Supplementary

Table S1 Previous therapies received in each group

Characteristics	HAIC (n=70)	Systemic ICI (n=46)	HAIC and ICI (n=14)	P value
Previous therapies received, n (%)				
Surgical resection	8 (24.24)	13 (39.39)	2 (33.33)	0.409
TACE	17 (51.52)	17 (51.52)	5 (83.33)	0.379
RFA/PEI	14 (42.42)	16 (48.48)	1 (16.67)	0.406
HAIC	0 (0.00)	9 (27.27)	0 (0.00)	0.002
TKI	22 (66.67)	26 (78.79)	5 (83.33)	0.556
Systemic chemotherapy	1 (3.03)	1 (3.03)	0 (0.00)	1.000
Immunotherapy	2 (6.06)	0 (0.00)	0 (0.00)	0.574
Radiotherapy	3 (9.09)	4 (12.12)	1 (16.67)	0.860
Clinical trial	0 (0.00)	0 (0.00)	1 (16.67)	0.083
Previous systemic therapies received, n (%)				0.071
Naïve	48 (68.6)	20 (43.5)	9 (64.3)	
1	21 (30.0)	24 (52.2)	5 (35.7)	
2	1 (1.4)	2 (4.3)	0	
Kind of previous systemic therapy, n (%)				0.872
Sorafenib	19 (27.1)	22 (47.8)	4 (28.6)	
Lenvatinib	2 (2.9)	2 (4.3)	1 (7.1)	
Sorafenib + regorafenib	0	1 (2.2)	0	
Sorafenib + lenvatinib	1 (1.4)	1 (2.2)	0	
Systemic chemotherapy	1 (1.4)	0	0	

HAIC, hepatic arterial infusion chemotherapy; ICI, immune checkpoint inhibitor; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; TKI, tyrosine kinase inhibitor.

https://dx.doi.org/10.21037/jgo-22-858

Table S2 Category and dosage of PD-1 inhibitors used in the ICI alone and HAIC combined with ICI groups

Category	ICI (n=46)	HAIC and ICI (n=14)	P value
Nivolumab, n (%)	25 (54.4)	5 (35.7)	0.360
Median ICIs cycle [range]	5 [1–35]	3 [1–28]	0.466
Median cumulative dose [range] (mg)	800 [140–5,250]	600 [100–5,600]	0.717
Pembrolizumab, n (%)	11 (23.9)	8 (57.1)	0.046
Median ICIs cycle [range]	6 [3–13]	4 [1–17]	0.135
Median cumulative dose [range] (mg)	700 [300–1,300]	400 [100–1,800]	0.237
Nivolumab plus ipilimumab, n (%)	4 (8.7)	0 (0.0)	0.564
Median ICIs cycle [range]	2 [2–4]	–	–
Median cumulative dose [range] (nivolumab/ipilimumab)	200/400 [200–400/400–800]	–	–
Atezolizumab plus bevacizumab, n (%)	5 (10.9)	1 (7.1)	1.000
Median ICIs cycle [range]	15 [2–17]	7 [7–7]	0.558
Median cumulative dose [range] (atezolizumab/bevacizumab) (mg)	12,000/4,800 [2,400–20,400/2,000–9,000]	8,400/3,176.5 [8,400–8,400, 3,176.5–3,176.5]	1.000
Spartalizumab, n (%)	1 (2.2)	0 (0.0)	1.000
Median ICIs cycle [range]	2 [2–2]	–	–
Median cumulative dose [range] (mg)	200 [200–200]	–	–

HAIC, hepatic arterial infusion chemotherapy; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein-1.

Table S3 Overall tumour response to immunotherapy and hepatic arterial infusion chemotherapy in HCC patients with MVI

Response	Overall RECIST, n (%)			Overall mRECIST, n (%)		
	HAIC (n=70)	Systemic ICI (n=46)	P value	HAIC (n=70)	Systemic ICI (n=46)	P value
ORR	16 (22.86)	12 (26.09)	0.860	17 (24.29)	13 (28.26)	0.794
DCR	29 (41.43)	18 (39.13)	0.958	29 (41.43)	18 (39.13)	0.958

DCR, disease control rate; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; MVI, macrovascular invasion; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; mRECIST, modified Response Evaluation Criteria in Solid Tumours.

Table S4 Vascular response to immunotherapy and hepatic arterial infusion chemotherapy in HCC patients with MVI

Variables	Vessel response, n (%)			PVTT response, n (%)			IVCTT response, n (%)		
	HAIC (n=70)	Systemic ICI (n=46)	P value	HAIC (n=60)	Systemic ICI (n=40)	P value	HAIC (n=16)	Systemic ICI (n=11)	P value
ORRT	27 (38.57)	21 (45.65)	0.572	24 (40.00)	20 (50.00)	0.435	7 (43.75)	7 (63.64)	0.533
DCRT	37 (52.86)	27 (58.70)	0.669	33 (55.00)	24 (60.00)	0.773	11 (68.75)	9 (81.82)	0.662

DCRT, disease control rate of tumour thrombi; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; IVCTT, inferior vena cava vein tumour thrombus; MVI, macrovascular invasion; ORRT, objective response rate of tumour thrombi; PVTT, portal vein tumor thrombus.

https://dx.doi.org/10.21037/jgo-22-858

Table S5 Cox regression for death

Variables	Crude HR (95% CI)	P value	Adjusted HR[†] (95% CI)	P value
Treatment				
HAIC	Ref.		Ref.	
Systemic ICI	1.10 (0.71–1.70)	0.678	0.83 (0.49–1.40)	0.481
HAIC and ICI	0.48 (0.22–1.06)	0.068	0.47 (0.21–1.04)	0.062
Overall response				
No	Ref.		Ref.	
Yes	0.11 (0.05–0.21)	<0.001	0.11 (0.05–0.22)	<0.001
Vascular response				
No	Ref.		Ref.	
Yes	0.22 (0.14–0.36)	<0.001	0.22 (0.14–0.36)	<0.001
Gender				
Female	Ref.		–	–
Male	0.95 (0.57–1.56)	0.833	–	–
Age (years)				
<55	Ref.		–	–
≥55	1.33 (0.80–2.23)	0.276	–	–
ECOG PS				
0	Ref		–	–
≥1	1.42 (0.92–2.17)	0.112	–	–
Alpha-fetoprotein (ng/mL)				
<400	Ref.		–	–
≥400	1.19 (0.80–1.78)	0.386	–	–
Etiology of chronic liver disease				
No	Ref.		–	–
Yes	0.83 (0.42–1.65)	0.595	–	–
CLIP				
0–1	Ref.		Ref.	
2–5	2.19 (1.10–4.37)	0.025	2.26 (1.10–4.65)	0.027
Child-Pugh stage				
A	Ref.		Ref.	
B	1.73 (1.09–2.76)	0.021	1.57 (0.96–2.56)	0.072
Distant metastases				
No	Ref.		–	–
Yes	1.24 (0.80–1.93)	0.337	–	–
Previous treatment TKI				
No	Ref.	–	–	–
Yes	1.26 (0.84–1.88)	0.260	–	–
Treatment combined with TKI				
No	Ref.		Ref.	
Yes	0.62 (0.40–0.95)	0.030	0.51 (0.31–0.86)	0.011

[†], variables with P<0.05 in the univariate analysis and variables of treatment modalities entered the multivariate analysis. Treatment modality, overall response, vascular response, CLIP score, Child-Pugh stage and treatment combined with TKI entered the multivariate analysis. CI, confidence interval; CLIP, Cancer of the Liver Italian Program Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor.

https://dx.doi.org/10.21037/jgo-22-858

Table S6 Cox regression for progression or death

Variables	Crude HR (95% CI)	P value	Adjusted HR[†] (95% CI)	P value
Treatment				
HAIC	Ref.		Ref.	
Systemic ICI	1.03 (0.69–1.55)	0.881	0.90 (0.59–1.38)	0.639
HAIC and ICI	0.48 (0.24–0.97)	0.040	0.46 (0.23–0.94)	0.032
Gender				
Female	Ref.		–	–
Male	0.82 (0.52–1.28)	0.380	–	–
Age (years)				
<55	Ref.		–	–
≥55	1.13 (0.69–1.84)	0.620	–	–
ECOG PS				
0	Ref.		–	–
≥1	1.30 (0.87–1.93)	0.202	–	–
Alpha-fetoprotein (ng/mL)				
<400	Ref.		–	–
≥400	1.14 (0.78–1.67)	0.493	–	–
Etiology of chronic liver disease				
No	Ref.		–	–
Yes	0.89 (0.46–1.70)	0.719	–	–
CLIP				
0–1	Ref.		–	–
2–5	1.66 (0.91–3.03)	0.099	–	–
Child-Pugh stage				
A	Ref.		Ref.	
B	1.77 (1.15–2.73)	0.009	1.81 (1.15–2.84)	0.010
Distant metastases				
No	Ref.		–	–
Yes	1.25 (0.83–1.89)	0.283	–	–
Previous treatment TKI				
No	Ref.		–	–
Yes	1.11 (0.76–1.63)	0.577	–	–
Treatment combined with TKI				
No	Ref.		–	–
Yes	0.74 (0.49–1.11)	0.143	–	–

[†], variables with P<0.05 in the univariate analysis and variables of treatment modalities entered the multivariate analysis. Treatment modality and Child-Pugh stage entered the multivariate analysis. CI, confidence interval; CLIP, Cancer of the Liver Italian Program Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor.

https://dx.doi.org/10.21037/jgo-22-858

Table S7 The levels of serum bilirubin before and after treatment

Time points	HAIC (n=70), mean ± SD	Systemic ICI (n=46), mean ± SD	HAIC and ICI (n=14), mean ± SD	P values[‡]
Before treatment, mg/dL	1.08±0.70	1.22±0.88	1.06±0.45	0.570
After treatment, mg/dL				
4 weeks	1.91±2.31	1.97±3.43	1.71±1.32	0.956
8 weeks	2.36±4.19	3.16±5.58	1.83±1.49	0.553
12 weeks	2.08±2.27	3.71±7.28	1.55±1.45	0.166
β-coefficient (P value)[†]	0.40 (0.001)*	0.94 (0.010)*	0.23 (0.120)	–

*, P<0.05; [†], regression coefficient indicating time trend by using generalized estimating equation model; [‡], comparison of serum bilirubin levels at each follow-up point between groups using one-way ANOVA. ANOVA, analysis of variance; HAIC, hepatic arterial infusion chemotherapy; ICI, immune checkpoint inhibitor; SD, standard deviation.

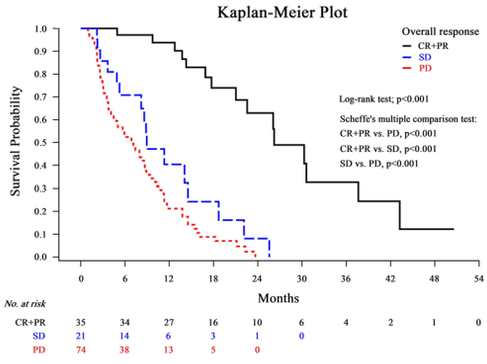

Figure S1 Kaplan-Meier curve for overall survival by overall RECIST. CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

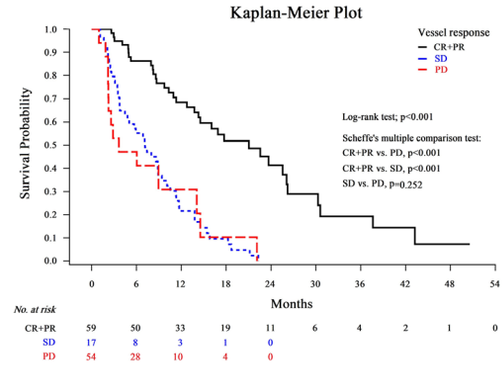

Figure S3 Kaplan-Meier curve for overall survival by vessel RECIST. CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

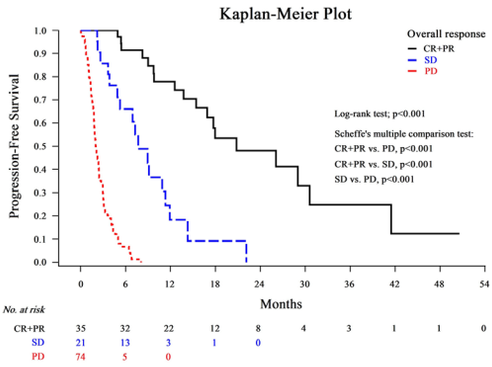

Figure S2 Kaplan-Meier curve for progression-free survival by overall RECIST. CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

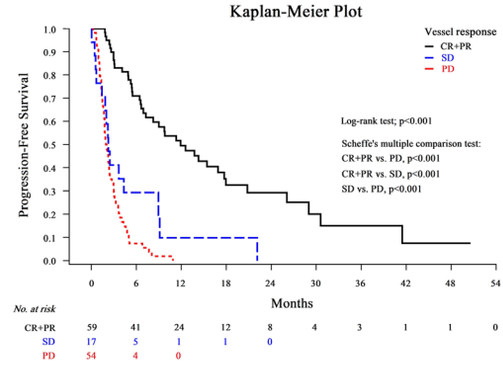

Figure S4 Kaplan-Meier curve for progression-free survival by vessel RECIST. CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

https://dx.doi.org/10.21037/jgo-22-858

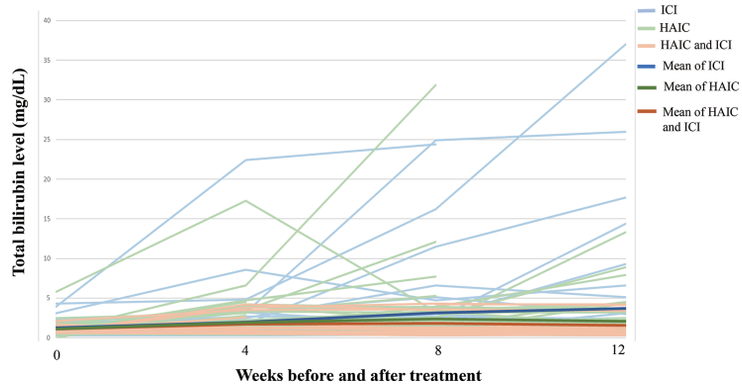

Figure S5 Dynamic changes in the levels of serum total bilirubin before and after treatment. HAIC, hepatic arterial infusion chemotherapy; ICI, immune checkpoint inhibitor.

https://dx.doi.org/10.21037/jgo-22-858