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ORIGINAL RESEARCH

Population Sensitive to Lenvatinib Plus Anti-PD-1 for Unresectable Hepatocellular Carcinoma Infected with Hepatitis B Virus

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Background: We explore the dose–efficacy relationship of lenvatinib plus anti-PD-1 in patients with unresectable hepatocellular carcinoma (u-HCC) infected with hepatitis B virus (HBV) in real-world practice. Furthermore, we identify the population sensitive to lenvatinib plus anti-PD-1 treatments.

Methods: This retrospective study included 70 patients treated with lenvatinib plus at least 3 cycles of anti-PD-1 and 140 with lenvatinib alone. Stabilized inverse probability of treatment weighting (SIPTW) was used to balance clinical features between the two groups. The overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs) were analyzed. Subpopulation treatment effect pattern plot (STEPP) estimated treatment-effect differences between the two groups.

Results: The median age was 54 years, and 189 (90%) cases were male. A total of 180 (85%) patients were infected with HBV. A slowly increasing 12-month survival rate was with the cycles of anti-PD-1, and 5 cycles and more of anti-PD-1 appeared the most beneficial and stable survival rate. The lenvatinib plus at least 3 cycles anti-PD-1 group had better OS (21.4 vs 14 months, $p = 0.041$), PFS (8.0 vs 6.3 months, $p = 0.015$) than the lenvatinib alone group in unadjusted cohorts, and the SIPTW adjusted cohorts had confirmed it. For patients with portal vein trunk invasion (PVTI) or extrahepatic spread (EHS) combined with Child-Pugh class B (CPB), lenvatinib plus anti-PD-1 made the 12-month survival rate increase by 38%, while, in the other population, it did only 18%. The two groups had similar AEs ($p \geq 0.05$).

Conclusion: The lenvatinib combined with at least 3 cycles of anti-PD-1 was efficacy and safe for u-HCC patients infected with HBV. Especially, patients with PVTI or EHS combined with CPB may benefit most from the combination therapy.

Keywords: hepatocellular carcinoma, real-world study, anti-PD-1, lenvatinib

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death globally.[1] For most patients, the opportunity for complete resection is lost at the first diagnosis due to the lack of early symptoms. Therefore, about half of the HCC patients receive systemic therapies that are the standard for unresectable hepatocellular carcinoma (u-HCC) according to official guidelines.[2–5]

Notably, the systemic therapies of immune checkpoint inhibitors (ICI) with anti-angiogenic or tyrosine kinase inhibitors (TKIs) have been found promising for u-HCC. The combination therapy with ICI is superior to the monotherapy of TKIs in clinical trials and real-world studies.[6–8] The clinical trials, atezolizumab plus bevacizumab

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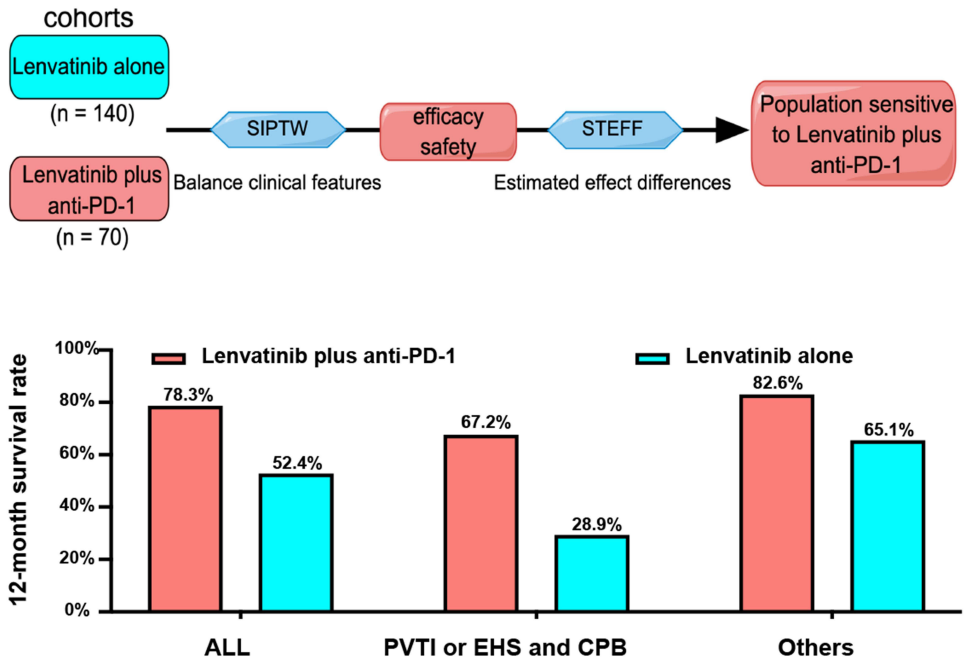
Graphical Abstract



(IMbrave150), apatinib plus camrelizumab (RESCUE), and lenvatinib plus pembrolizumab (the Phase IIb KEYNOTE-524) showed improved survival rates and controllable tolerability in advanced HCC patients.[6,9,10] Lenvatinib with pembrolizumab has been recommended for advanced HCC in the clinical guideline, the diagnosis and treatment of HCC, from the Chinese Society of Clinical Oncology (CSCO).[10]

Recently, the LEAP-002 trial released a negative result about lenvatinib plus pembrolizumab versus lenvatinib alone in the European Society for Medical Oncology (ESMO). The subgroup analysis showed that the patients infected with hepatitis B virus (HBV) may benefit from lenvatinib plus pembrolizumab treatments. Besides, the real-world study in 378 u-HCC patients, 90% infected with HBV, showed that the lenvatinib plus anti-PD-1 had long survival and considerable objective response rate (ORR) and disease control rate (DCR).[11]

In addition, just as the duration of lenvatinib is a key factor in the efficacy, the number of cycles of anti-PD-1 may be important for the efficacy and safety of combination therapy of lenvatinib and anti-PD-1. However, few studies mentioned the number of cycles for anti-PD-1. Therefore, the dose–efficacy relationship of anti-PD-1 was unknown.

Although the systemic therapy of the targeted drug combined with ICI is a promising therapy for advanced HCC, only less than half of patients would benefit from it. So far, there are no indicators to identify the population sensitive to combination therapy. Subpopulation treatment effect pattern plot (STEPP) methodology was commonly used to explore the treatment-effect heterogeneity along continuous variations of biomarker expression.[12,13] Specifically, STEPP analysis can estimate the absolute effect difference between two treatment groups' survival curves at a specified time point, and then identify the sensitive population.[14] For example, STEPP was used in hormone receptor-positive breast cancer to compare letrozole with tamoxifen, and it showed patients with higher Ki-67 levels may benefit most from letrozole, not tamoxifen.[15]

In the real-world study, we explored the dose–efficacy relationship of lenvatinib plus anti-PD-1 and identified the population sensitive to lenvatinib plus anti-PD-1 treatment. It will help physicians to individualize lenvatinib combined with anti-PD-1 decision-making for u-HCC patients infected with HBV.

Materials and Methods

Study Design and Patients

This study collected data from consecutive hospital u-HCC patients treated with lenvatinib with or without anti-PD-1. A total of 210 eligible patients came from the Fifth Medical Center of Chinese PLA General Hospital and Electric Power Hospital of Beijing from October 2018 to February 2021. They were diagnosed as HCC by the international guidelines.[2,3] Of these, 70 patients had received lenvatinib plus at least 3 cycles anti-PD-1, and 140 patients with lenvatinib alone (Figure S1).

The eligibility criteria were as follows: 1) age >18 years and u-HCC patients, including intermediate-stage HCC and advanced HCC (BCLC staging system),[16] 2) treatment with lenvatinib more than 1 month with or without at least 3 cycles anti-PD-1 treatment, 3) patients assessed by multi-phase dynamic contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) study within 1 month before initiation of lenvatinib with or without anti-PD-1, and tumor response evaluated every 2 months after treatments, and at least once, 4) at least one measurable target lesion, 5) patients with Child-Pugh class A (CPA), Child-Pugh class B (CPB) ≤7 and with ECOG performance status (ECOG-PS) ≤2. Patients with incomplete medical information, failed follow-up, autoimmune disease, severe coagulation dysfunction (platelet count $<50\times10^9$/L, prothrombin activity <40%), other malignancies, and HIV were excluded.

This study was approved by the ethics committee of the Fifth Medical Center of Chinese PLA General Hospital and Electric Power Hospital of Beijing, approval number [KY-2021-12-33-1]. Written informed consent was obtained from patients. The study adhered to the Declaration of Helsinki.

Data Collection and Definition of Variables

Clinical parameters were collected from electronic medical records and images as follows: clinical features within 1 month before initiation of treatments (age, sex, weight, etiology, antivirus therapy, prothrombin time (PT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), total bilirubin (TBIL), platelet count (PLT), α-fetoprotein (AFP), ECOG performance status (PST), Child-Pugh (CP), ALBI, BCLC stage, etc.); tumor characteristics from images (tumor size, number, intrahepatic tumor occupation, extrahepatic spread (EHS), and portal vein trunk invasion (PVTI)); treatments (the dose of initiation of lenvatinib, relative dose intensity for initial 8 weeks, modification or interruption of lenvatinib and anti-PD-1, duration with lenvatinib and cycles of anti-PD-1, discontinuation, and subsequent anticancer medicine).

HBV infected was defined as patients with positive HBsAg for more than six months. HCV infected was defined as patients with hepatitis C antibody positive. Patients with detectable HBV DNA received nucleotide analogs. Here, none of the patients had detectable HCV RNA. Cirrhosis was diagnosed when ultrasonography, MRI, or CT found a blunted, nodular liver edge with splenomegaly (length of spleen >12 cm) and platelet counts of $<100\times10^9$/L. According to the 1999 World Health Organization criteria, diabetes was diagnosed by endocrinologists.

The follow-up ended in March 2022. Overall survival (OS) was defined as the time from baseline to the date of patients' last follow-up or death and was collected through the phone. Progression-free survival (PFS) was defined as the time from the start of treatment to the date of disease progression or death.

Tumor response was independently evaluated blindly by one independent radiologist and one hepatologist through CT/MRI images according to RECIST (Response Evaluation Criteria in Solid Tumor) v1.1.[17] Relative dose intensity for the initial 8 weeks of lenvatinib therapy (8W-RDI) was defined as the ratio of actual dose to recommended dose in the first 8 weeks.[18,19]

Adverse events (AEs) were assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.[20] Treatment-related AEs were collected from the start of treatments to 3 months after the last dose, or the start of new anticancer agents, whichever came up first.

Treatment Regiments

Lenvatinib was from Eisai (Tokyo, Japan), and anti-PD-1 was from sintilimab (IBI308, Innovent Biologics [Suzhou] Co. Ltd.) and tislelizumab (BGB-A317, BeiGene). The dosing schedule of lenvatinib and anti-PD-1 was as per the drug

instructions. Lenvatinib was administered as per the patient's weight: 8mg/day for <60kg, 12mg/day for ≥60kg, and 200mg for weighting ≥50kg or 3mg/kg for <50kg every 21 days of anti-PD-1, except for patients with Child-Pugh class B, in which, 8mg/day of lenvatinib was administered for all patients.

The dose reduction and interruption of lenvatinib were based on the drug instructions. The dose reduction of anti-PD -1, from 200mg to 3mg/kg, was for patients with weight loss from ≥50kg to <50kg during treatments, and the dose interruption of anti-PD-1 was up to ≤12 weeks. In case of progressive disease or uncontrollable serious AEs, lenvatinib with or without anti-PD-1 was discontinued. When patients developed PD, the subsequent anticancer treatments were based on physicians' suggestions and patients' choices.

Statistical Analysis

Categorical variables were shown as percentages, testing with Chi-square, and continuous variables were displayed as the median with interquartile range (IQR), testing with Mann–Whitney *U*-test. The median follow-up was calculated by reverse Kaplan–Meier (KM-PF).[21] Standardized mean difference (SMD) was defined as the difference between two groups divided by the standard deviation. SMD < 0.1, 0.1~0.3, 0.3~0.5, > 0.5 indicate negligible, mild, moderate, and large differences, respectively.[22,23] Stability inverse probability of treatment weight (SIPTW) was used to balance the bias between the two groups, weighting clinical features using appropriate math of propensity score. OS and PFS were calculated using Kaplan–Meier analysis and compared by the Log rank test. Variables with p-value <0.10 in the SIPTW-weighted univariate analysis were entered into the SIPTW-weighted multivariate Cox regression analysis. Nonparametric sliding-window subpopulation treatment effect pattern plot (STEPP) methodology was used to estimate effect differences between the two groups at a 12-month survival rate.[22,23] In addition, power was calculated by PASS (software: release 11.0). All statistical analyses were conducted by R (4.1.2) using the packages of "survival", "survminer", "tidyverse", "stepp", "ggplot2" and "MatchIt". P < 0.05 (two-sided) denotes statistical significance.

Results

Patients Characteristics

In the unadjusted cohort, some of the clinical features had slight differences between the two groups. Mild differences (0.1 < SMD < 0.3) were observed on sex, PT, AFP, ALB, liver cirrhosis, BCLC stage, macrovascular invasion, 8W-RDI, and previous targeted therapy. Moderate differences (SMD of 0.303) were shown on ALT. SIPTW was used to balance the variable bias between the two groups. After SIPTW adjustment, the weighted cohort showed balanced clinical features between the two groups, all clinical features with SMD < 0.1 indicating negligible differences (Table 1).

The median age was 54 (IQR, 47–62) years, and 189 (90%) cases were male. The etiologies included HBV-infected (n = 180, 85.7%), chronic hepatitis C virus (HCV) infected (n = 8, 3.8%), and others (n = 22, 10.5%). Among 180 patients with HBV infected, 170 (94.4%) patients had received nucleotide analogs (NAs), 10 patients with HBV and 8 patients with HCV had an undetectable viral load. A total of 166 (79%) patients were classified at BCLC stage C and 44 (21%) were at stage B. 135 (64.3%) patients with CPA and 75 (35.7%) with CPB. Eighty-seven (41.1%) patients showed EHS. Forty-three (20.5%) patients had PVTI and 79 (37.6%) with portal vein branch invasion. For previous treatments, 39 (18.6%) received targeted therapies, 127 (60.5%) with TACE, 144 (68.6%) with radiotherapy, and 32 (15.2%) with surgery. Sixty-four (30.5%) patients had diabetes. A total of 137 (65.2%) patients did not meet REFLECT criteria for PVTI (n = 43, 20.5%), intrahepatic tumor occupation ≥50% (n = 50, 23.8%), previous targeted therapy (n = 39, 18.6%) and CPB (n = 75, 35.7%) (Table 1).

Efficacy

The respective median follow-up of the combination and monotherapy groups was 21.1 (95% CI: 15.6–32.4) and 22.9 (95% CI: 20.6–30.8) months (*P = 0.439*), respectively. At the end of the follow-up, 33 (47.1%) and 87 (62.1%) patients died in the combination and monotherapy groups, respectively. The respective median OS of the combination and monotherapy groups was 21.4 (95% CI: 16.4–31.4) and 14.0 (95% CI: 11.2–17.5) months (HR: 0.65, 95% CI: 0.44–0.97)

Table 1 Clinical Features of the Lenvatinib Alone Group (Monotherapy) and the Lenvatinib Plus Anti-PD-1 Group (Combination Therapy) Before and After SIPTW Adjustment

Characteristics	ALL Patients (n=210)	Unweighted Cohort			Weighted Cohort After SIPTW		
		Monotherapy (n=140)	Combination Therapy (n=70)	SMD value	Monotherapy (n=140.13)	Combination Therapy (n=69.68)	SMD value
Age (years)	54.5 (47.0–62.0)	54.0 (47.0–63.3)	55.0 (47.0–61.0)	0.073	53.0 (47.0–63.0)	55.0 (48.0–60.9)	0.028
Sex				0.139			0.024
Male	189 (90.0%)	128 (91.4%)	61 (87.1%)		126.7 (90.4%)	63.5 (91.1%)	
Female	21 (10.0%)	12 (8.6%)	9 (12.9%)		13.5 (9.6%)	6.2 (8.9%)	
Bodyweight (kg)	70.0 (63.0–75.4)	70.0 (63.0–75.0)	69.5 (62.5–77.4)	0.024	70.0 (63.1–75.0)	70.03 (64.0–77.5)	0.059
Etiology				0.061			0.009
Hepatitis B	180 (85.7%)	121 (86.4%)	59 (84.3%)		119.8 (85.5%)	59.7 (85.7%)	
Hepatitis C	8 (3.8%)	5 (3.6%)	3 (4.3%)		6.0 (4.3%)	2.8 (4.1%)	
Others	22 (10.5%)	14 (10.0%)	8 (11.4%)		14.4 (10.3%)	7.1 (10.2%)	
Antivirus therapy (Nucleotide analogs)	170/180 (94.4%)	115/121 (95.0%)	55/59 (93.2%)	0.09	114.1/119.8 (95.2%)	57.7/59.7 (96.6%)	0.036
ALT (U/L)	35.0 (22.3–49.7)	36.0 (24.0–51.2)	30.5 (20.0–47.0)	0.303	35.00 (22.8–49.0)	31.13 (22.5–58.0)	0.031
AST (U/L)	42.5 (31.2–70.2)	42.0 (31.7–72.2)	44.5 (29–75.6)	0.089	42.0 (32.3–68.0)	45.0 (30.3–74.0)	0.006
GGT (U)	97.5 (52.2–190.7)	106.0 (53.7–181.5)	83.5 (47.2–203.7)	0.032	108.3 (53.0–179.3)	107.5 (49.7–208.9)	0.003
PLT (10^9/L)	128.5 (87.0–174.7)	131.0 (88.5–172.2)	125.0 (86.2–198.2)	0.091	133.8 (88.1–173.1)	125.3 (86.1–176.4)	0.032
PT (s)	12.1 (11.4–13.0)	11.9 (11.4–12.9)	12.4 (11.6–13.3)	0.156	12.1 (11.4–12.9)	12.4 (11.6–13.3)	0.047
ALP (U/L)	135.0 (96.0–184.7)	137.5 (98–189.2)	122.5 (92–175.7)	0.023	137.0 (98.0–189.8)	122.8 (92.0–167.8)	0.015
ALB (g/L)	35 (33–38)	35 (32–38)	36 (33–38.8)	0.133	35 (32–38)	35 (32–38)	0.031
TBIL (umol/L)	16.4 (11.3–23.3)	16.70 (11.6–23.5)	16.10 (10.8–22.6)	0.027	17.56 (11.6–23.6)	18.05 (11.49–29.3)	0.052
AFP (ng/mL)				0.176			0.015
<400	123 (58.6)	78 (55.7)	45 (64.3)		81.4 (58.1)	39.9 (57.3)	
≥400	87 (41.4)	62 (44.3)	25 (35.7)		58.8 (41.9)		
Child-pugh				0.09			0.021
A	135 (64.3%)	88 (62.9%)	47 (67.1%)		88.8 (63.4%)	43.4 (62.3%)	
B	75 (35.7%)	52 (37.1%)	23 (32.9%)		51.3 (36.6%)	26.2 (37.7%)	
ALBI grade				<0.001			0.012
1	33 (15.7%)	22 (15.7%)	11 (15.7%)		21.0 (15.0%)	10.1 (14.6%)	
2 or 3	177 (84.3%)	118 (84.3%)	59 (84.3%)		119.2 (85.0%)	59.5 (85.4%)	
ECOG-PS				0.077			0.039
0 or 1	202 (96.2%)	134 (95.7%)	68 (97.1%)		134.8 (96.2%)	66.5 (95.4%)	
2	8 (3.8%)	6 (4.3%)	2 (2.9%)		5.3 (3.8%)	3.2 (4.6%)	
Cirrhosis	189 (90.0%)	128 (91.4%)	61 (87.1%)	0.139	126.5 (90.3%)	63.6 (91.3%)	0.035
BCLC stage				0.173			0.025
B	44 (21.0)	26 (18.6)	18 (25.7)		28.3 (20.2)	13.4 (19.2)	
C	166 (79.0)	114 (81.4)	52 (74.3)		111.8 (79.8)	56.3 (80.8)	

(*Continued*)

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Table 1 (Continued).

Characteristics	ALL Patients (n=210)	Unweighted Cohort			Weighted Cohort After SIPTW		
		Monotherapy (n=140)	Combination Therapy (n=70)	SMD value	Monotherapy (n=140.13)	Combination Therapy (n=69.68)	SMD value
Maximum tumor diameter (cm)	7.6 (3.3–10.7)	7.6 (3.7–10.7)	7.3 (2.3–10.5)	0.034	7.6 (3.4–10.7)	8.0 (3.3–10.2)	0.058
Number of tumor lesions				0.049			0.005
Single	54 (25.7)	37 (26.4)	17 (24.3)		36.0 (25.7)	17.7 (25.5)	
Multiple	156 (74.3)	103 (73.6)	53 (75.7)		104.1 (74.3)	51.9 (74.5)	
Extrahepatic spread	87 (41.4)	58 (41.4)	29 (41.4)	<0.001	57.4 (40.9)	28.9 (41.5)	0.011
Tumor occupation≥50%	50 (23.8)	33 (23.6)	17 (24.3)	0.017	34.0 (24.3)	19.1 (27.5)	0.074
Macrovascular invasion				0.229			0.08
No	88 (41.9)	54 (38.6)	34 (48.6)		58.0 (41.4)	28.5 (40.9)	
Trunk	43 (20.5)	32 (22.9)	11 (15.7)		28.4 (20.2)	12.3 (17.6)	
Brunch	79 (37.6)	54 (38.6)	25 (35.7)		53.7 (38.4)	28.9 (41.5)	
Previous targeted therapy	39 (18.6)	24 (17.1)	15 (21.4)	0.164	27.0 (19.3)	13.2 (18.9)	0.009
Previous locoregional therapies							
Previous TACE	127 (60.5)	86 (61.4)	41 (58.6)	0.058	84.3 (60.1)	42.6 (61.1)	0.02
Previous radiotherapy	144 (68.6)	96 (68.6)	48 (68.6)	<0.001	96.9 (69.1)	49.3 (70.7)	0.035
Previous surgery	32 (15.2)	21 (15.0)	11 (15.7)	0.02	21.0 (15.0)	10.8 (15.5)	0.015
Diabetes	64 (30.5%)	42 (30.0%)	22 (31.4%)	0.031	43.3 (30.9%)	23.6 (33.8%)	0.063
Unfilled REFLECT criteria	137 (65.2%)	90 (64.3%)	47 (67.1%)	0.043	90.9 (64.9%)	45.4 (65.1%)	0.027

Notes: SMD < 0.1, 0.1~0.3, 0.3~0.5, > 0.5 indicate negligible, mild, moderate and large differences, respectively.

Abbreviations: ALT, aspartate aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; PLT, blood platelet; PT, prothrombin time; ALP, alkaline phosphatase; AFP, α-fetoprotein; ALB, albumin; TBIL, total bilirubin; ALBI grade, Albumin-Bilirubin Grade; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC stage, Barcelona Clinic Liver Cancer; TACE, transcatheter arterial chemoembolization.

(Figure 1A). After SIPTW adjustment, the combination group still showed a superior survival over the monotherapy group (Combination vs Monotherapy: 22.3 vs 14.2 months, HR = 0.58, 95% CI: 0.38–0.89, $p = 0.014$, Figure 1B).

At the end of follow-up, 52 (74.3%) and 119 (85%) patients developed PD or death in combination and monotherapy groups, respectively. The respective median PFS was 8.03 (95% CI: 6.97–12.1) and 6.33 (95% CI: 5.03–7.6) months in the combination and monotherapy groups (HR = 0.67, 95% CI: 0.47–0.92, $p= 0.015$) (Figure 1C). After SIPTW adjustment, the combination group still had better PFS than the monotherapy group (Figure 1D).

Among patients with PD, 30 (57.7%) patients accepted subsequent anticancer treatments in the combination group and 60 (50.4%) did in the monotherapy group (*P = 0.381*). The subsequent anticancer drugs mainly were regorafenib or anti-PD-1. In addition, 8 patients received TACE after PD, including 4 and 4 patients in combination and monotherapy groups, and there were no statistical differences between them (P = 0.45).

Interestingly, the STEPP analysis showed a slowly increasing 12-month survival rate with the cycles of anti-PD-1, and 5 cycles and more of anti-PD-1 appeared the most beneficial and stable survival rate (Figure 2A). This suggested that patients with 5 cycles and more of anti-PD-1 may benefit most from the combination therapy.

We defined lenvatinib plus 4 cycles of anti-PD-1 as the combination therapy group. Eleven patients with lenvatinib plus 3 cycles of anti-PD-1 were excluded from the combination group and then entered into the monotherapy group. Then, the respective median OS was 24.2 (95% CI:21.4-NA) and 13.6 (95% CI: 11.2–16.4) months in the combination and monotherapy groups (HR: 0.44, 95% CI: 0.28–0.70) (Figure 2B).

The best tumor responses are shown in Table 2. As per RECIST v1.1, the combination group had superior DCR and ORR over the monotherapy group (DCR: 80% vs 63.6%, $p = 0.023$; ORR: 25.7% vs 12.1%, $p = 0.013$). The SIPTW adjustment cohort confirmed it (Combination vs Monotherapy: DCR:78.1% vs 62.4%, $p = 0.046$; ORR: 24.5% vs 12.5%, $p = 0.043$). Nobody achieved CR in the two groups (Table 2).

Prognostic Factors of Overall Survival and Progression-Free Survival for u-HCC

The associated factors with OS were analyzed by the SIPTW-weighted univariate and multivariate Cox regression analyses. Collinearity between variables did not exist. The results showed that duration of treatments (≥7.6 vs <7.6 months: HR 0.28, 95% CI 0.18–0.43, $p < 0.001$), combination therapy (yes vs no: HR 0.44, 95% CI 0.27–0.72, $p = 0.001$) and EHS (yes vs no: HR 1.69, 95% CI 1.01–2.85, $p = 0.046$) were independent factors of OS (Table S1). Also, the duration of treatments (≥7.6 vs <7.6 months: HR 0.33, 95% CI 0.23–0.49, $p < 0.001$), the combination therapy (yes vs no: HR 0.65, 95% CI 0.46–0.92, $p = 0.014$), and the previous radiotherapy (yes vs no: HR 0.67, 95% CI 0.47–0.96, $p = 0.027$) were independent protective factors of PFS. 8W-RDI showed no relevance to the OS and PFS (Table S2). The results suggested that the duration of treatments and lenvatinib combined with anti-PD-1, not 8W-RDI, were key to the OS and PFS for u-HCC patients.

After the factors associated with treatments were removed, multivariate Cox regression analysis showed that PVTI (Trunk invasion vs No vascular invasion: HR 2.18, 95% CI 1.21–3.92, $p = 0.009$), EHS (yes vs no: HR 2.07, 95% CI 1.33–3.22, $p = 0.001$) and Child-Pugh class (CPB vs CPA: HR 1.68, 95% CI 1.10–2.55, $p = 0.015$) were independent risk factors of OS (Table 3). Patients with CPB have a poorer OS than that with CPA (11.5 vs 21.4 months, P < 0.001). However, the combination therapy group (Lenvatinib plus 3 cycles anti-PD-1) have a slightly longer overall survival compared with the monotherapy group in patients with CPA (the combination therapy vs Monotherapy: 22.3 vs 18.3 months, P = 0.16) or CPB 7 scores (the combination therapy vs Monotherapy: 13.2 vs 11.2 months, P = 0.16) (Figure S2A and B), but not reach statistically significant. Moreover, the combination therapy group (Lenvatinib plus 4 cycles anti-PD-1) has an evident longer overall survival than the monotherapy group in patients with CPA (the combination therapy vs Monotherapy: 24.4 vs 16.7 months, P = 0.014) or CPB 7 scores (the combination therapy vs Monotherapy: 21.3 vs 11.2 months, P = 0.014) (Figure S2C and D). Therefore, although patients with CPB have a poor prognosis, they may benefit from the combination therapy.

The Population Sensitive to Lenvatinib Plus Anti-PD-1

The features associated with OS were integrated into a composite risk score according to the coefficients of the variables from the above multivariate Cox regression analysis. The composite risk score was calculated as follows:

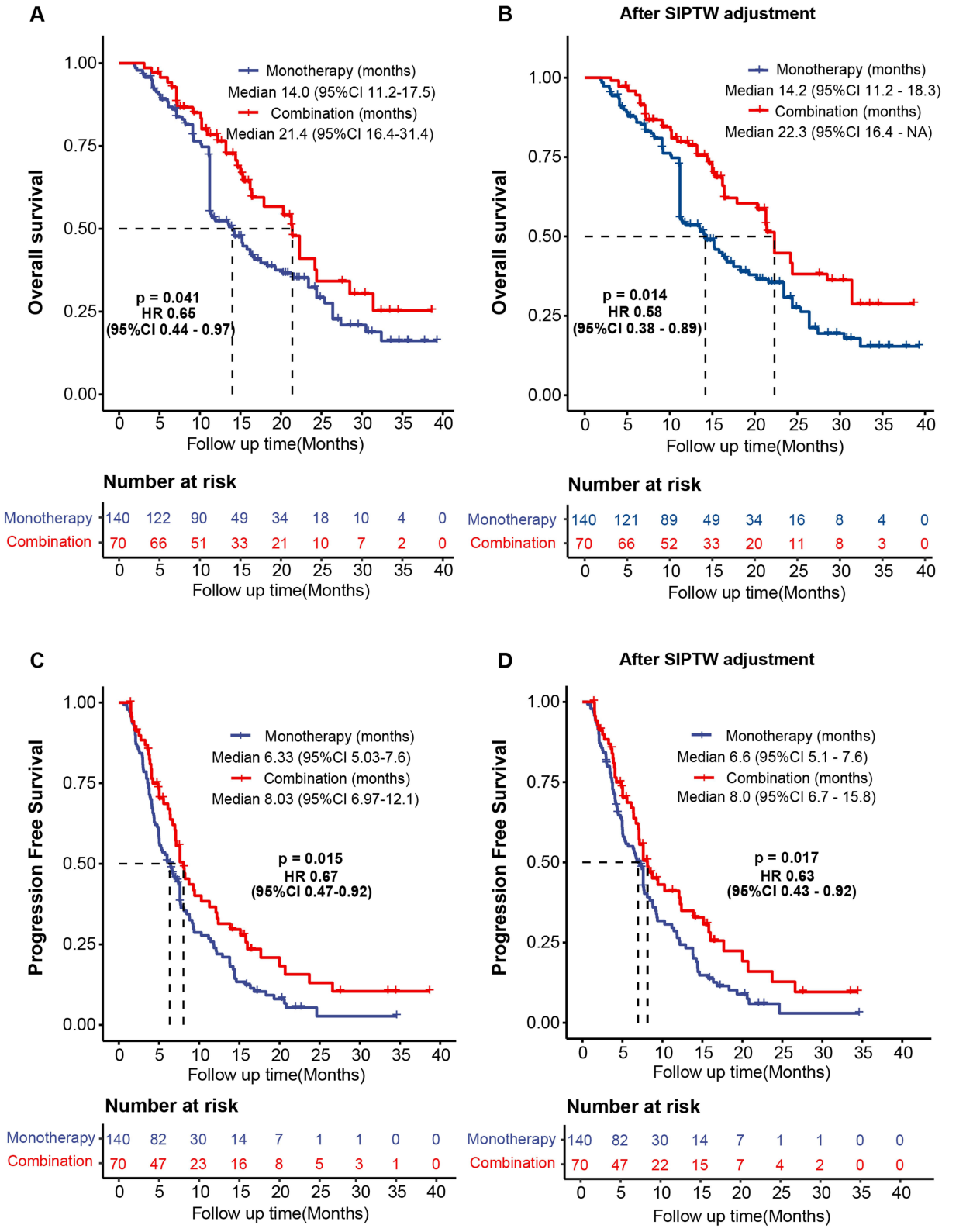

Figure 1 Survival outcomes in the combination and monotherapy groups. (**A**) Overall survival. (**B**) Overall survival after SIPTW adjustment. (**C**) Progression-free survival. (**D**) Progression-free survival after SIPTW adjustment.

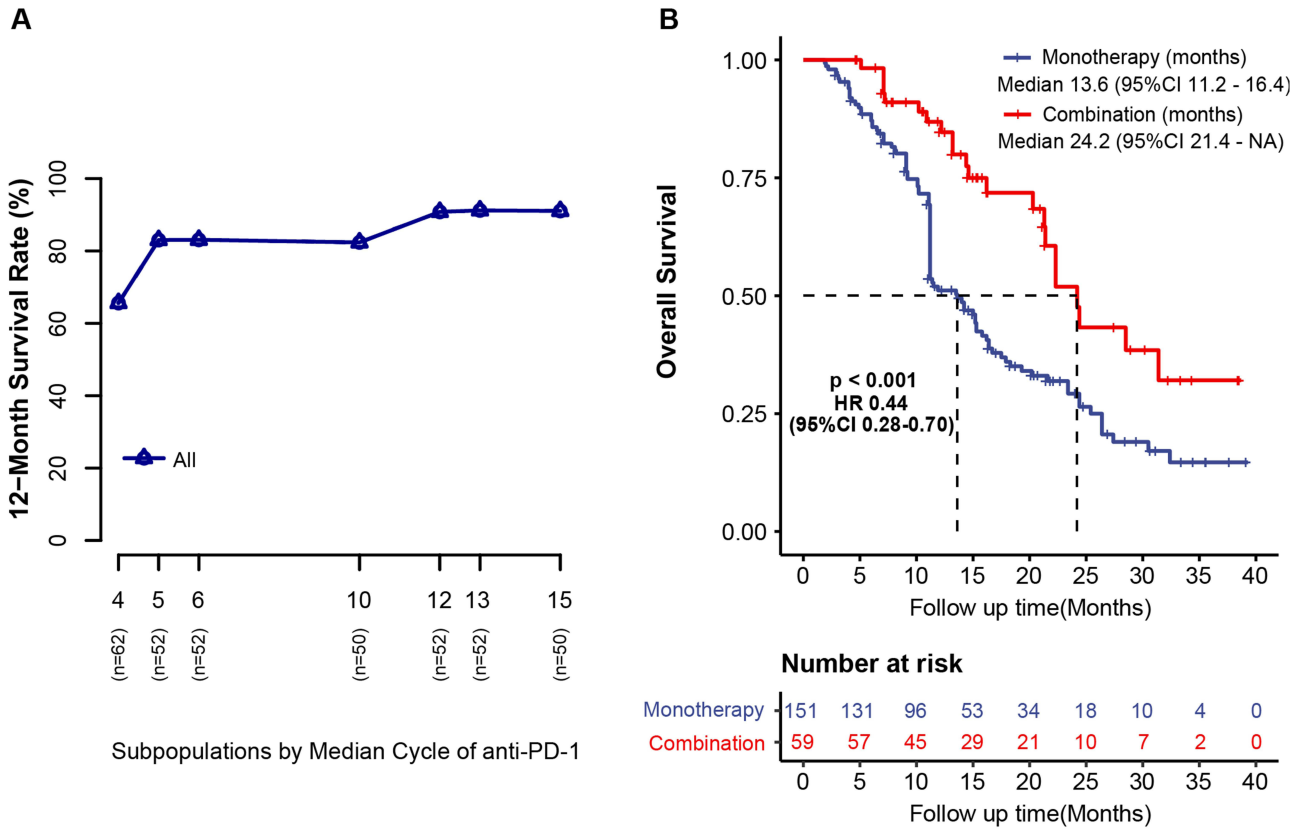

Figure 2 12-month survival rate according to cycles of anti-PD-1. (**A**) The 12-month survival rate (y-axis) according to the median cycles of anti-PD-1 in subpopulations (x-axis) through subpopulation treatment effect pattern plot analysis (STEFF). (**B**) Overall survival of the monotherapy and combination groups.
Notes: The combination group only included 59 patients with 4 cycles anti-PD-1 plus lenvatinib, while the other 11 patients with 3 cycles anti-PD-1 plus lenvatinib were put into the monotherapy group.

Composite risk score = portal vein trunk invasion (No vascular invasion = 0, existence = 1) * 0.83 + extrahepatic spread (nonexistence = 0, existence = 1) * 0.74+ Child-Pugh (class A = 0, class B = 1) * 0.54 + portal vein branch invasion (No vascular invasion = 0, existence = 1) * 0.34.

Across the composite risk score, the STEPP analysis revealed that the 12-month survival rate of all patients was 61% (120 of 210 patients died), increasing from 27.8% in the highest quartile of the composite risk score to 76% in the lowest quartile (Figure 3A and B). The median composite risk score was 0.74. For patients with a composite risk score >0.74, the combination therapy made the 12-month survival rate increase by 38%. On the contrary, the combination therapy made the 12-month survival rate increase by only 18% (Figure 3C and D).

Table 2 Tumor Responses in the Lenvatinib Alone Group (Monotherapy%) and the Lenvatinib Plus Anti-PD-1 Group (Combination Therapy%) by Response Evaluation Criteria in Solid Tumors v1.1 Before and After SIPTW Adjustment

Best Overall Response	Unweighted Study Population				Weighted Study Population After SIPTW			
	Monotherapy (n=140)	Combination Therapy (n=70)	P-value	SMD value	Monotherapy (n=140.13)	Combination Therapy (n=69.68)	P-value	SMD value
CR	0 (0.0%)	0 (0.0%)	NA	NA	0 (0.0%)	0 (0.0%)	NA	NA
PR	17 (12.1%)	18 (25.7%)	0.013	0.417	17.5 (12.5%)	17.0 (24.5%)	0.043	0.313
SD	72 (51.4%)	38 (54.3%)	0.696	<0.001	69.9 (49.9%)	37.2 (53.6%)	0.655	0.075
PD	51 (36.4%)	14 (20.0%)	0.023	0.371	52.1 (37.1%)	11.1 (15.9%)	0.002	0.494
ORR	17 (12.1%)	18 (25.7%)	0.013	0.417	17.5 (12.5%)	17.0 (24.5%)	0.043	0.313
DCR	89 (63.6%)	56 (80.0%)	0.023	0.371	87.5 (62.4%)	54.3 (78.1%)	0.046	0.35

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table 3 The Independent Factors of Over Survival by SIPTW-Weighted Cox Regression Analysis

Characteristics	Univariate		Multivariate	
	HR (95CI)	P-value	HR (95CI)	P-value
Extrahepatic spread (Yes vs No)	2.16 (1.49–3.13)	<0.001	2.07 (1.33–3.22)	0.001
Child-pugh (B vs A)	2.08 (1.45–2.99)	<0.001	1.68 (1.10–2.55)	0.015
No vascular invasion (Reference)	1		1	
Trunk invasion	2.60 (1.62–4.18)	<0.001	2.18 (1.21–3.92)	0.009
Branch invasion	1.64 (1.08–2.50)	0.020	1.41 (0.84–2.37)	0.199
GGT (U/L)	1 (1–1)	0.002	1 (1–1)	0.118
ALBI grade (1 vs 2 or 3)	1.66 (0.95–2.90)	0.076	1.26 (0.70–2.28)	0.436
Maximum tumor diameter (cm)	1.04 (1–1.07)	0.052	0.99 (0.95–1.03)	0.712
BCLC stage (C vs B)	1.97 (1.22–3.19)	0.006	0.90 (0.47–1.71)	0.742
Previous targeted therapy (Yes vs No)	1.46 (0.96–2.21)	0.074	1.07 (0.69–1.68)	0.755
ALP (U/L)	1 (1–1.01)	0.003	1 (1–1)	0.899
Number of tumor lesions (Multiple vs Single)	1.43 (0.93–2.21)	0.101		
Previous targeted therapy (Yes vs No)	1.37 (0.89–2.09)	0.148		
PT (s)	1.11 (0.96–1.29)	0.158		
ECOG-PS (2 vs 0 or 1)	2.25 (0.70–7.15)	0.171		
Tumor occupation (≥50% vs <50%)	1.30 (0.87–1.95)	0.207		
ALT (U/L)	1 (0.99–1)	0.217		
Sex (Male vs Female)	1.39 (0.78–2.47)	0.267		
Liver cirrhosis (Yes vs No)	1.39 (0.70–2.74)	0.347		
HCV infected (Yes vs No)	0.61 (0.20–1.83)	0.377		
HBV infected (Yes vs No)	0.78 (0.46–1.35)	0.379		
AFP (≥400 vs <400) ng/mL	1.17 (0.82–1.68)	0.393		
Bodyweight (kg)	0.99 (0.98–1.01)	0.441		
Previous surgery (Yes vs No)	0.84 (0.50–1.40)	0.504		
AST (U/L)	1 (1–1)	0.565		
Previous radiotherapy (Yes vs No)	0.92 (0.63–1.34)	0.657		
Antivirus therapy (Yes vs No)	0.91 (0.59–1.41)	0.683		
Age (years)	1 (0.98–1.02)	0.817		
Diabetes (Yes vs No)	1.04 (0.71–1.54)	0.825		
PLT (10^9/L)	1 (1–1)	0.864		
Previous TACE (Yes vs No)	0.99 (0.68–1.43)	0.940		

Abbreviations: GGT, γ-glutamyl transpeptidase; ALBI grade, Albumin-Bilirubin Grade; BCLC stage, Barcelona Clinic Liver Cancer; ALP, Alkaline phosphatase; PT, Prothrombin time; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ALT, Aspartate aminotransferas; AFP, α-fetoprotein; AST, Aspartate aminotransferase; PLT, Blood platelet; TACE, Transcatheter arterial chemoembolization.

For the convenience of application, the composite risk score was simplified as three factors, PVTI, EHS, and CPB. Meanwhile, portal vein branch invasion was removed for no statistical significance. Patients with PVTI or EHS combined with CPB had a lower OS than the other population (11.2 vs 22.3 months) (Figure 4A). However, for patients with PVTI or EHS combined with CPB, the combination therapy made the 12-month survival rate increased by 38%, while, in the other population, it did only 18% (Figure 4B and C).

Safety Profile

The respective median duration of the combination therapy and monotherapy was 8.5 and 6.6 months. The respective median lenvatinib 8W-RDI was 83.3% and 91.7% in the combination and monotherapy groups. Grade 3 and more treatment-related AEs with a frequency ≥1% were presented in Table S3 and any grade treatment-related AEs with frequent ≥10% in Table S4. Treatment-related deaths or serious AEs were not observed. Serious immune-related adverse events (irAE) were not observed: myocarditis, pneumonia, and myositis. Any grade treatment-related AEs of the combination group were comparable to that of the monotherapy group (any grade: 70 (100%) vs 135 (96.4%), $p = 0.26$; Grade 3 and more AEs: 42 (60.0%) vs 69 (49.3%),

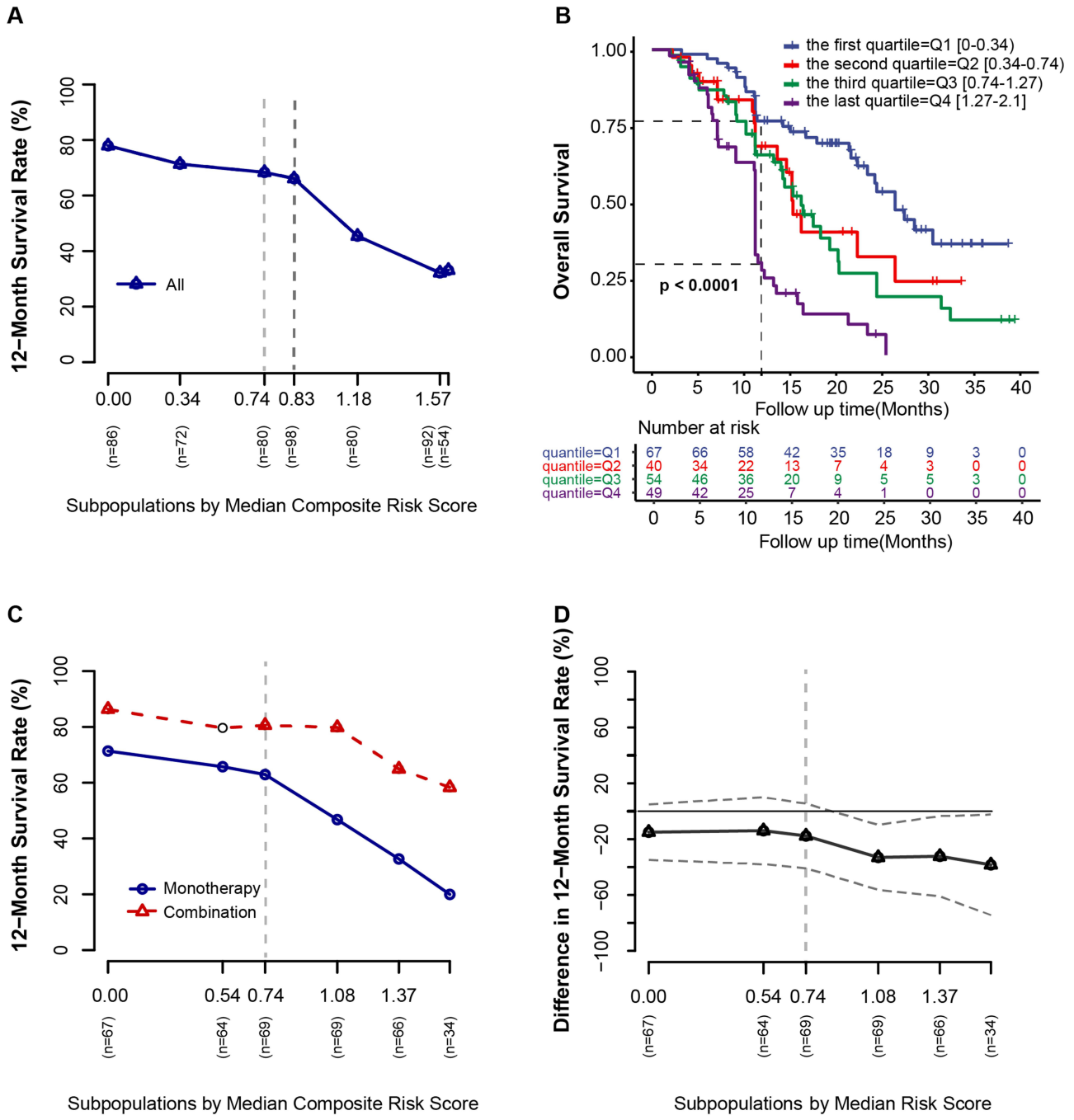

Figure 3 Overall survival according to the composite risk scores. (**A**) 12-month survival rate (y-axis) by median composite risk scores in subpopulations (x-axis). (**B**) Overall survival by the quartile of the composite risk scores. (**C**) 12-month survival rate (y-axis) according to the median composite risk scores in subpopulations (x-axis) through subpopulation treatment effect pattern plot analysis (STEFF). (**D**) The difference in 12-month survival rate (y-axis) between the combination and monotherapy groups according to the median composite risk scores in subpopulations (x-axis). The light grey vertical dashed lines indicate the median composite risk score of 0.74.

p = 0.143). The most common AEs included hypertension (n = 88, 42%), fatigue (n = 87, 41%), decreased appetite (n = 81, 39%), diarrhea (n = 75, 36%), hand-foot syndrome (n = 73, 35%) and proteinuria (n = 67, 32%). The combination group had similar adverse events leading to interruption or dose reduction/discontinuation to the monotherapy group (Table S4).

Discussion

This study showed that a slowly increasing 12-month survival rate was with the cycles of anti-PD-1, and 5 cycles and more of anti-PD-1 appeared the most beneficial and stable survival rate. The lenvatinib plus at least 3 cycles anti-PD-1

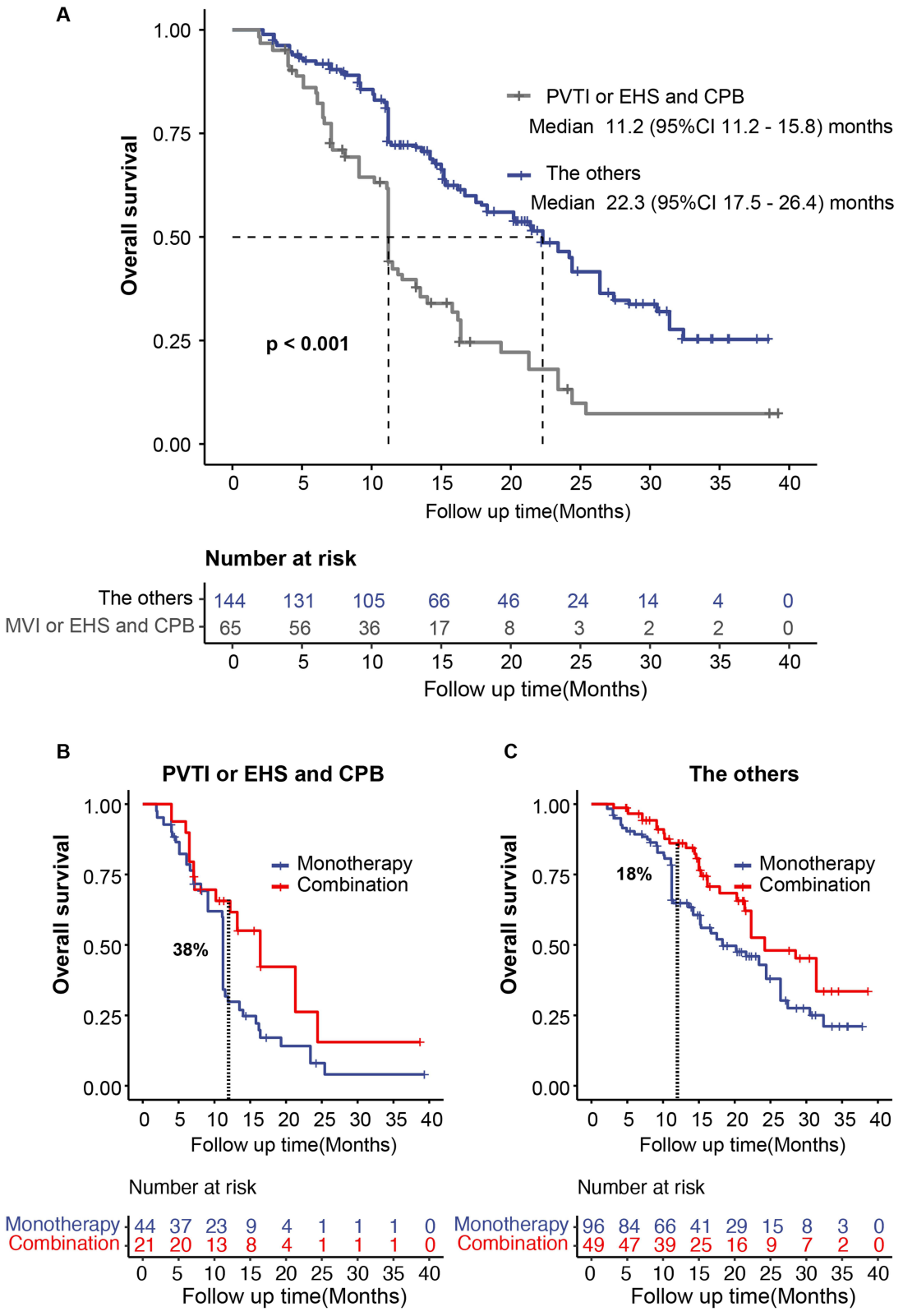

Figure 4 The lenvatinib plus anti-PD-1 made overall survival improvement. (**A**) Overall survival grouping by PVTI or EHS combined with CPB. (**B**) For patients with PVTI or EHS combined with CPB, lenvatinib plus anti-PD-1 made overall survival improvement, (**C**) while, for the others, it did.
Abbreviations: PVTI, portal vein trunk invasion; CPB, Child-Pugh class B; EHS, extrahepatic spread.

group had better OS (21.4 vs 14 months), PFS (8.0 vs 6.3 months), ORR (25.7% vs 12.1%), and DCR (80% vs 63.6%) than the monotherapy group. For patients with PVTI or EHS combined with CPB, lenvatinib plus anti-PD-1 made the 12-month survival rate increase by 38%, while, in the other population, it did only 18%. The two groups showed a similar toxicity profile.

The median OS and PFS of the lenvatinib plus pembrolizumab group were 22 and 9.3 months in the KEYNOTE-524 trial (phase Ib).[10] However, ESMO released a negative result (lenvatinib plus pembrolizumab vs lenvatinib) in the LEAP-002 trial (phase III). The reason may be that only 48% of patients enrolled were infected with HBV in the LEAP-002 trial. A meta-analysis of systemic therapies of Phase III RCTs (2002–2020) suggests that immunotherapies may be more effective in viral-related HCC than non-viral-related HCC.[24] Interestingly, the subgroup analysis of the LEAP-002 trial also showed consistent results with this study in the population with HBV, extrahepatic spread, or macrovascular portal vein invasion/extrahepatic spread: the lenvatinib plus pembrolizumab had a superior OS over the lenvatinib alone. Besides, in a real-world study, Yang reported that lenvatinib plus anti-PD-1 had long survival and considerable ORRs and DCRs in 378 u-HCC patients, and 90% infected with HBV.[11] Some real-world studies reported consistent results: lenvatinib plus ICI had superior efficacy over lenvatinib alone.[25–27]

Furthermore, we explored the dose–efficacy relationship between lenvatinib and anti-PD-1. The SIPTW-weighted multivariate Cox regression analysis indicated that the duration of lenvatinib, not 8W-RDI of lenvatinib, can prolong the OS and PFS for u-HCC patients. A study also reported that the duration of lenvatinib was a protective factor of OS.[28] In addition, the STEPP analysis suggested that a slowly increasing 12-month survival rate was with the cycles of anti-PD-1, and patients with 5 cycles and more of anti-PD-1 may benefit most from the combination therapy, which was one very important finding.

Although lenvatinib plus anti-PD-1 may be a promising therapy for u-HCC, only less than half of patients would benefit from it. Therefore, individualized therapy decisions should weigh benefits against high costs and adverse effects. However, there were no indicators to clarify who was sensitive to Lenvatinib plus anti-PD-1 treatments. In this study, the other important finding was that patients with PVTI or EHS combined with CPB would benefit most from the lenvatinib plus anti-PD-1 treatments. Similarly, a real-world study also reported that lenvatinib plus anti-PD-1 can improve OS for HCC patients with invasion in Vp4.[26] Although patients with PVTI or EHS combined with CPB had a poor prognosis, they may benefit most from the combination therapy. This finding may help physicians to individualize the choice of lenvatinib plus anti-PD-1.

The mechanism of synergy between TKIs and ICI is being increasingly characterized. Vascular abnormalities are a hallmark of most solid tumors and stem from elevated levels of VEGF and angiopoietin 2 (ANG2). Lenvatinib targets these molecules and then normalizes the abnormal tumor vasculature, to increase the infiltration of immune effector cells into tumors. It promotes the efficacy of anti-PD-1, which depends on the increment and activity of immune effector cells in the tumor microenvironment (TME). Vascular normalization and immune responses may be reciprocally regulated.[29] For example, lenvatinib plus anti-PD-1 can increase the percentage of early-activated CD8+T cells.[30] Therefore, it may be the reason that patients with metastasizes or vascular invasion would benefit more from the lenvatinib plus anti-PD-1.

In addition, this study showed that the two groups had similar AEs and interruption and/or modification of treatment. A real-world study reported a similar result for the interruption and/or modification of treatment.[31]

The common limitations were bias from the retrospective design. However, information from electronic medical records and overall survival were objective. Besides, we performed rigorous statistical analyses to balance the clinical features between two groups by the SIPTW and adjust possible prognostic factors by the SIPTW-weighted multivariate Cox regression analysis. Although SIPTW could not deal with unmeasured confounding variables, such as the economic background of patients, the results still provided robust information. In addition, this study included two kinds of anti-PD -1, sintilimab and tislelizumab, which are more affordable than pembrolizumab. Although both are common anti-PD-1, there may be slight differences between them. Therefore, the multicentre randomized controlled trial (RCT) needs to be inspired to further verify the efficacy and safety of lenvatinib plus at least 3 cycles of anti-PD-1 in the dominant population.

Conclusions

The lenvatinib plus at least 3 cycles of anti-PD-1 treatment was efficacy and safe for u-HCC patients infected with HBV in real-world studies. Especially, patients with PVTI or EHS combined with CPB may benefit most from the combination therapy.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study protocol was reviewed and approved by the institution review board of the Fifth Medical Center of Chinese PLA General Hospital and Electric Power Hospital of Beijing, approval number [KY-2021-12-33-1]. Written informed consent was obtained from patients. The study was performed by the ethics standards of the institutional research committee and the recent Declaration of Helsinki.

Consent for Publication

All subjects gave written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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