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

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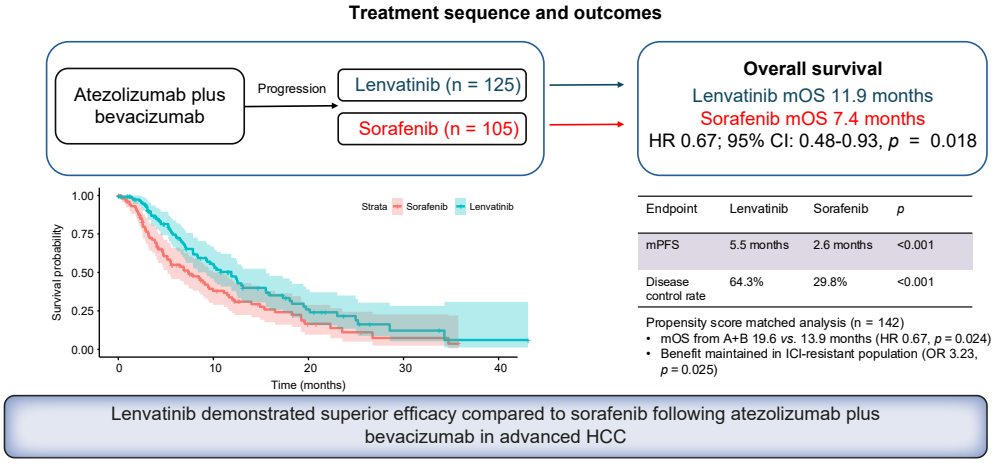
Graphical abstract



Highlights:

- Lenvatinib demonstrated superior OS compared to sorafenib as second-line therapy following atezolizumab +bevacizumab progression.
- Benefits persisted after propensity score matching and even in patients with primary resistance to immunotherapy.
- Multinational real-world data supports lenvatinib as the preferred second-line treatment option in advanced HCC.

Impact and implications:

Continuing active treatment after progression on frontline atezolizumab plus bevacizumab (A+B) can benefit patients with advanced hepatocellular carcinoma (HCC), but evidence to guide second-line therapy remains limited. The LEVIATHAN study addresses this gap by evaluating real-world outcomes in a large, prospective, multinational cohort treated with lenvatinib or sorafenib after A+B discontinuation. Our findings show that lenvatinib provides significantly longer progression-free and overall survival than sorafenib, even after adjusting for baseline imbalances with propensity scores. Lenvatinib also achieved higher disease control rates, including in patients with primary resistance to immunotherapy. These results challenge the assumption that all VEGFR-targeting TKIs are equivalent post-ICI and suggest lenvatinib may be superior to sorafenib following anti-VEGF–based immunotherapy. While prospective randomised trials are still needed, these real-world data offer valuable guidance for clinicians and help refine treatment sequencing in advanced HCC.

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Research article

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

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Background & Aims: Atezolizumab plus bevacizumab (A+B) is a standard first-line systemic therapy for unresectable hepatocellular carcinoma (HCC). However, optimal sequencing strategies after A+B failure remain undefined.

Methods: LEVIATHAN is a multicentre, observational study evaluating efficacy and survival outcomes in patients who progressed on A+B and subsequently received either lenvatinib or sorafenib as second-line therapy. Of 1,210 patients treated with first-line A+B between May 2018 and August 2024, 230 eligible patients were included (lenvatinib, n = 125 [54.3%]; sorafenib, n = 105 [45.7%]). Propensity score matching was applied to adjust for baseline imbalances, incorporating independent predictors of overall survival (OS) and response to prior treatment.

Results: In the overall second-line cohort, lenvatinib was associated with superior median progression-free survival (5.5 *vs.* 2.6 months, hazard ratio [HR] 0.41, p <0.001) and median OS (11.9 *vs.* 7.4 months, HR 0.67, p = 0.018) compared to sorafenib. From the start of A+B, the A+B-lenvatinib sequence achieved a median OS of 22.4 months *vs.* 14.3 months with A+B-sorafenib (HR 0.54, p <0.001). These differences persisted in the propensity score-matched cohort (median OS: 19.6 *vs.* 13.9 months, HR 0.67, p = 0.024). Multivariate analysis identified treatment with lenvatinib as an independent predictor of improved OS alongside alpha-fetoprotein ≤400 ng/ml, neutrophil-to-lymphocyte ratio <3, and absence of portal vein thrombosis.

Conclusions: The LEVIATHAN study supports lenvatinib as a more effective second-line option than sorafenib following A+B in unresectable HCC, including in patients with primary resistance to immunotherapy. While limited by the observational study design, these findings highlight the importance of treatment sequencing to optimise outcomes in advanced HCC.

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Introduction

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, with a dismal prognosis in patients with advanced or unresectable disease.[1] The introduction of immune checkpoint inhibitor (ICI) combinations has significantly reshaped the therapeutic landscape of this tumour, affording a median overall survival (OS) approaching 2 years[2] and long-term survivorship in a proportion of patients.[3–5] The phase III IMbrave150 trial established the combination of atezolizumab plus bevacizumab (A+B) as a standard first-line systemic therapy for unresectable HCC, demonstrating superior OS and progression-free survival (PFS) compared to sorafenib.[5,6] Whilst benefit from these highly effective therapies is confirmed by clinical trials[7] and routine practice,[8] some patients do not respond to treatment and others ultimately experience disease progression after a period of benefit, highlighting the urgent need to define optimal non-cross-resistant second-line treatment strategies.

Unlike first-line, where randomised clinical trials provide robust evidence to guide treatment selection, the optimal sequencing of therapies after A+B discontinuation remains undefined. Our group has previously demonstrated the benefit of tyrosine kinase inhibitors (TKI) in this disease setting.[9] However, agents with recognised activity in second-line including regorafenib, cabozantinib, and ramucirumab were evaluated in clinical trials that exclusively enrolled patients who had progressed on sorafenib rather than immunotherapy[10–12] or in phase II, non-randomised clinical trials.[13–15] As a result,

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there is no high-level evidence to guide treatment decisions after immunotherapy discontinuation and off-label use of therapies approved in the context of other sequencing strategies is dictated by physician preference, reimbursement and expected adverse event profile from the agents considered. In clinical practice, TKIs targeting vascular endothelial growth factor receptors (VEGFR), such as lenvatinib and sorafenib, remain widely used as second-line options after immunotherapy.[13–20] However, the mechanism of action of each agent is different and it is unclear whether VEGF pathway inhibition continues to lead to therapeutic benefit beyond first-line discontinuation.

Differing from sorafenib, lenvatinib is a pan-FGFR inhibitor, and FGF signalling inhibition may offer distinct advantages following ICI exposure.[21] The interplay between VEGF and FGF signalling in resistance to anti-angiogenic and immune-based therapies remains an area of active investigation, which may yield approaches to improve clinical outcomes in patients progressing after immunotherapy-based treatment. Clinically, while lenvatinib is non-inferior to sorafenib in extending the OS of treatment-naïve patients with unresectable HCC, its longer progression-free survival (PFS), as well as superior objective response rate and disease control rate (DCR), may offer particular benefit in patients discontinuing immunotherapy.[22] High-quality evidence to support the comparative efficacy of lenvatinib *vs*. sorafenib is sparse.

To address this knowledge gap, we designed LEVIATHAN, a multicentre, observational study evaluating survival outcomes in patients treated with A+B who subsequently received either sorafenib or lenvatinib as second-line therapy. Patient data were collected through the AB-real registry, allowing for a comprehensive assessment of treatment effectiveness and potential prognostic factors associated with patients' survival. By leveraging a large, multinational cohort, our findings seek to inform clinical decision-making and optimise treatment sequencing for patients with HCC who progress after first-line A+B therapy.

Patients and methods

LEVIATHAN is a multicentre, observational study designed to collect and describe response and survival outcomes in patients with HCC receiving lenvatinib or sorafenib as a second-line treatment following A+B discontinuation within the AB-real dataset.

Consecutive patients with unresectable HCC who received A+B as part of routine clinical care at 26 tertiary care centres across Europe, the USA and Asia between May 2018 and October 2024 were enrolled in the prospectively maintained AB-real database[8] and evaluated for eligibility to LEVIATHAN.

Eligibility criteria included all patients who were 18 years of age or older, had radiographic or histologic diagnosis of HCC according to the American Association for the Study of Liver Diseases criteria,[23] and had unresectable or advanced HCC based on BCLC (Barcelona Clinic Liver Cancer) criteria.[24] We identified patients who were treated with first-line A+B. From this population, we selected patients who had progression of disease or permanent discontinuation of A+B treatment; patients who discontinued due to adverse events or other non-progression-related causes were included only if radiological progression occurred prior to initiation of second-line therapy. Patients who died while on A+B therapy, those with Child-Pugh class B or C cirrhosis, and those who received combination treatments including anti-CTLA-4 agents, were excluded. Patients who underwent locoregional therapies (*e.g*. transarterial chemoembolisation, radiation) during A+B treatment, in the interval between A+B discontinuation and second-line therapy, or during TKI treatment were also excluded. Demographic, clinical, and biochemical characteristics were collected, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG-PS), BCLC stage, presence of cirrhosis, aetiology of liver disease, Child-Pugh score, and baseline blood tests.

A+B in first line and lenvatinib or sorafenib in second-line were administered according to the schedules reported in the SHARP study[25] and REFLECT study.[22] Treatment initiation followed multidisciplinary assessment and was administered per the local practice of each participating institution. Toxicity management, including dose modifications, was conducted in accordance with the summary of product characteristics for the agents considered. Treatment continued until disease progression or unacceptable toxicity.

Baseline tumour status was assessed using CT or MRI as clinically indicated. Tumour response was evaluated by treating investigators every 8–12 weeks and per local guidelines using the same imaging modalities as at baseline, following RECIST version 1.1.

PFS was defined as the time from treatment initiation to disease progression or death from any cause, whichever occurred first. PFS to first line was defined as the time from A+B treatment initiation to disease progression. PFS to second line was defined as the time from second-line treatment initiation to disease progression or death from any cause. OS was defined as the time from A+B initiation to death, while OS to second line was defined as the time from second-line initiation to death.

Baseline patient characteristics were reported as median (IQR) for continuous variables and as proportions (%) for categorical variables. The chi-squared and Mann-Whitney *U* tests were used to compare categorical and continuous variables, respectively. The Kaplan-Meier method was used to estimate median survival times with 95% CIs. Median survival estimates were compared using univariate Cox regression analysis, and variables with a p value <0.05 in the univariate model were included in the multivariate analysis. Univariate and multivariate Cox regression analyses were performed to assess the impact of baseline patient demographics and disease characteristics on OS.

To mitigate selection bias between patients receiving lenvatinib or sorafenib as second-line therapy, we performed a propensity score matching (PSM). Matching was based on independent predictors of OS identified in the multivariate analysis, best response to first-line treatment, and overall benefit from A+B therapy for primary *vs.* secondary resistance.[26] Primary and secondary resistance were defined accordingly to Society for Immunotherapy of Cancer criteria.[26] Primary resistance was defined as progressive disease or stable disease (SD) lasting less than 6 months. In contrast, secondary resistance was defined by complete response, partial response or SD lasting more than 6 months. Matching was conducted using a 1:2 ratio with a calliper of 0.15.

To evaluate treatment efficacy, we calculated the relative risk for DCR defined as the composite of complete response,

partial response and SD. The relative risk was computed as the ratio of the DCR in lenvatinib-treated patients to that in sorafenib-treated patients. The odds ratio for clinical benefit was calculated as the ratio of odds between the treatment groups. Statistical significance was assessed using Fisher's exact test, with p <0.05 considered statistically significant.

All statistical analyses were performed using R software (version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the institutional review board of each participating site.

Results

A total of 1,210 patients treated with A+B between May 2018 and October 2024 were identified in the AB-Real dataset and assessed for eligibility to LEVIATHAN. Of the 1,210 patients treated with A+B, 344 patients were excluded because they had ECOG-PS >2 or Child-Pugh other than A. In total, 636 patients were excluded either because they had received A+B as a second line or later treatment, had not yet experienced progression on A+B by data cut-off, or received a second-line treatment other than sorafenib or lenvatinib. The remaining 230 patients who were alive after progression on A+B were included in the final analysis (Fig. 1).

Patient characteristics

Baseline characteristics of the overall cohort are shown in Table 1. At the initiation of the first line with A+B, patients had a median age of 61.5 (standard deviation 10.8) years and were predominantly male (81.2%). Most patients had BCLC stage C (55.2%), ALBI grade 1 (61.8%) and a neutrophil-to-lymphocyte ratio (NLR) <3 (60.8%). Compared to those who received sorafenib, patients treated with lenvatinib had better ECOG-PS, a lower incidence of ascites, a more favourable BCLC stage, and better ALBI grade at the time of diagnosis. Patients treated at Eastern centres were also more likely to receive lenvatinib than sorafenib as second-line therapy (Table 1).

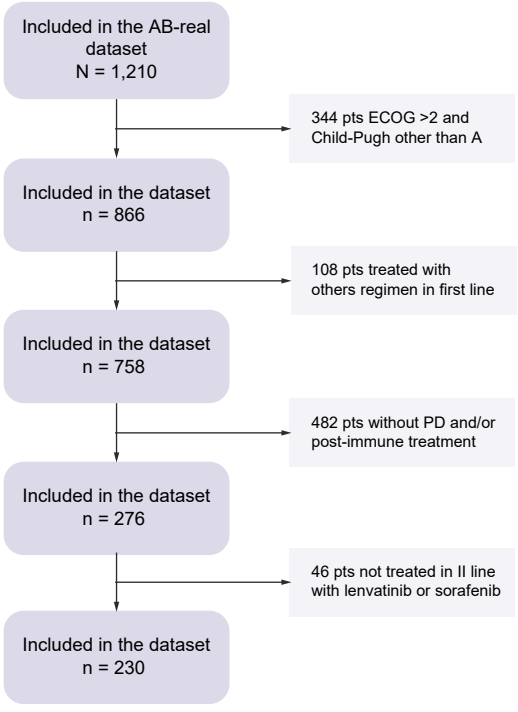


Fig. 1. Patient flow. ECOG, Eastern Cooperative Oncology Group.

First-line treatment

After a median follow-up of 29.5 months (95% CI 25.1-34.2) for OS, the median PFS (mPFS) of A+B was 4.2 months (95% CI 3.8-5), while the median OS (mOS) was 18.6 months (95% CI 15.7-20.99) in the entire cohort of patients. The DCR associated with A+B was 68.4%. Reasons for permanent A+B discontinuation included radiological progression (n = 192), clinical deterioration (n = 6), toxicity (n = 15), others and/or unknown (n = 16).

Within the analysed cohort, 125 patients (54.3%) received lenvatinib, while 105 patients (45.7%) received sorafenib after progression on A+B (Table 1). Compared to patients who received sorafenib, those who continued with lenvatinib after A+B discontinuation had a lower ALBI score (ALBI grade 1: 73.6% *vs.* 47.6%, respectively, p <0.001) and BCLC stage (BCLC A+B: 28.7% *vs.* 21% respectively, p = 0.005). In addition, patients treated with lenvatinib had achieved a higher proportion of disease control whilst on A+B compared to those treated with sorafenib in second line (81.4% *vs.* 53.4%, respectively p <0.001) (Table 1). No substantial differences in adverse events during first-line treatment were observed between patients subsequently treated with lenvatinib or sorafenib (Fig. S1A and B).

Second-line treatment

In the overall cohort of patients treated with lenvatinib or sorafenib as second-line treatment, the mPFS was 3.6 months (95% CI 3.15-4.8), while mOS from second line was 9.32 months (95% CI 7.82-11.89). In unmatched analyses, patients treated with lenvatinib achieved a superior mPFS of 5.5 months (95% CI, 3.97–8.2) compared with 2.6 months (95% CI, 2.03–3.45) in the sorafenib group (HR 0.41; 95% CI, 0.29–0.59; p <0.001). Similarly, mOS from second line was 11.9 months (95% CI 9.23-15.54) in the lenvatinib group *vs.* 7.4 months (95% CI 5.16-9.95) in the sorafenib group (0.67; 95% CI 0.48-0.93, p = 0.018, Fig. 2).

To evaluate the survival outcomes associated with AB +sorafenib *vs.* AB+lenvatinib sequencing strategies, we compared estimates calculated from the time of A+B initiation.

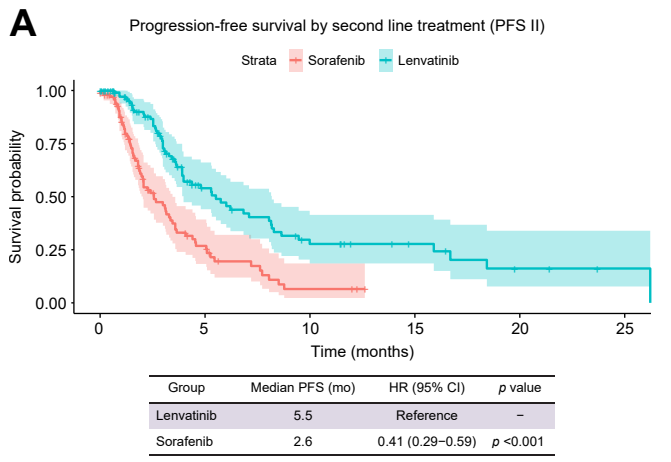
Patients who received lenvatinib after A+B achieved an overall mOS from the first line of 22.4 months (95% CI 18.63-26.31), whereas those treated with sorafenib after A+B had an overall mOS from the first line of 14.3 months (95% CI 11.17-18.95; HR 0.54; 95% CI 0.39-0.75, p <0.001, Fig. 2). In patients who were evaluable for response (164, 65.5%), lenvatinib was also associated with a better control of the disease, with a lower rate of progressive disease as best response compared to sorafenib (29.8% *vs.* 64.3%, p <0.001) (Fig. S2).

On univariate Cox regression analysis, alpha-fetoprotein (AFP) level ≤400 ng/ml, second-line treatment with lenvatinib, NLR low, absence of portal vein thrombosis (PVT), ALBI grade 1 and male sex were associated with improved mOS from the

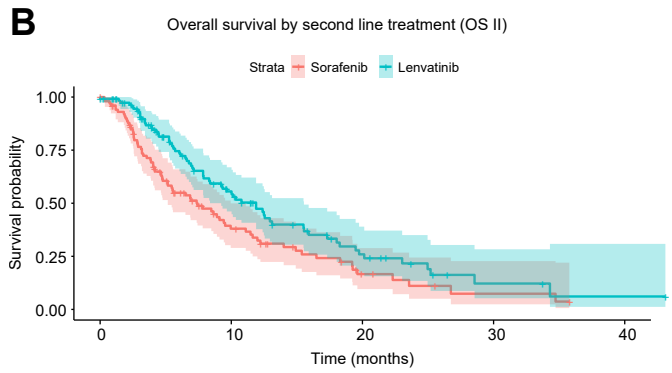
Table 1. Baseline characteristics of patients treated with lenvatinib or sorafenib after atezolizumab-bevacizumab.

Variable	Total	Lenvatinib	Sorafenib	*p* values
N	230	125	105	
Centre (%)				
Eastern	164 (71.3)	97 (77.6)	67 (63.8)	**0.031**
Western	66 (28.7)	28 (22.4)	38 (36.2)	
Age (mean [standard deviation])	61.53 (10.80)	61.48 (11.10)	61.58 (10.51)	0.948
Sex (%)				
Female	43 (18.8)	22 (17.6)	21 (20.2)	0.741
Male	186 (81.2)	103 (82.4)	83 (79.8)	
BMI (mean [standard deviation])	24.77 (4.06)	24.62 (3.91)	24.95 (4.24)	0.548
ECOG diagnosis (%)				
0	102 (44.3)	69 (55.2)	33 (31.4)	**<0.001**
1	128 (55.7)	56 (44.8)	72 (68.6)	
HCC etiology (%)				
Non-viral	73 (31.7)	36 (28.8)	37 (35.2)	0.367
Viral	157 (68.3)	89 (71.2)	68 (64.8)	
Cirrhosis (%)				
No	56 (24.5)	23 (18.5)	33 (31.4)	0.075
Unknown	3 (1.3)	2 (1.6)	1 (1.0)	
Yes	170 (74.2)	99 (79.8)	71 (67.6)	
Diabetes (%)				
No	161 (89.4)	74 (89.2)	87 (89.7)	0.990
Unknown	2 (1.1)	1 (1.2)	1 (1.0)	
Yes	17 (9.4)	8 (9.6)	9 (9.3)	
Ascites (%)				
No	188 (81.7)	109 (87.2)	79 (75.2)	**0.029**
Previous and now resolved	1 (0.4)	1 (0.8)	0 (0.0)	
Yes	41 (17.8)	15 (12.0)	26 (24.8)	
Number of nodules (%)				
2-3	52 (24.2)	32 (28.3)	20 (19.6)	0.312
Multifocal	127 (59.1)	64 (56.6)	63 (61.8)	
Single	36 (16.7)	17 (15.0)	19 (18.6)	
BCLC (%)				
Stage A	16 (7.0)	9 (7.2)	7 (6.7)	**0.005**
Stage B	50 (21.7)	35 (28.0)	15 (14.3)	
Stage C	127 (55.2)	56 (44.8)	71 (67.6)	
Unknown	37 (16.1)	25 (20.0)	12 (11.4)	
Neoplastic PVT (%)				
No	176 (76.9)	100 (80.0)	76 (73.1)	0.280
Yes	53 (23.1)	25 (20.0)	28 (26.9)	
Extrahepatic spread (%)				
No	107 (46.5)	60 (48.0)	47 (44.8)	0.721
Yes	123 (53.5)	65 (52.0)	58 (55.2)	
AFP level (%)				
<400 ng/ml	144 (63.4)	78 (62.9)	66 (64.1)	0.964
≥400 ng/ml	83 (36.6)	46 (37.1)	37 (35.9)	
NLR grade (%)				
High	85 (39.2)	46 (38.3)	39 (40.2)	0.888
Low	132 (60.8)	74 (61.7)	58 (59.8)	
ALBI grade (%)				
1	141 (61.8)	92 (73.6)	49 (47.6)	**<0.001**
2	86 (37.7)	32 (25.6)	54 (52.4)	
3	1 (0.4)	1 (0.8)	0 (0.0)	
Prior locoregional treatments (%)				
No	34 (18.8)	19 (19.4)	15 (18.1)	0.972
Yes	147 (81.2)	79 (80.6)	68 (81.9)	
Type of resistance to immunotherapy (%)				
Unknown	1 (0.5)	1 (0.8)	0 (0.0)	0.016
Primary resistance	126 (57.5)	60 (49.2)	66 (68.0)	
Secondary resistance	92 (42.0)	61 (50.0)	31 (32.0)	
BR immunotherapy (%)				
CR	5 (2.2)	5 (4.1)	0 (0.0)	**<0.001**
NE	8 (3.5)	1 (0.8)	7 (6.7)	
PD	64 (28.1)	22 (17.9)	42 (40.0)	
PR	39 (17.1)	28 (22.8)	11 (10.5)	
SD	112 (49.1)	67 (54.5)	45 (42.9)	

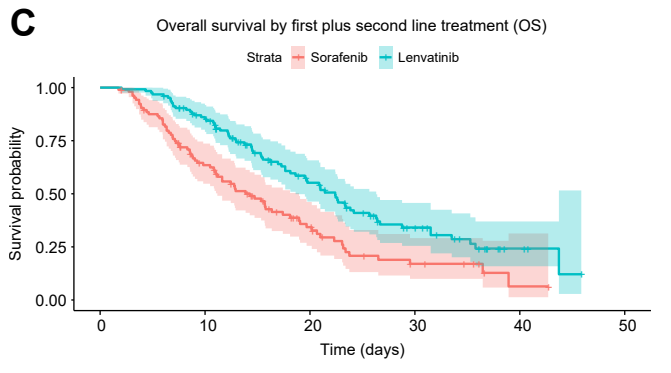
AFP, alpha-fetoprotein; BR, best response; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
Continuous variables are presented as means with standard deviation and compared using the independent samples *t* test. Categorical variables are expressed as counts and percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. An alpha level of 0.05 was considered statistically significant.



Group	Median PFS (mo)	HR (95% CI)	*p* value
Lenvatinib	5.5	Reference	–
Sorafenib	2.6	0.41 (0.29–0.59)	*p* <0.001



Group	Median OS (mo)	HR (95% CI)	*p* value
Lenvatinib	11.9	Reference	–
Sorafenib	7.4	0.67 (0.48–0.93)	*p* = 0.018



Group	Median OS (mo)	HR (95% CI)	*p* value
Lenvatinib	22.4	Reference	–
Sorafenib	14.3	0.54 (0.39–0.75)	*p* <0.001

Fig. 2. Kaplan-Meier curves for PFS and OS in patients treated with lenvatinib or sorafenib as second-line therapy after A+B. (A). Kaplan-Meier curves for PFS in patients treated with lenvatinib or sorafenib as second-line therapy after A+B; (B). Kaplan-Meier curves for OS in patients treated with lenvatinib or sorafenib as second line after A+B; (C). Kaplan-Meier curves for OS in patients treated with the sequence of A+B- lenvatinib or A+B– sorafenib. HRs, 95% CIs, and *p* values were calculated using Cox proportional hazards models. A two-sided alpha level of 0.05 was considered statistically significant. HRs, hazard ratios; OS, overall survival; PFS, progression-free survival.

first line. On multivariate analysis, second-line treatment with lenvatinib, AFP level ≤400 ng/ml, NLR <3 and absence of PVT remained independent predictors of a better OS outcome (Table 2).

Outcomes in the propensity score-matched cohort

Due to the imbalance in baseline characteristics between sorafenib and lenvatinib recipients and the observational, non-randomised nature of this study, we performed a PSM analysis to mitigate the risk of selection bias in influencing survival outcomes. Groups were matched based on independent predictors of OS identified in the multivariate analysis, best response to first-line treatment, and overall benefit from A+B therapy for primary *vs*. secondary resistance. The baseline features of the matched patient population are presented in Table S1.

In the PSM population, mPFS to second line was 5.5 in the levantinib group compared to 2.1 months in sorafenib group (HR 0.41, 95% CI 0.29-0.59, *p* <0.001) (Fig. 3). Notably, the AB +lenvatinib and AB+sorafenib matched groups did not differ in terms of median PFS to A+B (4.1 *vs.* 3.4 months, respectively; HR 0.8, 95% CI 0.54-1.07, *p* = 0.1) (Fig. S3). mOS from the first line was also significantly improved with the lenvatinib treatment strategy: 19.6 (95% CI 15.4-25.6) months for AB +lenvatinib *vs.* 13.9 (95% CI 10.8-18.1) months for AB +sorafenib (HR 0.67, 95% CI 0.48-0.93, *p* = 0.024) (Fig. 3). Lenvatinib exposure after A+B discontinuation was associated with a superior radiological outcome compared to sorafenib. In patients who were evaluable for radiologic response (n = 103, 72.5% of the PSM population), lenvatinib was associated with better DCR than sorafenib (68.9% *vs.* 32.8%, *p* <0.001) (Fig. S4).

In further analyses, we assessed whether characteristics of response to lenvatinib and sorafenib depended on whether patients were primary resistant to first-line immunotherapy (*i.e.* those achieving progressive disease as best overall response to A+B or short-lived SD <6 months). In this small sub-group (n = 57, 40.1% of the PSM population), lenvatinib exposure after A+B was associated with a statistically significant improvement in DCR compared to sorafenib. Lenvatinib achieved a higher DCR than sorafenib (57.7% *vs.* 29.3%, *p* = 0.025), with an odds ratio of 3.23 (95% CI 1.05–10.46), indicating a significantly greater likelihood of disease control (Figs 4, and S5, S6).

Finally, we looked at the features contributing to survival in the PSM-refined population using uni- and multivariable Cox regression models. Exposure to second-line treatment with lenvatinib, baseline AFP levels ≤400 ng/ml, NLR <3 and absence of PVT were all independently associated with improved mOS (Table S2).

Discussion

The introduction of immunotherapy combinations in clinical practice has significantly transformed the therapeutic landscape of unresectable HCC,[27,28] revolutionising first-line treatment paradigms while leaving uncertainty regarding subsequent treatment strategies. Current second-line options were established in the sorafenib era and the optimal treatment sequence following progression on A+B remains undefined. Evidence from HCC and other malignancies, including colorectal cancer, suggests that TKIs following bevacizumab-based therapy may continue to provide clinical benefit across lines of therapy, underscoring the need to identify the most effective therapeutic sequences in HCC.[13–15,18,29,30]

Table 2. Univariate and multivariate Cox regression analyses of factors associated with OS.

		Univariate analysis			Multivariate analysis		
Variable	**Level**	**HR**	**95% CI**	***p* values**	**HR**	**95% CI**	***p* values**
Second-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			

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PVT, portal vein thrombosis. Results are presented as HR with 95% CI. Multivariate analysis was conducted including variables with *p* value <0.05 in univariate analysis. An alpha level of 0.05 was considered statistically significant. Statistically significant *p* values are highlighted in bold.

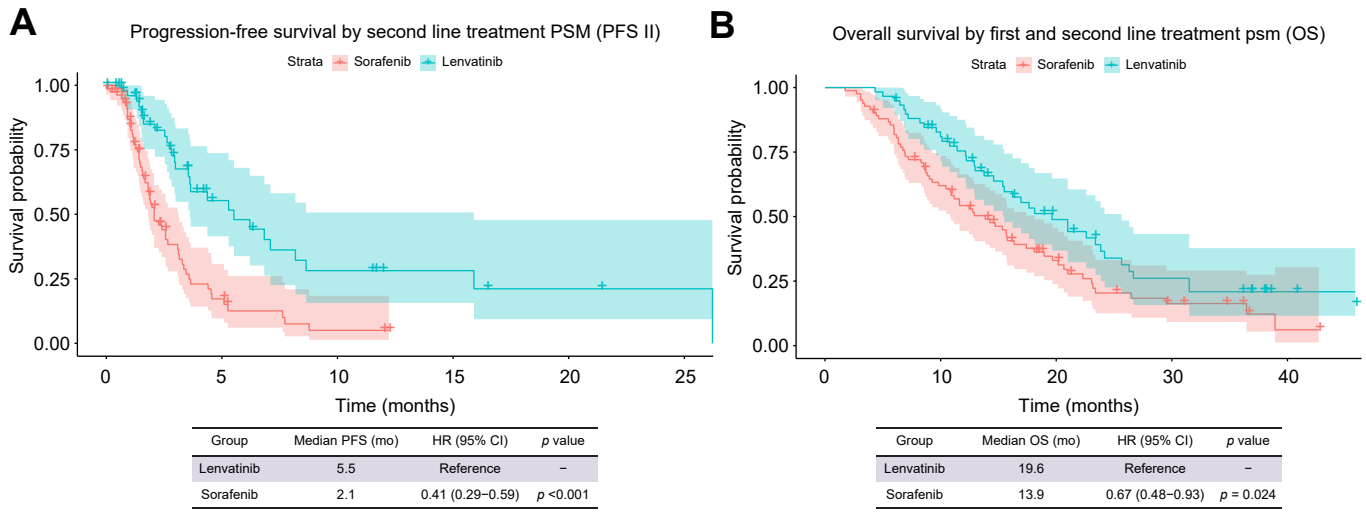


Fig. 3. Kaplan-Meier curves for PFS and OS in patients treated with lenvatinib or sorafenib as second-line therapy after A+B in PSM population. (A). Kaplan-Meier curves for PFS in patients treated with lenvatinib or sorafenib as second-line therapy after A+B in PSM population; (B) Kaplan-Meier curves for OS in patients treated with the sequence of A+B - lenvatinib or A+B – sorafenib in PSM population. HRs, 95% CIs, and *p* values were calculated using Cox proportional hazards models. A two-sided alpha level of 0.05 was considered statistically significant. HRs, hazard ratios; OS, overall survival; PFS, progression-free survival; PSM, propensity score matching.

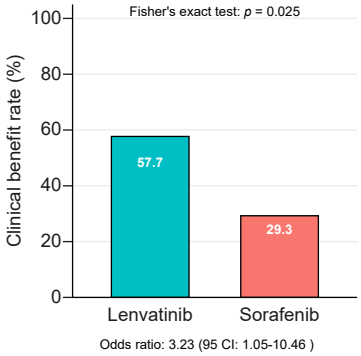


Fig. 4. Disease control rate with lenvatinib compared to sorafenib in primary resistance patient to A+B. Bar plot showing the proportion of patients achieving disease control with lenvatinib *vs.* sorafenib in the subset of patients with primary resistance to A+B. Statistical comparison between groups was performed using Fisher's exact test (two-sided). An alpha level of 0.05 was considered statistically significant.

To address this knowledge gap, we designed LEVIATHAN to evaluate the survival outcomes of patients who received either sorafenib or lenvatinib as second-line therapy after A+B. It is accepted that continuing active therapy after A+B progression leads to an incremental improvement in survival.[9] Previous evidence suggests that patients receiving lenvatinib achieve a longer PFS[9] and OS compared to those treated with sorafenib.[17,18,31] However, most studies adopted a descriptive approach, and the representativity of the survival estimates is heavily influenced by selection bias, geographic heterogeneity and different reimbursement strategies.

In our multicentre, globally conducted study, we overcame this issue by incorporating robust PSM modelling which included patient stratification based on response to A+B and focused our analysis on therapeutic sequencing rather than on efficacy outcomes from second-line strategies. Here, we demonstrate that lenvatinib is associated with improved outcomes compared to sorafenib following progression on A+B in

patients with advanced HCC, offering insights into optimal treatment sequencing in the current therapeutic landscape. The observed improvements in PFS and OS with lenvatinib, in both unadjusted and PSM populations, highlight the importance of selecting the most effective treatment sequence to optimise the chances of obtaining a longer survivorship even beyond immunotherapy discontinuation. Sorafenib and lenvatinib have a partly non-overlapping spectrum of kinase inhibition. We speculate that pan-FGFR inhibition, together with VEGFR and RET blockade –targets more selectively inhibited by lenvatinib than sorafenib – may more effectively counteract resistance mechanisms emerging after prior anti-VEGF therapy, thereby contributing to the observed differences in clinical outcomes.[21] These findings are consistent with results from a recent prospective Korean phase II trial, in which lenvatinib demonstrated clinical activity following progression on A+B, with a mPFS of 5.4 months and mOS of 8.6 months, further supporting its role in this setting.[14] Interestingly, our data also suggest that, beyond its superiority in the general population, lenvatinib could also provide benefits in a subpopulation with a particularly poor prognosis. Specifically, patients who were primarily resistant to first-line immunotherapy and subsequently treated with lenvatinib in the second-line setting had a higher chance of disease control compared to those receiving sorafenib (60% *vs.* 30%). While this observation should be interpreted with caution due to the small sample size, it raises the hypothesis that lenvatinib may retain antitumour activity in immunotherapy-refractory disease.

Preclinical evidence has shown that lenvatinib may exert immunomodulatory effects, including promotion of T-cell infiltration and modulation of immune checkpoints, potentially overcoming some mechanisms of resistance to immunotherapy.[21] Nevertheless, we recognise that these considerations are speculative in the absence of mechanistic data from our cohort. Future studies incorporating biomarker and translational analyses will be required to test this hypothesis and define the biological rationale for treatment selection in the post-A+B setting.

Despite the strengths of this study, several limitations must be acknowledged. Data were derived from an observational study rather than a randomised trial, potentially introducing confounding factors that cannot be fully controlled through propensity score adjustment. Significant baseline imbalances between treatment groups – particularly the fact that patients treated with lenvatinib were generally fitter and enriched in good prognostic factors – may have influenced survival outcomes. In addition, sorafenib may have been more frequently selected in patients with impaired liver or kidney function, given its longer-standing safety data and broader experience in these populations.[32,33] Variability in patient management across centres may also influence treatment outcomes. Furthermore, while our study focuses on lenvatinib and sorafenib, other VEGFR-targeting multikinase inhibitors, such as cabozantinib and regorafenib – both approved for patients previously treated with sorafenib – have not been widely investigated in the post-immunotherapy setting, particularly in large, randomised clinical trials.[13–15,34,35] However, recent single-arm phase II studies suggest that cabozantinib and regorafenib may be effective in patients progressing after immunotherapy, reporting a mPFS of 4.3 and 3.5 months and mOS of 9.9 and 9.7 months, respectively.[13,36] Notably, among patients treated with cabozantinib in the second-line setting, the mPFS and mOS were 4.3 months (95% CI 3.9–6.7) and 14.3 months (95% CI 8.9–NR), respectively.[13]

Lastly, the lack of biomarker-driven selection for treatment strategy remains a critical challenge, underscoring the need for further research into predictive markers to refine treatment algorithms. Further studies are required to validate our observations, identify predictive biomarkers, and better define which patients may derive the greatest benefit from the A+B-lenvatinib sequence.

Despite the acknowledged limitations and in the absence of randomised trials, LEVIATHAN helps bridge the existing knowledge gap, demonstrating that TKIs should not be considered interchangeable therapeutic options post-immunotherapy. Our study reinforces previous observations from simulation models,[37] observational[16–18] and non-randomised studies,[14] strengthening these findings with a large, multinational cohort analysis utilizing PSM. The significant differences in survival outcomes observed suggest that lenvatinib should be preferred over sorafenib following discontinuation of atezolizumab plus bevacizumab, given its consistent benefits in PFS, OS, and DCR, even in patients with primary resistance to immunotherapy.

Ongoing trials, such as IMbrave251 (NCT04770896) and ACCRU-GI-2008 (NCT05168163), are currently evaluating the continuation of atezolizumab in combination with TKIs compared to TKI monotherapy after A+B discontinuation. While these studies will provide important evidence on optimal post-immunotherapy strategies, our real-world data offer preliminary but compelling evidence to support lenvatinib as a superior second-line treatment option and as a benchmark for future studies evaluating post-immunotherapy treatment strategies. These findings contribute to the evolving treatment landscape of advanced HCC, reinforcing the importance of optimised sequencing strategies to improve patient outcomes.

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Abbreviations

A+B, atezolizumab plus bevacizumab; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; DCR, disease control rate; ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; PSM, propensity score matching; PVT, portal vein thrombosis; SD, stable disease; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

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Conflict of interest

GFM reports travel expenses from Roche. TUM currently or has previously in the past 3 years served on Advisory and/or Data Safety Monitoring Boards for Rockefeller University, Regeneron, AbbVie, Merck, EMD Serono, Geneos, AstraZeneca, Genentech, Glenmark, Arrowhead, G1 Therapeutics, NGMbio, DBV Technologies, Arcus, Fate, Ono, Storm, Replimmune, Avammune, Tubulis, NaturesToolbox, EvolveImmune, Abdera, AN2 Therapeutics and Astellas, and has or has had research grants from the National Institutes of Health (NCI), the Cancer Research Institute, Regeneron, Genentech, Bristol-Myers Squibb, Merck, and Boehringer Ingelheim. He holds stock options in Natures Toolbox. MP received speaker honoraria from AstraZeneca, Bayer, BMS, Eisai, Ipsen, Lilly, MSD, and Roche; he is a consultant/advisory board member for AstraZeneca, Bayer, BMS, Eisai, Ipsen, Lilly, MSD, and Roche; he received grants from AstraZeneca, Bayer, BMS, Eisai, and Roche; he received travel support from Bayer, BMS, Ipsen, and Roche. WF Hsu reports lecture fees from AbbVie, AstraZeneca, BMS, Gilead, and Roche. AD reports consulting or advisory board role with MSD/Eisai, Astrazeneca, Roche, MSD. AP reports consultant/advisory board member fee from AstraZeneca, Amgen, MSD, Incyte and travel support from Merck, Daiichi-Sankio, Accord. LR reports consulting fees from AbbVie, AstraZeneca, Basilea, Bayer, BMS, Eisai, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, Zymeworks; lecture fees from AstraZeneca, Bayer, BMS, Guerbet, Incyte, Ipsen, Roche, Servier; travel expenses from AstraZeneca and Servier; research grants (to Institution) from AbbVie, AstraZeneca, BeiGene, Exelixis, Fibrogen, Incyte, Ipsen, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, TransThera Sciences, Zymeworks. FB reports consulting or advisory board role with Astrazeneca, Bracco, BMS, ESAOTE, EISAI, GE, Gilead, IPSEN, MSD, Nerviano, Roche, Samsung, Signant Health, Siemens Healthineers. MK reports consulting fees from Chugai, Roche, Eisai, AstraZeneca; lecture fees from Chugai, Eisai, AstraZeneca; Research grant from Otsuka, Taiho, Chugai, GE Healthcare, Eisai. GC participated in advisory board and received speaker fees for Eisai, and AstraZeneca, MSD, Roche, Gilead. DJP received lecture fees from Bayer Healthcare, EISAI, BMS, Roche, Boston Scientific, travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, DaVolterra, Mursla, IPSEN, Exact Sciences, Avamune, EISAI, Roche, Starpharma, LiFT biosciences and Astra Zeneca; received research funding (to institution) from MSD, GSK and BMS. JvF has received honoraria from AstraZeneca.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

P.L. and J.S.K. contributed equally to this work and share first authorship. H.J.C. and D.J.P. jointly supervised the project and share senior authorship. P.L., H.J.C., and D.J.P. conceived and designed the study. All authors contributed to patient enrolment, provided clinical data, or supported local coordination. P.L. performed the statistical analysis. P.L., J.S.K., H.J.C., and D.J.P. interpreted the data. P.L. drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version for submission.

Data availability

Individual, de-identified participant raw data and data dictionary can be made available at the request of external investigators who propose to use the data in a way that has been approved by the HCC steering committee following review of a methodologically sound research proposal. Data will be made available 6 months after article publication, with no end date. Requests for de-identified data should be made to the study Chief Investigator.

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Supplementary data

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