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Effectiveness and safety of angiogenesis inhibitors combined with PD-1/PD-L1 blockades in the first-line treatment of patients with advanced hepatocellular carcinoma

A single-center retrospective study

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Abstract

The combination of immune checkpoint inhibitors targeting anti-programmed cell death-1 (anti-PD-1) or anti-programmed death ligand-1 (anti-PD-L1) with antiangiogenic agents has emerged as a revolutionary therapy for advanced hepatocellular carcinoma (aHCC). Key antiangiogenic medications encompass monoclonal antibodies targeting vascular endothelial growth factor (anti-VEGF mAbs) and multiple kinase inhibitors (MKIs). The aim of this study is to assess the difference of efficacy and safety between 2 combination therapies. This study retrospectively examined the outcomes of 57 patients with aHCC who underwent first-line treatment with a combination of immune checkpoint inhibitors and antiangiogenic therapy at the First Affiliated Hospital of Anhui Medical University, from September 2018 to July 2023. The analysis, conducted using SPSS software, focused on patient outcomes such as tumor response (assessed according to modified Response Evaluation Criteria in Solid Tumors criteria), objective response rate, disease control rate, progression-free survival, overall survival, and safety. Comparisons among different groups were also made. The anti-PD-1/anti-PD-L1–anti-VEGF mAbs group showed a trend of higher partial response rate (37.50% vs 22.45%), objective response rate (37.50% vs 24.49%), disease control rate (62.50% vs 59.18%), and seemed to achieve longer median progression-free survival (14.93 vs 14.90 months) and median overall survival (15.80 vs 11.10 months) without higher grade 3 or higher adverse events comparing to anti-PD-1/anti-PD-L1–MKIs group. Subgroup analysis showed that the anti-PD-1–lenvatinib group achieved longer median progression-free survival (23.97 months), while the anti-PD-1–regorafenib group achieved longer median overall survival (37.97 months). The anti-PD-1/anti-PD-L1 combined with anti-VEGF mAbs was effective and tolerable compared to anti-PD-1/anti-PD-L1–MKIs in aHCC. The addition of lenvatinib or regorafenib may provide promising incremental benefit for patients with aHCC.

Abbreviations: aHCC = advanced hepatocellular carcinoma, anti-PD-1 = anti-programmed cell death-1, anti-PD-L1 = anti-programmed death ligand-1, anti-VEGF mAbs = monoclonal antibodies targeting vascular endothelial growth factor, CR = complete response, DCR = disease control rate, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, HCC = hepatocellular carcinoma, ICIs = immune checkpoint inhibitors, MKIs = multiple kinase inhibitors, mOS = median overall survival, mPFS = median progression-free survival, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PR = partial response, RCCEP = reactive cutaneous capillary endothelial proliferation, TRAEs = treatment-related adverse events, VEGF = vascular endothelial growth factor.

Keywords: advanced hepatocellular carcinoma, angiogenesis inhibitors, anti-VEGF mAbs, MKIs, PD-1/PD-L1 blockades

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study received approval from the ethics committee of the First Affiliated Hospital of Anhui Medical University in accordance with ethical standards.

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1. Introduction

Based on statistics from the GLOBOCAN 2020 database, liver cancer poses a significant global health burden, standing as the 6th most common cancer in terms of incidence (accounting for 4.7% of all cases) and the 3rd leading cause of cancer-related deaths (representing 8.3% of all fatalities).[1] Among primary liver cancer cases, hepatocellular carcinoma (HCC) comprises a substantial proportion, ranging from 75% to 85%.[2] Due to the challenges in early-stage detection, the prognosis for HCC is unfavorable.[3] Specially, in advanced hepatocellular carcinoma (aHCC), the treatment options are limited. Over the past few years, there has been a notable breakthrough in tumor drug development, particularly for HCC, with the advent of therapy involving immune checkpoint inhibitors (ICIs) targeting anti-programmed cell death-1 (anti-PD-1) or anti-programmed death ligand-1 (anti-PD-L1).[4,5] Nonetheless, in first-line treatment, nivolumab was unable to demonstrate its superiority in terms of survival benefit when compared to sorafenib.[6] Likewise, in the context of second-line treatment, patients who received pembrolizumab (anti-PD-1 monotherapy) along with the best supportive care did not demonstrate a notable enhancement in overall survival (OS) when compared to those who received placebo in combination with the best supportive care, with survival durations of 13.9 months versus 10.6 months (P = .0238), respectively.[7] Hence, it is imperative to investigate combined approaches with other therapies in order to augment the effectiveness of ICIs in the management of aHCC. Prominent potential medications encompass monoclonal antibodies targeting vascular endothelial growth factor (anti-VEGF mAbs) and multiple kinase inhibitors (MKIs).[8] The ongoing research and investigation focus on combining ICIs with antiangiogenic agents. Preliminary studies and clinical trials have shown promising benefits of this combined therapy in improving treatment outcomes for patients with aHCC.[9,10] However, no studies have yet compared the therapeutic efficacy of ICIs in combination with anti-VEGF mAbs versus ICIs combined with MKIs in the first-line treatment of aHCC.

Angiogenesis and immune evasion are 2 fundamental characteristics of cancer, including HCC.[11] The majority of HCC exhibit hypervascularity, and the increased expression of vascular endothelial growth factor (VEGF) has been associated with the onset and advancement of the disease.[12] Apart from its involvement in angiogenesis, VEGF also exerts an immunomodulatory influence, and research has confirmed that antiangiogenic medications can modulate immune-related cells within the tumor microenvironment, thereby influencing the clinical effectiveness of ICIs.[13]

Monoclonal antibodies against VEGF, like bevacizumab, are designed to target VEGF,[14] thereby suppressing angiogenesis and tumor growth.[15] In single-agent phase 2 trials involving patients with advanced liver cancer, they demonstrated response rates ranging from 13% to 14%.[11] In the IMbrave150 phase III clinical trial,[16] the combination therapy of atezolizumab (a PD-L1 antibody) and bevacizumab (a VEGF inhibitor) exhibited improved OS compared to sorafenib, with a hazard ratio of 0.58 (95% CI, 0.42–0.79; P = .0006). Additionally, it achieved response rates (objective response rate [ORR] and disease control rate [DCR]) exceeding 27% according to RECIST v1.1 criteria. This combination therapy has now been incorporated into the National Comprehensive Cancer Network guidelines for hepatobiliary cancer.

Sorafenib and lenvatinib, both classified as MKIs, have received approval as the primary systemic treatments for unresectable hepatocellular carcinoma. This approval was grounded in research demonstrating a slightly extended survival period with sorafenib compared to placebo[17] and the non-inferiority of lenvatinib when compared to sorafenib.[18] Both drugs come with significant side effects that adversely affect the quality of life. The blocking of the VEGF pathway by MKIs not only boosts the activities of effector T cells within the tumor microenvironment but also reduces the presence of suppressive immune cells.[19,20] Furthermore, HCC tissue treated with MKIs exhibited a substantial increase in PD-L1 expression within immune cells.[21] When used in conjunction with anti-PD-1, MKIs suppressed tumor growth by stimulating the activity of natural killer cells effectively.[22] This data indicates that MKIs could serve as a promising option for combination therapy with ICIs.

The combination of ICIs with antiangiogenic agents is a topic of ongoing research and investigation. Early investigations and clinical trials have demonstrated promising advantages associated with this combination therapy for enhancing treatment outcomes in patients with aHCC. Nonetheless, there has not been any research comparing the therapeutic effectiveness of anti-PD-1/anti-PD-L1 combined with anti-VEGF mAbs therapy and anti-PD-1/anti-PD-L1 combined with MKIs therapy in the first-line treatment of aHCC. This study aims to assess the disparities in both effectiveness and safety between these 2 combination therapies.

2. Methods

2.1. Patients and study design

During September 2018 to July 2023, a retrospective review was conducted on 57 patients with aHCC who received first-line treatment involving the combination of ICIs and antiangiogenic therapy at the First Affiliated Hospital of Anhui Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study protocol was approved by the Institutional Review Boards of the First Affiliated Hospital of Anhui Medical University and the requirement for informed consent was waived due to the retrospective nature of this study.

The study encompassed individuals aged 18 years or older, who had been diagnosed with aHCC based on either histopathological or clinical confirmation, following the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition) in China. Additionally, they had undergone a minimum of 2 cycles of therapy involving the combination of ICIs and antiangiogenic treatment. Patients meeting the eligibility criteria were also mandated to possess survival data, records of adverse events, and at least 1 set of follow-up radiological data. Patients who had previously undergone radical surgery or local therapy, had a comorbidity of autoimmune disease or other malignant tumor, as well as those without efficacy assessment, were excluded from this study. Patient characteristics, including age, gender, history of viral hepatitis, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score, Child-Pugh scale, tumor stage (cTNM stage), portal vein tumor thrombus, intrahepatic spread, and metastatic site, were collected and analyzed.

2.2. Outcome assessment

Treatment responses were assessed through computed tomography scans or magnetic resonance imaging every 2 to 3 months, following the modified Response Evaluation Criteria in Solid Tumors criteria.[23] When a patient had multiple tumors, the effectiveness of the treatment was assessed based on the overall tumor response, encompassing a comprehensive evaluation of both target and nontarget lesions, as well as any new lesions. The outcomes of tumor response to treatment were categorized into 4 groups: complete response (CR), partial response (PR), progressive disease, and stable disease. The study's endpoints comprised the ORR, DCR, progression-free survival (PFS), OS, and safety. ORR was determined by calculating the percentage of patients who achieved either a CR or a PR. DCR

Table 1

Baseline characteristics of 57 patients with aHCC who received anti-PD-1/anti-PD-L1 combined anti-VEGF mAbs therapy or anti-PD-1/anti-PD-L1 combined MKIs therapy.

Characteristic	Anti-PD-1/anti-PD-L1 plus anti-VEGF mAbs (n = 8)No. of patient (%)	Anti-PD-1/anti-PD-L1 plus MKIs (n = 49)No. of patient (%)	*P*-value*
Age(year)			.404
≤57	5(62.50%)	24(48.98%)	
>57	3(37.50%)	25(51.02%)	
Gender			.311
Male	6(75.00%)	43(87.76%)	
Female	2(25.00%)	6(12.24%)	
History of viral hepatitis			.808
None	2(25.00%)	18(36.73%)	
CHB	6(75.00%)	28(57.14%)	
CHC	0(0%)	3(6.12%)	
ECOG-PS score			.239
0	5(62.50%)	17(34.69%)	
1	3(37.50%)	32(65.31%)	
Child-Pugh scale			.841
A	6(75.00%)	31(63.27%)	
B	2(25.00%)	11(22.45%)	
C	0(0%)	1(2.04%)	
cTNM stage			.572
Stage I	1(12.50%)	2(4.08%)	
Stage II	0(0%)	3(6.12%)	
Stage III	1(12.50%)	14(28.57%)	
Stage IV	6(75.00%)	30(61.22%)	
Metastatic site			.922
Distant lymph node	4(50.00%)	24(48.98%)	
Lung	1(12.50%)	5(10.20%)	
Bone	3(37.50%)	10(20.41%)	
Brain	0(0%)	1(2.04%)	
Adrenal gland	0(0%)	2(4.08%)	
PVTT	5(62.50%)	20(40.82%)	
Intrahepatic spread	3(37.50%)	22(44.90%)	

Anti-PD-1 = anti-programmed cell death-1, anti-PD-L1 = anti-programmed death ligand-1, anti-VEGF mAbs = monoclonal antibodies targeting vascular endothelial growth factor, CHB = chronic hepatitis B, CHC = chronic hepatitis C, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, MKIs = multiple kinase inhibitors, PVTT = portal vein tumor thrombus.

* Chi-squared test; Fisher exact test.

was calculated as the percentage of patients who achieved a confirmed CR, PR, or stable disease as their best response. PFS was defined as the duration from the initiation of therapy to the occurrence of radiographic disease progression or death from any cause. OS was defined as the period from the initiation of therapy until the date of death from any cause. Complications after treatment were documented using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 5.0)[24]: grade 1, mild or asymptomatic adverse events; grade 2, moderate adverse events requiring minimal, local, and noninvasive intervention; grade 3, severe or disabling adverse events with prolonged hospitalization indicated; grade 4, life-threatening adverse events requiring urgent intervention; and grade 5, death related to adverse events.

2.3. Statistical analysis

The statistical analysis was performed using the SPSS software (version 21.0, SPSS Institute, IL). The normality of data distribution was assessed using the Shapiro–Wilk test. Continuous variables were reported as the mean with standard deviation for data that followed a normal distribution or as the median and interquartile range for data that exhibited a skewed distribution. Categorical variables were represented as counts and percentages. Between-group comparisons for continuous variables with a normal distribution were conducted using Student *t* test, while those with a skewed distribution were assessed using the Mann–Whitney *U* test. For categorical variables, between-group comparisons were performed using either Chi-squared tests or Fisher exact tests. Kaplan–Meier methodology was employed to calculate PFS and OS, followed by a stratified Log rank test for comparisons. The analysis of ORR and DCR was predicated on the best overall response. A *P*-value of <.05 was considered significant.

3. Results

3.1. Patient characteristics

We conducted this retrospective review on a total of 57 aHCC patients at the First Affiliated Hospital of Anhui Medical University between September 2018 and July 2023, these patients underwent anti-PD-1/anti-PD-L1 combined angiogenesis inhibitors therapy and had not previously received systemic treatment. Among these patients, 8 individuals received a combination therapy of anti-PD-1/anti-PD-L1 and anti-VEGF mAbs. Specifically, there were 5 cases of bevacizumab and 3 cases of HLX04. Additionally, 49 patients underwent treatment with anti-PD-1/anti-PD-L1 in combination with MKIs. This included 8 cases of sorafenib, 18 cases of lenvatinib, 8 cases of donafenib, 12 cases of apatinib, 2 cases of anlotinib, and 1 case of regorafenib. The patient baseline characteristics, including age, gender, history of viral hepatitis, ECOG-PS score, Child-Pugh scale, tumor stage (cTNM stage), portal vein tumor thrombus, intrahepatic spread, and metastatic site, were found to be generally well balanced between the 2 groups ($P > .05$) (Table 1).

3.2. Treatment response after combined ICIs with antiangiogenic agent therapy in aHCC

The anti-PD-1/anti-PD-L1–anti-VEGF mAbs group showed a trend of higher PR rate (37.50% vs 22.45%), ORR (37.50%

vs 24.49%), and DCR (62.50% vs 59.18%) compared to the anti-PD-1/anti-PD-L1–MKIs group. However, this difference was not statistically significant ($P > .05$) (Table 2).

Among the 8 patients who received anti-PD-1/anti-PD-L1 combined anti-VEGF mAbs treatment, 6 patients were treated with anti-PD-1 therapy and 2 patients were treated with anti-PD-L1 therapy. The ORR in the anti-PD-1 group was 33.33% (2 out of 6 patients), while in the anti-PD-L1 group it was 50.00% (1 out of 2 patients). The *P*-value for the comparison of ORR between the 2 groups was 1.000, indicating no statistically significant difference. Similarly, the DCR in the anti-PD-1 group was 50.00% (3 out of 6 patients), while in the anti-PD-L1 group it was 100.00% (2 out of 2 patients). The *P*-value for the comparison of DCR between the 2 groups was .464, also indicating no statistically significant difference (Table 3).

Among the 55 patients who received anti-PD-1 combined anti-VEGF treatment, 6 patients were treated with anti-VEGF mAbs therapy and 49 patients were treated with MKIs therapy. The anti-PD-1–anti-VEGF mAbs group showed a higher PR rate of 33.33% compared to the anti-PD-1–MKIs group with a PR rate of 22.45%. The ORR in the anti-PD-1–anti-VEGF mAbs group was 33.33%, while in the anti-PD-1–MKIs group it was 24.49%. On the other hand, the DCR in the anti-PD-1–anti-VEGF mAbs group was 50.00%, which was lower than the DCR of 59.18% in the anti-PD-1–MKIs group (Table 4).

Table 2

Treatment response to anti-PD-1/anti-PD-L1 combined anti-VEGF mAbs therapy or anti-PD-1/anti-PD-L1 combined MKIs therapy.

Outcome	Anti-PD-1/anti-PD-L1 plus anti-VEGF mAbs No. of patient (%)	Anti-PD-1/anti-PD-L1 plus MKIs No. of patient (%)	*P*-value*
n	8	49	
CR	0(0)	1(2.04%)	1.000
PR	3(37.50%)	11(22.45%)	.391
SD	2(25.00%)	17(34.69%)	.706
PD	3(37.50%)	20(40.82%)	1.000
ORR	3(37.50%)	12(24.49%)	.422
DCR	5(62.50%)	29(59.18%)	1.000

Anti-PD-1 = anti-programmed cell death-1, anti-PD-L1 = anti-programmed death ligand-1, anti-VEGF mAbs = monoclonal antibodies targeting vascular endothelial growth factor, CR = complete response, DCR = disease control rate, MKIs = multiple kinase inhibitors, ORR = objective response rate, PD = progressive disease, PR = partial response, SD = stable disease.

* Chi-squared test; Fisher exact test.

Table 3

Treatment response to anti-PD-1 combined anti-VEGF mAbs therapy or anti-PD-L1 combined anti-VEGF mAbs therapy.

Outcome	Anti-PD-1 plus anti-VEGF mAbs No. of patient (%)	Anti-PD-L1 plus anti-VEGF mAbs No. of patient (%)	*P*-value*
n	6	2	
CR	0(0)	0(0)	–
PR	2(33.33%)	1(50.00%)	1.000
SD	1(16.67%)	1(50.00%)	.464
PD	3(50.00%)	0(0)	.464
ORR	2(33.33%)	1(50.00%)	1.000
DCR	3(50.00%)	2(100%)	.464

Anti-PD-1 = anti-programmed cell death-1, anti-PD-L1 = anti-programmed death ligand-1, anti-VEGF mAbs = monoclonal antibodies targeting vascular endothelial growth factor, CR = complete response, DCR = disease control rate, ORR = objective response rate, PD = progressive disease, PR = partial response, SD = stable disease.

* Chi-squared test; Fisher exact test.

In the group of patients receiving anti-PD-1 combined with MKIs treatment (n = 49), the specific MKIs utilized included regorafenib (1 case), sorafenib (8 cases), lenvatinib (18 cases), donafenib (8 cases), apatinib (12 cases), and anlotinib (2 cases). Among the different MKIs used in the anti-PD-1 combined MKIs treatment group, the specific ORR rates were as follows: regorafenib: 0% (0 out of 1 patient), sorafenib: 37.50% (3 out of 8 patients), lenvatinib: 22.22% (4 out of 18 patients), donafenib: 37.50% (3 out of 8 patients), apatinib: 8.33% (1 out of 12 patients), anlotinib: 50.00% (1 out of 2 patients). The Chi-square value was 4.900, and the *P*-value was .430, suggesting no statistically significant difference in the distribution of MKIs used. The DCR for the different MKIs used in the anti-PD-1 combined MKIs treatment group were as follows: regorafenib: 0% (0 out of 1 patient), sorafenib: 62.50% (5 out of 8 patients), lenvatinib: 55.56% (10 out of 18 patients), donafenib: 87.50% (7 out of 8 patients), apatinib: 50.00% (6 out of 12 patients), anlotinib: 50.00% (1 out of 2 patients). The Chi-square value for the comparison of DCR between these different MKIs was 4.898, and the *P*-value was .430, indicating no statistically significant difference in the distribution of MKIs used (Table 5).

3.3. PFS and OS after combined ICIs with antiangiogenic agent therapy in aHCC

The median progression-free survival (mPFS) of the anti-PD-1/anti-PD-L1–anti-VEGF mAbs was 14.93 months (95% CI: 13.36–16.51), which was slightly longer than the mPFS of the anti-PD-1/anti-PD-L1–MKIs group, which was 14.90 months (95% CI: 7.82–21.98). However, this difference was not statistically significant ($P = .675$). The median overall survival (mOS) for the 2 groups were 15.80 months (95% CI: 0–33.86) and 11.10 months (95% CI: 7.12–15.08), respectively. Again, there was no statistically significant difference between the 2 groups ($P = .743$) (Fig. 1).

The mPFS for the anti-PD-1–anti-VEGF mAbs group was 14.20 months (95% CI: 5.94–22.47), while the mPFS for the anti-PD-1–MKIs group was 14.90 months (95% CI: 7.82–21.98). There was no statistically significant difference between the 2 groups ($P = .985$). However, the anti-PD-1–anti-VEGF mAbs group exhibited a longer mOS of 18.67 months compared to the mOS of 11.10 months in the anti-PD-1–MKIs group ($P = .469$) (Fig. 2).

The PFS and OS were assessed among different anti-PD-1–MKIs groups. The mPFS for regorafenib was 10.13 months, for sorafenib was 16.40 months, for lenvatinib was 23.97 months, for apatinib was 11.10 months, and for anlotinib was 0.67 months. The mOS for these groups were 37.97 months for regorafenib, 6.13 months for sorafenib, 23.90 months for lenvatinib, 7.10 months for apatinib, 11.10 months for anlotinib, and 6.30 months for donafenib. In summary, the anti-PD-1–lenvatinib group achieved longer mPFS, while the anti-PD-1–regorafenib group achieved longer mOS. However, these differences among different anti-PD-1–MKIs groups were not statistically significant ($P > .05$).

3.4. Adverse events of aHCC patients after combined ICIs with antiangiogenic agent therapy

Among the 57 patients, 40 of them (70.18%) reported adverse events of any grade, regardless of causality. The most common treatment-related adverse events (TRAEs) were diarrhea, elevated aspartate aminotransferase, hypertension, reactive cutaneous capillary endothelial proliferation (RCCEP), anemia, and increased blood bilirubin, with incidences of 22.81%, 19.30%, 17.54%, 15.79%, 15.79%, and 15.79%, respectively. In terms of grade 3 or higher adverse events, 23 patients (57.50%) experienced TRAEs of this severity. These included elevated aspartate aminotransferase (5.26%), hypertension

(5.26%), anemia (5.26%), increased blood bilirubin (5.26%), leukocytopenia (5.26%), and upper gastrointestinal bleeding (5.26%). Unfortunately, 1 fatal adverse event occurred due to upper gastrointestinal bleeding. In the anti-PD-1/anti-PD-L1–anti-VEGF mAbs group, the incidence of adverse events was 50.00% (4/8), while in the anti-PD-1/anti-PD-L1–MKIs group, it was 73.47% (36/49). Nonetheless, there was no statistically significant distinction observed between the 2 groups (P = .221). The most common TRAEs among patients who received anti-PD-1/anti-PD-L1–anti-VEGF mAbs were diarrhea (37.50%), elevated aspartate aminotransferase (25.00%), increased blood bilirubin (25.00%), proteinuria (25.00%), leukocytopenia (25.00%), and decreased platelet count (25.00%). In the anti-PD-1/anti-PD-L1–MKIs group, the most common TRAEs were diarrhea (20.41%), elevated aspartate aminotransferase (18.37%), hypertension (18.37%), RCCEP (16.33%), anemia (16.33%), and rash (16.33%). anti-PD-1/anti-PD-L1 combined MKIs therapy tended to yield a slightly higher grade 3 or higher toxicity (42.86%) compared with anti-PD-1–anti-VEGF mAbs group (25.00%) (P = .453).

In the anti-PD-1/anti-PD-L1–anti-VEGF mAbs group, TRAEs resulted in drug interruption in 1 patient (12.50%) and dose reduction in 1 patient (12.50%). In the anti-PD-1/anti-PD-L1–MKIs group, TRAEs led to drug interruption in 6 patients (12.24%), drug withdrawal in 5 patients (10.20%), dose reduction in 5 patients (10.20%), glucocorticoid intervention in 5 patients (10.20%), and unfortunately, death in 1 patient (2.04%) (Table 6).

4. Discussion

In recent years, ICIs have become a breakthrough treatment for aHCC. While single-agent ICIs have exhibited extended disease control with tolerable side effects in a specific patient subset,[25,26] phase III trials have not achieved their primary objectives in the initial treatment compared to sorafenib[6] and in the secondary treatment compared to placebo.[7] Without the presence of biomarkers, the option of combining ICIs with other medications emerges as a practical treatment approach. Key potential drugs in this context encompass anti-VEGF mAbs, as well as MKIs.[8] Combining ICIs with antiangiogenic agents is an area of active research. Preliminary studies and clinical trials have shown potential benefits of this combination therapy in improving treatment outcomes for patients with aHCC. In the GO30140 phase 1b trial, the incorporation of bevacizumab with atezolizumab revealed extended PFS when compared to atezolizumab by itself. This outcome rendered the combination a promising therapeutic choice for HCC.[9] The results of KEYNOTE-524 study indicated that multikinase inhibition with lenvatinib plus PD-1 inhibition with pembrolizumab results in improved antitumor activity.[10] In the RESCUE phase II study presented here, it was demonstrated that the combination of camrelizumab and apatinib exhibited remarkable effectiveness in terms of ORR, DOR, and OS in aHCC, whether in the first-line or second-line treatment scenarios. Furthermore, the safety profile of this combination was found to be well-tolerated.[27] In the phase III IMbrave150 clinical trial,[16] the treatment involving atezolizumab (a PD-L1 antibody) in combination with bevacizumab (a VEGF inhibitor) led to improved OS compared to sorafenib, with a hazard ratio of 0.58 (95% CI, 0.42 to 0.79; P = .0006). Additionally, it achieved response rates (ORR and DCR) exceeding 27% based on RECIST v1.1 criteria. This combination therapy is now a part of the National Comprehensive Cancer Network guidelines for hepatobiliary cancer. Given these findings, both domestic and international guidelines have recommended the use of immunotherapy in conjunction with antiangiogenic therapy as a first-line treatment option for aHCC.

In this study, we compared the therapeutic efficacy of anti-PD-1/anti-PD-L1 combined anti-VEGF mAbs therapy and anti-PD-1/anti-PD-L1 combined MKIs therapy in the first-line treatment of aHCC, and found that the combination of anti-PD-1/anti-PD-L1 and anti-VEGF mAbs therapy demonstrated better tumor control, longer mPFS and mOS comparing with anti-PD-1/anti-PD-L1 combined MKIs treatment group, indicating that anti-PD-1/anti-PD-L1 plus anti-VEGF mAbs therapy brought more long-term benefits to patients than anti-PD-1/anti-PD-L1 combined MKIs therapy. The PR rate, ORR, and DCR in anti-PD-1/anti-PD-L1–anti-VEGF mAbs group were 37.50%, 37.50%, and 62.50%, respectively, while in anti-PD-1/anti-PD-L1–MKIs group them were 22.45%, 24.49%, and 59.18%, respectively. Compared with previous clinical studies, the ORR was slightly higher and the DCR was slightly lower in both groups.[8,9,28] The mPFS and mOS for anti-PD-1–anti-VEGF mAbs group were 14.93 months (95% CI: 13.36–16.51) and 15.80 months (95% CI: 0–33.86), while for anti-PD-1–MKIs group was 14.90 months (95%

Table 4

Treatment response to anti-PD-1 combined anti-VEGF mAbs therapy or anti-PD-1 combined MKIs therapy.

Outcome	Anti-PD-1 plus anti-VEGF mAbs No. of patient (%)	Anti-PD-1 plus MKIs No. of patient (%)	*P*-value*
n	6	49	
CR	0(0)	1(2.04%)	1.000
PR	2(33.33%)	11(22.45%)	.619
SD	1(16.67%)	17(34.69%)	.651
PD	3(50.00%)	20(40.82%)	.686
ORR	2(33.33%)	12(24.49%)	.638
DCR	3(50.00%)	29(59.18%)	.686

Anti-PD-1 = anti-programmed cell death-1, anti-PD-L1 = anti-programmed death ligand-1, anti-VEGF mAbs = monoclonal antibodies targeting vascular endothelial growth factor, CR = complete response, DCR = disease control rate, MKIs = multiple kinase inhibitors, ORR = objective response rate, PD = progressive disease, PR = partial response, SD = stable disease.

* Chi-squared test; Fisher exact test.

Table 5

Treatment response to anti-PD-1 combined different MKIs therapy.

Outcome	Anti-PD-1 plus regorafenib	Anti-PD-1 plus sorafenib	Anti-PD-1 plus lenvatinib	Anti-PD-1 plus donafenib	Anti-PD-1 plus apatinib	Anti-PD-1 plus anlotinib	χ^2-value	*P*-value*
Total	1	8	18	8	12	2		
CR	0(0)	0(0)	1(5.56%)	0(0)	0(0)	0(0)	6.040	1.000
PR	0(0)	3(37.50%)	3(16.67%)	3(37.50%)	1(8.33%)	1(50.00%)	5.540	.329
SD	0(0)	2(25.00%)	6(33.33%)	4(50.00%)	5(41.67%)	0(0)	2.736	.834
PD	1(100%)	3(37.50%)	8(44.44%)	1(12.50%)	6(50.00%)	1(50.00%)	4.898	.430
ORR	0(0)	3(37.50%)	4(22.22%)	3(37.50%)	1(8.33%)	1(50.00%)	4.900	.430
DCR	0(0)	5(62.50%)	10(55.56%)	7(87.50%)	6(50.00%)	1(50.00%)	4.898	.430

Anti-PD-1 = anti-programmed cell death-1, anti-PD-L1 = anti-programmed death ligand-1, anti-VEGF mAbs = monoclonal antibodies targeting vascular endothelial growth factor, CR = complete response, DCR = disease control rate, MKIs = multiple kinase inhibitors, ORR = objective response rate, PD = progressive disease, PR = partial response, SD = stable disease.

* Chi-squared test; Fisher exact test.

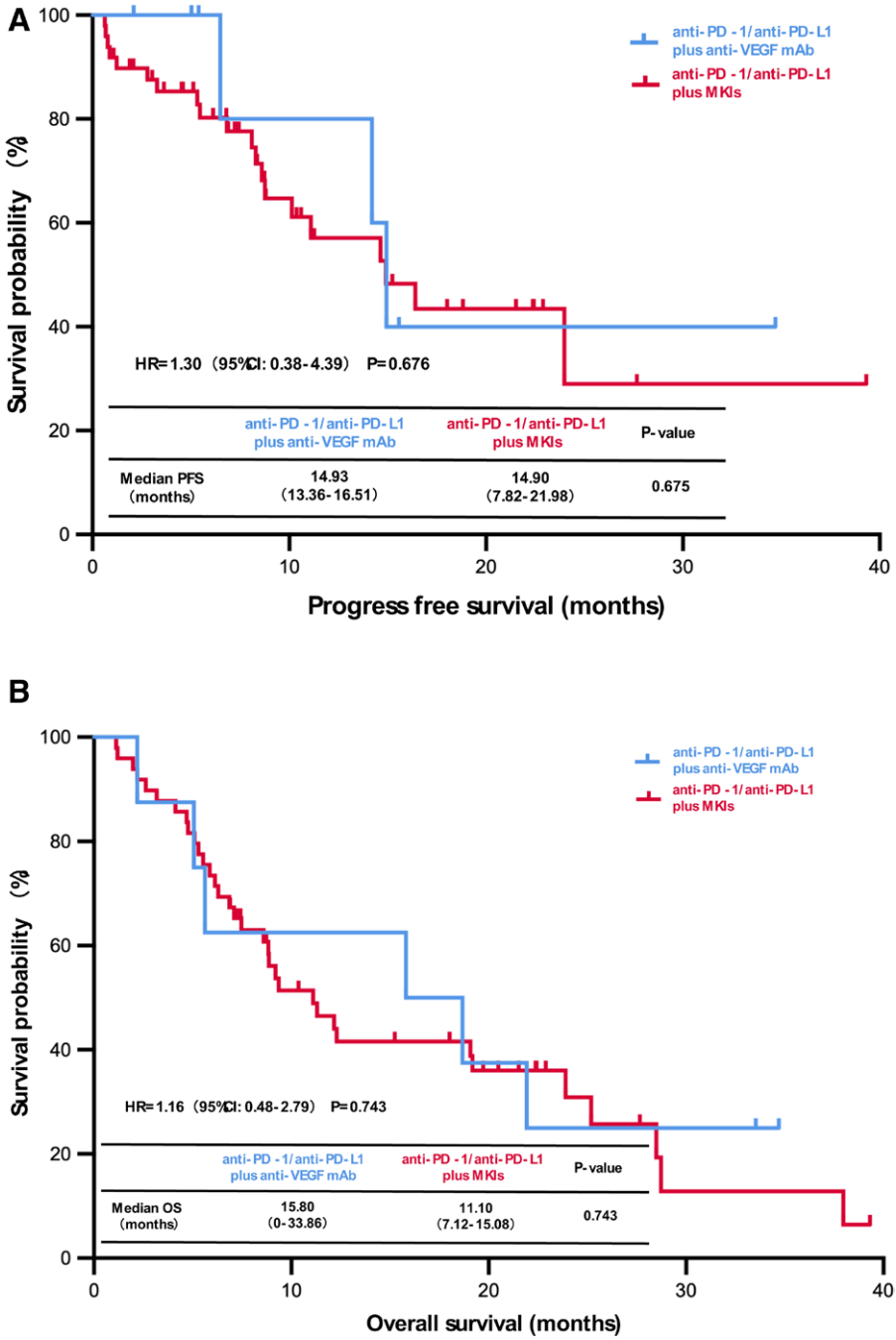

Figure 1. Kaplan–Meier curves according to therapeutic regimens. (A) PFS according to therapeutic regimens (anti-PD-1/anti-PD-L1 and anti-VEGF mAbs combination therapy vs anti-PD-1/anti-PD-L1 and MKIs combination therapy). (B) OS according to therapeutic regimens (anti-PD-1/anti-PD-L1 and anti-VEGF mAbs combination therapy vs anti-PD-1/anti-PD-L1 and MKIs combination therapy). Anti-PD-1 = anti-programmed cell death-1, anti-PD-L1 = anti-programmed death ligand-1, anti-VEGF mAbs = monoclonal antibodies targeting vascular endothelial growth factor, MKIs = multiple kinase inhibitors, OS = overall survival, PFS = progression-free survival.

CI: 7.82–21.98) and 11.10 months (95% CI: 7.12–15.08), respectively. Again, this study exhibited a longer mPFS compared with the results of previous clinical studies.[10,29,30] Among the patients included in this study, all of them had an ECOG-PS score of 0 to 1, 64.91% with Child-Pugh grade A, and 64.91% present with chronic viral hepatitis. The overall condition of the patients was better than in previous studies,[8–10,28–30] which may have led to a high treatment response rate in this study, and the improvement in mPFS may be related to the combination of antiangiogenic therapy in all patients in this study.

Combining anti-PD-1/PD-L1 with anti-VEGF mAbs and MKIs offers promising therapeutic strategies for aHCC. Both combinations have shown efficacy, but they differ in clinical implications. The combination of anti-PD-1/PD-L1 with anti-VEGF mAbs has demonstrated significant improvements in OS and PFS in aHCC. This regimen was associated with a higher ORR and DCR compared to monotherapies.[31,32] This combination tended to have a better safety profile with fewer TRAEs compared to combinations involving MKIs.[32] The combination works by shifting the tumor microenvironment from immunosuppressive to immune-permissive, enhancing the efficacy of ICIs.[33,34] Anti-PD-1/PD-L1 combined with MKIs showed enhanced antitumor activity and longer survival in preclinical models. This combination is

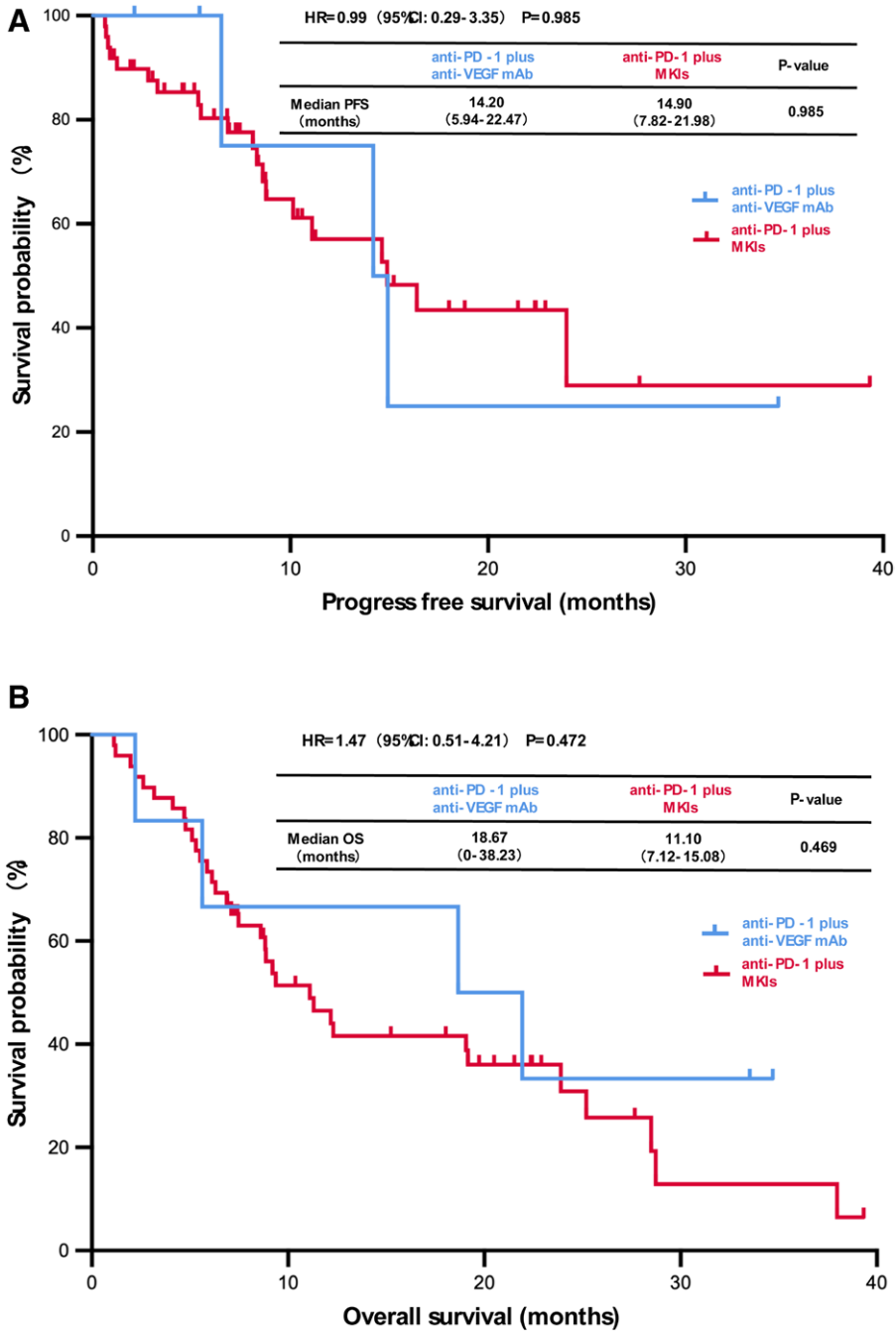

Figure 2. Kaplan–Meier curves according to therapeutic regimens. (a) PFS according to therapeutic regimens (anti-PD-1 and anti-VEGF mAbs combination therapy vs anti-PD-1 and MKIs combination therapy). (b) OS according to therapeutic regimens (anti-PD-1 and anti-VEGF mAbs combination therapy vs anti-PD-1 and MKIs combination therapy). Anti-PD-1 = anti-programmed cell death-1, anti-PD-L1 = anti-programmed death ligand-1, anti-VEGF mAbs = monoclonal antibodies targeting vascular endothelial growth factor, MKIs = multiple kinase inhibitors, OS = overall survival, PFS = progression-free survival.

particularly effective in modulating the tumor microenvironment and enhancing T cell function.[33,35] While effective, this combination was associated with a higher incidence of TRAEs compared to anti-VEGF mAbs combinations.[32] MKIs target multiple pathways, including VEGFR and FGFR, which can lead to a more comprehensive modulation of the tumor microenvironment, potentially offering benefits in cases with specific genetic backgrounds.[33,35] Both combinations offered significant clinical benefits in aHCC, with anti-PD-1/PD-L1 plus anti-VEGF mAbs providing a safer profile and anti-PD-1/PD-L1 plus MKIs offering potentially greater efficacy in certain genetic contexts. The choice between these regimens may depend on patient-specific factors, including genetic mutations and tolerance to adverse events. Further research and clinical trials are needed to optimize these combination therapies for individual patients.

VEGF is identified as having a role within the tumor microenvironment. Inhibiting the VEGF pathway promotes the infiltration of effector immune cells by normalizing the irregular tumor vasculature.[36] Additionally, the suppression of the VEGF pathway by MKIs not only boosts the activities of effector T cells within the tumor microenvironment but also diminishes the presence of suppressive immune cells.[19,20] Moreover, when administered in combination with anti-PD-1, MKIs suppressed tumor growth by activating efficient natural killer cells.[22] These findings imply that MKIs could be a promising choice

Table 6

Incidence of TRAEs in 57 patients with aHCC who underwent anti-PD-1/anti-PD-L1 combined anti-VEGF mAbs therapy or anti-PD-1/anti-PD-L1 combined MKIs therapy.

	All patients (n = 57)		Anti-PD-1/anti-PD-L1 combined anti-VEGF mAbs therapy(n = 8)		Anti-PD-1/anti-PD-L1 combined MKIs therapy(n = 49)	
Adverse event	**Any grades**	**Grade 3–5**	**Any grades**	**Grade 3–5**	**Any grades**	**Grade 3–5**
AEs to drug interruption	7(12.28%)	5(8.77%)	1(12.50%)	1(12.50%)	6(12.24%)	4(8.16%)
AEs to drug withdrawal	5(8.77%)	4(7.02%)	0(0)	0(0)	5(10.20%)	4(8.16%)
AEs to dose reduction	6(10.53%)	4(7.02%)	1(12.50%)	1(12.50%)	5(10.20%)	3(6.12%)
AEs to glucocorticoid intervention	5(8.77%)	4(7.02%)	0(0)	0(0)	5(10.20%)	4(8.16%)
AEs to death	1(1.75%)	1(1.75%)	0(0)	0(0)	1(2.04%)	1(2.04%)
AEs						
Diarrhea	13(22.81%)	1(1.75%)	3(37.50%)	1(12.50%)	10(20.41%)	0(0)
Elevated AST	11(19.30%)	3(5.26%)	2(25.00%)	0(0)	9(18.37%)	3(6.12%)
Hypertension	10(17.54%)	3(5.26%)	1(12.50%)	0(0)	9(18.37%)	3(6.12%)
RCCEP	9(15.79%)	0(0)	1(12.50%)	0(0)	8(16.33%)	0(0)
Anaemia	9(15.79%)	3(5.26%)	1(12.50%)	0(0)	8(16.33%)	3(6.12%)
Increased blood bilirubin	9(15.79%)	3(5.26%)	2(25.00%)	1(12.50%)	7(14.29%)	2(4.08%)
Rash	8(14.04%)	1(1.75%)	0(0)	0(0)	8(16.33%)	1(2.04%)
Proteinuria	8(14.04%)	2(3.51%)	2(25.00%)	0(0)	6(12.24%)	2(4.08%)
Abdominal pain	7(12.28%)	1(1.75%)	1(12.50%)	0(0)	6(12.24%)	1(2.04%)
Decreased appetite	7(12.28%)	1(1.75%)	1(12.50%)	0(0)	6(12.24%)	1(2.04%)
Leukocyte count decrease	7(12.28%)	3(5.26%)	2(25.00%)	1(12.50%)	5(10.20%)	2(4.08%)
Platelet count decrease	7(12.28%)	2(3.51%)	2(25.00%)	1(12.50%)	5(10.20%)	1(2.04%)
Hypoproteinemia	7(12.28%)	0(0)	1(12.50%)	0(0)	6(12.24%)	0(0)
Fatigue	6(10.53%)	1(1.75%)	1(12.50%)	1(12.50%)	5(10.20%)	0(0)
Hypothyroidism	6(10.53%)	0(0)	0(0)	0(0)	6(12.24%)	0(0)
Nausea	5(8.77%)	0(0)	1(12.50%)	0(0)	4(8.16%)	0(0)
Vomit	5(8.77%)	0(0)	0(0)	0(0)	5(10.20%)	0(0)
HFS	5(8.77%)	2(3.51%)	0(0)	0(0)	5(10.20%)	2(4.08%)
Bleeding	5(8.77%)	3(5.26%)	0(0)	0(0)	5(10.20%)	3(6.12%)
Pyrexia	4(7.02%)	0(0)	1(12.50%)	0(0)	3(6.12%)	0(0)
Constipation	4(7.02%)	0(0)	1(12.50%)	0(0)	3(6.12%)	0(0)
Weight decrease	4(7.02%)	0(0)	1(12.50%)	0(0)	3(6.12%)	0(0)
Elevated ALT	4(7.02%)	1(1.75%)	1(12.50%)	0(0)	3(6.12%)	1(2.04%)
Hypokalemia	4(7.02%)	1(1.75%)	1(12.50%)	0(0)	3(6.12%)	1(2.04%)
Pruritus	3(5.26%)	0(0)	0(0)	0(0)	3(6.12%)	0(0)
Pneumonia	3(5.26%)	1(1.75%)	1(12.50%)	0(0)	2(4.08%)	1(2.04%)
Alopecia	2(3.51%)	0(0)	0(0)	0(0)	2(4.08%)	0(0)
Hyperkalemia	2(3.51%)	1(1.75%)	0(0)	0(0)	2(4.08%)	1(2.04%)
Flatulency	2(3.51%)	0(0)	1(12.50%)	0(0)	1(2.04%)	0(0)
Hyponatremia	2(3.51%)	1(1.75%)	1(12.50%)	0(0)	1(2.04%)	1(2.04%)
Mucositis	1(1.75%)	0(0)	0(0)	0(0)	1(2.04%)	0(0)
UIT	1(1.75%)	0(0)	0(0)	0(0)	1(2.04%)	0(0)
Oliguria	1(1.75%)	1(1.75%)	0(0)	0(0)	1(2.04%)	1(2.04%)

Data are n (%).

AEs = adverse events, ALT = alanine aminotransferase, anti-PD-1 = anti-programmed cell death-1, anti-PD-L1 = anti-programmed death ligand-1, anti-VEGF mAbs = monoclonal antibodies targeting vascular endothelial growth factor, AST = aspartate aminotransferase, HFS = hand-foot syndrome, MKIs = multiple kinase inhibitors, RCCEP = reactive cutaneous capillary endothelial proliferation, UIT = urinary tract infection.

for combination therapy with anti-PD-1. Among the different MKIs used in the anti-PD-1 combined MKIs treatment group, anti-PD-1–lenvatinib group achieved longer PFS, while the anti-PD-1–regorafenib group achieved longer OS. Lenvatinib, classified as a multikinase inhibitor targeting VEGF receptors 1 to 3, fibroblast growth factor (FGF) receptors 1 to 4, platelet-derived growth factor receptor-α, RET, and KIT,[37–39] gained approval for the initial treatment of unresectable hepatocellular carcinoma. This approval was grounded on the phase III REFLECT study, which demonstrated that lenvatinib brought about substantial and clinically relevant enhancements when compared to sorafenib in terms of ORR, PFS, and time to progression.[18] Compared to sorafenib, regorafenib boasts higher biological activity and a broader range of targets, inhibiting multiple kinases related to angiogenesis and tumorigenesis, including VEGF receptor VEGFR1-3, tyrosine-protein kinase receptors TIE and Ret, platelet-derived growth factor receptor platelet-derived growth factor receptor-β, basic fibroblast growth factor receptor FGFR-1/2, serine/threonine protein kinase Raf, and mitogen-activated protein kinase p38, thereby exerting antitumor effects.[40–43] Additionally, regorafenib optimizes the tumor microenvironment by modulating macrophages, enhancing CD8 + T cell proliferation and activation, and boosting NK cell cytolytic activity to inhibit STAT3 signaling, ultimately leading to HCC cell apoptosis.[44–46] Compared with lenvatinib, regorafenib targets TIE2, CSF1R, and RAF to improve tumor immune microenvironment-related pathways, enhancing immunity and inhibiting tumor cell proliferation.[47] When used as a first-line treatment, either alone or in combination with ICIs, regorafenib has demonstrated promising results in terms of PFS and OS, with the combination therapy appearing to further enhance survival outcomes compared to monotherapy.[48] This study collected and analyzed real-world clinical data, however, due to the relatively small sample size, differences may not be reliably detected. Even if a true effect exists, it may not be captured due to inadequate sample size, resulting in a non-significant *P*-value. Importantly, even when the *P*-value lacks statistical significance, the research findings can still hold

value if the effect size is meaningful in practical terms. In future studies, we aim to increase the sample size and gather more data to enhance statistical power, thereby improving the likelihood of detecting differences and aiding readers in better understanding the potential implications of our research results.

The results of CARES-310 study indicated that the most common grade 3 or 4 TRAEs were hypertension (102 [38%] of 272 patients in the camrelizumab–rivoceranib group vs 40 [15%] of 269 patients in the sorafenib group), palmar-plantar erythrodysaesthesia syndrome (33 [12%] vs 41 [15%]), increased aspartate aminotransferase (45 [17%] vs 14 [5%]), and increased alanine aminotransferase (35 [13%] vs 8 [3%]).[30] Chen et al developed a real-world study for aHCC and concluded that the most frequently observed adverse events of any grade were anorexia (12/14, 85.71%), thrombocytopenia (7/14, 50.00%), hypertension (6/14, 42.86%), diarrhea (4/14, 28.57%), fatigue (4/14, 28.57%), and anemia (2/14, 14.29%) in the anlotinib and PD-1 blockade combination group.[49] The study conducted by Burgio et al revealed that the main drug-related adverse events in the lenvatinib arm were fatigue (41.0%), hypertension (35.4%) and decreased appetite (32.6%), and the main drug-related adverse events in the sorafenib arm were diarrhea (38.2%) and fatigue (29.2%).[50] The adverse events in our study were similar to those described in prophase studies and the existing benchmarks for safety in advanced HCC therapies. The most frequently observed adverse events of any grade were diarrhea (13/57, 22.81%), elevated aspartate aminotransferase (11/57, 19.30%), hypertension (10/57, 17.54%), RCCEP (9/57, 15.79%), anemia (9/57, 15.79%), and increased blood bilirubin (9/57, 15.79%). Most TRAEs were regarded as grade 1 to 2 and the combination treatment was generally well tolerated for our patients with aHCC. As bleeding was the main concern of any antiangiogenic treatment, the only fatal adverse event reported in our study was upper gastrointestinal bleeding. Moreover, anti-PD-1/anti-PD-L1 combined MKIs therapy tended to yield a slightly higher incidence of TRAEs (73.47%) compared with anti-PD-1–anti-VEGF mAbs group (50.00%), similar to the grade 3/4 toxicities (42.86% vs 25.00%). Achieving a harmony between effectiveness and side effects remains a significant concern at present.

In our investigation, it is essential to consider the following limitations. Firstly, this study is retrospective in nature, which inevitably introduces selection bias. Secondly, it's worth noting that this study was carried out at a single institution in China, which could potentially impact the applicability of the findings to a wider demographic. Thirdly, the ability to conduct subgroup analysis with adequate statistical power was constrained due to the relatively small sample size. Lastly, we did not delve into an analysis of patient characteristics to identify which individuals might derive greater benefits from various combination therapies. Hence, there are plans to conduct a meticulously structured prospective randomized trial on a more extensive cohort to further assess the effectiveness and safety of combining ICIs with different antiangiogenic agents for individuals dealing with aHCC.

5. Conclusions

When compared to the treatment regimen combining anti-PD-1/anti-PD-L1 with MKIs, the therapy that pairs anti-PD-1/anti-PD-L1 with anti-VEGF mAbs exhibited superior tumor control, as well as prolonged PFS and OS. The combination of anti-PD-1/anti-PD-L1 with MKIs was associated with a higher incidence of TRAEs and grade 3/4 toxicities. Among the various MKIs used in conjunction with anti-PD-1, the anti-PD-1–lenvatinib combination resulted in a longer mPFS, whereas the anti-PD-1–regorafenib combination led to a longer mOS. However, these findings require confirmation through a well-designed, prospective, randomized study.

Author contributions

Conceptualization: Guoping Sun.
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Formal analysis: Jing Xu.
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Investigation: Jing Xu, Zhenya Jia, Guoping Sun.
Methodology: Jing Xu, Xin Wang.
Project administration: Jing Xu, Guoping Sun.
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Software: Jing Xu, Xin Wang.
Supervision: Zhenya Jia, Guoping Sun.
Validation: Jing Xu, Xin Wang.
Visualization: Jing Xu.
Writing – original draft: Jing Xu, Xin Wang.
Writing – review & editing: Jing Xu, Zhenya Jia, Guoping Sun.

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