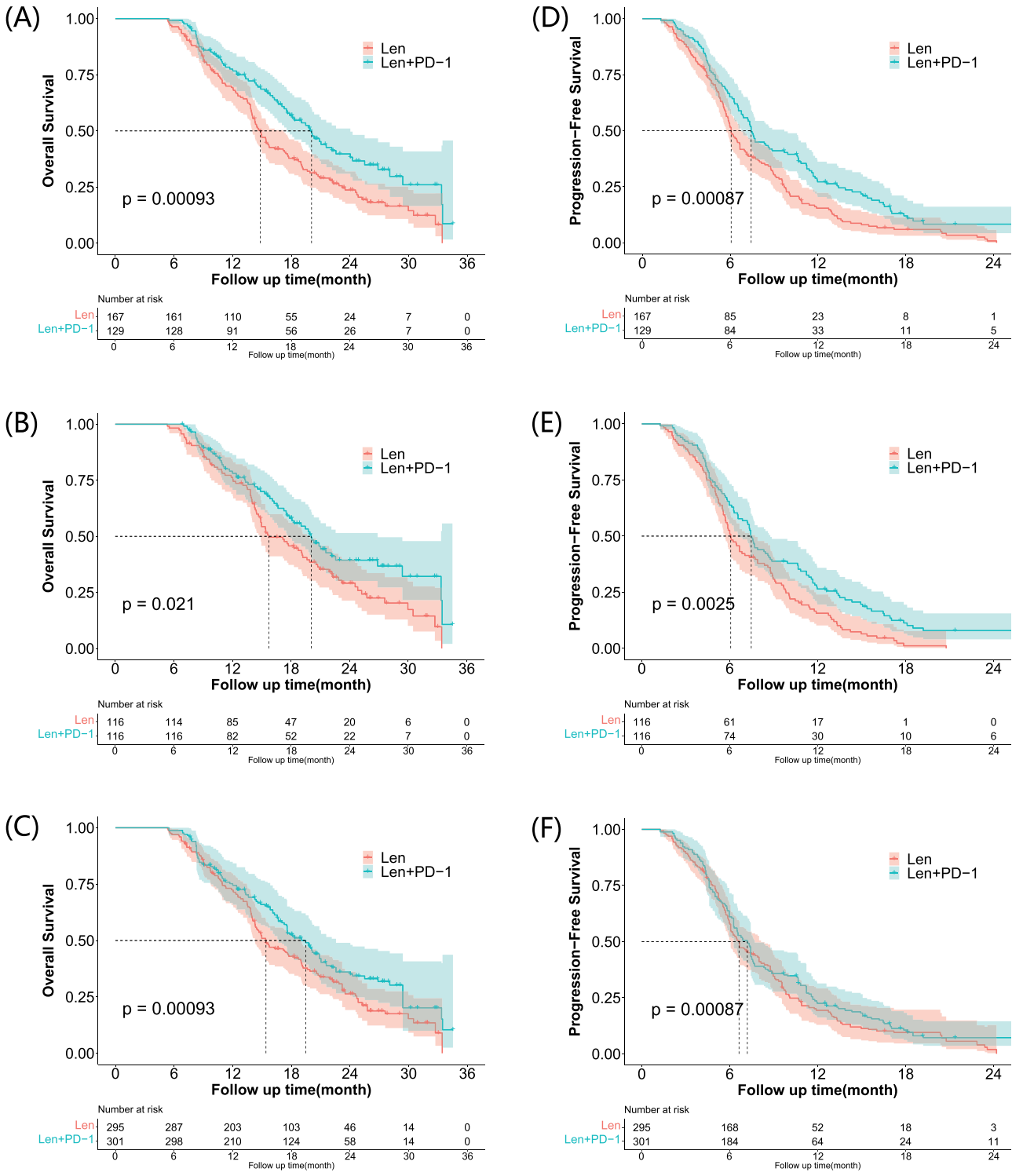

Figure 2 Figure 2. Survival curve of OS in entire cohort (**A**), PSM cohort (**B**), and IPTW cohort (**C**). Survival curve of PFS in entire cohort (**D**), PSM cohort (**E**), and IPTW cohort (**F**).

Subgroup Analysis of HAIC Treatment on Survival Between the Two Groups

HAIC therapy was a protective factor for OS and PFS based on Cox analysis. We further analyzed the efficacy of HAIC on the survival between the two groups. For the PSM cohort, there were 60 patients in the Len group and 70 patients in the Len+PD-1 group that underwent HAIC. The OS was markedly different between the patients with and without HAIC

Table 2 Tumor Evaluation by RECIST v 1.1 in the Entire and PSM Cohorts

Evaluation		Entire cohort			PSM cohort		
		Len (n=167)	Len+PD-1 (n=129)	*P* value	Len (n=116)	Len+PD-1 (n=116)	*P* value
3-month evaluation	CR	0	2 (1.6)	0.001	0 (0.0)	2 (1.7)	0.002
	PR	37 (22.2)	54 (41.9)		24 (20.7)	49 (42.2)	
	SD	93 (55.6)	55 (42.6)		70 (60.3)	50 (43.2)	
	PD	37 (22.2)	18 (13.9)		22 (19.0)	15 (12.9)	
6-month evaluation	CR	0	2 (1.6)	0.016	0 (0.0)	2 (1.7)	0.030
	PR	38 (22.8)	47 (36.4)		24 (20.7)	41 (35.4)	
	SD	32 (19.1)	24 (18.6)		23 (19.8)	21 (18.1)	
	PD	97 (58.1)	56 (43.4)		69 (59.5)	52 (44.8)	

Abbreviations: CR, complete response; PD-1, programmed cell death protein-1; PD, progressive disease; PR, partial response; SD, stable disease.

(HR, 0.45; 95% CI, 0.32–0.64; $P < 0.001$) (Figure 3A). PFS was also significant (HR, 0.49; 95% CI, 0.37–0.65; $P < 0.007$) (Figure 3B). OS and PFS were markedly different between the Len and Len+PD-1 groups with HAIC (HR, 0.57; 95% CI, 0.36–0.90; $P = 0.016$) (Figure 3C) and (HR, 0.52; 95% CI, 0.36–0.75; $P < 0.001$) (Figure 3D), respectively. However, the OS and PFS was not different between the Len and Len+PD-1 groups without HAIC (HR, 1.11; 95% CI, 0.68–1.80; $P = 0.689$) (Figure 3E) and (HR, 1.19; 95% CI, 0.80–1.78; $P = 0.430$), respectively (Figure 3F).

Safety

In the entire cohort, most patients experienced treatment-related AEs, which are listed in Table S5. No treatment-related deaths occurred in either group. For grade 3 to 4 AEs, patients suspended Lenvatinib or PD-1 inhibitor treatment until the adverse effects were alleviated or disappeared, and continued system treatment after recovery.

Discussion

Treatment options for advanced HCC have evolved rapidly.[18] Ten years after sorafenib was the only available treatment for treating advanced HCC, there are now new treatment options for patients in a variety of settings.[19] Since 2021, the Food and Drug Administration has approved atezolizumab plus bevacizumab as first-line treatment for advanced HCC.[20] In China, most patients cannot afford this regimen, and molecular targeted therapy combined with immunotherapy is recommended.[21] Lenvatinib and PD-1 inhibitor are cheaper and available compared with atezolizumab plus bevacizumab. For HCC with oligometastasis, there is an urgent need to control tumor progression because of the high tumor burden in the liver and other organs.[5] Thus, any therapy that can improve efficacy should be administered to improve survival. Lenvatinib plus PD-1 inhibitor have been recommended in China for patients with extrahepatic metastases.[22] However, not all patients receive Lenvatinib and PD-1 inhibitor simultaneously, which involves the recommendation of the doctor, patient preference, and economic circumstances; thus, some patients undergo Lenvatinib treatment alone. Therefore, we compared the outcomes of Lenvatinib plus PD-1 inhibitor with Lenvatinib monotherapy in a real-world study. The combination of Lenvatinib and PD-1 inhibitor was associated with a positive outcome for HCC with beyond oligometastasis.

In this multicenter retrospective analysis, we demonstrated that the combination conferred a significantly better OS (20.1 months vs 15.7 months) and PFS (7.4 months vs 6.1 months) compared with Lenvatinib alone. The combination group also exhibited a higher ORR (37.1% vs 20.1%) and superior tumor inhibition. However, in the subgroup analysis, Lenvatinib plus PD-1 inhibitor showed no significant difference in OS and PFS for patients without HAIC treatment. Although the LAEP-002 trial demonstrated that Lenvatinib and PD-1 inhibitor did not meet the pre-specified significance for improved OS and PFS compared with Lenvatinib alone, the combination still exhibited a survival benefit. We analyzed the OS and PFS in LEAP-002, and the OS curves within 18 months were similar, with no significant difference.

Table 3 Univariable and Multivariable Analysis of Prognostic Factors for OS in PSM Cohort

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Treatment type				
Len vs Len+PD-1	1.48 (1.06–2.06)	0.021	1.45 (1.08–2.02)	0.040
Age				
>60 vs ≤60	1.17 (0.81–1.70)	0.394		
Sex				
Male vs Female	1.40 (0.85–2.29)	0.188		
ALT, U/L				
>40 vs ≤40	1.47 (1.06-2.05)	0.022	1.08 (0.72-1.49)	0.839
AST, U/L				
>40 vs ≤40	1.22 (0.88–1.71)	0.239		
Type of HCC				
Primary vs Recurrent	1.36 (0.90–2.07)	0.141		
Tumor size in liver, cm				
≤5	Reference		Reference	
>5, ≤10	1.56 (1.07–2.26)	0.020	1.42 (0.91–2.17)	0.120
>10	1.84 (1.18–2.87)	0.008	1.47 (0.86–2.36)	0.181
Tumor number in liver				
>3 vs ≤3	1.84 (1.27–2.66)	0.008	1.41 (0.95–2.08)	0.088
HAIC				
Absence vs Presence	1.52 (1.09–2.10)	0.002	2.10 (1.45–3.05)	<0.001
AFP, ng/mL				
> 400 vs ≤ 400	1.40 (1.01–1.94)	0.046	1.39 (0.98–1.97)	0.065
PVTT type				
No	Reference		Reference	
I	0.96 (0.35–2.63)	0.941	0.70 (0.24–2.08)	0.526
II	1.41 (0.89–2.23)	0.144	1.24 (0.72–2.13)	0.445
III	2.32 (1.45–3.71)	<0.001	1.61 (0.89–2.91)	0.113
HVTT				
Absence vs Presence	1.65 (1.01–2.69)	0.045	1.39 (0.75–2.57)	0.300
Child-Pugh				
Grade B vs Grade A	1.60 (1.15–2.23)	0.006	1.09 (0.85–1.39)	0.392
ALBI grade				
Grade I	Reference		Reference	
Grade II	1.47 (1.02–2.12)	0.042	1.47 (0.93–2.18)	0.069
Grade III	2.76 (1.56–4.88)	<0.001	1.91 (1.04–3.51)	0.037
Organs involved				
Multiple vs Single	1.51 (1.09–2.40)	0.014	1.66 (1.16–2.39)	0.006
HBV DNA				
Positive vs Negative	1.46 (1.04–2.06)	0.031	1.24 (0.86–1.79)	0.241
Anti-virus				
No vs Yes	1.21 (0.81–1.79)	0.351		
Cirrhosis				
Yes vs No	1.39 (1.01–1.93)	0.048	1.20 (0.83–1.75)	0.333
Portal hypertension				
Yes vs No	1.21 (0.82–1.78)	0.338		

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV DNA, hepatitis B virus deoxyribonucleic acid; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumor thrombus; PD-1, programmed cell death protein-1; PSM, propensity score-matching; PVTT, portal vein tumor thrombus.

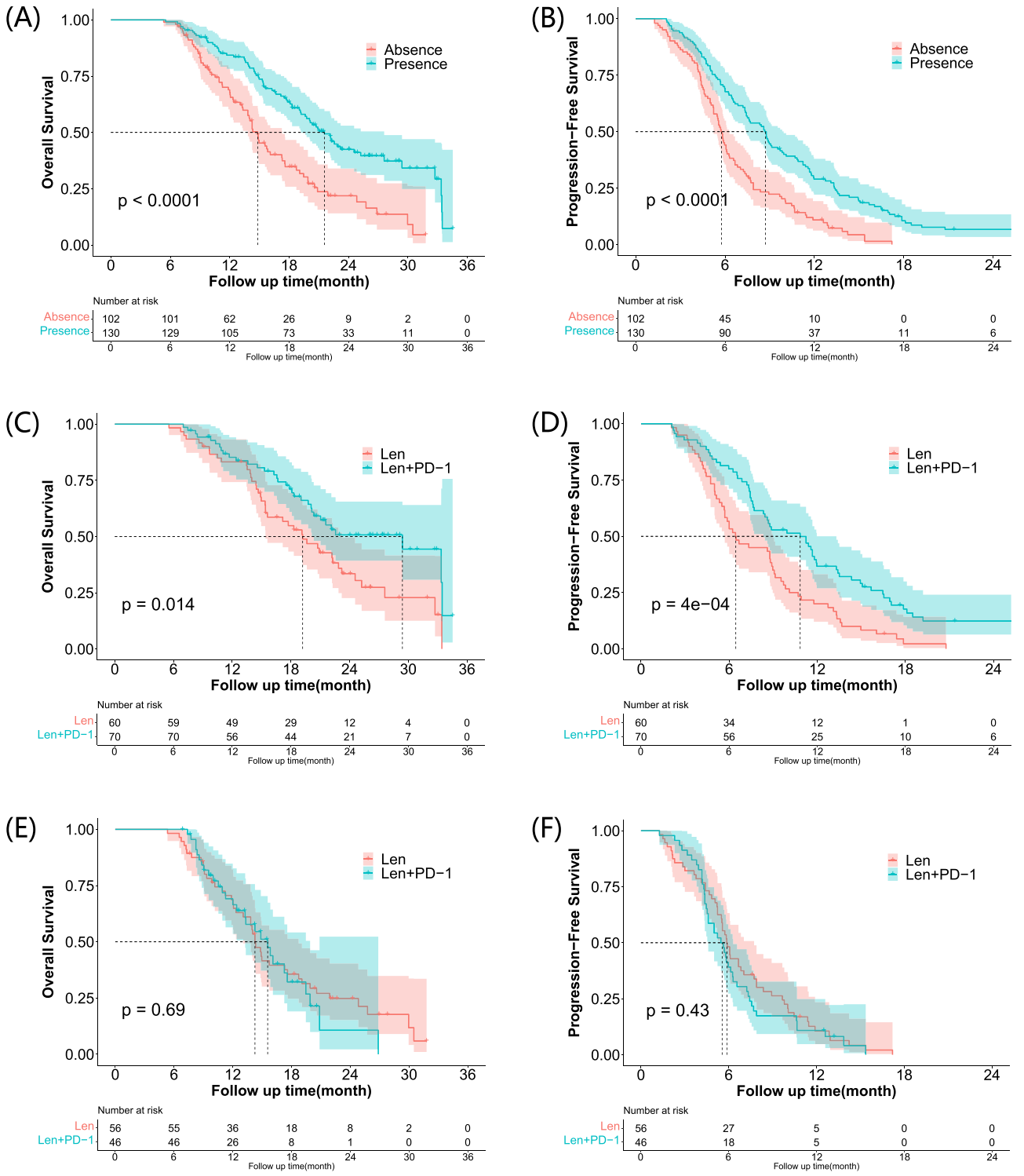

Figure 3 Survival curve of OS (**A**) and PFS (**B**) in the patients with and without HAIC treatment. Survival curve of OS (**C**) and PFS (**D**) in patients with HAIC treatment between Len and Len+PD-1 groups. Survival curve of OS (**E**) and PFS (**F**) in patients without HAIC treatment between Len and Len+PD-1 groups.

This indicates that these patients did not receive survival benefit from Lenvatinib and PD-1 inhibitor.[7] Thus, the high invasiveness and advanced tumor stage of HCC beyond oligometastasis are associated with limited survival benefit from systemic therapy.

Locoregional therapy may enhance immunotherapy.[23] FOLFOX-HAIC is an effective treatment for advanced HCC and has been reported to significantly improve OS.[24] HIAC combined with immunotherapy and molecular targeted therapy were effective in advanced HCC.[25] In the present study, we found that HAIC was a protective factor both for OS and PFS by Cox analysis. In a subgroup analysis, HAIC combined with Lenvatinib and PD-1 inhibitor had a significantly better survival compared with HAIC combined with Lenvatinib. The significance may be attributed to the following factors. First, HAIC may induce tumor apoptosis and immunogenic cell death, and this effect could augment tumor-specific T-cell stimulation and recruitment.[26] Second, PD-1 inhibitor may enhance the anti-tumor immune response and relieve immunosuppression within the tumor, which inhibits metastases.[27] Third, Lenvatinib may decrease regulatory T cells and myeloid-derived suppressor cells, and this effect produces a synergetic effect with PD-1 inhibitor.[28]

Many factors can affect the OS of advanced HCC, including primary tumor, underlying liver disease, inflammatory or immune status of patients, and treatment modalities.[29,30] In the present study, a multivariate analysis revealed that a liver tumor number >3 and multiple involved organs were risk factors for the OS of HCC beyond oligometastasis. Our previous study showed that the lung along with other organs was a risk indicator for OS.[5] Multiple tumors in the liver and organs indicate an aggressive tumor status and a high metastatic tumor burden, which indicates poorer and reduced survival.[31,32]

It should be noted that this study had several limitations. First, this was a retrospective study, rather than a randomized study, which may lead to selection bias and confounding variables. Second, it was a real-world study of Lenvatinib and PD-1 inhibitor, which cannot completely rule out the influence of doctors and patients in patient registration and self-selected medication. Third, although we included data from multiple centers, the results should be further verified in a randomized controlled trial.

Conclusion

In summary, we demonstrated that Lenvatinib combined with PD-1 inhibitor significantly improved both the OS and PFS of HCC with beyond oligometastasis. A subgroup analysis revealed that OS and PFS were improved in the Len+PD-1 versus the Len group with HAIC treatment, whereas the OS and PFS were similar between the Len and Len+PD-1 groups without HAIC.

Data Sharing Statement

Data available was from the Feng Duan and with permission of four hospitals authority in China.

Ethics Statement

The Ethics Committee Board of the Chinese PLA General Hospital approved this retrospective study and waived the requirement for patient consent for this retrospective review. We solemnly promised that this study strictly abided by relevant laws and regulations and did not disclose patient personal information and related information to any other personnel and organizations to ensure the security and confidentiality of patient information.

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Disclosure

The authors declare no conflicts of interest in this work.

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