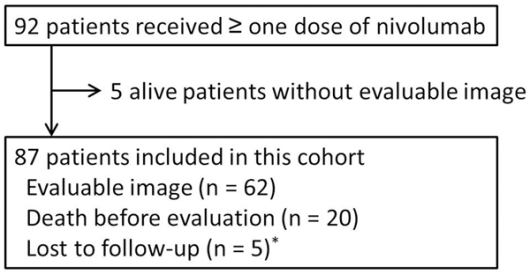


Supplementary Figure 1. Flow chart of patients enrolled in this study. * Five patients were lost to follow-up for more than 3 months.

Supplementary Table 1. Demographics of patients with evaluable radiological imaging data or death before evaluation

Character (N = 82)	Evaluable imaging (N = 62)	Death before evaluation (N = 20)	*P* value
Age (years)	62.1 (54.8-67.6)	66.8 (58.9-69.9)	.214
Sex, M/F (% male)	56 (90.3)	19 (95.0)	.518
Body mass index (kg/m^2)	24.80 (21.89-27.05)	20.83 (19.72-22.85)	<.001
NLR	4.76 (2.98-8.34)	9.96 (5.68-15.40)	.002
Platelet count (10^9/L)	141 (91-198)	175 (150-265)	.039
AST (U/L)	60 (41-100)	147 (96-274)	<.001
ALT (U/L)	50 (28-62)	61 (33-129)	.042
Total bilirubin (mg/dL)	1.1 (0.7-1.7)	1.9 (1.2-12.2)	.003
Albumin (g/dL)	3.7 (3.2-4.0)	3.0 (2.5-3.5)	.002
INR	1.09 (1.04-1.20)	1.24 (1.14-1.58)	<.001
Etiology			
Alcohol	16 (25.8)	7 (35.0)	.429
HBV	40 (64.5)	8 (40.0)	.054
HCV	14 (22.6)	6 (30.0)	.504
Diabetes mellitus	18 (29.0)	6 (30.0)	.934
Liver cirrhosis	45 (72.6)	17 (85.0)	.264
Child-Pugh score	6 (5-7)	8 (6-11)	<.001
Class A	37 (59.7)	5 (25.0)	
Class B	20 (32.3)	9 (45.0)	
Class C	3 (4.8)	6 (30.0)	
ALBI grade 1/2/3	15 (25.4)/37 (62.7)/7 (11.9)	3 (15.0)/9 (45.0)/8 (40.0)	.023
AFP (ng/mL)	337.6 (11.8-6963.0)	1651.9 (41.8-36835.5)	.261
AFP ≥400 ng/mL	28 (45.2)	10 (50.0)	.474
BCLC stage			<.001
A	6 (9.7)	0 (0)	
B	8 (12.9)	0 (0)	
C	45 (72.6)	13 (65.0)	
D	3 (4.8)	7 (35.0)	
CLIP score	2 (1-4)	4 (3-5)	<.001
Max. tumor size (cm)	4.6 (2.7-7.8)	7.3 (5.1-10.3)	.017
Tumor number			.141
1	16 (25.8)	2 (10.0)	
2	6 (9.7)	2 (10.0)	
3	7 (11.3)	2 (10.0)	
≥4	33 (53.2)	14 (70.0)	

Total tumor volume (cm^3)	667.2 (185.8-2675.2)	2794.8 (703.6-5886.8)	.011
MVI	34 (54.8)	15 (75.0)	.112
VP3	12 (19.4)	5 (25.0)	
VP4	20 (32.3)	10 (50.0)	
Hepatic vein	2 (3.2)	0 (0)	
EHM	34 (54.8)	16 (80.0)	.046
Prior therapy			.011
Sorafenib	33 (53.2)	6 (30.0)	
Lenvatinib	7 (11.3)	0 (0)	
Surgery	14 (22.6)	2 (10.0)	
TACE/TARE	41 (66.1)/2 (3.2)	5 (25.0)/0 (0)	
RFA	13 (21.0)	0 (0)	
PEI	4 (6.5)	0 (0)	
RT	41 (66.1)	7 (35.0)	
Nivolumab dose	6 (5-10)	2 (1-3)	<.001
Treatment duration	3.62 (2.39-6.03)	0.70 (0.30-1.03)	<.001
Concurrent therapy	46 (74.2)	7 (35.0)	.002
Sorafenib	20 (32.3)*	3 (15.0)	
Regorafenib	4 (6.5)*	3 (15.0)	
Lenvatinib	15 (24.2)*	1 (5.0)	
Chemotherapy	7 (11.3)	0 (0)	
Radiotherapy	11 (17.7)	1 (5.0)	
TACE	11 (17.7)	0 (0)	
irAEs	9 (14.5)	2 (10.0)	.609
Progression-free survival (months)	4.43 (2.33-8.70)	1.13 (0.43-1.93)	<.001
Overall survival (months)	8.70 (4.53-20.60)	1.27 (0.47-1.93)	<.001

Data are presented as the median (first quartile-third quartile). AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; EHM, extrahepatic metastasis; F, female; CLIP, Cancer of the Liver Italian Program; HBV, hepatitis B virus; HCV, hepatitis C virus; irAEs, immune-related adverse events; IQR, interquartile range; M, male; MVI, macrovascular invasion; RT, radiotherapy; 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. *Seven patients received sequential TKI therapy: sorafenib→regorafenib (3), sorafenib→lenvatinib (3), and sorafenib→lenvatinib→regorafenib (1).

Supplementary Table 2. IrAEs in 87 patients with hepatocellular carcinoma

Type of irAE (N = 40)	irAE, N (%)	
	Any grade	Grade ≥3
Hepatitis	14 (16.1)	5 (5.7)
Fatigue	12 (13.8)	2 (2.3)
Dermatitis	11 (12.6)	3 (3.4)
Colitis	9 (10.3)	1 (1.1)
Hand foot syndrome	4 (4.6)	0 (0)
Fever	4 (4.6)	0 (0)
Pneumonitis	2 (2.3)	2 (2.3)
Gastric necrosis	1 (1.1)	1 (1.1)
Myalgia	1 (1.1)	0 (0)
Dizziness	1 (1.1)	0 (0)

irAE, immune-related adverse event.

Supplementary Table 3. List of patients with ≥ grade 3 irAEs

Age (years)	Sex	Nivolumab		Time of irAE (after nivolumab initiation, months)	Type of irAE	Best response	Final status[a]	COD
		Total dose	Average dosage (mg/kg)					
67.6	M	1	2.80	0.40	Gastric necrosis	DBE	E	Infection
65.4	M	6	2.96	4.17	Hepatitis	PR	S	
56.6	M	6	3.11	3.27	Hepatitis	CR	E	irAE
78.1	F	5	3.19	2.70	Colitis	LFU	C	
64.2	M	6	4.02	3.63	Dermatitis	PR	C	
58.2	M	4	1.56	2.17	Fatigue	LFU	C	
67.5	M	13	2.37	5.00	Pneumonitis	CR	E	Liver failure
78.5	M	10	3.53	5.00	Hepatitis	PR	E	Liver failure
76.4	M	2	2.67	2.30	Fatigue	LFU	C	
61.7	M	6	1.57	2.00	Dermatitis	PD	S	
56.4	F	15	3.30	8.00	Dermatitis	CR	E	Liver failure
51.0	M	6	2.94	5.00	Pneumonitis	PD	E	ICH
67.0	M	10	3.06	5.13	Hepatitis	PR	E	irAE
36.9	M	2	2.96	0.93	Hepatitis	DBE	E	irAE

C, censored (lost to follow-up before Dec 31, 2019); COD, cause of death; CR, complete response; DBE, death before evaluation; E, expired; F, female; ICH, intracranial hemorrhage; irAE, immune-related adverse event; LFU, lost to follow-up; M, male; PD, progressive disease; PR, partial response; S, survival. [a]Final status as of Dec 31, 2019.

Supplementary Table 4. Factors associated with irAEs (grade ≥3) in 87 patients with HCC

Character		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (year)		1.012 (0.960-1.067)	.651		
Sex	Female vs male	1.861 (0.335-10.333)	.478		
Alcohol	No vs yes	0.880 (0.247-3.138)	.843		
HBV	No vs yes	0.513 (0.147-1.786)	.294		
HCV	No vs yes	1.290 (0.325-5.126)	.717		
TTV (cm^3)	≤1000 vs >1000	2.065 (0.631-6.760)	.231		
Tumor number	Single vs multiple	2.148 (0.627-7.636)	.224		
MVI	No vs yes	1.517 (0.481-4.781)	.477		
EHM	No vs yes	1.607 (0.509-5.070)	.418		
CLIP score	0-2 vs ≥3	3.981 (1.025-15.459)	.046		
AFP (ng/mL)	<400 vs ≥400	1.189 (0.374-3.785)	.769		
NLR	≤3.0 vs >3.0	1.238 (0.302-5.074)	.767		
AST (U/L)	≤40 vs >40	0.333 (0.040-2.784)	.310		
ALT (U/L)	≤40 vs >40	0.607 (0.174-2.120)	.434		
Child-Pugh class	A vs B/C	3.524 (0.895-13.874)	.072		
ALBI grade	1 vs 2/3	0.935 (0.230-3.797)	.925		
Prior therapy					
Sorafenib	No vs yes	1.370 (0.432-4.344)	.592		
Lenvatinib	No vs yes	0.441 (0.077-2.541)	.360		
Concurrent therapy	No vs yes	0.681 (0.195-2.386)	.549		
TKI	No vs yes	0.434 (0.132-1.421)	.168		
TACE	No vs yes	0.451 (0.103-1.968)	.290		
Radiotherapy	No vs yes	1.556 (0.230-10.534)	.651		
AFP response	Yes vs no	1.500 (0.455-4.946)	.505		

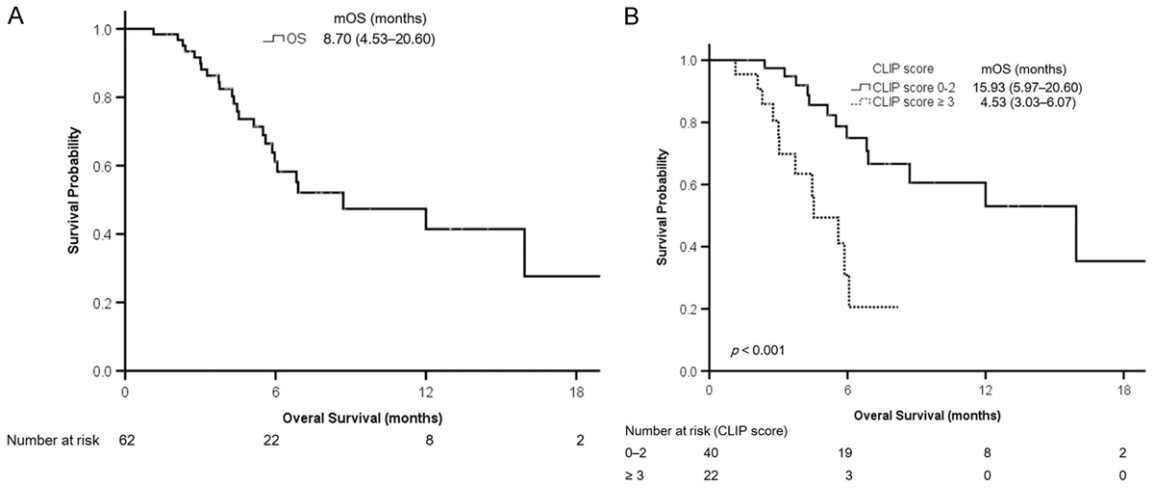
Best response	CR + PR vs none	4.227 (1.226-14.573)	.022

AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIP, Cancer of the Liver Italian Program; CR + PR, complete response plus partial response; EHM, extrahepatic metastasis; HBV, hepatitis B virus; HCV, hepatitis C virus; irAEs, immune-related adverse events; MVI, macroscopic vascular invasion; NLR, neutrophil-lymphocyte ratio; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TTV, total tumor volume.

Supplementary Table 5. Factors associated with objective response in 62 patients with HCC who underwent radiological assessment

Character		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (year)		1.038 (0.982-1.097)	.192		
Sex	Female vs male	1.367 (0.226-8.247)	.733		
Alcohol	No vs yes	0.776 (0.224-2.697)	.690		
HBV	No vs yes	0.686 (0.206-2.290)	.540		
HCV	No vs yes	1.510 (0.365-6.248)	.570		
Any irAEs	Yes vs no	2.095 (0.661-6.646)	.209		
Grade 1-2 irAEs	Yes vs no	0.625 (0.188-2.079)	.443		
Grade ≥3 irAEs	Yes vs no	7.636 (1.643-35.503)	.010		
TTV (cm^3)	≤1000 vs >1000	4.879 (1.231-19.337)	.024		
Tumor number	Single vs multiple	9.286 (2.549-33.832)	.001	9.542 (1.537-59.255)	.015
MVI	No vs yes	6.500 (1.806-23.393)	.004		
EHM	No vs yes	2.143 (0.689-6.668)	.188		
CLIP score	0-2 vs ≥3	6.000 (1.226-29.371)	.027		
AFP (ng/mL)	<400 vs ≥400	0.9338 (0.305-2.879)	.910		
NLR	≤3.0 vs >3.0	6.107 (1.754-21.268)	.004		
AST (U/L)	≤40 vs >40	3.000 (0.820-10.978)	.097		
ALT (U/L)	≤40 vs >40	1.611 (0.520-4.993)	.409		
Child-Pugh class	A vs B/C	4.058 (1.017-16.186)	.047		
ALBI grade	1 vs 2/3	6.750 (1.865-24.425)	.004		
Prior therapy					
Sorafenib	No vs yes	2.750 (0.862-8.771)	.087		
Lenvatinib	No vs yes	2.2462 (0.274-22.116)	.421		
Concurrent therapy	No vs yes	0.846 (0.230-3.108)	.801		
TKI	No vs yes	0.670 (0.217-2.071)	.486		
TACE	No vs yes	0.369 (0.096-1.427)	.149		
Radiotherapy	No vs yes	2.333 (0.393-13.845)	.351		
AFP response	Yes vs no	3.808 (1.153-12.575)	.028	5.997 (1.070-33.600)	.042

AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIP, Cancer of the Liver Italian Program; EHM, extrahepatic metastasis; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macroscopic vascular invasion; NLR, neutrophil-lymphocyte ratio; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TTV, total tumor volume.



Supplementary Figure 2. Kaplan-Meier analyses of the overall survival in patients evaluable through radiological imaging. A. All patients. B. Patients with higher (≥3) or lower (0-2) CLIP score. Continuous variables are presented as the median (first quartile-third quartile). CLIP, Cancer of the Liver Italian Program; mOS, median overall survival.

Supplementary Table 6. Comparison between the present study and other studies

Status	This study	Finkelmeier *et al.* [13][a]	Scheiner *et al.* [14][b]	Shao *et al.* [18][c]	Lee *et al.* [15][d]
Number of patients	87	34	65	43	95
Age	63.4 (55.4-68.6)	65 (range 40-77)	65.2 ± 11.1	55 ± 11.9	65.5 (57.2-72.9)
Sex (male), *n* (%)	79 (90.8)	26 (76.5)	49 (75.4)	35 (81.4)	73 (76.8)
Child-Pugh class A/B/C (%)	51.7/34.5/11.5	55.9/41.2/2.9	49.2/43.1/7.7	100/0/0	72.6/24.2/3.2
AFP ≥400 ng/mL	39 (44.8)	N/A	28 (43.1)	23 (53.5)	53 (55.8)
BCLC stage A/B/C/D (%)	8.0/10.3/69.0/12.6	11.8/38.2/50/0	0/12.3/78.5/9.2	0/7.0/93.0/0	0/21.1/78.9/0
CLIP 0-2/≥3 (%)	52.9/47.1	N/A	N/A	79.1/20.9	N/A
Max. tumor size (cm)	5.2 (2.7-8.3)	N/A	N/A	N/A	5.2 (2.3-8.8)
Multiple tumors, *n* (%)	67 (77.0)	N/A	N/A	N/A	89 (93.7)
MVI, *n* (%)	51 (58.6)	19 (55.9)	24 (36.9)	17 (39.5)	51 (53.7)
EHM, *n* (%)	52 (59.8)	19 (55.9)	35 (53.8)	38 (88.4)	48 (50.5)
Prior treatment					
Sorafenib, *n* (%)	40 (46.0)	25 (73.5)	56 (86.2)	N/A	56 (58.9)
Lenvatinib, *n* (%)	7 (8.0)	N/A	N/A		N/A
TACE, *n* (%)	49 (56.3)	15 (44.1)	30 (46.2)		55 (57.9)
RT, *n* (%)	44 (50.6)				23 (24.2)
Surgery, *n* (%)	16 (18.4)	9 (26.5)	15 (23.1)		35 (36.8)
RFA, *n* (%)	15 (17.2)		9 (13.8)		31 (32.6)
Objective response, *n* (%)	17 (19.5)	4 (11.8)	8 (12.3)	15 (34.9)	22 (24.4)
Disease control, *n* (%)	34 (39.1)	12 (35.3)	32 (49.2)	25 (58.1)	33 (36.7)

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; EHM, extrahepatic metastasis; MVI, macrovascular invasion; N/A, not applicable; RT, radiotherapy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation. [a]All patients received nivolumab therapy. [b]A total of 34 patients received nivolumab, and 34 patients received pembrolizumab therapy. [c]Enrolled patients from several clinical trials conducted in one hospital. In total, 27 patients received program cell death-1 (PD1) blockade, 1 patient received anticytotoxic T-lymphocyte antigen 4 (CTLA4), and 15 patients received PD1 blockade plus anti-CTLA4 therapy. [d]A total of 92 patients received nivolumab, and 3 patients received pembrolizumab therapy.