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Original Article

Comparison of survival benefit and safety profile between lenvatinib and donafenib as conversion therapy in patients with hepatocellular carcinoma

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Abstract: Objective: To compare the survival benefit and safety profiles between lenvatinib and donafenib when used as conversion therapies for patients with hepatocellular carcinoma (HCC) at the China National Liver Cancer (CNLC) stages I-III. Methods: A retrospective comparative study was conducted on 76 patients diagnosed with HCC at CNLC stage I-III. Among them, 40 patients were treated with lenvatinib, and the other 36 patients received donafenib. Key outcomes, including overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events, were evaluated. Results: Patients treated with lenvatinib showed significantly longer OS (14.9 vs. 7.9 months, P=0.010) and PFS (4.6 vs. 2.9 months, P<0.001) compared to those treated with donafenib. The ORR was 15% in the lenvatinib group and 5.6% in the donafenib group (P=0.551). Lenvatinib was also associated with a lower incidence of grade ≥3 adverse events (P<0.05). Specifically, severe adverse events such as hepatotoxicity, hematological toxicity, hand-foot syndrome, and diarrhea were less frequent in the lenvatinib cohort. Univariate and multivariate analyses identified elevated alpha-fetoprotein (AFP) levels and the presence of hepatic vein tumor thrombus as significant predictors of poorer PFS, with hazard ratios (HR) of 1.45 and 1.80, respectively. Furthermore, multivariate analysis revealed that higher Child-Pugh scores and elevated AFP levels were associated with worse OS (all P<0.05). Conclusion: Lenvatinib demonstrates superior survival outcomes compared to donafenib as a conversion therapy in patients with CNLC stage I-III HCC. While the two therapies are comparable in overall safety profiles, lenvatinib is more tolerated, with a lower incidence of severe adverse events.

Keywords: Hepatocellular carcinoma, conversion therapy, lenvatinib, donafenib, survival benefit

Introduction

Hepatocellular carcinoma (HCC), the sixth leading cause of cancer-related mortality globally, presents a significant clinical challenge due to its aggressive nature and rising incidence rates [1, 2]. HCC predominantly affects individuals with chronic liver conditions, such as hepatitis B or C virus infection and cirrhosis [3, 4]. Conventional treatments for HCC include surgical resection, liver transplantation, and radiofrequency ablation [5]. However, these options are not feasible for all patients, underscoring the need for alternative therapeutic strategies.

In recent years, conversion therapy has gained recognition as a promising approach for HCC patients at CNLC (Chinese National Liver Cancer Committee) stages I-III, aiming to downstage tumors and enhance surgical eligibility [6, 7]. Consistent with CNLC guidelines, molecular targeted agents such as tyrosine kinase inhibitors (TKIs) have become integral to the management of advanced HCC [8, 9]. Among these, lenvatinib and donafenib are two clinically validated TKIs with distinct molecular targets [10]. Lenvatinib inhibits VEGFR1-3, PDGFRβ, FGFR1-4, and RET, while donafenib primarily targets VEGFR2, PDGFRβ, and FGFR2 [11-13]. Both drugs have shown encouraging

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efficacy in improving overall survival (OS) and progression-free survival (PFS) in phase III trials [14, 15].

Despite their parallel regulatory approvals and similar efficacy endpoints in registration trials, direct comparative data on lenvatinib and donafenib in the context of conversion therapy remain scarce. Specifically, differences in survival outcomes, safety profiles, and conversion success rates between the two TKIs have not been thoroughly investigated [16]. To address this gap, we conducted a retrospective cohort study to evaluate and compare the therapeutic efficacy and safety of lenvatinib versus donafenib in patients with CNLC stage I-III HCC undergoing conversion therapy.

Methods

Study design and patient selection

This retrospective comparative cohort study was conducted at Shijiazhuang People's Hospital between January 2020 and December 2022. Eligible patients were diagnosed with HCC at CNLC stage I-III and received either lenvatinib or donafenib as conversion therapy. Conversion therapy was defined as the initiation of targeted therapy following systemic chemotherapy or best supportive care, with the primary goal of achieving partial response (PR) or stable disease (SD). Patients were excluded if they had received prior TKI treatment, were concurrently taking strong CYP3A inhibitors, or declined participation. Additionally, patients undergoing other anticancer therapies, such as chemotherapy, radiotherapy, or surgery, during the study period were excluded to ensure that outcomes could be attributed solely to lenvatinib or donafenib. This study was approved by the Institutional Review Board and Ethics Committee of Shijiazhuang People's Hospital.

Therapeutic interventions and outcome measures

Treatment protocols: Patients received either: (1) lenvatinib (AB12345; Eisai Co., Ltd.) at an initial daily dose of 8 mg (bodyweight <60 kg) or 12 mg (≥60 kg), with dose adjustments (2-4 mg/day) based on toxicity tolerance, or (2) donafenib (GH246; Zhejiang Hisun Pharmaceutical Co., Ltd.) administered orally at 400-600 mg/day in divided doses. Both regimens were continued for at least two treatment cycles (minimum 8 weeks), unless disease progression or intolerable toxicity necessitated discontinuation.

Assessment timeline: Radiological evaluations using contrast-enhanced CT or MRI were performed at baseline and every 8 weeks thereafter. Tumor responses were evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) by independent radiologists blinded to treatment allocation.

Primary endpoints: OS: Time from treatment initiation to all-cause mortality; patients still alive were censored at the date of the last follow-up (minimum follow-up: 12 months). PFS: Time from therapy initiation to the earliest occurrence of radiological progression (per mRECIST) or death.

Secondary endpoints: Objective Response Rate (ORR) [17]: Proportion of patients achieving complete response (CR) or partial response (PR). Disease Control Rate (DCR): Proportion of patients achieving CR, PR, or stable disease (SD) sustained for at least 8 weeks. Safety Profile: Incidence and severity of treatment-emergent adverse events (TEAEs), according to NCI CTCAE v5.0. Particular attention was given to hypertension, hand-foot syndrome, and proteinuria.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 24.0 and GraphPad Prism version 8.0. Baseline and clinical characteristics were compared between the two treatment groups. Categorical variables were expressed as n (%) and compared between groups using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation and compared between groups using the independent samples t-test. Non-normally distributed variables were reported as median (range) and analyzed with the Mann-Whitney U test (Wilcoxon rank-sum test).

OS and PFS were estimated using the Kaplan-Meier method, and survival curves were com-

pared using the log-rank test. Univariate and multivariate analyses were conducted using Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). A *P* value <0.05 was considered statistically significant.

Results

Comparison of patient characteristics between the two groups

A total of 76 patients were included in this study, with 40 receiving lenvatinib and 36 receiving donafenib. As presented in **Table 1**, there were no statistically significant differences in the baseline clinical characteristics between the two groups. This balanced distribution strengthens the validity of subsequent comparisons of treatment efficacy and safety outcomes.

Comparison of therapeutic efficacy between the two groups

As shown in **Table 2**, in the Lenvatinib group, one patient achieved CR, five had PR, nineteen achieved SD, and seventeen experienced progressive diseases (PD). The ORR was 15% in the lenvatinib group and 5.6% in the patient achieved (*P*=0.551). Moreover, the DCR was 62.5% in the lenvatinib group and 47.22% in the donafenib group (*P*=0.239).

Comparison of safety profiles between the two groups

Lenvatinib was associated with a significantly lower incidence of adverse events with grade 3 or higher compared to donafenib (*P*<0.05, **Table 3**). Notably, the lenvatinib group demonstrated fewer severe adverse events, particularly in terms of hepatotoxicity, hematological toxicity, hand-foot syndrome, and diarrhea. These findings suggest that lenvatinib may offer a more favorable safety profile, which is a critical concern when selecting an appropriate treatment regimen for patients with HCC.

Comparison of progression-free survival between the two groups

During the follow-up period, tumor progression occurred in 70.8% (34/48) of patients in the lenvatinib group and 86.7% (26/30) in the donafenib group. The median PFS was 4.6 months (95% CI: 4.3-5.1) in the lenvatinib group, significantly higher than 2.9 months (95% CI: 2.6-3.3) in the donafenib group (P<0.001) (**Figure 1**).

Comparison of overall survival between the two groups

A total of 16 patients (40%) in the lenvatinib group and 20 patients (55.6%) in the donafenib group died during follow-up. The median OS was significantly longer in the lenvatinib group at 14.9 months (95% CI: 11.9-16.9), compared to 7.9 months (95% CI: 6.3-9.3) (*P*=0.010) (**Figure 2**).

Univariate and multivariate analysis of factors influencing patient PFS

Elevated AFP levels (HR=1.45, 95% CI: 1.18-1.79, *P*=0.008) and the presence of hepatic vein tumor thrombus (HR=1.80, 95% CI: 1.02-1.15, *P*=0.003) were identified as significant predictors of shorter PFS in both univariate and multivariate analyses (**Table 4**). Although age and cirrhosis showed association with PFS in univariate analysis, these factors did not retain significance in the multivariate model.

Univariate and multivariate analysis of factors influencing patient OS

Univariate analysis identified that lower performance status (PS score ≥1 vs. 0), higher Child-Pugh scores (B/C vs. A), presence of cirrhosis, hepatic vein tumor thrombus, advanced CNLC stage (III vs. I/II), and elevated AFP levels (≥400 ng/mL vs. <400 ng/mL) were significantly associated with poorer OS (all P<0.05; **Table 5**). In multivariate analysis, higher Child-Pugh scores (HR=1.06, 95% CI: 1.02-1.10, P=0.006) and elevated AFP levels (HR=3.03, 95% CI: 1.10-9.09, P=0.039) remained independent predictors of worse OS. Notably, the presence of hepatic vein tumor thrombus showed a paradoxical protective effect in the adjusted model (HR=0.88, P=0.002), possibly due to confounding by other covariates.

Discussion

HCC is a leading cause of cancer-related deaths globally, characterized by a poor prognosis due to its late detection and limited therapeutic

Table 1. The comparison of baseline clinical characteristics between the lenvatinib and donafenib groups

Characteristic	Lenvatinib group (n=40)	Donafenib group (n=36)	t/χ^2	*p*-value
Age (year)	55.2±10.3	54.8±9.8	1.094	0.863
Gender (males)	25 (62.5%)	21 (58.33%)	0.851	0.711
Etiology of hepatocellular carcinoma			1.360	0.596
Hepatitis B Infection	31	26		
Other	9	10		
PS score			0.850	0.769
0	29	25		
1	11	11		
Microvascular invasion			1.651	0.655
Nonexistence	27	26		
Incidence	13	10		
Cirrhosis			1.088	0.606
Nonexistence	33	28		
Incidence	7	8		
AFP			1.490	0.981
≥400 ng/mL	19	17		
<400 ng/mL	21	19		
Hepatic vein cancer embolism			1.177	0.708
Nonexistence	32	30		
Incidence	8	6		
Extrahepatic metastasis			0.893	0.901
Nonexistence	15	14		
Incidence	25	22		
Liver Function (Child-Pugh)			2.110	0.909
A	45%	44.44%		
B	37.5%	36.12%		
C	17.5%	19.44%		
Tumor Stage (CNLC)			1.366	0.937
I	40%	38.89%		
II	30%	30.56%		
III	25%	25%		
Pathology Type			0.858	0.958
Squamous	40%	38.89%		
Adenocarcinoma	35%	33.33%		
Prior Treatment History			0.842	0.756
Chemotherapy	12 (30%)	10 (27.8%)		
Surgery	5 (12.5%)	6 (16.7%)		
Radiotherapy				
ECOG Performance Status			1.571	0.853
0	55%	52.78%		
1	30%	30%		
2	10%	11.11%		
3	5%	2.78%		

CNLC: China Liver Cancer Staging; PS Score: Baseline Performance Status Score; AFP: Alpha-fetoprotein; ECOG Performance Status: Eastern Cooperative Oncology Group Performance Status.

Table 2. The efficacy outcomes of the lenvatinib and the donafenib group

Efficacy outcomes	Lenvatinib group (n=40)	Donafenib group (n=36)	χ^2	*p*-value
Best Efficacy Response			1.760	0.538
CR	1	0		
PR	5	2		
SD	19	15		
PD	17	18		
ORR (%)	15%	5.6%	0.149	0.551
DCR (%)	62.5%	47.22%	1.357	0.239

ORR: objective response rate; DCR: Disease control rate; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table 3. Incidence of grade ≥3 adverse events of the lenvatinib and the donafenib group

Adverse Event	Lenvatinib (%)	Donafenib (%)	χ^2	*p*-value
Any Grade ≥3 Adverse Event	36.9	45.6	1.249	0.046
Hepatotoxicity	13.9	39.7	1.038	<0.001
Hematological Toxicity	15.8	2	0.091	0.023
Hand-Foot Syndrome	12.4	19.8	2.118	0.04
Diarrhea	6.8	15.6	3.021	<0.001
Stomatitis	6.1	12.9	0.093	0.027
Proteinuria	5.6	4.8	1.018	0.46
Thrombocytopenia	5.2	3.7	1.320	0.37
Hypothyroidism	4.7	3.2	0.071	0.2
Fatigue	3.9	3.1	1.069	0.7

options [16]. The management of HCC has evolved, with a growing emphasis on personalized therapeutic strategies [18]. Conversion therapy, which involves altering the treatment approach for HCC patients, is crucial in optimizing patient outcomes [19]. This study included a diverse cohort of HCC patients encompassing a broad spectrum of clinical characteristics and disease stages. All patients initially underwent transarterial chemoembolization (TACE) as the standard first-line therapy for HCC. However, due to disease progression or intolerable side effects, they subsequently received conversion therapy with either lenvatinib or donafenib. Both lenvatinib and donafenib are molecularly targeted agents with demonstrated anti-tumor activity in HCC. Lenvatinib is a multikinase inhibitor that targets multiple receptor tyrosine kinases, whereas donafenib selectively inhibits VEGFR2 and PDGFRβ [20].

The primary endpoint of the study was OS, with secondary endpoints including PFS, ORR, DCR, and safety profiles. The study found that lenvatinib provided a superior survival benefit over donafenib when used as conversion therapy in patients with HCC at CNLC stages I-III. Notably, the median OS was significantly longer in the lenvatinib group (14.9 months) than in the donafenib group (7.9 months), indicating a clear survival advantage for lenvatinib. This suggests that lenvatinib may have a more favorable impact on patient survival compared to donafenib within the context of conversion therapy for HCC. In terms of PFS, elevated AFP levels and the presence of hepatic vein tumor thrombus were identified as independent predictors of poorer prognosis in both univariate and multivariate analyses. These clinical factors may play a critical role in stratifying patients and tailoring conversion therapy strategies. These findings align with previous reports comparing lenvatinib with donafenib. For instance, Meng et al. reported that lenvatinib was associated with prolonged PFS and OS in patients with advanced HCC [21]. Similarly, Guan et al. demonstrated that lenvatinib achieved a higher DCR and a longer PFS than donafenib [13].

In the comparative analysis of safety profiles between lenvatinib and donafenib in the treatment of HCC, lenvatinib was associated with a lower incidence of grade ≥3 adverse events compared to donafenib. Notably, lenvatinib demonstrated a lower incidence of hepatotoxicity, hematological toxicity, hand-foot syndrome, and diarrhea. Additionally, adverse events such as stomatitis, proteinuria, thrombocytopenia, hypothyroidism, and fatigue were less common in the lenvatinib group, although some of these differences did not reach statistical significance. In a randomized trial by

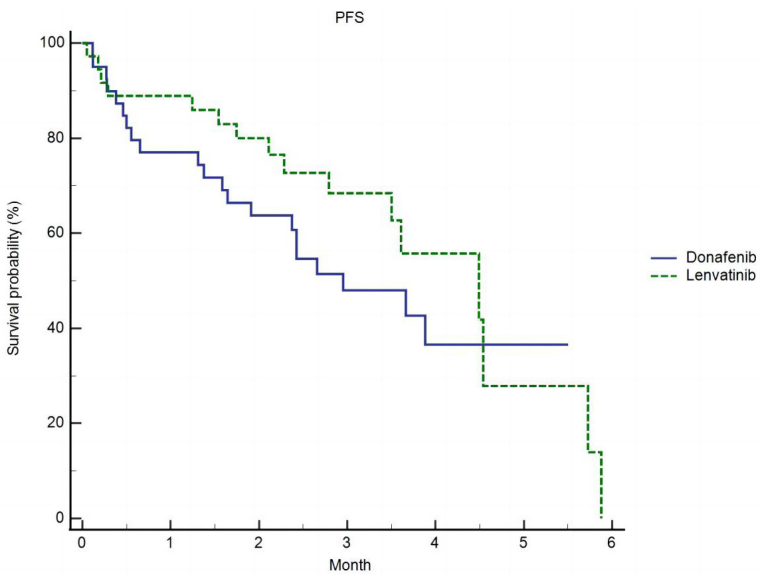

Figure 1. Kaplan-Meier curves of median progression-free survival between two groups (Time-month). PFS: progression-free survival.

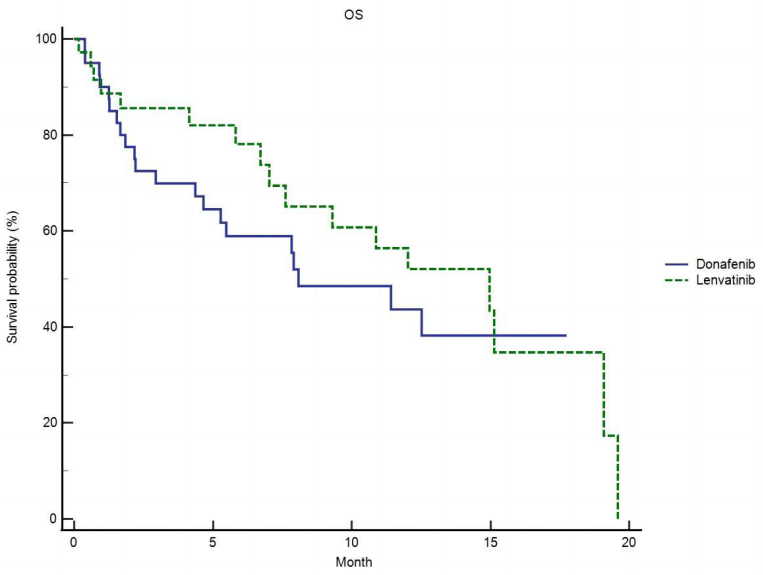

Figure 2. Kaplan-Meier curves of median overall survival between two groups (Time-month).

Han et al. [22], patients with unresectable HCC treated with lenvatinib experienced significantly fewer grade ≥3 adverse events, including hepatotoxicity, diarrhea, and hand-foot syndrome, than those treated with sorafenib. Similarly, Xie et al. reported a lower incidence of hypertension, hand-foot syndrome, and diarrhea with lenvatinib compared to sorafenib in advanced HCC patients [23]. A meta-analysis by Liu et al., incorporating data from multiple clinical trials, also found that lenvatinib posed a lower risk of hepatotoxicity and diarrhea than other systemic agents, including donafenib [24]. In contrast, a study by Yi et al. observed that while lenvatinib and sorafenib yielded similar overall survival, lenvatinib was associated with a higher incidence of hypertension and diarrhea [25]. Lenvatinib, a multi-kinase inhibitor, targets several angiogenic and growth factor receptors, including VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT [26]. This broad spectrum of inhibition may contribute to its antitumor effects by blocking tumor angiogenesis and inhibiting tumor cell proliferation and survival. In contrast, donafenib, another multi-kinase inhibitor, primarily targets VEGFR1-3, PDGFRα, and c-Kit, with weaker activity against FGFR and RET [27]. These differences in target selectivity may underlie the variations in efficacy and toxicity observed between the two agents. In conclusion, the superior safety profile of lenvatinib compared to donafenib may be related to its broader and more potent inhibition of tumor-related signaling pathways. Further research is needed to elucidate the molecular mechanisms and to identify predictive biomarkers that may guide treatment selection in patients with HCC.

This study has several limitations. First, it was conducted at a single center, which may limit its generalizability to a broader patient population. Second, the relatively small sample size increases the risk of type II errors, potentially obscuring statistically significant differences between treatment groups. Lastly, the retrospective design may have introduced biases related to patient selection and data collection. However, to minimize confounding factors,

Table 4. Univariate and multivariate analysis for PFS prognosis

Characteristic	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (</≥65)	1.05	1.01-1.10	0.035	1.03	0.99-1.07	0.621
Gender (males/females)	1.12	1.04-1.20	0.062			
Hepatitis B (infected/uninfected)	1.20	1.05-1.35	0.521			
PS score (0/1)	0.98	0.86-1.11	0.766			
Microvascular invasion (nonexistence/incidence)	0.57	0.31-1.04	0.069			
Cirrhosis (nonexistence/incidence)	1.08	1.02-1.15	0.039	1.06	1.01-1.10	0.602
AFP (≥/<400 ng/mL)	1.50	1.20-1.85	<0.001	1.45	1.18-1.79	0.008
Hepatic vein cancer embolism (nonexistence/incidence)	1.80	1.30-2.50	<0.001	1.75	1.28-2.40	0.003
Extrahepatic metastasis (nonexistence/incidence)	1.03	0.97-1.09	0.260			
Child-Pugh (A/B/C)	1.02	0.96-1.08	0.632			
CNLC (I/II/III)	1.04	0.97-1.12	0.247			
Pathology Type (Squamous/Adenocarcinoma/Others)	0.92	0.80-1.05	0.210			
ECOG (0/1/2/3)	0.90	0.82-1.00	0.598			

HR: Hazard Ratio; CNLC: China Liver Cancer Staging; PS Score: Baseline Performance Status Score; AFP: Alpha-fetoprotein; ECOG: Eastern Cooperative Oncology Group.

Table 5. Univariate and multivariate analysis for overall survival prognosis

Characteristic	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (</≥65)	1.20	1.05-1.35	0.150			
Gender (males/females)	1.02	0.96-1.08	0.182			
Hepatitis B (infected/uninfected)	1.46	0.51-4.14	0.478			
PS score (0/1)	0.32	0.18-0.55	0.001	0.29	0.16-0.55	0.518
Microvascular invasion (nonexistence/incidence)	0.92	0.36-1.51	0.346			
Cirrhosis (nonexistence/incidence)	0.69	0.32-1.51	0.009	0.88	0.36-2.16	0.783
AFP (≥/<400 ng/mL)	0.35	0.12-0.98	0.045	0.33	0.10-1.03	0.039
Hepatic vein cancer embolism (nonexistence/incidence)	1.18	1.12-1.24	0.001	0.88	0.81-0.95	0.002
Extrahepatic metastasis (nonexistence/incidence)	0.88	0.31-2.49	0.803			
Child-Pugh (A/B/C)	1.08	1.03-1.14	0.002	1.06	1.02-1.10	0.004
CNLC (I/II/III)	0.41	0.20-0.85	0.016	0.70	0.25-1.94	0.941
Pathology Type (Squamous/Adenocarcinoma/Others)	0.70	0.24-1.99	0.479			
ECOG (0/1/2/3)	0.53	0.27-1.07	0.075			

HR: Hazard Ratio; CNLC: China Liver Cancer Staging; PS Score: Baseline Performance Status Score; AFP: Alpha-fetoprotein; ECOG: Eastern Cooperative Oncology Group.

patients who received concurrent chemotherapy, radiotherapy, or surgical interventions were excluded, allowing for a more isolated assessment of the therapeutic effects of lenvatinib and donafenib.

Conclusions

Lenvatinib offers superior survival benefits over donafenib as a conversion therapy in patients with HCC at CNLC stages I-III. Moreover, lenvatinib is linked to a reduced incidence of grade ≥3 adverse events compared to donafenib, suggesting a more favorable safety profile. Despite these promising findings, prospective multicenter studies with larger sample sizes and longer follow-up periods are necessary to validate these results. Future research should also explore predictive biomarkers and patient subgroups that may benefit most from lenvatinib, while providing a more comprehensive evaluation of long-term safety and efficacy outcomes.

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Disclosure of conflict of interest

None.

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