Supplementary Material: Sorafenib Versus Lenvatinib-Based Sequential Systemic Therapy for Advanced Hepatocellular Carcinoma: A Real-World Analysis

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Supplemental Materials

Table S1. Baseline characteristics of patients with only one vs. two or more systemic therapies.

	1 Systemic Therapy (*n* = 80)	**>1 Systemic Therapy (*n* = 84)**	***p* Value**
Age (years), median (IQR)	66 (59–73)	68.52 (61.25–73)	0.3
Male gender, *n* (%)	66 (82.5)	74 (88)	0.3
ECOG PS			0.052
0, *n* (%)	37 (47)	55 (67)	
1, *n* (%)	38 (48)	26 (32)	
2, *n* (%)	3 (4)	1 (1)	
3, *n* (%)	1 (1)	0 (0)	
Liver cirrhosis, *n* (%)	62 (78)	61 (73)	0.5
Child-Pugh score			**0.01**
CPS A, *n* (%)	60 (76)	72 (91)	
CPS B, *n* (%)	19 (24)	7 (9)	
CPS C, *n* (%)	0	0	
ALBI grade			0.051
1, *n* (%)	27 (34)	38 (50)	
2, *n* (%)	49 (62)	36 (47)	
3, *n* (%)	3 (4)	2 (3)	
Bilirubin (mg/dl), median (IQR)	1.2 (0.7–1.9)	0.8 (0.6–1.4)	0.2
Albumin (g/dl), median (IQR)	3.8 (3.4–4.2)	4.0 (3.6–4.3)	0.053
MELD Score, median (IQR)	9 (7–12)	7 (6–10)	**0.04**
Ascites, *n* (%)	25 (31)	15 (18)	0.062
Refractory ascites, *n* (%)	5 (6)	2 (2)	0.1
Esophageal varices, *n* (%)	29 (37)	30 (37)	0.9
Tumor stage			0.6
BCLC A, *n* (%)	0 (0)	1 (1)	
BCLC B, *n* (%)	28 (35)	29 (35)	
BCLC C, *n* (%)	52 (65)	53 (64)	
Macrovascular invasion, N (%)	30 (38)	19 (23)	**0.04**
Prior locoregional therapy, N (%)	44 (55)	62 (74)	**0.01**

IQR: interquartile range, ECOG PS: Eastern Cooperative Oncology Group performance status, CPS: Child-Pugh score, ALBI grade: albumin-bilirubin grade, MELD: model of end stage liver disease, BCLC: Barcelona Clinic Liver Cancer.

Table S2. Univariate and multivariate analysis using Cox regression.

Parameter	Univariate Analysis		Multivariate Analysis	
	p Value	Hazard Ratio (95% CI)	*p* value	Hazard Ratio (95% CI)
1st-line Sorafenib vs. Lenvatinib	0.99	1.0 (0.689–1.452)	0.398	1.194 (0.791–1.802)
ECOG PS 1 vs. 0	0.0002	2.075 (1.415–3.042)	0.001	2.018 (1.333–3.055)
Sequential therapy no vs. yes	0.001	1.879 (1.282–2.754)	0.032	1.557 (1.039–2.335)
ALBI grade 2 vs. 1	0.0001	2.489 (1.669–3.710)	0.0001	2.337 (1.511–3.613)
BCLC B vs BCLC C	0.293	1.226 (0.838–1.794)		
CPS B vs A	0.001	2.287 (1.421–3.679)	0.466	1.239 (0.696–2.204
Pretreatment no vs. yes	0.149	0.749 (0.507–1.109)		
Ascites	0.014	1.674 (1-108–2.528)		
Macrovascular invasion	0.006	1.739 (1.171–2.583)		

95% CI: 95% confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status, CPS: Child-Pugh score, ALBI grade: albumin-bilirubin grade, BCLC: Barcelona Clinic Liver Cancer.

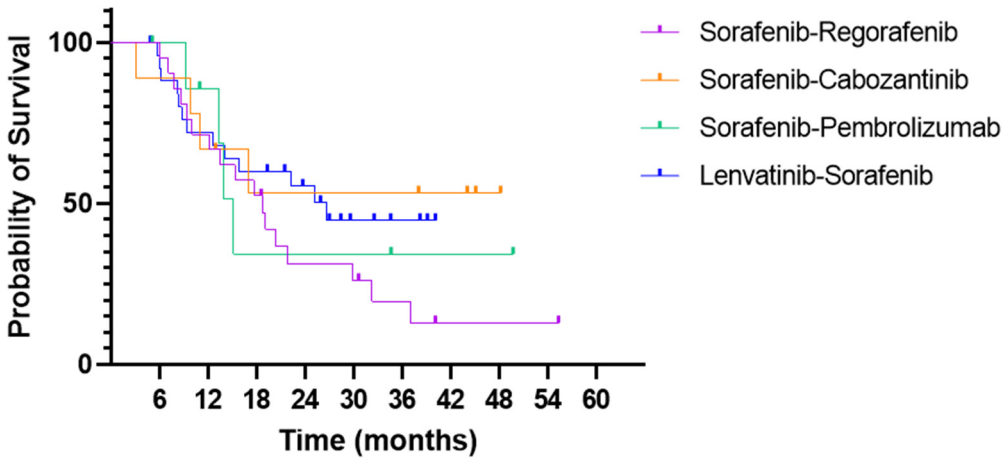

Figure S1. Kaplan Meier Curve of median overall survival (mOS) for patients with more than 1 therapy line with regard to the sequence of 1st and 2nd line therapy. The four most common sequences were analyzed. (mOS Sorafenib-Regorafenib 567 days; mOS Sorafenib-Cabozantinib undefined; mOS Sorafenib-Pembrolizumab 458 days; mOS Lenvatinib-Sorafenib 811 days; *p* value ns)

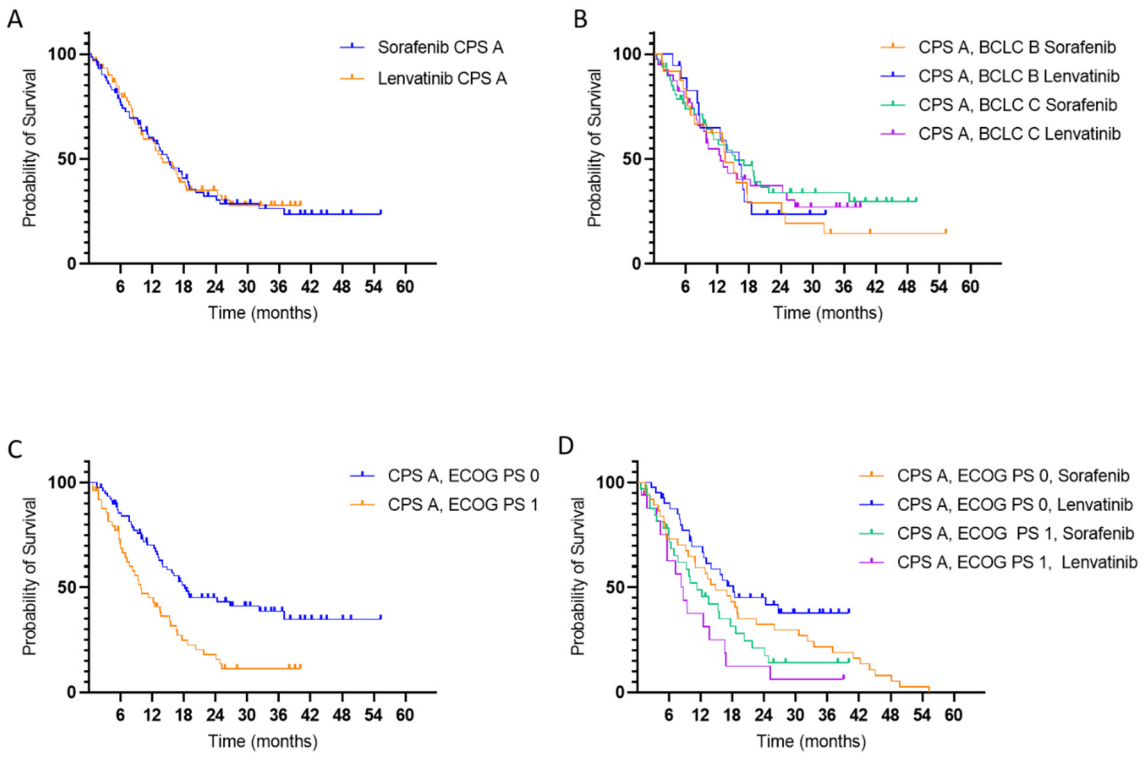

Figure S2. Kaplan-Meier Curves of median overall survival (mOS) in a subgroup-analysis including only patients presenting with preserved liver function (CPS A). (**A**) mOS was not significantly different regarding choice of 1st-line therapy. (**B**) mOS was not significantly different regarding choice of 1st-line and tumor stage. (**C**) Patients with CPS A and better performance status as indicated by ECOG-PS 0 showed significantly better mOS (mOS ECOG PS 0 554 days vs. mOS ECOG PS 1 298 days; *p* value 0.0003). (**D**) Patients with ECOG PS 1 show worse survival as compared to patients with ECOG PS 0 irrespective of choice of 1st-line therapy.

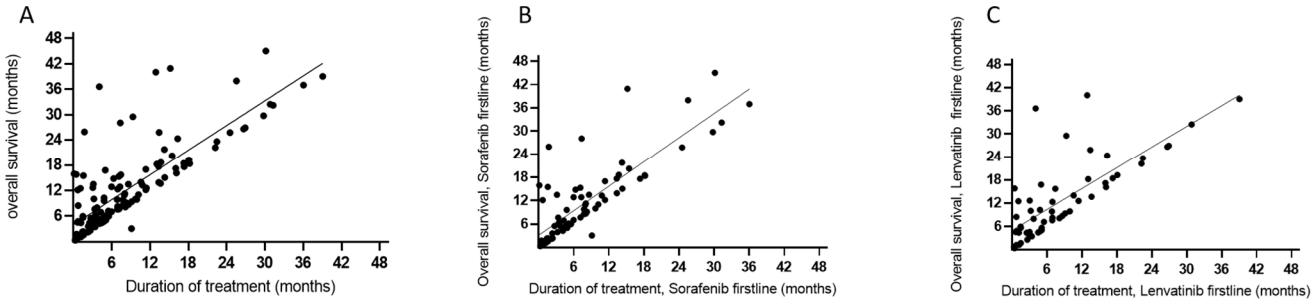

Figure S3. Correlation analysis between duration of entire TKI treatment and mOS. (**A**) whole cohort (r = 0.79, 95% CI 0.7231–0.8512, P value <0.0001); (**B**) Patients starting with Sorafenib as 1st-line (r = 0.76, 95% CI 0.6503–0.8496, *p* value <0.0001). (**C**) Patients starting with Lenvatinib as 1st-line (r = 0.78, 95% CI 0.6499–0.8678, *p* value <0.0001)

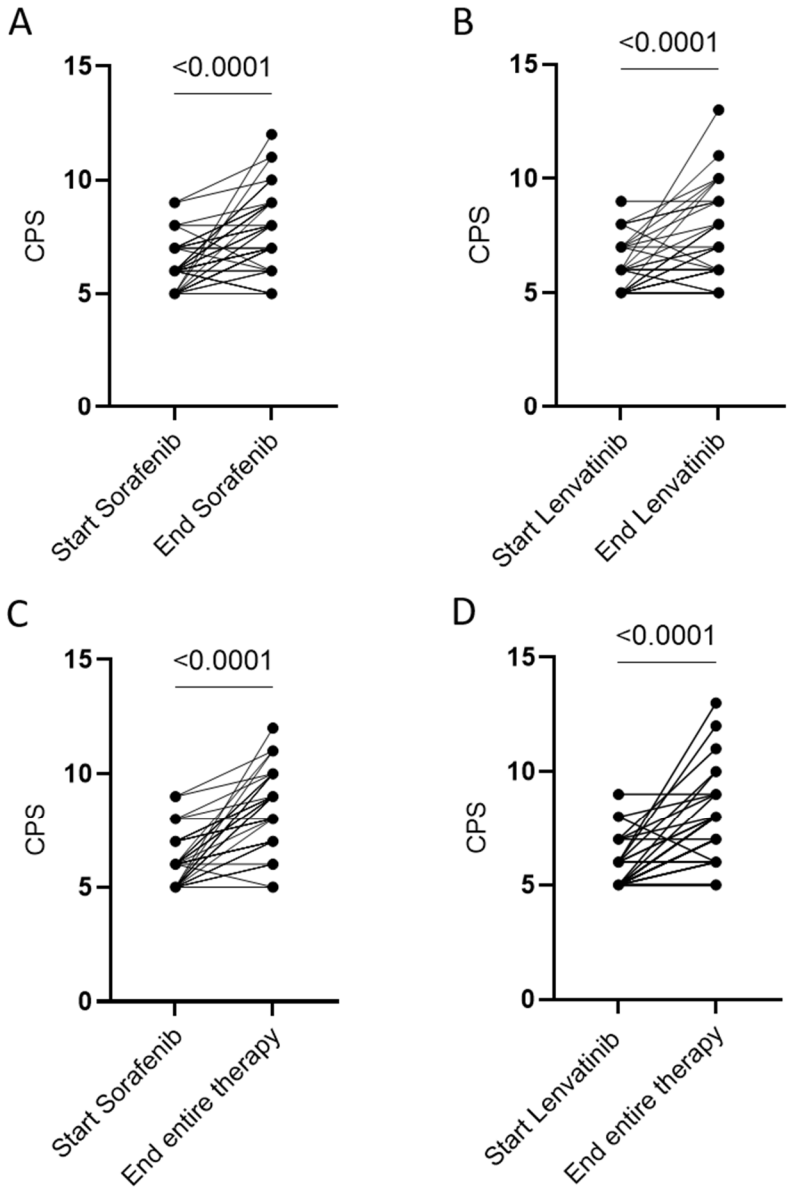

Figure S4 Liver function deterioration represented by differences in Child-Pugh score (**A**) after 1st line therapy with Sorafenib (mean of differences end-start 1.1 points; *p* value < 0.0001; median treatment duration 99.5 days); (**B**): after 1st line therapy with Lenvatinib (mean of differences end-start 0.9 points; *p* value < 0.0001; median treatment duration 120 days); (**C**): after the entire systemic therapy when started with Sorafenib (mean of differences end-start 2.1 points; *p* value <0.0001; median treatment duration 157.5 days); (**D**): after the entire systemic therapy when started with Lenvatinib (mean of differences end-start 1.9 points; *p* value < 0.0001; median treatment duration 155 days); Y-axis = Child-Pugh score (points)

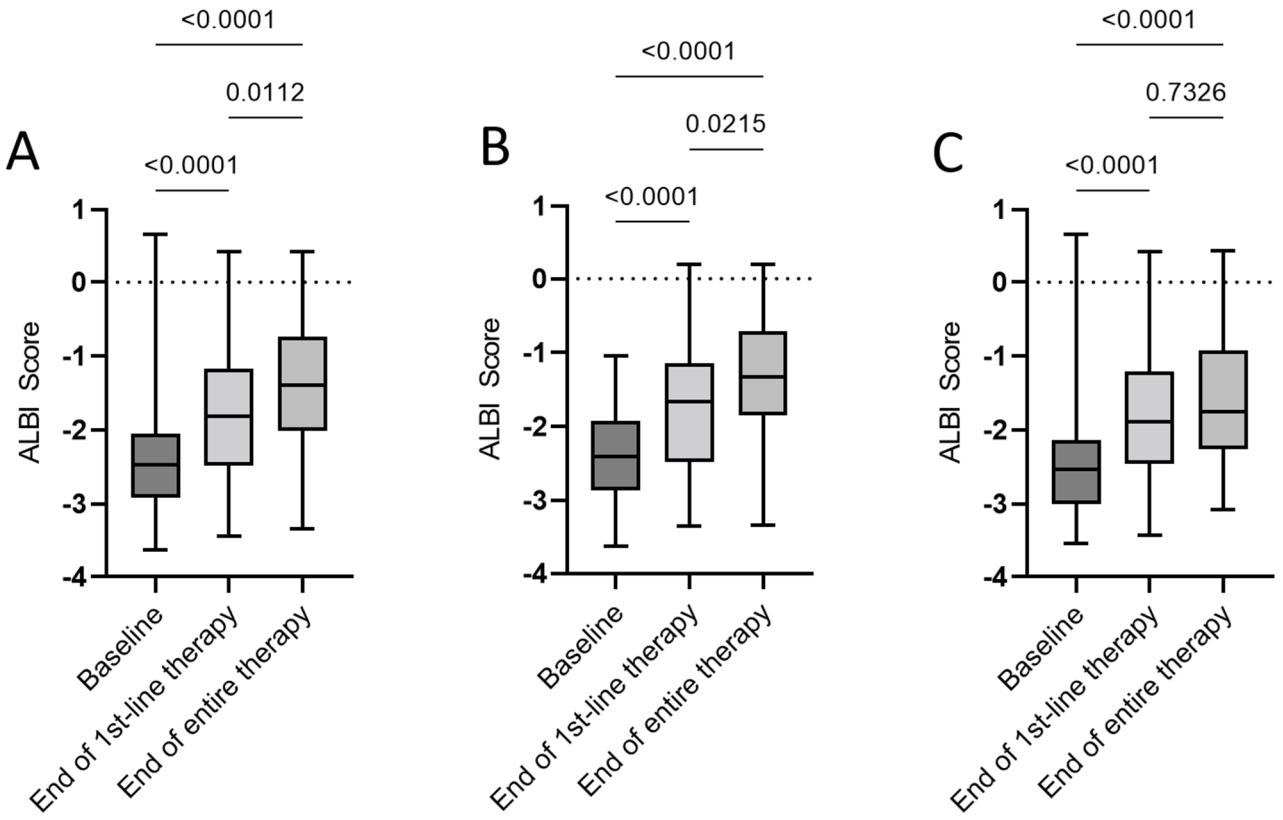

Figure S5. Liver function deterioration as represented by ALBI score. (**A**) Entire cohort. (**B**) Patients with Sorafenib as 1st-line. (**C**). Patients with Lenvatinib as 1st-line.