Journal of Hepatocellular Carcinoma

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Triple Therapy with Interventional Treatment, Donafenib, and Anti-PD-1 Antibodies in Unresectable Hepatocellular Carcinoma: A Retrospective Real-World Study in China

Qiuwen Ye[1,*], Zhengrui Song[1,*], Tingdong Yu[1], Yong Li[1], Liang Ai[1], Guangjun Yang[2], Kun Su[3], Dong Chen[4], Wentao Zhao[5], Rong Ding[6], Yong Zha[1], Gang Li[1]

[1]Department of Hepatobiliary and Pancreatic Surgery, Yunnan Cancer Hospital, Kunming, Yunnan, People's Republic of China; [2]Department of Radiology, Yunnan Cancer Hospital, Kunming, Yunnan, People's Republic of China; [3]Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, People's Republic of China; [4]Department of Ultrasound Medicine, Yunnan Cancer Hospital, Kunming, Yunnan, People's Republic of China; [5]Department of Gastrointestinal Oncology, Yunnan Cancer Hospital, Kunming, Yunnan, People's Republic of China; [6]Department of Minimally Invasive Interventional Therapy, Yunnan Cancer Hospital, Kunming, Yunnan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yong Zha; Gang Li, Department of Hepatobiliary and Pancreatic Surgery, Yunnan Cancer Hospital, No. 519 Kunzhou Road, Xishan District, Kunming, Yunnan, 650031, People's Republic of China, Email zhayong888@sina.com; gangli315@163.com

Background: Unresectable hepatocellular carcinoma (uHCC) remains a major clinical challenge with limited effective therapeutic options. Triple therapy combining interventional treatments, donafenib, and anti-PD-1 monoclonal antibodies has shown promise in recent studies, but real-world data remain limited.

Objective: To evaluate the real-world efficacy and safety of triple therapy with interventional treatment, donafenib, and anti-PD-1 monoclonal antibodies in patients with uHCC.

Methods: This retrospective study included 89 patients with uHCC who received donafenib, anti-PD-1 monoclonal antibodies (tislelizumab or sintilimab), and interventional therapies (TACE and/or HAIC) between March 2022 and December 2023. Outcomes included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. Efficacy was assessed using modified RECIST (mRECIST) criteria; prognostic factors were analyzed using Cox regression models.

Results: Among 89 patients, the ORR was 75.3% and the disease control rate was 100%. The median PFS was 18.5 months (95% CI: 15.0–NA); median OS was not reached after a median follow-up of 13.7 months. PFS rates at 6, 12, and 18 months were 87.6%, 72.4%, and 52.7%, and OS rates were 93.3%, 81.6%, and 72.4%, respectively. Conversion surgery was achieved in 15.7% of patients. Subgroup analysis indicated that ECOG PS 1, extrahepatic metastases, and high baseline AFP were associated with worse survival outcomes, while interventional modality did not significantly affect prognosis. Multivariate analysis confirmed ECOG PS 1 and extrahepatic metastases as independent predictors of shorter PFS, and ECOG PS 1 and elevated AFP as independent predictors of worse OS. Grade ≥3 treatment-related adverse events occurred in 30.3% of patients; no treatment-related deaths were reported.

Conclusion: The combination of interventional therapies, donafenib, and anti-PD-1 monoclonal antibodies demonstrated promising efficacy and manageable safety in uHCC, warranting further validation in prospective trials.

Keywords: hepatocellular carcinoma, donafenib, tyrosine kinase inhibitors, interventional therapies, immune checkpoint inhibitors

Introduction

Hepatocellular carcinoma (HCC) is a leading global health challenge, ranking as the sixth most common cancer and the third leading cause of cancer-related deaths worldwide. In China, the burden of HCC is particularly high, with over 370,000 new cases and 320,000 deaths annually.[1] The majority of patients are diagnosed at advanced stages, precluding

Received: 3 April 2025
Accepted: 9 August 2025
Published: 24 August 2025

surgical resection. Even for those eligible for surgery, the five-year recurrence rate exceeds 60%,[2] underscoring the urgent need for more effective systemic and multimodal therapeutic strategies.

Interventional therapies, such as transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC), remain pivotal in the management of unresectable HCC (uHCC).[3] These techniques leverage the dual blood supply of liver, delivering targeted therapy directly to the tumor while sparing healthy tissue. Although effective in controlling tumor growth, these approaches often yield limited long-term benefits when used as monotherapies, highlighting the importance of combining them with systemic therapies to improve outcomes. Donafenib, a deuterated derivative of sorafenib, represents an important advancement in the systemic treatment of advanced HCC. As a multi-target tyrosine kinase inhibitor (TKI), donafenib inhibits several critical signaling pathways involved in tumor proliferation and angiogenesis, and has demonstrated improved pharmacokinetics, safety, and superior overall survival compared with sorafenib.[4,5] Notably, donafenib is the only molecular targeted drug that has demonstrated superior overall survival (OS) compared to sorafenib in a head-to-head trial.[5]

Recent studies have further established the value of combining locoregional and systemic therapies in advanced HCC. FOLFOX-based HAIC combined with targeted agents such as sorafenib or lenvatinib has been shown to significantly improve response rates, survival outcomes, and surgical conversion rates compared to monotherapy, with objective response rate (ORR) exceeding 40% and conversion rates up to 12.8% for HAIC plus sorafenib.[6,7] Similarly, large randomized trials have demonstrated that TACE combined with targeted agents, including sorafenib or lenvatinib, confers significant benefits in progression-free survival (PFS), OS, and ORR compared to monotherapy.[8,9] Further, triple therapy regimens incorporating HAIC, targeted agents, and immune checkpoint inhibitors (ICIs) have yielded even higher response and conversion rates in retrospective and prospective studies. A retrospective study showed that, compared with lenvatinib monotherapy, the combination of HAIC, lenvatinib, and toripalimab achieved a significantly higher ORR (59.2% vs 9.3%) and a higher surgical conversion rate (12.7% vs 0).[10] Furthermore, Phase II clinical studies reported at ASCO 2022 demonstrated favorable efficacy of such triple regimens: the TRIPLET study of HAIC combined with apatinib and camrelizumab reported an ORR of 70.96%,[11] while another phase II study of HAIC combined with sintilimab and the bevacizumab biosimilar IBI305 in initially unresectable HCC achieved an ORR of 66.7% and a surgical conversion rate of 66.7%.[12]

Despite these encouraging advances, evidence from real-world clinical practice regarding the efficacy and safety of triple therapy combining interventional treatments, donafenib, and anti-PD-1 monoclonal antibodies in patients with unresectable HCC remains limited. Therefore, this study aims to supplement and expand the real-world evidence regarding the use of triple therapy in patients with unresectable HCC in Chinese patients.

Materials and Methods

Study Design

This study was conducted as a retrospective, real-world clinical investigation to evaluate the effectiveness and safety of donafenib combined with anti-PD-1 monoclonal antibodies and interventional surgery as a first-line therapy for patients with unresectable HCC. The study retrospectively included patients who received this combination therapy at Yunnan Cancer hospital between March 2022 and December 2023. This study adheres to the STROBE guidelines for the reporting of observational studies.[13] Ethical approval for this study was obtained from the Ethics committee of Yunnan Cancer hospital (Approval No.: KYLX2025-01) and the need for individual patient consent was waived due to the retrospective nature of the study.

Study Population

Patients were eligible for inclusion if they were between 18 and 80 years of age, irrespective of gender, and had been diagnosed with HCC according to the *2024 Guidelines for Diagnosis and Treatment of Primary Liver Cancer*[14] or via histological or cytological confirmation. Additional inclusion criteria included the presence of unresectable HCC, no prior systemic or local therapy, and at least one measurable lesion defined by the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[15] Patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1, and a Child-Pugh score of ≤8. To

ensure reliable data analysis, only patients with complete baseline data and at least one follow-up evaluation was included. Exclusion criteria were histological confirmation of fibrolamellar or sarcomatoid HCC or cholangiocarcinoma components, a Child-Pugh score >8 after hepatoprotective therapy, or an ECOG PS score ≥2. Patients with severe comorbidities affecting critical organs or systems or incomplete data records were also excluded.

Treatment Procedures

All patients included in this study received the triple therapy regimen consisted of interventional therapy (TACE or HAIC) combined with anti-PD-1 monoclonal antibody (tislelizumab or sintilimab) and donafenib. Donafenib was administered orally at an initial dose of 200 mg twice daily. The choice of interventional regimen (TACE or HAIC) was determined by the treating physician based on each patient's clinical characteristics. The criteria for selecting TACE or HAIC were as follows: (1) HAIC was administered to patients with large, localized tumors or tumors accompanied by surrounding satellite lesions; it was also used as a subsequent local therapy following initial TACE and HAIC sessions, as well as for patients with diffuse hepatocellular carcinoma or those with portal vein tumor thrombus. (2) TACE was chosen for patients with well-demarcated, localized lesions exhibiting a rich arterial blood supply, or for those with multiple tumors adjacent to the liver capsule and a relatively low overall tumor burden but a high risk of tumor rupture. (3) Combined HAIC and TACE was employed in cases where numerous tumors were distributed across different liver lobes with blood supply from multiple arteries. In these situations, TACE was performed on the non-dominant feeding arteries, while HAIC was administered through the dominant feeding artery. The interval between interventional therapy and the initiation of anti-PD-1 monoclonal antibodies plus donafenib did not exceed one month. All treatment decisions were made in accordance with routine clinical practice and were tailored to optimize therapeutic outcomes for each individual patient.

Data Collection and Follow-Up

Data were retrospectively extracted from electronic medical records, including demographic details, clinical history, laboratory test results, imaging findings, and treatment outcomes. Tumor characteristics, including size, number, and vascular invasion, were recorded. Liver function was assessed using the Child-Pugh score, and disease staging was determined according to the BCLC staging system.

Follow-up assessments were conducted every 12 weeks until disease progression, initiation of a new anticancer therapy, withdrawal of consent, loss to follow-up, death, or study termination. Regular assessments included imaging evaluations (CT/MRI), laboratory tests and ECOG PS scoring. Safety follow-up included monitoring adverse events (AEs) and serious adverse events (SAEs) for up to 30 days after the last dose or until initiation of new therapy, with continued monitoring for unresolved events.

Outcomes

The primary endpoint was the objective response rate (ORR), defined as the proportion of patients achieving a complete response (CR) or partial response (PR) according to mRECIST criteria. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and disease control rate (DCR; including CR, PR, and stable disease [SD]). Progression-free survival was defined as the time from initiation of combination therapy to documented disease progression or death. Patients lost to follow-up without confirmed radiological progression or death were censored at the date of last follow-up with no evidence of progression. Patients who were alive without tumor progression at the data cutoff date were censored at the date of the last imaging assessment. Overall survival was defined as the time from initiation of combination therapy to death from any cause; patients still alive at the data cutoff were censored at their last known follow-up. Safety was evaluated based on the incidence and severity of treatment-emergent adverse events (TEAEs), which were documented and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

Descriptive statistics were used to summarize baseline demographic and clinical characteristics. Continuous variables, such as age, were described as means, medians, and standard deviations, while categorical variables were reported as frequencies and percentages. Survival analyses were conducted using the Kaplan-Meier method, with differences analyzed using the Log rank test. All variables with $p < 0.2$ during univariate analyses were included in multivariate analyses, which included a Cox regression analysis to identify factors independently associated with PFS and OS. The proportional hazards assumption was verified using Schoenfeld residuals andglobal tests. The missing data in this study were missing at random, attributable to loss to follow-up. All statistical tests were two-sided, with a significance level set at 0.05. Safety analyses were descriptive, focusing on the type, incidence, and severity of adverse events during the treatment period.

Results

Patient Characteristics

Between March 2022 and December 2023, 171 patients with advanced HCC were screened. A total of 82 patients were excluded due to prior alternative therapies, poor adherence, or incomplete data, resulting in 89 patients with uHCC being included in the final analysis (Figure 1). The median age of the cohort was 56 years (range, 34–79 years), and 87.6% were male. Most patients were classified as Barcelona Clinic Liver Cancer (BCLC) stage C (51.7%) or stage B (34.8%). The majority of patients (91.0%) had a Child-Pugh class A liver function, and 75.3% had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0. Hepatitis B virus (HBV) infection was the predominant etiology, accounting for 83.1% of cases. Notably, 52.8% of patients presented with more than three lesions, and 82.0% had tumors with a maximum diameter greater than 5 cm. Extrahepatic metastases were observed in 11.2% of patients (Table 1). Among them, 88 patients were treated with tislelizumab and 1 patient with sintilimab. Regarding interventional modalities, 10 patients underwent hepatic arterial infusion chemotherapy (HAIC), 42 received transarterial chemoembolization (TACE), and 37 were treated with a combination of TACE and HAIC.

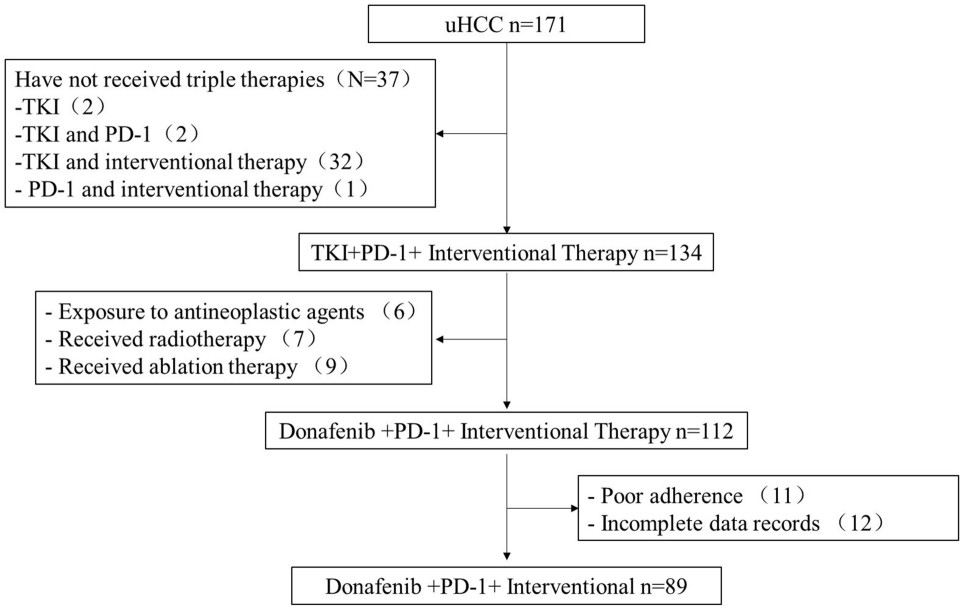

Figure 1 Flowchart of patients selection. Poor adherence: the anti-PD-1 monoclonal antibody was used for less than two times or was not followed up regularly.

Table 1 Patient Demographics and Baseline Characteristics

Characteristics	Patients (N=89)
Age (years), median (min-max)	56 (34–79)
Sex, n (%)	
Male	78 (87.6%)
Female	11 (12.4%)
BCLC staging, n (%)	
A	12 (13.5%)
B	31 (34.8%)
C	46 (51.7%)
CNLC staging, n (%)	
Ia	2 (2.2%)
Ib	10 (11.2%)
IIa	9 (10.1%)
IIb	22 (24.7%)
IIIa	36 (40.4%)
IIIb	10 (11.2%)
Chlid-pugh score, n (%)	
A	81 (91.0%)
B	8 (9.0%)
ECOG PS score, n (%)	
0	67 (75.3%)
1	22 (24.7%)
Etiology, n (%)	
HBV	74 (83.1%)
HCV	3 (3.4%)
Others	12 (13.5%)
Tumor number, n (%)	
1	28 (31.5%)
2	10 (11.2%)
3	4 (4.5%)
>3	47 (52.8%)
Maximum tumor size (mm), n (%)	
≤5cm	16 (18.0%)
>5cm	73 (82.0%)
AFP, n (%)	
<400	46 (51.7%)
≥400	43 (48.3%)
Tumor thrombus, n (%)	
Yes	41 (46.1%)
No	48 (53.9%)
Extrahepatic metastasis, n (%)	
Yes	10 (11.2%)
No	79 (88.8%)
Anti-PD-1 monoclonal antibodies, n (%)	
Tislelizumab	88(98.9%)
Sintilimab	1(1.1%)
Interventional therapy	
TACE	42(47.2%)
HAIC	10(11.2%)
TACE and HAIC	37(41.6%)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging system; CNLC, China Liver Cancer staging system; Child-Pugh, Child-Pugh Score for liver function assessment; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; AFP, Alpha-Fetoprotein. TACE, transarterial chemoembolization; HAIC, Hepatic Arterial Infusion Chemotherapy.

https://doi.org/10.2147/JHC.S532120

Treatment Efficacy

The combination therapy demonstrated substantial efficacy. The best overall response (BOR) rates were as follows: complete response (CR) in 14.6% of patients, partial response (PR) in 60.7%, and stable disease (SD) in 24.7%, leading to an ORR of 75.3% and a disease control rate (DCR) of 100% (Figure 2). The median time to response (TTR) was 2.3 months (95% CI: 2.0–3.2), and the median time to progression (TTP) was 12.0 months (95% CI: 10.9–13.9). The median duration of response (DOR) was 11.1 months (95% CI: 9.1–11.7). Additionally, 15.7% of patients underwent successful conversion surgery, with 57.1% achieving a major pathological response (MPR) and 40.0% achieving a pathological complete response (pCR) (Table 2).

Subgroup analyses revealed significant variations in the objective response rate (ORR) among different clinical and tumor-related characteristics (Figure 3). Patients with an ECOG PS of 0 exhibited a significantly higher ORR of 83.4% (95% CI: 72.5–91.5) compared to 50.0% (95% CI: 28.2–71.7) in those with a PS of 1 ($\chi^2 = 10.037$, $P = 0.002$). Similarly, the BCLC stage significantly influenced ORR, with patients in stages A or B achieving 88.4% (95% CI: 74.9–96.1) compared to 63.0% (95% CI: 47.5–76.8) in stage C ($\chi^2 = 7.662$, $P = 0.006$). Baseline alpha-fetoprotein (AFP) levels were also predictive of response, as patients with AFP ≤400 μg/mL demonstrated an ORR of 84.7% (95% CI: 71.1–93.7), which was significantly higher than the 69.2% (95% CI: 49.4–79.0) observed in those with AFP >400 μg/mL ($\chi^2 = 4.619$, $P = 0.032$). The presence or absence of tumor thrombus further impacted ORR. Patients without tumor thrombus achieved an ORR of 85.4% (95% CI: 72.2–93.9), whereas those with tumor thrombus had a lower ORR of 63.4% (95% CI: 46.7–77.9) ($\chi^2 = 5.752$, $P = 0.016$). Additionally, extrahepatic metastases were associated with significantly lower efficacy, as patients without metastases had an ORR of 79.7% (95% CI: 62.9–88.0), compared to 40.0% (95% CI: 12.1–73.8) in those with metastases ($\chi^2 = 5.551$, $P = 0.018$). In contrast, no significant differences in ORR were observed when stratified by sex, age, HBV infection status, Child-Pugh grade, number of target lesions, or the maximum diameter of target lesions ($P > 0.05$ for all). These findings suggest that clinical characteristics such as ECOG PS of 0, BCLC stage A or B, AFP ≤400 μg/mL, and absence of tumor thrombus or extrahepatic metastases are strong predictors of superior therapeutic response in patients with unresectable HCC.

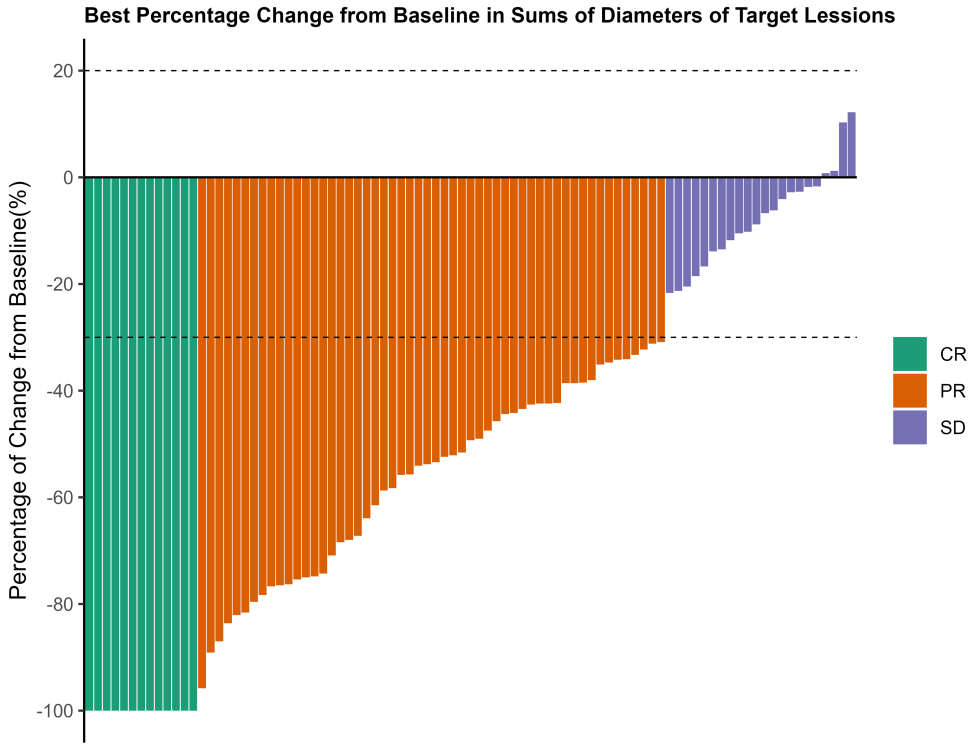

Figure 2 Best Percentage Change from Baseline in the Sum of Diameters of Target Lesions This waterfall plot illustrates the best percentage change from baseline in the sum of diameters of target lesions among evaluable patients treated with the study regimen. Bars are color-coded to indicate the best overall response: complete response (CR, green), partial response (PR, Orange), and stable disease (SD, purple). The dashed lines at −30% and +20% denote the thresholds for partial response (PR) and progressive disease (PD), respectively, as defined by RECIST criteria. Negative values represent tumor shrinkage, while positive values reflect tumor growth.

Table 2 Treatment Efficacy Outcomes of Patients

Treatment Efficacy	N (89)
BOR, n (%)	
CR	13 (14.6%)
PR	54 (60.7%)
SD	22 (24.7%)
ORR, n (%)	67 (75.3%)
DCR, n (%)	89 (100%)
TTR/ month, median (95% CI)	2.3 (2.0–3.2)
TTP/ month, median (95% CI)	12.0 (10.9–13.9)
DOR/ month, median (95% CI)	11.1 (9.1–11.7)
Conversion rate, n (%)	14 (15.7%)
MPR, n (%)	8 (57.1%)
pCR, n (%)	6 (40.0%)

Abbreviations: BOR, Best Overall Response; CR, Complete Response; PR, Partial Response; SD, Stable Disease; ORR, Objective Response Rate; DCR, Disease Control Rate; TTR, Time to Response; TTP, Time to Progression; DOR, Duration of Response; MPR, Major Pathological Response; pCR, Pathological Complete Response.

Long-Term Survival outcomes

The median follow-up duration was 13.7 months (range: 3.6–27.5). The median PFS was 18.5 months (95% CI: 15.0–NA), while the median overall survival (OS) had not yet been reached. The PFS rates at 6, 12, and 18 months were 87.6%, 72.4%, and 52.7%, respectively, and the corresponding OS rates were 93.3%, 81.6%, and 72.4% (Figure 4). Univariate survival analyses using Kaplan-Meier curves and Log rank tests revealed that several clinical factors were significantly associated with survival outcomes. As shown in Supplementary Figure 1, patients with ECOG PS 1 had significantly worse OS than those with ECOG PS 0 (P = 0.0055), and patients with baseline AFP ≥400 ng/mL also had worse OS than those with AFP <400 ng/mL (P = 0.0012). Supplementary Figure 2 further demonstrated that PFS was significantly shorter in patients with ECOG PS 1 compared to those with ECOG PS 0 (P = 0.024), and in patients with extrahepatic metastases compared to those without (P = 0.044). The detrimental effect of ECOG PS 1 and elevated AFP on OS was consistently observed across analyses. Importantly, as shown in Supplementary Figure 3, there were no statistically significant differences in PFS or OS among patients who received different interventional modalities (TACE, HAIC, or the combination of TACE and HAIC). The median PFS was 13.0 months for HAIC, not reached for TACE, and 15.0 months for the combination group (P = 0.16). The median OS was 16.3 months for HAIC, not reached for TACE, and not reached for the combination group (P = 0.063).

Prognostic Factors

The proportional hazards assumption was satisfied for all covariates (Supplementary Tables 1 and 2), and visual inspection of Schoenfeld residual plots confirmed no systematic deviation from proportionality over time (Supplementary Figures 4 and 5). In univariate Cox regression analysis, several factors were found to be significantly associated with poorer PFS, including a higher number of target lesions (>3 vs ≤3; HR: 2.06, 95% CI: 1.03–4.13, P = 0.041), ECOG performance status (PS) of 1 versus 0 (HR: 2.19, 95% CI: 1.09–4.42, P = 0.028), and the presence of extrahepatic metastases (HR: 2.41, 95% CI: 1.00–5.83, P = 0.051). For overall survival (OS), univariate analysis showed that a higher number of target lesions (>3; HR: 2.58, 95% CI: 1.00–6.65, P = 0.05), ECOG PS of 1 (HR: 3.23, 95% CI: 1.35–7.72, P = 0.008), the presence of extrahepatic metastases (HR: 3.32, 95% CI: 1.20–9.15, P = 0.02), and baseline AFP ≥400 ng/mL (HR: 4.62, 95% CI: 1.67–12.77, P = 0.003) were associated with worse outcomes (Table 3).

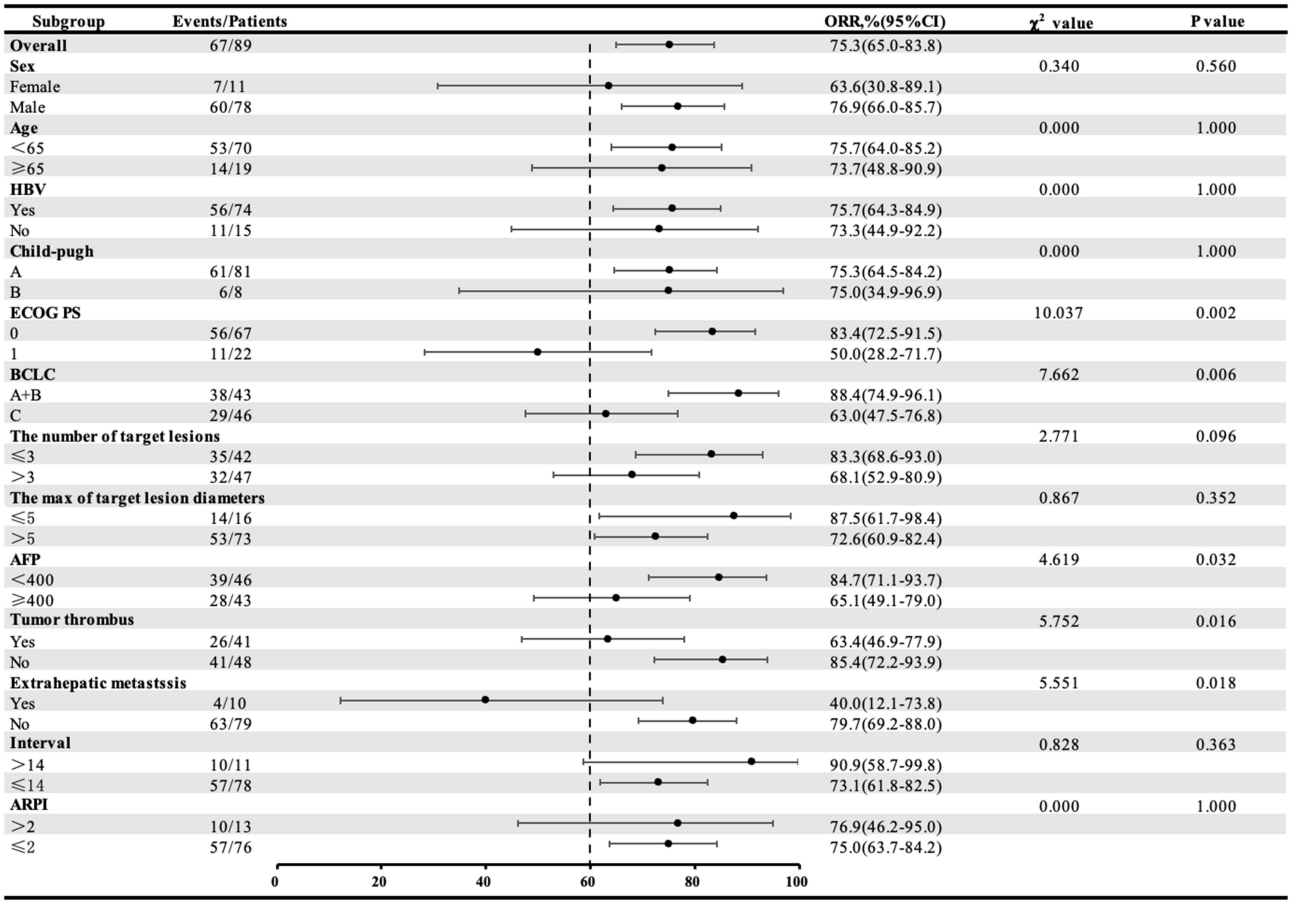

Figure 3 Subgroup Analysis of Objective Response Rate (ORR). Forest plot summarizing the subgroup characteristics analysis of objective response rate (ORR) in patients treated with triple therapy. Subgroups include sex, age, hepatitis B virus (HBV) infection status, Child-Pugh classification, Eastern Cooperative Oncology Group (ECOG) performance status (PS), Barcelona Clinic Liver Cancer (BCLC) stage, number of target lesions, maximum diameter of target lesions, baseline alpha-fetoprotein (AFP) levels, presence of tumor vascular invasion, extrahepatic metastases, and interval from diagnosis to treatment. Significant differences in ORR were observed in subgroups stratified by ECOG PS, BCLC stage, AFP levels, tumor vascular invasion, and extrahepatic metastases ($P < 0.05$). Data are presented as ORR percentages with 95% confidence intervals.

In multivariate Cox regression analysis, ECOG PS of 1 (HR: 2.51, 95% CI: 1.14–5.51, P = 0.022) and the presence of extrahepatic metastases (HR: 2.66, 95% CI: 1.04–6.79, P = 0.04) remained independent prognostic factors for shorter PFS. For OS, ECOG PS of 1 (HR: 2.78, 95% CI: 1.08–7.17, P = 0.034) and baseline AFP ≥400 ng/mL (HR: 5.21, 95% CI: 1.81–14.98, P = 0.002) were identified as independent predictors of poorer survival (Table 3). Although extrahepatic metastases and the number of target lesions were significant in univariate analysis for OS, they did not retain significance in the multivariate model. These findings highlight the prognostic value of baseline performance status, tumor burden, and AFP level in patients with unresectable HCC treated with triple therapy.

Safety

TEAEs occurred in 97.8% of patients, with 30.3% experiencing grade 3 or higher TEAEs. The most common TEAEs (≥10%) included elevated alanine aminotransferase (50.6%), hand-foot skin reaction (49.4%), elevated aspartate aminotransferase (47.2%), hyperbilirubinemia (44.9%), thrombocytopenia (37.1%), diarrhea (21.3%), rash (12.4%), and leukocytosis (11.2%). Severe TEAEs (≥3 grade) included thrombocytopenia (7.9%), elevated aspartate transaminase AST (6.7%), hyperbilirubinemia (5.6%), rash (5.6%), hand-foot skin reaction (4.5%), and elevated alanine transaminase (ALT) (3.4%). No treatment-related deaths or grade 5 events were reported (Table 4).

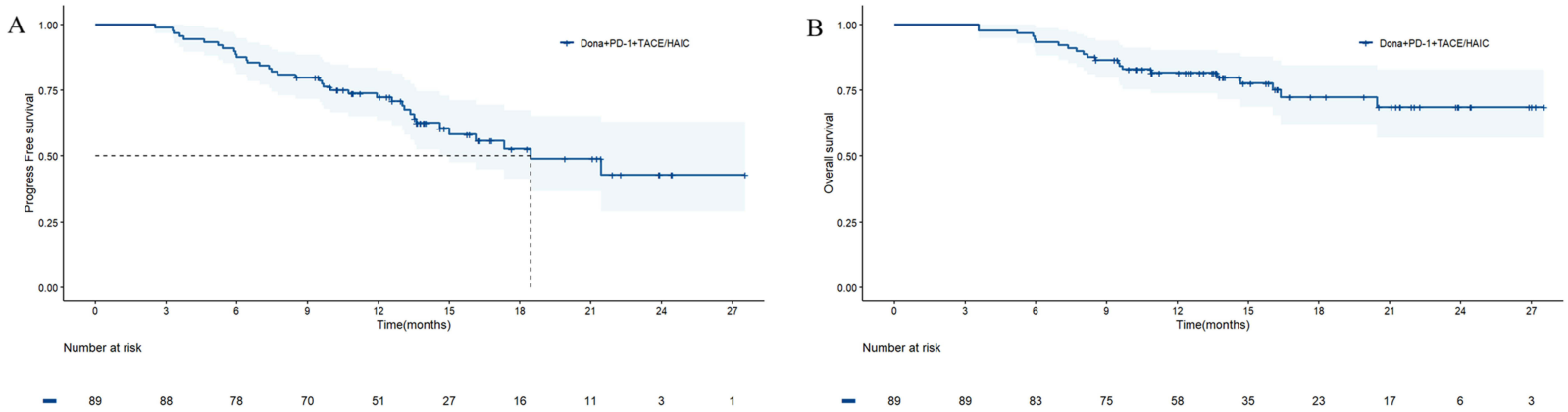

Figure 4 Kaplan-Meier Curves for Progression-Free Survival (PFS) and Overall Survival (OS). (**A**) The Kaplan-Meier curve illustrates the progression-free survival (PFS) of patients treated with the combination therapy of donafenib, Anti-PD-1 monoclonal antibodies, and TACE/HAIC. The median PFS was 18.5 months (95% CI: 15.0–NA). (**B**) The Kaplan-Meier curve shows the overall survival (OS) of the same cohort. The median OS was not reached during the follow-up period. Shaded areas represent 95% confidence intervals. The number at risk is shown below each time point.

https://doi.org/10.2147/JHC.S532120

Table 3 Univariate and Multivariate Regression Analysis of Progression-Free Survival (PFS) and Overall Survival (OS)

Variable	PFS				OS			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	p_value	HR (95% CI)	p_value	HR (95% CI)	p_value	HR (95% CI)	p_value
Age	0.47 (0.18–1.20)	0.114	0.41 (0.15–1.14)	0.087	0.56 (0.17–1.92)	0.359		
The number of target lesions(>3 vs.≤3)	2.06(1.03–4.13)	0.041	1.49 (0.69–3.21)	0.309	2.58 (1.00–6.65)	0.05	2.02 (0.71–5.72)	0.186
The max of target lesions diameters(>5 vs.≤5cm)	0.75(0.34–1.65)	0.471			1.41 (0.41–4.78)	0.583		
The sum of target lesions diameters(>9 vs.≤9cm)	1.05(0.54–2.04)	0.892			2.03 (0.79–5.24)	0.144	1.16 (0.42–3.17)	0.775
Tumor thrombus (yes vs.no)	0.98(0.51–1.89)	0.946			1.66 (0.70–3.95)	0.249		
Metastasis (yes vs.no)	2.41(1.00–5.83)	0.051	2.66 (1.04–6.79)	0.04	3.32 (1.20–9.15)	0.02	2.77 (0.97–7.96)	0.058
Child-pugh (B vs A)	0.75(0.23–2.44)	0.629			0.51 (0.07–3.81)	0.512		
ECOG PS (1 vs.0)	2.19(1.09–4.42)	0.028	2.51 (1.14–5.51)	0.022	3.23 (1.35–7.72)	0.008	2.78 (1.08–7.17)	0.034
AFP (≥400 vs <400ng/mL)	1.79(0.93–3.48)	0.084	1.75 (0.87–3.52)	0.115	4.62 (1.67–12.77)	0.003	5.21 (1.81–14.98)	0.002
The interval between first systematic treatment and first interventional surgery (≤14 vs.>14d)	1.66(0.58–4.72)	0.343			1.73 (0.40–7.50)	0.461		

Notes: Variables showing statistical significance at $p < 0.2$ in univariate analysis were entered intothe multivariate analysis model.

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; PFS, Progression-Free Survival; OS, Overall Survival; BCLC, Barcelona Clinic Liver Cancer staging system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, Hepatitis B Virus; AFP, Alpha-Fetoprotein.

https://doi.org/10.2147/JHC.S532120

Table 4 Incidence of Treatment-Emergent Adverse Events (TEAEs)

TEAE	All Grades	≥ Grade 3
At least one TEAE	87 (97.8%)	27 (30.3%)
Elevated ALT	45 (50.6%)	3 (3.4%)
Hand-foot skin reaction	44 (49.4%)	4 (4.5%)
Elevated AST	42 (47.2%)	6 (6.7%)
Elevated total bilirubin	40 (44.9%)	5 (5.6%)
Decreased platelet count	33 (37.1%)	7 (7.9%)
Diarrhea	19 (21.3%)	2 (2.2%)
Rash	11 (12.4%)	5 (5.6%)
Increased WBC count	10 (11.2%)	1 (1.1%)
Hypertension	5 (5.6%)	1 (1.1%)
Anorexia	5 (5.6%)	0
Fatigue	4 (4.5%)	0
Periodontitis	3 (3.4%)	0
Oral mucositis	2 (2.2%)	0
Weight loss	2 (2.2%)	0
Acute kidney injury	1 (1.1%)	1 (1.1%)
Stroke	1 (1.1%)	1 (1.1%)
Gastrointestinal bleeding	1 (1.1%)	1 (1.1%)
Limb edema	1 (1.1%)	0
Abdominal distension	1 (1.1%)	0
Abdominal pain	1 (1.1%)	0
Stomach bloating	1 (1.1%)	0
Gastrointestinal pain	1 (1.1%)	0

Notes: Adverse events are presented as the number and incidence.
Abbreviations: TEAE, Treatment-Emergent Adverse Event; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; WBC, White Blood Cell.

Discussion

In this real-world retrospective study, triple therapy with interventional treatment, donafenib, and anti-PD-1 monoclonal antibodies demonstrated notable efficacy and safety in patients with uHCC. The ORR was 75.3% and DCR reached 100%. Median PFS was 18.5 months, while median OS was not reached after a median follow-up of 13.7 months. Conversion surgery was achieved in 15.7% of patients, with most resected cases showing major or complete pathological response. Grade ≥3 TRAEs occurred in 30.3% of patients, with no treatment-related deaths. These findings suggest that triple therapy can achieve sustained tumor control and provide surgical opportunities for a subset of patients with advanced HCC in real-world clinical practice.

This study's findings are consistent with prior research demonstrating the efficacy of triple therapies involving TACE, TKIs, and ICIs in uHCC. The observed ORR of 75.3% and DCR of 100% align closely with Shang et al, who reported an

ORR of 70.5% and a DCR of 95.1% in a multicenter study using TACE, donafenib, and ICIs.[16] Similarly, Li et al demonstrated the benefit of adding ICIs to systemic therapies, with their TACE+donafenib+PD-1 inhibitors (TACE+DP) group achieving an ORR of 50.6%, significantly higher than the 41.4% observed in the TACE+donafenib (TACE+D) group.[17] In terms of survival outcomes, this study observed a median PFS of 18.5 months, which significantly exceeds the 12.7 months reported by Shang et al and the 10.6 months achieved in Li et al's TACE+DP group.[16,17] This may be attributed to a greater proportion of patients with Child-Pugh A liver function and ECOG PS 0, earlier tumor stage, and fewer with extrahepatic metastasis or elevated AFP. Individualized multidisciplinary management may have also contributed to these favorable results. Conversion surgery remains a critical endpoint for evaluating the potential curative impact of triple therapies. In this study, 15.7% of patients underwent conversion surgery, a rate slightly lower than the 19.7% reported by Shang et al.[16] However, the pCR rate of 40% among resected patients in this study demonstrates effective tumor cytoreduction. Recent research using HAIC-based regimens reported conversion rates ranging from 12.8% to 38.9%, depending on the systemic agents used. For example, in a real-world study of lenvatinib, tislelizumab, and HAIC, the ORR reached 94.4%, with a conversion rate of 38.9%.[18,19]

Other recent studies provide additional context for evaluating triple therapy strategies. Wu et al reported an ORR of 76.4% and a conversion rate of 52.7% with lenvatinib, camrelizumab, and TACE in a multicenter prospective study, highlighting the versatility of triple therapy regimens across different systemic agents.[20] Zhang et al observed an ORR of 53.6% and a PFS of 8.9 months with lenvatinib and Anti-PD-1 monoclonal antibodies alone, emphasizing the added value of integrating TACE to achieve higher response rates and extended survival outcomes.[21] Furthermore, Qi et al, focusing on an adjuvant setting with donafenib, TACE, and tislelizumab, reported favorable results in reducing recurrence risk in high-risk patients following resection, further underscoring the utility of triple therapy across various disease stages.[22] The safety profile observed in this study aligns with findings from related research. TEAEs ≥ Grade 3 occurred in 30.3% of patients, lower than the 36.1% reported by Shang et al and comparable to the 33.8% in Li et al's TACE+DP group.[16,17] The absence of Grade 5 TEAEs in this study further supports the tolerability of triple therapy regimens, comparable to that observed in recent trials such as LAUNCH, where lenvatinib combined with TACE also demonstrated an acceptable safety profile alongside significant survival benefits.[9]

The triple therapy used in this study combines TACE, donafenib, and anti-PD-1 antibodies to integrate locoregional and systemic approaches for synergistic treatment of HCC. TACE induces tumor necrosis and immunogenic cell death, which enhances antigen presentation and immune activation.[23] Donafenib inhibits VEGF signaling, resulting in vascular normalization, improved immune cell infiltration, and reduced recruitment of immunosuppressive cells.[24,25] Anti-PD-1 antibodies restore T-cell function by blocking the PD-1/PD-L1 pathway.[26] The inhibition of VEGF further enhances anti-tumor immunity and works synergistically with PD-1 blockade, while TACE-induced hypoxia upregulates VEGF and PD-L1 expression, providing a mechanistic basis for this combination.[27–29] Overall, these three modalities complement each other at both local and systemic levels.

Multivariate analysis in our study demonstrated that ECOG PS 1, extrahepatic metastasis, and elevated baseline AFP (>400 ng/mL) were independent adverse prognostic factors for both PFS and OS among patients with unresectable HCC receiving triple therapy. This aligns with recent large-scale studies and prognostic models in this field. For example, multiple retrospective and multicenter studies have consistently found that patients with impaired performance status, the presence of extrahepatic spread, or high baseline AFP have significantly worse survival outcomes after triple or combination therapies.[30–32] Elevated AFP is recognized as a marker of aggressive tumor biology, while extrahepatic metastasis reflects advanced disease burden and is repeatedly associated with reduced benefit from locoregional and systemic therapies. Similarly, an ECOG PS above 0 indicates decreased functional reserve, which is linked to both lower treatment tolerance and poorer prognosis. These findings reinforce the importance of comprehensive risk assessment before initiating triple therapy, and suggest that individualized treatment strategies and more intensive monitoring may be needed for patients with these high-risk features in clinical practice.

In real-world clinical practice, patients with unresectable HCC often present with heterogeneous tumor burdens, necessitating individualized selection of local treatment modalities (such as TACE or HAIC) based on comprehensive clinical assessment. In this study, different interventional approaches (TACE, HAIC, or their combination) were employed, which may have introduced variability in the treatment procedures. However, subgroup analysis revealed no significant differences in treatment efficacy among the different interventional modalities (TACE vs HAIC vs TACE

combined with HAIC) ($P > 0.05$; see Supplementary Figure 3). Therefore, despite variations in interventional approaches, the choice of local treatment modality did not appear to affect efficacy outcomes in this cohort.

This study has several limitations that should be acknowledged. First, as a retrospective analysis without a control arm, it is subject to inherent biases, including potential selection bias in patient inclusion, which may limit the generalizability of the findings. Importantly, the absence of a comparator arm (such as TACE plus TKI or TKI plus ICI) precludes direct comparison of efficacy and safety outcomes with other commonly used treatment regimens. As a result, it is not possible to determine whether the observed outcomes are superior to those of alternative therapeutic strategies, and efficacy claims should therefore be interpreted with caution. Second, the relatively small sample size might influence the robustness of the observed outcomes. Third, the current follow-up duration may not be sufficient to fully assess long-term efficacy and safety trends. Ongoing follow-up will be conducted to provide more comprehensive data on long-term efficacy and survival in the future. While the promising efficacy and safety profiles of the triple therapy were demonstrated, larger randomized controlled trials are needed to validate these findings and establish the definitive role of this approach in the management of unresectable HCC. Furthermore, the identification and validation of predictive biomarkers could refine patient selection and guide individualized treatment strategies, ultimately improving therapeutic outcomes and minimizing unnecessary toxicities. Future research should focus on addressing these gaps to optimize the clinical utility of this promising therapeutic approach.

Conclusion

This real-world study demonstrates that triple therapy with interventional treatment, donafenib, and anti-PD-1 antibodies achieves high response rates, favorable survival, and manageable safety in unresectable HCC. ECOG PS 1, extrahepatic metastasis, and elevated AFP independently predict poorer outcomes. These findings warrant further investigation to confirm the clinical utility of this approach and its potential role in future treatment strategies.

Data Sharing Statement

The datasets used and analyzed in this study are available from the corresponding author upon request.

Ethics Approval and Informed Consent

The study was approved by the Ethics committee of Yunnan Cancer hospital (Approval No.: KYLX2025-01) and complied with the Declaration of Helsinki 1975. Informed consent was waived due to the retrospective nature of the study, with assurance that data was either anonymized or kept confidential.

Funding

This study was funded by Yunnan Provincial Science and Technology Department Basic Research Special Project - General Program (Grant No.: 202301AY070001-096); Yunnan Provincial Science and Technology Department - Kunming Medical University Joint Special Project - General Program (Grant No.: 202501AT070128); Yunnan Province Science and Technology Talents and Platform Plan Project (Grant No.: 202305AF150067); The Scientific and technological innovation team building program of Yunnan Provincial Education Department (Grant No.: K1322149); and Yunnan Province Talent Support Program (Grant No.: CZ0096-901264).

Disclosure

The authors declare that there is no conflict of interest in this work.

References

1. Bray F, Laversanne M, Sung H. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca Cancer J Clin*. 2024;74:229–263. doi:10.3322/caac.21834
2. Akateh C, Black SM, Conteh L, et al. Neoadjuvant and adjuvant treatment strategies for hepatocellular carcinoma. *World J Gastroenterol*. 2019;25:3704–3721. doi:10.3748/wjg.v25.i28.3704
3. Si T, Huang Z, Khorsandi SE, Ma Y, Heaton N. Hepatic arterial infusion chemotherapy versus transarterial chemoembolization for unresectable hepatocellular carcinoma: a systematic review with meta-analysis. *Front Bioeng Biotechnol*. 2022;10:1010824. doi:10.3389/fbioe.2022.1010824
4. Keam SJ, Duggan S. Donafenib: first approval. *Drugs*. 2021;81:1915–1920. doi:10.1007/s40265-021-01603-0

5. Qin S, Bi F, Gu S. Donafenib versus sorafenib in first-line treatment of unresectable or metastatic hepatocellular carcinoma: a randomized, open-label, parallel-controlled Phase II-III trial. *J Clin Oncol*. 2021;39:3002–3011. doi:10.1200/JCO.21.00163
6. He M, Li Q, Zou R, et al. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin vs sorafenib alone for hepatocellular carcinoma with portal vein invasion: a randomized clinical trial. *JAMA Oncol*. 2019;5:953–960. doi:10.1001/jamaoncol.2019.0250
7. Zheng K, Zhu X, Fu S, Cao G, Li WQ. sorafenib plus hepatic arterial infusion chemotherapy versus sorafenib for hepatocellular carcinoma with major portal vein tumor thrombosis: a randomized trial. *Radiology*. 2022;303:455–464. doi:10.1148/radiol.211545
8. Kudo M, Ueshima K, Ikeda M, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut*. 2020;69:1492–1501. doi:10.1136/gutjnl-2019-318934
9. Peng Z, Fan W, Zhu B. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: a phase III, randomized clinical trial (LAUNCH). *J Clin Oncol*. 2023;41:117–127. doi:10.1200/JCO.22.00392
10. He MK, Liang RB, Zhao Y, et al. Lenvatinib, toripalimab, plus hepatic arterial infusion chemotherapy versus lenvatinib alone for advanced hepatocellular carcinoma. *Therapeut Adv Med Oncol*. 2021;13:17588359211002720. doi:10.1177/17588359211002720
11. Zhang TQ, Geng ZJ, Zuo MX, Li JB. Camrelizumab (a PD-1 inhibitor) plus apatinib (an VEGFR-2 inhibitor) and hepatic artery infusion chemotherapy for hepatocellular carcinoma in Barcelona Clinic Liver Cancer stage C (TRIPLET): a phase II study. *Signal Trans a Targeted Ther*. 2023;8:413. doi:10.1038/s41392-023-01663-6
12. Liu D, Mu H, Liu C, et al. Hepatic artery infusion chemotherapy (HAIC) combined with sintilimab and bevacizumab biosimilar (IBI305) for initial unresectable hepatocellular carcinoma (HCC): a prospective, single-arm phase II trial. *J clin oncol*. 2022;40:4073. doi:10.1200/JCO.2022.40.16_suppl.4073
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–1457. doi:10.1016/S0140-6736(07)61602-X
14. Department of Medical Administration, National Health Commission of the People's Republic of China. Guidelines for diagnosis and treatment of primary liver cancer (2024 edition). *Chin J Gen Surg*. 2024;33:475–530 doi:10.7659/j.issn.1005-6947.2024.04.001.
15. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Seminars in liver disease. *Seminars Liver Dis*. 2010;30:52–60. doi:10.1055/s-0030-1247132
16. Shang C, Zhong J, Luo X, et al. Efficacy and safety of transarterial therapy combined with donafenib plus immune checkpoint inhibitors for unresectable hepatocellular carcinoma: a multicenter retrospective study. *J Clin Oncol*. 2024;42:e16133–e. doi:10.1200/JCO.2024.42.16_suppl.e16133
17. Li H, Wang J, Zhang G, et al. Transarterial chemoembolization combined donafenib with/without PD-1 for unresectable HCC in a multicenter retrospective study. *Front Immunol*. 2023;14:1277329. doi:10.3389/fimmu.2023.1277329
18. Tan K, He X, Zhang H et al. Chicago, 2023 June 2-6, 2023 ASCO Annual Meeting . Efficacy and safety of tislelizumab combined with lenvatinib and FOLFOX4-HAIC in conversion therapy of middle-advanced stage hepatocellular carcinoma (HCC): a real-world retrospective study. *J Clin Oncol*. 2023 ;41: e16137-e16137. doi:10.1200/JCO.2023.41.16_suppl.e16137
19. Dong W, Zhang S, Huo Z et al. Chicago, 2023 June 2-6, 2023 ASCO Annual Meeting, Lenvatinib in combination with PD-1 inhibitor and hepatic arterial infusion chemotherapy (HAIC) for patients with potentially resectable hepatocellular carcinoma: a retrospective analysis. *J Clin Oncol*. 2023;41:e16160-e16160: doi:10.1200/JCO.2023.41.16_suppl.e16160
20. Wu XK, Yang LF, Chen YF, et al. Transcatheter arterial chemoembolisation combined with lenvatinib plus camrelizumab as conversion therapy for unresectable hepatocellular carcinoma: a single-arm, multicentre, prospective study. *EClinicalMedicine*. 2024;67:102367. doi:10.1016/j.eclinm.2023.102367
21. Zhang W, Tong S, Hu B, et al. Lenvatinib plus anti-PD-1 antibodies as conversion therapy for patients with unresectable intermediate-advanced hepatocellular carcinoma: a single-arm, phase II trial. *J ImmunoTher Cancer*. 2023;11.
22. Qi W, Peng W, Qi X, Qiu Z, Wen T, Li C. TIDE: adjuvant tislelizumab plus donafenib combined with transarterial chemoembolization for high-risk hepatocellular carcinoma after surgery: protocol for a prospective, single-arm, phase II trial. *Front Oncol*. 2023;13:1138570. doi:10.3389/fonc.2023.1138570
23. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. *Ann Rev Immunol*. 2013;31:51–72. doi:10.1146/annurev-immunol-032712-100008
24. Viallard C, Larrivée B. Tumor angiogenesis and vascular normalization: alternative therapeutic targets. *Angiogenesis*. 2017;20:409–426. doi:10.1007/s10456-017-9562-9
25. Yang J, Yan J, Liu B. Targeting VEGF/VEGFR to Modulate Antitumor Immunity. *Front Immunol*. 2018;9:978. doi:10.3389/fimmu.2018.00978
26. Hato T, Goyal L, Greten TF, Duda DG, Zhu AX. Immune checkpoint blockade in hepatocellular carcinoma: current progress and future directions. *Hepatology*. 2014;60:1776–1782. doi:10.1002/hep.27246
27. Li L, Wen Q, Ding R. Therapeutic targeting of VEGF and/or TGF-β to enhance anti-PD-(L)1 therapy: the evidence from clinical trials. *Front Oncol*. 2022;12:905520. doi:10.3389/fonc.2022.905520
28. Montasser A, Beaufrère A, Cauchy F. Transarterial chemoembolisation enhances programmed death-1 and programmed death-ligand 1 expression in hepatocellular carcinoma. *Histopathology*. 2021;79:36–46. doi:10.1111/his.14317
29. Liu K, Min XL, Peng J, Yang K, Yang L, Zhang XM. The Changes of HIF-1α and VEGF Expression After TACE in Patients With Hepatocellular Carcinoma. *J Clin Med Res*. 2016;8:297–302. doi:10.14740/jocmr2496w
30. Liu DY, Li YN, Wu J-Y. Efficacy and safety of transcatheter arterial chemoembolization combined with lenvatinib plus anti-PD-1 inhibitors for hepatocellular carcinoma patients with extrahepatic metastases: a multicenter retrospective study. *J Hepatocell Carcinoma*. 2024;11:2339–2349. doi:10.2147/JHC.S480958
31. Zeng ZX, Wu JY, Wu J-Y, et al. The TAE score predicts prognosis of unresectable HCC patients treated with TACE plus lenvatinib with PD-1 inhibitors. *Hepatol Internat*. 2024;18:651–660. doi:10.1007/s12072-023-10613-x
32. Li X, Sun W, Ding X, Li W, Chen J. Prognostic model of immune checkpoint inhibitors combined with anti-angiogenic agents in unresectable hepatocellular carcinoma. *Front Immunol*. 2022;13:1060051. doi:10.3389/fimmu.2022.1060051