

Supplementary Table 1. Baseline characteristics of patients with advanced HCC in cohort 3 (patients with both MVI and EHM).

Demographics/characteristics	Unmatched			Matched		
	HAIC n = 48 (%)	Sorafenib n = 167 (%)	SMD	HAIC n = 44 (%)	Sorafenib n = 44 (%)	SMD
Age, mean	64.1	67.5	0.348	64.4	69.0	0.495
Gender, male	43 (89.6)	149 (89.2)	-0.012	39 (88.6)	37 (84.1)	-0.133
HCV positive	18 (37.5)	61 (36.5)	0.020	15 (34.1)	15 (34.1)	0.000
HBV positive	12 (25.0)	43 (25.7)	-0.017	12 (27.3)	13 (29.5)	-0.050
Alcohol abuse	7 (14.6)	20 (12.0)	0.077	7 (15.9)	4 (9.1)	0.207
Major MVI*	39 (81.3)	106 (63.5)	0.406	35 (79.5)	37 (84.1)	-0.118
Size of intrahepatic lesion, >50 mm*	20 (41.7)	65 (39.2)	0.051	18 (40.9)	13 (29.5)	0.240
Number of intrahepatic lesions, >3*	34 (70.8)	126 (75.4)	-0.104	32 (72.7)	34 (77.3)	-0.105
Number of metastatic sites >1*	6 (12.5)	47 (28.1)	0.354	5 (11.4)	6 (13.6)	0.050
Child–Pugh class A*	31 (66.0)	135 (81.3)	-0.068	31 (70.5)	32 (72.7)	0.093
AFP, >400 ng/mL	28 (58.3)	103 (61.7)	-0.396	28 (63.6)	26 (59.1)	0.495

Abbreviations: AFP, alfa-fetoprotein; EHM, extrahepatic metastasis; HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; SMD, standardized mean difference.

*Major MVI, size of intrahepatic lesion, number of intrahepatic lesions, number of metastatic sites, Child–Pugh class, and AFP were matched in cohort 3.

Supplementary Table 2. Baseline characteristics of patients with advanced HCC patients in cohort 4 (patients without MVI and with EHM).

Demographics/characteristics	Unmatched			Matched		
	HAIC n = 22 (%)	Sorafenib n = 424 (%)	SMD	HAIC n = 9 (%)	Sorafenib n = 19 (%)	SMD
Age, mean	68.1	69.7	0.174	70.2	68.4	-0.188
Gender, male	19 (86.4)	341 (80.4)	-0.160	7 (78.6)	17 (89.5)	0.320
HCV positive	9 (40.9)	192 (45.3)	-0.088	3 (32.1)	6 (31.6)	0.037
HBV positive	3 (13.6)	93 (21.9)	-0.218	1 (10.7)	8 (42.1)	-0.749
Alcohol abuse	3 (13.6)	39 (9.2)	0.140	2 (21.4)	5 (26.3)	-0.096
Size of intrahepatic lesion, >50 mm*	5 (22.7)	57 (14.1)	0.225	4 (42.9)	4 (21.1)	0.515
Number of intrahepatic lesions, >7*	15 (68.2)	143 (35.2)	0.699	5 (57.1)	11 (57.9)	-0.047
Number of metastatic sites, >1*	3 (13.6)	105 (24.8)	-0.285	2 (21.4)	4 (21.1)	0.028
Child–Pugh class A*	14 (66.7)	389 (92.8)	0.689	6 (64.3)	12 (63.2)	-0.074
AFP, >400 ng/mL*	14 (63.6)	272 (64.2)	0.011	6 (64.3)	11 (57.9)	-0.182

Abbreviations: AFP, alfa-fetoprotein; EHM, extrahepatic metastasis; HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; SMD, standardized mean difference.

*Size of intrahepatic lesion, number of intrahepatic lesions, number of metastatic sites, Child–Pugh class, and AFP were matched in cohort 4

Supplementary Table 3. Subgroup analyses of patients with advanced HCC according to MVI

Subgroup	HAIC (month, 95%CI)	Sorafenib (month, 95% CI)	HR (95%CI)	P-value (Log-rank)
Cohort 1 (matched)				
Minor MVI	15.4 (8.8–21.0)	10.0 (5.8–15.2)	0.669 (0.458–0.978)	0.036
Major MVI	9.6 (7.7–12.3)	8.4 (5.9–12.3)	0.831 (0.608–1.136)	0.244
VP≤2	14.1 (8.8–10.9)	9.5 (6.1–14.4)	0.710 (0.505–0.999)	0.048
VP≥3	9.3 (7.7–12.3)	8.2 (5.8–12.3)	0.792(0.562–1.116)	0.182
Cohort 3 (matched)				
Minor MVI	6.6 (1.5–9.3)	9.8 (2.2–22.1)	1.318 (0.461–3.759)	0.606
Major MVI	5.0 (4.2–14.4)	4.9 (3.5–5.6)	0.592 (0.349–1.005)	0.049
VP≤2	6.6 (4.2–7.7)	5.9 (3.4–14.9)	0.814 (0.391–1.693)	0.580
VP≥3	11.5 (3.5–15.3)	4.6 (3.4–5.6)	0.496 (0.265–0.927)	0.025

Abbreviations: CI, confidence interval; HR, hazard ratio; MVI, macrovascular invasion.

Supplementary Table 4. Multivariate survival analyses of HAIC in patients with advanced HCC

Covariate	All populations		
	HR	95%CI	P-value
Age (years)			
≤69.2	Reference		
>69.2	1.140	0.889–1.461	0.303
Sex			
Male	Reference		
Female	0.899	0.663–1.219	0.493
HCV			
Negative	Reference		
Positive	0.778	0.596–1.014	0.063
HBV			
Negative	Reference		
Positive	0.830	0.599–1.150	0.263
Alcohol abuse			
Negative	Reference		
Positive	0.874	0.624–1.224	0.434
Tumor status			
MVI (+), EHM (-)	Reference		
MVI (-), EHM (-)	0.946	0.673–1.330	0.750
MVI (+), EHM (+)	1.383	0.962–1.962	0.080
MVI (-), EHM (+)	1.640	0.985–2.732	0.057
Child–Pugh Class			
A	Reference		
B	1.654	1.285–2.130	<0.001
AFP (ng/mL)			
≤400	Reference		
>400	1.026	0.806–1.306	0.835
Number of previous TACEs			
0	Reference		
>1	0.957	0.742–1.235	0.736
Regimen			
5FU + CDDP	Reference		
5FU + IFN	0.839	0.612–1.152	0.278
CDDP	1.072	0.760–1.512	0.693
Other	0.661	0.160–2.729	0.567

Abbreviations: AFP, alfa-fetoprotein; CDDP, cisplatin; EHM, extrahepatic metastasis; 5FU, 5-fluorouracil; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IFN, interferon; MVI, macrovascular invasion; TACE, transarterial chemoembolization.

Supplementary Table 5. Multivariate survival analyses of HAIC in patients with advanced HCC

(subpopulation of patients with MVI and without EHM).

Covariate	Patients with MVI and without EHM		
	HR	95%CI	P-value
Age (years)			
≤68.0	Reference		
>68.0	1.065	0.777–1.460	0.694
Sex			
Male	Reference		
Female	0.932	0.640–1.357	0.713
HCV			
Negative	Reference		
Positive	0.725	0.517–1.017	0.063
HBV			
Negative	Reference		
Positive	0.742	0.497–1.106	0.143
Alcohol abuse			
Negative	Reference		
Positive	0.720	0.472–1.098	0.127
MVI			
Minor	Reference		
Major	1.310	0.952–1.801	0.097
Maximum size of intrahepatic lesion(mm)			
≤50	Reference		
>50	1.149	0.806–1.638	0.442
Number of intrahepatic lesions			
≤3	Reference		
>3	1.431	1.031–1.986	0.032
Child–Pugh Class			
A	Reference		
B	1.405	1.026–1.925	0.034
AFP (ng/mL)			
≤400	Reference		
>400	1.048	0.778–1.410	0.758
Number of previous TACEs			
0	Reference		
>1	0.964	0.700–1.328	0.823
Regimen			
5FU + CDDP	Reference		
5FU + IFN	0.819	0.553–1.214	0.320
CDDP	1.102	0.691–1.758	0.683
Other	0.922	0.207–4.112	0.915

Abbreviations: AFP, alfa-fetoprotein; CDDP, cisplatin; EHM, extrahepatic metastasis; 5FU, 5-fluorouracil; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IFN, interferon; MVI, macrovascular invasion; TACE, transarterial chemoembolization.

Supplementary Table 6. Post treatments of patients with advanced HCC in cohort 1 (patients with MVI and without EHM).

Post treatment	Unmatched		Matched	
	HAIC n = 270 (%)	Sorafenib n = 263 (%)	HAIC n = 170 (%)	Sorafenib n = 170 (%)
Sorafenib	54 (20.4)	–	40 (23.5)	–
HAIC	–	59 (24.1%)	–	38 (24.2)
TACE	46 (17.4)	31 (12.7)	34 (20.0)	21 (13.5)
Radiation	27 (10.2)	12 (5.0)	18 (10.6)	10 (6.5)
Other systemic therapies (including clinical trials)	28 (10.6)	27 (11.1)	23 (13.5)	21 (13.6)

Abbreviations: HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization.

Supplementary Table 7. Post treatments of advanced HCC patients with cohort 2 (patients without both MVI and EHM).

Post treatment	Unmatched		Matched	
	HAIC n = 89 (%)	Sorafenib n = 492 (%)	HAIC n = 76 (%)	Sorafenib n = 76 (%)
Sorafenib	16 (18.6)	–	15 (19.7)	–
HAIC	–	102 (21.7)	–	13 (18.3)
TACE	14 (16.3)	136 (28.9)	11 (14.5)	24 (33.3)
Radiation	6 (7.0)	18 (3.9)	6 (7.9)	4 (5.7)
Other systemic therapies (including clinical trials)	11 (12.8)	83 (17.7)	10 (13.2)	13 (18.3)

Abbreviations: HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization.

Supplementary Table 8. Post treatments of advanced HCC patients with cohort 3 (patients without both MVI and EHM).

Post treatment	Unmatched		Matched	
	HAIC n = 89 (%)	Sorafenib n = 492 (%)	HAIC n = 76 (%)	Sorafenib n = 76 (%)
Sorafenib	16 (18.6)	–	15 (19.7)	–
HAIC	–	102 (21.7)	–	13 (18.3)
TACE	14 (16.3)	136 (28.9)	11 (14.5)	24 (33.3)
Radiation	6 (7.0)	18 (3.9)	6 (7.9)	4 (5.7)
Other systemic therapies (including clinical trials)	11 (12.8)	83 (17.7)	10 (13.2)	13 (18.3)

Abbreviations: HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization.

Supplementary Table 9. Post treatments of advanced HCC patients with cohort 4 (patients without MVI and with EHM).

Post treatment	Unmatched		Matched	
	HAIC n = 22 (%)	Sorafenib n = 424 (%)	HAIC n = 19 (%)	Sorafenib n = 19 (%)
Sorafenib	6 (27.3)	–	5 (26.3)	–
HAIC	–	40 (10.0)	–	7 (36.8)
TACE	2 (9.1)	57 (14.1)	1 (5.3)	0 (0.0)
Radiation	3 (13.6)	58 (14.5)	2 (10.5)	0 (0.0)
Other systemic therapies (including clinical trials)	2 (9.1)	96 (23.6)	2 (10.5)	4 (21.1)

Abbreviations: HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization.