

Lenvatinib vs. sorafenib as second-line treatment post atezolizumab plus bevacizumab for hepatocellular carcinoma: the LEVIATHAN study

Pasquale Lombardi, Jung Sun Kim, Giulia F. Manfredi, Ciro Celsa, Claudia A. M. Fulgenzi, Antonio D'Alessio, Bernardo Stefanini, Niraj C. Doshi, Emily Warmington, Thomas U. Marron, Matthias Pinter, Bernhard Scheiner, Beodeul Kang, Ho Yeong Lim, Wei-Fan Hsu, Brooke Wietharn, Marianna Silletta, Alessandro Parisi, Chun-Yen Lin, Andrea Dalbeni, Gianluca Masi, Martin Schönlein, Johann von Felden, Fabio Piscaglia, Peter R. Galle, Masatoshi Kudo, Tiziana Pressiani, Lorenza Rimassa, Mario Pirisi, Giuseppe Cabibbo, Hong Jae Chon, David J. Pinato

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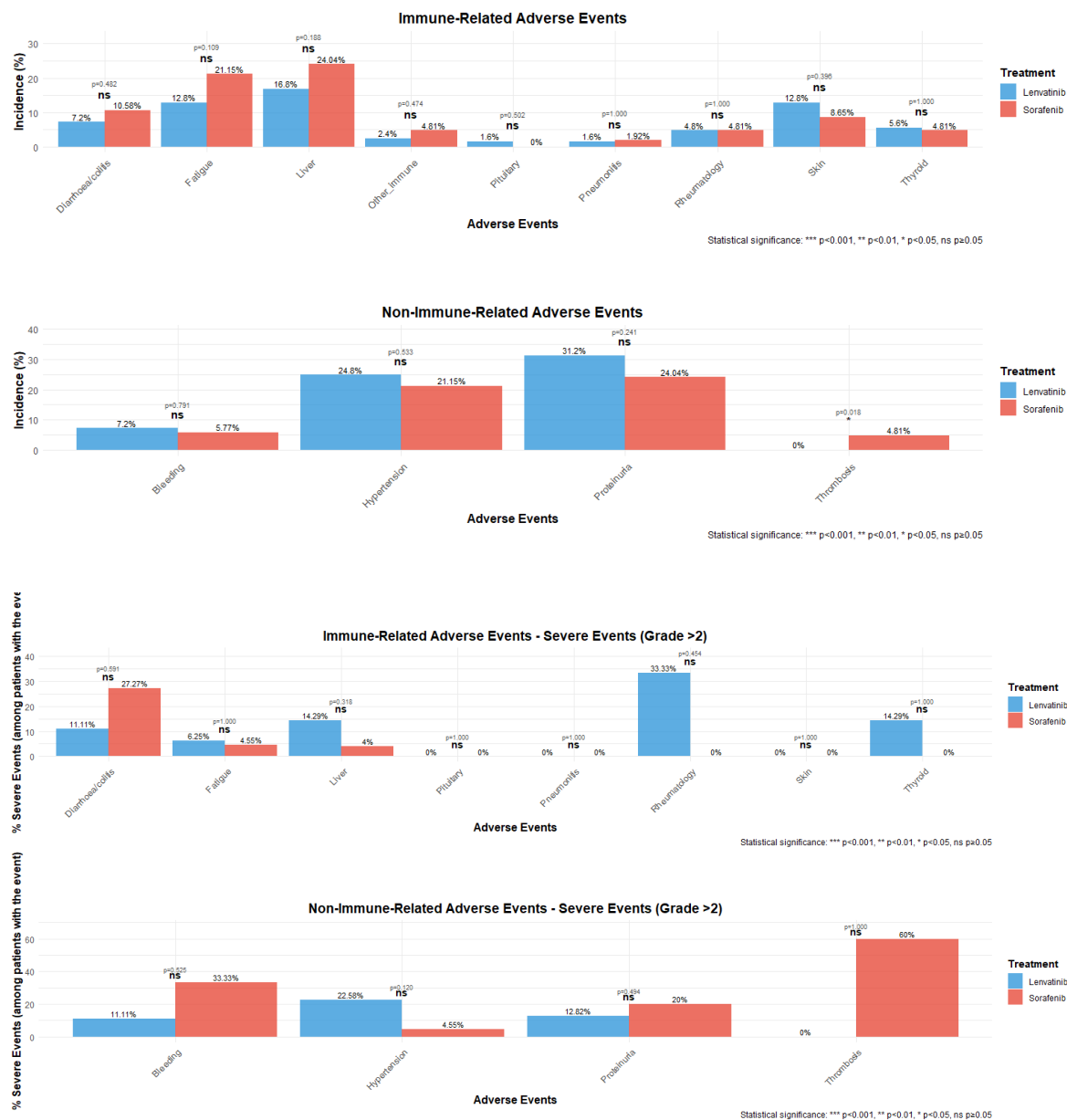


Fig. S1.
Incidence of all grades Adverse Event (A) and Adverse Events Grade >2 (B) during Atezolizumab-Bevacizumab Therapy, Stratified by Subsequent Second-Line Treatment

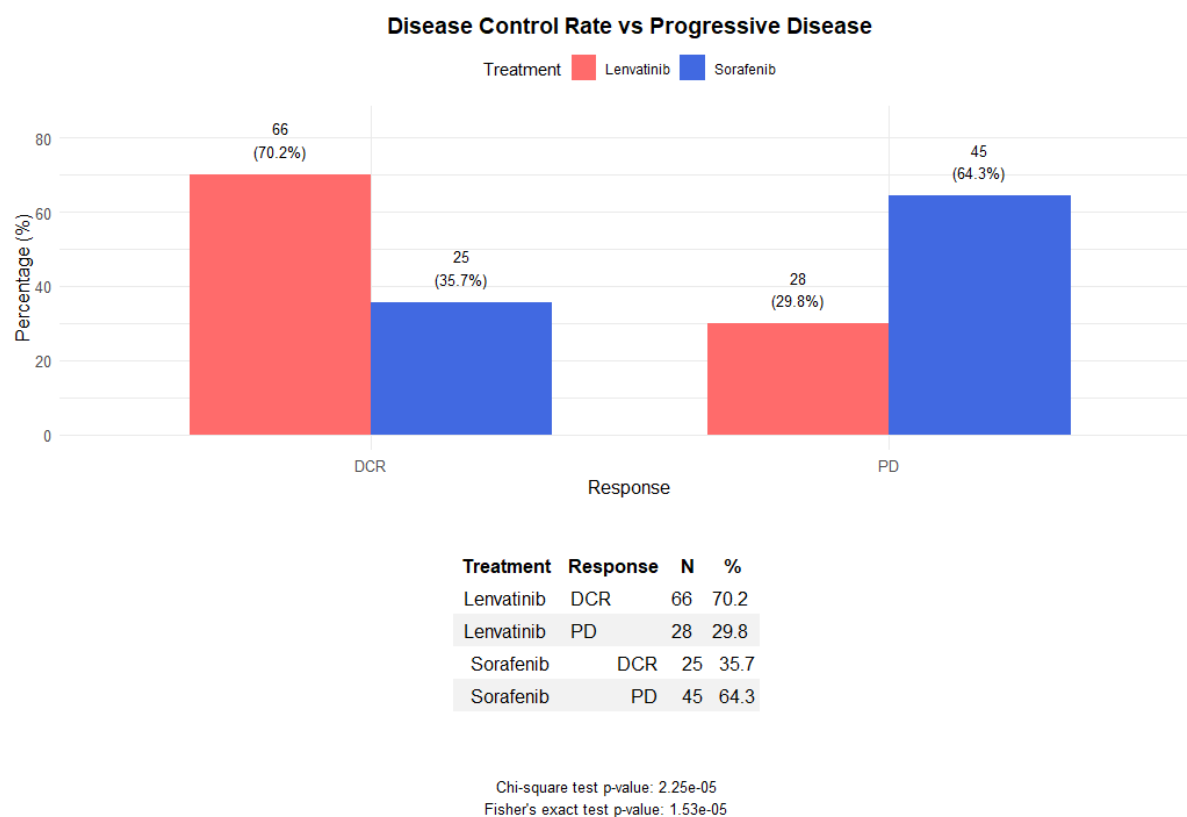


Fig. S2.
Disease control rate and progressive disease with lenvatinib compared to sorafenib.

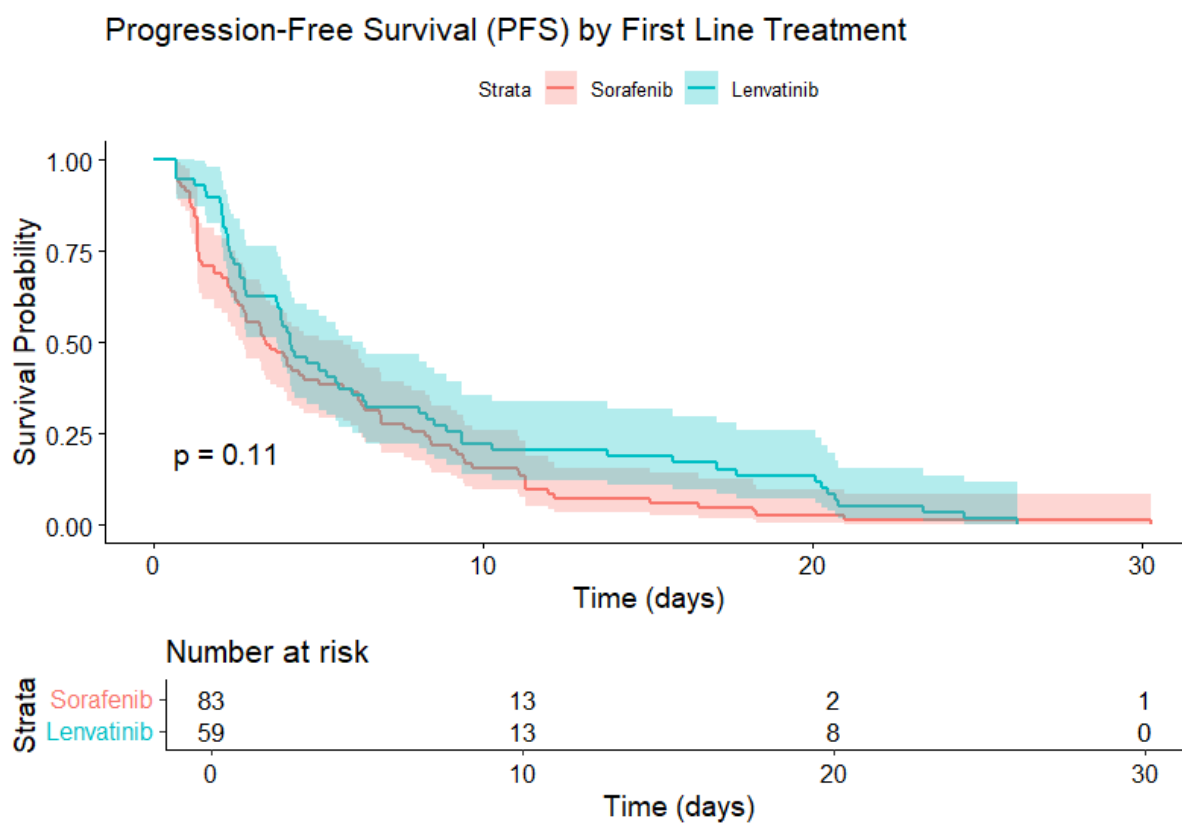


Fig. S3.
Kaplan-Meier curves for PFS by first-line treatment in patients treated with lenvatinib or sorafenib as second-line therapy.

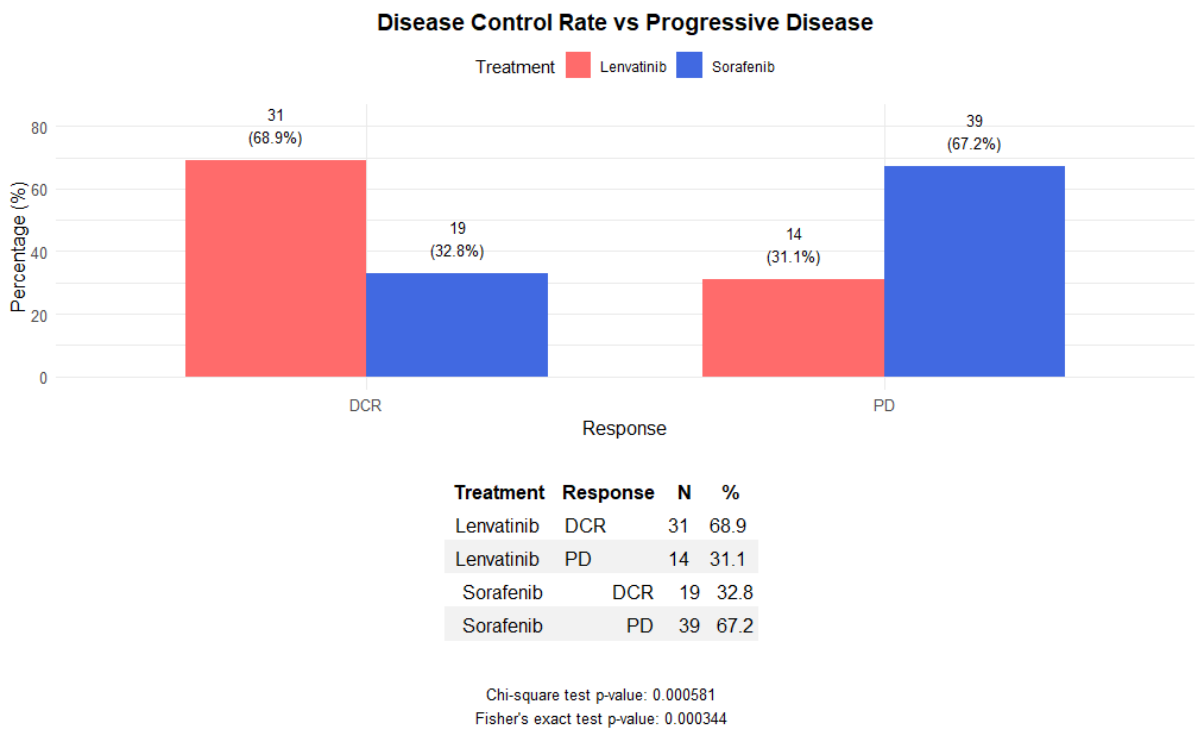


Fig. S4.
Disease control rate and progressive disease with lenvatinib compared to sorafenib in PSM population.

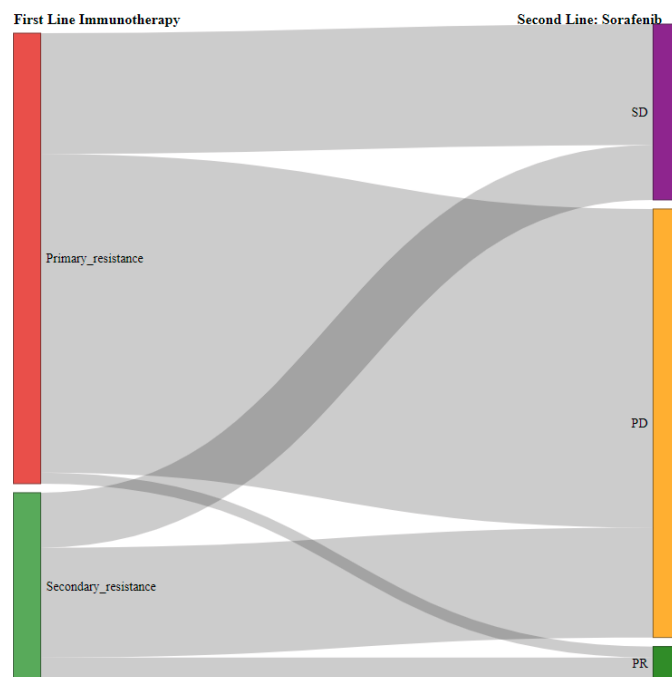
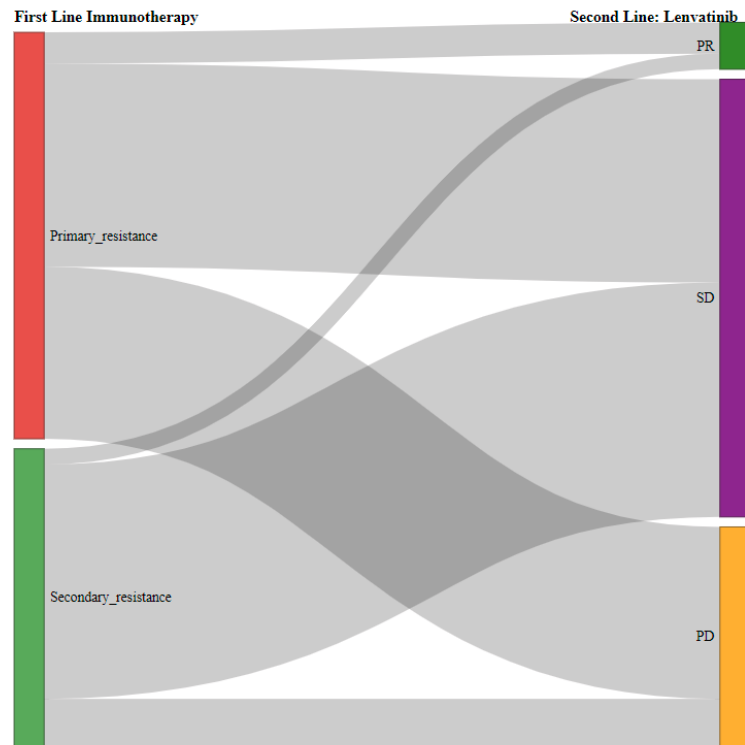


Fig. S5.

Sankey diagram of the illustrates patient flow from first line A+B to second line (A) lenvatinib or (B) sorafenib.

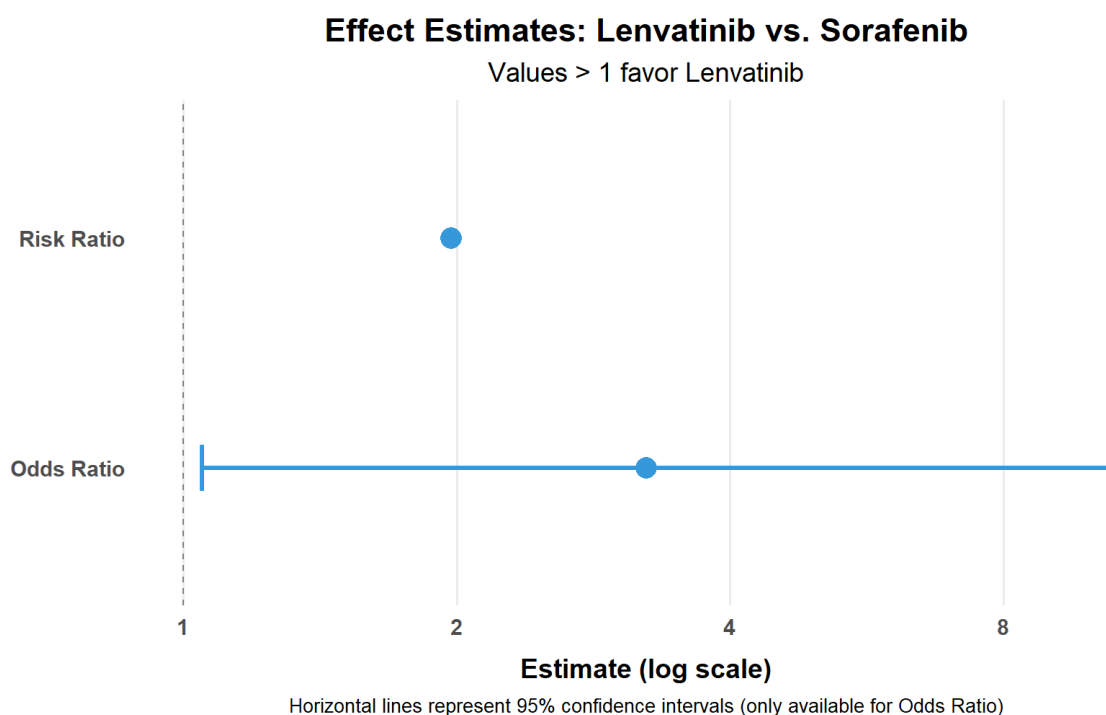


Fig. S6.
Effect Estimates of lenvatinib vs. sorafenib.

Table S1.
Baseline characteristics in PSM population.

Variable		Lenvatini b	Sorafeni b	p
n		59	83	
Center (%)	eastern	47 (79.7)	60 (72.3)	0.420
	western	12 (20.3)	23 (27.7)	
Age (mean (SD))		60.50 (11.33)	60.89 (10.19)	0.832
Sex (%)	Female	13 (22.0)	17 (20.7)	1.000
	Male	46 (78.0)	65 (79.3)	
BMI (mean (SD))		24.30 (4.02)	24.79 (3.98)	0.467
ECOG diagnosis (%)	0	27 (45.8)	23 (27.7)	0.041
	1	32 (54.2)	60 (72.3)	

Variable		Lenvatini b	Sorafenib b	p
HCC Etiology (%)	Non viral	12 (20.3)	29 (34.9)	0.088
	Viral	47 (79.7)	54 (65.1)	
Cirrhosis (%)	No	9 (15.3)	27 (32.5)	0.037
	Unknown	1 (1.7)	0 (0.0)	
	Yes	49 (83.1)	56 (67.5)	
Diabetes (%)	No	37 (92.5)	67 (88.2)	0.550
	Unknown	1 (2.5)	1 (1.3)	
	Yes	2 (5.0)	8 (10.5)	
Ascites (%)	No	52 (88.1)	61 (73.5)	0.030
	Previous and now resolved	1 (1.7)	0 (0.0)	
	Yes	6 (10.2)	22 (26.5)	
Number of nodules (%)	2-3	11 (20.0)	15 (18.3)	0.887
	Multifocal	34 (61.8)	54 (65.9)	
	Single	10 (18.2)	13 (15.9)	
BCLC (%)	Stage A	2 (3.4)	4 (4.8)	0.089
	Stage B	18 (30.5)	12 (14.5)	
	Stage C	32 (54.2)	60 (72.3)	
	Unknown	7 (11.9)	7 (8.4)	
Neoplastic PVT (%)	No	45 (76.3)	60 (72.3)	0.735
	Yes	14 (23.7)	23 (27.7)	
Extrahepatic spread (%)	No	25 (42.4)	37 (44.6)	0.929
	Yes	34 (57.6)	46 (55.4)	
AFP grade (%)	<400 ng/mL	36 (61.0)	52 (62.7)	0.982
	≥400 ng/mL	23 (39.0)	31 (37.3)	
NLR grade (%)	high	28 (47.5)	32 (38.6)	0.376
	low	31 (52.5)	51 (61.4)	
ALBI grade (%)	grade 1	34 (57.6)	42 (50.6)	0.512
	grade 2	25 (42.4)	41 (49.4)	
Prior locoregional treatments (%)	No	11 (22.9)	9 (13.6)	0.300
	Yes	37 (77.1)	57 (86.4)	

Variable		Lenvatini b	Sorafenib b	p
Type of resistance to immunotherapy (%)	Primary resistance	35 (59.3)	55 (66.3)	0.503
	Secondary resistance	24 (40.7)	28 (33.7)	
BR immunotherapy (%)	PD	18 (30.5)	31 (37.3)	0.264
	PR	13 (22.0)	13 (22.0)	
	SD	28 (47.5)	42 (50.6)	

Table S2.

Univariate and multivariate Cox regression analyses of factors associated with OS in PSM population.

		Univariate analysis			Multivariate analysis		
Variable	Level	HR	CI	P value	HR	CI	P value
II line treatment	Sorafenib vs Lenvatinib	1.55	1.03-2.33	0.034	1.85	1.22-2.82	0.003
Sex	Male vs Female	0.70	0.44-1.12	0.14			
ECOG	1 vs 0	1.22	0.79-1.89	0.37			
Age	(median)	1.03	0.69-1.53	0.87			
Etiology	Viral vs Non Viral	1.37	0.87-2.16	0.17			
Cirrhosis	Yes vs No	0.67	0.43-1.04	0.07			
Ascites	Yes vs No	1.16	0.71-1.90	0.54			
Number of nodules	Single vs Multiple	0.67	0.37-1.24	0.21			
Neoplastic PVT	Yes vs No	1.85	1.19-2.88	0.006	1.77	1.13-2.77	0.011
Extrahepatic spread	Yes vs No	1.08	0.72-1.60	0.71			
AFP grade	≥400 vs < 400	1.72	1.16-2.56	0.007	2.01	1.34-3.03	<0.001
NLR grade	NLR low vs high	0.60	0.421-0.89	0.013	0.56	0.37-0.84	0.005

ALBI grade	2-3 vs 1	1.11	0.75-1.64	0.60
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Table S3.

Distribution of treatment across the years

YEAR	LENVATINIB	SORAFENIB	TOTAL
2019	3	1	4
2020	6	9	15
2021	36	46	82
2022	48	21	69
2023	16	25	41
2024	9	1	10

Test di Mann-Whitney p-value: 0.1267

Table S4.

Baseline characteristics at initiation of second-line treatment, stratified by treatment group

Variable	Lenvatinib (n = 125)	Sorafenib (n = 104)	p-value
ECOG PS, n (%):			0.003
0	43 (34.4)	18 (17.3)	
1	75 (60.0)	75 (72.1)	
Missing	7 (5.6)	11 (10.6)	
Child-Pugh at Second-line, n (%):			0.034
Class A	13 (10.4)	24 (23.1)	
Class B	5 (4.0)	4 (3.8)	
Missing	107 (85.6)	76 (73.1)	
Ascites, n (%):			0.232
No	51 (40.8)	42 (40.4)	
Yes	6 (4.8)	1 (1.0)	
Missing	68 (54.4)	61 (58.7)	
AFP level, n (%):			0.399

<400 ng/mL	31 (24.8)	28 (26.9)	
≥400 ng/mL	18 (14.4)	21 (20.2)	
Missing	76 (60.8)	55 (52.9)	
NLR grade, n (%):			0.390
High	52 (41.6)	41 (39.4)	
Low	65 (52.0)	51 (49.0)	
Missing	8 (6.4)	12 (11.5)	
ALBI grade, n (%):			0.158
Grade 1	56 (44.8)	39 (37.5)	
Grade 2	64 (51.2)	53 (51.0)	
Grade 3	2 (1.6)	6 (5.8)	
Missing	3 (2.4)	6 (5.8)	
Progression pattern – New intrahepatic lesion, n (%):			0.300
Present	22 (17.6)	25 (24.0)	
Absent	103 (82.4)	79 (76.0)	
Progression pattern – Intrahepatic growth of pre-existing lesions, n (%):			0.514
Present	62 (49.6)	57 (54.8)	
Absent	63 (50.4)	47 (45.2)	
Progression pattern – New extrahepatic lesion, n (%):			1.000
Present	16 (12.8)	13 (12.5)	
Absent	109 (87.2)	91 (87.5)	
Progression pattern – Extrahepatic growth of pre-existing lesions, n (%):			0.942
Present	38 (30.4)	33 (31.7)	
Absent	87 (69.6)	71 (68.3)	
Progression pattern – New vascular invasion, n (%):			1.000

Present	4 (3.2)	3 (2.9)	
Absent	121 (96.8)	101 (97.1)	

ECOG PS: Eastern Cooperative Oncology Group Performance Status; AFP level: Alpha-fetoprotein level; NLR grade: Neutrophil-to-Lymphocyte Ratio grade; ALBI grade: Albumin-Bilirubin grade.