

# Efficacy and Safety Analysis of Transarterial Chemoembolization Plus Donafenib With or Without Immune Checkpoint Inhibitors for Unresectable Hepatocellular Carcinoma: A Prospective, Single-Arm, Single-Center, Phase II Clinical Study

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**Purpose:** To observe and assess the efficacy and safety of donafenib combined with transarterial chemoembolization (TACE) to treat unresectable hepatocellular carcinoma (HCC).

**Patients and Methods:** This prospective, single-arm, single-center, phase II clinical study enrolled 36 patients with initial unresectable HCC who had not undergone any systemic treatment. The patients received donafenib plus TACE (n = 26) or donafenib plus TACE plus programmed death receptor 1 inhibitors (n = 10). The primary endpoint was short-term efficacy, with secondary endpoints including progression-free survival (PFS), time to response (TTR), disease control rate (DCR), and adverse events. The tumor feeding artery diameter was also measured.

**Results:** Efficacy evaluation of all 36 patients revealed 6 cases of complete response, 19 of partial response, 8 of stable disease, and 3 of progressive disease. Six (16.7%) patients successfully underwent conversion surgery, all achieving R0 resection, and 2 (5.6%) achieved a complete pathological response. The objective response rate (ORR) was 69.4% and the DCR was 91.7%. The median PFS was 10.7 months, the median overall survival was not reached, and the median TTR was 1.4 months. The median survival rates at 6, 12, and 18 months were 85.0%, 77.6%, and 71.3%, respectively. The median PFS rates at 6, 12, and 18 months were 65.3%, 45.6%, and 34.2%, respectively. Treatment-related adverse events (TRAEs) occurred in all 25 subjects, including 4 (11.3%) grade 3 TRAEs. No grade 4 or 5 TRAEs occurred. The tumor feeding artery diameter was significantly decreased following treatment (P = 0.036). Multivariable analysis revealed the sum of baseline target lesion diameters, best tumor response, and combined immunotherapy as independent predictors of PFS.

**Conclusion:** TACE plus donafenib reduced the tumor feeding artery diameter in patients with unresectable HCC. The safety profile was good, and a high ORR was achieved.

**Keywords:** hepatocellular carcinoma, donafenib, transarterial chemoembolization, immune checkpoint inhibitors, safety, efficacy

## Introduction

Hepatocellular carcinoma (HCC) accounts for 75–85% of primary liver cancer cases and is a major cause of cancer-related deaths worldwide, seriously threatening human health.<sup>1,2</sup> Great advancements in the treatment modes for HCC have been made in recent years, and factors such as the patient body strength, degree of cirrhosis, tumor load, and cancer stage require full consideration. Surgical resection, liver transplantation, local ablation, and other treatments are generally used for early HCC, with local and systemic treatments mainly reserved for advanced HCC. Comprehensive treatment further improves the curative effect and prolongs patient survival.<sup>3,4</sup> However, for patients with advanced HCC who are unsuitable or refuse treatment, the main local treatment method is transarterial chemoembolization (TACE), which significantly improves the outcomes of patients with Barcelona Clinic Liver Cancer (BCLC) stage B and some with stage C.<sup>5–7</sup>

In recent years, targeted therapy, immunotherapy, and other innovative methods have provided new treatment options for patients with advanced liver cancer, and these have become the standard first-line treatment for patients with advanced HCC.<sup>8–11</sup> Donafenib, an oral small-molecule multitarget tyrosine kinase inhibitor (TKI), is an improved form of sorafenib, with significantly enhanced molecular stability and improved pharmacokinetics.<sup>12</sup> It is also the only single-agent targeted drug superior to sorafenib in first-line head-to-head studies on advanced HCC. The positive results of the ZGDH3 trial, which showed improved overall survival (OS) compared with sorafenib, led to the approval of donafenib for treating unresectable or metastatic HCC.<sup>3</sup> Like sorafenib, lenvatinib, and atiluzumab plus bevacizumab, donafenib is recommended as first-line systemic therapy for patients with unresectable HCC.<sup>13</sup>

With the advent of the immune era, the use of systemic therapies, such as TKIs<sup>9</sup> and immune checkpoint inhibitors (ICIs),<sup>14,15</sup> have shown good effects in HCC treatment. Compared with a single-agent treatment, combination therapy shows a better trend in tumor response rate, survival outcome, and transformation resection in patients with advanced liver cancer due to the combination of the different antitumor mechanisms of TACE, TKIs, and immune checkpoint inhibitors, which may exert synergistic and toxic effects.<sup>16–18</sup> To the best of our knowledge, there are few clinical studies on TACE combined with donafenib with or without immune checkpoint inhibitors in the treatment of advanced liver cancer. Thus, this real-world study aimed to evaluate the efficacy and safety of donafenib combined with TACE with or without immune checkpoint inhibitors in the treatment of advanced HCC with a view to providing novel therapeutic approaches for clinical diagnosis and treatment.

## Materials and Methods

### Patient Selection

This prospective, single-arm, single-center phase II clinical trial was initiated by the researcher. The study subjects were selected from patients at the Affiliated Tumor Hospital of Shandong First Medical University. This study was conducted in accordance with the Declaration of Helsinki. The study received approval from the Ethics Committee of Affiliated Tumor Hospital of Shandong First Medical University, and all patients provided informed consent. After discussion by the multidisciplinary team (MDT), it was deemed unresectable (unresectable was defined as fulfilling any of the following conditions: large tumor; multiple tumors involving both the left and right lobes of the liver; invasion of major blood vessels such as the main portal vein and inferior vena cava; the patient was unable to tolerate surgical treatment; there were extrahepatic metastatic lesions).<sup>19</sup>

The inclusion criteria were as follows: (1) patients with liver cancer who strictly met the clinical diagnostic criteria for primary liver cancer as per the Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition)<sup>20</sup> or were diagnosed by histopathology or cytology, (2) patients who received TACE plus donafenib or TACE plus donafenib with immune checkpoint inhibitors as the first-line treatment, (3) patients aged 18–75 years with a survival time >3 months, (4) patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 before TACE and Child–Pugh grade A or B, and (5) patients with least one measurable lesion.

The exclusion criteria were as follows: (1) previous systemic antitumor therapy, (2) diffuse liver cancer, (3) intractable hepatic encephalopathy, refractory ascites, or hepatorenal syndrome, (4) previous tumor history, (5) and (5) incomplete data.

## Treatment Protocol

According to the judgment of the investigator, TACE was administered conventionally or using drug-eluting beads. The administration of multiple TACE treatments depended on evidence of viable tumors or intrapathological recurrence as observed by contrast-enhanced computed tomography or magnetic resonance imaging.

Donafenib was administered orally 3 days after TACE at an initial dose of 200 mg twice daily. An immune checkpoint inhibitor (carrelizumab or tislelizumab: 200 mg, once every 3 weeks, 1 cycle) was administered within 1–2 weeks after TACE treatment. If patients experienced side effects during the use of immune checkpoint inhibitors and donafenib, the dose was reduced or drug administration was suspended or stopped. If donafenib-related adverse reactions could be tolerated, the dose was adjusted to 200 mg/day.

## Evaluation of Treatment Response and Follow-Up

All patients were regularly followed up at intervals of 4–6 weeks after the first treatment until reaching the OS endpoint or the last follow-up date (December 31, 2023).

All patients underwent a comprehensive examination before and after treatment, including tests for serum tumor markers, an electrocardiogram, and an examination of the chest, abdomen, and pelvis. Routine blood analysis, blood biochemistry, urine, stool, and liver and kidney function tests were performed before each treatment cycle. Tumor responses were evaluated by two radiologists, both with >10 years' experience, using the modified Response Evaluation Criteria in Solid Tumors (mRECIST)<sup>21</sup> to compare tumor response between the two groups, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) and disease control rate (DCR) were also assessed. Progression-free survival (PFS) was defined as the time between the first TACE treatment and the date of disease progression or death.<sup>21</sup> OS was defined as the time from the first TACE treatment to death from any cause or the date of the last follow-up.<sup>21</sup> Treatment-related adverse events (TRAEs) were assessed using Common Terminology Criteria for Adverse Events (version 5.0).<sup>22</sup> The occurrence of common adverse events (AEs), such as hand–foot syndrome, rash, fatigue, diarrhea, hypertension, alopecia, and gastrointestinal bleeding, as well as any other AEs, were recorded.

## Statistical Methods

Data were analyzed using SPSS version 25.0 statistical software (IBM Corp., Armonk, NY, USA). Continuous data were presented as the mean  $\pm$  standard deviation, and comparisons between the two groups were performed by *t*-test. Categorical data were compared using chi-square test or Fisher exact test. The Kaplan–Meier method was used to draw survival curves, and log rank tests were used to compare the differences in survival between the two groups. The prognostic risk factors of OS and PFS were analyzed by Cox regression. P-values <0.05 were considered statistically significant.

## Results

### Patients

Figure 1 presents a flowchart showing the participant selection process. From September 2021 to December 2023, 50 patients received TACE combined with donafenib with or without immune checkpoint inhibitor. Screening according to the inclusion criteria resulted in the exclusion of 14 patients, including 3 due to incomplete data and 3 due to lack of follow-up data. The remaining 36 patients participated in the study (TACE + donafenib, *n* = 26; TACE + donafenib + immune checkpoint inhibitors, *n* = 10). Appropriate PD-1 drugs were selected according to the patient's medical insurance and condition. Among the 36 patients, 33 were male (91.7%), and the median age was 62.0 years. There were 17 (47.2%) cases with an ECOG PS of 1. Complications included 33 (91.7%) cases with hepatitis B virus infection and 11 (30.6%) with portal vein tumor thrombus. Baseline alpha-fetoprotein (AFP) levels  $\geq$ 400 ng/mL were present in 18 (50.0%) cases. The median maximum tumor diameter value was 9.1 cm (interquartile range: 5.1–12.4). The institutional distribution is presented in Table 1.

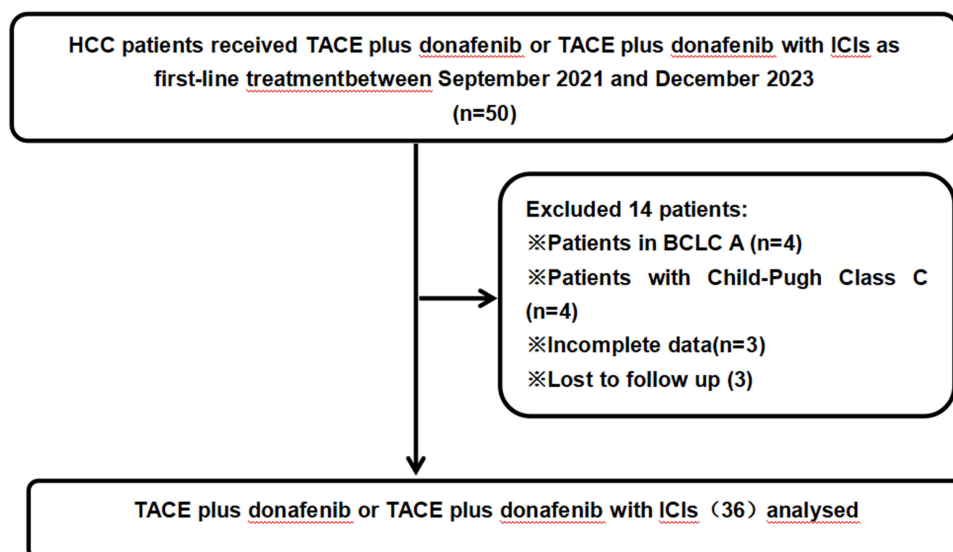


Figure 1 Patient flow chart.

### Effectiveness Analysis

As of February 11, 2024, the median follow-up time was 17.6 months. All 36 subjects were eligible for efficacy evaluation, and the median number of TACE treatments was 2.3 (range: 1–5). According to mRECIST, the ORR was 69.4% (25/36) and the DCR was 91.7% (33/36) (Table 2). Compared with the baseline, the target lesion burden decreased in 32 (88.9%) patients (Figure 2). CR was achieved in 6 (16.7%) patients, PR in 19 (52.8%), SD in 8 (22.2%), and PD in 3 (8.8%) (Table 2). Six (16.7%) patients successfully underwent conversion surgery and achieved R0 resection. Complete pathological response was achieved in two patients. Figure 3 presents the time change from baseline in target lesions (mRECIST). The tumor feeding artery diameter decreased from  $3.9 \pm 1.2$  mm to  $3.1 \pm 1.1$  mm at 4 weeks after TACE treatment, and the difference was statistically significant ( $P = 0.004$ ).

### Survival Analysis

The median PFS was 10.7 months (95% confidence interval [CI]: 8.37–NA months) (Figure 4), the median duration of response was 11.4 months, the median OS time was not reached (Figure 5), the median time to response (TTR) was 1.4 months (95% CI: 0.8–6.9 months), and the onset time was relatively fast. Furthermore, patients in the early tumor response group (CR+PR) had longer median PFS (23.4 vs 7.43 months,  $P < 0.014$ ) (95% CI: 10.67–NA months vs 95% CI: 4.83–NA months) compared with those in the late tumor group (SD+PD) (Figure 6). Patients in the BCLC B group had longer median PFS (10.67 vs 5.63 months,  $P = 0.048$ ) (95% CI: 7.43–NA months vs 95% CI: 2.67–NA months) compared with those in the BCLC C group, the median OS time was not reached. The median survival rates at 6, 12, and 18 months were 85.0%, 77.6%, and 71.3%, respectively. The median PFS rates at 6, 12, and 18 months were 65.3%, 45.6%, and 34.2%, respectively. The ORR was consistent among all subgroups, including those with a tumor size  $\geq 9$  cm or extrahepatic metastasis (Figure 7).

### Analysis of Prognostic Factors

Table 3 presents the results of univariate and multivariate analyses of the matched cohorts. Cox proportional hazards model showed that the sum of baseline target lesion diameters ( $<9$  vs  $\geq 9$  cm) (hazard ratio [HR] = 0.13 [95% CI: 0.03–0.68];  $P = 0.016$ ), immune checkpoint inhibitor (yes vs no) (HR = 0.327 [95% CI: 0.116–0.922];  $P = 0.034$ ), and best tumor response (CR+PR vs SD+PD) (HR = 0.09 [95% CI: 0.02–0.48];  $P = 0.032$ ) were independent prognostic factors for PFS.

**Table 1** Baseline Characteristics of Patients

Characteristic	All Patients (N = 36)
Age (years), median (IQR)	62 (52–69)
Sex	
Male	33 (91.7%)
Female	3 (8.3%)
ECOG PS	
0	19 (52.8%)
I	17 (47.2%)
China liver cancer staging (CNLC)	
Ib	9 (25.0%)
IIa	3 (8.3%)
IIb	13 (36.1%)
IIIa	7 (19.4%)
IIIb	4 (11.1%)
HBsAg positive	33 (91.7%)
BCLC stage	
B	25 (69.4%)
C	11 (30.6%)
Child–Pugh class	
A	32 (88.9%)
B	4 (11.1%)
AFP (ng/mL)	
≥400	18 (50.0%)
<400	13 (36.1%)
NA	5 (13.9%)
ALBI grade	
I	11 (30.6%)
2	23 (63.9%)
NA	2 (5.5%)
Vascular invasion	
Yes	11 (30.6%)
No	25 (69.4%)
Maximum tumor diameter (cm), median (IQR)	9.1 (5.2–12.4)
Extrahepatic metastasis, n (%)	
Yes	4 (11.1%)
No	32 (88.95)
Type of combination therapy	
TACE+D	26 (72.2%)
TACE+D+I	10 (27.8%)

**Notes:** Unless indicated otherwise, values are presented as n (%).

**Abbreviations:** IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status; HBsAg, hepatitis B surface antigen; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; TACE+D, transarterial chemoembolization plus donafenib; TACE+D+I, transarterial chemoembolization plus donafenib with immune checkpoint inhibitors.

## Safety

All 25 patients experienced TRAEs (Table 4), including 5 (14.7%) with TRAEs  $\geq$  grade 3, which were mainly manifested by elevated alanine aminotransferase (2.9%) and aspartate aminotransferase (5.9%) serum levels, hypertension (2.9%), and rash (2.9%). Hypertension related to donafenib (mainly grade 1 and 2) developed in 11 (32.3%) patients. A reduction in platelet count induced by hepatic arterial infusion chemotherapy combined with target immunity was observed in 15 patients, reaching grade 3 in 2 patients, which was relieved after treatment with drugs such as avatipopa. Two patients (5.9%) developed immune-related serious AEs, including one case of immune-related pneumonia (grade 2) and one case

**Table 2** Tumor Response According to mRECIST

Variables	All patients (N = 36)
Best objective response, n (%)	
Complete response	6 (16.7%)
Partial response	19 (52.8%)
Stable disease	8 (22.2%)
Progressive disease	3 (8.8%)
Objective response rate, n (%), 95% CI	25 (69.4%) (51.9–83.7)
Disease control rate, n (%), 95% CI	33 (91.7%) (77.5–98.2)
TTR, months, range	1.4 (1.1–4.4)
DOR, months, median (95% CI)	11.4 (9.23–NA)
Follow-up (months), median (95% CI)	17.6 (13.9–23.7)
OS, months, median (95% CI)	NA (NA–NA)
6-month OS rate	85.0%
12-month OS rate	77.6%
18-month OS rate	71.3%
PFS, months, median (95% CI)	10.7 (7.43–NA)
6-month PFS rate	65.3%
12-month PFS rate	45.6%
18-month PFS rate	34.2%

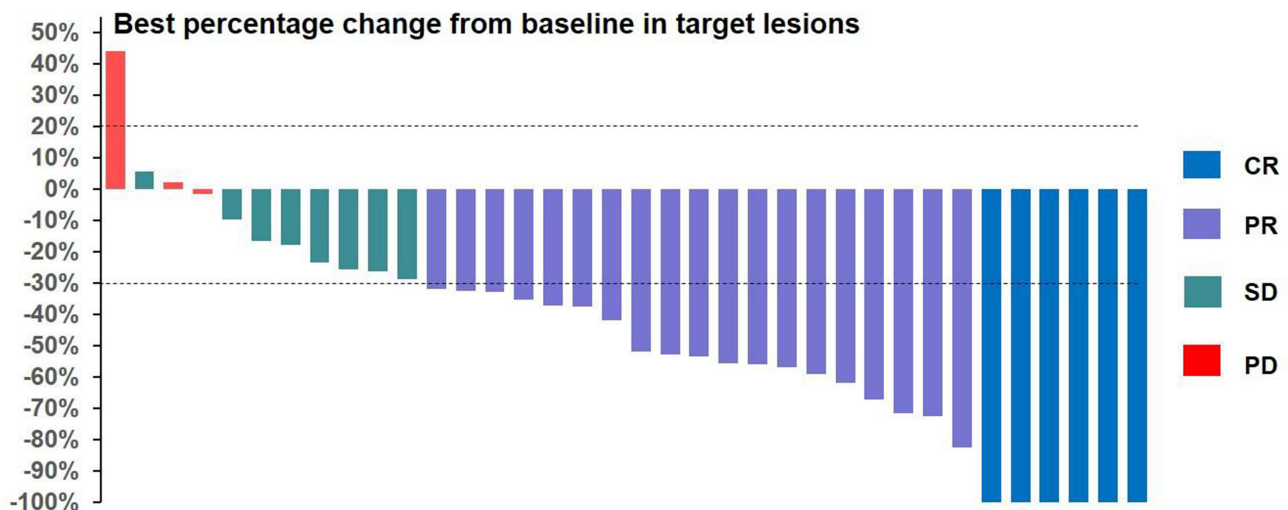
**Note:** Unless indicated otherwise, values are presented as n (%).

**Abbreviations:** CI, confidence interval; TTR, time to response; DOR, duration of response; OS, overall survival; PFS, progression-free survival.

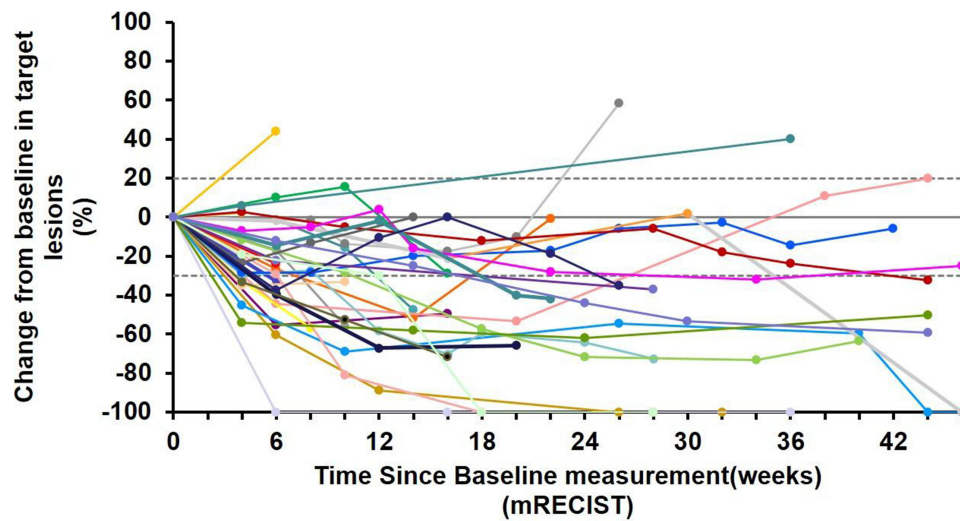
of hypothyroidism (grade 2). All patients recovered after drug withdrawal and steroid treatment. There were no treatment-related deaths and no TRAEs >grade 4. All TRAEs were relieved following symptomatic treatment or discontinuation of drug administration.

## Discussion

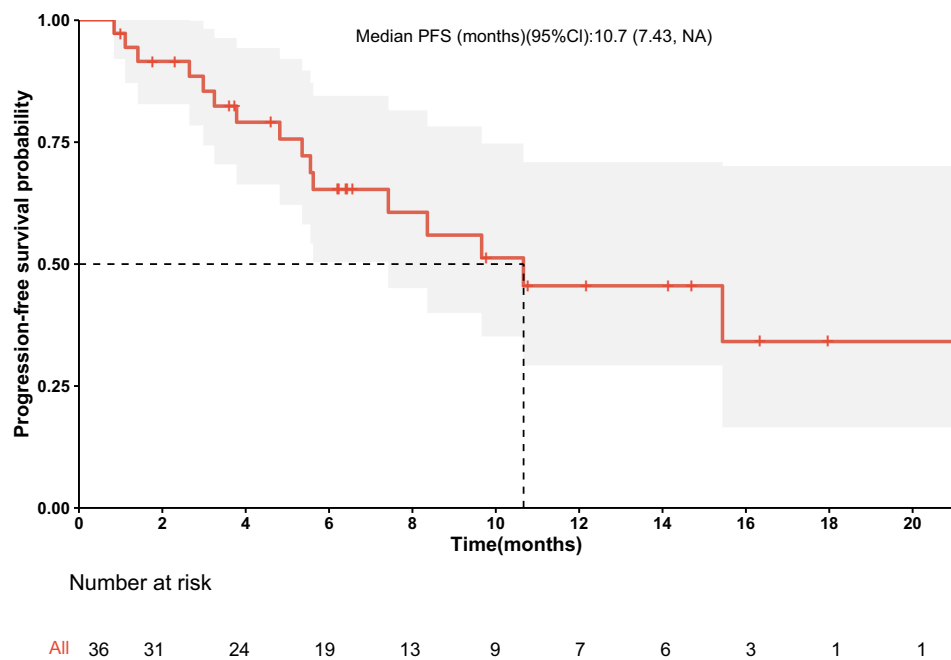
Due to the high malignancy and complexity of liver cancer, its poor prognosis, and its serious impact on human health, there is an urgent need for effective treatment. TACE-based comprehensive treatment is gradually evolving,<sup>23</sup> particularly for patients with BCLC stage B, where the ORR of TACE alone is as high as 50%.<sup>8</sup> However, as the number of TACE



**Figure 2** Best change from baseline in the sum of the target lesion diameter per patient.



**Figure 3** Change from baseline in target lesions.



**Figure 4** Progression-Free survival for all patients.

treatments increases, the effective rate decreases and liver damage occurs, with tumor recurrence and distant metastasis developing in some patients. The application of targeted drugs and immunotherapy has led to significant progress in treatment prospects for HCC. The current treatment trend for advanced HCC is combination therapy. Thus, our study evaluated the efficacy and safety of TACE combined with donafenib with or without immune checkpoint inhibitors for the treatment of advanced liver cancer. The treatment regimens achieved satisfactory tumor remission and good efficacy, with some patients achieving transformation resection, providing further evidence for the treatment of initial unresectable HCC.

At present, there are many different molecular targeted drugs and ICIs available to treat HCC. Many studies have focused on whether different drug combinations can achieve good therapeutic effects and which combination regimen provides greater survival benefits for HCC patients. There are many limitations to using TACE treatment alone. However,

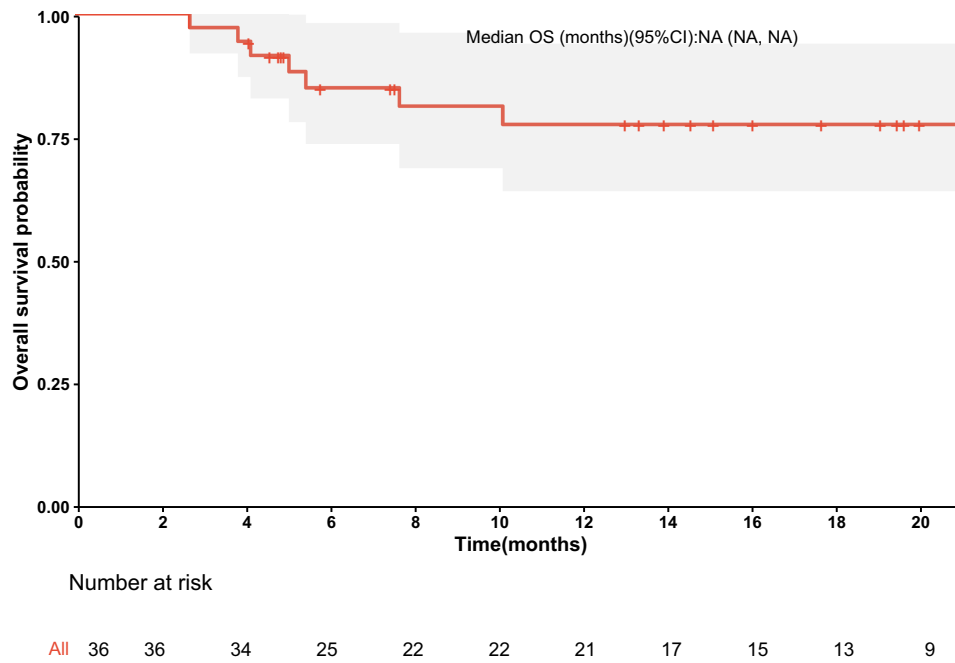


Figure 5 Overall survival for all patients.

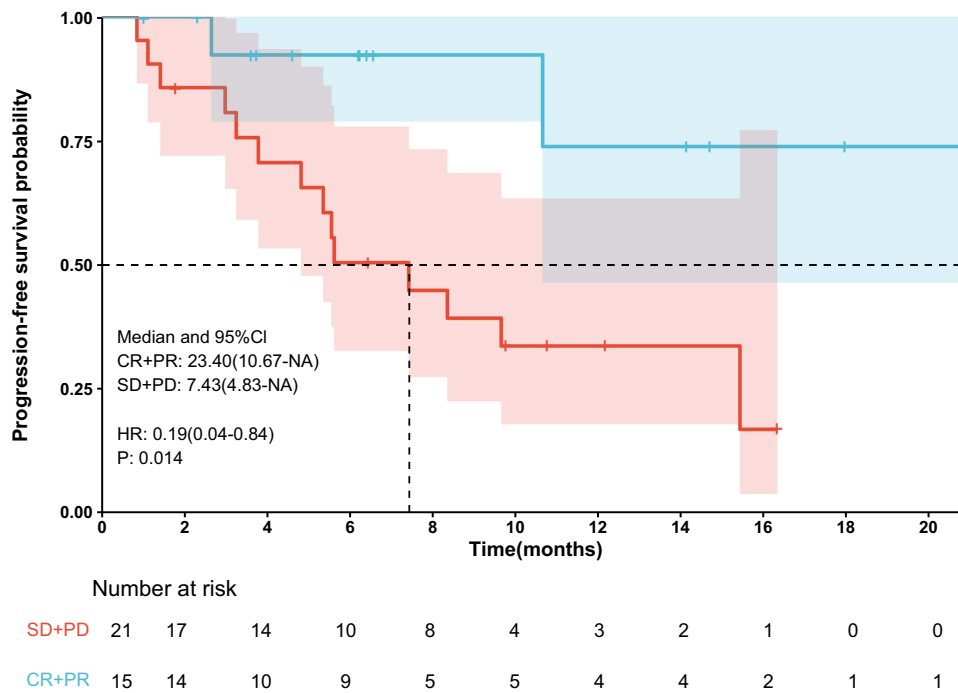


Figure 6 PFS in patients with early tumor response compared with patients with late tumor response (CR+PR vs. SD+PD).

the ORR and DCR of TACE combined with systemic therapy for unresectable HCC ranges from 35–70% and 75%–96%, respectively, which fully shows the synergistic effect between local therapy and systemic therapy, and that combination therapy achieves a higher tumor control rate compared with TACE alone.<sup>24,25</sup> The IMbrave150 study showed that atezolizumab plus bevacizumab achieved an ORR of 27.3% and a median PFS of 6.8 months for HCC.<sup>16</sup> Likewise, the CARES-310 study showed that camrelizumab plus apatinib achieved an ORR of 25.4% and a median PFS of 5.6

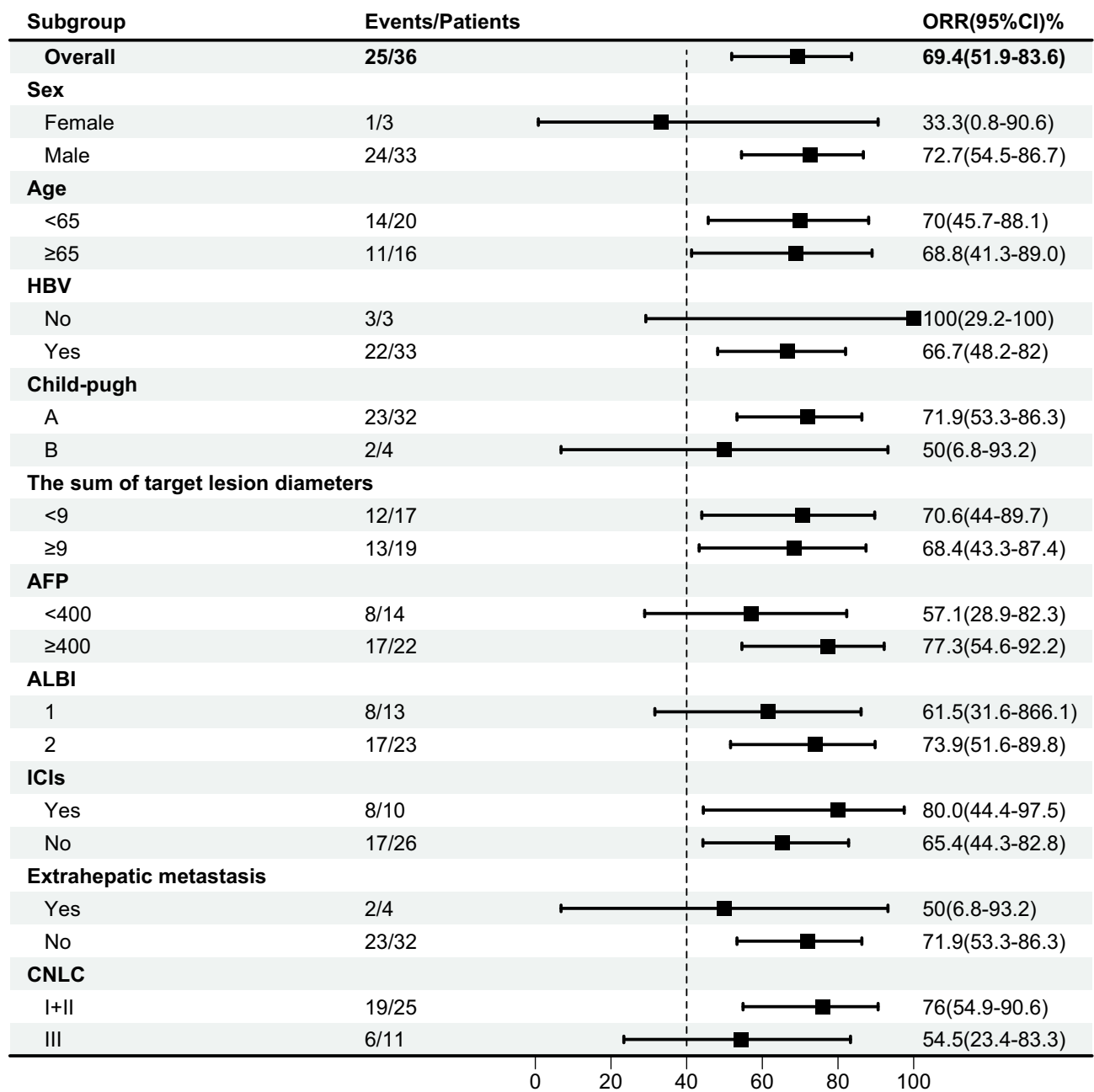


Figure 7 Subgroup analysis of ORR according to baseline characteristics.

months.<sup>26</sup> In our study, TACE combined with donafenib with or without immune checkpoint inhibitors achieved a high ORR (69.4%) and DCR (91.7%). Six patients successfully underwent conversion surgery and achieved R0 resection, and two patients achieved complete pathological remission. Moreover, the therapeutic onset time was short, with a median TTR of 1.4 months. The results also showed a long-term survival benefit, with a median PFS of 10.7 months. The median survival rates at 6, 12, and 18 months were 85.0%, 77.6%, and 71.3%, respectively, exceeding those of most monotherapy and targeted combined immunotherapy. Compared with different combinations of systemic therapies, local therapy combined with systemic therapy appears to further improve efficacy. The basic principle is clear: TACE reduces the tumor burden and activates immunogenic cell death.<sup>27</sup> Similar to sorafenib and other TKIs, donafenib inhibits platelet-derived growth factor receptors and vascular endothelial growth factor receptors and also blocks the RAF/MEK/

**Table 3** Univariate and Multivariate Predictors of PFS

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age, years ( $\geq 65$ vs $< 65$ )	1.47	0.47–4.59	0.511			
Sex (male vs female)	1.37	0.17–10.8	0.766			
Hepatitis B virus (yes vs no)	0.63	0.14–2.95	0.561			
Sum of baseline target lesion diameters ( $< 9$ vs $\geq 9$ cm)	0.19	0.04–0.90	0.037	0.13	0.03–0.68	0.016
Metastasis (yes vs no)	3.70	0.75–18.10	0.107			
Child–Pugh (B vs A)	0.95	0.12–7.63	0.958			
AFP ( $\geq 400$ vs $< 400$ ng/mL)	1.07	0.34–3.41	0.903			
Immune checkpoint inhibitor (yes vs no)	0.263	0.094–0.733	0.011	0.327	0.116–0.922	0.034
Best tumor response (CR+PR vs SD+PD)	0.19	0.04–0.62	0.008	0.09	0.020.48	0.032

**Abbreviations:** HR, Hazard ratio; CI, confidence interval; AFP, alpha-fetoprotein; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

**Table 4** Treatment-Related Adverse Events

Adverse Events	Any Grade		Grades 3 and 4	
	N	%	N	%
Any TRAE	25	69.4%	5	13.9%
Increased ALT	17	47.2%	1	2.8%
Increased AST	18	50.0%	2	5.6%
Increased blood bilirubin	14	38.9%		
Anemia	3	8.3%		
Proteinuria	6	16.7%		
Pain	16	44.4%		
Nausea	13	36.1%		
Fatigue	10	27.7%		
Hypertension	11	30.6%	1	2.8%
Hand and foot syndrome	2	5.6%		
Leukopenia	4	11.1%		
Hypothyroidism	1	2.8%		
Gastrointestinal hemorrhage	1	2.8%		
Immune-related pneumonia	1	2.8%		
Rash	3	8.3%	1	2.8%
Platelet count decreased	15	41.7%	2	5.6%
Ascites	4	11.1%		
Weight loss	2	5.6%		

**Abbreviations:** TRAE, treatment-related adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransaminase.

ERK signaling pathway, leading to vascular normalization.<sup>28</sup> The normalization of tumor vasculature promotes immune cell infiltration of the tumor area and enhances immune killing, further controlling tumor recurrence and metastasis.<sup>29</sup>

Although multimodal treatment may improve the curative effect, the side effects and serious adverse reactions cannot be ignored because they affect patients' quality of life. The quality of life of cancer patients is crucial, particularly because it has been shown to affect long-term prognosis.<sup>30</sup> The REFLECT study reported that clinical responders had a lower risk of exacerbation and higher quality of life scores compared with clinical nonresponders.<sup>31</sup> In our study, TACE combined with donafenib with or without PD-1 did not show new safety signals and was well-tolerated by patients. The combination of multiple treatment modes did not appear to cause any unusual overlapping toxicity, and no grade 4 or 5 TRAEs occurred. The above results were comparable to those previously reported,<sup>32,33</sup> indicating the safety and tolerability of combined TACE treatment.

Our clinical study has certain limitations. First, the sample size is small, so the possibility of bias in the results cannot be ruled out. Second, the follow-up time is relatively short. Third, because this is a single-arm study, there is no control group, and the level of evidence is somewhat poor. Thus, large, multicenter prospective clinical studies are necessary to further verify the efficacy and safety of TACE combined with donafenib with or without immune checkpoint inhibitors in patients with unresectable HCC.

## Conclusion

To summarize, TACE combined with donafenib with or without immune checkpoint inhibitors had a short therapeutic onset time for patients with unresectable HCC, showing high ORR, PFS, and DCR, as well as controllable toxicity. Additionally, treatment resulted in significant narrowing of the tumor feeding artery. Thus, TACE combined with donafenib with or without immune checkpoint inhibitors is a potentially safe and effective first-line treatment for HCC and is worthy of further promotion in clinical practice.

## Abbreviations

AE, Adverse events; BCLC, Barcelona Clinic Liver Cancer; CI, Confidence interval; CR, Complete response; DCR, Disease control rate; ICI, Immune checkpoint inhibitors; ORR, Objective response rate; OS, Overall survival; PD, Progressive disease; PFS, Progression-free survival; PR, Partial response; SD, Stable disease; TKI, Tyrosine kinase inhibitor; TRAE, Treatment-related adverse events; TTR, Time to response.

## Data Sharing Statement

The data that support the findings of this study are available via a data access agreement. Please contact the corresponding author for this request.

## Ethics Approval and Informed Consent

This study was approved by the Medical Ethics Committee of our hospital and registered in the Chinese Clinical Trial Registry (ChiCTR2100054041). All subjects voluntarily enrolled and signed 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 report no conflicts of interest in this work.

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