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ORIGINAL RESEARCH

PD(L)1 Inhibitors Plus Lenvatinib Vs Atezolizumab Plus Bevacizumab Combined With HAIC for Unresectable HCC: A Propensity Score Matching Study

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Purpose: To compare the clinical outcomes of different systemic therapies, specifically PD(L)1 inhibitors plus Lenvatinib versus Atezolizumab plus Bevacizumab, when combined with hepatic arterial infusion chemotherapy (HAIC) based on the FOLFOX regimen (oxaliplatin, fluorouracil, and leucovorin) as first line treatment for unresectable hepatocellular carcinoma.

Patients and Methods: This real-world retrospective study enrolled 294 patients with unresectable HCC. All patients received HAIC in combination with either PD(L)1 inhibitors plus Lenvatinib (PLEN-HAIC) or Atezolizumab plus Bevacizumab (AT-HAIC). Propensity score matching (PSM) was performed to balance patient characteristics. The overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) were compared.

Results: After PSM, 80 and 130 patients received AT-HAIC and PLEN-HAIC, respectively. No significant differences were found in ORR between the AT-HAIC and PLEN-HAIC groups (50.0% vs 40.0% per RECIST, p = 0.202; 60.0% vs 57.7% per mRECIST, p = 0.853). Both groups showed similar disease control rates. Median PFS was 14.3 months for PLEN-HAIC versus 8.8 months for AT-HAIC (p = 0.018). Median OS was significantly better in the PLEN-HAIC group (p = 0.045, both not reached). Subgroup analysis revealed that Lenvatinib showed a better OS compared to Bevacizumab when combined with HAIC and PDL1 inhibitors (p = 0.023).

Conclusion: PLEN-HAIC offers significant survival benefits over AT-HAIC in advanced HCC. Given its remarkable efficacy, PLEN-HAIC could be a promising first-line option for unresectable HCC.

Keywords: hepatocellular carcinoma, immunotherapy, hepatic arterial infusion chemotherapy, propensity score matching, real-world study

Introduction

Primary liver cancer is the eighth most prevalent cancer worldwide, with hepatocellular carcinoma(HCC) constituting the majority histological type and accounting for 98% of all liver cancer cases.[1] For HCC patients, surgical treatment remains crucial for achieving the best prognosis.[2] However, due to the insidious development of liver cancer, only a small fraction of patients can undergo curative treatment. Patients with Portal Vein Tumor Thrombus (PVTT) or extra-hepatic metastasis are classified as advanced stage (BCLC stage C) by most guidelines.[3,4] Despite the wide range of surgical and locoregional therapy options available, approximately 50% of patients with unresectable HCC will eventually require systemic therapies, and their prognosis remains poor.[5]

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Lenvatinib, an oral multi-kinase inhibitor, has been approved worldwide after the REFLECT trial demonstrated its noninferiority to Sorafenib.[6] However, the moderate efficacy of single-agent therapy limits its clinical application. Although the LEAP-002 trial did not improve overall survival compared to Lenvatinib monotherapy, Pembrolizumab plus Lenvatinib did provide better survival outcomes among Asian populations and those with HBV infection.[7] Oral TKIs are of interests due to their convenient administration and improved dosing flexibility in treating hepatocellular carcinoma. Several clinical trials have reported that the combination of PD(L)1 inhibitors plus oral TKIs resulted in impressive ORR(ORR) and conversion-to-resection rates while with manageable safety.[8–10] Immune-based combination therapies have also shown promising antitumor activity. In the IMbrave150 clinical trial, the immune combination regimen of the PD-L1 inhibitor Atezolizumab plus the VEGF inhibitor Bevacizumab(AT) demonstrated significant efficacy in unresectable HCC, and became the new standard of care for first line systemic therapy.[11]

In recent years, Hepatic Arterial Infusion Chemotherapy (HAIC) based on the FOLFOX regimen has proven effective in treating unresectable HCC. With advantages in tumor shrinkage, excellent efficacy among PVTT cohorts, and manageable toxicity, HAIC is recommended and widely performed in the Asia-Pacific region.[12] Notably, compared to Transarterial Chemoembolization (TACE), FOLFOX-HAIC can significantly improve the overall survival of HCC patients with high tumor burden.[13] On the basis of the concept that HAIC can increase antigenicity and modulate the tumor environment when combined with systemic therapy, emerging studies have assessed the triple regimen of HAIC combined with TKIs and anti-PD1 immunotherapy, demonstrating impressive ORR and conversion-to-resection rates.[14–18] Few studies have also revealed the potent efficacy and tolerable safety of combining AT with intra-arterial therapy in patients with unresectable HCC.[19–22] Notwithstanding the various anti-angiogenic agents and immune checkpoint inhibitors options, there is no consensus on which systemic therapy exerts the most efficacy when paired with HAIC. Although AT is the current standard first-line systemic treatment for unresectable HCC, its widespread use may be limited by pharmacoeconomic considerations and cost-effectiveness. In contrast, PD-(L)1 inhibitors plus Lenvatinib (PLEN) are more commonly utilized in real-world clinical practice and are often combined with HAIC.[15,16,23–27] Yet, the relative superiority of PLEN versus AT when combined with HAIC in treating unresectable HCC remains unclear.

Hence, our study aims to compare these two different treatment patterns in combination with HAIC to identify the most suitable immuno-targeted strategy for integration with HAIC.

Methods

Study Population

This retrospective study included patients with unresectable HCC who received at least two cycle of hepatic arterial infusion chemotherapy combined with different systemic treatments (Atezolizumab plus Bevacizumab, AT; or PD-(L)1 inhibitors plus Lenvatinib, PLEN) between January 2022 and June 2023 from Sun Yat-sen University Cancer Center(SYSUCC). This study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 1983, and approved by the Institutional Review Board of SYSUCC. The Ethics Committee granted approval for this study (approval number: B2023-648-01). The HCC was diagnosed by pathology or image based on criteria of the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL).[28,29]

The inclusion criteria were as follows: patients with unresectable HCC and (a) treated by HAIC combined with AT or PLEN as initial treatment for at least two cycles; (b) aged 18–75 years; (c) patients had a tumor classification of Barcelona Clinic Liver Cancer (BCLC) B or C; (d) Child-Pugh (CP) was classified as A or B; (d) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and (e) adequate hematologic blood counts (white blood cell count > 3 × 109/L, absolute neutrophil count > 1.5 × 109/L, platelet count > 10 × 109/L, hemoglobin concentration > 85 g/L). The exclusion criteria were as follows: (a) prior systemic treatment or locoregional therapies; (b) other concomitant malignancies; (c) incomplete medical data; and (d) loss to follow-up.

Treatment Procedure

The HAIC procedure was performed using a microcatheter placed in the tumor-feeding arteries. Subsequently, patients were transferred to the inpatient ward, and the FOLFOX-based chemotherapeutic agents were infused into the hepatic

artery through an arterial pump at the following dosages: leucovorin 400 mg/m2, oxaliplatin 85 mg/m2, fluorouracil bolus 400 mg/m2 for 2 hours, and fluorouracil infusion 1200 mg/m2 for 23 or 46 hours. The catheter and sheath were removed after the completion of the HAIC procedure. HAIC was performed at intervals of 4–6 weeks, and continued until disease progression or serious treatment related toxicity occurred.

Patients received intravenous Atezolizumab (1200 mg) plus Bevacizumab (15 mg/kg), along with other PD(L)-1 inhibitors such as Camrelizumab (200 mg), Sintilimab (200 mg), Toripalimab (240 mg), Tislelizumab (200 mg), and Durvalumab (1500 mg), in combination with HAIC. In AT-HAIC group, the timeframe criteria for combination therapy was defined as the administration of HAIC concurrently with or up to 30 days before Atezolizumab (1200 mg) plus Bevacizumab (15 mg/kg).At least one cycle of Atezolizumab plus Bevacizumab should be used after the HAIC procedure. For the PLEN-HAIC group, Lenvatinib was administrated orally, at a dose of 12 mg/d for bodyweight ≥ 60 kg or 8 mg/d for bodyweight < 60 kg orally once daily. The administration of HAIC should be concurrently with or up to 30 days before PD(L)-1 inhibitors (Camrelizumab, Sintilimab, Tislelizumab, Toripalimab, Pembrolizumab, Durvalumab), and Lenvatinib was concomitant with HAIC or PD(L)-1 inhibitors.

Patients typically received 2–8 cycles of HAIC, with the total number of HAIC treatment times determined by a multi-discipline team (MDT). Efficacy evaluations were performed every 1–2 treatment cycles, and additional cycles administered based on the tumor response, liver function, physical condition and continued clinical benefit from HAIC. When patients achieved complete response(CR), partial response(PR), showed no further benefit from HAIC, or experienced intolerance to HAIC, the treatment regimen was transitioned from triple combination therapy to maintenance immuno-targeted therapy. For patients who developed progressive disease (PD) or unacceptable toxicity, the MDT recommended appropriate second-line treatments. The Immuno-target therapy(PLEN or AT) were administered until disease progression, death, unacceptable toxicity, patient request, physician's decision, or loss to follow-up.

Follow-up and Data Collection

Baseline characteristics and follow-up data were collected through hospital information system, including age, sex, ECOG PS score, etiology, cirrhosis, tumor diameter, tumor number, AFP and PIVKA-II level, alanine aminotransferase (ALT), albumin-bilirubin (ALBI) grade, albumin (ALB), aspartate aminotransferase (AST), total bilirubin (TBIL), presence of macrovascular invasion or extra-hepatic metastasis. Liver computed tomography (CT) or MRI scans were conducted to evaluate tumor response every 1–2 treatment cycles, with the patient's follow-up data also recorded until disease progression or death.

Response Assessments

The primary endpoints were ORR and PFS. Tumor responses were classified as progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR) according to mRECIST and RECIST version 1.1. The ORR was defined as the sum of PR and CR. The disease control rate (DCR) was defined as the sum of PR, SD, and CR. PFS referred to the time from the beginning of the initial combination therapy to the progression of the disease or death. The secondary endpoint was overall survival (OS). OS referred to the time interval from initial combination therapy to death from any cause.

Statistical Analysis

We used propensity score matching (PSM) to minimize the impact of confounding factors that may influence treatment decisions and to balance patient characteristics, including demographics (sex and age), tumor features (diameter, number, imaging cirrhosis, extra-hepatic metastasis, macrovascular invasion), and laboratory test levels, including platelet count (PLT), neutrophil count (NEU), lymphocyte count (LYM), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), and total bilirubin (TBIL), alpha f alpha fetoprotein (AFP). Continuous variables were analyzed using independent-sample or paired-sample t-tests, while categorical variables were analyzed using the $\chi 2$ test. Clinical parameters between the two groups were compared using the Mann–Whitney *U*-test and the $\chi 2$ test. Kaplan–Meier curves were used to analyze OS and PFS, and the Log rank test was employed for comparisons. To identify predictors of survival, both univariate and multivariate analyses were conducted using the Cox proportional hazards model. All

statistical tests were two-sided, with P values less than 0.05 deemed statistically significant. Statistical and propensity score matching (PSM) analyses were conducted using R version 4.3.2.

Results

Patients Characteristics

A total of 294 patients with advanced HCC under combination therapy were finally enrolled in this study. The flowchart of this study is illustrated in Figure 1. 93 patients in the AT-HAIC group received Hepatic Arterial Infusion Chemotherapy(HAIC) combined with Atezolizumab plus Bevacizumab(AT), while 201 patients in the PLEN-HAIC group received HAIC combined the PD(L)-1 plus Lenvatinib(PLEN). The PD(L)-1 inhibitor categories in PLEN-HAIC group are summarized in Supplementary Table 1.

Prior to PSM, more tumor numbers($p = 0.013$) and lower incidence of macro-vascular invasion($p = 0.007$) were observed in the AT-HAIC group. After performing 1:2 ratio matching, 80 patients in the AT-HAIC group and 130 patients in the PLEN-HAIC group were obtained. Baseline patient characteristics, including demographic(sex and age), tumor features(diameter, number, imaging cirrhosis, extra-hepatic metastasis, macro-vascular invasion) and laboratory test levels(PTL, NEU, LYM, ALT, AST, ALB, TBIL) were well matched between the groups after PSM (all $P > 0.3$, SMD <0.2). Both groups showed similar rates of conversion resection (13.8% vs 16.2%, after PSM, $p = 0.785$; Table 1).

Treatment Efficacy

The tumor responses before PSM are shown in Table 2. Based on the RECIST 1.1 criteria, the ORR and DCR of the AT-HAIC group were 48.4% and 96.8%, while those of the PLEN-HAIC group were 42.8% and 97.0%, respectively

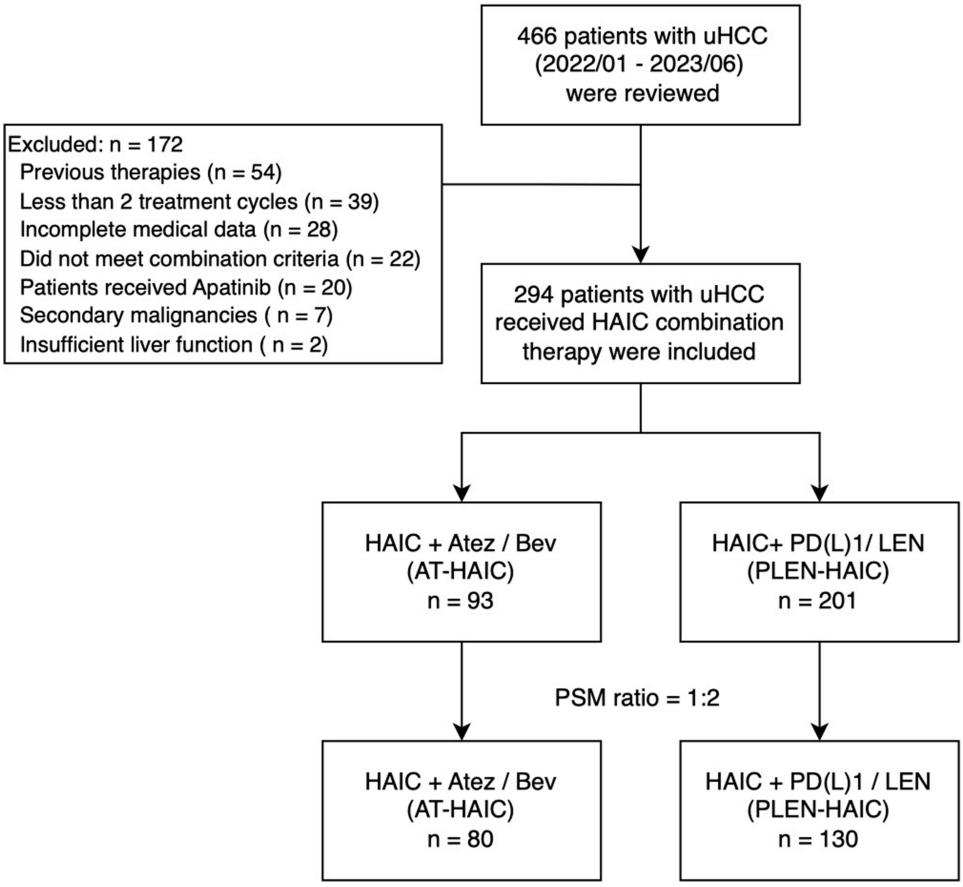

Figure 1 Flow chart of patients with unresectable HCC. **Abbreviations**: HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; LEN, Lenvatinib; Atez, atezolizumab; Bev, bevacizumab; PSM, propensity score matching.

Table 1 Baseline Characteristics of Unresectable HCC Received HAIC Combined With Different Systemic Therapy Before and After PSM

Variables	Before PSM		p	PSM		p
	AT-HAIC (n = 93)	PLEN-HAIC (n = 201)		AT-HAIC (n = 80)	PLEN-HAIC (n = 130)	
Sex			0.578			0.737
female	5 (5.4)	16 (8.0)		4 (5.0)	4 (3.1)	
male	88 (94.6)	185 (92.0)		76 (95.0)	126 (96.9)	
Age			0.370			0.860
<60	65 (69.9)	152 (75.6)		58 (72.5)	97 (74.6)	
≥60	28 (30.1)	49 (24.4)		22 (27.5)	33 (25.4)	
HBsAg			0.938			0.935
negative	28 (30.1)	63 (31.3)		24 (30.0)	37 (28.5)	
positive	65 (69.9)	138 (68.7)		56 (70.0)	93 (71.5)	
Diameter (cm)			0.589			0.663
<10cm	32 (36.8)	82 (41.0)		30 (37.5)	54 (41.5)	
≥10cm	55 (63.2)	118 (59.0)		50 (62.5)	76 (58.5)	
Numbers			0.013			0.936
<3	14 (15.1)	59 (29.4)		13 (16.2)	23 (17.7)	
≥3	79 (84.9)	142 (70.6)		67 (83.8)	107 (82.3)	
Cirrhosis			0.428			0.812
No	53 (57.0)	103 (51.2)		44 (55.0)	68 (52.3)	
Yes	40 (43.0)	98 (48.8)		36 (45.0)	62 (47.7)	
BCLC stage			0.354			0.999
B	15 (16.1)	23 (11.4)		12 (15.0)	20 (15.4)	
C	78 (83.9)	178 (88.6)		68 (85.0)	110 (84.6)	
Extra-hepatic metastasis			0.143			0.783
absent	55 (59.1)	138 (68.7)		50 (62.5)	85 (65.4)	
present	38 (40.9)	63 (31.3)		30 (37.5)	45 (34.6)	
Macro-vascular invasion			0.007			0.450
absent	30 (32.3)	35 (17.4)		23 (28.7)	30 (23.1)	
present	63 (67.7)	166 (82.6)		57 (71.2)	100 (76.9)	
PLT (10^9/L)			0.999			0.999
<100	88 (94.6)	191 (95.0)		75 (93.8)	123 (94.6)	
≥100	5 (5.4)	10 (5.0)		5 (6.2)	7 (5.4)	
NEU (10^9/L)			0.801			
<1.8	2 (2.2)	7 (3.5)		2 (2.5)	3 (2.3)	
≥1.8	91 (97.8)	194 (96.5)		78 (97.5)	127 (97.7)	
LYM (10^9/L)			0.950			0.694
<1.1	20 (21.5)	41 (20.4)		18 (22.5)	25 (19.2)	
≥1.1	73 (78.5)	160 (79.6)		62 (77.5)	105 (80.8)	
ALT (U/L)			0.720			0.451
<40	37 (39.8)	74 (36.8)		32 (40.0)	44 (33.8)	
≥40	56 (60.2)	127 (63.2)		48 (60.0)	86 (66.2)	
AST (U/L)			0.271			0.307
<40	22 (23.7)	35 (17.4)		21 (26.2)	25 (19.2)	
≥40	71 (76.3)	166 (82.6)		59 (73.8)	105 (80.8)	
TBIL (μmol/L)			0.999			0.565
<17.1	46 (49.5)	99 (49.3)		41 (51.2)	60 (46.2)	
≥17.1	47 (50.5)	102 (50.7)		39 (48.8)	70 (53.8)	
ALB (g/L)			0.231			0.615
<40	26 (28.0)	72 (35.8)		23 (28.7)	43 (33.1)	
≥40	67 (72.0)	129 (64.2)		57 (71.2)	87 (66.9)	

(*Continued*)

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Table 1 (Continued).

Variables	Before PSM		p	PSM		p
	AT-HAIC (n = 93)	PLEN-HAIC (n = 201)		AT-HAIC (n = 80)	PLEN-HAIC (n = 130)	
AFP (ng/mL)			0.341			0.680
<400	38 (40.9)	69 (34.3)		32 (40.0)	47 (36.2)	
≥400	55 (59.1)	132 (65.7)		48 (60.0)	83 (63.8)	
Conversion to resection			0.479			0.785
No	81 (87.1)	167 (83.1)		69 (86.2)	109 (83.8)	
Yes	12 (12.9)	34 (16.9)		11 (13.8)	21 (16.2)	
Treatment cycles			0.208			0.391
< 4 cycles	48 (51.6)	121 (60.2)		43 (53.8)	79 (60.8)	
≥ 4 cycles	45 (48.4)	80 (39.8)		37 (46.2)	51 (39.2)	

Notes: Values are presented as n (%). P values were calculated using a two-sided $\chi 2$ test.
Abbreviations: HBsAg, hepatitis B surface antigen; PLT, platelet; NEU, neutrophils; LYM, lymphocyte; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; AFP, alpha-fetoprotein; TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

Table 2 Treatment Efficacy Evaluated by RECIST and mRECIST Criteria Before PSM

	RECIST		p	mRECIST		p
	AT-HAIC (n = 93)	PLEN-HAIC (n = 201)		AT-HAIC (n = 93)	PLEN-HAIC (n = 201)	
Complete Response (%)				8 (8.6)	12 (6.0)	0.559
Partial Response (%)	45 (48.4)	86 (42.8)	0.440	45 (48.4)	107 (53.2)	0.517
Stable disease (%)	45 (48.4)	109 (54.2)	0.420	37 (39.8)	76 (37.8)	0.846
Progressive disease (%)	3 (3.2)	6 (3.0)	0.999	3 (3.2)	6 (3.0)	0.999
ORR (%)	45 (48.4)	86 (42.8)	0.440	53 (57.0)	119 (59.2)	0.817
DCR (%)	90 (96.8)	195 (97.0)	0.999	90 (96.8)	195 (97.0)	0.999

(p-value for ORR= 0.440, p-value for DCR = 1.00). According to mRECIST criteria, AT-HAIC group demonstrated an ORR and DCR of 57.0% and 96.8%, whereas the PLEN-HAIC group showed achieved 59.2% and 97.0%, respectively (p-value for ORR= 0.817, p-value for DCR = 1.00).

After PSM (Table 3), patients in the AT-HAIC group exhibited similar rates of ORR (50.0% vs 40.0%, p = 0.202) based on the RECIST 1.1 criteria, while the DCRs were 100% and 97.7%, respectively (p = 0.441). However, no

Table 3 Treatment Efficacy Evaluated by RECIST and mRECIST Criteria After PSM

	RECIST		p	mRECIST		p
	AT-HAIC (n = 80)	PLEN-HAIC (n = 130)		AT-HAIC (n = 88)	PLEN-HAIC (n = 130)	
Complete Response (%)				7 (8.8)	9 (6.9)	0.828
Partial Response (%)	40 (50.0)	52 (40.0)	0.202	41 (51.2)	66 (50.8)	0.999
Stable disease (%)	40 (50.0)	75 (57.7)	0.345	32 (40.0)	52 (40.0)	0.999
Progressive disease (%)	0 (0.0)	3 (2.3)	0.441	0 (0.0)	3 (2.3)	0.441
ORR (%)	40 (50.0)	52 (40.0)	0.202	48 (60.0)	75 (57.7)	0.853
DCR (%)	80 (100.0)	127 (97.7)	0.441	80 (100.0)	127 (97.7)	0.441

Notes: Summary of best response. Values are presented as n (%). P values were calculated using a two-sided $\chi 2$ test.
Abbreviations: mRECIST, modified response evaluation criteria in solid tumors; PSM, propensity score matching; RECIST, response evaluation criteria in solid tumors.

significant differences of the ORRs(60.0% vs 57.7%, p = 0.853) and DCRs(100% vs 97.7%, p = 0.441) were observed according to the mRECIST criteria.

Survival Outcomes

The median follow-up was 15.3 months(range, 2.3–27.3). During the follow-up, a total of 1079 cycles of HAIC combination therapy were administered, with a median of 4 cycles in both AT-HAIC (range, 2–6) and PLEN-HAIC group(range, 3–8). As shown in Table 1, the number of HAIC used in both groups did not show any statistical significance, either before (p = 0.208) or after PSM (p = 0.391). At the end of follow-up, 59 (63.4%) patients in the AT-HAIC group and 123 (61.2%) patients in the PLEN-HAIC group had disease progression or died. Median PFS was 8.8 months (95% CI, 7.1–12.5) in the AT-HAIC group, which was significantly shorter than that in the PLEN-HAIC group (11.7 months [95% CI, 10.7–14.7]; p = 0.036) (Figure 2A). There is no significant difference in terms of OS between the two groups (p = 0.13) (Figure 2B).

After matching, the median PFS was 8.8 (95% CI, 7.1–14.2) and 14.3 (95% CI, 11.4–16.7) months in the AT-HAIC and PLEN-HAIC groups, respectively (p = 0.018) (Figure 2C). The 6-month, 12-months, 24-months PFS rates were 65.0%, 40.6%, 24.7% in the AT-HAIC group and 84.1%, 57.4%, 32.2% in the PLEN-HAIC group, respectively. Although the median survival was not reached in either group, the OS of PLEN-HAIC group was better than that of the AT-HAIC group (p = 0.045, Figure 2D).The 6-month, 12-months, 24-months OS rates were 94.9%, 71.8%, 50.8% in the AT-HAIC group and 98.4%, 82.5%, 61.9% in the PLEN-HAIC group, respectively. The duration of response (DOR) for both groups before and after PSM are shown in Supplementary Figure 1A and B. There was no significant difference between the two groups (before PSM: p = 0.75; after PSM: p = 0.53).

Prognostic Factor Analysis

The multivariate analysis demonstrated that treatment group (PLEN-HAIC; HR = 0.64, 95% CI 0.45–0.93, p =0.018), and conversion to resection (yes; HR = 0.56, 95% CI 0.33–0.69, p = 0.035) were independent prognostic factors for PFS, while imaging cirrhosis (present; HR = 1.82, 95% CI 1.12–2.97, p = 0.015), extra-hepatic metastasis (present; HR = 1.93, 95% CI 1.20–3.10, p = 0.006) and conversion to resection (yes; 95% CI 0.07–0.72, p = 0.012) were predictive factors for OS. (Table 4)

Subgroup Analysis

Subgroup analysis revealed a persistent trend toward superior survival benefits in the PLEN-HAIC group compared to the AT-HAIC group (Figure 3). Additionally, PLEN-HAIC provided better clinical efficacy in both PFS and OS among patients with large tumor size, BCLC stage C and negative AFP levels. Given that some patients in the PLEN-HAIC group received the PD-L1 inhibitor(Durvalumab), as well as in the AT-HAIC group(Atezolizumab), we further investigated the prognosis of HAIC combined with PD-L1 inhibitor plus either Lenvatinib or Bevacizumab. The LEN combination group showed better OS compared to Bev combination group both before(p = 0.025) and after (p = 0.023) PSM (Supplementary Figure 2).

Discussion

This retrospective study aims to evaluate the efficacy of different systemic therapies, including PD(L)1 plus Lenvatinib or Atezolizumab plus Bevacizumab in combination with hepatic arterial infusion therapy (HAIC) in real-life settings for patients with unresectable HCC. Our findings indicate that the combination of PD-(L)1 inhibitors with Lenvatinib results in superior PFS and OS compared to the Atez/Bev combination when paired with HAIC.

Systemic therapy is considered the definitive treatment strategy for unresectable HCC.[3] Although Lenvatinib plus Pembrolizumab did not demonstrate superiority over Lenvatinib monotherapy, it showed strong efficacy in patients with unresectable HCC, particularly within Asian populations, with a median PFS of 8.3 months and a median OS of 26.3 months.[30] The CARES-310 study is the first to demonstrate significant improvements in survival outcomes over Sorafenib by using an anti-PD-1 antibody paired with an orally administered small-molecule anti-angiogenic agent. In this Phase 3 trial, the combination of Camrelizumab and Rivoceranib as first-line treatment for unresectable HCC resulted in a median overall survival of 22.1 months, the longest reported in any global phase 3 trial for systemic treatment.[10]

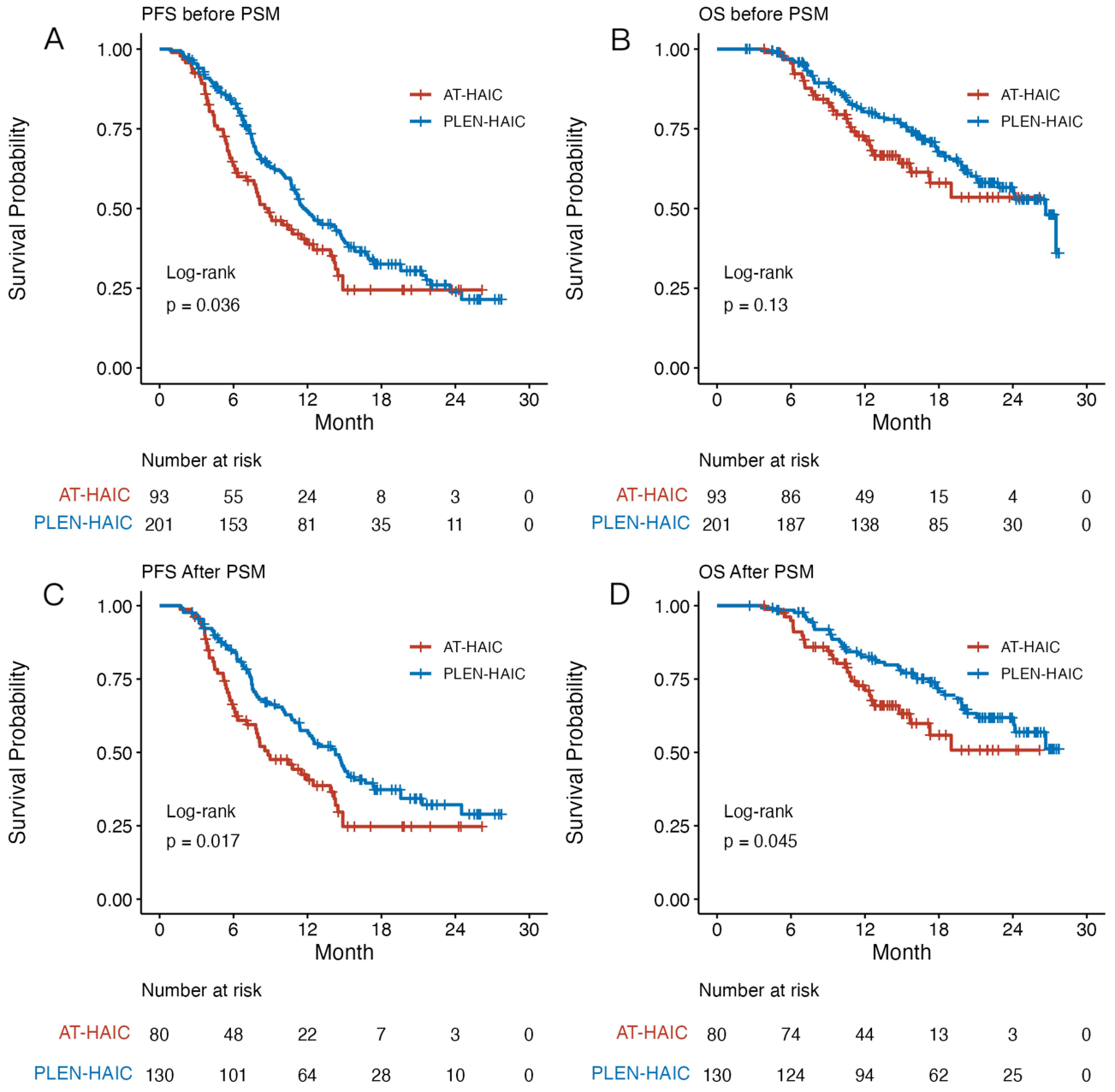


Figure 2 Kaplan–Meier survival curves comparing PFS and OS among unresectable HCC patients who underwent AT-HAIC versus PLEN-HAIC. **(A)** Progression free survival rate before propensity score matching; **(B)** Overall survival rate before propensity score matching; **(C)** Progression free survival rate after propensity score matching; **(D)** Overall survival rate after propensity score matching.

Despite the revolutionary success of immune checkpoint inhibitor-based therapy, there remains an urgent need to achieve deep and durable tumor responses.[31] The triple combination therapy of Lenvatinib, PD(L)-1 inhibitor and intra-arterial therapy is emerging as a pivotal treatment option in real-world clinical practice.[15,21,27] Several studies have explored the efficacy and safety of triple combination therapy, which has shown promising results in treating intermediate and advanced HCC, outperforming dual therapy with Lenvatinib and PD-1 inhibitors.[26,32] Currently, there is no clear consensus on the optimal immuno-targeted therapy regimen for triple combination conversion therapy. AT is recognized as the first-line standard treatment for unresectable HCC. On the other hand, On the other hand, the LEAP-002 trial showed that PLEN exhibited a trend toward greater benefit in the Asian subgroup compared with the overall population. Its lower cost and favorable pharmacoeconomic profile have led to its frequent utilization in clinical practice, particularly

Table 4 Univariate and Multivariate Analyses of Prognostic Factors for PFS and OS After PSM

Variables	PFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p	HR [95% CI]	p
Treatment (PLEN-HAIC)	0.65 [0.45–0.93]	0.018	0.64 [0.45–0.93]	0.018	0.61 [0.37–0.99]	0.047	0.63 [0.38–1.02]	0.062
Sex (male)	0.69 [0.28–1.70]	0.423			0.74 [0.23–2.36]	0.614		
Age (≥60)	0.91 [0.61–1.37]	0.652			0.89 [0.52–1.53]	0.679		
HBsAg (positive)	1.14 [0.77–1.67]	0.518			1.32 [0.77–2.28]	0.318		
Diameter (≥10cm)	1.47 [1.02–2.12]	0.039	1.37 [0.94–2.00]	0.105	1.47 [0.90–2.40]	0.127		
Numbers (≥3)	1.52 [0.93–2.49]	0.094			1.25 [0.67–2.33]	0.488		
Cirrhosis (present)	1.13 [0.80–1.61]	0.488			2.15 [1.33–3.47]	0.002	1.82 [1.12–2.97]	0.015
BCLC (stage C)	0.90 [0.56–1.44]	0.662			1.06 [0.54–2.07]	0.868		
Extra-hepatic metastasis (present)	1.36 [0.95–1.95]	0.093			2.31 [1.45–3.69]	<0.01	1.93 [1.20–3.10]	0.006
Macro-vascular invasion (present)	0.69 [0.46–1.01]	0.057			0.63 [0.38–1.06]	0.079		
ALT (≥40)	1.13 [0.78–1.64]	0.504			1.05 [0.64–1.71]	0.849		
AST (≥40)	1.58 [1.01–2.49]	0.047	1.40 [0.87–2.26]	0.165	1.81 [0.95–3.45]	0.071		
TBIL (≥17.1)	1.04 [0.73–1.48]	0.818			1.06 [0.66–1.68]	0.817		
ALB (≥40)	1.18 [0.80–1.74]	0.39			0.79 [0.49–1.29]	0.348		
PLT (≥100)	0.85 [0.37–1.92]	0.69			0.21 [0.03–1.51]	0.121		
NEU (≥1.8)	1.60 [0.39–6.46]	0.511			1.66 [0.23–11.96]	0.615		
LYM (≥1.1)	0.96 [0.61–1.50]	0.85			0.83 [0.46–1.49]	0.528		
AFP (≥400)	1.26 [0.88–1.82]	0.207			1.07 [0.66–1.73]	0.773		
Conversion to resection (yes)	0.50[0.29–0.84]	0.009	0.56 [0.33–0.96]	0.035	0.18 [0.06–0.56]	0.003	0.23 [0.07–0.72]	0.012
Treatment Cycles (≥4)	1.36 [0.94–1.97]	0.099			0.83 [0.52–1.32]	0.428		

Notes: The multivariable analysis includes the variables with P-value ≤0.05 from the univariable analysis.

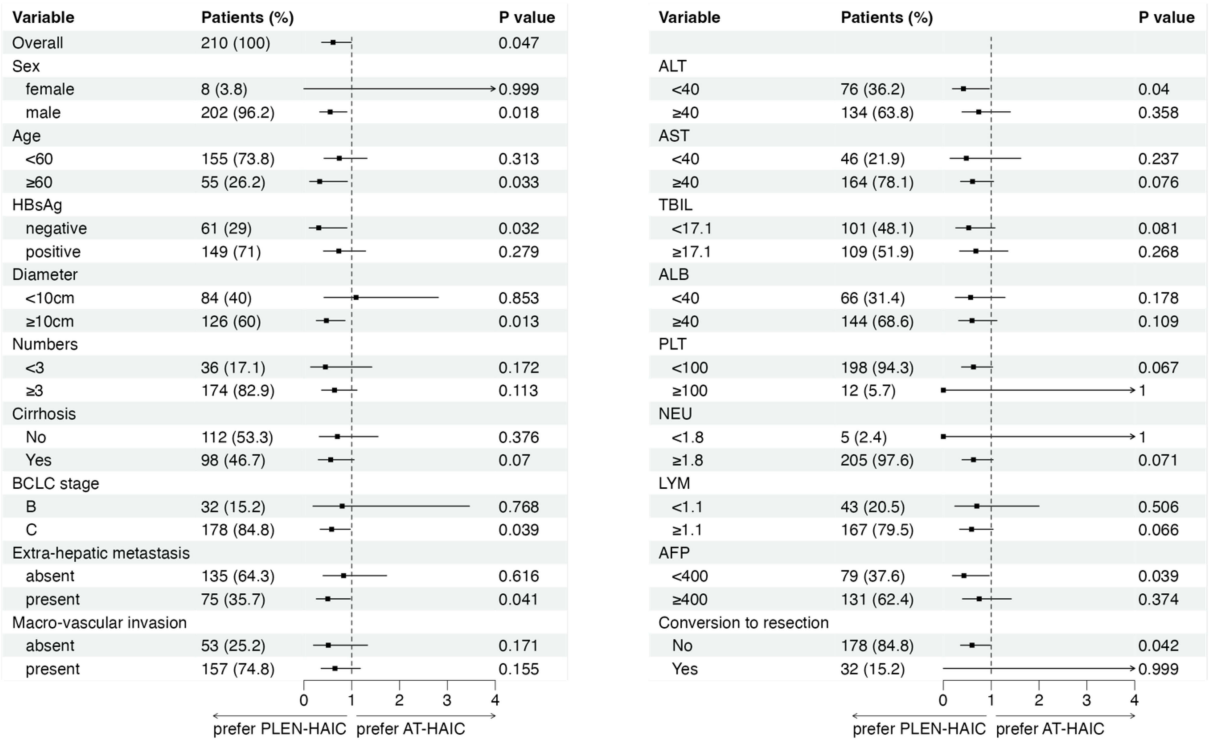
when combined with HAIC.[15,23,24,33] Based on this background, these two treatment regimens were compared to evaluate their efficacy and identify the most suitable approach for integration with HAIC.

In this study, PLEN-HAIC achieved remarkable efficacy, with an ORR of 40%(per RECIST) and 57.7%(per mRECIST), a median DOR of 13.6 months, a median PFS of 14.3 months, and a 1-year OS rate of 82.5%. The combination of HAIC, Lenvatinib and PD(L)1 inhibitors has significantly prolonged both progression-free survival and overall survival in patients with unresectable HCC. Notably, limited data are available regarding the combination of Atezolizumab plus Bevacizumab with HAIC. Such combination group in this study achieved an ORR of 50.0% (RECIST 1.1, after PSM) and a median PFS of 8.8 months, consistent with previous reports.[19,20] In addition, the AT-HAIC as first-line treatment in advanced HCC patients significantly improved ORR and PFS compared to the IMbrave150 trials and other real-world retrospective studies.[11]

The significant PFS and OS benefits observed in the PLEN group of our study suggest that Lenvatinib plus PD(L)1 inhibitors may be a more effective option for combination with HAIC. In the subgroup analysis, PLEN-HAIC versus AT-HAIC demonstrated better clinical benefits in both PFS and OS among patients with large tumor size, BCLC stage C and negative AFP levels.

The DurHope trial reported a median PFS of 5.5 month and an ORR of 47.4% in advanced HCC patients receiving HAIC combined with Lenvatinib plus Durvalumab(PD-L1 inhibitor).[27] Despite differing inclusion criteria, the corresponding subgroup in our study yielded an ORR of 60.9% and a median PFS of 14.7 months. Interestingly, this regimen outperformed in comparison to the Bevacizumab based regimen, suggesting that, compared to large-molecule monoclonal antibodies, small molecule targeted drugs combined with PD-L1 inhibitors and HAIC may provide additional benefits.

In this study, the combination of HAIC and immuno-targeted therapy demonstrated favorable outcomes, aligning with previous reports on triple combination therapy.[15,19,24,25,32] These results may stem from the synergistic effects of systemic and locoregional therapies. Tumor vasculature, unlike normal vascular structures, is characterized by high permeability and tortuous, dilated vessels. The combination of PD-(L)1 inhibitors and anti-angiogenic agents helps



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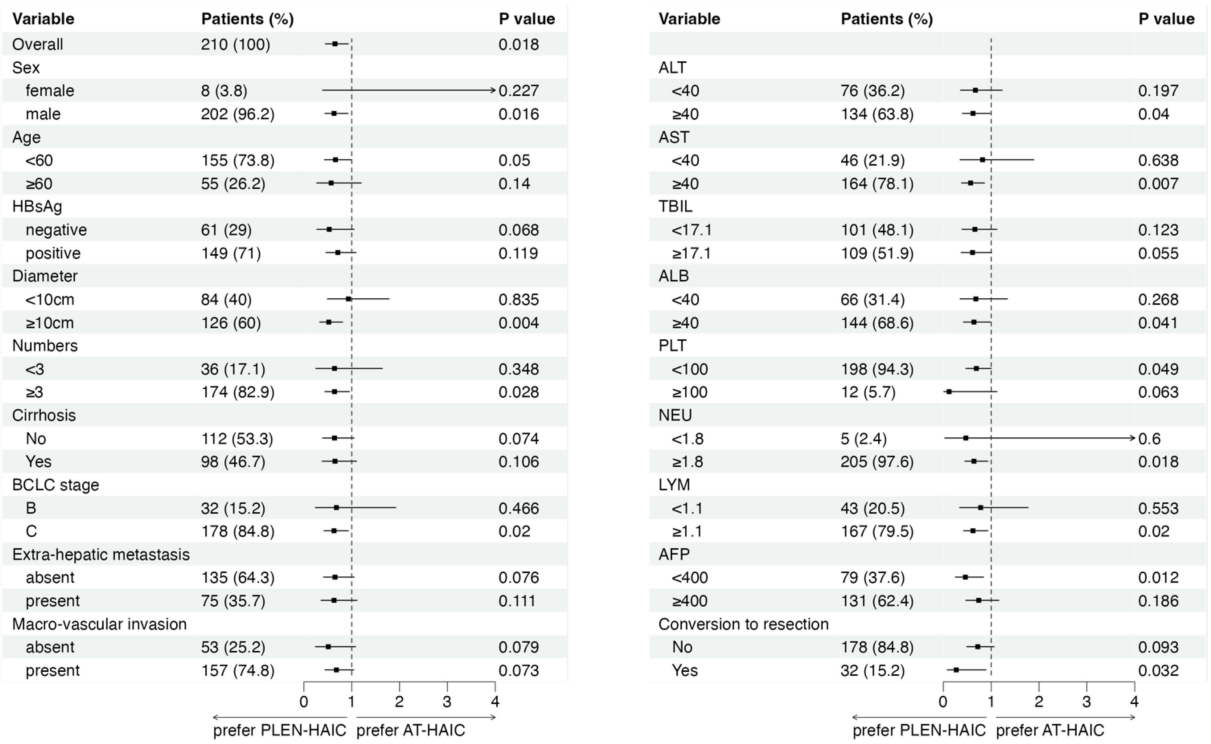

B

Figure 3 Forest plot of subgroup analysis. (**A)** Forest Plot of Subgroup Analysis for Progression free survival; (**B)** Forest Plot of Subgroup Analysis for Overall survival.

normalize tumor vasculature, reprogramming its structure and function, thereby increasing the drug delivery of cytotoxic agents.[34] FOLFOX-based HAIC enhances the antitumor effects of PD-(L)1 inhibitors by inducing the production and release of tumor antigens and ensuring a high concentration of chemotherapeutic agents within the tumor.

However, the efficacy of the two immuno-targeted regimens varies when combined with HAIC, potentially due to the distinct response patterns of Lenvatinib versus AT in combination with HAIC. Lenvatinib is a small-molecule multi-tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT. It acts intracellularly after crossing the cell membrane. In contrast, Bevacizumab, a large-molecule monoclonal antibody targeting VEGFR, functions extracellularly by binding to VEGFR on the cell surface.[35] Multi-kinase inhibitors are considered to exhibit relatively stronger tumor-killing and tumor-necrosis activity compared to anti-angiogenic agents.[36] It is reported that Lenvatinib primarily induces tumor necrosis by normalizing vasculature and reducing blood flow, while AT induces tumor response primarily through shrinkage and anti-VEGF effects before HAIC.[37] Compared to the tumor response pattern induced by AT, Lenvatinib-induced tumor necrosis may synergize with HAIC in stimulating the production and release of tumor antigens, further increasing the tumor's immunogenicity. As a result, this process promotes immune cell infiltration, further enhancing the efficacy of PD-(L)1 immune checkpoint inhibitors. In contrast, AT-induced tumor shrinkage may not fully maximize the advantages of HAIC, especially considering that HAIC tends to be more effective in patients with a high tumor burden.[13]

In addition, post-hoc analysis of FOHAIC-1 trial indicated that HAIC therapy was more cost-effective than targeted sorafenib.[38] Indeed, the high cost of the Atezolizumab plus Bevacizumab regimen limits its widespread use among patients with advanced HCC. In the contrast, the combination of Lenvatinib with PD-1 inhibitors not only offers superior efficacy but also significantly reduces expenses. This cost effectiveness allows more patients to afford and complete their treatments, ultimately improving their quality of life and health outcomes.

The combination of Lenvatinib with PD-(L)1 inhibitors has been widely adopted in clinical practice, and numerous studies have demonstrated its efficacy in treating HCC. Although the ICIs in the PLEN group were quite heterogeneous, this variability reflects the current real-world clinical practice, where treatment regimens often differ based on patient characteristics and clinician preferences. Taken together, when paired with HAIC, integrating an orally administered anti-angiogenic tyrosine kinase inhibitor into an immunotherapy combination regimen not only provides clinicians greater flexibility in treatment selection, but also significantly improve survival outcomes compared to a large-molecule immunotherapy regimen.

There are some limitations in current study. First, it was a retrospective study conducted at a single center, inherently carrying biases related to patient selection and data collection. Second, the follow-up period in the AT-HAIC group was not long enough, resulting in the median OS not yet being reached. Third, the study primarily focused on efficacy endpoints and lacked a detailed analysis of treatment-related adverse events. In the future, efforts should be made to extend the follow-up period to assess long-term efficacy and survival benefits. Additionally, basic research should be conducted to explore the molecular mechanisms underlying these differences.

In summary, when combined with hepatic arterial infusion chemotherapy, systemic therapy that incorporates an orally administered small-molecule anti-angiogenic drug with PD-(L)1 inhibitors outperforms large-molecule immunotherapy in controlling disease progression and prolonging overall survival. This approach may prove more effective in real-world clinical settings, positioning it as a promising alternative therapeutic strategy for HCC.

Abbreviations

HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; AT, Atezolizumab plus Bevacizumab; PLEN, PD(L)1 inhibitors plus Lenvatinib; PLT, platelet count; NEU, neutrophil count; LYM, lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; AFP, alpha fetoprotein; PIVKA-II, protein-II induced by vitamin K absence.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Study Approval Statement

This study protocol was reviewed and approved by Sun Yat-sen University Cancer Center, approval number: B2023-648-01

Consent to Participate Statement

The study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center. Given its retrospective nature, the requirement for written informed consent was waived by the Ethics Committee. This study does not include any patient-identifiable data, and individual consent was not required.

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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The authors have no conflicts of interest to declare for this work.

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