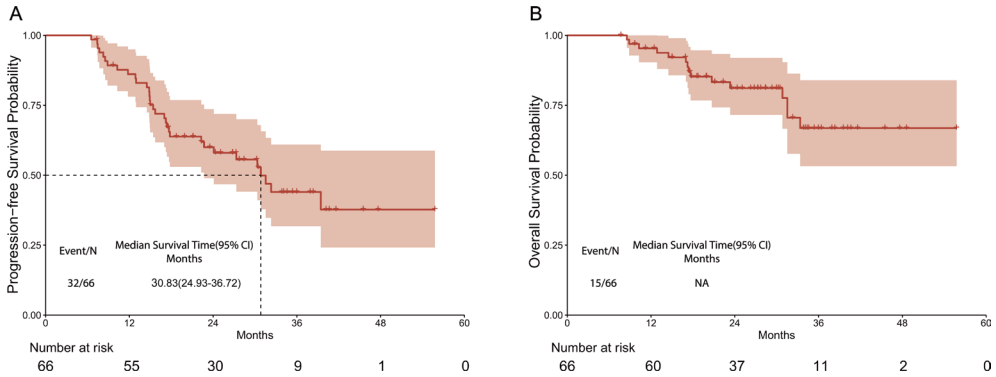

Figure S1 KM survival analysis for HCC patients after ICI discontinuation. (A) KM analysis of PFS in HCC patients with ICI discontinuation. The median PFS were 30.83 months (95% CI: 24.93–36.72). (B) KM analysis of OS in HCC patients with ICI discontinuation. The median OS were not reached. HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival.

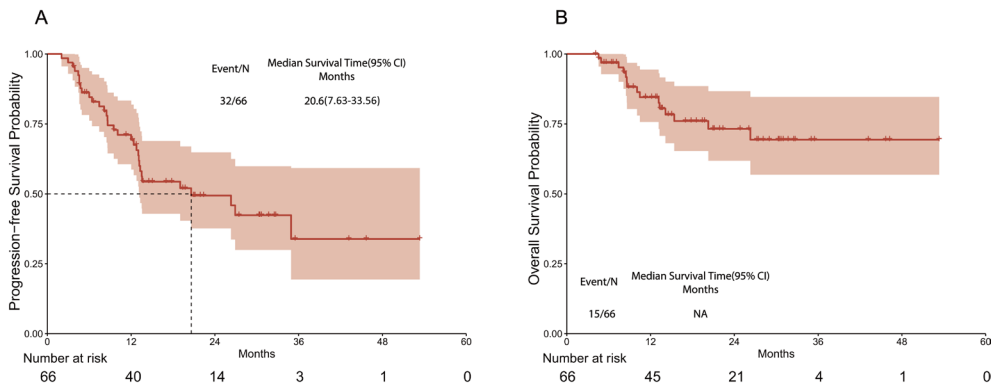

Figure S2 KM analysis of PFS_{Dis} (A) and OS_{Dis} (B) in HCC patients with ICI discontinuation, the median PFS_{Dis} was 20.6 months (95% CI: 7.63–33.56), and the median OS_{Dis} was not reached. KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor.

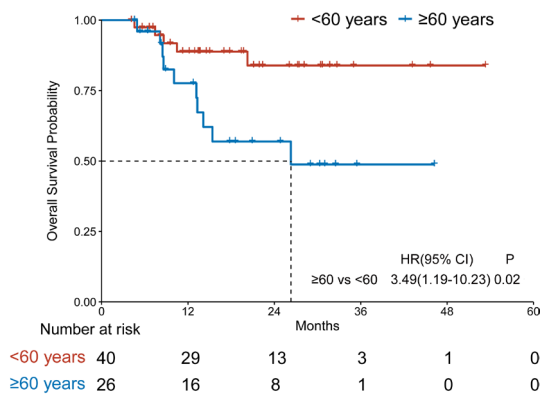

Figure S3 KM analysis of OS_{Dis} in HCC patients stratified by age. HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier; OS, overall survival; HCC, hepatocellular carcinoma.

https://dx.doi.org/10.21037/jgo-24-216

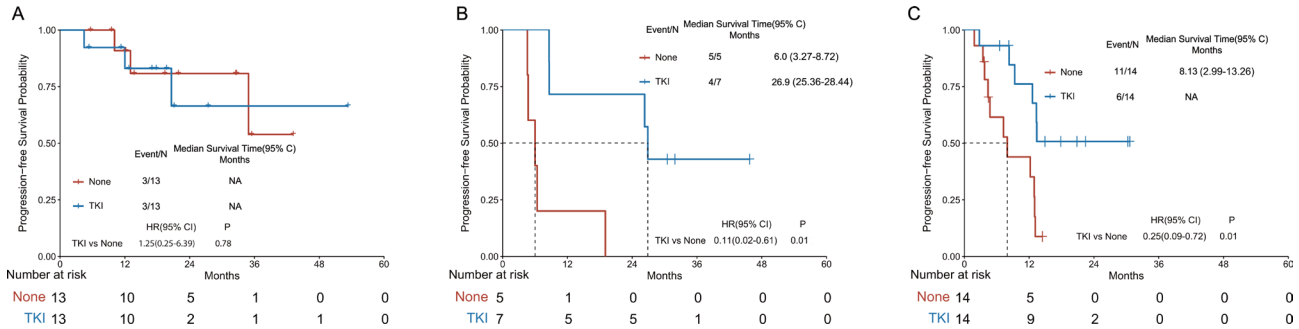

Figure S4 Subgroup analysis of PFS_{Dis} in patients with a response of mCR (A), mPR (B) or mSD (C), patients were stratified by maintenance therapy after discontinuation. mCR, complete response per mRECIST; mPR, partial response per mRECIST; mSD, stable disease per mRECIST.

Table S1 ICIs used in patients

Medication	n (%)
Nivolumab	9 (13.6)
Pembrolizumab	3 (4.5)
Toripalimab	41 (62.1)
Sintilimab	10 (15.1)
Tislelizumab	3 (4.5)

ICI, immune checkpoint inhibitor.

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Table S2 Univariable and multivariable Cox proportional hazards regression model of PFS since ICI start

Characteristic	Median survival time (months)	Univariate analysis		Multivariable Cox regression	
		HR (95% CI)	P	HR (95% CI)	P
Age, years					
≥60 *vs.* <60	22.3 *vs.* NR	2.37 (1.18–4.78)	0.01	NA	0.35
Gender					
Male *vs.* female	30.8 *vs.* NR	1.20 (0.36–3.94)	0.76		
ECOG PS					
1 *vs.* 0	NR *vs.* 30.8	0.95 (0.46–1.94)	0.88		
Child-Pugh score					
B *vs.* A	NR *vs.* 30.8	0.71 (0.10–5.24)	0.74		
HBV					
Yes *vs.* no	31.5 *vs.* 26.3	0.74 (0.29–1.93)	0.54		
HCV					
Yes *vs.* no	NR *vs.* 30.8	0.60 (0.08–4.41)	0.61		
MVI					
Yes *vs.* no	NR *vs.* 30.3	0.63 (0.27–1.45)	0.27		
Extrahepatic metastasis					
Yes *vs.* no	NR *vs.* 24.1	0.46 (0.20–1.08)	0.07		
BCLC					
B *vs.* A	17.8 *vs.* 30.3	1.43 (0.55–3.73)	0.46		
C *vs.* A	NR *vs.* 30.3	0.56 (0.21–1.48)	0.24		
AFP, μg/L					
≥400 *vs.* <400	NR *vs.* 30.3	0.56 (0.25–1.25)	0.15		
DCP, mAU/mL					
≥400 *vs.* <400	32.3 *vs.* 30.3	0.85 (0.41–1.74)	0.65		
First-line					
Yes *vs.* no	30.8 *vs.* 39.4	0.93 (0.43–2.01)	0.85		
Treatment-naïve					
Yes *vs.* no	31.5 *vs.* 30.3	0.70 (0.29–1.71)	0.43		
Combinational therapy of LRT and ICI					
Yes *vs.* no	27.3 *vs.* NR	2.00 (0.82–4.89)	0.12		
Combinational therapy of TKI and ICI					
Yes *vs.* no	31.5 *vs.* 17.2	0.60 (0.29–1.25)	0.17		
Duration of ICIs[#]	NA	0.93 (0.87–1.00)	0.07		
TRAE					
Yes *vs.* no	30.8 *vs.* 39.4	1.15 (0.56–2.35)	0.70		

Table S2 (*continued*)

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Table S2 (*continued*)

Characteristic	Median survival time (months)	Univariate analysis		Multivariable Cox regression	
		HR (95% CI)	P	HR (95% CI)	P
Previous surgery					
Yes *vs.* no	30.3 *vs.* 31.5	0.95 (0.47–1.91)	0.87		
Previous TACE					
Yes *vs.* no	30.3 *vs.* 31.5	1.32 (0.57–3.08)	0.52		
Previous PMCT					
Yes *vs.* no	17.4 *vs.* 31.5	1.04 (0.44–2.50)	0.92		
Previous radiotherapy					
Yes *vs.* no	15.7 *vs.* 31.5	1.40 (0.45–4.30)	0.56		
Previous TKI					
Yes *vs.* no	NR *vs.* 30.8	1.07 (0.48–2.39)	0.86		
Reason for ICI discontinuation					
CR *vs.* SD	NR *vs.* 24.1	NR	0.98		
PR *vs.* SD	39.4 *vs.* 24.1	0.43 (0.16–1.11)	0.08		
AE *vs.* SD	14.9 *vs.* 24.1	1.64 (0.72–3.77)	0.24		
Other *vs.* SD	27.3 *vs.* 24.1	1.56 (0.35–6.88)	0.55		
Response at ICI discontinuation					
CR *vs.* SD	NR *vs.* 22.3	NR	0.98	NA	0.18
PR *vs.* SD	39.4 *vs.* 22.3	0.34 (0.14–0.79)	0.01	NA	0.55
mResponse at ICI discontinuation*					
mCR *vs.* mSD	NR *vs.* 17.7	0.23 (0.09–0.57)	0.002	0.16 (0.06–0.42)	<0.001
mPR *vs.* mSD	29.1 *vs.* 17.7	0.75 (0.33–1.70)	0.48	0.79 (0.35–1.81)	0.59
Treatment after ICI discontinuation					
TKI *vs.* none	NR *vs.* 22.3	0.46 (0.23–0.95)	0.03	0.30 (0.14–0.64)	0.002

[#], duration of ICIs was defined as quantitative variable; *, mResponse, response per mRECIST. Age, Response at ICI discontinuation, mResponse at ICI discontinuation and Treatment after ICI discontinuation were included in the final multi-variable model for PFS. 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.

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Table S3 Univariable and multivariable Cox proportional hazards regression model of OS since ICI start

Characteristic	Median survival time (months)	Univariate analysis		Multivariable Cox regression	
		HR (95% CI)	P	HR (95% CI)	P
Age, years					
≥60 *vs.* <60	33.4 *vs.* NR	3.53 (1.20–10.35)	0.02	3.53 (1.20–10.34)	0.02
Gender					
Male *vs.* female	NR	0.71 (0.16–3.17)	0.65		
ECOG PS					
1 *vs.* 0	NR	1.11 (0.39–3.13)	0.84		
Child-Pugh score					
B *vs.* A	NR	1.65 (0.22–12.57)	0.62		
HBV					
Yes *vs.* no	NR *vs.* 33.4	0.38 (0.12–1.21)	0.10		
HCV					
Yes *vs.* no	NR	1.56 (0.20–11.88)	0.66		
MVI					
Yes *vs.* no	NR	1.67 (0.60–4.71)	0.32		
Extrahepatic metastasis					
Yes *vs.* No	NR	0.66 (0.21–2.08)	0.47		
BCLC					
B *vs.* A	NR	1.42 (0.28–7.35)	0.67		
C *vs.* A	NR	1.17 (0.25–5.50)	0.84		
AFP, μg/L					
≥400 *vs.* <400	NR	0.29 (0.07–1.29)	0.10		
DCP, mAU/mL					
≥400 *vs.* <400	NR	0.65 (0.22–1.92)	0.43		
First-line					
Yes *vs.* no	NR	1.17 (0.37–3.68)	0.78		
Treatment-naïve					
Yes *vs.* no	NR	1.18 (0.38–3.70)	0.77		
Combinational therapy of LRT and ICI					
Yes *vs.* no	NR	1.29 (0.41–4.11)	0.66		
Combinational therapy of TKI and ICI					
Yes *vs.* no	NR	0.52 (0.19–1.46)	0.21		
Duration of ICIs[#]	NA	1.00 (0.92–1.09)	0.85		
TRAE					
Yes *vs.* no	NR	1.04 (0.37–2.93)	0.94		

Table S3 (*continued*)

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Table S3 (*continued*)

Characteristic	Median survival time (months)	Univariate analysis		Multivariable Cox regression	
		HR (95% CI)	P	HR (95% CI)	P
Previous surgery					
Yes *vs.* no	NR	0.77 (0.28–2.11)	0.60		
Previous TACE					
Yes *vs.* no	33.4 *vs.* 31.5	1.25 (0.54–2.91)	0.60		
Previous PMCT					
Yes *vs.* no	30.0 *vs.* 34.4	1.18 (0.51–2.72)	0.69		
Previous radiotherapy					
Yes *vs.* no	20.7 *vs.* 33.4	1.41 (0.48–4.17)	0.53		
Previous TKI					
Yes *vs.* no	NR	0.97 (0.31–3.06)	0.96		
Reason for ICI discontinuation					
CR *vs.* SD	NR	NR	0.99		
PR *vs.* SD	NR	0.49 (0.13–1.83)	0.28		
AE *vs.* SD	NR	1.28 (0.39–4.27)	0.68		
Other *vs.* SD	NR	NR	0.99		
Response at ICI discontinuation					
CR *vs.* SD	NR	NR	0.99		
PR *vs.* SD	NR	0.36 (0.10–1.29)	0.11		
mResponse at ICI discontinuation*					
mCR *vs.* mSD	NR	0.15 (0.03–0.70)	0.01	NA	0.03
mPR *vs.* mSD	NR	0.62 (0.19–2.04)	0.43	NA	0.87
Treatment after ICI discontinuation					
TKI *vs.* none	NR	0.38 (0.13–1.13)	0.08		

[#], duration of ICIs was defined as quantitative variable; *, mResponse, response per mRECIST. Age, mResponse at ICI discontinuation were included in the final multi-variable model for OS. OS, overall 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.

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Table S4 Univariable and multivariable Cox proportional hazards regression model of OS after ICI discontinuation (OS_{Dis})

Characteristic	Median survival time (months)	Univariate analysis		Multivariate Cox regression	
		HR (95% CI)	P	HR (95% CI)	P
Age, years					
≥60 *vs.* <60	26.3 *vs.* NR	3.49 (1.19–10.23)	0.02	3.49 (1.19–10.22)	0.02
Gender					
Male *vs.* female	NR	0.55 (0.12–2.43)	0.42		
ECOG PS					
1 *vs.* 0	NR	0.97 (0.34–2.72)	0.94		
Child-Pugh score					
B *vs.* A	NR	2.27 (0.29–17.61)	0.43		
HBV					
Yes *vs.* no	NR *vs.* 15.4	0.38 (0.12–1.19)	0.09		
HCV					
Yes *vs.* no	NR	1.50 (0.20–11.42)	0.69		
MVI					
Yes *vs.* no	NR	1.76 (0.63–4.98)	0.28		
Extrahepatic metastasis					
Yes *vs.* no	NR	0.61 (0.20–1.93)	0.40		
BCLC					
B *vs.* A	NR	1.25 (0.24–6.48)	0.79		
C *vs.* A	NR	1.02 (0.22–4.83)	0.97		
AFP, μg/L					
≥400 *vs.* <400	NR	0.29 (0.07–1.31)	0.10		
DCP, mAU/mL					
≥400 *vs.* <400	NR	0.68 (0.23–1.98)	0.47		
First-line					
Yes *vs.* no	NR	1.17 (0.37–3.70)	0.78		
Treatment-naïve					
Yes *vs.* no	NR	1.18 (0.37–3.71)	0.78		
Combinational therapy of LRT and ICI					
Yes *vs.* no	NR	1.19 (0.38–3.76)	0.76		
Combinational therapy of TKI and ICI					
Yes *vs.* no	NR	0.54 (0.19–1.51)	0.23		
Duration of ICIs[#]	NA	1.06 (0.97–1.15)	0.19		
TRAE					
Yes *vs.* no	NR	1.22 (0.43–3.42)	0.71		

Table S4 (*conyinued*)

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Table S4 (*conyinued*)

Characteristic	Median survival time (months)	Univariate analysis		Multivariate Cox regression	
		HR (95% CI)	P	HR (95% CI)	P
Previous surgery					
Yes *vs.* no	NR	0.77 (0.28–2.14)	0.62		
Previous TACE					
Yes *vs.* no	27.2 *vs.* 26.1	1.06 (0.46–2.48)	0.89		
Previous PMCT					
Yes *vs.* no	15.4 *vs.* 27.2	1.08 (0.47–2.52)	0.85		
Previous radiotherapy					
Yes *vs.* no	13.2 *vs.* 27.2	1.63 (0.55–4.86)	0.38		
Previous TKI					
Yes *vs.* no	NR	0.96 (0.31–3.02)	0.94		
Reason for ICI discontinuation					
CR *vs.* SD	NR	NR	0.99		
PR *vs.* SD	NR	0.58 (0.15–2.17)	0.41		
AE *vs.* SD	NR	1.14 (0.34–3.80)	0.82		
Other *vs.* SD	NR	NR	0.99		
Response at ICI discontinuation					
CR *vs.* SD	NR	0.00 (0.00–NR)	0.99		
PR *vs.* SD	NR	0.45 (0.13–1.59)	0.21		
mResponse at ICI discontinuation*					
mCR *vs.* mSD	NR	0.16 (0.03–0.74)	0.01	NA	0.03
mPR *vs.* mSD	NR	0.76 (0.23–2.50)	0.64	NA	0.56
Treatment after ICI discontinuation					
TKI *vs.* none	NR	0.35 (0.12–1.04)	0.06		

[#], duration of ICIs was defined as quantitative variable; *, mResponse, response per mRECIST. Age, mResponse at ICI discontinuation were included in the final multi-variable model for OS_{Dis}. OS, overall 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.

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Table S5 TKIs used as maintenance therapy after ICI discontinuation

TKIs (n=34)	n (%)
Lenvatinib	26 (76.5)
Sorafenib	8 (23.5)

TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

Table S6 Treatment related adverse effects leading to ICI discontinuation in patients

TRAEs (n=13)	n (%)
Pneumonitis	1 (7.7)
Dermatitis	1 (7.7)
Hepatitis	5 (38.5)
Fever	1 (7.7)
Gastric hemorrhage	1 (7.7)
Rash	2 (15.4)
Gastritis	1 (7.7)
Thrombocytopenia	1 (7.7)

ICI, immune checkpoint inhibitor; TRAE, treatment-related adverse event.

Table S7 Association between liver function with previous treatments

Baseline characteristics of patients (n=66)	Child-Pugh score (n, %)		P value
	A	B	
Previous TACE (n=46)	45 (97.83)	1 (2.17)	0.44
Previous PMCT (n=20)	19 (95.0)	1 (5.0)	0.90
Previous radiotherapy (n=8)	7 (87.5)	1 (12.5)	0.24

TACE, transarterial chemoembolization; PMCT, percutaneous microwave coagulation therapy.

Table S8 Multicollinearity analysis of RECIST and mRECIST

Variable	Tolerance	Variance inflation factor (VIF)
RECIST	0.788	1.27
RECIST	0.591	1.693
mRECIST	0.514	1.947
mRECIST	0.635	1.575

Dependent variable: PFS_{Dis}, OS_{Dis}. PFS_{Dis}, progression-free survival at discontinuation; OS_{Dis}, overall survival at discontinuation.

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