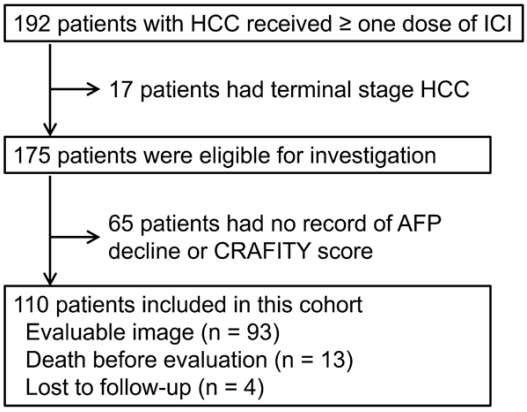


Supplementary Figure 1. Flowchart of patient recruitment. AFP, α-fetoprotein; CRAFITY, C-reactive protein and α-fetoprotein in immunotherapy; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor.

Supplementary Table 1. Patient demographics, baseline characteristics, and therapeutic response

Character	Eligible for investigation (n = 175)	Enrolled (n = 110)	Excluded (n = 65)	*P* value
Age (years)	64.9 (55.9-72.0)	64.5 (54.6-72.4)	65.3 (58.4-70.5)	.461
Sex (male), *n* (%)	148 (84.6)	94 (85.5)	54 (83.1)	.675
Body mass index (kg/m^2)	23.67 (21.38-26.35)	23.43 (20.96-26.72)	24.05 (22.18-26.16)	.387
NLR	5.02 (2.96-7.91)	5.34 (3.01-8.28)	4.43 (2.78-6.41)	.126
Platelet count (× 10^9/L)	159 (104-239)	174 (109-251)	137 (88-207)	.014
AST (U/L)	50 (32-89)	48 (32-92)	52 (32-82)	.912
ALT (U/L)	37 (25-60)	35 (23-57)	39 (27-66)	.211
Total bilirubin (mg/dL)	0.93 (0.69-1.40)	0.97 (0.66-1.60)	0.92 (0.70-1.35)	.627
Albumin (g/dL)	3.6 (3.3-4.0)	3.6 (3.3-4.0)	3.7 (3.3-4.1)	.467
INR	1.07 (1.01-1.17)	1.06 (1.01-1.17)	1.08 (1.02-1.16)	.507
Etiology				
Alcohol	45 (25.7)	35 (31.8)	10 (15.4)	.017
HBV	95 (54.3)	62 (56.4)	33 (50.8)	.474
HCV	47 (26.9)	27 (24.5)	20 (30.8)	.371
Diabetes mellitus	58 (33.1)	29 (26.4)	29 (44.6)	.013
Liver cirrhosis	134 (76.6)	84 (76.4)	50 (76.9)	.933
Child-Pugh score	6 (5-7)	6 (5-7)	6 (5-7)	.945
Child-Pugh class A	113 (64.6)	72 (66.1)	41 (64.1)	
Child-Pugh class B	60 (34.3)	37 (33.9)	23 (35.9)	
ALBI grade				.680
1	52 (30.2)	33 (30.6)	19 (29.7)	
2	105 (61.0)	67 (62.0)	38 (59.4)	
3	15 (8.7)	8 (7.4)	7 (10.9)	
AFP (ng/mL)	114.53 (8.84-3220.50)	126.48 (12.25-5056.0)	103.61 (6.39-1548.92)	.197
BCLC stage				.766
A	11 (6.3)	6 (5.5)	5 (7.7)	
B	25 (14.3)	16 (14.5)	9 (13.8)	
C	139 (79.4)	88 (80.0)	51 (78.5)	
Max. tumor size (cm)	4.7 (2.5-8.9)	4.7 (2.7-9.7)	4.4 (1.8-7.7)	.097
Total tumor volume (cm^3)	703.9 (124.3-4042.1)	740.4 (143.1-5339.6)	680.2 (48.0-2755.5)	.102
MVI[a]	89 (50.9)	65 (59.1)	24 (36.9)	.005
VP3	30 (17.1)	24 (21.8)	6 (9.2)	
VP4	50 (28.6)	34 (30.9)	16 (24.6)	
Hepatic vein	9 (5.1)	7 (6.4)	2 (3.1)	
EHM[a]	102 (58.3)	61 (55.5)	41 (63.1)	.324

Prior therapy				
Sorafenib	102 (58.3)	63 (57.3)	39 (60.0)	
Lenvatinib	28 (16.0)	19 (17.3)	9 (13.8)	
Surgery	37 (21.1)	21 (19.1)	16 (24.6)	
PEI/RFA	12 (6.9)/38 (21.7)	7 (6.4)/20 (18.2)	5 (7.7)/18 (27.7)	
TACE[b]/TARE	109 (62.3)/3 (1.7)	66 (60.0)/3 (2.7)	43 (66.2)/0 (0)	
Radiotherapy	3 (1.7)	3 (2.7)	0 (0)	
ICI duration (months)	3.27 (1.70-8.40)	2.85 (1.67-6.63)	4.20 (1.90-11.87)	.118
Nivolumab[c]	157 (89.7)	100 (90.9)	57 (87.7)	
Nivolumab + ipilimumab[c]	5 (2.9)	3 (2.7)	2 (3.1)	
Pembrolizumab[c]	19 (10.9)	12 (10.9)	7 (10.8)	
Reduction > 25%	92 (52.6)	59 (53.6)	33 (50.8)	
As 1st/2nd/3rd/4th-line systemic therapy	55 (31.4)/88 (50.3)/ 24 (13.7)/8 (4.6)	35 (31.8)/53 (48.2)/ 16 (14.5)/6 (5.5)	20 (30.8)/35 (53.8)/ 8 (12.3)/2 (3.1)	
Concurrent therapy	135 (77.1)	87 (79.1)	48 (73.8)	.426
Sorafenib[d]	62 (35.4)	43 (39.1)	19 (29.2)	
Lenvatinib[d]	52 (29.7)	32 (29.1)	20 (30.8)	
Regorafenib[d]	27 (15.4)	17 (15.5)	10 (15.4)	
RFA	3 (1.7)	3 (2.7)	0 (0)	
TACE	26 (14.9)	14 (12.7)	12 (18.5)	
Liver radiotherapy	35 (20.0)	20 (18.2)	15 (23.1)	
Therapeutic response				
Best Response				
Complete response	14 (8.0)	7 (6.4)	7 (10.8)	
Partial response	29 (16.6)	17 (15.5)	12 (18.5)	
Stable disease	46 (26.3)	27 (24.5)	19 (29.2)	
Progressive disease	86 (49.1)	59 (53.6)	27 (41.5)	
Not evaluable				
Death before evaluation	23 (13.1)	13 (11.8)	10 (15.4)	
Lost to follow-up[e]	5 (2.9)	4 (3.6)	1 (1.5)	
Objective response	43 (24.6)	24 (21.8)	19 (29.2)	.272
Disease control	89 (50.9)	51 (46.4)	38 (58.5)	.123
Progression-free survival (months)*	3.63 (2.27-5.00)	2.87 (2.16-3.58)	5.87 (2.47-9.26)	.127
Overall survival (months)*	14.53 (9.68-19.38)	8.20 (4.23-12.17)	23.23 (16.00-30.47)	.010

Data presented as median (first quartile-third quartile). *Data presented as median (95% confidence interval). AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; EHM, extrahepatic metastasis; HBV, hepatitis B virus; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor; MVI, macrovascular invasion; NLR, neutrophil-lymphocyte ratio; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor; PEI, percutaneous ethanol injection; INR, international normalized ratio; RFA, radiofrequency ablation. [a]Fifty-two patients with HCC had both macrovascular invasion and extrahepatic metastasis. [b]The median number of TACE sessions was 3 (2-5). [c]Seven patients received sequential ICI therapy because of progressive disease: nivolumab→atezolizumab plus bevacizumab (1), nivolumab→pembrolizumab→atezolizumab plus bevacizumab (n = 1), nivolumab→pembrolizumab→nivolumab (2), nivolumab→atezolizumab plus bevacizumab→nivolumab plus ipilimumab (1), nivolumab→atezolizumab plus bevacizumab→pembrolizumab (1), and nivolumab plus ipilimumab→nivolumab plus sorafenib (1). [d]Twenty-eight patients received sequential TKI therapy because of progressive disease: sorafenib→regorafenib (13), sorafenib→lenvatinib (4), sorafenib→regorafenib→lenvatinib (2), lenvatinib→sorafenib (2), lenvatinib→regorafenib (1), sorafenib→ramucizumab (1), and lenvatinib→cabozantinib (5). [e]Five patients were lost to follow-up because of immune-related adverse events.

Supplementary Table 2. TRAEs in 110 patients with hepatocellular carcinoma

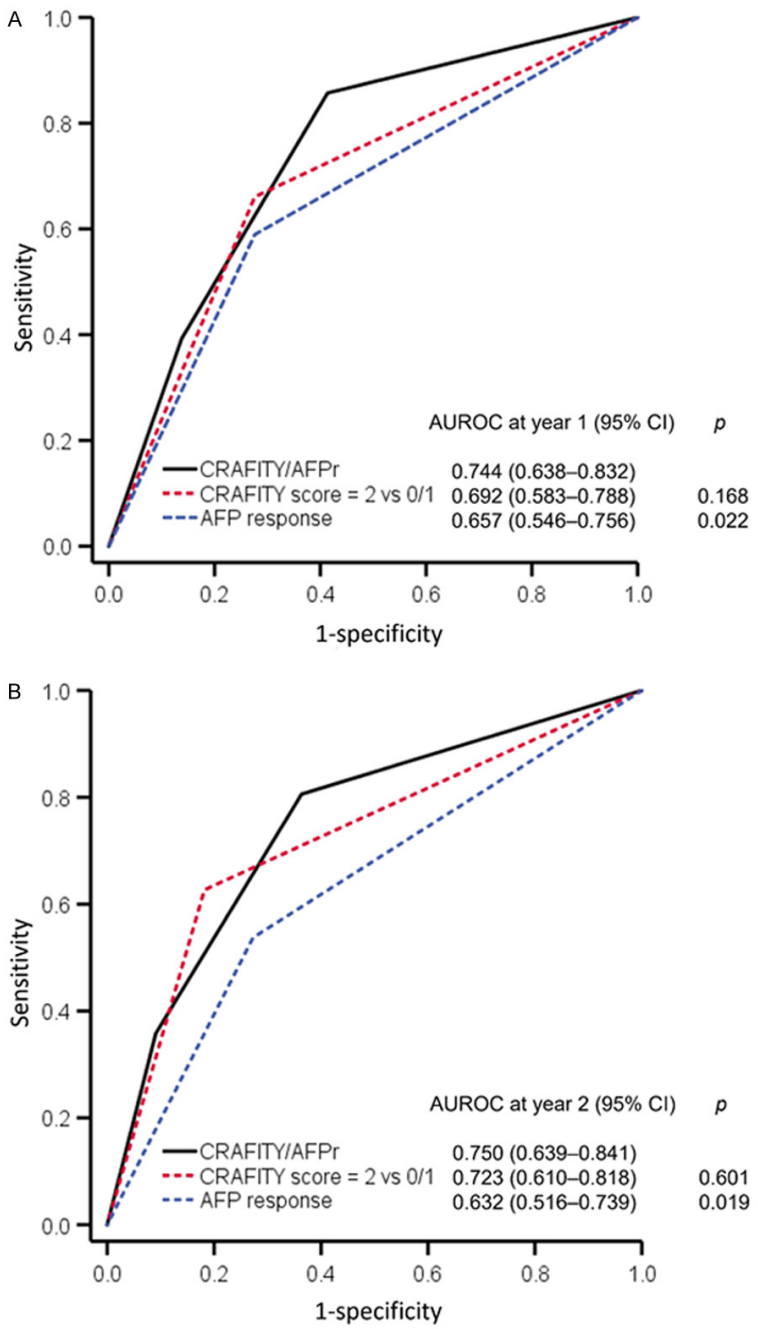
Type of TRAE (n = 74)	TRAE, n (%)	
	Any grade	Grade ≥ 3
Hepatitis*	25 (22.7)	12 (10.9)
Fatigue	16 (14.5)	3 (2.7)
Dermatitis	15 (13.6)	5 (4.5)
Hand foot syndrome	15 (13.6)	3 (2.7)
Colitis	10 (9.1)	2 (1.8)
Fever	8 (7.3)	1 (0.9)
Pneumonitis*	5 (4.5)	4 (3.6)
Proteinuria	2 (1.8)	0 (0)
Gastric necrosis	1 (0.9)	1 (1.1)
Thyroid disorder	1 (0.9)	0 (0)
Edema	1 (0.9)	0 (0)

*Among seven patients who died from TRAEs, five and two died from severe hepatitis and pneumonitis, respectively. TRAEs, treatment-related adverse events.

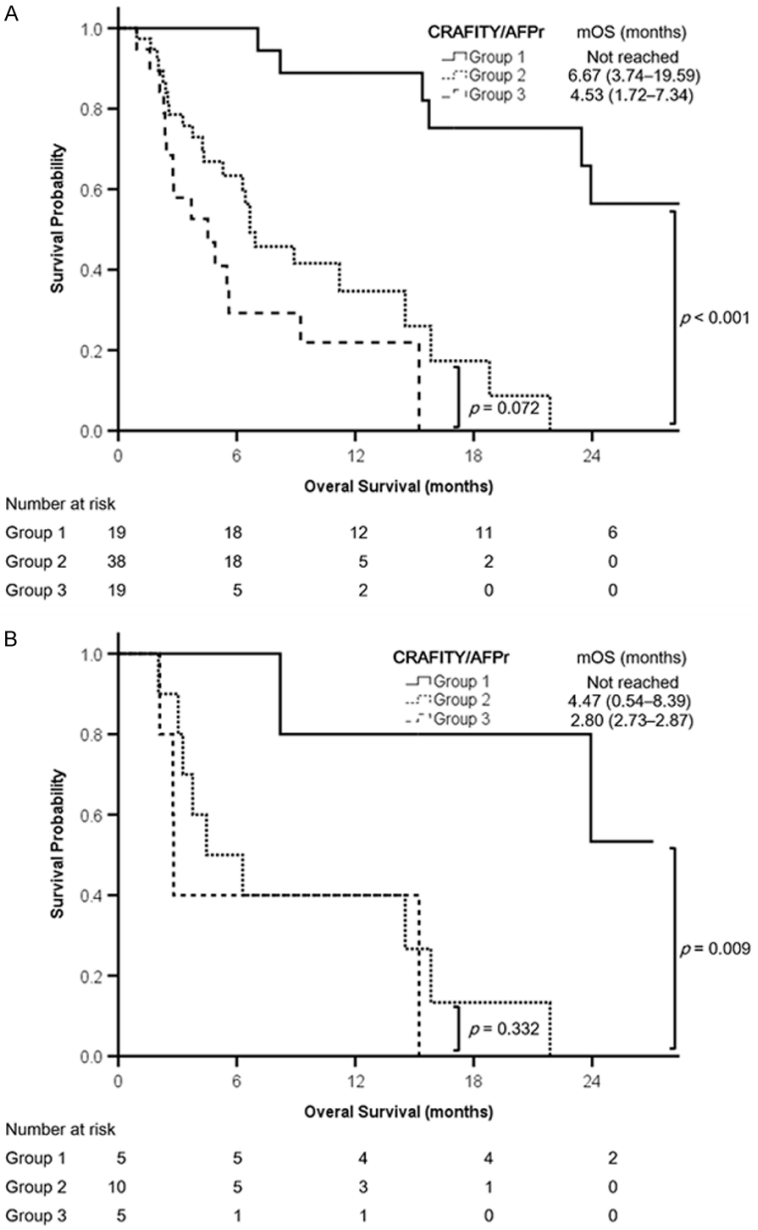
Supplementary Table 3. Factors associated with disease control in 93 patients with HCC who underwent radiological imaging

Character		Univariate analysis		Multivariable analysis 1		Multivariable analysis 2	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (year)		1.027 (0.993-1.062)	.128				
Sex	M vs F	2.045 (0.663-6.309)	.213				
Alcohol	Yes vs no	0.914 (0.382-2.188)	.840				
HBV	Yes vs no	0.896 (0.391-2.053)	.796				
HCV	Yes vs no	1.387 (0.531-3.623)	.504				
DM	Yes vs no	1.211 (0.473-3.098)	.690				
Grade 1-2 TRAEs	Yes vs no	1.828 (0.797-4.196)	.155				
Grade ≥ 3 TRAEs	Yes vs no	0.880 (0.332-2.332)	.797				
TTV (cm^3)	> 1000 vs ≤ 1000	0.792 (0.344-1.823)	.583				
MVI	Yes vs no	0.269 (0.111-0.651)	.004	0.363 (0.127-1.035)	.058		
EHM	Yes vs no	0.547 (0.238-1.255)	.155				
AST (U/L)	> 40 vs ≤ 40	0.863 (0.367-2.030)	.736				
ALT (U/L)	> 40 vs ≤ 40	0.594 (0.259-1.361)	.218				
NLR	> 3.0 vs ≤ 3.0	0.258 (0.092-0.724)	.010				
Child-Pugh class	B vs A	0.827 (0.329-2.078)	.686				
ALBI grade	2/3 vs 1	0.695 (0.282-1.712)	.429				
AFP decline > 15%	Yes vs no	7.680 (3.027-19.487)	< .001	7.177 (2.504-20.573)	< .001	Not assessed	
CRAFITY score	2 vs 0/1	0.636 (0.279-1.449)	.282			Not assessed	
Combined CRAFITY score and AFP response[a]	Group 1	Referent		Not assessed		Referent	
	Group 2	0.433 (0.145-1.292)	.134	Not assessed		0.568 (0.173-1.872)	.353
	Group 3	0.083 (0.022-0.320)	< .001	Not assessed		0.136 (0.032-0.576)	.007
Combination therapy[b]	Yes vs no	1.765 (0.560-5.564)	.332				

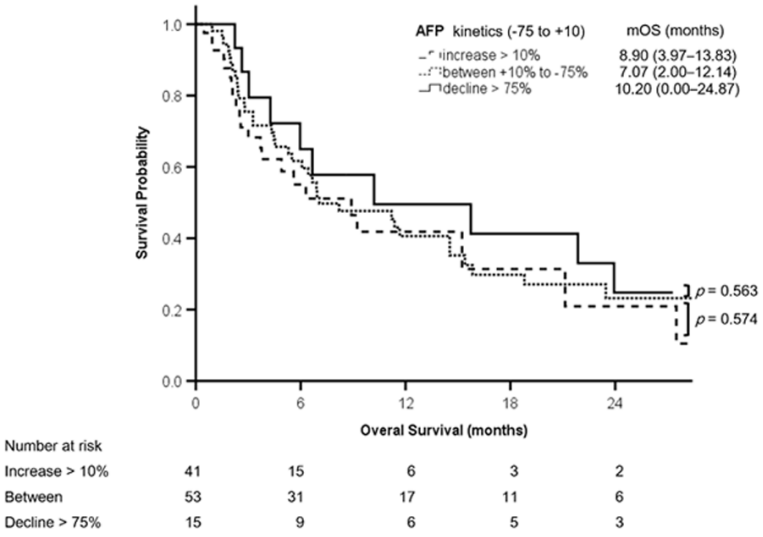
[a]Group 1: patients with a CRAFITY score of 0 or 1 and AFP response; Group 3: patients with a CRAFITY score of 2 and no AFP response; Group 2: patients who did not belong to Group 1 or 3. [b]Combination therapy includes tyrosine kinase inhibitors, radiofrequency ablation, transarterial chemoembolization, and stereotactic body radiotherapy for hepatocellular carcinoma. AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; EHM, extrahepatic metastasis; HBV, hepatitis B virus; HCV, hepatitis C virus; TRAEs, treatment-related adverse events; M vs F, male versus female; MVI, macroscopic vascular invasion; NLR, neutrophil-to-lymphocyte ratio; TTV, total tumor volume.



Supplementary Figure 2. Time-dependent AUROCs for the predictive performance of combined CRAFITY score and AFP response, CRAFITY score, or AFP response alone for OS. A. AUROCs at year 1. B. AUROCs at year 2. AFP, α-fetoprotein; AUROC, area under the receiver operating characteristic curve; CRAFITY, C-reactive protein and α-fetoprotein in immunotherapy; CRAFITY/AFPr, combined CRAFITY score and AFP response; OS, overall survival. The *P* values relate to the other two parameters compared with CRAFITY response using the DeLong test.



Supplementary Figure 3. Kaplan-Meier analyses of overall survival in different groups of patients according to the combination of CRAFITY score and AFP response (CRAFITY/AFPr). A. A subgroup of patients receiving combined immune checkpoint inhibitor (ICI) and tyrosine kinase inhibitor therapy (n = 76). B. A subgroup of patients receiving combined ICI and liver radiotherapy (n = 20). Survival is presented as median (95% confidence interval). AFP, α-fetoprotein; CRAFITY, C-reactive protein and α-fetoprotein in immunotherapy; mOS, median overall survival.



Supplementary Figure 4. Kaplan-Meier analysis of overall survival among groups stratified by Zhu's proposed AFP response [24]. AFP, α-fetoprotein; mOS, median overall survival.