Original Article

Discontinuation of immune checkpoint inhibitors in hepatocellular carcinoma: a retrospective cohort study

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Background: The optimal timing to discontinue immune checkpoint inhibitor (ICI) therapy in hepatocellular carcinoma (HCC) patients with clinical benefits remains unclear. This study aimed to assess the outcomes of HCC patients after ICI discontinuation.

Methods: Patients with HCC were retrospectively screened and those discontinued ICI therapy in the absence of progressive disease (PD) were included. Responses at discontinuation were evaluated per response evaluation criteria in solid tumors (RECIST) version 1.1 and modified RECIST (mRECIST). Patients were classified into five subgroups according to the cause of discontinuation: complete response (CR), partial response (PR), stable disease (SD) per RESICT version 1.1, adverse event (AE), or others. Progression-free survival (PFS) and overall survival (OS) since ICI start or after ICI discontinuation were assessed.

Results: A total of 66 patients were included. The median follow-up was 29.33 months. The median PFS since ICI start was 30.83 months [95% confidence interval (CI): 24.93–36.72], and the median OS was not reached. The median PFS after discontinuation was 20.6 months (95% CI: 7.63–33.56), and the median OS after discontinuation was not reached. Univariate analysis showed that age, treatment after discontinuation, Response (RECIST version 1.1) at discontinuation and modified response (mResponse per mRECIST) at discontinuation were significantly associated with PFS after discontinuation, while age and mResponse at discontinuation were significantly associated with OS after discontinuation. Multivariate analysis further demonstrated that mResponse at discontinuation and treatment after discontinuation were independently associated with PFS after discontinuation, while age was independently associated with OS after discontinuation.

Conclusions: ICIs might be discontinued in HCC patients with a response of CR per mRECIST. Patients with a response of PR/SD per mRECIST or elder age could continue ICI therapy after achieving clinical benefits. Tyrosine kinase inhibitor (TKI) maintenance therapy might help to prevent progression after ICI discontinuation.

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Keywords: Hepatocellular carcinoma (HCC); immune checkpoint inhibitors (ICIs); programmed death protein 1 (PD-1); discontinuation

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Introduction

Patients with hepatocellular carcinoma (HCC) are frequently diagnosed at an advanced stage of disease beyond potentially curative treatments including surgical resection, transplantation, or ablation (1). Sorafenib and lenvatinib are multi-target tyrosine kinase inhibitors (TKIs) that used to be the first-line treatment for patients with advanced HCC (2). Recently, the therapeutic landscape has dramatically changed with the introduction of immune checkpoint inhibitors (ICIs) both in the first-line and second-line setting for HCC (3). Currently, the ICI combination regimen (atezo-bevacizumab and durvalumab-tremelimumab) is considered as the front-line treatment option in HCC (2,4). marking a new era in which ICI-based combination therapies dominate clinical research across all stages of HCC (3).

The COSMIC-312 trial compared cabozantinib plus atezolizumab with sorafenib as a first-line treatment for advanced HCC, but the study did not show a significant difference in median overall survival (OS) (5). The LEAP-002 trial which compared the combination of pembrolizumab and lenvatinib with lenvatinib alone also did not meet its primary endpoints of OS and progression-free survival (PFS) (6). However, increasing evidence have demonstrated a significantly improved anti-tumor efficacy of combination treatment strategy based on ICIs plus TKI due to the synergistic effects (7). Furthermore, with the wide use of ICIs in HCC, there is still no consensus on the optimal duration of ICIs as well as the timing of the cessation of ICIs in patients with clinical benefit. Concerns have also been raised in clinical practice about the potentially accumulating risk of severe immune-related adverse events (irAEs) and the increasing economic burden associated with the long-term use of ICIs (8,9). More importantly, the risk of disease progression with the discontinuation of ICIs in HCC patients with clinical benefit is also unclear.

Therefore, in this study, we aimed to assess the outcome of patients with HCC after discontinuation of ICIs in the absence of progression and to explore potential predictive factors associated with the outcomes following discontinuation. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-216/rc).

Highlight box

Key findings

- Patients with complete response per mRECIST (mCR) at discontinuation or received tyrosine kinase inhibitor (TKI) maintenance therapy after immune checkpoint inhibitor (ICI) discontinuation had a more favorable prognosis, while elderly patients had a poor prognosis after ICI discontinuation.

What is known and what is new?

- ICIs have profoundly transformed the therapeutic landscape of hepatocellular carcinoma (HCC). However, the optimal timing to discontinue ICI therapy in patients with clinical benefits remains inconclusive.

What is the implication, and what should change now?

- ICIs might be discontinued in HCC patients with mCR. Patients with a response of partial response/stable disease per mRECIST or elder age could continue ICI therapy after achieving clinical benefits.
- TKI maintenance therapy might help to prevent progression after ICI discontinuation.

Methods

Study design and patients

We conducted a single-center, retrospective cohort study. Patients with HCC were first screened with the following criteria for eligibility: (I) diagnosis of HCC was confirmed by pathological examinations, or radiological examinations by liver imaging reporting and data system (LI-RADS) criteria without biopsy confirmation; (II) patients who have not been treated with ICIs previously; (III) previous Surgery, loco-regional therapy (LRT), systemic treatment recipients prior to ICIs were eligible for the study; (IV) treated with anti-programmed death protein 1 (anti-PD-1)/programmed cell death-ligand 1 (PD-L1) monoclonal antibody, at least 3 cycles from 2016 to 2021 in Eastern

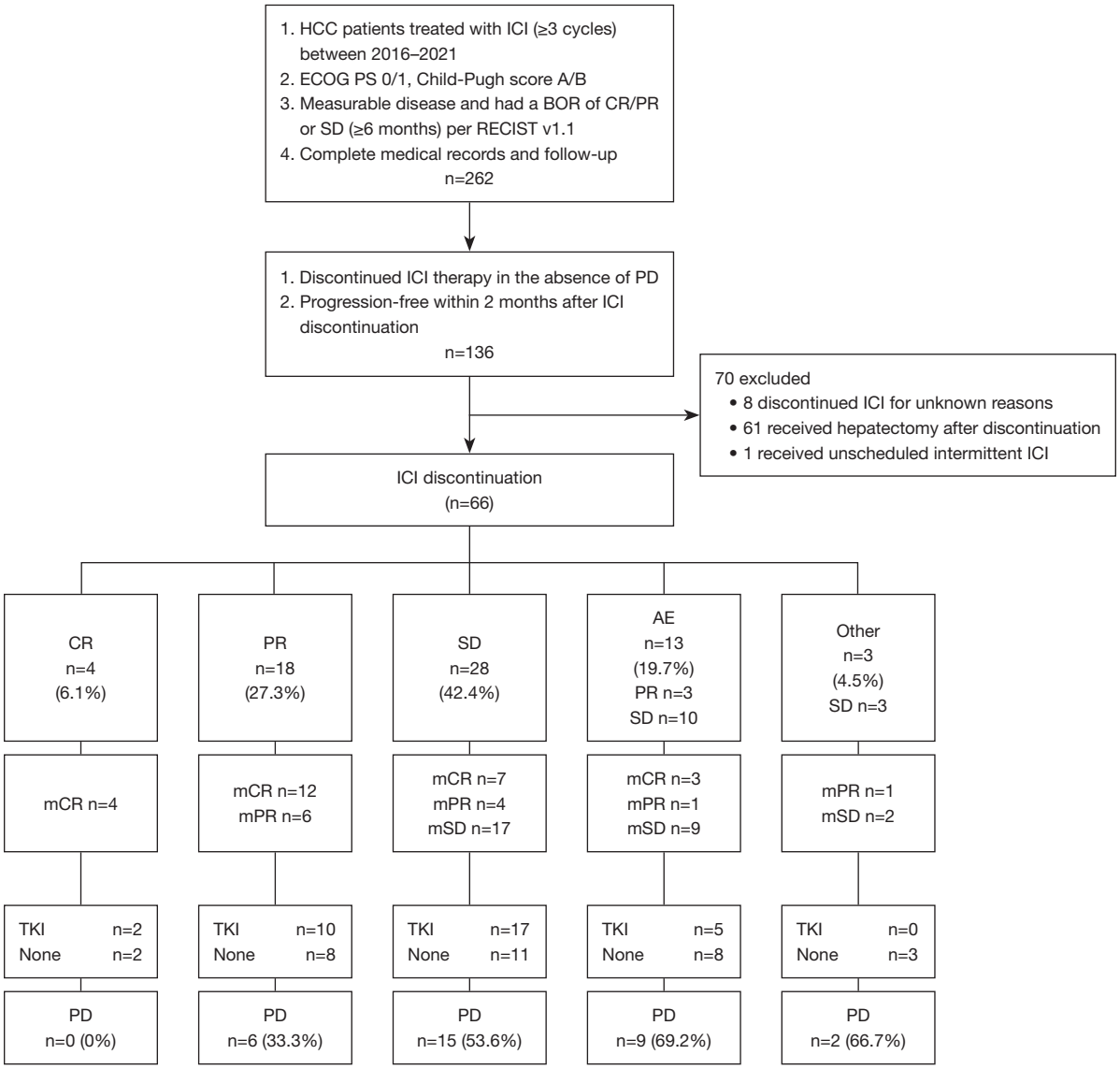

Figure 1 Flow chart of patients. HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; AE, adverse event; mCR, complete response per mRECIST; mPR, partial response per mRECIST; mSD, stable disease per mRECIST; TKI, tyrosine kinase inhibitor.

Hepatobiliary Surgery Hospital; (V) Eastern Cooperative Oncology Group performance status 0 or 1, Child-Pugh score A or B; (VI) patients who have received definitive treatments (surgical resection, transplantation, or liver-directed therapies) after ICI therapy were excluded; (VII) measurable disease at the start of ICI treatment and had a best overall response (BOR) of complete response/partial response (CR/PR) or stable disease (SD) (≥6 months) per response evaluation criteria in solid tumors (RECIST) version 1.1; (VIII) complete medical records and follow-up. The included patients who met the additional criteria: (I) discontinued ICI therapy in the absence of progressive disease (PD); (II) progression-free within 2 months after ICI discontinuation) were then included in the cohort to investigate the effect of ICI discontinuation on patient outcomes (*Figure 1*). This study was approved by the institutional review board of the Eastern Hepatobiliary Surgery Hospital (No. EHBHKY2023-K050-P002). This

study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patients' informed consent was not required, as this is a retrospective study. Data were collected from medical files, anonymized, and protected for analysis during the study.

Assessments

Responses were defined as CR, PR, SD, and PD by RECIST version 1.1. Responses at the time of discontinuation were also evaluated by modified RECIST (mRECIST), which were defined as mCR, mPR, and mSD. At the time of ICI discontinuation, patients were classified into five subgroups according to the cause of discontinuation: CR, PR, SD (≥6 months) per RESICT version 1.1, adverse event (AE), or others (economic or personal reasons). PFS was defined as the interval between ICI initiation and tumor progression or death, whichever comes first. OS was defined as the interval between ICI initiation and death. PFS after ICI discontinuation (PFS_{Dis}) was defined as the interval between ICI discontinuation and tumor progression or death, whichever comes first. OS after ICI discontinuation (OS_{Dis}) was defined as the interval between ICI discontinuation and patient death. The patients were followed up until 30 June, 2022. Duration of ICIs was the interval from the initiation to the last dose of ICI treatment. Common Terminology Criteria for Adverse Events Criteria Version 4.03 were used to evaluate treatment-related AEs (TRAEs).

Statistical analysis

The characteristics of patients were described by median and 95% confidence interval (CI) for quantitative variables and by numbers and percentages for qualitative variables. Swimmer plot was used to describe the whole state of the study population. Survival was estimated using the Kaplan-Meier method and log-rank test. The Cox proportional risk model was used to explore the effects of factors on the PFS rate and OS rate, with results presented as hazard ratio (HR) and 95% CI. In the univariate analysis, variables with a P value <0.05 were considered statistically significant and were subsequently included in the multi-variable analysis (Cox proportional risk model). Statistical analysis was performed using SPSS 23.0 software (IBM Corp., Armonk, NY, USA). All P values were double-tailed, and P<0.05 was considered statistically significant.

Results

Patient characteristics

A total of 262 patients with HCC met the inclusion criteria and underwent eligibility screening. Among them, 136 patients discontinued ICI therapy without experiencing disease progression and without the presence of PD within 2 months after discontinuation. Seventy patients were subsequently excluded from the study (8 discontinued ICI therapy for unknown reasons, 61 received hepatectomy after discontinuation, and 1 patient received unscheduled intermittent ICI therapy). Finally, 66 patients who had discontinued ICI therapy were enrolled (*Figure 1*). Thirty-two patients experienced disease progression, and 15 patients died during the follow-up period. Eleven patients with BCLC stage A HCC who were deemed unresectable, unsuitable for ablation, and also refused to receive liver transplantation were included. The median duration of ICI treatment was 5.16 months. The median follow-up was 29.33 months (95% CI: 7.7–55.8). Baseline characteristics of patients are summarized in *Table 1*. The detailed information on the ICIs used in this study is listed in Table S1. A total of 34 patients have received TKI maintenance therapy immediately after ICI discontinuation.

Among patients who discontinued ICI treatment due to AEs, 3 patients achieved PR, and 10 patients achieved SD at the time of ICI discontinuation. Patients who discontinued ICI treatment for other reasons achieved SD at the time of discontinuation. Overall, 4 (6.1%), 21 (31.8%), and 41 (62.1%) patients achieved CR, PR, and SD at the time of ICI discontinuation, respectively. According to mRECIST, 26 patients (39.4%), 12 patients (18.2%), and 28 patients (42.4%) achieved mCR, mPR, and mSD at the time of ICI discontinuation, respectively. After discontinuation, 34 patients were treated with TKI maintenance therapy, while 32 patients did not receive any treatment (*Figure 1*).

Patient outcome

At data cutoff (June 30, 2022), the median PFS was 30.83 months (95% CI: 24.93–36.72), and the median OS was not reached (Figure S1). Univariate analysis demonstrated significant associations between PFS and variables such as age (≥60 *vs.* <60 years, HR 2.37, 95% CI: 1.18–4.78, P=0.01), response at discontinuation (PR *vs.* SD, HR 0.34, 95% CI: 0.14–0.79, P=0.01), mResponse

Table 1 Baseline characteristics of patients

Characteristic	Value
Age (years)	
≥60	26 (39.39)
<60	40 (60.61)
Gender	
Male	58 (87.88)
Female	8 (12.12)
ECOG PS	
0	40 (60.61)
1	26 (39.39)
Child-Pugh score	
A	63 (95.45)
B	3 (4.55)
HBV	
Yes	58 (87.88)
No	8 (12.12)
HCV	
Yes	3 (4.55)
No	63 (95.45)
MVI	
Yes	19 (28.79)
No	47 (71.21)
Extrahepatic metastasis	
Yes	22 (33.33)
No	44 (66.67)
BCLC	
A	11 (16.67)
B	20 (30.30)
C	35 (53.03)
AFP, μg/L	
≥400	22 (33.33)
<400	44 (66.67)
DCP, mAU/mL	
≥400	28 (42.42)
<400	38 (57.58)
First-line	
Yes	48 (72.73)
No	18 (27.27)
Treatment-naïve	
Yes	15 (22.73)
No	51 (77.27)
Combinational therapy of LRT and ICI	
Yes	49 (74.24)
No	17 (25.76)
Combinational therapy of TKI and ICI	
Yes	50 (75.76)
No	16 (24.24)
Duration of ICIs[#] (months)	5.16 (0.97–22.23)
TRAE	
Yes	39 (59.09)
No	27 (40.91)
Previous surgery	
Yes	39 (59.09)
No	27 (40.91)
Previous TACE	
Yes	46 (69.70)
No	20 (30.30)
Previous PMCT	
Yes	20 (30.30)
No	46 (69.70)
Previous radiotherapy	
Yes	8 (12.12)
No	58 (87.88)
Previous TKI	
Yes	17 (25.76)
Lenvatinib	6 (35.29)
Sorafenib	10 (58.82)
Apatinib	1 (5.88)
No	49 (74.24)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Value
Reason for ICI discontinuation	
CR	4 (6.06)
PR	18 (27.27)
SD	28 (42.42)
AE	13 (19.70)
Other	3 (4.55)
Response at ICI discontinuation	
CR	4 (6.06)
PR	20 (30.30)
SD	42 (63.64)
mResponse at ICI discontinuation*	
mCR	26 (39.39)
mPR	12 (18.18)
mSD	28 (42.42)
Treatment after ICI discontinuation	
TKI	34 (51.52)
None	32 (48.48)

Data are presented as n (%) unless otherwise specified. #, duration of ICIs was defined as quantitative variable and expressed as median (range); *, mResponse, response per mRECIST. ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; BCLC stage, Barcelona Clinic Liver Cancer stage; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; LRT, loco-regional therapy; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event; TACE, transarterial chemoembolization; PMCT, percutaneous microwave coagulation therapy; CR, complete response; PR, partial response; SD, stable disease; AE, adverse event; mCR, complete response per mRECIST; mPR, partial response per mRECIST; mSD, stable disease per mRECIST.

at discontinuation (mCR *vs.* mSD, HR 0.23, 95% CI: 0.09–0.57, P=0.002), and maintenance treatment after ICI discontinuation (TKI *vs.* none, HR 0.46, 95% CI: 0.23–0.95, P=0.03) (Table S2). Similarly, age (≥60 *vs.* <60 years, HR 3.53, 95% CI: 1.20–10.35, P=0.02) and mResponse at discontinuation (mCR *vs.* mSD, HR 0.15, 95% CI: 0.03–0.70, P=0.01) were also found to be statistically significant predictors of OS (Table S3). Kaplan-Meier analysis further supported these findings, showing that patients with mCR and TKI therapy after discontinuation had significantly improved PFS (*Figure 2A,2B*) and patients with younger age had significantly improved OS (*Figure 2C*). Multivariable analysis revealed that mResponse at discontinuation (mCR *vs.* mSD, HR 0.16, 95% CI: 0.06–0.42, P<0.001) and TKI maintenance after ICI discontinuation (TKI *vs.* none, HR 0.30, 95% CI: 0.14–0.64, P=0.002) was independently associated with PFS (Table S2), while age (≥60 *vs.* <60 years, HR 3.53, 95% CI: 1.20–10.35, P=0.02) was independently associated with OS (Table S3).

Patient outcome after ICI discontinuation

The median PFS_{Dis} was 20.6 months (95% CI: 7.63–33.56), and the median OS_{Dis} was not reached (Figure S2). Univariate analysis showed that age (≥60 *vs.* <60 years, HR 2.39, 95% CI: 1.18–4.84, P=0.01), TKI maintenance after ICI discontinuation (TKI *vs.* none, HR 0.46, 95% CI: 0.23–0.95, P=0.03), Response at discontinuation (PR *vs.* SD, HR 0.36, 95% CI: 0.15–0.88, P=0.02), and mResponse at discontinuation (mCR *vs.* mSD, HR 0.22, 95% CI: 0.09–0.58, P=0.002) were significantly associated with PFS_{Dis} (*Table 2*). Kaplan-Meier analysis also revealed that patients with mCR at discontinuation or TKI treatment after discontinuation had improved PFS_{Dis} (*Figure 3A,3B*). Multivariate analysis further demonstrated that mResponse at discontinuation (mCR *vs.* mSD, HR 0.15, 95% CI: 0.05–0.43, P<0.001) and TKI maintenance after ICI discontinuation (TKI *vs.* none, HR 0.28, 95% CI: 0.13–0.61, P=0.001) were independently associated with PFS_{Dis} (*Table 2*). Univariate analysis showed that age (≥60 *vs.* <60 years, HR 3.49, 95% CI: 1.19–10.23, P=0.02) and mResponse at discontinuation (mCR *vs.* mSD, HR 0.16, 95% CI: 0.03–0.74, P=0.01) were significantly associated with OS_{Dis}, and only age (≥60 *vs.* <60 years, HR 3.49, 95% CI: 1.19–10.22, P=0.02) remained statistically significant in the multivariate analysis (Table S4). Consistent with these findings, Kaplan-Meier analysis demonstrated that patients under the age of 60 years had remarkably improved OS_{Dis} (Figure S3). The detailed information of TKIs used as maintenance therapy were listed in Table S5, which only included lenvatinib and sorafenib.

The detailed AEs leading to discontinuation were listed in Table S6, which included pneumonitis, rash, dermatitis, hepatitis, fever, gastric hemorrhage, gastritis, and thrombocytopenia. Previous treatments and Child-Pugh score were also not associated with survival (*Table 2* and Table S7). Additionally, we examined the

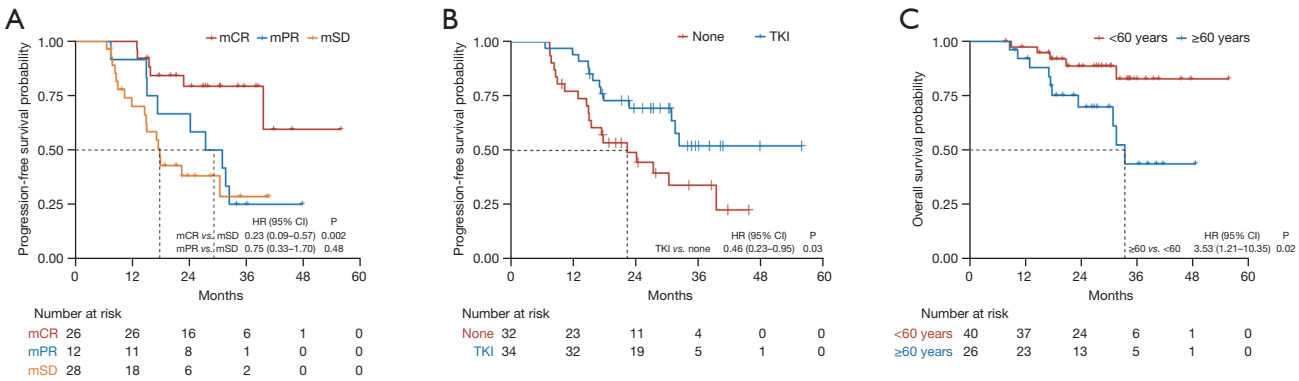

Figure 2 Kaplan-Meier analysis of PFS and OS in HCC patients. (A) Kaplan-Meier estimates of PFS curves in HCC patients stratified by response per mRECIST. (B) Kaplan-Meier estimates of PFS curves in HCC patients stratified by treatment after discontinuation. (C) Kaplan-Meier estimates of OS curves in HCC patients stratified by age. mCR, complete response per mRECIST; mPR, partial response per mRECIST; mSD, stable disease per mRECIST; HR, hazard ratio; CI, confidence interval; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; OS, overall survival; HCC, hepatocellular carcinoma.

multicollinearity issues between RECIST and mRECIST assessment criteria in predicting survival. As shown in Table S8, the variance inflation factor (VIF) values for independent variables, including RECIST and mRECIST, were significantly below 5, suggesting that multicollinearity is unlikely to be a concern in our statistical model. Furthermore, the swimmer plot of patients after ICI discontinuation clearly showed that patients with mCR or younger age had notably improved outcome (*Figure 4*). Additionally, the swimmer plot and subgroup analysis further revealed that TKI after ICI discontinuation only improved PFS_{Dis} in patients with mPR (HR 0.11, 95% CI: 0.02–0.61, P=0.01) and mSD (HR 0.25, 95% CI: 0.09–0.72, P=0.01) (*Figure 4* and Figure S4A-S4C).

Discussion

Currently, the optimal duration of immunotherapy for HCC patients with evident clinical benefits remains unclear. For the first time, our study provides the insights into the prognosis of patients after ICI discontinuation and demonstrates that ICIs might be discontinued in HCC patients who have achieved a response of mCR. Furthermore, patients who have received TKI maintenance therapy after ICI discontinuation had a more favorable PFS, but TKI maintenance therapy did not show a benefit in OS. On the other hand, elderly patients had a poor prognosis after ICI discontinuation.

The optimal duration of treatment and appropriate timing to discontinue ICI therapy remain a critical issue for patients with cancer. The risk of severe late-phase immune-related toxicities, the economic burden of long-term treatment, and most importantly, the risk of progression, all might influence the decision of clinicians and patients to discontinue ICIs. For metastatic melanoma, the European Society of Medical Oncology recommends that patients with confirmed CR may be considered for discontinuation of therapy after at least 6 months of anti-PD-1 treatment, whereas patients with PR or SD are recommended to be considered for discontinuation after at least 2 years of treatment (10). However, the study by Ellebaek *et al.* reported that patients with metastatic melanoma who obtained an early response and discontinued immunotherapy early still had an excellent prognosis, especially in the absence of fluorodeoxyglucose (FDG) positron emission tomography (PET)-avid lesions when discontinuing treatment (11). Discontinuation of anti-PD-1 therapy after 12 months of treatment when no active disease is observed on computed tomography (CT) scan, PET/CT scan, or tumor biopsy may have low rates of disease relapse in patients with advanced melanoma (12). A multi-center prospective Safe Stop trial suggested that from a healthcare and economic perspective, shorter treatment duration is preferred and overtreatment should be prevented, early discontinuation of PD-1 blockade upon achieving a CR or PR is recommended in patients with advanced melanoma (13). In short, recent research reports have explored the optimal timing for discontinuing ICIs, but such studies remain inconclusive and fail to clarify when to discontinue ICIs for HCC patients. The median

Table 2 Univariable and multivariate Cox proportional hazards regression model of PFS after ICI discontinuation (PFS_{Dis})

Characteristic	Median survival time (months)	Univariate analysis		Multivariate Cox regression	
		HR (95% CI)	P	HR (95% CI)	P
Age, years					
≥60 *vs.* <60	13.1 *vs.* 34.9	2.39 (1.18–4.84)	0.01	NA	0.25
Gender					
Male *vs.* female	20.6 *vs.* NR	0.99 (0.30–3.27)	0.98		
ECOG PS					
1 *vs.* 0	NR *vs.* 20.6	0.86 (0.42–1.76)	0.68		
Child-Pugh score					
B *vs.* A	NR *vs.* 20.6	0.87 (0.12–6.43)	0.89		
HBV					
Yes *vs.* no	26.3 *vs.* 12.7	0.80 (0.31–2.08)	0.64		
HCV					
Yes *vs.* no	NR *vs.* 20.6	0.59 (0.08–4.35)	0.60		
MVI					
Yes *vs.* no	NR *vs.* 19.0	0.70 (0.30–1.62)	0.40		
Extrahepatic metastasis					
Yes *vs.* no	NR *vs.* 13.6	0.44 (0.19–1.03)	0.059		
BCLC					
B *vs.* A	13.2 *vs.* 12.4	1.29 (0.49–3.39)	0.60		
C *vs.* A	NR *vs.* 12.4	0.53 (0.20–1.42)	0.20		
AFP, μg/L					
≥400 *vs.* <400	NR *vs.* 13.5	0.51 (0.23–1.16)	0.10		
DCP, mAU/mL					
≥400 *vs.* <400	26.9 *vs.* 19	0.91 (0.44–1.88)	0.80		
First-line					
Yes *vs.* no	20.6 *vs.* 34.9	0.94 (0.43–2.03)	0.86		
Treatment-naïve					
Yes *vs.* no	26.3 *vs.* 19	0.80 (0.33–1.94)	0.62		
Combinational therapy of LRT and ICI					
Yes *vs.* no	19.0 *vs.* NR	1.97 (0.81–4.82)	0.13		
Combinational therapy of TKI and ICI					
Yes *vs.* no	26.3 *vs.* 13.1	0.66 (0.32–1.38)	0.27		
Duration of ICIs[#]	NA	0.99 (0.92–1.06)	0.77		
TRAE					
Yes *vs.* no	19.0 *vs.* 34.9	1.26 (0.61–2.57)	0.53		

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	Median survival time (months)	Univariate analysis		Multivariate Cox regression	
		HR (95% CI)	P	HR (95% CI)	P
Previous surgery					
Yes *vs.* no	20.6 *vs.* 26.3	0.84 (0.41–1.70)	0.62		
Previous TACE					
Yes *vs.* no	24.7 *vs.* 31.1	1.18 (0.53– 2.62)	0.69		
Previous PMCT					
Yes *vs.* no	23.9 *vs.* 27.5	1.22 (0.59–2.54)	0.59		
Previous radio					
Yes *vs.* no	15.3 *vs.* 28.6	1.86 (0.71–4.86)	0.21		
Previous TKI					
Yes *vs.* no	13.5 *vs.* 20.6	1.08 (0.48–2.43)	0.84		
Reason for ICI discontinuation					
CR *vs.* SD	NR *vs.* 13.2	NR	0.98		
PR *vs.* SD	NR *vs.* 13.2	0.43 (0.16–1.20)	0.10		
AE *vs.* SD	13.3 *vs.* 13.2	1.34 (0.58–3.06)	0.49		
Other *vs.* SD	6.4 *vs.* 13.2	2.03 (0.46–8.94)	0.35		
Response at ICI discontinuation					
CR *vs.* SD	NR *vs.* 13.2	NR	0.98	NA	0.24
PR *vs.* SD	34.9 *vs.* 13.2	0.36 (0.15–0.88)	0.02	NA	0.68
mResponse at ICI discontinuation*					
mCR *vs.* mSD	NR *vs.* 13.1	0.22 (0.09–0.58)	0.002	0.15 (0.05–0.43)	<0.001
mPR *vs.* mSD	13.8 *vs.* 13.1	0.86 (0.37–1.97)	0.71	1.00 (0.43–2.32)	0.99
Treatment after ICI discontinuation					
TKI *vs.* none	26.9 *vs.* 13.1	0.46 (0.23–0.95)	0.03	0.28 (0.13–0.61)	0.001

#, duration of ICIs was defined as quantitative variable; *, mResponse, response per mRECIST. In the univariate analysis, variables with a P value <0.05 were considered statistically significant and were subsequently included in the multi-variable analysis (Cox proportional risk model). Age, response at ICI discontinuation, mResponse at ICI discontinuation and treatment after ICI discontinuation were included in the final multi-variable model for PFS_{Dis}. PFS, progression-free survival; ICI, immune checkpoint inhibitor; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; BCLC stage, Barcelona Clinic Liver Cancer stage; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; LRT, loco-regional therapy; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event; TACE, transarterial chemoembolization; PMCT, percutaneous microwave coagulation therapy; CR, complete response; PR, partial response; SD, stable disease; AE, adverse event; mCR, complete response per mRECIST; mPR, partial response per mRECIST; mSD, stable disease per mRECIST; NR, not reached; NA, not applicable.

durations of ICI treatment were 10.65, 7.84, 5.09, 3.57 and 4.20 months in the CR, PR, SD, AE and Other groups, respectively. The relatively short median duration in all patients (5.16 months) was probably due to the notable short median duration in the AE group (AE versus CR + PR + SD + Other, P=0.04). However, our analysis showed that treatment duration of ICI was not associated with PFS_{Dis} or OS_{Dis} (*Table 2* and Table S2), suggesting that the

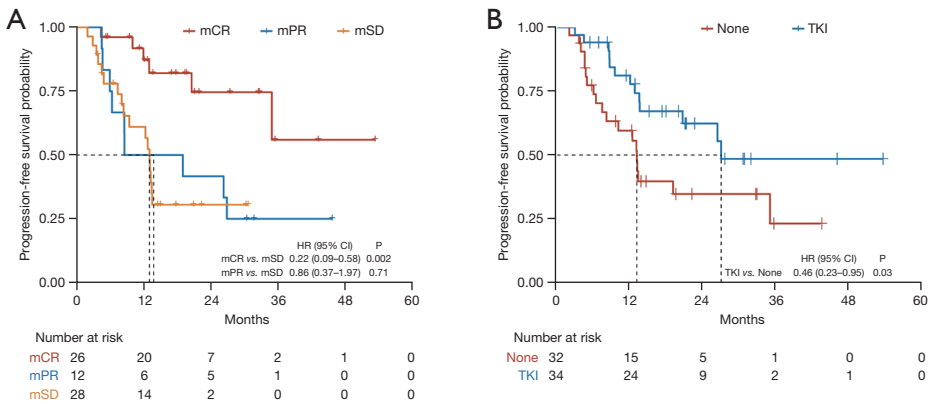

Figure 3 Kaplan-Meier analysis of PFS_{Dis} in HCC patients. (A) The PFS_{Dis} was compared in patients with different responses per mRECIST at discontinuation. (B) The PFS_{Dis} was compared in patients treated with TKI or none after discontinuation. mCR, complete response per mRECIST; mPR, partial response per mRECIST; mSD, stable disease per mRECIST; HR, hazard ratio; CI, confidence interval; TKI, tyrosine kinase inhibitor; PFS_{Dis}, progression-free survival after immune checkpoint inhibitor discontinuation; HCC, hepatocellular carcinoma.

duration of ICI treatment may not influence the outcome of patients. According to our study, patients with HCC who discontinued ICIs after achieving mCR had a better prognosis than those who did not, irrespective of the duration of ICI treatment, suggesting that mCR could serve as a potential indicator for ICI discontinuation. Additional studies are necessary to address this issue and provide more conclusive evidence.

Studies from other cancers have shown that after the cessation of immunotherapy, patients with PR should receive intensified therapy when tumor lesions no longer regress, for most of them eventually develop secondary resistance, whereas patients with CR can remain long-term progression-free (14-16). Consistently, this study also showed that patients with mCR had markedly superior survival compared with mPR or mSD, further indicating that patients with mPR or mSD required a lengthier period of observation and evaluation before discontinuation was considered. Moreover, it might be beneficial to achieve mCR with intensive combinational therapies to get long-term progression-free.

A recent meta-analysis has shown that mRECIST outperformed RECIST (version 1.1) in evaluating objective response rate (ORR) and predicting prognosis in patients with HCC who underwent molecular targeted therapies (17). mRECIST not only considers the lesion diameter, but also provides more detailed imaging features, including the average lesion density, lesion margin clarity, and tumor vascular sensitivity (18). Compared with RECIST, mRECIST can objectively and accurately assess the response of HCC after treatment and help to adjust treatment strategies promptly and predict patient prognosis (19). Accordingly, in our study, multivariate analysis revealed that the response based on mRECIST but not RECIST criteria was significantly associated with PFS_{Dis}, and patients with mCR could be candidates for ICI discontinuation. However, the cessation criteria based on imaging were still not perfect. The combination of imaging and minimal residual disease (MRD) detection with ctDNA/cfDNA or AFP/DCP levels may provide better indicators and guidance for cessation of treatment, which indeed warrants further investigation.

Maintenance therapy approaches after a good response to initial treatment has attracted increasing interests in metastatic colorectal cancer (20,21). However, the maintenance therapy with TKIs after ICI discontinuation is still unclear for HCC. In addition to the synergistic effects of ICIs and TKIs, first-line TKIs (lenvatinib and sorafenib) alone can also bring survival benefits for patients with HCC. Herein, we revealed for the first time that patients who have received TKI maintenance therapy after ICI discontinuation had a more favorable PFS, but TKI maintenance therapy did not show a benefit in OS, which could be attributed to the small sample size. Consequently, while TKI maintenance therapy demonstrates some short-term advantages in disease control, these findings must be further validated in studies with larger samples and longer follow-up periods to assess its long-term effects on OS.

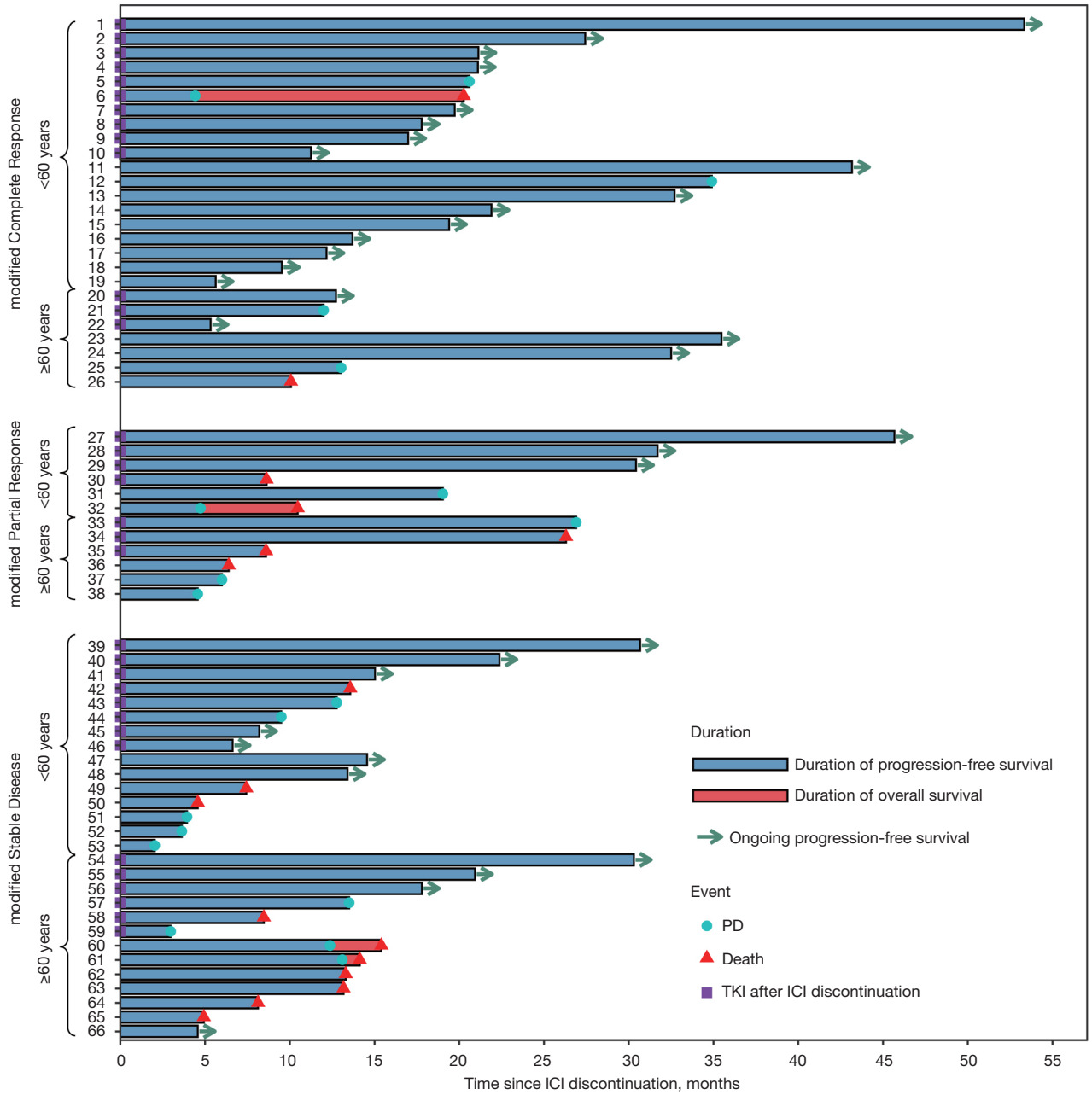

Figure 4 The swimmer plot of patients with ICI discontinuation. The patients were grouped with response per mRECIST, age and treatment after discontinuation. PD, progressive disease; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

Some studies and case reports indicate that the efficacy of immunotherapy may differ between elder and younger populations. However, in large-scale clinical trials of ICIs treating HCC, either completed or ongoing, age has not been verified as a potential factor affecting OS (22-24). The present study indicated that individuals (over the age of 60 years) treated with ICIs displayed a short OS, and a short OS_{Dis}. A possible explanation could be that elderly patients tend to suffer from underlying diseases like hypertension, diabetes, and cardiovascular disease, which may affect the treatment and prognosis of HCC. Additionally, age-related physiological changes could potentially influence the pharmacodynamics and pharmacokinetics of ICIs, leading to variations in treatment efficacy (25,26). However,

due to the small sample size in our study, the association between age and OS in patients treated with ICIs merits further investigations. Importantly, previous treatments might impact the residual liver function and thus the OS as well the efficacy and safety of subsequent systemic therapy. Patients with compromised baseline liver function tend to experience worse OS (27). However, in our study, there was no significant correlation between previous treatments and Child-Pugh score at baseline. Previous treatments and Child-Pugh score were also not associated with survival (*Table 2* and Table S7). One possible explanation could be that only 3 (4.55%) patients with Chil-Pugh B score were included in our study. The association between residual liver function and previous treatments as well as HCC treatment outcome indeed requires further investigation in larger prospective studies.

It is reported that the development of irAEs during ICI treatments is related to the effects of ICIs on $CD4^+$ CD25 Foxp3 regulatory T cells, which play a crucial role in controlling the immune response (28). In addition, the onset of irAEs was reported to be associated with superior outcomes in cancer patients treated with ICIs (7,25,26). However, in our study, improved survival was not observed in the patients who discontinued ICI treatment due to AEs.

This study has some limitations. Firstly, our study was limited by the relatively small sample size and the presence of significant heterogeneity among patients in terms of baseline characteristics and objective response. In addition, although other studies have reported that the efficacy and safety of ICI might be different according to the etiology of liver disease (29,30). We haven't detected a significant correlation between hepatitis B virus (HBV), hepatitis C virus (HCV) etiologies and survival, which was possibly due to that the patients in this study were mainly with HBV etiologies (87.88%), and the number of patients with HCV (4.55%) or non-viral etiologies was limited. Future multicenter studies with different etiologies are warranted. The efficacy of ICI rechallenge and the use of other medications after progression was not available. Further investigations of ICI rechallenge after ICI discontinuation in large cohorts are warranted. Ultimately, there was a lack of clinical use of the combination of atezolizumab and bevacizumab in China before 2021, primarily attribute to economic burden and health insurance coverage, therefore patients receiving the combination were not included in our analysis.

Conclusions

The present study represents the first report regarding the prospects and optimal timing for ICI discontinuation in HCC patients. The decision-making of ICI discontinuation could consider factors like patient age and response per mRECIST. Subsequent maintenance therapy with TKI after discontinuation might prevent progression.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-216/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-216/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the institutional review board of the Eastern Hepatobiliary Surgery Hospital (No. EHBHKY2023-K050-P002). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patients' informed consent was not required, as this is a retrospective study.

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