

# A retrospective study of transarterial chemoembolization (TACE) combined with lenvatinib compared with TACE monotherapy for BCLC B2 stage hepatocellular carcinoma

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**Abstract.** The present study aimed to compare the efficacy and safety of combination therapy with lenvatinib (Len) plus transarterial chemoembolization (TACE) and TACE alone in patients with Barcelona Clinic Liver Cancer (BCLC) B2 stage hepatocellular carcinoma (HCC). A total of 66 patients with BCLC B2 stage HCC were retrospectively reviewed in the present study, of which 34 patients received Len + TACE, while 32 patients received TACE alone between May 2018 and May 2020. Survival outcome, tumor response and adverse events (AEs) were compared between the two treatment groups. The 6-month, 1- and 2-year overall survival (OS) rates were significantly higher in the Len + TACE group (97.1, 85.3 and 76.3%, respectively) compared with those in the TACE group [93.8, 81.1 and 45.4%, respectively]; hazard ratio (HR), 0.395; 95% confidence interval (CI), 0.180-0.867;  $P=0.023$ ], but no significant difference in progression-free survival rate was observed between the two groups (HR, 0.815; 95% CI, 0.437-1.520;  $P=0.510$ ). Patients receiving Len + TACE demonstrated a higher objective response rate compared with those receiving TACE alone (64.7 vs. 34.4%;  $P=0.014$ ). Therefore, Len + TACE combination therapy was associated with increased OS and tumor response compared with that of TACE monotherapy in patients with BCLC B2 stage HCC. However, large-scale, multicenter, prospective studies are needed to further confirm these results.

## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of cancer and third leading cause of cancer-related deaths worldwide in 2020 (1). HCC has emerged as one of the top five cancer types with regards to incidence, mortality and disability-adjusted life year of cancer in China; HCC is ranked tenth and fourteenth in the US and UK, respectively, although the disability-adjusted life year burden of HCC has decreased by 41.5%, and its ranking dropped from second to fifth between 1990 and 2019 (2). Currently, a number of options are recommended as treatments for HCC including surgical resection, liver transplantation and radiofrequency ablation (3). However, ~66% of patients with HCC are already at intermediate or advanced stage of disease at the time of diagnosis, and qualify for non-curative types of treatment, such as transarterial chemoembolization (TACE) and tyrosine kinase inhibitors (TKIs) (4).

The Barcelona Clinical Liver Cancer (BCLC) staging system is classified based on tumor load (tumor size, tumor number, vascular invasion and extrahepatic metastasis), liver function status (Child-Pugh class) and performance status (Eastern Cooperative Oncology Group-performance status), and is widely used for HCC staging (5). According to current recommendations, TACE is the global standard treatment for BCLC B stage HCC (5). However, due to the presence of heterogeneity with regards to tumor burden, liver function and clinical characteristics, as well as the recommendation for this treatment for a wide range of patients with intermediate stage HCC, there are several limitations associated with this type of treatment. Based on varying liver function and tumor burden, Bolondi *et al* (6) reclassified BCLC B stage HCC into four substages. Subsequently, various staging systems have since emerged, and appropriate treatments for different subgroups have been recommended (7). Based on the criteria recommended by Bolondi *et al* (6), Kudo *et al* (8) modified and improved the Kinki criteria, which subclassified intermediate HCC into three substages. The Kinki criteria are based on the Child-Pugh score, Milan criteria (solitary tumor  $\leq 5$  cm, or two or three nodules  $\leq 3$  cm) and up-to-seven criteria (the sum of the size in cm, and the number of tumors  $\leq 7$ ). The B2 substage includes patients with HCC with a Child-Pugh score of 5-7,

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beyond Milan criteria and exceeding the up-to-seven criteria. In 2018, Kudo (9) proposed the Kindai criteria (Table I), which were modified on the basis of the original version of the Kinki criteria in order to provide more suitable treatment decision-making in patients with intermediate-stage HCC.

According to both the Bolondi and Kinki criteria, TACE and sorafenib are recommended as the first and/or alternative treatment options for patients with B2 stage HCC. However, >66.6% of patients with HCC exhibit resistance and a high rate of recurrence after TACE. Thus, repeated TACE is needed for such patients, and resistance to this treatment may lead to a poor prognosis. Previous studies suggested that TACE causes tumor cells to be surrounded by a hypoxic environment, which may elevate expression levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (FGF), and ultimately lead to tumor angiogenesis (10-12). TKIs targeting VEGF receptor (VEGFR) and other related receptors, inhibit receptor activity and the activation of downstream signaling pathways, and achieve anti-angiogenesis by blocking multiple signaling pathways (13,14). Previous randomized controlled trials in patients with HCC reported that combination therapy with TACE and sorafenib significantly prolonged progression-free survival time compared with TACE monotherapy (15,16). A recent meta-analysis reported a significantly increased efficacy of TACE plus sorafenib for patients with unresectable HCC (uHCC) compared with TACE alone (17). However, a multicenter retrospective observational study enrolled 1,719 patients with uHCC and divided these patients into three groups, namely low, moderate and high tumor burden, based on tumor size and number, and reported that TACE plus sorafenib provided notable survival benefits compared with TACE alone, only in patients with a moderate tumor burden (18).

As a novel member of multi-kinase inhibitor agents, targeting VEGF, FGF and platelet-derived growth factor receptors, lenvatinib (Len) was reported to show non-inferiority or superiority in both efficacy and safety measured compared with sorafenib, and has been recommended as a first-line treatment for patients with uHCC in Japan, America, China and other countries (19-22). In addition, TACE plus Len also demonstrated improved efficacy compared with that of TACE plus sorafenib in patients with HCC (23). Kudo *et al* (24) recommended Len-TACE sequential therapy as the first option for patients with uHCC deemed unsuitable for TACE treatment. Recently, a number of studies made a comparison between TACE plus Len, and Len alone for patients with uHCC, and the combination therapy achieved improved clinical outcomes (25,26). However, to the best of our knowledge, no studies focused on comparing the efficacy of the two treatments in subgroups of patients, especially those with moderate tumor burden.

Therefore, the present retrospective study was conducted to compare the efficacy and safety of combination therapy with TACE and Len against TACE monotherapy in patients with BCLC B2 stage HCC.

## Materials and methods

**Study design and patient population.** A total of 66 patients with BCLC B2 stage HCC who received Len + TACE or TACE

alone at the Affiliated Hospital of North Sichuan Medical College between May 2018 and May 2020 were retrospectively reviewed (Fig. 1). The cohort of patients in the present study was not included in other clinical trial studies. HCC was diagnosed using histopathological and/or imaging examinations, and was classified using the BCLC staging system (5). BCLC B2 stage HCC was defined as intermediate-stage HCC with Child-Pugh scores of 5-7, beyond the Milan criteria and up-to-seven criteria (8,9).

The inclusion criteria were as follows: i) Diagnosis of BCLC B2 stage HCC; ii) age  $\geq 18$  but  $< 75$  years; and iii) no other history of malignant tumors. The exclusion criteria were as follows: i) Received previous local or systemic therapy, such as TACE, TKIs or programmed death-1 (PD-1); and iii) incomplete data or loss of follow-up.

Baseline data were collected including age, sex, hepatitis B virus (HBV) status,  $\alpha$ -fetoprotein (AFP) level, Child-Pugh score, liver cirrhosis, largest tumor size, tumor number and distribution.

**TACE.** After the assessment of routine blood tests, liver and kidney function, and PS, a 5-F infusion catheter was selectively inserted into the tumor-feeding hepatic arteries. An injection of an emulsion of epirubicin (20-40 mg; Pharmorubicin<sup>®</sup>; Pfizer, Inc.) and lipiodol (2-10 ml; Guerbet Laboratories Ltd.) into the intrahepatic arterial was performed, and small gelatin sponge particles were used for embolization. Biochemical indicators such as AFP, bilirubin, albumin and others were reviewed on day 3 post-operation, and patients were evaluated for changes in the tumor using CT or MRI scans 4 weeks after TACE. TACE was repeated until progression to either TACE-refractory criteria (27,28), unacceptable toxicity or withdrawal of consent.

**Len + TACE.** In principle, doctors recommended Len + TACE combination therapy for all patients with BCLC B2 stage HCC. However, patients who refused Len accepted TACE monotherapy for either economic or personal reasons, such as a fear of complications or disagreement with the doctor's decisions. If no obvious abnormalities in biochemical indicators, such as abnormal elevation of liver transaminase, and other symptoms, such as severe nausea and anaphylaxis, were observed on day 3 post operation, Len was administered on the same day, otherwise, Len was administered after symptoms had ceased. Len (Eisai Co., Ltd) was administered orally at 8 mg once per day in patients with weight  $< 60$  kg or at 12 mg per day in patients with weight  $\geq 60$  kg based on the recommended doses published by the REFLECT trial (20). If serious adverse events (AEs; grade  $\geq 3$ ) or any unacceptable treatment-related AEs occurred, the dose of Len was reduced, delayed or discontinued according to the manufacturer's instructions.

**Follow-up and assessment.** The first follow-up was conducted 4 weeks after TACE and included analysis of related biochemical indicators and CT or MRI. Follow-up was repeated every 4-8 weeks to detect any recurrence or metastasis. Follow-up was censored in April 2022.

Overall survival (OS) was defined as the period from the date of initial TACE to death or last follow-up, whereas progression-free survival (PFS) was defined as the period from

Table I. Subclassification of BCLC B stage hepatocellular carcinoma [Kindai criteria (9)].

Criteria or clinical strategy	Subclassification			
	B1	B2	B3a	B3b
Milan criteria	Beyond	Beyond	Beyond	Beyond
Up-to-seven criteria	In	Out	In	Out
Child-Pugh score	5-7	5-7	8-9	8-9
Concept of treatment strategy	Curative	Non-curative, palliative	Curative if within up-to-7	Palliative, no treatment
Treatment option	Resection, ablation, superselective c-TACE	Lenvatinib <sup>a</sup>	Transplantation, ablation, superselective c-TACE	HAIC, selective DEB-TACE, BSC
Alternative	DEB-TACE <sup>b</sup> , B-TACE <sup>c</sup>	Sorafenib <sup>a</sup> , TACE + sorafenib, DEB-TACE <sup>d</sup> , bland TAE <sup>d</sup> followed by MTA	DEB-TACE, B-TACE, HAIC	BSC

<sup>a</sup>Both lenvatinib and sorafenib recommended for patients with liver function of Child-Pugh score 5 and 6; <sup>b</sup>DEB-TACE is recommended for patients with relatively large tumors and Child-Pugh score 7; <sup>c</sup>B-TACE is recommended for fewer tumors; <sup>d</sup>Both DEB-TACE and bland TAE are recommended for huge tumors that are >6 cm (9). BCLC, Barcelona Clinic Liver Cancer; TACE, Transcatheter arterial chemoembolization; c-TACE, Conventional subsegmental lipiodol TACE; HAIC, Hepatic arterial infusion chemotherapy; DEB-TACE, TACE with drug-eluting beads; BSC, Best supportive care; B-TACE, Balloon occluded TACE; MTA, multi-targeted agent.

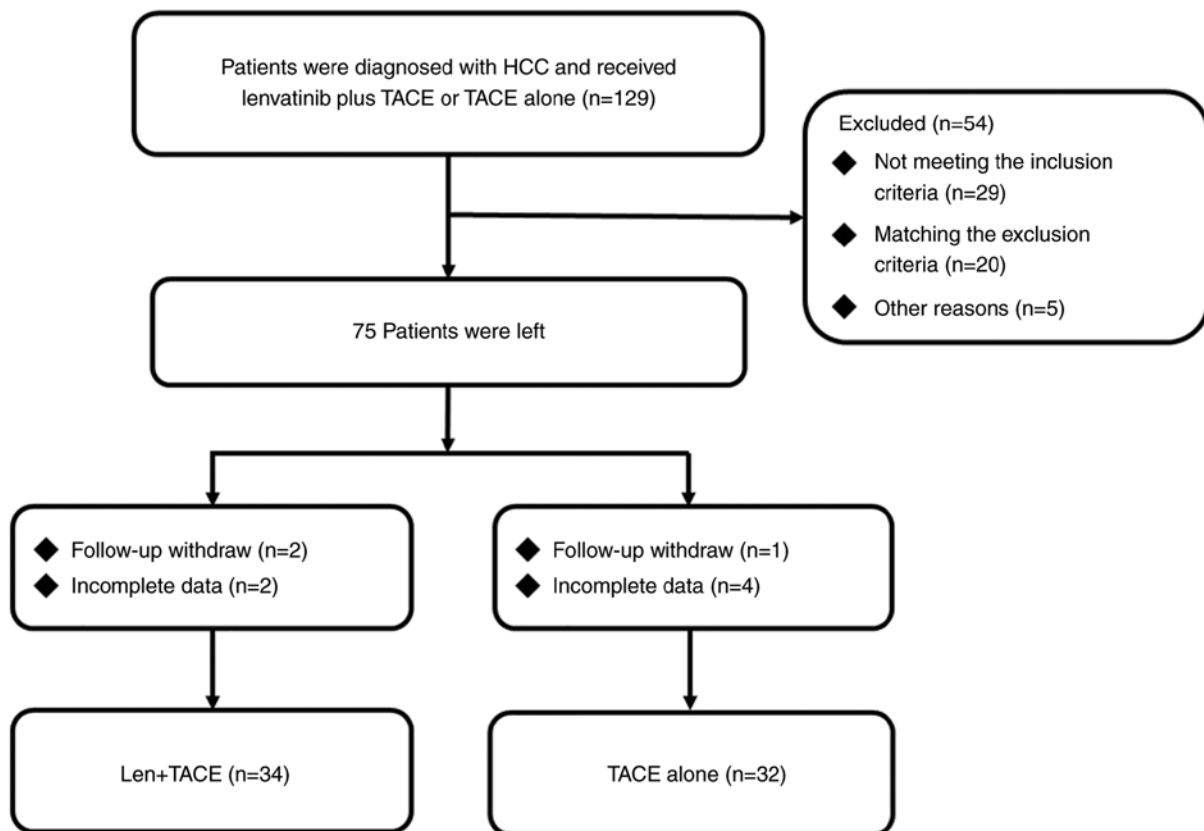


Figure 1. Flow chart for selecting patients with BCLC B2 stage HCC for the present study. BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; Len, lenvatinib; TACE, transarterial chemoembolization.

the date of initial TACE to the time of disease progression or last follow-up. Tumor response was assessed every 4-8 weeks

according to the modified response evaluation criteria for solid tumors (mRECIST) (29), including complete response (CR),

Table II. Baseline patient characteristics.

Patient characteristic	Lenvatinib + TACE (n=34)	TACE (n=32)	Total (n=66)	P-value
Age, years <sup>a</sup>	51.79±12.30	53.34±14.72	52.55±13.45	0.643
Sex, n (%)				0.710
Female	5 (14.7)	3 (9.4)	8 (12.1)	
Male	29 (85.3)	29 (90.6)	58 (87.9)	
HBV, n (%)				>0.999
Negative	5 (14.7)	4 (12.5)	9 (13.6)	
Positive	29 (85.3)	28 (87.5)	57 (86.4)	
AFP (ng/l), n (%)				0.013
≤400	13 (38.2)	22 (68.8)	35 (53.0)	
>400	21 (61.8)	10 (31.2)	31 (47.0)	
Child-Pugh score, n (%)				0.977
5	13 (38.2)	13 (40.6)	26 (39.4)	
6	13 (38.2)	12 (37.5)	25 (37.9)	
7	8 (23.5)	7 (21.9)	15 (22.7)	
Liver cirrhosis, n (%)				0.709
No	11 (32.4)	9 (28.1)	20 (30.3)	
Yes	23 (67.6)	23 (71.9)	46 (69.7)	
Tumor number, n (%)				0.654
≤3	4 (11.8)	6 (18.8)	10 (15.2)	
>3	30 (88.2)	26 (81.3)	56 (84.8)	
Largest tumor size (cm), n (%)				0.622
≤4	18 (52.9)	15 (46.9)	33 (50.0)	
>4	16 (47.1)	17 (53.1)	33 (50.0)	
Tumor distribution, n (%)				0.420
Unilobar	8 (23.5)	5 (15.6)	13 (19.7)	
Bilobar	26 (76.5)	27 (84.4)	53 (80.3)	

TACE, transarterial chemoembolization; HBV, hepatitis B virus; AFP,  $\alpha$ -fetoprotein. <sup>a</sup>Data are presented as mean  $\pm$  SD.

partial response (PR), stable disease (SD) and progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients who achieved CR or PR, and the disease control rate (DCR) was defined as the proportion of patients who achieved either CR, PR or SD. Treatment-related AEs were evaluated according to the Common Terminology Criteria for Adverse Events (version 5) (30).

**Statistical analysis.** Continuous data with normal distribution were expressed as the mean and standard deviation and skewed distributions were expressed as medians and interquartile ranges. Categorical data are expressed as frequencies and percentages. Categorical variables were compared using the  $\chi^2$  or Fisher's exact tests and continuous variables were comparing using the unpaired Student's t-test. PFS and OS were calculated using the Kaplan-Meier method and the log-rank test was used to compare PFS and OS between the groups. Hazard ratios (HRs) and confidence intervals (CIs) were estimated using the Cox proportional hazards model. Statistical analysis was performed using the SPSS software (version 21; IBM Corp.) and RStudio (version 4.2.1; RStudio, Inc.).  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Patient characteristics.** In total, 66 patients were included in the present study with 34 patients receiving Len + TACE, and 32 patients receiving TACE alone (Table II). Most of the patients were male [n=58 (87.9%)] and had an HBV infection [n=57 (86.4%)], >3 tumors [n=56 (84.8%)], a bilobar distribution [n=53 (80.3%)] and a mean age of 52.55±13.45 years. In the Len + TACE group, the number of patients with higher AFP levels >400 ng/l [n=21 (61.8%)] was significantly higher compared with that in the TACE group [n=10 (31.2%)] ( $P=0.013$ ). Other patient characteristics of note included hepatitis C virus (HCV) infection [n=1 (1.5%)], alcohol abuse [n=1 (1.5%)], non-alcoholic fatty liver disease [n=2 (3.0%)] and other unknown background of liver damage [n=5 (7.5%)]. All patients infected with HBV were treated with 0.5 mg entecavir (Chia Tai Tianqing Pharmaceutical Group Co., Ltd.) once daily, while the patient infected with HCV received 400/100 mg sofosbuvir and velpatasvir (Gilead Sciences, Inc.) once daily.

**Overall survival.** As the number of deaths was so small that >50% of the patients still survived at the end of the follow-up,

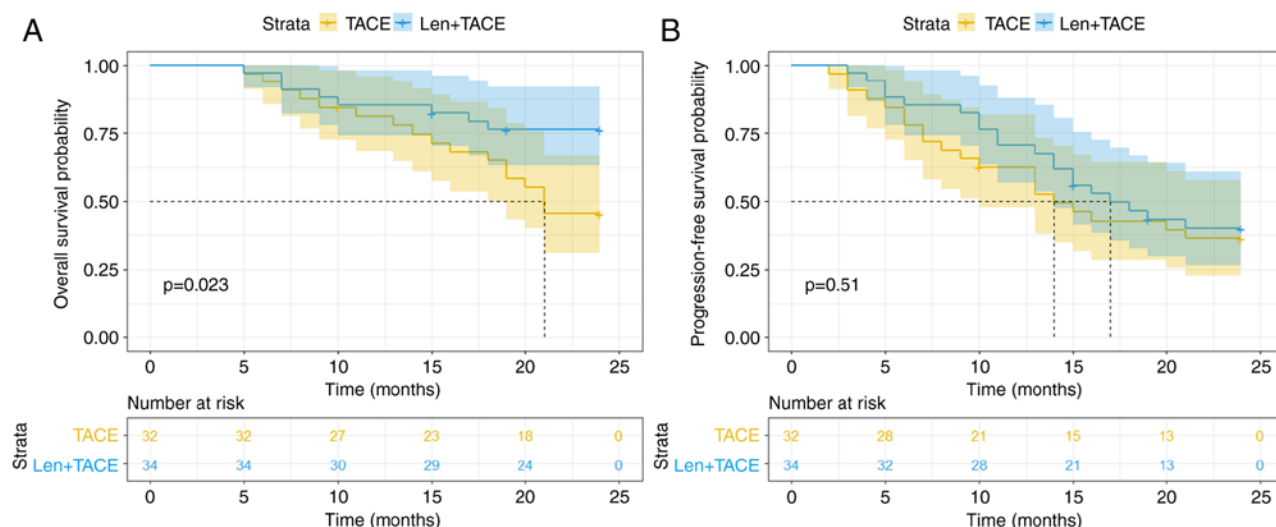


Figure 2. Kaplan-Meier survival curves in (A) overall survival and (B) progression-free survival of patients with BCLC B2 stage HCC and treated with Len + TACE combination therapy or TACE monotherapy. The shaded areas on the graph represent the confidence interval. Len, lenvatinib; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.

causing the inability to calculate the median value, the median OS time was not reached in the two treatment groups (Fig. 2A). The OS time was significantly longer in the Len + TACE group compared with that in the TACE group (HR, 0.395; 95% CI, 0.180-0.867;  $P=0.023$ ). The 6-month, 1- and 2- year OS rates in the Len + TACE group were 97.1, 85.3 and 76.3%, respectively. The 6-month, 1- and 2- year OS rates in the TACE group were 93.8, 81.1 and 45.4%, respectively. The subgroup analysis demonstrated that patients aged  $>60$  years, with lower levels of AFP ( $\leq 400$  ng/ml),  $>3$  tumors, largest tumor size  $\leq 4$  cm and without HBV infection and liver cirrhosis, benefited more from Len + TACE compared with TACE monotherapy ( $P<0.05$ ; Fig. 3).

**Progression-free survival.** The median PFS time of the entire patient cohort was 16.00 months (95% CI, 11.60-20.41 months). In the Len + TACE combination therapy group and the TACE monotherapy group, the median PFS time was 17.00 months (95% CI, 11.55-22.45 months) and 14.00 months (95% CI, 8.68-19.32 months), respectively, and no significant difference was observed between the two treatment groups (HR, 0.815; 95% CI, 0.437-1.520;  $P=0.510$ ; Fig. 2B). However, the PFS rates at 6 months, 1 and 2 years were higher in patients who received combination therapy (85.3, 70.6 and 40.1%, respectively) compared with those in patients who received monotherapy (78.1, 62.5 and 36.2%, respectively), however the difference was not statistically significant. A total of seven and two patients with disease progression received additional PD-1 treatment in the Len + TACE group and the TACE group, respectively. In total,  $\sim 70\%$  of patients chose to maintain their original treatment strategy after disease progression because of either economic or personal reasons.

**Tumor response.** Based on the mRECIST criteria, four and 18 patients exhibited CR and PR, respectively after receiving Len + TACE, and two and nine patients, respectively after TACE (Table III). The ORR in the Len + TACE group was

Table III. Tumor response in the combination and monotherapy treatment groups of patients.

Tumor response	Lenvatinib + TACE, n (%)	TACE, n (%)	P-value
CR	4 (11.8)	2 (6.3)	0.673
PR	18 (52.9)	9 (28.1)	0.040
SD	5 (14.7)	10 (31.3)	0.109
PD	7 (20.6)	11 (34.4)	0.209
ORR	22 (64.7)	11 (34.4)	0.014
DCR	27 (79.4)	19 (59.4)	0.066

TACE, transcatheter arterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

significantly higher compared with that in the TACE group (64.7 vs. 34.4%;  $P=0.014$ ). Furthermore, DCR was markedly increased in the Len + TACE group compared with the TACE group (79.4 vs. 59.4%;  $P=0.066$ ). Representative images of necrosis and regression of tumor lesion are shown in Fig. 4.

**Adverse events.** Occurrences of treatment-emergent AEs were recorded (Table IV). In the Len + TACE group, the most common AEs elevated were alanine aminotransferase (ALT)/aspartate transaminase (AST) (52.9%), fever (47.1%), pain (35.3%), hypertension (32.4%) and decreased white blood cells (WBCs; 23.5%), while grade 3/4 AEs included elevated ALT/AST (23.5%), hypertension (11.8%), decreased WBCs (5.9%), fever (2.9%) and diarrhea (2.9%). In the TACE group, fever was the most frequent event (46.9%), followed by elevated ALT/AST (43.8%), pain (25.0%), decreased WBCs (18.8%), diarrhea (9.4%) and rash (3.1%) and grade 3/4 AEs were reported in this patient group, including elevated

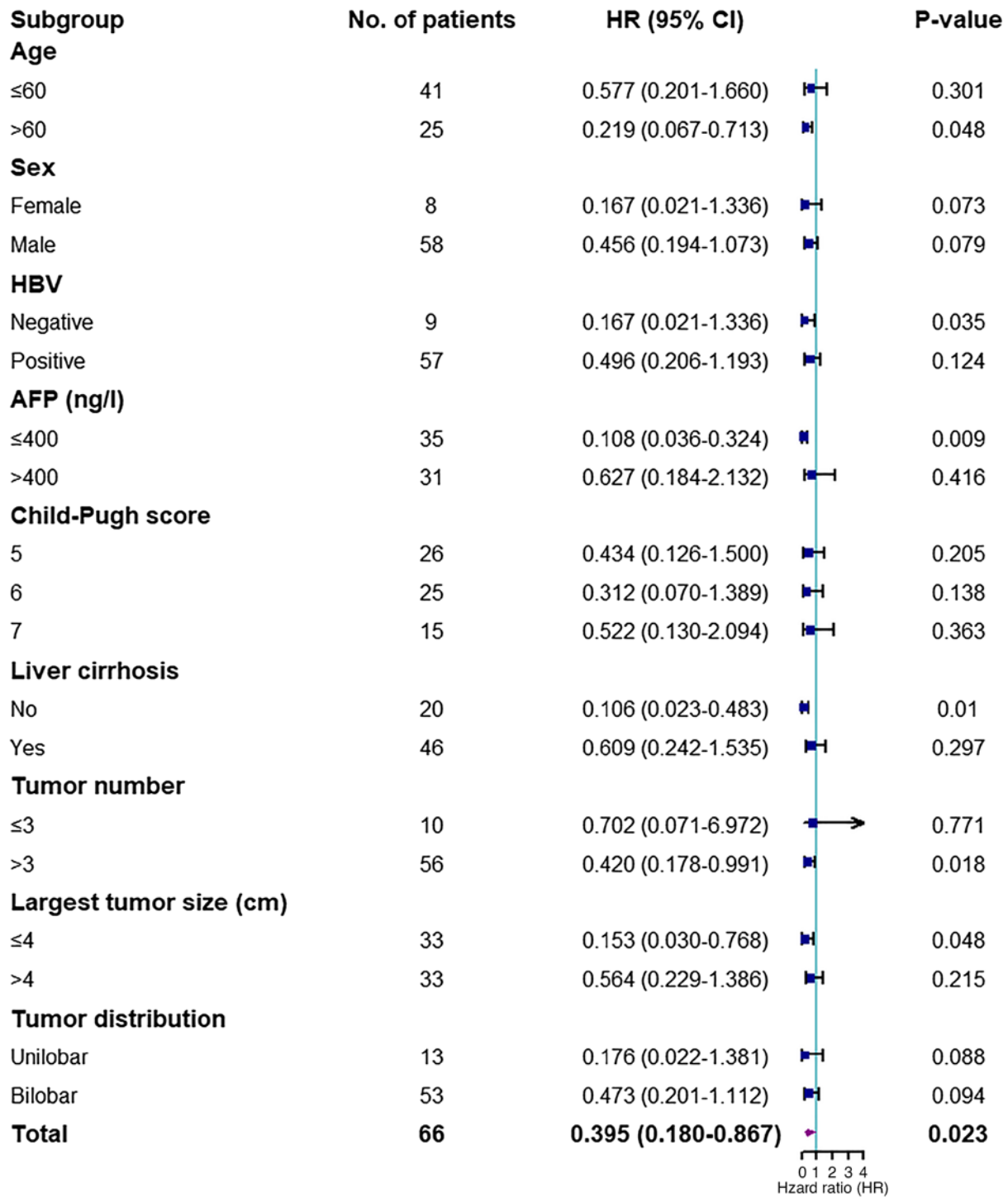


Figure 3. Forest plot of the overall survival in the subgroup of comparison between the Len + TACE group and the TACE monotherapy group. Len, lenvatinib; TACE, transarterial chemoembolization; HBV, hepatitis B virus; AFP,  $\alpha$ -fetoprotein; HR, hazard ratio; CI, confidence interval.

ALT/AST (18.8%), fever (3.1%) and decreased WBCs (3.1%). In the Len + TACE group, three patients reduced the dose of Len, and one patient temporarily withdrew Len because of intolerance to AEs, which led to the AEs becoming manageable for the patient.

**Univariate and multivariate analyses.** Univariate and multivariate Cox regression analyses of factors influencing OS and PFS were performed (Table V). Univariate analysis demonstrated that the use of Len + TACE and largest tumor

size  $\leq 4$  cm were shown to be significant prognostic factors for favorable OS, but the largest tumor size was the only significant prognostic factor for PFS. Multivariate Cox proportional hazards model for OS identified the largest tumor size ( $>4$  vs.  $\leq 4$  cm; HR, 4.086; 95% CI, 1.623-10.289;  $P=0.003$ ) and treatment strategy (Len + TACE vs. TACE; HR, 0.426, 95% CI, 0.184-0.990;  $P=0.047$ ) as independent risk factors. Similarly, for PFS, patients with largest tumor size  $\leq 4$  cm had significantly improved prognosis (HR, 2.548; 95% CI, 1.334-4.870;  $P=0.005$ ).



Table IV. Adverse events in the combination and monotherapy treatment groups of patients.

Adverse events	Lenvatinib + TACE (n=34)		TACE (n=32)	
	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)
Elevated ALT/AST	18 (52.9)	8 (23.5)	14 (43.8)	6 (18.8)
Fever	16 (47.1)	1 (2.9)	15 (46.9)	1 (3.1)
Pain	12 (35.3)	0 (0.0)	8 (25.0)	0 (0.0)
Hypertension	11 (32.4)	4 (11.8)	0 (0.0)	0 (0.0)
Decreased white blood cell count	8 (23.5)	2 (5.9)	6 (18.8)	1 (3.1)
Diarrhea	5 (14.7)	1 (2.9)	3 (9.4)	0 (0.0)
HFSR	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	2 (5.9)	0 (0.0)	1 (3.1)	0 (0.0)

TACE, transcatheter arterial chemoembolization; ALT, alanine aminotransferase; AST, aspartate transaminase; HFSR, hand-foot skin reaction.

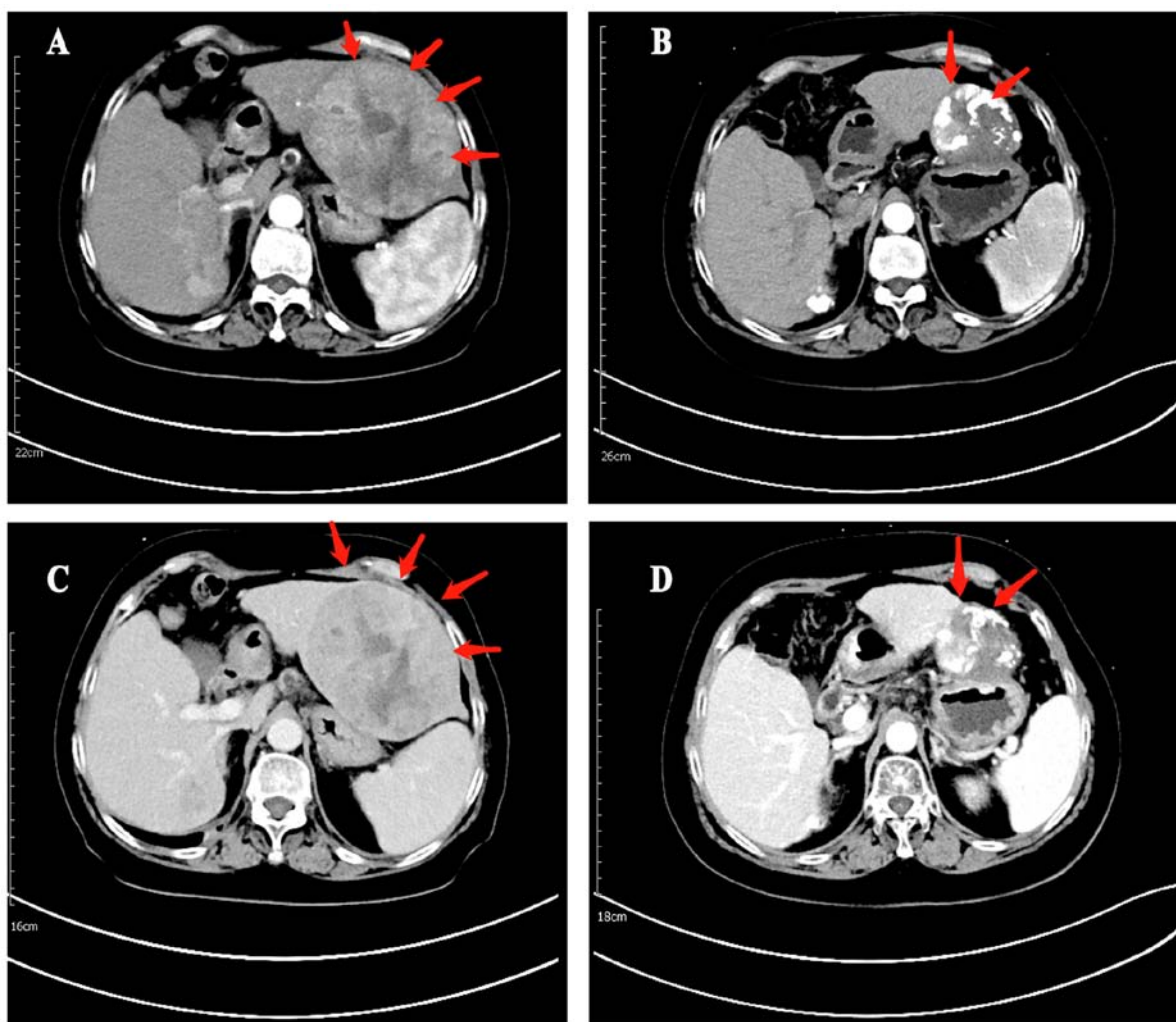


Figure 4. Enhanced CT images in arterial phase of tumor lesions (A) before Len + TACE combination therapy (B) and necrosis and regression of the tumor lesions after Len + TACE combination therapy. Enhanced CT images in portal venous phase of tumor lesions (C) before Len + TACE combination therapy (D) and necrosis and regression of the tumor lesions after Len + TACE combination therapy. Len, lenvatinib; TACE, transarterial chemoembolization; CT, computer tomography.

## Discussion

According to the updated BCLC guidelines that take into

consideration the extensive heterogeneity of tumor burden, intermediate stage HCC was divided into three groups (5). Among these groups, the BCLC B2 subgroup was defined as

Table V. Univariate and multivariate analysis of overall survival and progression-free survival of patients treated with combination Len + TACE and TACE monotherapy.

Patient characteristic	Overall survival				Progression-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years	0.998 (0.970-1.027)	0.892	N/A	N/A	1.020 (0.996-1.044)	0.107	N/A	N/A
Sex								
Male vs. female	0.643 (0.220-1.879)	0.419	N/A	N/A	0.774 (0.303-1.977)	0.592	N/A	N/A
HBV								
Positive vs. negative	0.756 (0.259-2.203)	0.608	N/A	N/A	0.726 (0.304-1.731)	0.470	N/A	N/A
AFP, ng/l								
>400 vs. ≤400	1.192 (0.544-2.613)	0.661	N/A	N/A	1.123 (0.604-2.091)	0.714	N/A	N/A
Child-Pugh score								
6 vs. 5	0.697 (0.265-1.833)	0.465	N/A	N/A	0.672 (0.326-1.385)	0.282	N/A	N/A
7 vs. 5	1.620 (0.638-4.111)	0.310	N/A	N/A	0.982 (0.449-2.150)	0.964	N/A	N/A
Liver cirrhosis								
Yes vs. no	1.201 (0.502-2.876)	0.681	N/A	N/A	0.816 (0.420-1.585)	0.548	N/A	N/A
Tumor number								
>3 vs. ≤3	1.437 (0.430-4.801)	0.556	N/A	N/A	1.664 (0.651-4.252)	0.287	N/A	N/A
Largest tumor size, cm								
>4 vs. ≤4	4.297 (1.709-10.806)	0.002	4.086 (1.623-10.289)	0.003 (1.334-4.870)	2.548 (1.334-4.870)	0.005	2.548	0.005
Tumor distribution								
Bilobar vs. Unilobar	1.394 (0.478-4.066)	0.543	N/A	N/A	1.099 (0.506-2.387)	0.811	N/A	N/A
Treatment								
Len + TACE vs. TACE	0.394 (0.170-0.914)	0.030	0.426 (0.184-0.990)	0.047 (0.438-1.515)	0.815	0.517	N/A	N/A

Only variables with P<0.05 at univariate analysis were analyzed by multivariate analysis. Len, lenvatinib; TACE, transarterial chemoembolization; HBV, hepatitis B virus; AFP,  $\alpha$ -fetoprotein; HR, hazard ratio; CI, confidence interval; N.A., not applicable.

patients with defined tumor burden, preserved portal flow and feasibility of selective access to feeding tumor arteries who did not meet the extended liver transplant criteria, and TACE was recommended as the first line treatment option for this group (5). However, the cut-off for the division into subgroups is still not sufficiently specific, and heterogeneity and limitations still exist. Based on the Bolondi criteria, Kudo (9) developed the Kindai criteria. Len was recommended as the first-line treatment, and either sorafenib alone or sorafenib plus TACE

were recommended as alternative options for patients categorized into the BCLC B2 substage, according to the Kindai criteria (8,9). As previously reported by Wang *et al* (18), no notable differences were observed in patient groups treated with TACE plus sorafenib and sorafenib alone in the BCLC B1 substage, as patients with low tumor burden responded favorably to TACE monotherapy. Although tumor burden was approved as an independent risk factor, TACE may cause a larger area of embolization and necrosis, and the addition of



sorafenib cannot offset these side effects for patients with a high tumor burden, which leads to not marked clinical effects of treatment (18,31). In the TACTICS clinical trial, TACE plus sorafenib notably prolonged PFS than TACE alone for whole patient population, but did not for those within up-to-seven criteria (low tumor burden) (32).

In a previous study by Kudo *et al* (24), it was reported that Len-treated patients with B2 stage disease had a significantly improved ORR (73.3 vs. 33.3%;  $P<0.001$ ) and DCR (100 vs. 53.3%;  $P<0.001$ ) compared with TACE alone. Additionally, four patients no longer received treatment with lenvatinib, achieving drug-free status, after CR in the Len group, of which three patients received additional selective TACE. It could be suggested that Len-TACE sequential therapy can achieve improved CR, but additional comparisons of specific survival data between Len-TACE sequential therapy and TACE alone were lacking (24). Previous retrospective studies demonstrated that Len + TACE combination therapy notably improved treatment efficacy compared to TACE monotherapy for patients with uHCC, however, Fu *et al* (26) reported that TACE combined with Len failed to prolong OS in patients with BCLC B or C stage ( $P=0.070$  and  $P=0.328$ , respectively) (25). Chen *et al* (25) further studied patients with BCLC B and C stage and Len + TACE combination therapy notably contributed to increased survival in this population.

However, to the best of our knowledge, there are still no studies for patients with BCLC B2 substage HCC comparing the efficacy of Len + TACE combination therapy and TACE monotherapy. Therefore, in the present retrospective study, the efficacy and safety between combination therapy and monotherapy in patients with BCLC B2 substage HCC were compared. The present study demonstrated that patients receiving Len + TACE had significantly longer OS compared with those receiving TACE alone, meanwhile, a similar tendency of PFS was also observed. In addition, patients in the combination therapy group had improved ORR and treatment safety compared with those the monotherapy group. Currently, multiple signaling pathways such as the  $\beta$ -catenin signaling pathway and the epidermal growth factor receptor (EGFR) system, have been reported to be involved in the tumorigenesis and progression of HCC, and crosstalk among various signal transduction pathways also exists (33). Therefore, combination therapy may circumvent these signal transduction pathways and possibly cause tumor suppression more effectively than single treatment agents limited to targeting single molecules or pathways (33). Previous studies have reported that TACE can induce tumor angiogenesis, which leads to a risk of tumor recurrence and metastasis, while TKIs serve a role in suppressing cell proliferation and tumor angiogenesis by targeting VEGFR and other related receptors (12-14,34). Based on these findings, a combination of TKIs and TACE has previously been used by researchers. Qu *et al* (35) treated 45 patients with advanced HCC with sorafenib in combination with TACE or TACE alone and combination therapy significantly prolonged the median OS time compared with monotherapy. Thereafter, a series of studies comparing the two treatment types were performed and reported the same outcomes in patients with intermediate-advanced HCC (36). The results of these studies provide a preliminary basis for the application of combination therapy.

The combination therapy of TACE and Len has also been used. Compared with the combination of TACE with sorafenib, Len possesses a stronger affinity for VEGFR2 and inhibits more targets, including FGF, which results in a difference in its higher efficacy in combination with TACE (19,37-39). Moreover, Len targets more signaling pathways, including FGFR-MAPK, ERK/MAPK and EGFR-PI3K-AKT compared with sorafenib, which results in a greater therapeutic advantage compared sorafenib (40-42). Previous studies reported the increased efficacy of Len + TACE combination therapy for patients with uHCC compared with TACE monotherapy (25,26). However, the diagnosis of uHCC has a wide range of presentations and characteristics, and combination therapy or monotherapy is not the best option for all patients. For example, Kim *et al* (43) studied 277 patients BCLC B stage disease treated with surgical resection or TACE, and reclassified patients into four subgroups on a basis of characteristics and estimated HRs. The aforementioned study reported a significantly increased survival in the surgical resection group compared with the TACE group (5-year survival rate, 53.6 vs. 26.1%;  $P=0.021$ ) at the B2 substage which was characterized as 'oligo' tumors (2-4 nodules) with intermediate size and low AFP level, or with small to intermediate size and high AFP level. According to the Kinki criteria, Kudo (44) recommended curative treatment such as surgical resection and ablation, as a first-line option for patients with BCLC B1 stage HCC. In the B2 substage, tumor size and number may affect survival in patients with HCC and patients treated with TACE who had  $>6$  tumors had a significantly shorter median time to progression than those with  $\leq 6$  tumors (10.4 vs. 14.0 months;  $P=0.002$ ) (45). Thus, the present study focused only on the comparison between Len + TACE combination therapy and TACE monotherapy for BCLC B2 stage HCC. The Len + TACE group exhibited significantly improved OS and tumor response compared with the TACE group, which was in accordance with previous studies in which the same treatment comparisons were performed in patients with uHCC (25,26). Although a significant difference in PFS was not observed between the two treatment groups, with increasing sample size, this difference may be statistically significant. A recent network meta-analysis by Zhang *et al* (46) compared the combination therapy of TACE plus TKIs with TACE or TKIs monotherapy for patients with uHCC and these results showed that Len + TACE combination therapy ranked the highest in terms of OS (rank probability, 0.7559), PFS (rank probability, 0.8595) and DCR (rank probability, 0.3857) and was considered the optimal treatment for patients with uHCC.

The present multivariate analysis demonstrated that the largest tumor size  $>4$  cm was an independent risk factor and was associated with OS and PFS. Additionally, a large tumor size and multiple tumors were regarded as poor prognostic factors for the survival of patients with HCC. A previous cohort study of 362 patients treated with TACE and reported that a maximal tumor size  $>4$  cm (OR, 1.66; 95% CI, 1.29-2.30;  $P=0.002$ ) and  $>5$  tumors (OR, 1.92; 95% CI, 1.44-2.55;  $P<0.001$ ) were significant prognostic risk factors and a larger sample size study with 8,410 patients also reported similar results (47,48). In addition, the subgroup analysis from the present study demonstrated that patients with  $>3$  tumors benefited more from Len + TACE compared with monotherapy. Patients

with a higher number of tumors are less likely to respond to TACE and achieve a limited effect from this treatment (47,49). Therefore, combination therapy may provide additional benefits to patients with multiple tumors. However, the sample size should be larger to further compare Len + TACE with TACE treatment alone in other subgroups, such as those of tumor distribution and Child-Pugh class. In subgroup analysis, it was demonstrated that patients aged >60 years benefited more from Len + TACE compared with patients aged ≤60 years. Mosconi *et al* (50) compared the efficacy and safety of TACE between patients aged greater and less than 70 years and no significant difference was observed in survival efficacy and complications between these age groups. In an additional retrospective study, patients aged >70 years old who received sorafenib had longer OS (16 vs. 12 months) and PFS (12 vs. 8 months) compared with those aged ≤70 years, although these results were not statistically significant (51). In addition, the same phenomenon was also observed in a CELESTIAL trial as patients aged >65 years benefited from cabozantinib, a type of TKI, in regard to increased OS, but younger patients did not (52). This may indicate that TKI improve the survival of the elderly population more effectively compared with younger patients. However, the phase III RESORCE trial yielded opposite results to the aforementioned study (53). Elderly patients were more likely to report comorbidities compared with younger patients, which may increase the risk of complications after receiving systemic therapy. In the present study, on the one hand, the follow-up time was not long enough to observe such complications, so the occurrence of complications in patients was not been fully explored, which leads to the possibility of exaggerating the treatment effect in the elderly patient population. On the other hand, only 25 patients ages >60 years were included in the subgroup analysis, which may introduce bias and potentially lead to inaccurate results. Thus, these results should be interpreted cautiously. Given that the prevalence and incidence of HCC is increasing in the elderly patient population (54), more randomized trials and prediction models concerning the treatment of HCC based on age factors are needed to explore suitable treatment strategies that balance efficacy and safety for the elderly patient population.

As presented in the current study, although AEs in the Len + TACE group were more frequent, amongst which mild to moderate AEs were the most predominant, AEs associated with combination therapy were classed as manageable. In addition, hand-foot-skin reactions and hypertension were observed only in the Len + TACE group, which were most likely attributable to Len. Due to the significantly increased survival benefit of combination therapy of TACE + TKIs compared with either TACE or TKIs alone, if serious AEs occur after using Len, sorafenib or other TKI drugs are a viable alternative option, rather than discontinuation of Len (45). In addition, previous studies have reported that the incidence of treatment-related AEs in the sorafenib plus TACE group were comparable to, or lower than, those in the Len + TACE group during the combination treatment (55-57).

The present study has several limitations. First, this was a retrospective study, therefore, selection biases were unavoidable. Second, the sample size was small, and the observation period was not long enough for the median OS time to be observed, which may have led to masking of the

true therapeutic effects. Therefore, large-scale, multicenter, randomized controlled studies are needed to confirm these results and apply these findings to further research.

In conclusion, Len + TACE combination therapy was associated with increased OS and tumor response compared with TACE monotherapy in patients with BCLC B2 stage HCC. Combination therapy and monotherapy were safe and manageable. Tumor number can be used as an independent risk factor for both OS and PFS.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

JL and PY conceived and designed the study. JL, SY, GZ and PY collected patient data. GZ, SW and LY analyzed and interpreted the data. JL, SY and PY drafted and revised the manuscript. All authors read and approved the final version of the manuscript. JL and PY confirm the authenticity of all the raw data.

## Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of Affiliated Hospital of North Sichuan Medical College (approval no. 2023ER059-1) according to the retrospective protocol and all procedures for the cohort in the present study were carried out in agreement with the Declaration of Helsinki. Written, informed consent was obtained from all subjects and/or their legal guardian(s).

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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