

Efficacy and safety of adebrelimab plus bevacizumab in combination with hepatic artery infusion chemotherapy for advanced stage hepatocellular carcinoma: a retrospective cohort study

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Hepatic arterial infusion chemotherapy using a combination of oxaliplatin, fluorouracil, and leucovorin (HAIC-FOLFOX) has shown promise for patients with advanced-stage hepatocellular carcinoma (HCC). In this study, we aim to evaluate the efficacy and safety of combining adebrelimab (anti-PD-L1 antibody) and bevacizumab with HAIC-FOLFOX for HCC patients in BCLC stage C. This retrospective study included 32 untreated advanced-stage HCC patients receiving HAIC-FOLFOX combined with adebrelimab and bevacizumab as first-line therapy. The primary endpoint is overall response rate (ORR) based on the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. From January 14th, 2024, to December 5th, 2024, a total of 32 patients received the triplet combination of HAIC-FOLFOX, adebrelimab, and bevacizumab. Median follow-up time was 6.1 months. According to RECIST v1.1 criteria, the confirmed ORR was 71.8% (95% CI: 55.4–88.3%), with a disease control rate (DCR) of 93.7% (95% CI: 84.9–99.9%). Only one case (3.1%) had a grade 3 treatment-related adverse event (rash), which could be alleviated after symptomatic management. The combination of adebrelimab, bevacizumab, and HAIC-FOLFOX demonstrated encouraging results and manageable safety concerns for patients with HCC at BCLC stage C.

Key words: hepatic arterial infusion chemotherapy; adebrelimab; bevacizumab; hepatocellular carcinoma

Primary liver cancer ranks as the sixth most prevalent cancer globally and represents the third leading cause of cancer-related mortality. Approximately 906,000 new cases and 830,000 deaths were recorded annually worldwide [1]. Notably, China contributes to approximately 55% of these global incidences. Hepatocellular carcinoma (HCC) constitutes the predominant pathological subtype of primary liver cancer, representing 75–85% of all hepatic malignancies. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, patients classified as stage C exhibit distinct clinical characteristics: a performance status score of 0–1 accompanied by macrovascular invasion and/or extrahepatic metastases. This advanced disease stage is strongly associated with poor clinical prognosis [2, 3]. Due to the hidden onset of liver cancer, as well as the differences in economic and medical levels in various regions, most HCC

patients had advanced stage disease when diagnosed, and a lack of effective treatment means, resulting in generally poor prognosis of patients [4, 5]. At present, the first-line targeted drugs mainly include sorafenib and lenvatinib etc. [6]. However, existing studies have found that the efficacy of targeted drugs in the treatment of advanced-stage HCC patients is dissatisfactory, with an overall response rate (ORR) less than 20% [7].

In recent years, the rapid development of immune checkpoint inhibitors (ICIs) has provided new hope for changing the treatment of advanced liver cancer [8, 9]. In the IMbrave 150 study, the combined use of PD-(L)1 inhibitors and drugs targeting VEGF marks a milestone in the treatment of HCC [10]. When anti-angiogenic drugs are used in combination with anti-PD-L1 therapy, they inhibit immune checkpoint activity and enhance T cell function, thereby generating



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more effective anti-tumor responses than anti-PD-1 therapy alone [11, 12]. Hepatic arterial infusion chemotherapy (HAIC) using a combination of oxaliplatin, fluorouracil, and calcium folinate (FOLFOX) is effective in reducing the tumor burden within the liver because it allows chemotherapeutic agents to be targeted and delivered to the tumor-feeding arteries. The FO-HAIC study demonstrated HAIC-FOLFOX resulted in significantly prolonged overall survival (OS) time compared to sorafenib alone [13]. The TRIPLET study, through a combination of HAIC-FOLFOX, camrelizumab, and apatinib, achieved an ORR of 77.1% for advanced-stage HCC [14]; meanwhile, the reported ORR of the combination of camrelizumab and apatinib stood at 25% according to RECISTv1.1 [15]. The PD-L1 antibody targets the PD-L1 antigen on the tumor surface, and with the combination of HAIC, which promotes the release of tumor antigens after directly killing tumor cells, it can enhance the anti-tumor response. The combination of the PD-L1 antibody adebrelimab and the VEGF antibody bevacizumab has demonstrated remarkable anti-tumor effects in cases of advanced colorectal cancer [15].

Based on the above theoretical basis, we infer that the combination of HAIC with adebrelimab and bevacizumab might have a synergistic anti-tumor effect in the treatment of advanced liver cancer, and can effectively enhance the therapeutic effect.

In this study, we aim to evaluate the efficacy and safety of combining adebrelimab (anti-PD-L1 antibody) and bevacizumab with HAIC-FOLFOX for HCC patients in BCLC stage C.

Patients and methods

Patients. This study was a retrospective study. Inclusion criteria were: a) clinical or pathological diagnosis of HCC in accordance with the standards of the American Association for the Study of Liver Diseases; b) BCLC stage C classification; c) no prior anti-tumor treatment; d) the presence of at least one measurable intrahepatic tumor as per RECIST v1.1; e) an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; f) and a Child-Pugh score of ≤ 7 points; g) receive at least one course of HAIC-FOLFOX combined with adebrelimab and bevacizumab treatment. Patients with autoimmune diseases, uncontrolled hypertension, or a high risk of bleeding were excluded.

Ethics statements. All participants gave their written consent prior to being included in the study. The requirement for informed consent was waived by the ethics committee due to the anonymized nature of the data and retrospective study design. The study protocol was approved by the Institutional Review Boards. This single-center retrospective clinical study was approved by the local Institutional Review Board of Sun Yat-sen University Cancer Center (Approval No. B2025-787-01), and informed consent was waived due to its retrospective nature.

Treatment. *HAIC-FOLFOX.* This regimen comprised a 2-hour infusion of oxaliplatin at 85 mg/m^2 , a 2–3-hour infusion of leucovorin at 400 mg/m^2 , and a 23-hour infusion of fluorouracil at $1,250 \text{ mg/m}^2$. HAIC was performed by inserting a 5-French Yashiro catheter (Terumo Corporation, Tokyo, Japan) through the femoral artery, with a 2.7-French microcatheter placed inside. The tip of the microcatheter was advanced to the tumor-feeding artery under the guidance of DSA. When the tumor displayed additional blood supply from extrahepatic sources, the tip of the catheter was placed in the main feeding artery. Additionally, blank microspheres were utilized to embolize the branch arteries. If the path from the intrahepatic artery to the chemotherapeutic agent flowing into the gastroduodenal artery was short, coils were employed for embolization. The chemotherapeutic drugs for HAIC were administered within 3 days after the placement of the liver catheter. The catheter and sheath were removed after each HAIC. The combined therapy was discontinued when disease progression occurred, when the disease was downstaged to enable curative treatment opportunities, when unacceptable toxicity emerged, or in the event of death. Dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was conducted every 3 weeks until the completion of treatment to assess tumor response, adhering to the RECIST v1.1 and mRECIST criteria. Adverse events (AEs) during treatment were recorded or graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Administration of adebrelimab and bevacizumab. All participants were administered with adebrelimab (intravenous injection of 1,200 mg; commencing on the second day of the first HAIC cycle and repeated every 3 weeks) and bevacizumab (intravenous injection of 700 mg, starting on the second day of the first HAIC cycle and repeated every 3 weeks). Additionally, the dosing sequence is the administration of adebrelimab injection precedes that of bevacizumab injection. The time interval between the administration of the two drugs should be more than 30 minutes.

Treatment discontinuation criteria. Treatment discontinuation criteria for the combination therapy included: 1) disease progression; 2) successful tumor downstaging enabling curative intervention; 3) onset of unacceptable toxicities; or 4) patient death. Specifically, in cases of grade ≥ 3 treatment-related adverse events (TRAEs) or serious TRAEs, HAIC was terminated while adebrelimab and bevacizumab systemic therapies were maintained.

Outcomes. The primary aim was to determine the ORR in accordance with RECIST v1.1, which is defined as the percentage of participants experiencing a complete response (CR) or a partial response (PR). The secondary outcomes encompassed ORR as defined by mRECIST, disease control rate (DCR), and duration of response (DoR).

Statistical analysis. All participants who received at least one study treatment were considered for efficacy and safety

analyses. Both the ORR and DCR were presented with their two-sided 95% confidence intervals (CIs), calculated using the Clopper-Pearson method. The median of the time-to-event variables was determined by the Kaplan-Meier technique, and their respective 95% CIs were derived using the Brookmeyer and Crowley method. All statistical evaluations were conducted using SPSS 25.0 (SPSS Inc., Chicago, IL, USA) or R version 4.1.0 software.

Results

Patients. From January 14th, 2024, to December 5th, 2024, 32 patients were enrolled. The majority of the participants (87.5%) were male, among whom the median age was 54.5. Among them, there were 18 patients with extrahepatic metastases. All cases had HBV infection. A total of 18 patients (56.2%) had PVTT at Vp3 or above (Table 1).

Efficacy. The median follow-up time was 6.1 months as of December 5th, 2024. Patients received an average of 3.57 cycles of treatment. ORR was determined to be 71.8% (95% CI: 55.4–88.3 %), DCR was 93.7% (95% CI: 84.9–99.9%) per RECIST1.1. The ORR was 78.1% (95% CI: 63–93.3%), DCR was 96.8% (95% CI: 90.1–99.9%) per mRECIST (Figures 1A–1D, Table 2). The median OS and median PFS have not yet been reached (Figures 2A–2D). After the triple therapy, 6 out of 32 patients achieved a CR according to mRECIST criteria and received combination maintenance therapy with adebrelimab and bevacizumab. In subgroup analysis, the ORR of patients above PVTT Vp3 was 83.3%; the ORR of patients with a newly diagnosed tumor larger than 10 cm was 75%; the ORR of patients with both was 72.7% (Figure 3).

Safety. All patients experienced TRAEs. One patient (3.1%) had ≥ 3 grade TRAEs and developed rash after treatment. Fifteen patients (46.8%) had increased aspartate aminotransferase, most of whom were grade 1. Fifteen patients (46.8%) had increased blood bilirubin. In 18 patients (56.2%) and 16 patients (50%), respectively, neutrophil and lymphocyte counts were observed to decrease after HAIC induction. Eleven patients experienced a decrease in platelet count (34.3%), but all were grade 1. Abdominal pain, vomiting, and anorexia were also common, occurring in 18 patients (56.3%), 15 patients (46.8%), and 8 patients (25%), respectively, usually during infusion of oxaliplatin.

Discussion

This retrospective cohort study demonstrated that the combination of adebrelimab, bevacizumab, and HAIC-FOLFOX has encouraging results and manageable safety concerns for patients with HCC at BCLC stage C, even in high-risk patients. Several triple combination treatment protocols have been registered previously. The LEAP-012 trial assessed the safety and efficacy of transarterial chemoembolization (TACE) combined with lenvatinib and pembrolizumab in participants with incurable or non-metastatic HCC compared to TACE alone [16]. Additionally, the EMERALD-1 global study evaluated the effectiveness of TACE combined with durvalumab and bevacizumab in patients with locoregional HCC, in contrast to TACE plus durvalumab or TACE alone. In our study, we opted for HAIC instead of TACE because it allows for a standardized operating procedure that is technically easier to replicate. Moreover, HAIC minimizes many variables that may affect TACE outcomes, such as inconsistencies in medication usage, varying skill levels among operators, and different operator habits.

Table 1. Baseline characteristics of patients.

Variables	All patients (n = 32)
Age, years, median (range)	54.5 (26–78)
≥ 50	20 (62.5%)
<50	12 (37.5%)
Sex, n (%)	
Male	28 (87.5%)
Female	4 (12.5%)
Etiology, n (%)	
Hepatitis B	32 (100.0%)
ECOG performance status score, n (%)	
0	11 (34.4%)
1	21 (65.6%)
Child-Pugh score, n (%)	
5	31 (96.9%)
6	1 (3.1%)
AFP, ng/ml, n (%)	
≥ 400	17 (53.1%)
<400	15 (46.9%)
Tumor size, cm, median (range)	10.1 (3.5–25.1)
≥ 10	16 (50.0%)
<10	16 (50.0%)
Venous tumor thrombus, n (%)	
PVTT, n (%)	
Vp2	6 (18.7%)
Vp3	8 (25.0%)
Vp4	10 (31.3%)
Absent	8 (25.0%)
IVCTT, n (%)	
Hepatic vein invasion	13 (40.6%)
IVC invasion	7 (21.9%)
Absent	12 (37.5%)
Extrahepatic metastasis, n (%)	
Present	18 (56.3%)
Absent	14 (43.7%)

Abbreviations: ECOG-Eastern Cooperative Oncology Group; AFP-alpha fetoprotein; PIVKA-II-prothrombin in vitamin K absence II, PVTT-portal vein tumor thrombosis

tinib and pembrolizumab in participants with incurable or non-metastatic HCC compared to TACE alone [16]. Additionally, the EMERALD-1 global study evaluated the effectiveness of TACE combined with durvalumab and bevacizumab in patients with locoregional HCC, in contrast to TACE plus durvalumab or TACE alone. In our study, we opted for HAIC instead of TACE because it allows for a standardized operating procedure that is technically easier to replicate. Moreover, HAIC minimizes many variables that may affect TACE outcomes, such as inconsistencies in medication usage, varying skill levels among operators, and different operator habits.

In this study, the ORR of the treatment was superior to that of current monotherapies, such as tyrosine kinase inhibitors (TKIs) or ICIs [17]. Specifically, ORR was 18.8% for lenva-

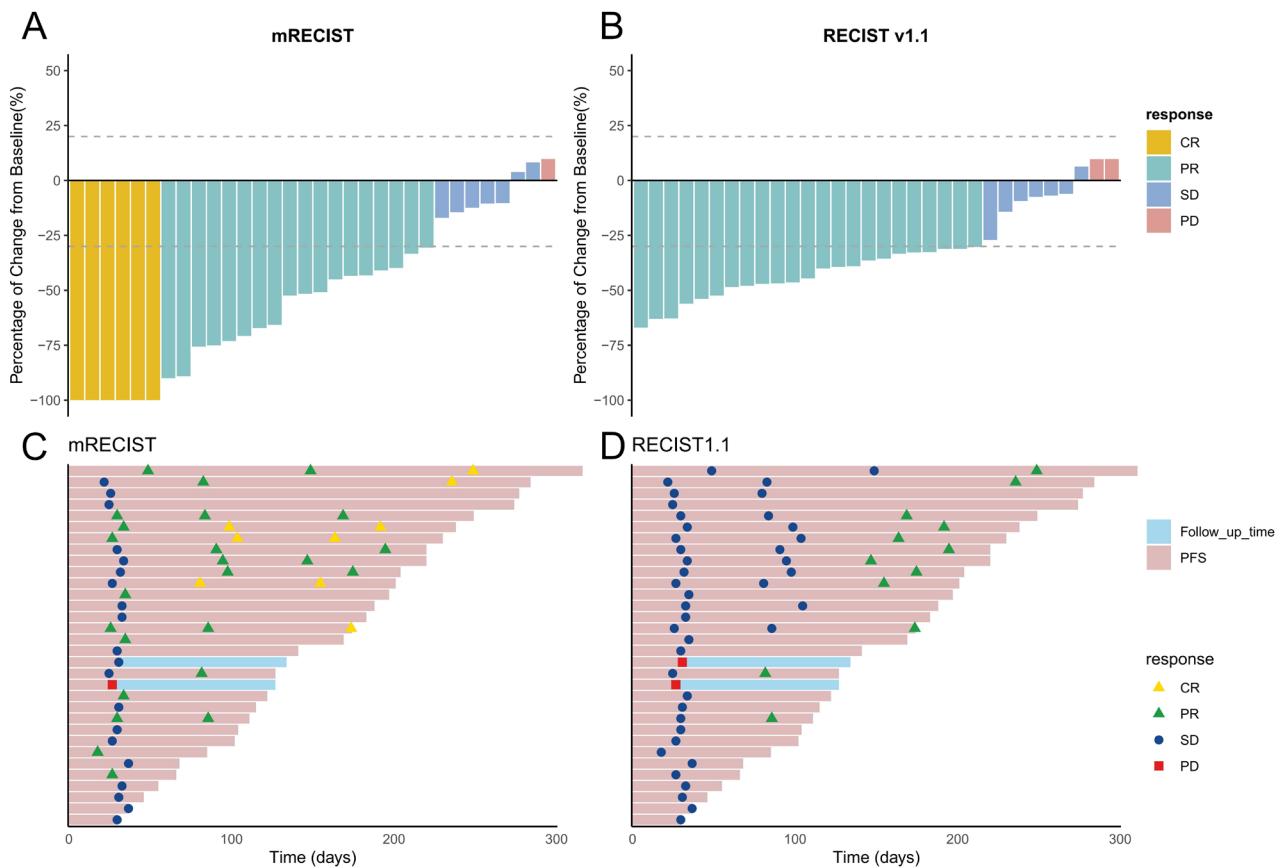


Figure 1. A) The best percentage change from baseline in target lesions as evaluated by RECIST v1.1. B) The best percentage change from baseline in target lesions according to mRECIST. C) An overview of treatment exposure and response duration assessed via RECIST v1.1. D) A summary of treatment exposure and response duration evaluated according to mRECIST.

Table 2. Tumor response.

Variables	All patients (n=32)	
	RECIST v1.1 (n=32)	mRECIST (n=32)
Best objective response, n (%)		
Complete response	0 (0.0%)	6 (18.7%)
Partial response	23 (71.8%)	19 (59.3%)
Stable disease	7 (21.8%)	6 (18.7%)
Progressive disease	2 (6.2%)	1 (3.1%)
Objective response rate, n (%)	71.8%	78.1%
95% CI	(55.4%, 88.3 %)	(63%, 93.3%)
Disease control rate, n (%)	93.7%	96.8%
95% CI	(84.9%, 99.9%)	(90.1%, 99.9%)
DOT, months, median (95% CI)	Not reached	
PFS, months, median (95% CI)		
6-month DOT rate, % (95% CI)	31.2% (14.3%, 48.2%)	
6-month PFS rate, % (95% CI)	46.9% (28.6%, 62.5%)	
Median follow-up time (months)	6.1	

Abbreviations: TTR-time to response; DOT-duration of response; PFS-progression-free survival; CI-confidence interval; RECIST-Response Evaluation Criteria in Solid Tumors; mRECIST-modified Response Evaluation Criteria in Solid Tumors

tinib in the REFLECT trial [18], 15% for nivolumab in the CheckMate 459 trial [19], and 18.3% for pembrolizumab in the KEYNOTE-240 trial [20]. With the combination of anti-angiogenic drugs and immunotherapy, significant progress has been made in the treatment landscape of HCC. The IMbrave150 study, which changed the first-line recommendation of BCLC guidelines, demonstrated that the ORR of PD-L1 inhibitor plus bevacizumab in the treatment of HCC was 27.3%, with a median PFS of 6.8 months [10]. In contrast to the IMbrave150 study, the triple therapy in our research exhibited a higher numerical ORR (71.8% / RECIST v1.1), suggesting that the addition of HAIC to PD-L1 inhibitor and bevacizumab might confer benefits to BCLC C-stage HCC.

Unlike intravenous chemotherapy, HAIC delivers chemotherapeutic drugs directly into the tumor. HAIC-FOLFOX can theoretically enhance the anti-tumor response of the PD-L1 antibody in combination with the bevacizumab regimen by stimulating tumor immunogenic antigen exposure. In HAIC, oxaliplatin can not only induce immunogenic cell death in HCC cells but also synergize with immune checkpoint blockade therapy at the same time by releasing tumor

Table 3. Treatment-related adverse events of all grades.

Events, n (%)	All patients (n = 32)			
	Any grade	Grade 1	Grade 2	Grade 3 or higher
Aspartate aminotransferase increased	15 (46.8%)	11(34.4%)	4 (12.5%)	0
Alanine aminotransferase increased	13 (40.6%)	9 (28.1%)	4 (12.5%)	0
Abdominal pain	18 (56.2%)	10 (31.3%)	8 (25%)	0
Blood bilirubin increased	15 (46.8%)	10 (31.3%)	5 (15.6%)	0
Platelet count decreased	11 (34.3%)	11 (34.4%)	0	0
Anemia	8 (25%)	8 (25%)	0	0
Neutrophil count decreased	18 (56.2%)	11 (34.4%)	7 (21.8%)	0
Lymphocyte count decreased	16 (50%)	13 (40.6%)	3 (9.4%)	0
Rash	7 (21.8%)	4 (12.5%)	2 (6.3%)	1 (3.1%)
Hypoalbuminemia	19 (59.4%)	18 (56.2%)	1 (3.1%)	0
Vomiting	15 (46.8%)	14 (43.8%)	1 (3.1%)	0
Fatigue	19 (59.4%)	15 (46.8%)	4 (12.5%)	0
Fever	9 (28.1%)	5 (15.6%)	4 (12.5%)	0
Ascites	5 (15.6%)	5 (15.6%)	0	0
Anorexia	15 (46.8%)	14 (43.8%)	1 (3.1%)	0

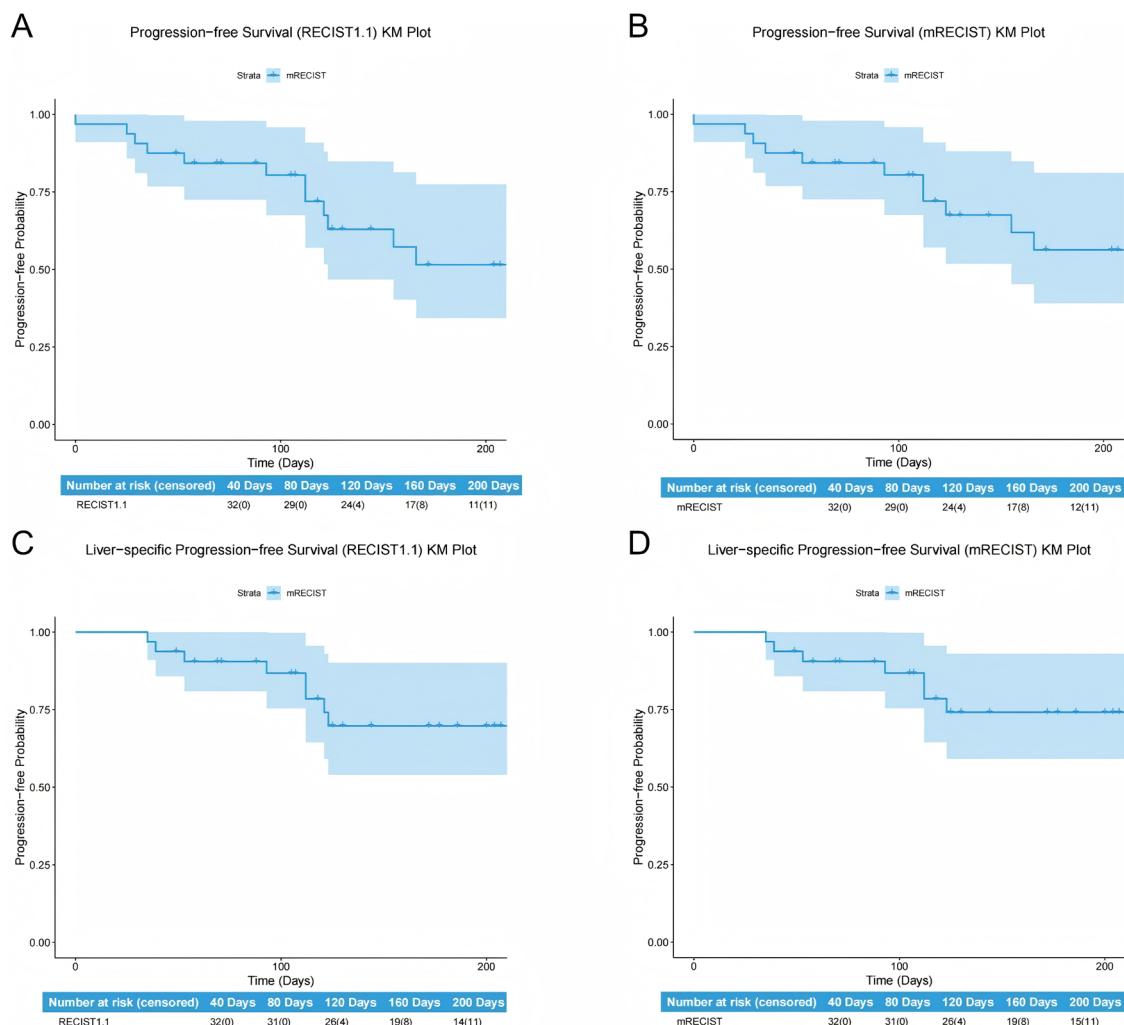


Figure 2. Survival analysis. A) Kaplan-Meier curves of progression-free survival (PFS) per RECIST v1.1. B) Kaplan-Meier curves of PFS per mRECIST. C) Kaplan-Meier curves of liver-specific PFS per RECIST v1.1. D) Kaplan-Meier curves of liver-specific PFS per mRECIST.

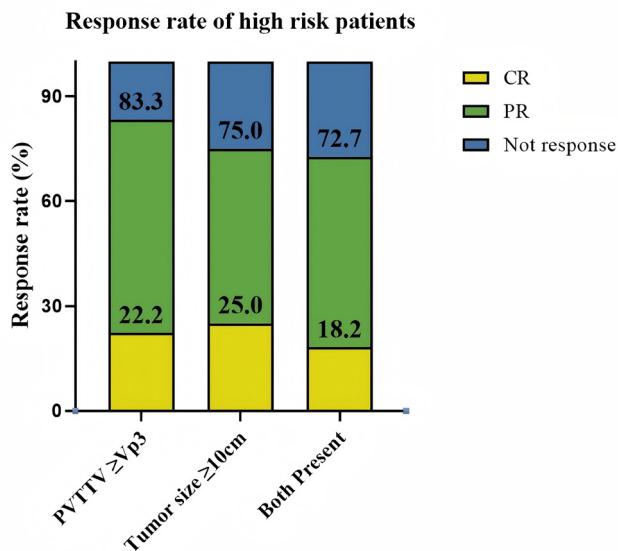


Figure3. The overall response rate of high-risk patients who have a PVTT \geq Vp3 or a tumor size \geq 10 cm at baseline.

antigens, transporting CRT to the cell surface, according to previous studies. Additionally, bevacizumab-induced vascular normalization prolongs, reduces tumor hypoxia and acidosis, and enhances the efficacy of infiltrating immune cells. Anti-PD-1 therapy targets immune checkpoints and activates the function of cytotoxic T lymphocytes, thereby providing more favorable anti-tumor activity [21, 22].

The ORR of the HAIC-FOLFOX, bevacizumab, and adebrelimab regimen was significantly higher than that of HAIC-FOLFOX, lenvatinib, and toripalimab (a PD-1 inhibitor) in LeToHAIC (78.1% vs. 67.7%) [23] and HAIC-FOLFOX, sintilimab (a PD-1 inhibitor) regimen (78.1% vs. 44.8%). As to PFS, the median PFS in our study has not yet been reached, showing great potential for progression-free survival benefit.

The prognosis of HCC patients with high-risk features remains poor. TRIPLET's ORR is higher than ours, but our study also included high-risk patients, such as 10 patients with Vp 3 PVTT and 11 patients with tumors larger than 10 cm. According to the subgroup analysis, the combination of adebrelimab, bevacizumab, and HAIC-FOLFOX elicited a high response rate of 72.7% (Figure 3) in these patients. Notably, one patient with an initially tumor diameter larger than 10 cm achieved a CR after three cycles of treatment. After triple therapy, 6 of 32 patients (18.8%) attained CR by mRECIST criteria, followed by maintenance therapy with adebrelimab and bevacizumab.

As to the AEs, previous studies have shown that the level of incidence of TRAE above grade 3 in similar studies is at a higher level, which is 15.5% and 74.3% according to the LeToHAIC study and TRIPLET study [14, 23]. Most of the AEs encountered in our study were generally well tolerated.

Only 1 patient (3.1%) had \geq 3 grade TRAEs and experienced rash after treatment, which is significantly lower than that in TRIPLET and LeToHAIC (3.1% vs. 74.3% and 15.5%). This trial also has its limitations. Firstly, this is a retrospective study, which may lead to data bias. Secondly, our study lacks biomarker analysis. Thirdly, the mean follow-up duration was not long enough.

Our study shows the combination of adebrelimab, bevacizumab, and HAIC-FOLFOX demonstrated encouraging results and manageable safety concerns for patients with HCC at BCLC stage C. HAIC results in high concentrations of local drugs through arterial perfusion of chemotherapeutic agents, and arterial perfusion of adebrelimab also has exciting potential that we will continue to explore in future studies.

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