SUPPLEMENTARY MATERIAL

Network mata-analysis

Study selection and data extraction of network meta-analysis: To fully assess the clinical benefit of different regimens in patients with advanced hepatocellular carcinoma (HCC), we conducted a meta-analysis including relevant randomized clinical trials (RCTs), which certified that , and that combination therapies were superior to monotherapies, in compliance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and reported results based on Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) reporting guideline.

An extensive literature search was performed from PubMed, Embase and the Cochrane Central Register of Controlled Trials databases for RCTs published in English from January 1, 2018, to January 1, 2023. We searched the abstracts of ESMO and ASCO from 2020 to 2022 as well. Data analysis began in January 2023. A combined search strategy of medical subject headings plus free-text terms was adopted to identify relevant studies. The full search strategy was detailed below: (1) research objective: history of HCC; (2) randomized-controlled studies with head-to-head comparisons of at least two treatment arms, and similar articles published by the same author recently; (3) systemic firstline therapy for unresectable, progressing or advanced HCC; (4) outcome indicators were OS or ORR per RECIST1.1 that could be obtained from the original article or supplementary materials; (5)reports of phase III RCTs certifying the monotherapies were not inferior to Sorafenib or other proven non-inferiority regimens such as Lenvatinib and HAIC in the first-line treatment of patients with advanced HCC or additional benefit of combination therapies versus monotherapies in the first-line treatment of patients with advanced HCC; and (6) not study on adjuvant or neoadjuvant therapy. If multiple publications of the

same study were retrieved, the most recent and informative publication was selected. Phase I, phase II, dose-finding, adjuvant and neoadjuvant, second or later-line setting trials were excluded. News, editorials, letters, commentaries, retrospective studies, review articles were also excluded. Two authors (Yu-Zhe Cao and Meng-Xuan Zuo) independently screened the trials for eligibility and extracted the following information from each trial: trial name, year of publication, sample size, treatment regimens in both arms and results of statistical testing of primary endpoints. Any discrepancies were resolved by consensus. The included RCTs were additionally assessed for risk of bias using the Cochrane Risk of bias (RoB 2) tool, which yielded low risk for all studies included (Supplementary Figure 1).

Although LEAP-002 study did not meet its superiority threshold, the study demonstrated Pembrolizumab combined with Lenvatinib could prolong overall survival compared with Lenvatinib alone for the patients with advanced HCC (21.2 months *vs* 19.0 months, HR = 0.840, Cl 0.708-0.997, P = 0.0227). So we still brought LEAP-002 study into network meta-analysis. However, the analysis only included the phase III RCT superior to sorafenib or lenvatinib published in the English, which may caused bias and limits the reliability of the analysis.

Search strategy

(1) PubMed

#1 controlled clinical trial [pt]

#2 randomized controlled trial [pt]

#3 randomized [tiab]

#4 randomly [tiab]

#5 trial* [tiab]

#6 rct [tiab]

#7 clinical trials [mh]

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 hepatocellular carcinoma [tiab]

#10 liver cancer [tiab]

#11 HCC [tiab]

#12 #9 OR #10 OR #11

#13 #8 AND #12

#14 advanced[tiab]

#15 unresectable[tiab]

#16 progressing[taib]

#17 #14 OR #15 OR #16

#18 #13 AND #17

#19 #English[la]

#20 #18 AND #19

#21animals [mh] NOT humans [mh]

#22 #20 NOT #21

((RCT[Title/Abstract]) OR (randomized controlled trial[Title/Abstract]) OR (controlled clinical tria[Title/Abstract]l) OR (clinical trials[Title/Abstract]) OR (trial*[Title/Abstract]) OR (clinical trials[MeSH Terms])) AND ((hepatocellular carcinoma[Title/Abstract]) OR (HCC[Title/Abstract]) OR (liver cancer[Title/Abstract])) AND ((advanced[Title/Abstract]) OR (unresectable[Title/Abstract]) OR (progressing[Title/Abstract])) AND (English[Language]) NOT ((animals[MeSH Terms]) NOT (humans[MeSH Terms]))

(2) Embase (Ovid)

#1 'liver cell carcinoma':ab,ti OR 'liver cell cancer':ab,ti OR 'hepatocellular carcinoma':ab,ti OR hcc:ab,ti

#2 'advanced' OR 'unresectable' OR 'progressing'

#3 'randomized controlled trial':de OR 'clinical study'

#4 'human' NOT 'animal'

#5 'phase 3 clinical trial'/de

#6 #1 AND #2 AND #3 AND #4

(3) Cochrane Central Register of Controlled Trials

#1 ('hepatocellular carcinoma' OR 'liver cancer' OR hcc):ti,ab,kw

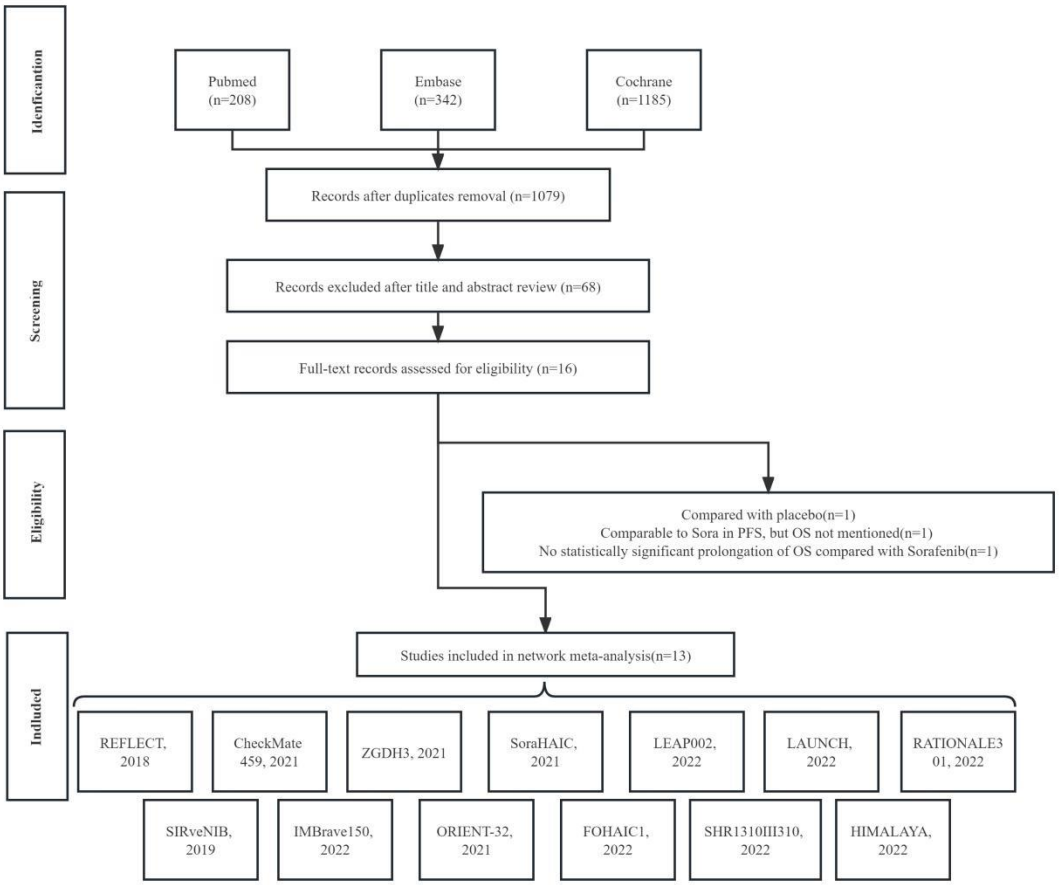
#2 ('progressing' OR 'advanced' OR 'unresectable'):ti,ab,kw

#3 English:la

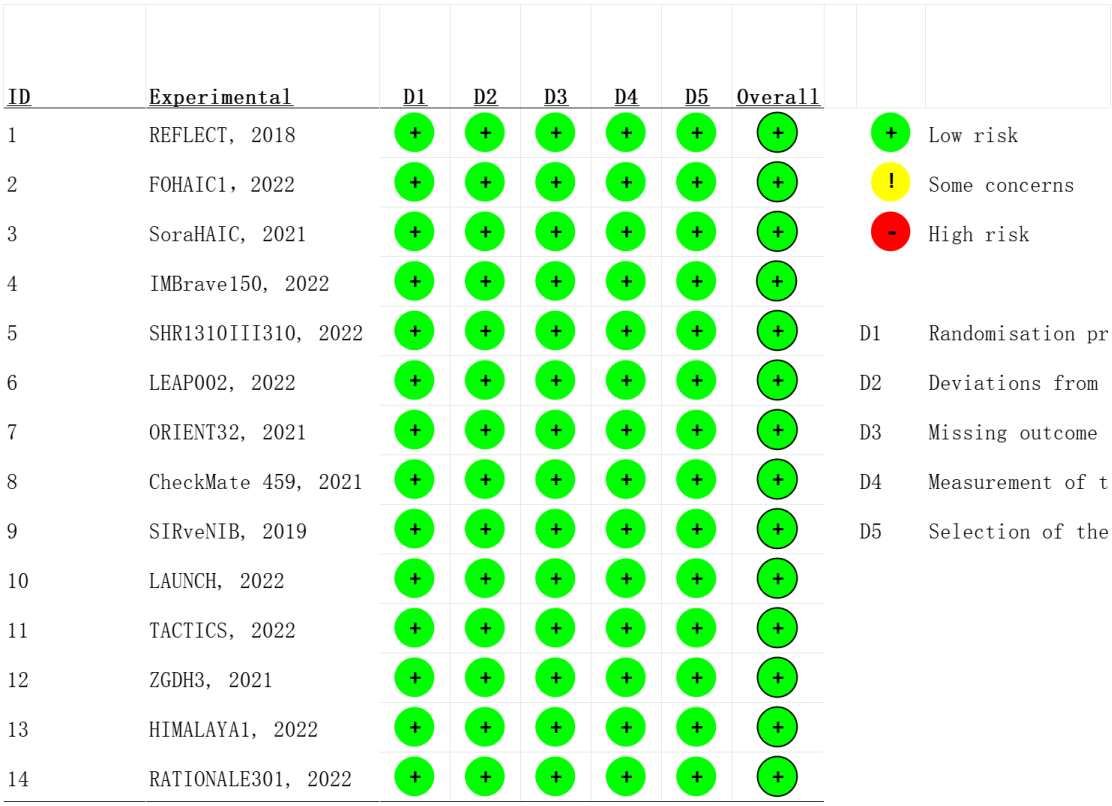
#4 ("RCT" OR "controlled clinical trial" OR "randomized controlled trial" OR "clinical trials"):ti,ab,kw

#5 #1 AND #2 AND #3 AND #4

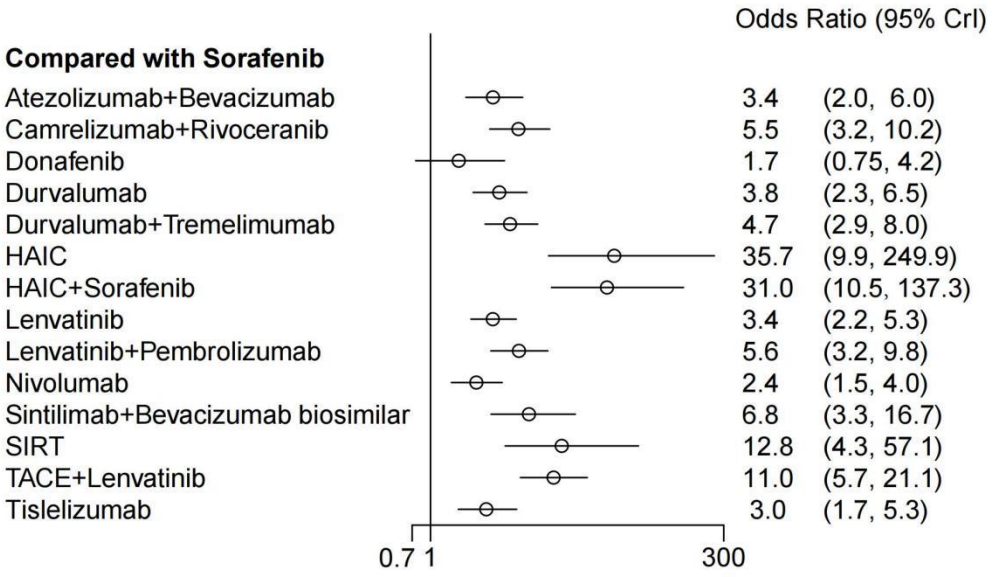
Supplementary Figures



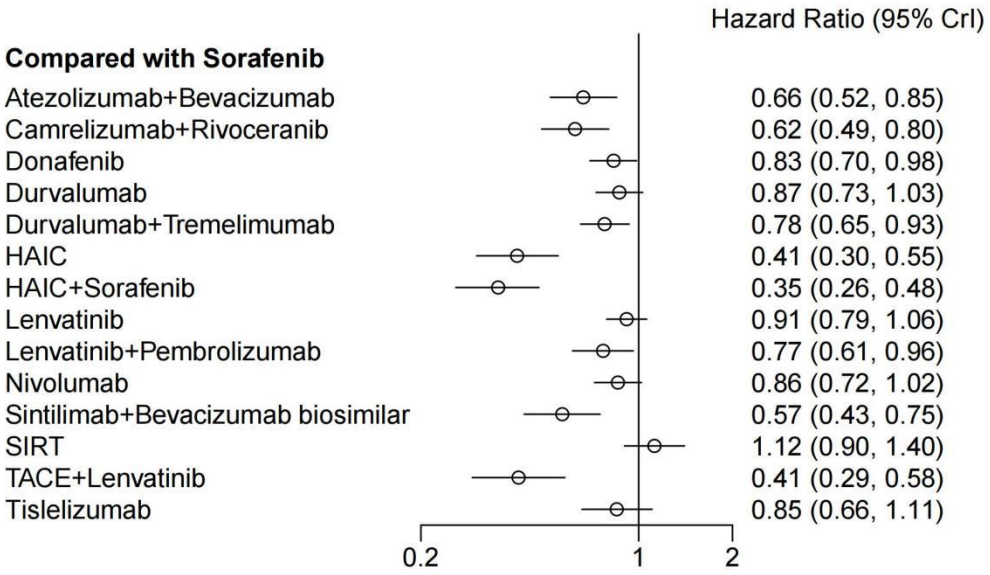
Supplementary Figure 1 Preferred reporting items for systematic reviews and meta-analyses flowchart of included studies.



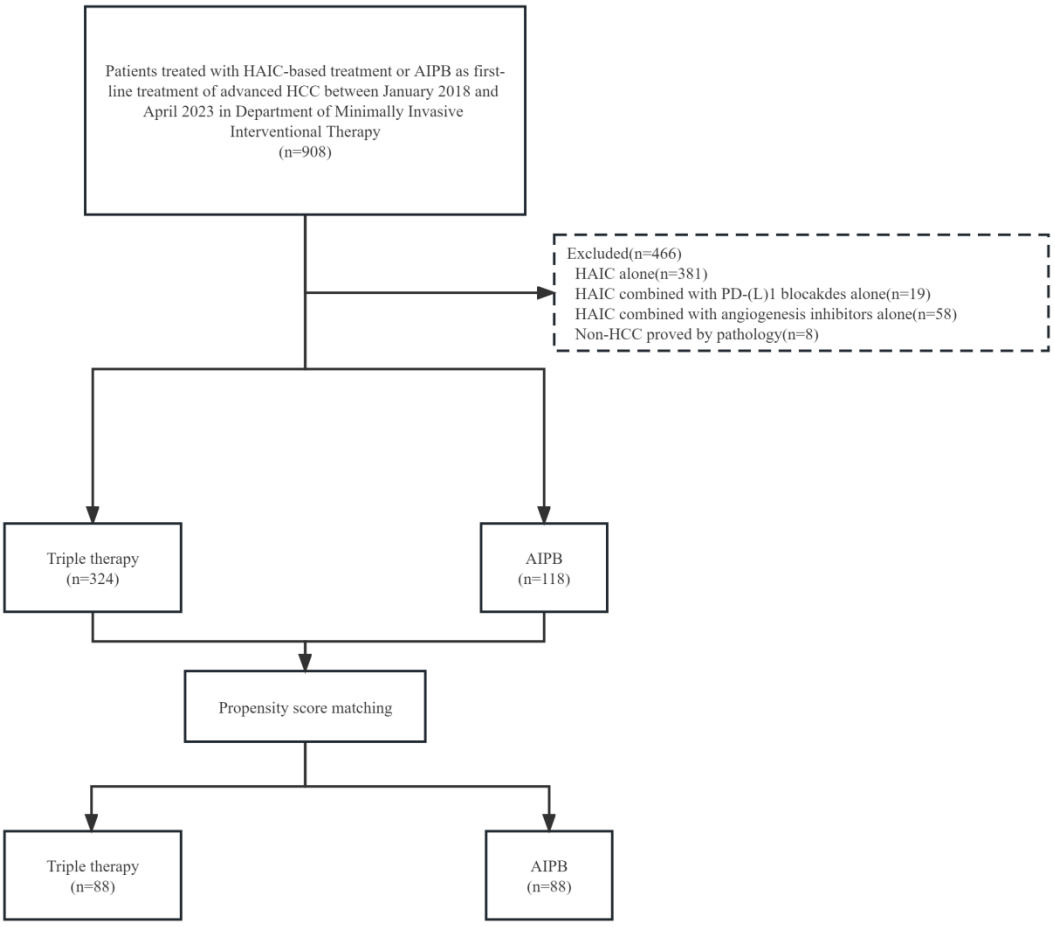
Supplementary Figure 2 Risk of bias of researches.



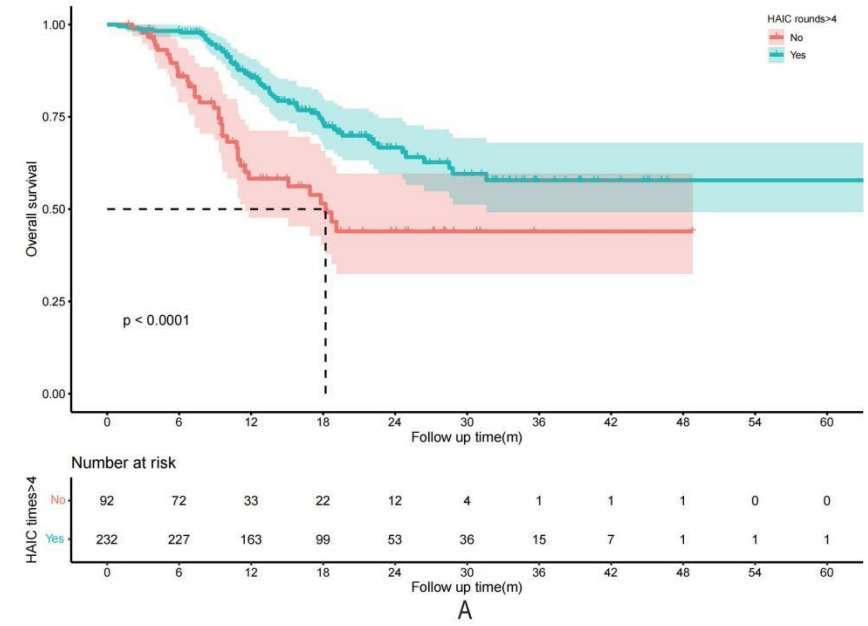
Supplementary Figure 3 Forest plot on odds ratios for objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 compared to sorafenib in the form of odds ratio.

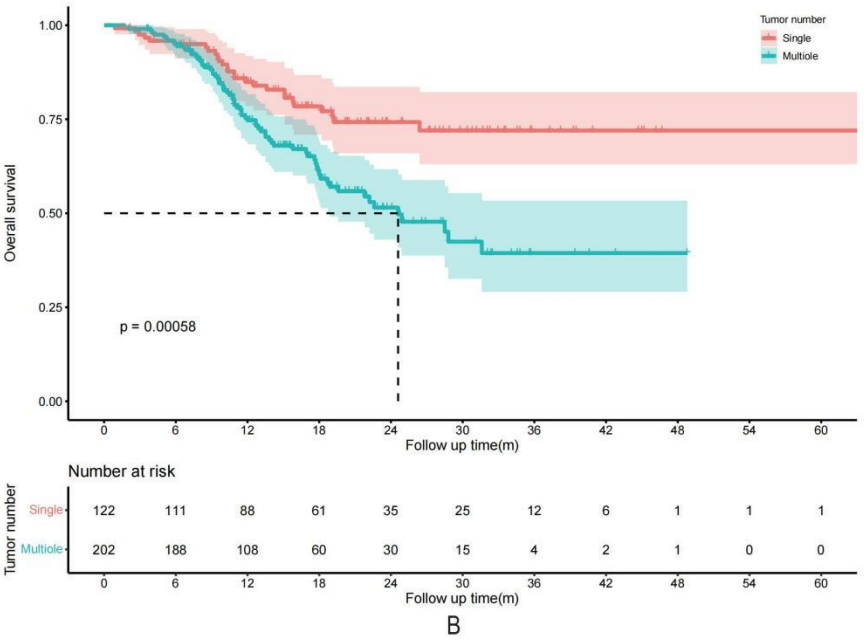


Supplementary Figure 4 Forest plot on hazrd ratios for overall survival compared to sorafenib in the form of hazard ratio.



Supplementary Figure 5 Patients' selection flow.





Supplementary Figure 6 Kaplan-Meier curves of overall survival in the triple therapy groups between different populations. A: the patients with HAIC

rounds more than 4 or not, not reached *vs* 18.2 mo; $P < 0.001$; B: the patients with single or multiple tumors, not reached *vs* 24.6 months; $P < 0.001$.

Supplementary Table 1 Baseline demographics of participants in included studies (%)

ID	Study	Yr	Arm	Patients number, *n*	Male	Age	ECOG PS > 0	Hepatitis virus	Child-Pugh A	BCLC C	MVI	EHM
1	REFLECT	2018	Lenvatinib	478	85	63 (20-88)[1]	100	72	99	78	23	61
			Sorafenib	476	84	62 (22-88)[1]	100	74	99	81	19	62
2	FOHAIC	2022	HAIC	130	89	54 (45-61)[2]	74	94	68	96	72	34
			Sorafenib	132	93	53 (45-62)[2]	82	89	71	93	69	35
3	SoraHAIC	2021	HAIC + Sorafenib	125	89	49 (41-55)[2]	73	85	100	100	100	30
			Sorafenib	122	92	49 (40-56)[2]	75	87	100	100	100	34
4	IMBrave150	2020	Atezolizumab + Bevacizumab	336	82	64 (56-71)[2]	100	70	100	82	38	63
			Sorafenib	165	83	66 (59-71)[2]	100	68	100	81	43	56
5	SHR1310III310	2022	Camrelizumab + Rivoceranib	272	83	58 (48-66)[2]	100	85	87	86	15	64

			Sorafenib	271	85	56 (47-64)[2]	100	83	85	85	19	66
6	LEAP002	2022	Lenvatinib + Pembrolizumab	395	80	66 (19-88)[1]	100	62	99	78	18	63
			Lenvatinib	399	82	66 (20-88)[1]	100	59	99	76	15	61
7	ORIENT-32	2021	Sintilimab + Bevacizumab biosimila	380	88	53 (21-82)[1]	100	96	96	85	28	73
			Sorafenib	191	90	54 (28-77)[1]	100	98	95	86	26	75
8	CheckMate 459	2021	Nivolumab	371	85	65 (57-71)[2]	100	55	98	82	33	60
			Sorafenib	372	85	65 (58-72)[2]	100	55	96	78	32	56
9	SIRveNIB	2019	SIRT	182	81	59.5 ± 12.93	100	68	91	48	31	0
			Sorafenib	178	85	57.7 ± 10.63	100	72	90	45	30	0
10	LAUNCH	2022	TACE + Lenvatinib	170	82	54 (46-64)[2]	100	89	100	100	72	55
			Lenvatinib	168	79	56 (48-63)[2]	100	89	100	100	70	56

11	ZGDH3	2021	Donafenib	328	86	53 (46-62)[2]	100	91	99	87	NA	NA
			Sorafenib	331	88	53 (46-61)[2]	100	93	96	88	NA	NA
12	HIMALAYA	2022	Durvalumab + Tremelimumab	393	83	65 (22-86)[1]	99	59	98	80	26	53
			Durvalumab	389	83	64 (20-86)[1]	99	57	98	79	24	54
			Sorafenib	389	87	64 (18-88)[1]	99	57	97	83	26	52
13	RATIONALE301 (26)	2022	Tislelizumab	342	84	62 (25-86)[1]	100	76	99	79	15	64
			Sorafenib	332	85	60 (23-86)[1]	100	76	100	76	15	60

[1]Ages are reported as median (range).

[2]Ages are reported as median (interquartile range).

[3]Ages are reported as mean ± SD.

BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; MVI: macrovascular invasion; EHM: extrahepatic metastasis; HAIC: hepatic arterial infusion chemotherapy; TACE: transcatheter arterial chemoembolization; SIRT: selective internal radiation therapy.

Supplementary Table 2 League table on odds ratio for objective per RECIST 1.1

Atezolizumab + Bevacizumab			
0.61 (0.27, 1.36)	Camrelizumab + Rivoceranib		
1.94 (0.69, 5.33)	3.2 (1.1, 9.04)	Donafenib	
0.88 (0.42, 1.9)	1.45 (0.67, 3.22)	0.46 (0.17, 1.26)	Durvalumab

0.71 (0.34, 1.53)	1.18 (0.54, 2.59)	0.37 (0.14, 1)	0.81 (0.56, 1.16)	Durvalumab + Tremelimumab			
0.09 (0.01, 0.39)	0.15 (0.02, 0.64)	0.05 (0.01, 0.23)	0.11 (0.01, 0.42)	0.13 (0.02, 0.52)	HAIC		
0.11 (0.02, 0.38)	0.18 (0.04, 0.62)	0.06 (0.01, 0.23)	0.12 (0.03, 0.42)	0.15 (0.03, 0.51)	1.17 (0.16, 10.5)	HAIC + Sorafenib	
1 (0.5, 2.07)	1.65 (0.8, 3.48)	0.51 (0.2, 1.38)	1.13 (0.58, 2.26)	1.4 (0.72, 2.8)	10.66 (2.71, 77.44)	9.25 (2.81, 43.05)	Lenvatinib

0.6 (0.28, 1.34)	0.99 (0.45, 2.25)	0.31 (0.11, 0.89)	0.68 (0.32, 1.47)	0.84 (0.4, 1.81)	6.44 (1.57, 47.94)	5.57 (1.61, 26.57)	0.6 (0.43, 0.85)	Lenvatinib + Pembrolizumab			
1.39 (0.67, 2.91)	2.26 (1.08, 4.95)	0.71 (0.27, 1.96)	1.56 (0.76, 3.25)	1.93 (0.96, 3.99)	14.77 (3.73, 106.5)	12.69 (3.78, 59.39)	1.39 (0.71, 2.69)	2.29 (1.09, 4.83)	Nivolumab		
0.5 (0.18, 1.27)	0.82 (0.28, 2.13)	0.26 (0.07, 0.8)	0.56 (0.2, 1.41)	0.69 (0.25, 1.74)	5.28 (1.11, 44.49)	4.58 (1.11, 23.9)	0.49 (0.18, 1.18)	0.83 (0.29, 2.09)	0.36 (0.13, 0.88)	Sintilimab + Bevacizumab biosimilar	
0.26 (0.05, 0.91)	0.43 (0.09, 1.54)	0.13 (0.02, 0.56)	0.29 (0.06, 1.02)	0.36 (0.08, 1.26)	2.8 (0.39, 24.93)	2.42 (0.38, 15.04)	0.26 (0.06, 0.87)	0.43 (0.09, 1.5)	0.19 (0.04, 0.64)	0.52 (0.1, 2.21)	SIRT

3.37 (1.99, 6.01)	5.53 (3.17, 10.18)	1.73 (0.75, 4.22)	3.81 (2.29, 6.53)	4.7 (2.89, 8.05)	35.66 (9.94, 249.91)	30.95 (10.52, 137.25)	3.36 (2.2, 5.31)	5.59 (3.23, 9.83)	2.44 (1.5, 4.03)	6.79 (3.25, 16.74)	12.84 (4.27, 57.15)	Sorafenib		
0.31 (0.13, 0.74)	0.51 (0.21, 1.21)	0.16 (0.05, 0.47)	0.35 (0.15, 0.81)	0.43 (0.19, 0.99)	3.29 (0.76, 25.27)	2.85 (0.79, 14.44)	0.31 (0.19, 0.49)	0.51 (0.28, 0.92)	0.22 (0.1, 0.51)	0.62 (0.23, 1.86)	1.18 (0.32, 5.75)	0.09 (0.05, 0.17)	TACE + Lenvatinib	
1.14 (0.52, 2.53)	1.87 (0.83, 4.25)	0.59 (0.21, 1.65)	1.29 (0.59, 2.78)	1.59 (0.74, 3.43)	12.18 (2.92, 92.03)	10.49 (2.98, 50)	1.14 (0.55, 2.31)	1.89 (0.85, 4.13)	0.82 (0.39, 1.74)	2.3 (0.9, 6.56)	4.37 (1.24, 21.55)	0.34 (0.19, 0.58)	3.69 (1.57, 8.84)	Tislelizumab

HAIC: hepatic arterial infusion chemotherapy; TACE: transcatheter arterial chemoembolization.

Supplementary Table 3 League table on hazard ratio for overall survival

Atezolizumab + Bevacizumab			
	Camrelizumab + Rivoceranib		
1.06 (0.75, 1.51)			
		Donafenib	
0.8 (0.59, 1.09)	0.75 (0.56, 1.02)		
0.77	0.72	0.96	Durv

(0.57, 1.04)	(0.54, 0.97)	(0.75, 1.22)	alumab				
0.85 (0.63, 1.16)	0.8 (0.59, 1.09)	1.07 (0.83, 1.37)	1.11 (0.87, 1.43)	Durvalumab + Tremelimumab			
1.63 (1.1, 2.4)	1.54 (1.04, 2.26)	2.04 (1.44, 2.88)	2.13 (1.5, 3)	1.91 (1.35, 2.71)	HAIC		
1.88 (1.27, 2.78)	1.77 (1.19, 2.63)	2.35 (1.66, 3.34)	2.45 (1.73, 3.49)	2.2 (1.54, 3.14)	1.15 (0.75, 1.77)	HAIC + Sorafenib	
0.73 (0.55, 0.97)	0.68 (0.51, 0.91)	0.91 (0.72, 1.14)	0.95 (0.76, 1.19)	0.85 (0.68, 1.07)	0.45 (0.32, 0.62)	0.39 (0.27, 0.54)	Lenvatinib

0.86 (0.62, 1.21)	0.81 (0.58, 1.14)	1.08 (0.81, 1.43)	1.13 (0.85, 1.49)	1.01 (0.76, 1.35)	0.53 (0.36, 0.78)	0.46 (0.31, 0.67)	1.19 (1, 1.41)	Lenvatinib + Pembrolizumab			
0.77 (0.57, 1.05)	0.73 (0.54, 0.98)	0.97 (0.76, 1.24)	1.01 (0.79, 1.29)	0.91 (0.71, 1.17)	0.47 (0.34, 0.67)	0.41 (0.29, 0.58)	1.07 (0.85, 1.34)	0.9 (0.67, 1.19)	Nivolumab		
1.17 (0.81, 1.7)	1.1 (0.76, 1.6)	1.46 (1.05, 2.03)	1.53 (1.1, 2.11)	1.37 (0.98, 1.91)	0.72 (0.48, 1.09)	0.62 (0.41, 0.94)	1.61 (1.17, 2.21)	1.35 (0.94, 1.95)	1.51 (1.09, 2.1)	Sintilimab + Bevacizumab biosimilar	
0.59	0.56	0.74	0.77	0.69	0.36	0.31	0.82	0.69	0.76	0.5	SIRT

(0.42, 0.82)	(0.4, 0.77)	(0.56, 0.98)	(0.58, 1.02)	(0.52, 0.92)	(0.25, 0.53)	(0.22, 0.46)	(0.62, 1.06)	(0.5, 0.94)	(0.58, 1.01)	(0.35, 0.72)				
0.66 (0.52, 0.85)	0.62 (0.49, 0.8)	0.83 (0.7, 0.98)	0.87 (0.73, 1.03)	0.78 (0.65, 0.93)	0.41 (0.3, 0.55)	0.35 (0.26, 0.48)	0.91 (0.79, 1.06)	0.77 (0.61, 0.96)	0.86 (0.72, 1.02)	0.57 (0.43, 0.75)	1.12 (0.9, 1.4)	Sorafenib		
1.61 (1.07, 2.46)	1.52 (1, 2.31)	2.02 (1.38, 2.96)	2.11 (1.44, 3.08)	1.89 (1.29, 2.77)	0.99 (0.63, 1.56)	0.86 (0.54, 1.36)	2.23 (1.63, 3.03)	1.87 (1.32, 2.66)	2.09 (1.43, 3.06)	1.38 (0.89, 2.14)	2.73 (1.83, 4.1)	2.43 (1.73, 3.42)	TACE + Lenvatinib	
0.78 (0.55, 1.11)	0.73 (0.51, 1.05)	0.98 (0.71, 1.33)	1.02 (0.75, 1.39)	0.91 (0.66, 1.24)	0.48 (0.32, 0.71)	0.42 (0.28, 0.62)	1.08 (0.8, 1.44)	0.9 (0.64, 1.27)	1.01 (0.74, 1.37)	0.67 (0.46, 0.98)	1.32 (0.94, 1.86)	1.18 (0.9, 1.52)	0.48 (0.32, 0.73)	Tislelizumab

HAIC: hepatic arterial infusion chemotherapy; TACE: transcatheter arterial chemoembolization.

Supplementary Table 4 Tumor response per modified Response Evaluation Criteria in Solid Tumors, *n* (%)

	Triple therapy group (*n* = 324)	AIPB group (*n* = 118)	Triple therapy group (*n* = 88)	AIPB group (*n* = 88)
Response	**Before PSM**		**After PSM**	
CR	21 (6.5)	4 (3.4)	6 (6.8)	4 (4.5)
PR	183 (56.5)	31 (26.3)	43 (48.9)	27 (30.7)
Stable disease	79 (24.4)	55 (46.6)	24 (27.3)	34 (38.6)
PD	41 (12.7)	28 (23.7)	15 (17.0)	23 (26.1)
ORR	204 (62.9)	35 (29.7)	49 (55.7)	31 (35.2)

AIPB: angiogenesis inhibitors plus programmed cell death protein 1/programmed death ligand 1 blockers; PSM: propensity score matching; CR: complete response; PR: partial response; PD: programmed death; ORR: objective response rate.