Journal of Hepatocellular Carcinoma

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy and Safety of Ipilimumab Plus Anti-PD-1/PD-L1 Antibodies Combination Therapy in Advanced Hepatocellular Carcinoma Patients Progressing After Multiple Lines of Treatment: A Retrospective Multicenter Study

Su-Su Zheng[1], Jing-Fang Wu[1], Zhen-Zhen Zhang[1], Yan-Fang Wu[1], Yi-Jie Chen[2], Sheng Qian[3], Bo-Heng Zhang[1,4,5]

[1]Department of Hepatic Oncology, Xiamen Clinical Research Center for Cancer Therapy, Clinical Research Center for Precision medicine of Abdominal Tumor of Fujian Province, Zhongshan Hospital, Fudan University (Xiamen Branch), Xiamen, Fujian, 361015, People's Republic of China; [2]Department of General Surgery, Strait Hospital of Huaqiao University (The 910th Hospital of the Joint Service Support Force of the Chinese People's Liberation Army), Quanzhou, Fujian, 362008, People's Republic of China; [3]Department of Interventional Radiology, Zhongshan Hospital, Fudan University (Xiamen Branch), Xiamen, Fujian, 361015, People's Republic of China; [4]The Liver Cancer Institute, Zhongshan Hospital and Shanghai Medical School, Fudan University, Key Laboratory for Carcinogenesis and Cancer Invasion, Shanghai, 200032, People's Republic of China; [5]Center for Evidence-Based Medicine, Shanghai Medical School, Fudan University, Shanghai, 200032, People's Republic of China

Correspondence: Bo-Heng Zhang, Email zhang.boheng@zs-hospital.sh.cn

Background: The combination of nivolumab and ipilimumab has demonstrated significant antitumor activity in first-line treatment for hepatocellular carcinoma (HCC) and in second-line treatment following progression on sorafenib. However, the efficacy and safety of ipilimumab plus anti-PD-1/PD-L1 antibodies combination therapy in advanced HCC patients who have progressed after multiple lines of treatment have not yet been reported.

Materials and Methods: We conducted a multicenter retrospective study that included 33 HCC patients who had progressed after multiple lines of immune-targeted therapy and received ipilimumab combination therapy. All patients had received at least one line of immunotherapy based combination therapy (excluding those treated with anti-CTLA-4 inhibitors). The primary endpoints were overall survival (OS) and progression-free survival (PFS). Efficacy was assessed using RECIST 1.1, while adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0).

Results: Among the patients, 29 (87.9%) received ipilimumab combination therapy as third-line or later line therapy. The median OS for the entire cohort was 14.07 months (95% CI: 5.57 months - not evaluable), and the median PFS was 2.36 months (95% CI: 1.97–5.64 months). Univariate survival analysis indicated that an NLR $\geq$ 3.1 and tumor size $\geq$ 63 mm are prognostic risk factors for OS (P=0.03 and P=0.027, respectively). Multivariate survival analysis revealed that an NLR $\geq$ 3.1 is the only independent prognostic risk factor for OS (P=0.048). The overall response rate (ORR) was 12.1%, and the disease control rate (DCR) was 48.5%. One patient experienced treatment-related death (3%), two had hyperprogression (6.1%), and three discontinued treatment due to adverse events (9.1%).

Conclusion: Ipilimumab combination therapy in very late lines is a viable treatment option, although careful monitoring for adverse events is essential. Earlier application of this combination may potentially benefit patients more effectively.

Keywords: advanced hepatocellular carcinoma, nivolumab, ipilimumab, immune checkpoint inhibitor, retrospective study

Introduction

Hepatocellular carcinoma (HCC) ranks as the seventh most common malignant tumor worldwide and has the second highest rate of cancer-related mortality.[1,2] Due to the insidious onset of the disease, more than half of the patients present

Received: 17 December 2024
Accepted: 25 February 2025
Published: 11 March 2025

with advanced HCC at the time of their initial diagnosis, rendering them ineligible for curative surgical interventions.[3] Consequently, systemic therapies, including targeted therapies and immunotherapy, have become critical treatment options for these patients.

Multitargeted tyrosine kinase inhibitors (TKIs) such as sorafenib, lenvatinib, and donafenib are commonly used first-line targeted agents.[4–6] Based on the results of clinical trials such as IMBRAVE150, CARES-310, and ORIENT-32, targeted therapy combined with immune checkpoint inhibitors (ICIs), including anti-PD-1/PD-L1 antibodies, has emerged as a first-line treatment strategy for advanced HCC.[7–9] Findings from the HIMALAYA trial suggest that the combination of PD-L1 antibodies with CTLA-4 antibodies (tremelimumab and durvalumab) holds promise as a new first-line treatment option for HCC.[10] Furthermore, based on the CHECKMATE-040 study, ipilimumab plus nivolumab is considered a viable second-line option following progression on first-line sorafenib.[11,12] In fact, dual immunotherapy regimens have already received first-line recommendations for HCC in several countries, with the nivolumab plus ipilimumab regimen approved in the United States as a second-line treatment for HCC following progression on sorafenib.[13–15]

However, all current second-line treatment options for HCC are based on clinical studies of progression after targeted therapy or chemotherapy. Agents such as regorafenib, apatinib, and ramucirumab are considered second-line treatments for HCC, their therapeutic efficacy is limited, and there is a lack of evidence supporting their combination with immunotherapy.[16–18] There are no standardized regimens for second-line or subsequent treatment following progression on prior-line immune based combination therapy. Dual immunotherapy, by simultaneously targeting the CTLA-4 and PD-1/PD-L1 pathways, may circumvent resistance mechanisms associated with TKIs and anti-PD-1/PD-L1 antibodies, thereby exerting its unique therapeutic effects. This study included advanced HCC patients who progressed after multiple lines of immune-targeted therapy and subsequently received ipilimumab combination therapy, aiming to explore the safety and efficacy of dual immunotherapy in later-line HCC treatment.

Materials and Methods

Patients Enrollment

From May 31, 2022, to October 30, 2024, we retrospectively included 33 patients with HCC who progressed after multiple lines of immune-targeted therapy and subsequently received ipilimumab combination therapy. These patients were recruited from two Chinese hospital centers (Zhongshan Hospital, Fudan University (Xiamen Branch) and Strait Hospital of Huaqiao University). The inclusion criteria were as follows: Diagnosis of HCC confirmed by pathology or imaging according to the American Association for the Study of Liver Diseases (AASLD) criteria.[14] Patients must have received at least one line of ICIs such as anti-PD-1/PD-L1 antibodies in combination with targeted therapy, with subsequent treatment adjusted to either nivolumab plus ipilimumab or continued use of the prior ICIs in conjunction with ipilimumab. Patients must have completed at least one cycle of ipilimumab combination therapy. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–1.

Exclusion criteria included patients who had previously received anti-CTLA-4 antibody therapy. All patients underwent comprehensive imaging and laboratory assessments to evaluate disease progression. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Zhongshan Hospital, Fudan University (Xiamen Branch) (protocol # B2019-026, 11 April 2023), and informed consent was obtained from all participants.

Treatment Protocol, Follow-Up, and Disease Monitoring

Ipilimumab was administered at a dose of 1 mg/kg, referencing the CheckMate 040 study arms B and C. The treatment regimen primarily consisted of either a 3-week schedule (four cycles of ipilimumab) or a 6-week schedule (ipilimumab every 6 weeks until intolerable side effects or disease progression).[12] The ICIs used in combination with ipilimumab included nivolumab (3 mg/kg Q3W for four doses in the 3-week schedule, 3 mg/kg Q2W for four doses in the 6-week schedule, followed by nivolumab 240 mg Q2W in both schedules), atezolizumab (1200mg), or similar agents

(carelizumab (200mg), sintilimab (200mg), tislelizumab (200mg), toripalimab (240mg), durvalumab (1500mg), pembrolizumab (200mg)), administered every three weeks.

Routine laboratory tests were conducted for each treatment cycle, and imaging assessments (such as abdominal enhanced CT or MRI) were performed every 6–12 weeks to evaluate disease status. Overall survival (OS) was defined as the time from the start of ipilimumab combination therapy to the date of death or the last follow-up. Progression-free survival (PFS) was defined as the time from the start of ipilimumab combination therapy to disease progression or death, with the last follow-up date being October 30, 2024. Treatment efficacy was assessed using RECIST v1.1 criteria, with the objective response rate (ORR) defined as the proportion of patients achieving either a partial response (PR) or a complete response (CR). Additionally, disease control rate (DCR) was calculated as the sum of CR, PR, and stable disease (SD).[19] Treatment-related adverse events were monitored using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Statistical Analysis

Statistical analyses were conducted using R (version 4.1.3), utilizing the survival and survminer packages to evaluate PFS and OS. Continuous variables were expressed as median, range, count, and percentage. The Kaplan-Meier method was employed to estimate median PFS and OS, while Log rank tests were used to compare PFS and OS among various subgroups, including treatment schedules (6-week vs 3-week) and treatment regimens (continuation of prior ICIs with ipilimumab vs nivolumab plus ipilimumab). Univariate and multivariate COX regression analyses were used to identify independent prognostic factors. A P-value of less than 0.05 indicated statistical significance for all analyses.

Results

Patient Characteristics

Based on the inclusion and exclusion criteria, a total of 33 hCC patients who experienced progression after multi-lines of immune-targeted therapy and subsequently received ipilimumab combination therapy were enrolled in this study. All patients underwent prior-line immune-targeted therapy, with 29 patients (87.9%) having received second-line or higher immune-targeted therapy, and 20 patients (60.6%) having received third-line or higher systemic therapy. Prior targeted agents included sorafenib, lenvatinib, apatinib, regorafenib, donafenib, and bevacizumab. Prior immunotherapy consisted of PD-1/PD-L1 inhibitors, including camrelizumab, nivolumab, durvalumab, pembrolizumab, sintilimab, tislelizumab, toripalimab, and atezolizumab. The median age of the patients was 53 years (range: 35–72), with 30 patients (90.9%) being male. Additionally, 31 patients (93.9%) were classified as Barcelona Clinic Liver Cancer (BCLC) stage C, and 28 patients (84.8%) presented with extrahepatic metastases. HBV infection was identified in 28 patients (84.8%), and the median level of alpha-fetoprotein (AFP) was 2528 ng/mL (range: 1.3–60500 ng/mL). Twenty-one patients (63.6%) continued to use prior ICIs in conjunction with ipilimumab treatment, while only 12 patients (36.4%) discontinued prior ICI therapy and switched to the nivolumab plus ipilimumab regimen. Detailed clinical characteristics are presented in Table 1.

Treatment Outcomes With Ipilimumab Combination Therapy

According to RECIST v1.1 criteria, the ORR in the total population was 12.1%, with 4 patients achieving a PR and no patients achieving a CR. The representative images and AFP levels collected from 4 patients who were evaluated as radiographic PR were shown in Figure S1. Twelve patients (36.4%) experienced SD, resulting in a DCR of 48.5%, while 51.5% of patients were assessed as having progressive disease (PD). In subgroup analysis, the response rates for the 6-week regimen and the 3-week regimen were comparable. The details were shown in Table 2.

Survival Analyses

The mOS for the total population was 14.07 months (95% CI, 5.57–Not evaluable), and the mPFS was 2.36 months (95% CI, 1.97–5.64) (Figure 1a and b). Survival analysis indicated a trend towards prolonged overall survival (OS) in patients receiving the 6-week regimen compared to the 3-week regimen, although this did not reach statistical significance

Table 1 Clinical Characteristics of Enrolled HCC Patients

Patients	Anti-PD-1/PD-L1+IPI Q3W (n=18)	Anti-PD-1/PD-L1+IPI Q6W (n=15)	Total (n=33)
Age(years), median (range)	58 (35–72)	50 (42–62)	53 (35–72)
Male, n (%)	16 (88.9)	14 (93.3)	30 (90.9)
BCLC stage, n (%)			
B	1 (5.6)	1 (6.6)	2 (6.1)
C	17 (94.4)	14 (93.3)	31 (93.9)
Child-Pugh score, n (%)			
A	14 (77.8)	13 (86.7)	27 (81.8)
B	4 (22.2)	2 (13.3)	6 (18.2)
NLR, median (range)	3 (1.1–9.4)	3.8 (0.8–10.3)	3.1 (0.8–10.3)
PLR, median (range)	148.3 (44.2–268.3)	154.4 (81.1–252.5)	151.7 (44.2–268.3)
Vascular invasion, n (%)	9 (50)	8 (53.3)	17 (51.5)
Extrahepatic spread, n (%)	14 (77.8)	14 (93.3)	28 (84.8)
AFP (ng/mL), median (range)	7837.5 (1.3–60,500)	850 (4.1–60,500)	2528 (1.3–60,500)
HBV positive, n (%)	15 (83.3)	13 (86.7)	28 (84.8)
Continue prior ICIs plus IPI, n (%)	15 (83.3)	6 (40)	21 (63.6)
Number of prior systemic regimens, n (%)			
1	3 (16.7)	1 (6.7)	4 (12.1)
2	5 (27.7)	4 (26.7)	9 (27.3)
≥3	10 (55.6)	10 (66.7)	20 (60.6)
Prior treatment, n (%)			
Surgical resection	8 (44.4)	5 (33.3)	13 (39.4)
Radiothearpy	6 (33.3)	6 (40)	12 (36.4)
Local therapy	16 (88.9)	15 (100)	31 (93.9)
ICIs	18 (100)	15 (100)	33 (100)
TKIs/Bevacizumab	18 (100)	15 (100)	33 (100)
Prior first-line systemic treatments, n (%)			
TKIs only[a]	9 (50)	4 (26.7)	13 (39.4)
Immune combination therapy[b]	9 (50)	11 (73.3)	20 (60.6)
Prior second-line systemic treatments, n (%)			
Immune combination therapy[c]	15 (83.3)	14 (93.3)	29 (87.9)
Prior third-line or more systemic treatments, n (%)			
Immune combination therapy[d]	6 (33.3)	8 (53.3)	14 (42.4)
Chemotherapy[e]	4 (22.2)	2 (11.1)	29 (18.2)

Notes: [a]TKIs only in the first-line setting were sorafenib, lenvatinib; [b]Immune combination therapies in the first-line setting were atezolizumab plus bevacizumab, carelizumab, sintilimab, tislelizumab, toripalimab, pembrolizumab, sorafenib, lenvatinib, apatinib; [c]Immune combination therapies in the second-line setting were atezolizumab plus bevacizumab, carelizumab, sintilimab, tislelizumab, toripalimab, pembrolizumab, nivolumab, durvalumab, sorafenib, lenvatinib, apatinib, regorafenib, gefitinib; [d]Immune combination therapies in the third-line or more setting were atezolizumab, carelizumab, sintilimab, tislelizumab, toripalimab, pembrolizumab, nivolumab, durvalumab, lenvatinib, apatinib, regorafenib, gefitinib; [e]Chemotherapies in the third-line or more settings were fluorouracil+leucovorin+oxaliplatin; fluorouracil+leucovorin+ irinotecan.

Abbreviations: IPI, ipilimumab; Q3W, every 3 weeks; Q6W, every 6 weeks; BCLC, Barcelona Clinic Liver Cancer; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; AFP, alpha-fetoprotein; HBV, hepatitis B virus; ICIs, immune checkpoint inhibitors; TKIs, tyrosine kinase inhibitors;

Table 2 Treatment Response of the Enrolled HCC Patients

All patients	Anti-PD-1/ PD-L1+IPI Q3W (n=18)	Anti-PD-1/ PD-L1+IPI Q6W (n=15)	Total (n=33)
CR, n (%)	0	0	0
PR, n (%)	2 (11.1)	2 (13.3)	4 (12.1)
SD, n (%)	5 (27.8)	7 (46.7)	12 (36.4)
PD, n (%)	11 (61.1)	6 (40)	17 (51.5)
ORR, n (%)	2 (11.1)	2 (13.3)	4 (12.1)
DCR, n (%)	7 (38.9)	9 (60)	16 (48.5)

Abbreviations: IPI, ipilimumab; Q3W, every 3 weeks; Q6W, every 6 weeks; ORR, objective response rate; PR, partial response; CR, complete response; DCR, disease control rate; SD, stable disease; PD, progressive disease.

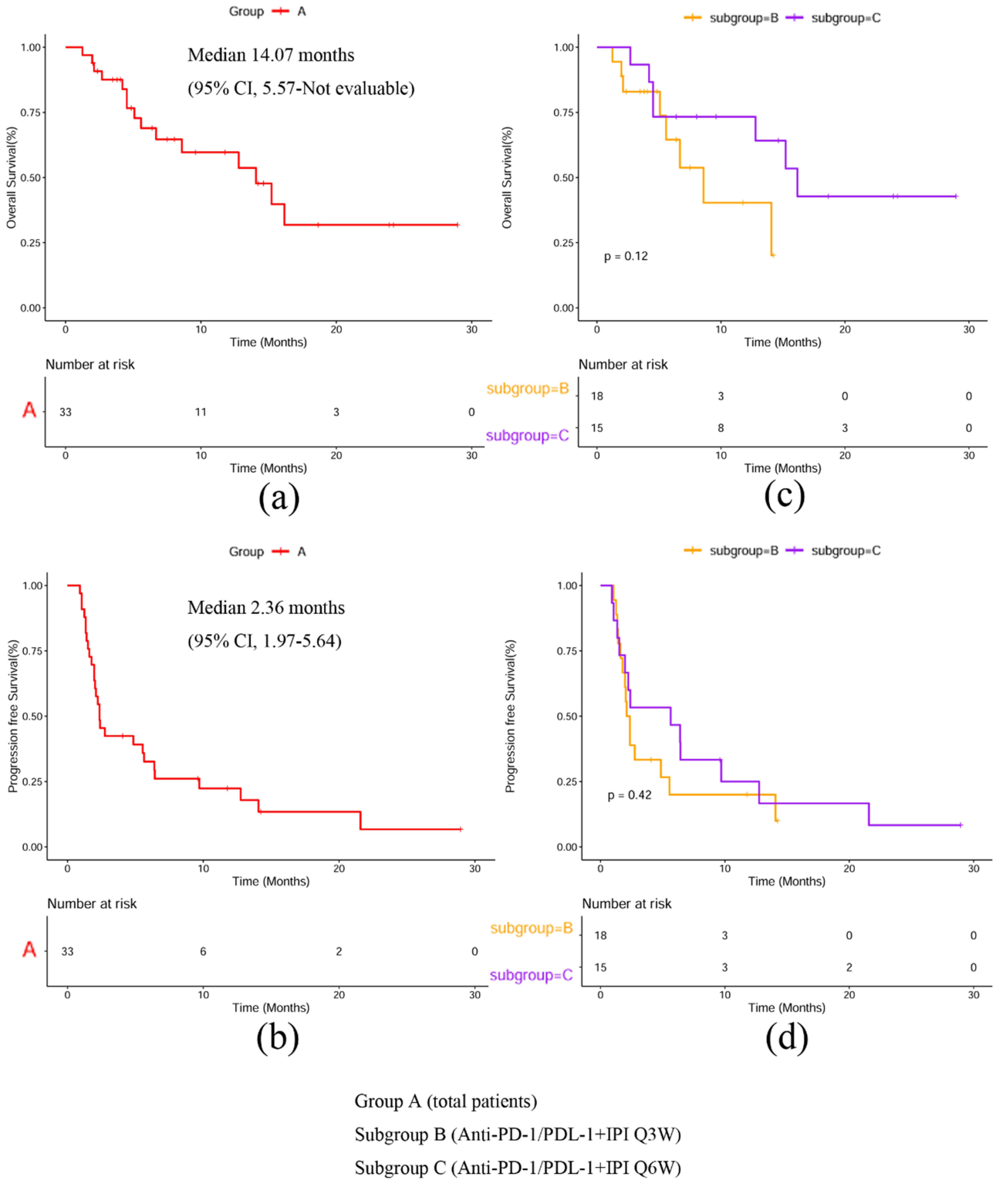

Figure 1 Survival analyses of the total and subgroup patients. (**a**) Overall survival of the total patients; (**b**) Progression free survival of the total patients; (**c**) Overall survival analysis between the IPI-Q3W and the IPI-Q6W; (**d**) Progression free survival analysis between the IPI-Q3W and the IPI-Q6W.
Abbreviation: CI, confidence interval; IPI, ipilimumab; Q3W, every 3 weeks; Q6W, every 6 weeks.

https://doi.org/10.2147/JHC.S512302

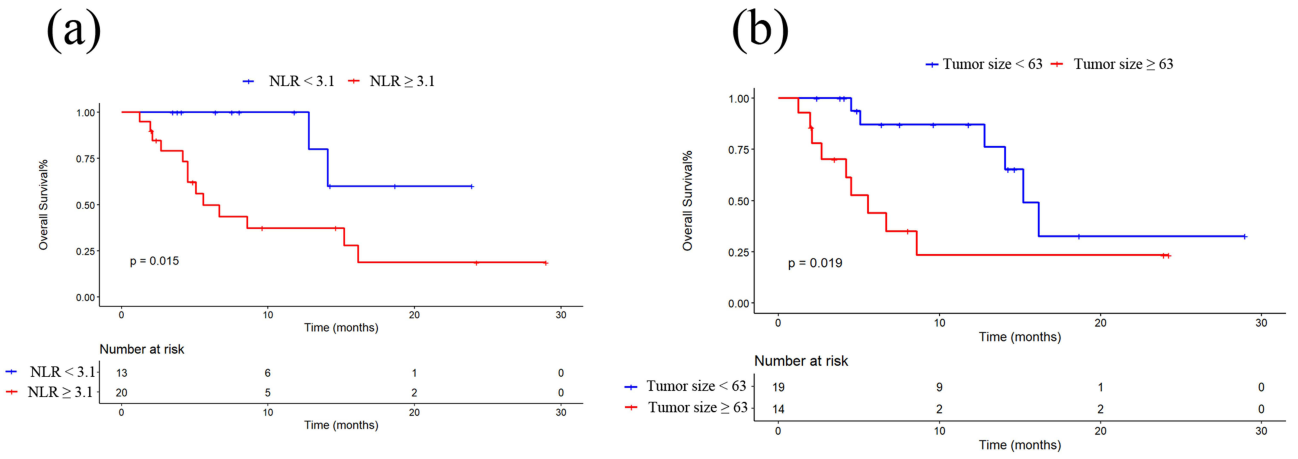

Figure 2 Survival analyses of the subgroup. (**a**) Overall survival analysis between the NLR groups; (**b**) Overall survival analysis between the tumor size groups.
Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

(P=0.12 for OS, P=0.42 for PFS) (Figure 1c and d). Subgroup analysis indicated that patients with an NLR≥3.1 or tumor size ≥63mm had worse OS (P=0.015 and P=0.019, respectively) (Figure 2a and b).Subgroup analysis based on the continuation of prior immunotherapy showed no statistically significant difference in survival between patients continuing prior ICIs plus ipilimumab and those switching to nivolumab plus ipilimumab (P=0.28 for OS, P=0.46 for PFS) (Figure 3a and b).

Safety and Adverse Events

Two patients (6.1%) experienced hyperprogression, with one patient resulting in death (3%), and the other patient discontinued immunotherapy and received intravenous chemotherapy, achieving a short-term disease control. Three patients (9.1%) discontinued treatment due to adverse drug reactions (including the two patients with hyperprogression). The most common treatment-related adverse events included ALT elevation (27.2%), dyspepsia (24.3%), and lipase elevation (15.2%). Additional adverse events are detailed in Table 3.

Prognostic Factors

Through COX univariate survival analysis, we found that only NLR and tumor size were associated with OS in HCC patients. Multivariate survival analysis confirmed that NLR ≥ 3.1 is an independent prognostic risk factor for OS. Due to the small sample size, no prognostic factors related to PFS were identified. A detailed summary of the prognostic analysis for each clinicopathological feature is provided in Table 4.

Discussion

The present study demonstrates that ipilimumab combination therapy may offer a survival benefit in patients with advanced HCC who have progressed after multiple lines of treatment, with a mOS of 14.07 months and a mPFS of 2.36 months. The ORR was 12.1% and the DCR was 48.5%. These results are lower compared to those reported in other studies involving nivolumab plus ipilimumab. Literature indicates that as a second-line treatment following progression on sorafenib, the mOS is reported to be between 12.5 and 22.8 months, with an ORR of 13–16%.[12] Another small-sample study on the use of nivolumab plus ipilimumab as second-line therapy after progression on first-line treatment with atezolizumab plus bevacizumab suggested a median overall survival (mOS) of 9.2 months and an objective response rate (ORR) of 22%.[20] The latest Check-Mate 9DW trial (NCT04039607) reported a mOS of 23.7 months and an ORR of 36% for patients with advanced HCC treated with nivolumab plus ipilimumab in the first line. The poor efficacy of subsequent lines of treatment may be attributed to the fact that these patients have progressed after multiple lines of therapy, indicating a change in the immune microenvironment compared to earlier treatments. This may also suggest that earlier

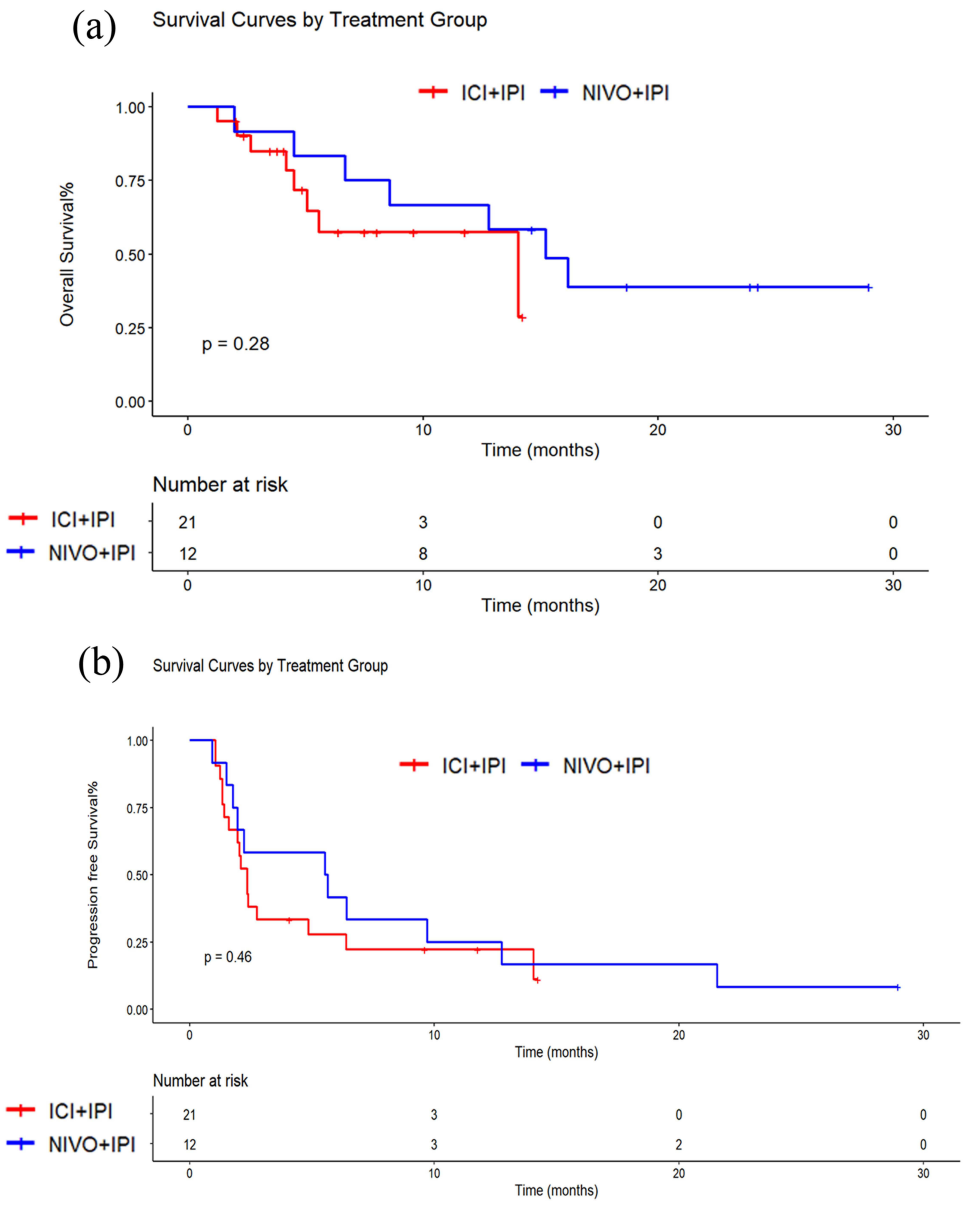

Figure 3 Survival analyses of the subgroup by treatment regimens. (**a**) Overall survival analysis between the treatment regimens; (**b**) Progression free survival analysis between the treatment regimens.
Abbreviation: ICI, immune checkpoint inhibitor; IPI, ipilimumab; NIVO, nivolumab.

application of the nivolumab plus ipilimumab regimen may yield greater survival benefits. However, the conclusions still warrant further validation.

There is currently no standard answer regarding whether patients with HCC who experience progression after the combination of targeted therapy plus immunotherapy can continue using the previously administered ICIs. The atezolizumab plus bevacizumab regimen is currently recommended as the first-line treatment for advanced HCC in several guidelines. Based on some expert consensus, it is suggested that after progression on atezolizumab plus bevacizumab, a switch to TKIs may be appropriate.[21] The subgroup analysis of this study indicates that continuing the prior ICIs combined with ipilimumab after progression yields similar outcomes to switching entirely to nivolumab plus ipilimumab (for OS, P=0.32). A study by Stephanie L et al also suggested that lack of response to frontline immunotherapy does not affect the benefits of subsequent treatment with nivolumab plus ipilimumab.[20] One possible explanation is that anti-CTLA-4 antibodies and anti-PD-1/PD-L1 antibodies exert their antitumor effects through different mechanisms, and their

https://doi.org/10.2147/JHC.S512302

Table 3 Adverse Events of the Enrolled HCC Patients

Adverse event	Anti-PD-1/PD-L1+IPI Q3W (n=18)		Anti-PD-1/PD-L1+IPI Q6W (n=15)		Total n(%)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Treatment leading to discontinuation	2 (11.1)		1 (6.7)		3 (9.1)	
Hyperprogressive	1 (5.6)		1 (6.7)		2 (6.1)	
Treatment-related deaths	1 (5.6)		0		1 (3)	
Rash	1 (5.6)	1 (5.6)	1 (6.7)	1 (6.7)	2 (6.1)	2 (6.1)
Dyspepsia/anorexia	4 (22.2)	1 (5.6)	2 (13.3)	1 (6.7)	6 (18.2)	2 (6.1)
Diarrhea	1 (5.6)	0	1 (6.7)	0	2 (6.1)	0
Fatigue	1 (5.6)	0	2 (13.3)	1 (6.7)	3 (9.1)	1 (3)
Cortisol decrease	1 (5.6)	0	1 (6.7)	0	2 (6.1)	0
Lipase elevation	2 (11.1)	0	3 (20)	0	5 (15.2)	0
ALT elevation	4 (22.2)	1 (5.6)	4 (26.7)	0	8 (24.2)	1 (3)
AST elevation	4 (22.2)	1 (5.6)	4 (26.7)	0	8 (24.2)	1 (3)
Hyponatremia	1 (5.6)	0	1 (6.7)	0	2 (6.1)	0
Thyroid dysfunction	5 (27.8)	0	0	0	5 (15.2)	0
Abdominal pain	2 (11.1)	0	3 (20)	0	5 (15.2)	0

Abbreviations: IPI, ipilimumab; Q3W, every 3 weeks; Q6W, every 6 weeks; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4 Prognostic Factors for OS and PFS

	Univariate Analysis for OS		*p* value	Multivariate Analysis for OS		*p* value	Univariate Analysis for PFS		*p* value
	HR	95% CI		HR	95% CI		HR	95% CI	
Gender (M/F)	0.61	0.079–4.680	0.634				1.608	0.478–5.415	0.443
Age (<60 vs ≥60)	0.803	0.217–2.967	0.742				0.533	0.214–1.327	0.176
HBV infection	1.175	0.264–5.226	0.832				1.122	0.384–3.275	0.834
TB (μmol/L)	1.025	0.971–1.082	0.368				0.98	0.934–1.027	0.397
Albumin (g/L)	0.965	0.923–1.008	0.109				0.98	0.932–1.031	0.438
WBC ($\times 10^9$/L)	0.875	0.57–1.344	0.971				1.063	0.807–1.399	0.665
PLT ($\times 10^9$/L)	0.996	0.985–1.007	0.5				1.003	0.996–1.01	0.441
Neu ($\times 10^9$/L)	1.096	0.677–1.775	0.709				1.053	0.732–1.514	0.781
L ($\times 10^9$/L)	0.335	0.089–1.262	0.106				1.023	0.447–2.343	0.956
NLR (<3.1 vs ≥3.1)	5.239	1.178–23.295	**0.03**	4.54	1.013–20.333	**0.048**	1.686	0.766–3.713	0.194
PLR (<151.7 vs ≥151.7)	2.045	0.695–6.024	0.194				1.153	0.546–2.438	0.708
Tumor size (<63 mm vs ≥63mm)	3.259	1.146–9.265	**0.027**	2.776	0.964–8.001	0.059	2.103	0.979–4.517	0.057
Vascular invasion	2.173	0.74–6.385	0.158				1.661	0.783–3.521	0.186
Extrahepatic spread	3.237	0.425–24.654	0.257				1.543	0.581–4.099	0.384
AFP (<400 ng/L, ≥400 ng/L)	2.012	0.566–7.152	0.28				1.197	0.535–2.679	0.662
ECOG (0/1)	0.443	0.160–1.232	0.119				0.611	0.278–1.341	0.219
Child–Pugh class (A/B)	1.976	0.624–6.248	0.247				0.629	0.216–1.835	0.396
Number of prior systemic regimens (1, 2/>2)	1.395	0.590–3.300	0.449				0.842	0.388–1.828	0.663
Anti-PD-1/PD-L1+IPI Q6W vs Anti-PD-1/PD-L1+IPI Q3W	0.412	0.121–1.298	0.13				0.729	0.337–1.575	0.421
Continue prior ICIs plus IPI vs NIVO+IPI	0.533	0.165–1.721	0.293				0.743	0.337–1.638	0.461

Note: Data in bold represents a P value of less than 0.05.

Abbreviations: IPI, ipilimumab; Q3W, every 3 weeks; Q6W, every 6 weeks; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; ICIs, immune checkpoint inhibitors; TKIs, tyrosine kinase inhibitors.

combined use may provide a synergistic antitumor effect.[22,23] Interestingly, our subgroup analysis suggested that the 6-week ipilimumab regimen might provide better outcomes than the 3-week regimen, although this did not reach statistical significance (P=0.12). However, in the CheckMate 040 Clinical Trial, there was no difference in survival benefit between arms B and C (mOS 12.5 months vs 12.7 months).[12] This trend warrants further investigation in larger cohorts to determine whether extended intervals between doses might mitigate toxicity while preserving antitumor efficacy.

In recent years, ICIs and their combination therapy regimens have made significant breakthroughs in the treatment of HCC, markedly improving patient survival. However, the efficacy of monotherapy with ICIs does not exceed 20%, indicating that the majority of patients do not benefit from immunotherapy. Therefore, there is an urgent need to explore biomarkers that can predict the clinical efficacy and prognosis of ICIs.[24,25] Markers of systemic inflammation, such as elevated NLR and PLR, have been associated with poor prognosis in HCC.[26,27] Research by Celina et al found that an NLR $\geq$ 5 is an independent prognostic factor for OS in HCC patients receiving nivolumab treatment.[28] Additionally, a study by Namiki et al suggested that NLR can predict PFS in patients with unresectable HCC receiving atezolizumab in combination with bevacizumab, particularly in those classified as mALBI grade 1 or 2a.[29] The results of our study confirm that an NLR $\geq$ 3.1 is an independent risk factor for prognosis in HCC patients receiving ipilimumab combination therapy (dual immunotherapy). Given that there are currently no definitive biomarkers to predict the efficacy of dual immunotherapy, the findings of this study may provide guidance for clinical treatment, although further validation in larger clinical cohorts is needed.

Despite the clinical benefits associated with ipilimumab combination therapy, the occurrence of drug-related serious adverse events warrants caution. In this study, the incidence of grade 3 or higher adverse events was 21.2%, which is comparable to previous reports involving nivolumab plus ipilimumab. Notably, the study population experienced two cases (6.1%) of hyperprogression, with one case (3%) resulting in death due to rapid tumor progression, highlighting the importance of careful patient selection and monitoring. Prior literature has reported that the incidence of immune-related hyperprogression ranges from 9% to 29%,[30–32] with a hyperprogression rate of 12.7% associated with nivolumab monotherapy.[33] Although the mechanisms underlying hyperprogression following immunotherapy in HCC remain unclear, it is evident that patients who experience hyperprogression have significantly shortened survival times. Therefore, further research should explore biomarkers that predict response and adverse outcomes, aiming to refine the patient population that may derive the most benefit from ipilimumab combination therapy.

This study has several limitations. First, while multicenter retrospective data were utilized to increase the sample size, the small sample size limits statistical power, particularly for subgroup analyses, which may obscure significant trends. Additionally, as a retrospective, multicenter analysis, the study may be subject to selection and information bias, and causality cannot be firmly established. Finally, heterogeneous treatment backgrounds among patients may impact the generalizability of the findings, underscoring the need for larger, prospective trials to validate these results.

Conclusions

In conclusion, ipilimumab combination therapy represents a viable treatment option for patients with advanced hepatocellular carcinoma in very late lines of therapy. Our findings demonstrate that while this approach can yield beneficial outcomes, it is imperative to implement careful monitoring for adverse events to ensure patient safety. Additionally, the possibility of enhanced effectiveness when this combination therapy is administered earlier in the treatment course suggests that timing may play a critical role in optimizing patient outcomes. Besides, our study confirm that an NLR $\geq$ 3.1 is an independent risk factor for prognosis in HCC patients receiving ipilimumab combination therapy, which may provide guidance for clinical treatment. However, it is important to acknowledge the limitations of our study, including its retrospective design and small sample size, which may affect the generalizability of the results. Future research should focus on larger, prospective studies to validate our findings and further explore the optimal timing for ipilimumab combination therapy.

Data Sharing Statement

The datasets presented in the current study are available from the corresponding author on reasonable request.

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.

Funding

This research was supported by grants from the Natural Science Foundation of Fujian Province (2022J05332 to Su-Su Zheng and 2022J011428 to Bo-Heng Zhang); Science and Technology Bureau of Xiamen City (3502Z20224ZD1081 to Su-Su Zheng). Fujian Provincial Health Commission Science and Technology Planning Project (2023GGB11 to Su-Su Zheng).

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Vogel A, Meyer T, Sapisochin G, et al. Hepatocellular carcinoma. *Lancet*. 2022;400:1345–1362. doi:10.1016/S0140-6736(22)01200-4
3. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology*. 2021;73(Suppl 1):4–13. doi:10.1002/hep.31288
4. Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a Phase III trial. *J Hepatol*. 2012;57(4):821–829. doi:10.1016/j.jhep.2012.06.014
5. Nair A, Reece K, Donoghue MB, et al. FDA supplemental approval summary: lenvatinib for the treatment of unresectable hepatocellular carcinoma. *Oncologist*. 2021;26(3):e484–e491. doi:10.1002/onco.13566
6. Qin S, Bi F, Gu S, et al. Donafenib versus sorafenib in first-line treatment of unresectable or metastatic hepatocellular carcinoma: a randomized, open-label, parallel-controlled phase II-III Trial. *J Clin Oncol*. 2021;39(27):3002–3011. doi:10.1200/JCO.21.00163
7. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
8. Qin S, Chan SL, Gu S, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international Phase 3 study. *Lancet*. 2023;402(10408):1133–1146. doi:10.1016/S0140-6736(23)00961-3
9. Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, Phase 2-3 study. *Lancet Oncol*. 2021;22(7):977–990. doi:10.1016/S1470-2045(21)00252-7
10. Abou-Alfa SK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*. 2022;1(8):a2100070. doi:10.1056/EVIDoa2100070
11. Yau T, Kang YK, Kim TY, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. *JAMA Oncol*. 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564
12. Melero I, Yau T, Kang YK, et al. Nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma previously treated with sorafenib: 5-year results from CheckMate 040. *Ann Oncol*. 2024;35(6):537–548. doi:10.1016/j.annonc.2024.03.005
13. Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. *J Clin Oncol*. 2020;38(36):4317–4345. doi:10.1200/JCO.20.02672
14. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023;78(6):1922–1965. doi:10.1097/HEP.0000000000000466
15. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary cancers, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2021;19(5):541–565. doi:10.6004/jnccn.2021.0022
16. Finn RS, Merle P, Granito A, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: additional analyses from the phase III RESORCE trial. *J Hepatol*. 2018;69(2):353–358. doi:10.1016/j.jhep.2018.04.010
17. Zhang Y, Fan W, Wang Y, et al. Apatinib for patients with sorafenib-refractory advanced hepatitis B virus related hepatocellular Carcinoma: results of a pilot study. *Cancer Control*. 2019;26(1):1147307480. doi:10.1177/1073274819872216
18. Zhu AX, Nipp RD, Finn RS, et al. Ramucirumab in the second-line for patients with hepatocellular carcinoma and elevated alpha-fetoprotein: patient-reported outcomes across two randomised clinical trials. *ESMO Open*. 2020;5(4):e000797. doi:10.1136/esmoopen-2020-000797
19. Fournier L, Ammari S, Thiam R, et al. Imaging criteria for assessing tumour response: RECIST, mRECIST, Cheson. *Diagn Interv Imaging*. 2014;95(7–8):689–703. doi:10.1016/j.diii.2014.05.002
20. Alden SL, Lim M, Kao C, et al. Salvage ipilimumab plus nivolumab after anti-PD-1/PD-L1 therapy in advanced hepatocellular carcinoma. *Cancer Res Commun*. 2023;3(7):1312–1317. doi:10.1158/2767-9764.CRC-23-0072
21. Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update. *J Clin Oncol*. 2024;42(15):1830–1850. doi:10.1200/JCO.23.02745
22. Kudo M. Scientific rationale for combination immunotherapy of hepatocellular carcinoma with anti-PD-1/PD-L1 and anti-CTLA-4 antibodies. *Liver Cancer*. 2019;8(6):413–426. doi:10.1159/000503254
23. Alsaab HO, Sau S, Alzhrani R, et al. PD-1 and PD-L1 Checkpoint Signaling Inhibition for Cancer Immunotherapy: mechanism, Combinations, and Clinical Outcome. *Front Pharmacol*. 2017;8:561. doi:10.3389/fphar.2017.00561

24. Donne R, Lujambio A. The liver cancer immune microenvironment: therapeutic implications for hepatocellular carcinoma. *Hepatology*. 2023;77(5):1773–1796. doi:10.1002/hep.32740
25. Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2022;19:151–172. doi:10.1038/s41571-021-00573-2
26. Zheng J, Cai J, Li H, et al. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as prognostic predictors for hepatocellular carcinoma patients with various treatments: a meta-analysis and systematic review. *Cell Physiol Biochem*. 2017;44(3):967–981. doi:10.1159/000485396
27. Bruix J, Cheng AL, Meinhardt G, et al. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. *J Hepatol*. 2017;67(5):999–1008. doi:10.1016/j.jhep.2017.06.026
28. Dharmapuri S, Ozbek U, Lin JY, et al. Predictive value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in advanced hepatocellular carcinoma patients treated with anti-PD-1 therapy. *Cancer Med*. 2020;9(14):4962–4970. doi:10.1002/cam4.3135
29. Ochi H, Kurosaki M, Joko K, et al. Usefulness of neutrophil-to-lymphocyte ratio in predicting progression and survival outcomes after atezolizumab-bevacizumab treatment for hepatocellular carcinoma. *Hepatol Res*. 2023;53(1):61–71. doi:10.1111/hepr.13836
30. Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive disease in patients with advanced non-small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. *JAMA Oncol*. 2018;4(11):1543–1552. doi:10.1001/jamaoncol.2018.3676
31. Sasaki A, Nakamura Y, Mishima S, et al. Predictive factors for hyperprogressive disease during nivolumab as anti-PD1 treatment in patients with advanced gastric cancer.er. *Gastric Canc*. 2019;22(4):793–802. doi:10.1007/s10120-018-00922-8
32. Saada-Bouzid E, Defaucheux C, Karabajakian A, et al. Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. *Ann Oncol*. 2017;28(7):1605–1611. doi:10.1093/annonc/mdx178
33. Kim CG, Kim C, Yoon SE, et al. Hyperprogressive disease during PD-1 blockade in patients with advanced hepatocellular carcinoma. *J Hepatol*. 2021;74(2):350–359. doi:10.1016/j.jhep.2020.08.010