Supplementary

Table S1 Treatment response of patients with HCC during first-line lenvatinib-based therapy

Treatment response	Lenvatinib monotherapy (n=53)	Lenvatinib plus immunotherapy (n=19)	P value
Modified RECIST			
Complete response	7 (13.2)	4 (21.1)	0.47
Partial response	9 (17.0)	8 (42.1)	0.055
Stable disease	32 (60.4)	6 (31.6)	0.040
Objective response rate	16 (30.2)	12 (63.2)	0.03
Disease control rate	48 (90.6)	18 (94.8)	>0.99
RECIST v1.1			
Complete response	2 (3.8)	1 (5.3)	>0.99
Partial response	11 (20.8)	5 (26.3)	0.75
Stable disease	35 (66.0)	12 (63.2)	0.78
Objective response rate	13 (24.5)	6 (31.6)	0.56
Disease control rate	48 (90.6)	18 (94.8)	>0.99

HCC, hepatocellular carcinoma; RECIST, response evaluation criteria in solid tumors.

Table S2 Characteristics of patients with HCC receiving first-line lenvatinib-based therapy before and after inverse probability of treatment weighting

Variables	Before IPTW			After IPTW		
	Lenvatinib monotherapy (n=53)	Lenvatinib plus immunotherapy (n=19)	P value	Lenvatinib monotherapy (n=52)	Lenvatinib plus immunotherapy (n=15)	P value
Age ≥65 years	25 (47.2)	8 (42.1)	0.79	24 (46.2)	7 (46.7)	>0.99
Male	41 (77.4)	16 (84.2)	0.74	41 (78.8)	13 (86.7)	0.72
Etiologies, n (%)			0.76			>0.99
HBV	30 (56.6)	12 (63.2)		29 (55.8)	9 (56.3)	
HCV	14 (26.4)	3 (15.8)		15 (28.8)	4 (25.0)	
Others	9 (17.0)	4 (21.1)		8 (15.4)	3 (18.8)	
Child-Pugh class, n (%)			>0.99			>0.99
A	51 (96.2)	18 (94.7)		50 (96.2)	15 (100)	
B	2 (3.8)	1 (5.3)		2 (3.8)	0 (0)	
ECOG, n (%)			0.47			>0.99
0-1	46 (86.8)	15 (78.9)		46 (88.5)	13 (86.7)	
2-3	7 (13.2)	4 (21.1)		6 (11.5)	2 (13.3)	
FIB-4 >3.25, n (%)	19 (35.8)	3 (15.8)	0.15	17 (32.7)	2 (13.3)	0.20
ALBI, n (%)			0.22			0.50
Grade 1, 2a	42 (79.2)	12 (63.2)/7 (36.8)		42 (80.8)	11 (73.3)	
Grade 2b, 3	11 (20.8)	7 (36.8)		10 (19.2)	4 (26.7)	
BCLC stage, n (%)			0.17			0.55
B	21 (39.6)	4 (21.1)		17 (32.7)	7 (43.8)	
C	32 (60.4)	15 (78.9)		35 (67.3)	9 (56.3)	
PVT, n (%)	14 (26.4)	2 (10.5)	0.21	12 (23.1)	1 (6.7)	0.30
Vp4, n (%)	3 (5.7)	2 (10.5)	0.60	2 (3.8)	1 (6.7)	0.54
EHM, n (%)	22 (41.5)	16 (84.2)	0.001	27 (51.9)	9 (60.0)	0.77
REFLECT criteria, n (%)			0.34			>0.99
Without	10 (18.9)	6 (31.6)		10 (19.2)	3 (20.0)	
Within	43 (81.1)	13 (68.4)		42 (80.8)	12 (80.0)	
AFP >400 ng/mL, n (%)	15 (28.3)	3 (15.8)	0.36	13 (25.0)	2 (13.3)	0.49
NLR >5.8, n (%)	13 (25.5)	1 (5.3)	0.09	11 (21.2)	0 (0)	0.059

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group performance status; EHM, extrahepatic metastasis; FIB-4, fibrosis index based on four factors; HBV, hepatitis B virus; HCV, hepatitis C virus; IPTW, inverse probability of treatment weighting; NLR, neutrophil-lymphocyte ratio; PVT, portal vein thrombosis.

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Table S3 Univariate and multivariate linear regression analyses of predictors of objective response for patients with HCC receiving first-line lenvatinib monotherapy (n=53)

Variables	Objective response (complete response and partial response)			
	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age ≥65 *vs.* <65 (year)	0.869 (0.266–2.843)	0.82		
Gender, male *vs.* female	5.769 (0.671–49.61)	0.11	5.769 (0.671–49.61)	0.11
Etiologies, viral *vs.* non-viral hepatitis	1.154 (0.300–4.434)	0.84		
ECOG 2,3 *vs.* 0,1	0.333 (0.037–3.026)	0.33		
FIB-4 >3.25 *vs.* ≤3.25	1.556 (0.465–5.199)	0.47		
ALBI grade 2b,3 *vs.* 1,2a	0.808 (0.184–3.552)	0.78		
BCLC stage C *vs.* B	0.727 (0.219–2.411)	0.60		
Previous LRT, yes *vs.* no	0.857 (0.216–3.399)	0.83		
Portal vein thrombosis, yes *vs.* no	0.524 (0.124–2.218)	0.38		
Extrahepatic metastasis, yes *vs.* no	1.089 (0.331–3.577)	0.89		
REFLECT criteria, without *vs.* within	0.500 (0.093–2.675)	0.42		
Adverse event, yes *vs.* no	1.667 (0.390–7.118)	0.49		
AFP >9 *vs.* ≤9 (ng/mL)	0.636 (0.194–2.086)	0.46		
NLR >5.8 *vs.* ≤5.8	0.926 (0.237–3.623)	0.91		
ALBI grade 1,2a and NLR ≤5.8 *vs.* others	1.435 (0.376–5.482)	0.60		

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; LRT, locoregional therapy; NLR, neutrophil-lymphocyte ratio.

Table S4 Univariate and multivariate linear regression analyses of predictors of disease control for patients with HCC receiving first-line lenvatinib monotherapy (n=53)

Variables	Disease control (complete response, partial response and stable disease)			
	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age ≥65 *vs.* <65 (year)	0.259 (0.025–2.675)	0.26		
Gender, male *vs.* female	1.267 (0.119–13.52)	0.85		
Etiologies, viral *vs.* non-viral hepatitis	NA	>0.99		
ECOG 2,3 *vs.* 0,1	0.116 (0.013–1.016)	0.052	NA	>0.99
FIB-4 >3.25 *vs.* ≤3.25	1.800 (0.174–18.64)	0.62		
ALBI grade 2b,3 *vs.* 1,2a	0.789 (0.074–8.428)	0.85		
BCLC stage C *vs.* B	1.667 (0.216–12.89)	0.62		
Previous LRT, yes *vs.* no	1.121 (0.106–11.89)	0.92		
Portal vein thrombosis, yes *vs.* no	0.333 (0.042–2.631)	0.30		
Extrahepatic metastasis, yes *vs.* no	NA	>0.99		
REFLECT criteria, without *vs.* within	0.200 (0.024–1.636)	0.13	NA	>0.99
Adverse event, yes *vs.* no	1.000 (0.095–10.54)	>0.99		
AFP >9 *vs.* ≤9 (ng/mL)	1.400 (0.182–10.79)	0.75		
NLR >5.8 *vs.* ≤5.8	0.314 (0.040–2.500)	0.27		
ALBI grade 1,2a and NLR ≤5.8 *vs.* others	2.538 (0.323–19.96)	0.38		

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; LRT, locoregional therapy; NLR, neutrophil-lymphocyte ratio.

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Table S5 Univariate and multivariate Cox regression analyses of predictors of progression-free survival for patients with HCC receiving first-line lenvatinib-based therapy (n=72)

Variables	Univariate		Multivariate[†]			
			Model 1		Model 2	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age ≥65 *vs.* <65 (year)	0.693 (0.387–1.241)	0.22				
Gender, male *vs.* female	1.088 (0.539–2.197)	0.81				
Etiologies, viral *vs.* non-viral hepatitis	1.265 (0.589–2.718)	0.55				
ECOG 2,3 *vs.* 0,1	1.398 (0.673–2.903)	0.37				
FIB-4 >3.25 *vs.* ≤3.25	1.074 (0.578–1.994)	0.82				
ALBI grade 2b,3 *vs.* 1,2a	1.856 (0.962–3.583)	0.07	1.135 (0.269–4.796)	0.86		
BCLC stage C *vs.* B	0.748 (0.417–1.344)	0.33				
History of LRT, yes *vs.* no	0.661 (0.326–1.340)	0.25				
Portal vein thrombosis, yes *vs.* no	0.838 (0.425–1.652)	0.61				
Extrahepatic metastasis, yes *vs.* no	1.060 (0.594–1.892)	0.84				
REFLECT criteria, without *vs.* within	0.697 (0.359–1.354)	0.29				
Combination with ICI, yes *vs.* no	0.900 (0.465–1.741)	0.75				
Adverse event, yes *vs.* no	1.043 (0.461–2.361)	0.92				
AFP >9 *vs.* ≤9 (ng/mL)	1.580 (0.784–3.186)	0.20	1.127 (0.518–2.455)	0.76	1.097 (0.514–2.341)	0.81
NLR >5.8 *vs.* ≤5.8	2.534 (1.221–5.258)	0.01	1.948 (0.473–8.013)	0.36		
ALBI grade 1,2a and NLR ≤5.8 *vs.* others	0.445 (0.233–0.849)	0.01			0.382 (0.168–0.871)	0.02

Shaded cells indicate that the variable had a confounding effect on other factors and was therefore not included in the multivariate analysis. [†], Model 1: No combination of ALBI and NLR model. Model 2: Combination of ALBI and NLR model. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer staging; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status scale; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; LRT, locoregional therapy; NLR, neutrophil lymphocyte ratio; PFS, progression-free survival.

Table S6 Univariate and multivariate Cox regression analyses of predictors of overall survival for HCC patients receiving first-line lenvatinib-based therapy (n=72)

Variables	Univariate		Multivariate[†]			
			Model 1		Model 2	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age ≥65 *vs.* <65 (year)	1.115 (0.426–2.913)	0.83				
Gender, male *vs.* female	0.622 (0.219–1.765)	0.37				
Etiologies, viral *vs.* non-viral hepatitis	1.716 (0.391–7.521)	0.47				
ECOG 2,3 *vs.* 0,1	3.620 (1.262–10.38)	0.02	1.660 (0.136–20.33)	0.69	1.122 (0.094–13.46)	0.93
FIB-4 >3.25 *vs.* ≤3.25	1.278 (0.472–3.460)	0.63				
ALBI grade 2b,3 *vs.* 1,2a	6.493 (2.369–17.79)	<0.001	8.418 (0.699–101.3)	0.09		
BCLC stage C *vs.* B	1.124 (0.414–3.049)	0.82				
History of LRT, yes *vs.* no	0.385 (0.132–1.125)	0.08	0.979 (0.203–4.721)	0.98	0.691 (0.153–3.113)	0.63
Portal vein thrombosis, yes *vs.* no	2.529 (0.958–6.676)	0.06	1.653 (0.489–5.583)	0.42	1.559 (0.466–5.214)	0.47
Extrahepatic metastasis, yes *vs.* no	0.765 (0.290–2.015)	0.59				
REFLECT criteria, without *vs.* within	0.252 (0.094–0.679)	0.006	0.775 (0.068–8.785)	0.84	0.546 (0.052–5.771)	0.62
Combination with ICI, yes *vs.* no	0.949 (0.309–2.916)	0.93				
Adverse event, yes *vs.* no	2.679 (0.350–20.48)	0.34				
AFP >9 *vs.* ≤9 (ng/mL)	2.966 (0.808–10.89)	0.10	1.825 (0.398–8.379)	0.44	2.123 (0.473–9.527)	0.33
NLR >5.8 *vs.* ≤5.8	5.480 (1.889–15.90)	0.002	0.758 (0.067–8.547)	0.82		
ALBI grade 1,2a and NLR ≤5.8 *vs.* others	0.171 (0.061–0.482)	0.001			0.197 (0.043–0.910)	0.040

Table shading indicated that the variable has a confounding effect on other factors, and thus was not included in the multivariate analysis. [†], Model 1: No combination of ALBI and NLR model. Model 2: Combination of ALBI and NLR model. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; LRT, locoregional therapy; NLR, neutrophil-lymphocyte ratio; OS, overall survival.

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Table S7 Subgroup analysis of progression-free survival

Variables	Patient number	HR	95% CI		P value
			Lower	Upper	
Overall	72	0.900	0.465	1.741	0.75
Age (years)					
<65	39	0.926	0.384	2.232	0.86
≥65	33	0.849	0.310	2.329	0.75
Extrahepatic metastasis					
Yes	38	0.920	0.402	2.107	0.84
No	34	0.505	0.068	3.771	0.51
Cause of liver disease					
Hepatitis B	43	0.854	0.379	1.922	0.70
Non-hepatitis B	29	1.002	0.316	3.177	>0.99
α-fetoprotein (ng/mL)					
<400	54	0.881	0.407	1.904	0.75
≥400	18	0.975	0.265	3.586	0.97

HR, hazard ratio; CI, confidence interval.

Table S8 Subgroup analysis of overall survival

Variables	Patient number	HR	95% CI		P value
			Lower	Upper	
Overall	72	0.949	0.309	2.916	0.93
Age (years)					
<65	39	0.918	0.185	4.553	0.92
≥65	33	0.986	0.203	4.794	0.99
Extrahepatic metastasis					
Yes	38	0.988	0.221	4.420	0.99
No	34	1.500	0.184	12.22	0.71
Cause of liver disease					
Hepatitis B	43	1.399	0.428	4.572	0.58
Non-hepatitis B	29	0.031	0.000	422.2	0.47
α-fetoprotein (ng/mL)					
<400	54	1.351	0.336	5.43	0.67
≥400	18	0.776	0.092	6.511	0.82

HR, hazard ratio; CI, confidence interval.

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