#175P: Lenvatinib versus sorafenib as second-line treatment post-atezolizumab plus bevacizumab for hepatocellular carcinoma: the LEVIATHAN Study.

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Introduction

Atezolizumab plus bevacizumab (A+B) is a standard of care first-line (1L) systemic therapy for unresectable hepatocellular carcinoma (uHCC). Uncertainty remains regarding optimal sequencing post A+B.

Methods

LEVIATHAN is a multicentre, prospective registry examining efficacy and survival outcomes of patients with HCC post A+B. From 1210 patients treated with 1L A+B between May 2018 and August 2024, 230 who progressed on A+B and received either lenvatinib (n=125, 54.3%) or sorafenib (n=105, 45.7%) as second-line (2L) treatment were included. Propensity score matching (PSM) was performed to mitigate selection bias, with matching based on independent predictors of overall survival (OS) and response characteristics to investigated treatment.

Table 1. Patient characteristics

Variable		Lenvatinib	Sorafenib	p
		125	105	
Center (%)	eastern	97 (77.6)	67 (63.8)	**0.031**
	western	28 (22.4)	38 (36.2)	
Age (mean (SD))		61.48 (11.10)	61.58 (10.51)	0.948
Sex (%)	Female	22 (17.6)	21 (20.2)	0.741
	Male	103 (82.4)	83 (79.8)	
ECOG diagnosis (%)	0	69 (55.2)	33 (31.4)	**<0.001**
	1	56 (44.8)	72 (68.6)	
HCC Etiology (%)	Non viral	36 (28.8)	37 (35.2)	0.367
	Viral	89 (71.2)	68 (64.8)	
Cirrhosis (%)	No	23 (18.5)	33 (31.4)	0.075
	Unknown	2 (1.6)	1 (1.0)	
	Yes	99 (79.8)	71 (67.6)	
Ascites (%)	No	109 (87.2)	79 (75.2)	**0.029**
	Previous and now resolved	1 (0.8)	0 (0.0)	
	Yes	15 (12.0)	26 (24.8)	
BCLC (%)	Stage A	9 (7.2)	7 (6.7)	**0.005**
	Stage B	35 (28.0)	15 (14.3)	
	Stage C	56 (44.8)	71 (67.6)	
	Unknown	25 (20.0)	12 (11.4)	
Neoplastic PVT (%)	No	100 (80.0)	76 (73.1)	0.280
	Yes	25 (20.0)	28 (26.9)	
Extrahepatic spread (%)	No	60 (48.0)	47 (44.8)	0.721
	Yes	65 (52.0)	58 (55.2)	
AFP level (%)	<400 ng/mL	78 (62.9)	66 (64.1)	0.964
	>=400 ng/mL	46 (37.1)	37 (35.9)	
NLR grade (%)	high	46 (38.3)	39 (40.2)	0.888
	low	74 (61.7)	58 (59.8)	
ALBI grade (%)	grade 1	92 (73.6)	49 (47.6)	**<0.001**
	grade 2	32 (25.6)	54 (52.4)	
	grade 3	1 (0.8)	0 (0.0)	
Type of resistance to immunotherapy (%)	Unknown	1 (0.8)	0 (0.0)	**0.016**
	Primary resistance	60 (49.2)	66 (68.0)	
	Secondary resistance	61 (50.0)	31 (32.0)	

Results

In the overall 2L study population, lenvatinib exposure was associated with longer median progression-free survival (PFS) (5.5 versus 2.6 months, HR 0.41, p<0.001) and OS (11.9 versus 7.4 months, HR 0.67, p=0.018) compared to sorafenib (Fig. 1A-B). When considering OS from the time of A+B initiation, the A+B-lenvatinib sequence achieved a median OS of 22.4 months versus 14.3 months for A+B-sorafenib (HR 0.54, p<0.001) (Fig. 1C).

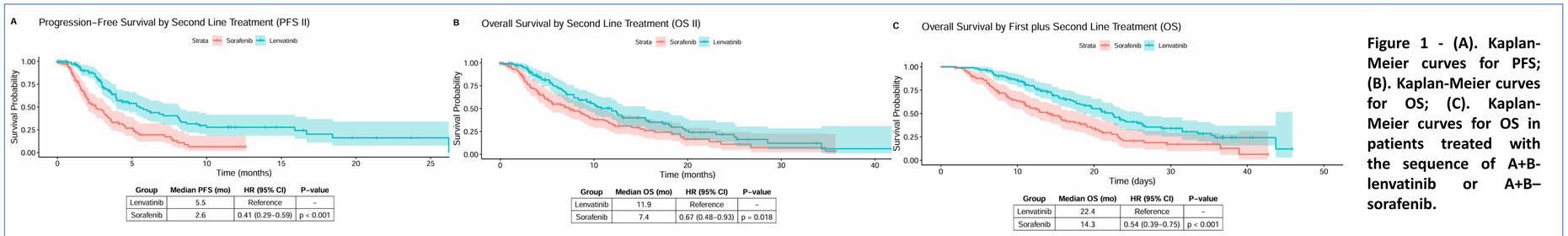

Figure 1 - (A). Kaplan-Meier curves for PFS; (B). Kaplan-Meier curves for OS; (C). Kaplan-Meier curves for OS in patients treated with the sequence of A+B-lenvatinib or A+B–sorafenib.

In PSM analyses, these differences remained significant, with median OS from 1L of 19.6 versus 13.9 months (HR 0.67, p=0.024) favouring lenvatinib (Fig. 2B). Notably, in patients with primary resistance to A+B, lenvatinib showed a superior disease control rate compared to sorafenib (57.7% vs 29.3%, p=0.025) (Fig. 4).

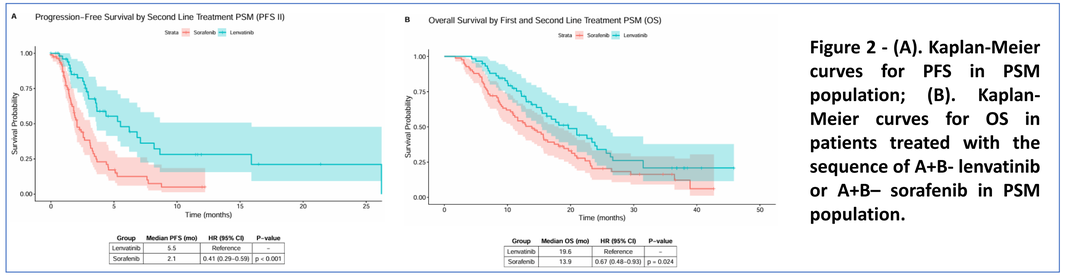

Figure 2 - (A). Kaplan-Meier curves for PFS in PSM population; (B). Kaplan-Meier curves for OS in patients treated with the sequence of A+B- lenvatinib or A+B– sorafenib in PSM population.

Multivariate analysis identified 2L treatment with lenvatinib, AFP ≤400 ng/ml, NLR <3, and absence of portal vein thrombosis as independent predictors of improved OS (Table 2).

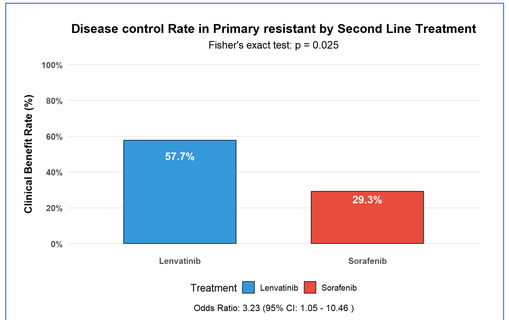

Figure 4 - Disease control rate with lenvatinib compared to sorafenib in primary resistance patient to A+B.

Table 2. Univariate and multivariate Cox regression analyses

		Univariate analysis			Multivariate analysis		
Variable	**Level**	**HR**	**CI**	**P_value**	**HR**	**CI**	**P value**
II line treatment	Sorafenib vs lenvatinib	1.92	1.36-2.70	<0.001	2.12	1.47-3.06	**<0.001**
Sex	Male vs Female	0.61	0.40-0.93	0.02	0.89	0.57-1.40	0.06
ECOG	1 vs 0	1.37	0.96-1.96	0.08			
Age	(median)	1.03	0.74-1.46	0.8			
Etiology	Viral vs Non Viral	1.30	0.88-1.93	0.2			
Cirrhosis	Yes vs No	0.77	0.53-1.13	0.2			
Ascites	Yes vs No	1.25	0.82-1.91	0.3			
Number of nodules	Single vs Multiple	0.82	0.50-1.34	0.4			
Neoplastic PVT	Yes vs No	1.69	1.14-2.50	0.008	1.64	1.10-2.46	**0.01**
Extrahepatic spread	Yes vs No	1.15	0.82-1.62	0.4			
AFP grade	>=400 vs < 400	1.83	1.30-2.59	<0.001	2.04	1.42-2.92	**<0.001**
NLR grade	NLR low vs high	0.60	0.42-0.85	0.004	0.59	0.41-0.85	**0.004**
ALBI grade	2-3 vs 1	1.41	0.99-2.03	0.054			

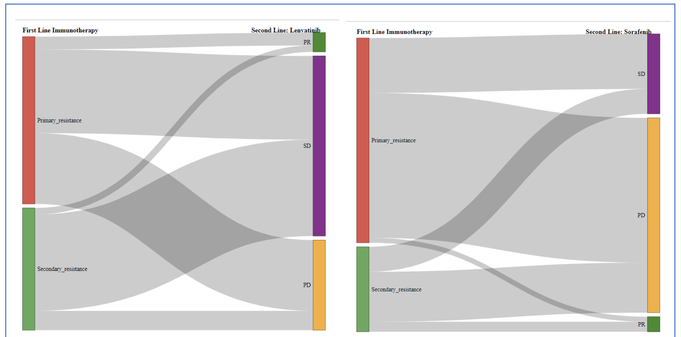

Figure 3 - Sankey diagram of the illustrates patient flow from first line A+B to second line (A) lenvatinib or (B) sorafenib.

Conclusions

The LEVIATHAN study suggests lenvatinib to be associated with improved outcomes compared to sorafenib as 2L treatment after A+B discontinuation in uHCC, including patients with refractory disease. Although observational in nature, these findings highlight the importance of optimized sequencing strategies in uHCC.

References

Finn RS, Qin S, Ikeda M et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020; 382 (20): 1894-1905;
Wu M, Fulgenzi CAM, D'Alessio A, Cortellini A, Celsa C, Manfredi GF, et al. Second-line treatment patterns and outcomes in advanced HCC after progression on atezolizumab/bevacizumab. JHEP Rep. 2025;7(2):101232.
Martirena A, Lombardi P, Pinato DJ, Rimassa L, Lamarca A. Systemic management of advanced HCC, 10.1016/j.esmogo.2025.100139, ESMO Gastrointestinal Oncology. 2025;7.

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