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ORIGINAL RESEARCH

Clinical Outcomes of Hepatic Arterial Infusion Chemotherapy Plus Lenvatinib and Tislelizumab for Treating Hepatocellular Carcinoma and Type IV Portal Vein Tumor Thrombus

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Purpose: To assess the activity and toxicity of hepatic arterial infusion chemotherapy (HAIC)+tislelizumab+lenvatinib (HAIC+tisle+len) in hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) type IV (Vp4 hCC) in a real-world context.

Methods: Fifty-five patients, with Vp4 hCC receiving HAIC+tisle+len therapy from April 2021 to December 2022, were analyzed retrospectively. Data on patient characteristics, adverse events (AEs), treatment, and survival were collected. Outcomes were disease control rate (DCR), overall response rate (ORR), overall survival (OS), progression-free survival (PFS), and treatment-related AEs (TRAEs).

Results: As of December 20, 2023, the median follow-up was 17.5 months (95% confidence interval [CI]: 14.7–22.5). The ORR was 52.7% (3 complete response [CR], 26 partial response [PR]) as per RECIST v1.1 and 65.5% (12 CR, 24 PR) as per mRECIST. The DCR was 94.5% using both RECIST v1.1 and mRECIST. The median PFS and the median OS were 8.0 months (95% CI: 6.2–12.3) and 16.7 months (95% CI: 12.0-not reached), respectively. Additionally, PFS was independently predicted only by the best tumor response. In patients with the best tumor response (PR or CR), the median PFS was 11.7 months (95% CI: 8.02-not reached) by mRECIST and 15.4 months (95% CI: 7.39-not reached) by RECIST v1.1. Hypertension (14.5%), decreased albumin levels (10.9%) and anorexia (9.1%) were the most frequently observed grade 3–4 TRAEs.

Conclusion: HAIC+tisle+len regimen demonstrated a promising efficacy and favorable safety for patients with HCC and Vp4, providing valuable real-world evidence to complement the trial data for Vp4 hCC.

Keywords: tislelizumab, portal vein tumor thrombus, lenvatinib, hepatocellular carcinoma, hepatic artery infusion chemotherapy

Introduction

Hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) is categorized as an advanced-stage disease (China liver cancer IIIa), depending on Chinese guidelines for the diagnosis and treatment of primary liver cancer.[1] PVTT, especially type IV (Vp4), represents a significant complication of HCC owing to its mortality and morbidity rates.[2] A subgroup analysis from the IMbrave 150 trial found that patients with Vp4 hCC receiving atezolizumab and bevacizumab had a median overall survival (OS) of just 7.6 months.[3] For advanced HCC patients treated with lenvatinib (len) or sorafenib, the median OS was approximately 10.7–15.0 months,[4] yet these therapies often fall short of providing adequate survival benefits for many patients.

For HCC with accompanying PVTT, transarterial chemoembolization (TACE) is an option.[1,5] However, this treatment carries a heightened risk of hepatic dysfunction due to the obstruction of arterial/portal venous blood flow, particularly in

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cases of portal trunk invasion. In contrast, hepatic arterial infusion chemotherapy (HAIC) is administered through a catheter directly into the arteries supplying the tumor, ensuring high drug concentrations in the tumor and tumor thrombus, leading to enhanced necrosis. This strategy presents a promising option for HCC and PVTT.[6,7]

With the development of systemic therapies, the approach to treating advanced HCC has also progressed rapidly. The sorafenib and tislelizumab (tisle; programmed cell death protein 1 inhibitor [PD-1]) in the RATIONALE-301 trial showed a median OS of 14.1 and 15.9 months, respectively. Compared to the sorafenib group, tisle group achieved a superior objective response rate (ORR) and exhibited more durable responses.[8] Len, an oral small-molecule tyrosine kinase inhibitor (TKI), was used as a 1st-line therapy for unresectable HCC in the REFLECT trial.[4] Recent advancements in HAIC with modified FOLFOX (5-fluorouracil, oxaliplatin, and leucovorin), along with PD-1 inhibitors and TKIs have brought new optimism for treating patients with Vp4 HCC.[9,10] Here, we aimed to evaluate the activity and toxicity of combining HAIC+tisle+len for patients with Vp4 hCC.

Patients and Methods

Study Design and Patients

This single-arm, observational retrospective study analyzed data from Vp4 hCC patients who received HAIC+tisle+len therapy from April 2021 to December 2022 at Eastern Hepatobiliary Surgery Hospital, China. HCC was diagnosed using pathological or non-invasive diagnostic methods, including magnetic resonance imaging (MRI), biopsy, cytology, or dynamic computed tomography (CT), as per the 2022 Guidelines for the Diagnosis and Treatment of Primary Liver Cancer[1] and AASLD standards.[11]

The criteria for inclusion were outlined as below: (a) aged 18–75 years; (b) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; (c) HCC with Vp4 PVTT diagnosed on the basis of imaging evidence (MRI/CT) supplemented by necessary clinical and laboratory information; (d) platelet count (PLT) ≥40 × 10^9/L, neutrophil count ≥1.5 × 10^9/L, hemoglobin (HB) ≥8.5 g/dL, serum albumin (ALB) ≥30 g/L, total bilirubin (TBIL) ≤50 μmol/L, alanine transaminase (ALT)/aspartate transaminase (AST) ≤5 times the upper limit of normal. Exclusion criteria were as follows: (a) decompensated liver function (eg, active gastrointestinal bleeding, significant ascites, or hepatic encephalopathy); (b) metastatic tumors in other organs; and (c) inadequate medical records missed follow-up.

The study received approval from the ethics review board of Eastern Hepatobiliary Surgery Hospital and was conducted according to the Declaration of Helsinki principles. In addition, informed consent was obtained from all patients for the HAIC+tisle+len regimen.

HAIC with Modified FOLFOX

Briefly, angiography was used to identify the tumor-feeding arteries, and a microcatheter was selectively advanced to the most prominent tumor-feeding artery. The treatment regimen consisted of a modified FOLFOX (leucovorin [400 mg/m^2], oxaliplatin [85 mg/m^2], 5-fluorouracil infusion [2400 mg/m^2 for 46 h], and 5-fluorouracil bolus [400 mg/m^2 on day 1]). HAIC was performed per 3–6 weeks, up to six times, by the same medical team. Post-HAIC evaluations and follow-ups were carried out before each subsequent treatment. HAIC could be repeated if the lesion was not completely necrotic and the active area exceeded 50% of the baseline. Dosage adjustments for chemotherapy drugs were considered if significant tumor reduction was observed. The tisle+len regimen was generally continued after HAIC. Surgical feasibility was evaluated by a specialist if the criteria for surgery were met.

Tisle and Len

Both tisle and len are covered by national health insurance. Physicians provided a comprehensive explanation of the drug's efficacy and potential adverse events (AEs) before treatment. With the patient consented, tisle (200 mg Q3W) was received 1–3 days after each HAIC treatment, based on the patient's response. Tisle was discontinued if serious immune-related AEs occurred, with corticosteroids used as necessary. Len was given orally at a dose of 8 mg/day for patients weighing less than 60 kg and 12 mg/day for those weighing 60 kg or more, commencing 1IMbrave 150 trial3 days following HAIC. The dose was adjusted or discontinued based on drug-related toxicity.

Antiviral Therapy

Antiviral therapy was vital for maintaining liver function and preventing viral activation during treatment. Antiviral medications (tenofovir or entecavir) were administered to patients with HBV infection before therapy, while sofosbuvir was given to those with HCV infection.

Outcomes and Assessments

The follow-up period concluded on December 20, 2023. Baseline and pretreatment HAIC assessments included routine blood counts, coagulation, alpha-fetoprotein (AFP), liver and kidney function, desgamma-carboxy prothrombin (DCP), thyroid function, and cardiac enzyme profiles. Clinical outcomes for HAIC+tisle+len treatment in Vp4 hCC were reported.

Tumor response was evaluated every 4–8 weeks using MRI/dynamic contrast-enhanced CT, evaluating changes in the tumor size and necrosis as per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and Modified RECIST (mRECIST). Treatment response referred to the best response achieved during the follow-up, including complete remission (CR), partial remission (PR), disease progression (PD), and stable disease (SD). Efficacy outcomes included disease control rate (DCR, the percentage of patients achieving PR, CR, or SD), overall response rate (ORR, the percentage of patients achieving PR or CR), progression-free survival (PFS, from the start of combination therapy to disease progression or death), and OS (the time between the start of the therapy and death from any cause). The Common Terminology Criteria for Adverse Events version 5.0, were applied to recorded and assessed AEs.

Statistical Analysis

Patients who received ≥1 hAIC+tisle+len treatment were analyzed for efficacy and safety. Means ± standard deviations were used to report data that were normally distributed, whereas the rank-sum test was used to analyze non-normally distributed data and shown as medians with interquartile ranges (IQR). Kaplan–Meier survival estimates were calculated, and subgroups survival was compared using the Log rank test. Univariate and multivariate Cox regression analyses were used to evaluate prognostic factors. To identify the prognostic factors affecting PFS, we collected the clinical data of 55 patients and performed Log rank tests for PFS based on variables such as the best tumor response (CR+PR vs SD+PD), age, sex, number of tumors, tumor diameter, baseline AFP, NLR, PLR, ALBI grade, CRAFITY score, extrahepatic metastasis, and HBV DNA level. Variables with a p-value <0.1 were incorporated into the Cox regression model, which included the best tumor response (CR+PR vs SD+PD) as per the mRECIST or RECIST v1.1, extrahepatic metastasis status, tumor number, and NLR. All analyses were conducted with SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA), with a p-value of less than 0.05 was regarded as statistically significant.

Results

Patient Characteristics

This study included 55 patients (Figure 1). Median age was 55 (range, 49–59) years, with 90.9% male. Tumor numbers 1, 2, and ≥3 were observed in 49.1%, 7.3%, and 43.6% of patients, respectively. Median tumor size was 9.5 cm (range, 6.8–11.6), with 83.4% of patients having tumors larger than the up-to-seven criteria. Hepatitis B surface antigen was detected in 80% (44/55) of patients, and hepatitis C antibody was found in 1.8% (1/55). Of the patients, 49 (89.1%) were in Child-Pugh stage A, and six (10.9%) were in stage B. The 20% of the patients had extrahepatic metastases. The median AFP and DCP levels were 267 (IQR: 17.9–11676) ng/mL and 3154 (IQR: 963–38253) mAU/mL, respectively. Table 1 provides an overview of the demographic and baseline characteristics.

Efficacy Outcomes

As of December 20, 2023, the median follow-up was 17.5 months (95% confidence interval [CI]: 14.7–22.5). During follow-up, 30 OS events occurred, with a median OS of 16.7 months (95% CI: 12.0-not reached) and a median PFS of 8.0 months (95% CI: 6.2–12.3; Figure 2). The patients received a total of 159 hAIC cycles, with a median of 3 cycles per patient; five patients (9.1%) received ≥6 cycles. The median duration of len treatment was 7.8 months (IQR: 5.4–13.4), and the median number of tisle cycles was 9 (IQR: 5–13).

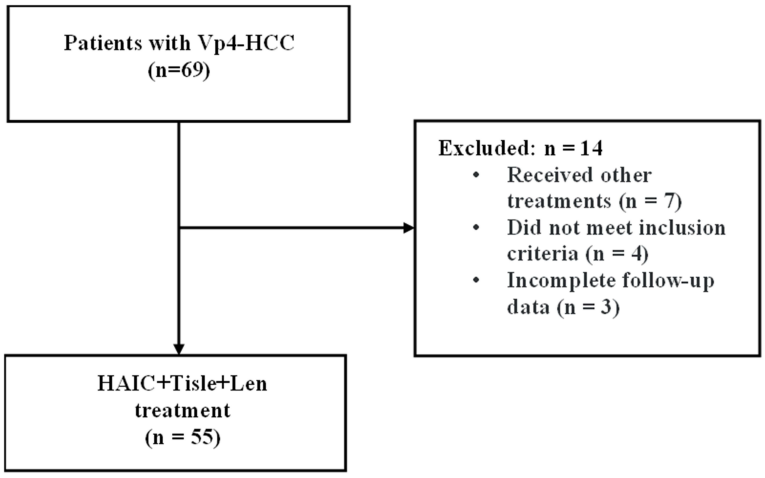

Figure 1 Flowchart demonstrating the process for selecting patients.

Patients receiving HAIC+tisle+len therapy achieved a CR in 5.5%, PR in 47.3%, and SD in 41.8% of patients, leading to an ORR of 52.7% and a DCR of 94.5%, based on RECIST v1.1 criteria. In addition, the ORR and DCR as per the mRECIST criteria were 65.5% and 94.5%, respectively (Table 2, Figure 3).

Changes in Liver Function and Tumor Markers

The hepatic functional reserve of patients was evaluated using ALBI classification both at baseline and at the last pre-HAIC before the follow-up cutoff. Hepatic functional reserve remained in most patients, with no further deterioration observed. ALBI grade was increased from 1 to 2 in 14 patients but decreased to 1 after treatment.

Analysis of tumor markers at baseline and the first follow-up revealed substantial reductions in both DCP and AFP levels post-treatment for most patients. At the baseline, the median AFP level was 267 ng/mL, which decreased

Table 1 Baseline Characteristics of the 55 Patients

Characteristics	Statistical Value
Gender	
Male	50 (90.9)
Female	5 (9.1)
Median age, years (range)	55 (49–59)
Etiology	
Hepatitis B	44 (80)
Hepatitis C	1 (1.8)
Non-B, Non-C	10 (18.2)
BCLC stage	
A	0 (0)
B	0 (0)
C	55 (100)
Child-Pugh class	
A	49 (89.1)
B	6 (10.9)
Number of tumors	
1	27 (49.1)
2	4 (7.3)
≥3	24 (43.6)

(*Continued*)

Table 1 (Continued).

Characteristics	Statistical Value
Largest tumor diameter (cm), Median (Q1, Q3)	9.5 (6.8, 11.6)
≤10	31 (56.4)
>10	24 (43.6)
Extrahepatic metastases	
Presence	11 (20)
Absence	44 (80)
Up to Steven status	
In	9 (16.4)
Beyond	46 (83.4)
AFP (ng/mL), median (Q1, Q3)	267 (17.9, 11676)
≥400	27 (49.1)
DCP (mAU/mL), median (Q1, Q3)	3154 (963, 38253)
≥40	52 (94.5)
TB (μmol/L), median (Q1, Q3)	17.5 (14.1, 24.7)
AST (U/L), median (Q1, Q3)	50.5 (36, 83)
ALT (U/L), median (Q1, Q3)	43 (25, 59)
ALB (g/L), median (Q1, Q3)	38.9 (34.5, 41.2)
WBC (×109), median (Q1, Q3)	5.49 (3.9, 6.2)
PLT (×109), median (Q1, Q3)	129 (97, 189)
NLR, median (Q1, Q3)	2.86 (2.01, 4.40)
PLR, median (Q1, Q3)	116.3 (81.97, 172.2)
ALBI grade (Patients analyzed)	54
Grade 1	17 (30.9)
Grade 2	37 (67.3)
Time of HAIC, median (Q1, Q3)	3 (2, 4)

Note: Data are presented as n (%) or median (Q1, Q3). Q1 and Q3 are 25th percent and 75th percent of the interquartile range.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; DCP, Des-gammacarboxy; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell; PLT, platelet; NLR, neutrophil–lymphocyte ratio; PLR, platelet lymphocyte ratio.

significantly to 16.1 ng/mL post-treatment ($p < 0.01$). Changes in AFP levels are shown in Figure 4. Similarly, the median baseline DCP level decreased from 3154 mAU/mL to 171 mAU/mL after treatment ($p < 0.01$), as shown in Figure 4.

Subsequent Treatments

During treatment, HAIC+tisle+len therapy was discontinued in 33 patients due to PD. Subsequently, 10 patients (18.5%) received TACE+tisle+len, 13 (23.6%) received tisle+len, and 4 (7.3%) received HAIC+tisle+regorafenib. Due to severe treatment-related AEs (TRAEs) with the triplet regimen, 12 patients were switched to other regimens, including tisle+len (n = 3), HAIC+tisle (n = 7), and HAIC+len (n = 2). Additionally, two patients underwent surgery after conversion, including one who received a liver transplant and remained tumor-free.

Safety Outcomes

No deaths related to the treatment occurred during the study. Almost all patients experienced various levels of AEs (Table 3). The most common TRAEs with HAIC+tisle+len were abdominal pain (16.4%, 9/55), hypertension (34.5%, 19/55), hypothyroidism (16.4%, 9/55), diarrhea (18.2%, 10/55), rash (18.1%, 10/55), and proteinuria (12.7%,7/55). The most frequent adverse laboratory reactions were leukopenia (38.2%, 21/55), PLT decreased (34.5%, 19/55), ALB decreased (29.1%, 16/55), alanine aminotransferase (ALT) increased (32.7%, 18/55), and aspartate aminotransferase (AST) increased (29.1%, 16/55). Grade 3–4 TRAEs most

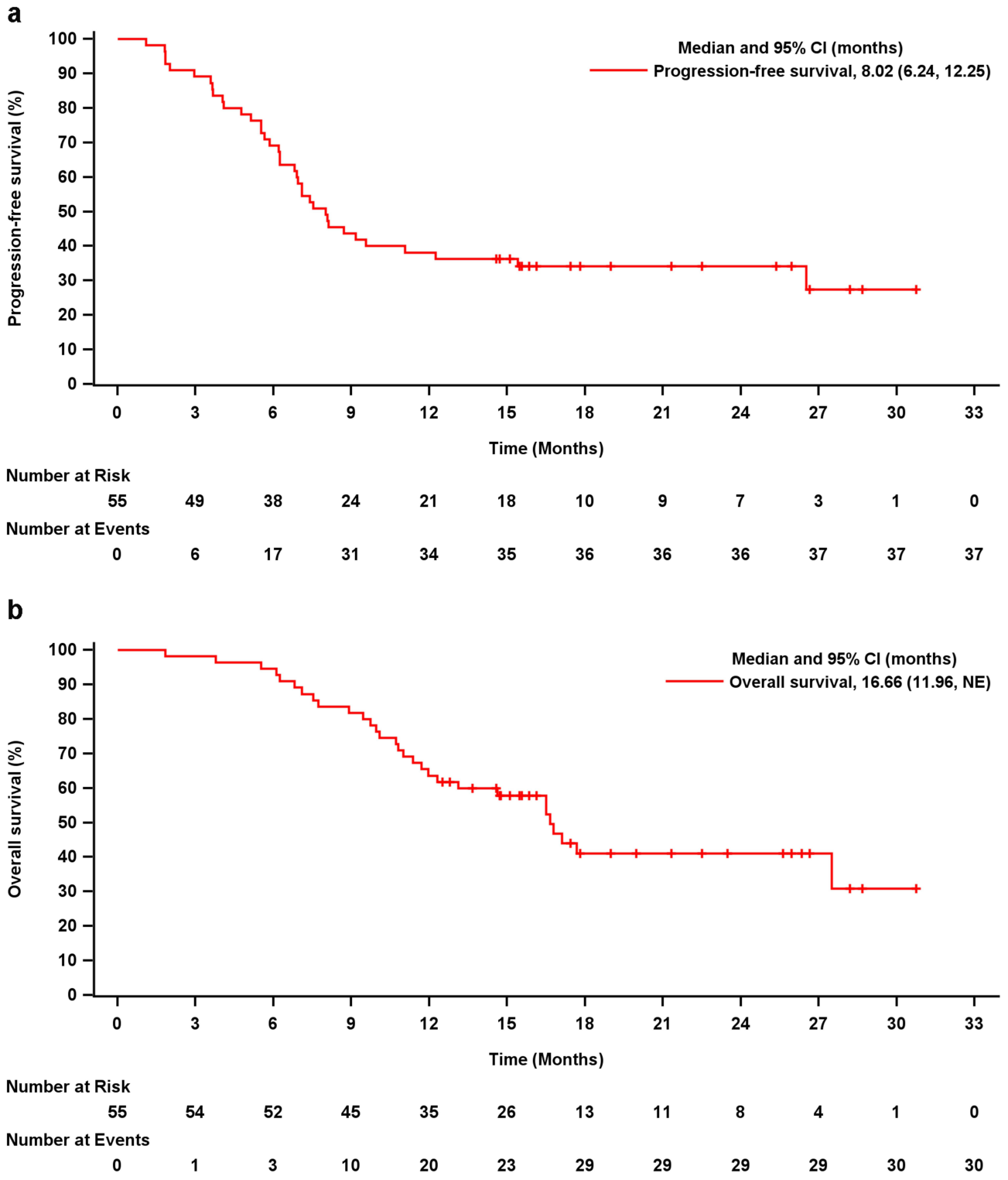

Figure 2 Kaplan-Meier curves demonstrating PFS (**a**) and OS (**b**) in patients treated with HAIC+Tisle+Len.

frequently observed were hypertension (14.5%, 8/55), ALB decreased (10.9%, 6/55), anorexia (9.1%, 5/55), leukopenia (9.1%, 5/55), abdominal pain (7.3%, 4/55), and AST/ALT increased (7.3%, 4/55). Most TRAEs were managed with dose reduction, treatment interruption, or standard drug therapy. Throughout the study, 21 patients (38.1%) experienced either dose reductions or interruptions.

Table 2 Best Tumor Response of the 55 Patients

Variable	Total (n = 55)
Best overall response by RECIST v 1.1 and mRECIST, n (%)	**RECIST v 1.1 mRECIST**
CR	3 (5.5) 12 (21.8)
PR	26 (47.3) 24 (43.6)
SD	23 (41.8) 16 (29.1)
PD	3 (5.5) 3 (5.5)
ORR, n (%)	29 (52.7) 36 (65.5)
DCR, n (%)	52 (94.5) 52 (94.5)

Note: Data are presented as n (%).
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; RECIST v 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Factors Associated with Disease Progression

Based on either the RECIST v1.1 or mRECIST, we observed a significant effect of the best tumor response (CR+PR vs SD+PD) on PFS (RECIST v1.1: hazard ratio [HR]=2.77, 95% CI: 1.24–6.16, p=0.0126; mRECIST: HR = 3.94, 95% CI: 1.79–8.69, p=0.0007) (Table 4). Sensitivity analyses were performed for all variables included in the Log rank test. After the within-model screening of all variables using the Cox stepwise regression model, only the best tumor response (CR +PR vs SD+PD) significantly affected PFS (HR = 3.00, 95% CI: 1.53–5.87, p=0.0014) according to the RECIST v1.1. Meanwhile, only the effect of the best tumor response (CR+PR vs SD+PD) and number of tumors on PFS was significant (mRECIST: HR = 4.10, 95% CI: 2.03–8.27, p<0.0001; the number of tumors [≥3 vs <3]: HR = 0.50, 95% CI: 0.26–0.98, p=0.0434) according to the mRECIST. Overall, the best tumor response (CR+PR vs SD+PD) was considered an independent risk factor for PFS.

Subsequent analyses of treatment outcomes based on the best tumor response (CR+PR vs SD+PD) revealed that patients with CR+PR exhibited a superior median PFS, compared to those with SD+PD. Specifically, the median PFS was 11.7 months vs 5.5 months (HR = 3.31, 95% CI: 1.70–6.43, p=0.0002) according to mRECIST (Figure 5a), and 15.4 months vs 5.8 months (HR = 2.82, 95% CI: 1.45–5.47, p=0.0014) according to RECIST v1.1 (Figure 5b).

Discussion

Despite the aggressive nature of Vp4 hCC, our study demonstrated that patients treated with HAIC+tisle+len achieved promising results. Median PFS was 8.0 months and the median OS was 16.7 months, which were comparable or superior to those from other studies on systemic therapy for advanced HCC.[12,13] The ORRs were 52.7% based on RECIST v1.1 and 65.5% per mRECIST, demonstrating a substantial positive response to therapy. These results were consistent with HAIC+PD-1 inhibitors and targeted agents in previous studies, which reported ORRs of 36.1%–100%.[9,12,14] Additionally, the DCR of 94.5% indicated that most patients achieved disease stabilization or remission, with a notable CR rate of 21.8% based on mRECIST. Furthermore, the observed reductions in DCP and AFP levels after treatment underscored the efficacy of this regimen in controlling tumor growth and improving clinical outcomes.

The prognosis for HCC patients with PVTT was closely related to its extent, with Vp4 involvement-where the portal vein's trunk was obstructed by cancer embolus-yielding a poor median OS of just 4.8 months. Effective treatment for Vp4 hCC remained uncertain, and no standardized approach has been established.[15,16] Western guidelines, including those from the European Association for the Study of the Liver, AASLD, and Barcelona Clinic Liver Cancer, primarily recommended systemic therapies-including atezolizumab, bevacizumab, sorafenib, Len, and durvalumab-as the 1st-line treatment options. By contrast, Eastern guidelines advocated for a more aggressive treatment approach. Some centers have explored treatment modalities such as radiotherapy +TACE or HAIC for patients with concomitant portal trunk thrombus, but the reported median OS was limited to 6 months to 1 year.[1,17,18]

For advanced HCC, single molecular targeted therapy or immunotherapy was usually insufficient to meet their long-term survival needs. Recent clinical trials, including the IMbrave150,[3] ORIENT-32,[19] and CARES-310 trials,[20] have

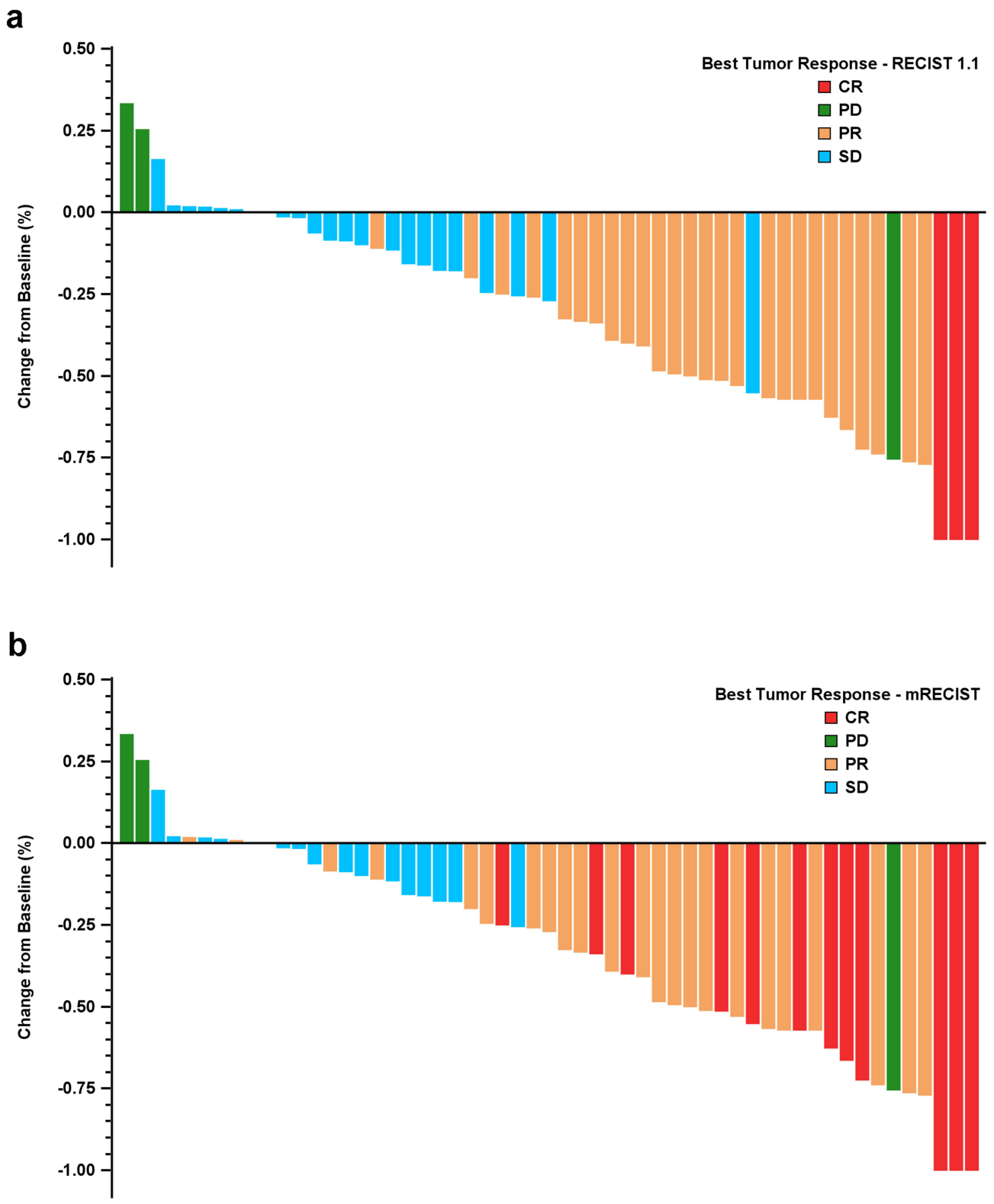

Figure 3 Best percentage changes from baseline in target lesions per RECIST v1.1 (**a**) and mRECIST (**b**).

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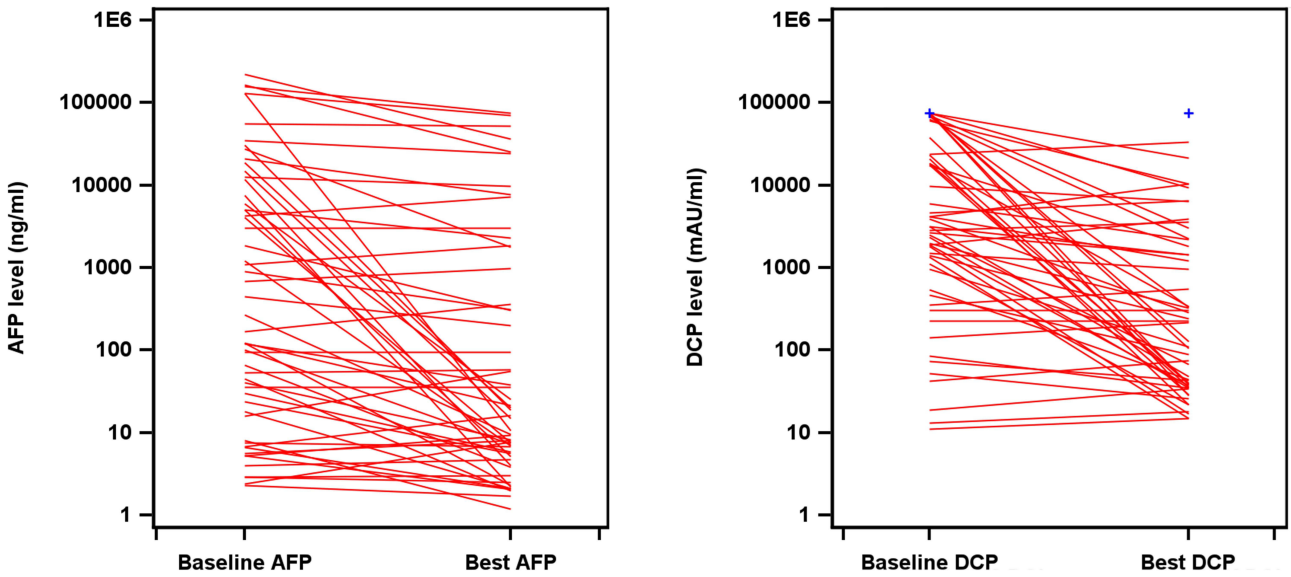

Figure 4 Changes in AFP and DCP levels from baseline to the first follow-up after HAIC+Tisle+Len treatment.

shown that immuno-combination targeted therapies offered superior efficacy and survival benefit. Trials such as EMERALD-1, CHANCE001,[21] and TRIPLET[9] have validated the clinical benefit of interventional therapy plus targeted therapies and PD-(L)1 inhibitors. HAIC, a localized chemotherapy treatment, delivered chemotherapeutic agents directly into the tumor's blood-supplying arteries, allowing the drugs to reach a high concentration locally in the tumors, killing tumor cells more effectively.[22] Simultaneously, because the drug was primarily locally within the tumor, AEs on other tissues throughout the body could be minimized. The integration of tisle and len-key agents in immunotherapy and targeted therapy for liver cancer[4,8]-with HAIC represented a potentially effective therapeutic option for Vp4 hCC.

Table 3 Treatment-Related Adverse Events

Adverse Events	All grades, n (%)	Grade 3–4, n (%)
Hypertension	19 (34.5)	8 (14.5)
Abdominal pain	9 (16.4)	4 (7.3)
Diarrhea	10 (18.2)	3 (5.5)
Dysphonia	5 (9.1)	0 (0)
Hand-foot skin reaction	8 (14.5)	2 (3.6)
Vomiting	9 (16.4)	3 (5.5)
Fatigue	6 (10.9)	0 (0)
Skin rash	10 (18.1)	2 (3.6)
Proteinuria	7 (12.7)	3 (5.5)
Epistaxis	3 (5.5)	0 (0)
Anorexia	23 (41.8)	5 (9.1)
Myocardial enzymes increased	7 (12.7)	0 (0)
Hypothyroidism	9 (16.4)	2 (3.6)
AST increased	16 (29.1)	4 (7.3)
ALT increased	18 (32.7)	4 (7.3)
Hyperbilirubinemia	14 (25.5)	2 (3.6)
Albumin decreased	16 (29.1)	6 (10.9)
PLT decreased	19 (34.5)	3 (5.5)
WBC decreased	21 (38.2)	5 (9.1)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase, PLT, platelet; WBC white blood cell.

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Table 4 Multivariable Cox Regression Analysis for Progression-Free Survival

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI) P value	HR(95% CI) P value
Gender (Male vs female)	0.77 (0.24–2.52)	0.6689		
Age (≤60 vs >60)	1.22 (0.53–2.79)	0.6355		
ALBI grade (1 vs 2+3)	1.55 (0.75–3.23)	0.2325		
Number of tumor (≥3 vs < 3)	0.55 (0.29–1.06)	0.0687	0.56 (0.27–1.17) 0.1221	0.60 (0.25-1.43) 0.2469
Largest tumor diameter (cm) (≤9.5 vs >9.5)	1.34 (0.70–2.57)	0.3680		
CRAFITY score (0+1 vs 2)	0.93 (0.49–1.79)	0.8306		
Baseline AFP (≤400 vs >400)	0.94 (0.50–1.80)	0.8629		
NLR level (≤ 3.65 vs >3.65)	0.46 (0.23–0.89)	0.0184	0.98 (0.43–2.25) 0.9712	1.04 (0.44-2.47) 0.9329
PLR level (≤139.13 vs >139.13)	0.58 (0.30–1.13)	0.1050		
Extrahepatic metastasis (presence vs absent)	0.50 (0.24–1.01)	0.0467	0.68 (0.29–1.57) 0.3617	0.60 (0.25-1.43) 0.2469
HBV DNA (≥100 vs <100)	0.58 (0.30–1.12)	0.1017		
Best tumor response assessed by mRECIST (CR+PR vs SD+PD)	3.31 (1.70–6.43)	0.0002	3.94 (1.79–8.69) 0.0007	
Best tumor response assessed by RECIST v 1.1. (CR +PR vs SD+PD)	2.82 (1.45–5.47)	0.0014		2.77 (1.24-6.16) 0.0126

The combination of HAIC and targeted immunotherapy showed a significant mechanistic synergy that could enhance treatment efficacy. HAIC activated the adaptive immune system, restored the immune surveillance function, and enhanced immunogenicity by prompting tumor cell death.[23,24] Compared to other PD-1 inhibitors, the Fc segment of tisle has been genetically engineered to eliminate antibody-dependent cell-mediated phagocytosis by binding to the Fcγ receptors on macrophages[25] This modification reduced T-cell depletion and enhanced cellular immune function, making tisle a preferred choice. Len enhanced anti-PD-1 therapy by blocking fibroblast growth factor receptor 4 (FGFR4), leading to decreased Treg differentiation and PD-L1 levels in tumors,[26] and by inhibiting interferon-γ signaling in tumor cells.[27] In addition, len normalized the tumor vasculature, reprogrammed the immune microenvironment, and transformed cold tumors into hot tumors. This combined therapeutic approach provided superior therapeutic outcomes due to its unique synergistic effects.

This study highlighted the importance of early and validated tumor response assessments in guiding treatment decisions. The finding of this study found that the best tumor response identified the only independently prognostic factor for PFS, emphasizing the importance of this assessment. Patients with CR or PR experienced notably longer PFS than those with SD or PD. Thus, treatment regimens should be adjusted if CR or PR was not achieved. Additionally, the study reported the adjustment of HAIC to TACE. With a 3-week HAIC treatment period, patients had sufficient time and good liver function reserve to switch to a new regimen if HAIC+tisle+len was ineffective, which contributed to prolonged OS. The choice of criteria can influence the interpretation of our findings and their relevance to different patient populations. By presenting results based on both mRECIST and RECIST v1.1, we aimed to provide a comprehensive view of treatment efficacy, applicable to both general and specific clinical settings. However, it is crucial to recognize that direct comparisons between these two criteria should be made with caution, as they assess different aspects of tumor response. The study found that the best tumor response was significantly associated with PFS as per mRECIST and RECIST v1.1, underscoring the importance of monitoring changes in tumor size and activity after this treatment. Previous studies had indicated that HAIC effectively induced tumor shrinkage,[7,28] while len combined with tisle might enhance tumor inactivation through angiogenesis inhibition.[29] Therefore, both response assessment criteria were valuable for evaluating the efficacy of HAIC+tisle+len triple therapy.

This study might provide valuable insights by incorporating liver function analyses. The ALBI grading method was employed to assess liver function reserve in patients receiving anticancer therapy and demonstrated effectiveness in accurately reflecting liver function status.[30] It was particularly suitable for monitoring changes in liver function during

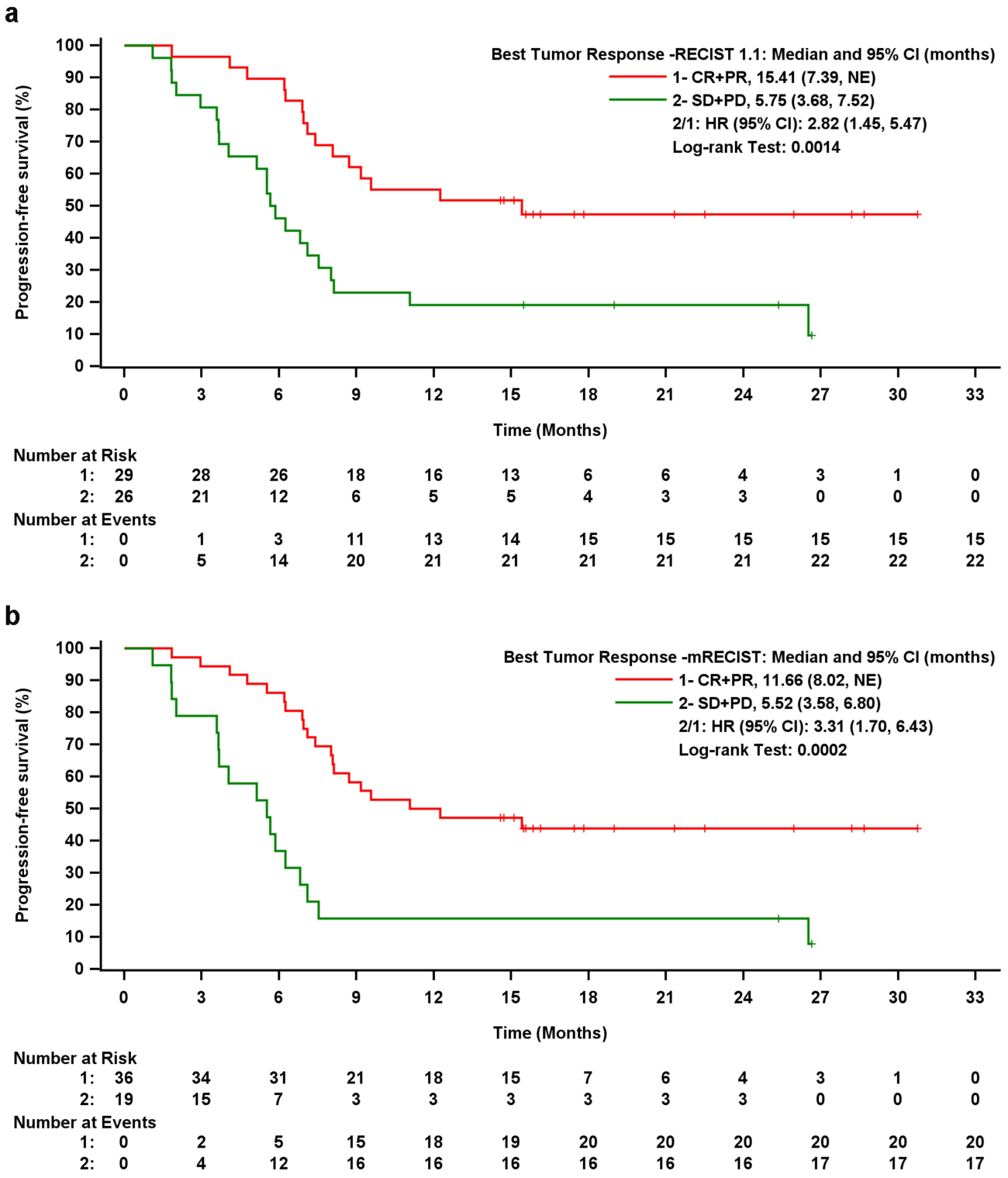

Figure 5 Progression-free survival with different stratified. The PFS in the best tumor response (CR+PR vs SD+PD) patients was assessed using RECIST v 1.1 (**a**). The PFS in the best tumor response (CR+PR vs SD+PD) patients was assessed using mRECIST (**b**).

therapy. The results of our study showed that most patients maintained stable liver function throughout HAIC+tisle+len therapy, suggesting that this regimen did not significantly impair liver function. Although the ALBI grade of 14 patients increased from 1 to 2 during treatment, it decreased to grade 1 at the end of treatment. This suggested that while liver

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function might be temporarily affected during certain stages of treatment, these changes were reversible with careful monitoring and appropriate treatment.

In addition, two patients underwent surgery following conversion therapy, and one patient underwent a liver transplantation and remained tumor-free. This underscores that our therapy might slow the course of the disease progression and make surgical resection or transplantation feasible, which was crucial for optimizing long-term survival for HCC. However, the conversion rate in this study was lower compared to other studies,[9,31] with only two patients undergoing surgery. This discrepancy might be due to that, while HAIC+tisle+len effectively controlled intrahepatic lesions in Vp4 hCC, complete regression of the cancerous thrombus in the main portal vein was often not achieved. Furthermore, a more reliable method to assess the activity of the portal vein cancerous thrombus post-treatment is lacking, leading surgeons to adopt a more conservative approach in such cases.

The HAIC+tisle+len regimen exhibited a manageable safety profile despite some common grade 3–4 TRAEs, including hypertension (14.5%), leukopenia (9.1%), abdominal pain (7.3%), and AST/ALT increased (7.3%). These AEs were consistent with the known safety profiles of tisle and len and the established tolerability of HAIC in advanced HCC.[4,6,19] The modified FOLFOX regimen (oxaliplatin and 5-fluorouracil) used in HAIC could cause myelosuppression, potentially leading to leukopenia and thrombocytopenia. In the treatment of hypertension, antihypertensive medications were provided to patients, the timing of administration was adjusted, and treatment regimens were suspended when necessary. Similarly, for leukopenia, regular blood count monitoring was emphasized, and prophylaxis with granulocyte stimulating factors or antibiotics was administered when appropriate to reduce the risk of infection. During HAIC therapy, approximately 7.3% of patients experienced severe epigastric pain, dyspnea, and emotional stress, primarily during oxaliplatin infusion. Most of these symptoms were alleviated with morphine analgesia or by adjusting the infusion rate. Persistent abdominal pain, if present after treatment, should be evaluated with gastroscopy. Transient AEs, including vomiting, fever, and nausea, were associated with the procedure but were relatively mild compared to those from systemic chemotherapy and generally improved with symptomatic management. Immune-related hepatitis occurred only in two patients, as evidenced by ALT and TBIL increased,[32] but resolved with glucocorticoid therapy and interruption of tisle. Despite these AEs, the regimen was generally manageable with proper monitoring, and most patients still experience meaningful benefits from this therapy.

Several limitations were present in this study. The retrospective design led to inherent biases, and the small sample size restricted the generalizability of the results, primarily because of the rarity of Vp4 hCC. The absence of a control group also hindered direct comparisons between the combination therapy and other treatment options. Future studies should address these issues by conducting larger randomized controlled trials to rigorously assess the activity and toxicity of HAIC+tisle+len for Vp4 hCC. Additionally, we needed long-term follow-up to assess the durability of the survival benefit and to identify any late-onset TRAEs.

Conclusions

To conclude, our real-world data supported the potential of HAIC+tisle+len as a promising treatment strategy for Vp4 hCC. Patients who achieved a CR or PR might experience better clinical outcomes than those with PD or SD. However, additional research is needed to confirm these outcomes and to establish the optimal regimen for this population.

Abbreviations

HCC, Hepatocellular carcinoma; TACE, Transarterial chemoembolization; HAIC, Hepatic arterial infusion chemotherapy; PD-1, Programmed cell death protein 1; OS, Overall survival; TKI, Tyrosine kinases; IQR, Interquartile range; ORR, Objective response rate; TBIL, Total bilirubin; AASLD, American Association for the Study of Liver Diseases; DCP, Desgamma-carboxy prothrombin; DCR, Disease control rate; AST, Aspartate transaminase; PLT, platelet count; HB, Hemoglobin concentration; ALT, Alanine transaminase; AFP, Alpha-fetoprotein; CR, Complete remission; SD, Stable disease; NLR, neutrophil–lymphocyte ratio; PR, Partial remission; PFS, Progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; PLR, Platelet–lymphocyte ratio; HR, Hazard ratio; ALBI, Albumin-bilirubin; AEs, Adverse events; FGFR4, Fibroblast Growth Factor Receptor 4.

Data Sharing Statement

Access to the materials and data generated and/or analyzed in this study can be requested from the corresponding author, Jian Zhai.

Informed Consent in Studies with Human Subjects

The study protocol was approved by the ethical committee of the Eastern Hepatobiliary Surgery Hospital, Second Military Medical University. Written informed consent was obtained from all included patients. All procedures complied with the ethical standards of the responsible committee (institutional and national) on human experimentation, as well as the 1975 helsinki Declaration, updated in 2008.

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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 in 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

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