Online-Only Supplement

Supplement to: Wenwen Zhang et al. **Lenvatinib plus anti-PD-1 antibodies as conversion therapy for patients with unresectable intermediate-advanced hepatocellular carcinoma: a single-arm, phase II trial**

Supplemental Methods

1 Conversion therapy

All eligible patients received oral lenvatinib (12 mg for bodyweight ≥ 60 kg; 8 mg for bodyweight < 60 kg) once daily and intravenous PD-1 inhibitors on day 1 of each 21-day treatment cycle. The anti-PD-1 antibodies and their single-dose infusion used in this study were sintilimab 200 mg, pembrolizumab 200 mg, tislelizumab 200 mg, or toripalimab 240 mg. The choice of anti-PD-1 antibodies was at the discretion of the patient.

If an adverse event occurred, interruption, discontinuation, or dose reduction was permitted for lenvatinib according to the trial protocol (appendix 1 pp 57-62); anti-PD-1 treatment was not dose reduced but interrupted or discontinued depending on tolerability. Treatment was resumed when protocol-defined criteria for treatment resumption were met. If hematological parameters did not recover on day 21 (±3 days), the next treatment cycle could be postponed for up to two weeks. In addition to unacceptable toxicity, treatment discontinuation also included the withdrawal of consent, disease progression, non-compliance, or other reasons that the investigators deemed would significantly compromise the patient's safety.

2 Surgery

Resectability was assessed mainly based on liver function, vascular structure, and tumor response evaluated by independent imaging review (IIR) according to HCC-specific modified RECIST (mRECIST) every 6-8 weeks (the first assessment before the fourth cycle) until conversion success, disease progression, unacceptable toxicity, or for 48 weeks. The resectability criteria (i.e., criteria for conversion success) were defined based on the "Chinese expert consensus on conversion therapy of immune checkpoint inhibitors combined anti-angiogenic targeted drugs for advanced hepatocellular carcinoma (2021 Edition)" and our previous study.[1, 2] The specific criteria were listed as follows.: 1) Child-Pugh class A or B; 2)

ECOG PS 0 or 1; 3) no extrahepatic lesions, extrahepatic lesions can be curatively resected, or extrahepatic lesions tend to be judged as inactive by the multidisciplinary team (MDT); 4) the estimated intact vascular structure of the reserved liver; and 5) the expected remnant liver volume ≥ 35% in patients without chronic liver disease and ≥ 45% in chronic liver disease patients.

Patients who satisfied the criteria for successful conversion were informed of the benefits and risks associated with surgery. Surgical treatment was performed after obtaining signed informed consent. Under the premise of radical resection, the type of surgery was chosen depending on the intraoperative exploration situation. Morbidity and mortality were monitored within 30 days following surgery. Post-hepatectomy liver failure was evaluated in accordance with the International Study Group of Liver Surgery criteria.[3] Post-operative complications were graded using the Clavien-Dindo classification.[4]

3 Post-operative management

The pathological response of all resected specimens was evaluated and classified as pathological complete response (pCR; no viable tumor cells in the resection specimens, including completely resected primary tumors, tumor thrombosis, and lymph nodes), pathological partial response (pPR; ≤50% viable tumor cells in the primary tumor), and pathological non-response (pNR; > 50% viable tumor cells in the primary tumor or appearance of new lesions).

At 2-4 weeks post-surgery, the patients with pCR were initiated with the PD-1 inhibitor monotherapy for ≥ 6 months, or until recurrence or unacceptable toxicity, whichever occurred first. Patients with pPR resumed the conversion therapy regimen for 6-12 months or until recurrence or unacceptable toxicity, whichever occurred first. Patients with pNR were treated with the regimes recommended by the MDT based on the results of the pathological examination and/or genetic testing. Tumors were assessed at 4 weeks after surgery, and every 12 weeks thereafter using the serum alpha-fetoprotein (AFP) level and imaging examination.

4 Clinical and radiographic assessment

All patients were monitored through imaging examination utilizing contrast-enhanced

magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT). Tumor response was assessed by the investigators and IIR per RECIST 1.1 and mRECIST, respectively, and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was calculated as the percentage of patients achieving CR or PR, and disease control rate (DCR) as the proportion of patients with CR, PR, or SD. Overall survival (OS) was the time from the initiation of conversion therapy to death due to any cause. Progression-free survival (PFS) was the time between the onset of conversion therapy and PD, recurrence, or death, whichever event occurred first. Recurrence-free survival (RFS) was the time from the curative-intended surgery to recurrence or death, whichever appeared first. The duration of response was the interval from the first documented CR or PR until PD, recurrence, or death, whichever came first.

5 Safety assessment

All patients underwent safety evaluations 14 days before initiating study treatment and within 3 days before the next treatment cycle. Adverse events and abnormal laboratory findings were assessed by the investigators following the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

6 Multiplex immunofluorescence

Multiplex immunofluorescence (mIF) staining was performed using the Akoya OPAL Polaris 7-Color Automation IHC kit (NEL871001KT). Formalin-fixed paraffin-embedded (FFPE) tissue slides were incubated with specific primary antibodies targeting pan-CK (ab7753, 1:100, Abcam), CD8 (ab178089, 1:100, Abcam), CD56 (ab75813, 1:100, Abcam), CD68 (ab213363, 1:1000, Abcam), and HLA-DR (ab20181, 1:300, Abcam). This was followed by interaction with horseradish peroxidase-conjugated secondary antibody and tyramide signal amplification. The slides were heat-treated after each round of amplification. Cell nuclei were counterstained with 4', 6-diamidino-2-phenylindole. Multiplex stained slides were scanned, and all scans for each slide were merged to determine the relative localization of the proteins. The quantities of various cell populations were expressed as the percentage of positively

stained cells in all nucleated cells.

Supplementary Table 1. Detailed clinicopathological characteristics of all 56 eligible HCC patients.

ID	Initials	Smoke	Drink	HBV+	HCV+	ECOG PS	Child-pugh	BCLC stage	CNLC stage	Baseline AFP (ng/mL)	Extrahepatic metastasis	PVTT	HVTT	Prior local therapy for HCC	Curative-intended surgery after conversion	mIF testing
P001	BHP	no	no	yes	no	0	A	C	IIIb	216.7	lymph node	yes	no	no	yes	yes
P002	CFJ	yes	no	no	no	0	A	C	IIIa	17008	no	yes	no	no	yes	no
P003	CSZ	yes	yes	NA	NA	1	A	C	IIIa	7.34	no	yes	no	surgery+TACE	no	no
P004	DGC	yes	yes	yes	no	1	A	C	IIIb	>1000	lung	yes	no	no	no	no
P005	DXF	yes	yes	yes	no	0	A	C	IIIa	12947	no	yes	no	no	no	yes
P006	FDJ	yes	no	yes	no	0	A	C	IIIa	5.01	no	yes	yes	no	yes	no
P007	FGS	yes	yes	no	no	0	A	B	IIb	11.96	no	no	no	surgery	yes	no
P008	GBRZ	no	no	yes	no	0	A	C	IIIa	60.82	no	yes	no	no	yes	no
P009	GHG	yes	yes	yes	no	0	A	C	IIIa	41828	no	yes	no	no	no	yes
P010	GZ	no	no	yes	no	0	A	C	IIIb	6.48	lymph node	yes	NA	no	no	no
P011	HB	yes	yes	yes	no	0	A	C	IIIb	2859	lymph node	yes	no	no	no	no
P012	HGR	yes	no	yes	no	0	A	C	IIIa	819.3	no	yes	no	no	no	yes
P013	HJY	yes	no	yes	no	0	A	C	IIIa	9026	no	no	yes	no	yes	yes
P014	HLJ	no	no	yes	no	0	A	C	IIIa	1320	no	yes	no	no	no	no
P015	HZJ	yes	yes	yes	no	0	A	C	IIIa	14.63	no	yes	yes	no	no	no
P016	LBM	yes	yes	yes	no	0	A	C	IIIa	430.3	no	yes	no	no	yes	yes
P017	LF	yes	yes	yes	no	1	A	C	IIIa	12.87	no	no	yes	no	no	no
P018	LMX	yes	yes	yes	no	0	A	C	IIIa	4.74	no	yes	no	no	no	yes
P019	LSS	no	no	yes	no	0	A	C	IIIa	542.2	no	yes	no	no	no	no
P020	LST	no	no	yes	no	0	A	C	IIIa	426.9	no	yes	no	no	no	no
P021	LSY	no	yes	yes	no	0	A	C	IIIa	31797	no	yes	no	no	Yes	yes
P022	LXC	no	no	yes	no	0	A	C	IIIb	86.78	lymph node	yes	no	no	yes	no
P023	MQC	no	yes	yes	no	0	A	C	IIIb	>60500	lung	yes	no	no	no	no
P024	MYH	yes	yes	yes	no	0	A	C	IIIa	33.78	no	yes	no	no	no	yes
P025	PMY	no	no	yes	yes	0	A	C	IIIa	338.4	no	yes	no	no	no	no
P026	QJF	no	no	yes	no	0	A	C	IIIa	>60500	no	yes	no	no	no	no
P027	QSM	yes	yes	yes	no	0	A	C	IIIa	56.9	no	yes	yes	no	no	no

P028	SG	yes	no	no	yes	0	A	C	IIIb	20.33	lymph node	no	no	no	no	no
P029	SHN	no	no	yes	no	0	A	C	IIIb	45544	lymph node	yes	no	no	no	no
P030	SKM	no	no	yes	no	0	A	C	IIIa	961.7	no	yes	no	no	no	no
P031	SLM	no	no	yes	no	0	A	C	IIIa	22.42	no	yes	no	no	no	no
P032	SXL	yes	F	yes	no	1	NA	C	IIIa	>60500	no	yes	no	no	no	no
P033	SY	yes	yes	yes	NA	0	A	C	IIIa	20.91	no	yes	no	no	no	yes
P034	SYP	yes	yes	yes	no	0	A	C	IIIa	2660	no	yes	no	no	yes	no
P035	TM	no	no	yes	no	0	A	C	IIIa	2.26	no	yes	no	surgery	yes	no
P036	TSQ	yes	no	yes	no	0	A	C	IIIa	>60500	no	yes	no	no	yes	yes
P037	WAF	no	no	yes	no	0	A	C	IIIb	436.6	lymph node	no	yes	no	yes	yes
P038	WJS	no	no	yes	no	0	B	C	IIIa	>60500	no	yes	NA	no	no	no
P039	WL	NA	no	yes	NA	0	A	C	IIIa	33577	no	yes	no	no	no	no
P040	WLJ	no	yes	yes	no	0	A	C	IIIb	448.3	lung	yes	no	no	no	no
P041	WXIL	yes	no	yes	yes	0	A	C	IIIb	7058	lymph node	yes	no	no	yes	yes
P042	WXJ	yes	no	yes	no	0	A	C	IIIa	>60500	no	yes	no	no	no	Yes
P043	WXL	yes	yes	yes	no	0	A	C	IIIa	4.27	no	yes	no	no	no	no
P044	WZQ	no	no	yes	no	0	A	C	IIIb	17020	lymph node	no	yes	no	yes	yes
P045	YSP	no	no	NA	yes	0	A	C	IIIb	NA	lymph node	yes	no	no	yes	yes
P046	YYB	yes	yes	yes	no	0	A	C	IIIb	3033	lymph node	yes	no	no	no	yes
P047	ZCH	yes	no	yes	no	0	A	C	IIIa	789	no	yes	no	no	yes	yes
P048	ZHF	no	no	yes	no	0	A	C	IIIb	960.4	lymph node	yes	yes	no	yes	no
P049	ZJY	yes	no	yes	no	0	A	C	IIIa	5440	no	yes	no	no	no	yes
P050	ZNZ	no	no	yes	no	0	A	C	IIIa	14.1	no	yes	no	no	no	yes
P051	ZXC	NA	NA	yes	no	0	A	C	IIIa	>60500	no	yes	no	no	no	no

P052	ZXJ	yes	no	no	no	0	A	C	IIIb	4381	lymph node	no	yes	no	no	no
P053	ZXJG	yes	yes	yes	no	0	A	C	IIIa	1398	no	yes	no	no	no	no
P054	ZXL	yes	no	yes	no	0	A	B	IIb	1060	no	no	no	no	yes	no
P055	ZXP	no	no	yes	no	0	A	C	IIIa	22.8	no	no	yes	no	yes	no
P056	ZYH	no	yes	no	yes	0	NA	C	IIIa	24246	no	yes	no	no	yes	no

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; PS: performance status; BCLC, Barcelona Clinic Liver Cancer; CNLC: China Liver Cancer; AFP: alpha-fetoprotein; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombosis; mIF: multiplex immunofluorescence.

Supplementary Table 2. Summary of overall response in 56 HCC patients receiving lenvatinib plus PD-1 inhibitors.

Parameter	HCC-specific mRECIST		RECIST 1.1	
	IIR	investigator	IIR	investigator
Objective response	30 (53.6)	33 (58.9)	25 (44.6)	26 (46.4)
Complete response	5 (8.9)	12 (21.4)	1 (1.8)	1 (1.8)
Partial response	25 (44.6)	21 (37.5)	24 (42.9)	25 (44.6)
Stable disease	14 (25.0)	9 (16.1)	19 (33.9)	19 (33.9)
Disease control[a]	44 (78.6)	42 (75.0)	44 (78.6)	45 (80.4)
Progressive disease	7 (12.5)	8 (14.3)	10 (17.9)	9 (16.1)
Could not be evaluated	4 (7.1)	5 (8.9)	1 (1.8)	1 (1.8)
Data missing	1 (1.8)	1 (1.8)	1 (1.8)	1 (1.8)

Data presented as no. (%).

[a] Disease control included complete response, partial response, and stable disease.

Abbreviations: IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST, Response Evaluation Criteria in Solid Tumors.

Supplementary Table 3 The characteristics of 21 conversion resection patients during the perioperative period.

Characteristics	Successful conversion
Before surgery	
Days from systemic therapy to surgery	109 (77, 219)
Lenvatinib withdrawal days before surgery	5 (2, 7)
Hepatectomy	
Number of hepatic segment excision	
1	2 (9.5%)
2	4 (19.0%)
≥3	15 (71.4%)
Portal vein thrombectomy	7 (33.3%)
Hepatic vein thrombectomy	3 (14.3%)
Retroperitoneal lymph node dissection	1 (4.8%)
Operation time (min)	260 (200, 390)
Intraoperatve blood loss (mL)	500 (50, 2400)
Intraoperative blood transfusion	6 (28.6%)
Blood transfusion volume (mL)	837.5 (450, 980)
After surgery	
Child-Pugh score (5 days post-sugery)	
A	18 (85.7%)
B	3 (14.3%)
Clavin-Dindo classification	
I	1 (4.8%)
III	2 (9.5%)
Post-hepatectomy liver failure	
A	4 (19.0%)
Post-operative hospital stay, days	10 (5,33)
Pathological response	
pCR	8 (38.1%)
pPR	9 (42.9%)
pNR	4 (19.0%)

Data presented as median (minimum-maximum) or no. (%).

Abbreviations: pCR, pathological complete response; pPR; pathological partial response; pNR, pathological non-response.

Supplementary Table 4 Univariate and multivariate analysis of the variables associated with PFS and OS in 56 HCC patients receiving lenvatinib plus PD-1 inhibitors.

Parameter	**PFS**				**OS**	
	Univariable analysis		**Multivariable analysis**		**Univariable analysis**	
	HR (95% CI)	P value	HR (95%CI)	P value	HR (95% CI)	P value
Age (≥ 60 vs. <60)	0.56 (0.28-1.14)	0.108			0.58 (0.23-1.43)	0.233
Sex (female vs. male)	1.29 (0.50-3.31)	0.595			1.09 (0.33-3.60)	0.892
Smoke (no vs. yes)	1.07 (0.57-2.00)	0.829			0.94 (0.44-1.97)	0.863
Drink (no vs. yes)	1.50 (0.80-2.79)	0.204			1.49 (0.71-3.14)	0.294
HBV infection (no vs. yes)	0.62 (0.22-1.76)	0.37			0.44 (0.13-1.49)	0.187
HCV infection (no vs. yes)	2.01 (0.68-5.94)	0.205			2.14 (0.63-7.19)	0.221
Baseline AFP (<400ng/ml vs. ≥400ng/ml)	2.21 (1.12-4.35)	0.022	2.33 (1.17-4.61)	**0.016**	1.81 (0.80-4.13)	0.156
Hepatic cyst (no vs. yes)	0.52 (0.18-1.47)	0.215			0.20 (0.03-1.50)	0.119
Extrahepatic disease (no vs. yes)	0.92 (0.50-1.67)	0.78			1.08 (0.52-2.25)	0.837
Concomitant medication (no vs. yes)	1.08 (0.52-2.27)	0.833			0.94 (0.36-2.47)	0.903
ECOG PS (0 vs. 1)	0.75 (0.23-2.43)	0.631			0.80 (0.19-3.37)	0.758
TNM stage (III vs. IV)	0.90 (0.49-1.66)	0.731			0.70 (0.33-1.50)	0.361
Extrahepatic metastasis						
no vs. Lymph node	1.00 (0.47-2.12)	0.998			0.69 (0.26-1.82)	0.452
no vs. lung	1.79 (0.54-5.96)	0.341			1.10 (0.26-4.73)	0.897
Multiple foci (single vs. multiple)	2.00 (1.09-3.67)	0.024	2.49 (1.30-4.76)	**0.006**	1.13 (0.54-2.37)	0.748
BCLC stage (B vs. C)	0.99 (0.24-4.13)	0.994			/	/

CNLC stage						
IIb vs. IIIa	0.96 (0.23-4.05)	0.96			/	/
IIb vs. IIIb	1.09 (0.24-4.91)	0.913			/	/
Vascular invasion	0.99 (0.24-4.13)	0.994			/	/
PVTT (no vs. yes)	1.73 (0.73-4.10)	0.215			3.43 (0.81-14.44)	0.093
HVTT (no vs. yes)	0.26 (0.06-1.06)	0.061			0.00 (0.00-Inf)	0.997
Vp status (no vs. yes)						
Vp2 vs. Vp3	0.65 (0.21-2.03)	0.457			0.71 (0.19-2.68)	0.611
Vp2 vs. Vp4	0.88 (0.30-2.61)	0.821			1.24 (0.36-4.26)	0.736
Vv status (Vv2 vs. Vv3)	0.94 (0.34-2.66)	0.913			0.44 (0.10-2.01)	0.29
Conversion success (no vs. yes)	0.37 (0.20-0.69)	**0.002**	**0.29 (0.15-0.57)**	**<0.001**	**0.31 (0.15-0.66)**	**0.002**

/ There were too few events to conduct a reliable analysis.

PFS was assessed by IIR according to mRECIST.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AFP: alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; PS: performance status; TNM, tumor-node-metastasis; BCLC, Barcelona Clinic Liver Cancer; CNLC: China Liver Cancer; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombosis; Vp, portal vein invasion; Vv, venous invasion; PFS, progression-free survival; OS, overall survival; IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

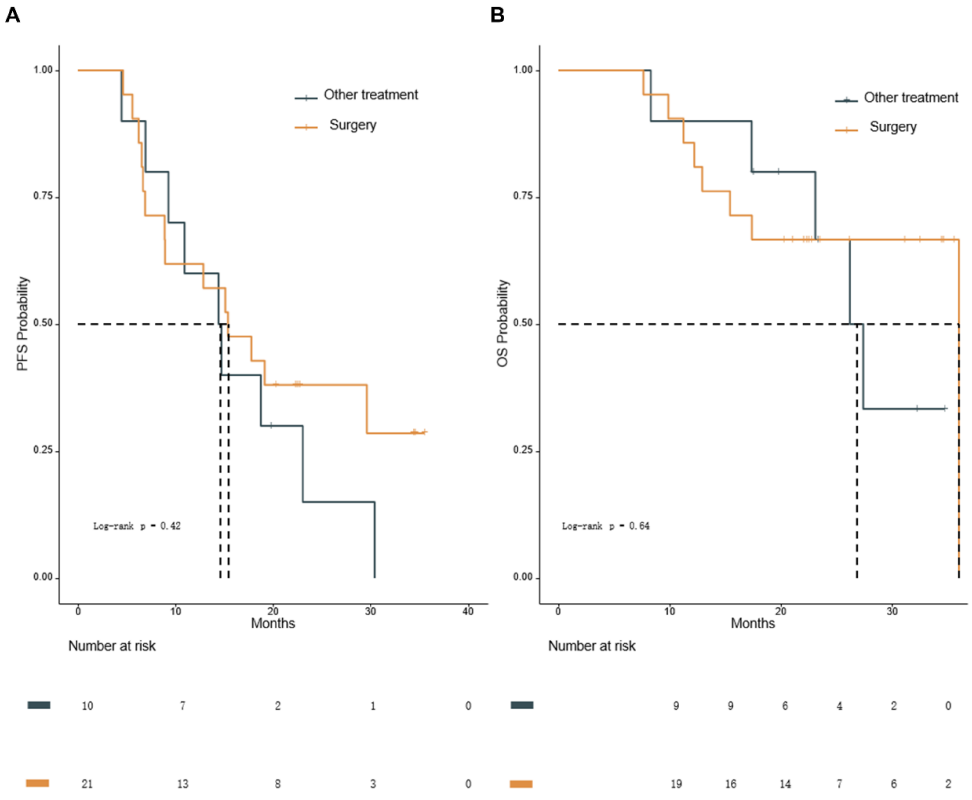
Supplementary Table 5 Treatment-related adverse events in 56 HCC patients receiving lenvatinib plus PD-1 inhibitors

Clinical characteristics	Lenvatinib plus PD-1 inhibitors				
	Any grade	Grade 1-2	Grade 3	Grade 4	Grade 5
Any treatment-related adverse event	50 (89.3%)	43 (76.8%)	22 (39.3%)	1 (1.8%)	2 (3.6%)[a]
Rash	17 (30.4%)	15 (26.8%)	2 (3.6%)		
Hand-foot syndrome	16 (28.6%)	12 (21.4%)	4 (7.1%)		
Fever	7 (12.5%)	6 (10.7%)	1 (1.8%)		
Nausea	6 (10.7%)	6 (10.7%)			
Proteinuria	5 (8.9%)	5 (8.9%)			
Abdominal pain	5 (8.9%)	5 (8.9%)			
Diarrhea	5 (8.9%)	4 (7.1%)	1 (1.8%)		
Hypothyroidism	4 (7.1%)	4 (7.1%)			
Hypertension	9 (16.1%)	3 (5.4%)	6 (10.7%)		
Blood bilirubin increased	4 (7.1%)	2 (3.6%)	2 (3.6%)		
Epistaxis	3 (5.4%)	2 (3.6%)	1 (1.8%)		
Myalgia	2 (3.6%)	2 (3.6%)			
Cough	2 (3.6%)	2(3.6%)			
Fatigue	2 (3.6%)	2 (3.6%)			
Periodontal disease	7 (12.5%)	1 (1.8%)	6 (10.7%)		
Hypoalbuminemia	1 (1.8%)	1 (1.8%)			
Lung infection	1 (1.8%)	1 (1.8%)			
Edema limbs	1 (1.8%)	1 (1.8%)			
Floaters	1 (1.8%)	1 (1.8%)			
Pharyngolaryngeal pain	1 (1.8%)	1 (1.8%)			
Intracranial hemorrhage	1 (1.8%)	1 (1.8%)			
Hoarseness	1 (1.8%)	1 (1.8%)			
Mammogenesis	1 (1.8%)	1 (1.8%)			
Leukocytosis	1 (1.8%)	1 (1.8%)			
Shingles	1 (1.8%)	1 (1.8%)			
Cholecystitis	1 (1.8%)	1 (1.8%)			
Hypohepatia	1 (1.8%)	1 (1.8%)			
Increased aminotransferases	1 (1.8%)	1 (1.8%)			
Hematuria	1 (1.8%)	1 (1.8%)			
Autoimmune disorder	2 (3.6%)		1 (1.8%)	1 (1.8%)	
Unknown death					2 (3.6%)
Liver dysfunction	1 (1.8%)		1 (1.8%)		
Psoriasis	1 (1.8%)		1 (1.8%)		
Gingival bleeding	1 (1.8%)		1 (1.8%)		
Platelet count decreased	1 (1.8%)		1 (1.8%)		
Arthralgia	1 (1.8%)		1 (1.8%)		

Data presented as no. (%).

[a] Two patients who experienced grade 5 treatment-related adverse events died during or after the treatment, and the causes of death were unknown. Thus, the relation to treatment could not be ruled out.

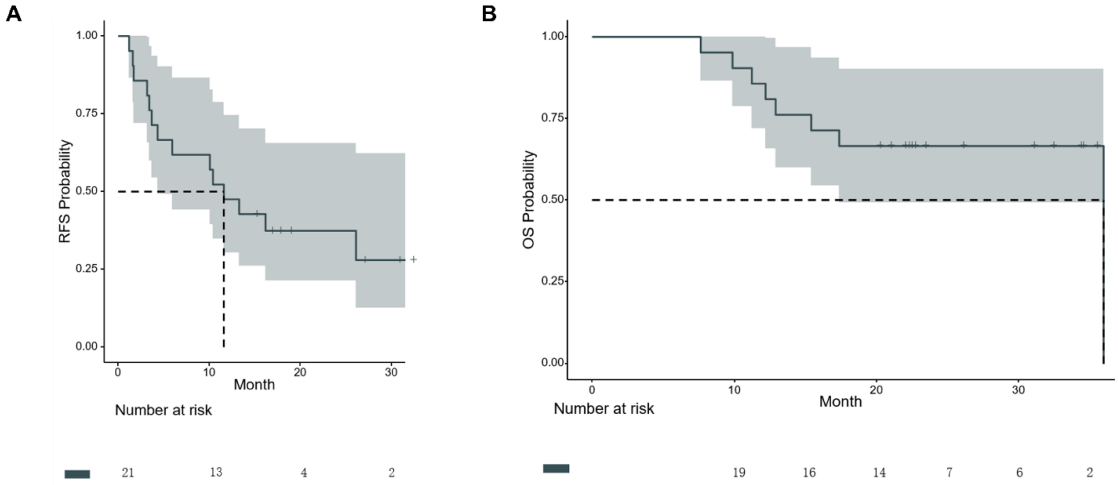
Supplementary Figure 1 Kaplan-Meier curves of PFS (A) and OS (B) of 31 conversion success patients stratified by post-operative therapy strategies.



PFS was assessed by IIR according to mRECIST.

Abbreviations: PFS, progression-free survival; OS, overall survival; IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

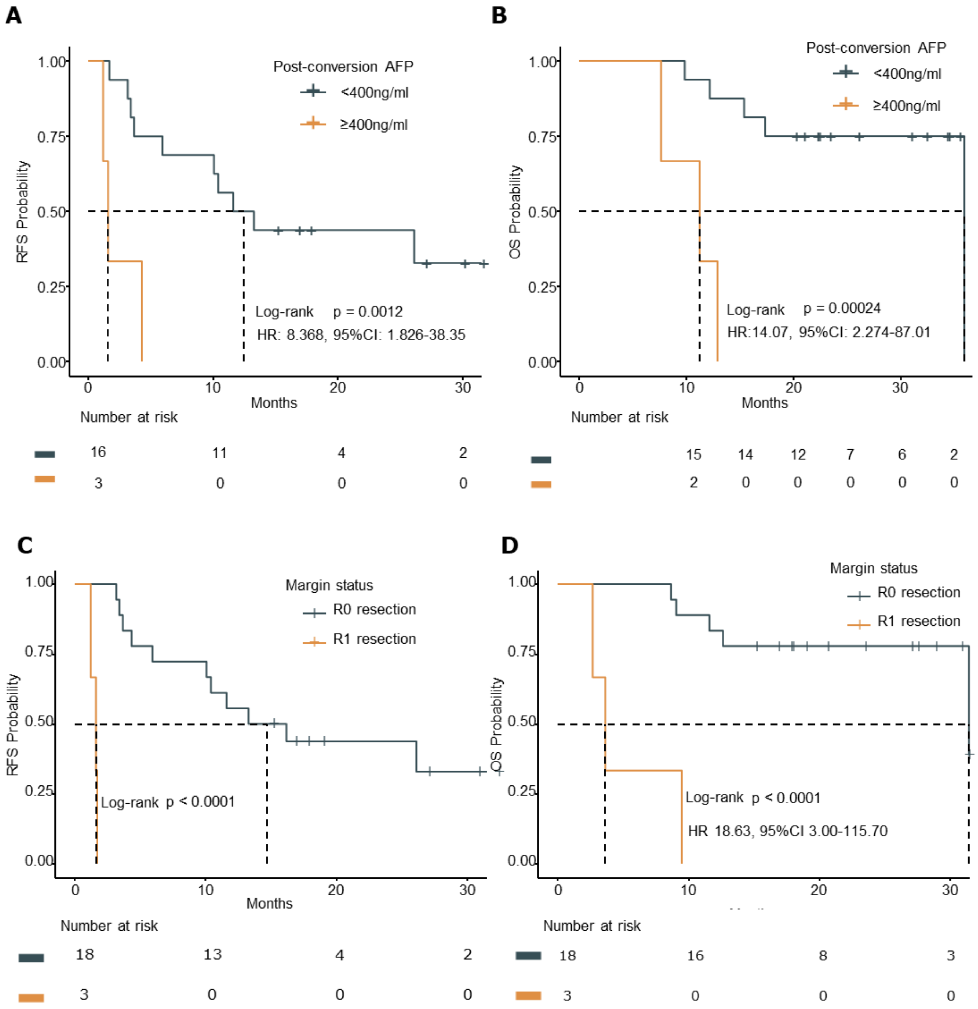
Supplementary Figure 2 Kaplan-Meier estimates of RFS (A) and post-operative OS (B) of 21 HCC patients with conversion resection



RFS assessment by IIR according to mRECIST.

Abbreviations: RFS: recurrence-free survival; OS, overall survival; IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

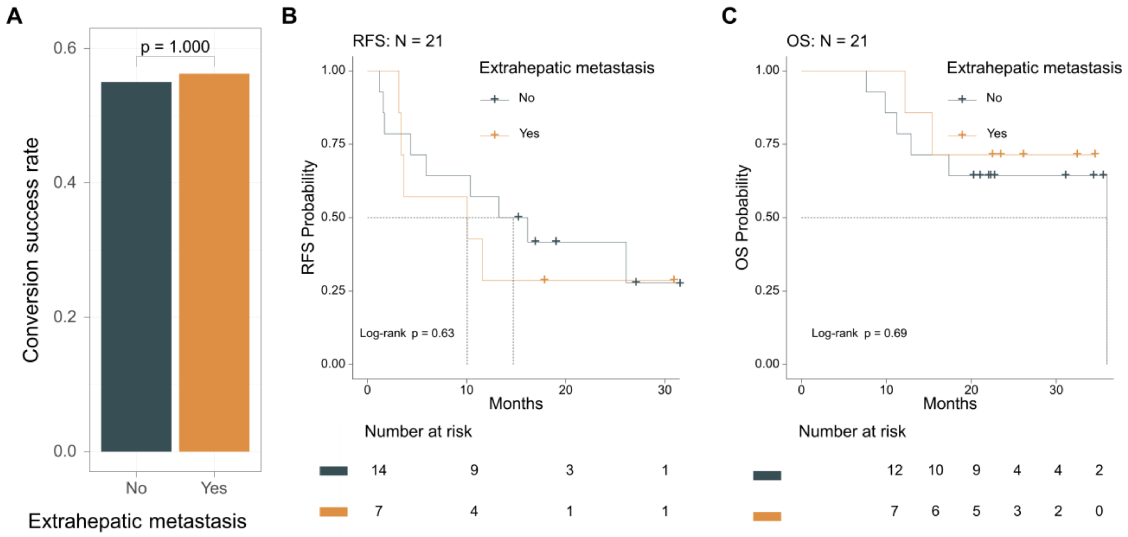
Supplementary Figure 3 Kaplan-Meier estimates of RFS (A and C) and post-operative OS (B and D) of 21 conversion resection patients stratified by post-conversion AFP level and surgical margin.



RFS was assessed by IIR according to mRECIST

Abbreviations: RFS: recurrence-free survival; OS, overall survival; IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Supplementary Figure 4 The effects of extrahepatic metastasis on conversion success rate and post-operative survival in 56 patients receiving lenvatinib plus PD-1 inhibitors.



(A) The conversion success rate of patients with or without extrahepatic metastasis following therapy with lenvatinib plus PD-1 inhibitors. (B and C) Kaplan-Meier curves for RFS (B) and post-operative OS (C) of conversion resection patients stratified by extrahepatic metastasis.

RFS was assessed by IIR according to mRECIST

Abbreviations: RFS: recurrence-free survival; OS, overall survival; IIR, independent imaging review; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

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