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Original article

Real-world efficacy of cabozantinib alone or in combination with ICIs in heavily pretreated hepatocellular carcinoma: potential role of AXL and MET expression
Cabozantinib ± ICIs in pretreated HCC patients

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ABSTRACT

Introduction and Objectives: Cabozantinib, a multi-kinase inhibitor targeting AXL and MET, is approved for second-line treatment of hepatocellular carcinoma (HCC). However, the combination of cabozantinib with immune checkpoint inhibitors (ICIs) remains controversial after the COSMIC-312 study. The role of AXL and MET expression in predicting cabozantinib response is unclear. This study aims to evaluate cabozantinib's efficacy with ICIs and the predictive value of AXL and MET expression.
Materials and Methods: From January 2019 and December 2023, 50 advanced HCC patients treated with cabozantinib were retrospectively enrolled.
Results: Overall, 74% of patients received prior immunotherapy, 72% had been treated with more than two different multiple kinase inhibitors (MKIs), and 58% received cabozantinib as a fifth-line or later therapy. Cabozantinib was used alone (60%), with ICIs (12%), or with chemotherapy (28%). A majority (70%) received a dosage exceeding 40 mg/day. The ORR to cabozantinib was 0%, while the DCR was 42.2%. median PFS was 3.3 months, and OS was 6.1 months. There was no significant difference in PFS or OS between patients receiving five or more lines of treatment and those receiving fewer. Cabozantinib plus ICIs showed longer PFS (6.7 vs. 3.2 months, p = 0.04) and a trend toward improved OS compared to cabozantinib alone. AXL expression may predict better outcomes. Common adverse effects included palmar-plantar erythrodysesthesia (24.2%) and hypertension.
Conclusions: This study highlights the potential of cabozantinib combined with immunotherapy in heavily pretreated HCC, with AXL expression as a possible predictive biomarker.

1. Introduction

Hepatocellular carcinoma (HCC), the seventh most common cancer worldwide in 2020, remains highly lethal, particularly in its advanced stages [1]. With the advent of immune checkpoint inhibitors (ICIs), the first-line treatment paradigm for unresectable HCC has shifted from tyrosine kinase inhibitors (TKIs) alone to combination therapies, such as atezolizumab/bevacizumab and durvalumab/tremelimumab [2,3]. Challenges persist despite advancements in novel immunotherapy combinations [4]. Furthermore, multiple lines of systemic therapy are available. Anti-vascular endothelial growth factor (anti-VEGF) agents—including sorafenib, lenvatinib, regorafenib, ramucirumab, and cabozantinib—are recommended. However, prognosis remains poor in later lines of treatment.

Abbreviation: ALBI, Albumin-Bilirubin score; AXL, AXL; BCLC, Barcelona Clinic Liver Cancer; CPS, Child-Pugh score; DCR, disease control rate; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ICIs, immune checkpoint inhibitors; IHC, immunohistochemistry; MET, MET receptor tyrosine kinase; MKIs, multiple kinase inhibitors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TKIs, tyrosine kinase inhibitors

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Cabozantinib, a multi-kinase inhibitor targeting VEGFR 1-3, RET, KIT, AXL, MET, and FLT3, has been approved for use in unresectable HCC as a second- or third-line treatment based on the results of the CELESTIAL trial [5]. However, in the COSMIC-312 study, the combination of cabozantinib and atezolizumab failed to demonstrate superior efficacy compared to sorafenib in patients who had not received prior systemic anticancer therapies [6]. In contrast, in renal cell carcinoma, the combination of cabozantinib and nivolumab showed significant survival benefit and likelihood of response over sunitinib monotherapy, suggesting that cabozantinib may have an immunomodulatory effect [7]. Thus, the potential of combining cabozantinib with ICIs remains controversial, particularly in heavily pretreated patients with HCC.

AXL and MET are key drivers of tumor progression in HCC. AXL promotes epithelial-mesenchymal transition (EMT), invasion, migration, angiogenesis, and immune evasion, while MET contributes to tumor growth, metastasis, angiogenesis, and drug resistance [8–10]. Cabozantinib, by targeting both AXL and MET pathways, can control tumor progression [11]. However, the role of AXL and MET expression in predicting response to cabozantinib remains uncertain, highlighting the need for further investigation.

This study aims to evaluate the real-world efficacy of cabozantinib, particularly in combination with immunotherapy, and to investigate the relationship between AXL and MET expression and treatment outcomes in patients with unresectable HCC.

2. Materials and methods

2.1. Study design and setting

This retrospective cohort study was conducted at the Department of Oncology, Taipei Veterans General Hospital, Taiwan. Patients with unresectable or advanced HCC, confirmed either histologically or clinically according to international guidelines, were identified from electronic medical records between January 2019 and December 2023. Eligible patients were 18 years or older at the time of diagnosis and received palliative systemic treatment with cabozantinib. Data collected included patient demographics (age, sex), underlying comorbidities, tumor histology, laboratory results, imaging reports, tumor stage, prior local and systemic treatments, cabozantinib dosage, treatment outcomes, drug-related toxicities, and date of death or last follow-up. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital. (TPEVGH IRB No.: 2024-10-004AC)

2.2. Immunohistochemistry

Four-micrometer whole tissue sections were used for immunohistochemistry (IHC) analysis. The IHC of AXL was performed using a HPA037422 antibody (dilution 1:100; Merck, Darmstadt, Germany). The IHC of MET was performed using an ab227637 antibody (dilution 1:100; Abcam, Cambridge, UK). IHC was performed using the Roche Ventana Benchmark ULTRA System (Roche Ventana, Tucson, AZ, USA). Membranous staining in tumor cells was considered positive and evaluated using the histochemical scoring system (H-score). H-score is the product of the percentage of tumor cells showing positive staining and staining intensity (0, no staining; 1, weak staining; 2, moderate staining; and 3, strong staining), ranging from 0 to 300. The results were further classified as negative (0–14), weak (15–99), moderate (100–199), or strong (200–300) for further analysis. Weak, moderate, and strong staining were collectively defined as positive.

2.3. Outcome measures

In this study, treatment response was assessed by using RECIST criteria by two specialist reviewers. The RECIST definitions were as follows: complete response (CR) indicated no viable tumor; partial response (PR) was defined as a tumor size decrease of more than 30%; stable disease (SD) was characterized by a tumor size change between +20% and -30%; and progressive disease (PD) was defined as an increase of more than 20%, based on the sum of the largest diameters of the target lesions. The objective response rate (ORR) was defined as the proportion of CR and PR, while the disease control rate (DCR) was defined as the proportion of CR, PR, and SD. This version clarifies the definitions and is aligned with standard academic writing conventions. Progression-free survival (PFS) was defined as the time from the initiation of cabozantinib to the onset of PD or death. Overall survival (OS) was measured from the start of cabozantinib treatment to death from any cause.

2.4. Statistical analysis

The patient's baseline characteristics are presented by calculating the mean, median, standard deviation, and interquartile range. The associations between cabozantinib treatment responses across groups were analyzed using the Fisher exact test and chi-square ($\chi 2$) test. A chi-square analysis with 1,000 bootstrap resamples was performed to assess the association between IHC expression and treatment response. The estimation of PFS and OS were conducted using the Kaplan–Meier method, and the differences in survival curves were assessed through the log-rank test. A Cox proportional-hazards model was used to calculate hazard ratios and assess prognostic factors on progression and mortality in univariate and multivariate analyses. Changes in the Albumin-Bilirubin (ALBI) score during the treatment course with cabozantinib were evaluated using paired t-tests. $P < 0.05$ was considered statistically significant. All the statistical analyses were performed by IBM® SPSS®, version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM).

2.5. Ethical statement

This study has been approved by the institutional review board of Taipei Veterans General Hospital (TPEVGH IRB No.: 2024-10-004AC), which is the appropriate regulatory agency to review research on both adults and children. All methods were carried out in accordance with relevant guidelines and regulations.

3. Results

3.1. Patient characteristics

A total of 50 HCC patients treated with cabozantinib were enrolled. The median age was 55 years (interquartile range: 48-65), and 76% of the patients were male. Hepatitis B virus (HBV) infection was present in 74% (37/50) of patients, while 8% (4/50) had hepatitis C virus (HCV) infection, with 4% (2/50) showing co-infection. In terms of liver function, 34% of patients were classified as Child-Pugh class (CPS) A, 52% as CPS B, and 14% as CPS C. The Barcelona Clinic Liver Cancer (BCLC) stage B accounted for 48% of patients, and stage C for 38%. Additionally, 48% of patients (24/50) were diagnosed with cirrhosis.

3.2. Use of cabozantinib in later line setting

Regarding prior systemic treatments, 74% of patients had previously undergone immunotherapy, and 72% had received more than

two different tyrosine kinase inhibitors prior to cabozantinib. With respect to combination regimens, 60% of patients received cabozantinib monotherapy, 12% received cabozantinib with ICIs (6 patients: 3 patients received durvalumab and 3 patients received atezolizumab), and 28% received cabozantinib with chemotherapy. A majority (70%) were treated with a cabozantinib dosage exceeding 40 mg/day, and 58% received cabozantinib as part of a fifth-line or later systemic treatment regimen. Detailed demographic and clinical characteristics are presented in Table 1.

3.3. Combination of cabozantinib with immunotherapy

The outcomes of cabozantinib therapy are presented in the swimmer's plot (Supplementary Fig. 1). The ORR to cabozantinib was 0%, and the DCR was 42.2%. The combination of cabozantinib with ICIs showed a significantly higher DCR compared to combination with chemotherapy or cabozantinib monotherapy (83.3%, 28.6%, and 33.3%, respectively, $p < 0.05$). Positive AXL expression was associated with a higher DCR, though this was not statistically significant (50% vs. 0%, $p = 0.13$). A chi-square analysis with 1,000 bootstrap resamples was conducted, revealing a contingency coefficient of 0.522 (95% CI: 0.31–0.71), indicating a moderate association between AXL expression and treatment response. The bias was 0.002, with a standard error of 0.11. Additionally, patients who achieved SD with prior targeted therapies, including lenvatinib, sorafenib, or regorafenib, showed a trend toward higher DCR with subsequent cabozantinib treatment (Table 2).

Table 1
Baseline characteristics.

Characteristics	N (%)
Median age, years (range)	55 (IQR: 48-65)
< 65	12 (24)
≥ 65	38 (76)
Sex (male)	38 (76)
Viral	43 (86)
HBV	37 (74)
HCV	4 (8)
Co-infection	2 (4)
Non-viral	7 (14)
CPS class	
A	17 (34)
B	26 (52)
C	7 (14)
ALBI grade	
I	16 (32)
II	26 (52)
III	8 (16)
Cirrhosis	24 (48)
Macrovascular invasion	24 (48)
BCLC stage	
B	24(48)
C	19(38)
D	7(14)
AFP	
≥ 400 ng/ml	25 (50)
< 400 ng/ml	25 (50)
Previous local treatment	
Surgery	17 (34)
RFA	13 (26)
TACE	33 (66)
RT	16 (32)
Transplantation	3 (6)
Previous immunotherapy	37 (74)
Previous chemotherapy	15 (30)
Previous TKIs	
≥ 2 TKIs	36 (72)
< 2 TKIs	14 (28)
Lenvatinib	39 (78)
Sorafenib	33 (66)
Regorafenib	20 (40)
Drugs combined with cabozantinib	
Immunotherapy	6 (12)
Chemotherapy	14 (28)
No	30 (60)
Cabozantinib dosage	
≥ 40 mg/day	35 (70)
< 40 mg/day	15 (30)
Treatment lines for cabozantinib	
≥ 5th	29 (58)
< 5th	21 (42)

IQR = Interquartile Range; CPS class: Child-Pugh Score Class; ALBI grade: Albumin-Bilirubin grade; BCLC stage: Barcelona Clinic Liver Cancer stage; AFP: Alpha-Fetoprotein; RFA: Radiofrequency Ablation; TACE: Transarterial Chemoembolization; RT: Radiotherapy; TKIs: Tyrosine Kinase Inhibitors

3.4. Progression-free survival and overall survival

The median PFS for the total population was 3.3 months (95% CI: 2.6–4.0), and the OS was 6.1 months (95% CI: 3.1–9.1). Patients with SD exhibited significantly longer PFS (6.2 vs. 2.8 months, $p < 0.01$) and OS (14.8 vs. 3.9 months, $p < 0.01$) compared to those with PD (Fig. 1A and B). No significant difference was observed in PFS or OS between patients who received five or more lines of treatment and those with fewer than five lines of treatment (Fig. 1C and D). When cabozantinib was combined with ICIs, patients demonstrated a longer PFS (6.7 vs. 3.2 months, $p = 0.04$) and a trend toward better OS compared to cabozantinib monotherapy (Fig. 1E and F). The dose of cabozantinib was not associated with clinical outcomes (Fig. 1G and H).

3.5. AXL expression

Both ALBI grade and CPS class were significantly associated with OS but not PFS. (Fig. 2A-D). The staining results showed that the proportion of AXL-positive cases was 40% (4/10), with 2 cases classified as weak positive and 2 cases as moderate positive. The proportion of MET expression was 2/7, with both cases classified as weak positive. The presence of AXL expression in cancer tissues showed a trend toward longer OS (14.6 vs. 5.0 months, $p = 0.25$). (Fig. 2E and F). In contrast, the presence of MET expression was not associated with clinical outcomes (Fig. 2G and H).

3.6. Prognostic factors for progression and death

Univariate analysis identified anti-HCV antibody positive, cirrhosis, alpha–fetoprotein (AFP) levels ≥ 400 ng/mL, serum albumin < 3.5 mg/dl as risk factors for progression. In the multivariate analysis, AFP levels ≥ 400 ng/mL and serum albumin < 3.5 mg/dl remained as independent predictors of risk. Although univariate analysis identified the combination with ICIs as a protective factor against progression, this association was not significant in multivariate analysis (Table 3). Regarding risk factors for death, univariate analysis revealed cirrhosis, serum albumin <3.5 mg/dl and total bilirubin ≥ 1.20 mg/dl as risk factors for death, while multivariate analysis merely indicated that serum albumin < 3.5 mg/dl (HR: 10.66) was independent poor risk factor (Table 4).

3.7. Safety

In this cohort, high grade adverse effect of cabozantinib was rare. The common adverse effects included palmar-plantar erythrodysesthesia (24.2%), hypertension (15.2%), elevated aspartate transaminase/alanine aminotransferase (15.2%) and diarrhea (12.1%). In addition, other adverse effects such as fatigue, nausea/vomiting, leukopenia, skin rash and hypothyroidism occurring at an incidence rate of less than 10 %. The detailed adverse events during treatment with cabozantinib are shown in supplementary table 1.

Table 2
Treatment response by RECIST 1.1 criteria.

	Cabozantinib				
	CR/PR	SD	PD	DCR	p value
All population	0%	42.2%	57.8%	42.2%	
Sex					
Male	0%	45.5%	54.5%	45.5%	0.73
Female	0%	36.4%	63.6%	36.4%	
CPS class					
A	0%	53.3%	46.7%	53.3%	0.50
B	0%	34.8%	65.2%	34.8%	
C	0%	50.0%	50.0%	50.0%	
Cirrhosis					
Absence	0%	46.2%	53.8%	46.2%	0.26
Presence	0%	29.2%	70.8%	29.2%	
Macrovascular invasion					
Yes	0%	38.1%	61.9%	38.1%	0.56
No	0%	47.8%	52.2%	47.8%	
Previous lenvatinib response					
Disease control group	0%	44.4%	55.6%	44.4%	0.12
Progression group	0%	11.1%	88.9%	11.1%	
Previous sorafenib response					
Disease control group	0%	41.7%	58.3%	41.7%	0.46
Progression group	0%	27.8%	72.2%	27.8%	
Previous regorafenib response					
Disease control group	0%	41.7%	58.3%	41.7%	0.66
Progression group	0%	28.6%	71.4%	28.6%	
Regimens					
Cabozantinib monotherapy	0%	33.3%	66.7%	33.3%	<0.05
Cabozantinib + chemotherapy	0%	28.6%	71.4%	28.6%	
Cabozantinib + immunotherapy	0%	83.3%	16.7%	83.3%	
Dosage of cabozantinib					
< 40 mg/day	0%	33.3%	66.7%	33.3%	0.76
≥ 40 mg/day	0%	40.0%	60.0%	40.0%	
Treatment lines for cabozantinib					
≥ 5^{th}	0%	29.4%	70.6%	29.4%	0.54
< 5^{th}	0%	42.4%	57.6%	42.4%	
Tissue AXL expression					
Positive	0%	50.0%	50.0%	50.0%	0.13
Negative	0%	0%	100%	0%	
Tissue MET expression					
Positive	0%	50.0%	50.0%	50.0%	1.0
Negative	0%	20.0%	80.0%	20.0%	

CPS class: Child-Pugh Score class

3.8. Liver function monitoring

First, we utilized the ALBI grade to monitor changes in liver function following cabozantinib treatment. Prior to initiating cabozantinib, liver function assessments classified 32% of patients as ALBI grade 1, 52% as ALBI grade 2, and 16% as ALBI grade 3. After four weeks of cabozantinib treatment, liver function assessment showed that 26% of patients were classified as ALBI grade 1, 48% as ALBI grade 2, and 26% as ALBI grade 3. After eight weeks of treatment with cabozantinib, 28% of patients were classified as ALBI grade 1, 53% as ALBI grade 2, and 20% as ALBI grade 3. The proportional changes in ALBI grade following cabozantinib treatment are illustrated in supplementary Fig. 2A. Second, we evaluated the ALBI score at baseline, 4 weeks, and 8 weeks after the initiation of cabozantinib. The ALBI score significantly worsened 4 weeks after treatment initiation (baseline vs. 4 weeks: −2.30 vs. −2.14; p = 0.003) but remained stable at 8 weeks with no significant statistical difference (4 weeks vs. 8 weeks: −2.14 vs. −2.04; p = 0.159) (supplementary Fig. 2B).

4. Discussion

The major findings of this study include: 1) Despite its use in fifth-line treatment and beyond, cabozantinib still demonstrated a favorable DCR, PFS, and OS; 2) The combination of cabozantinib with ICIs resulted in a higher DCR and longer PFS; and 3) AXL expression may serve as a potential predictor of cabozantinib efficacy.

The high-DCR achieving cabozantinib is the only drug approved for use after second-line treatment in HCC. In the CELESTIAL trial, the ORR was only 4%, but the DCR reached as high as 64%, with 28% of patients receiving cabozantinib as a third-line treatment [5]. However, real-world studies on cabozantinib remain limited. A retrospective cohort study involving 96 patients with unresectable HCC who received cabozantinib found that all patients were categorized as Child-Pugh A, and the majority received it as third-line systemic treatment. The ORR in this cohort was 4.2%, with a DCR of 63.5% [12]. Another retrospective study involving 88 HCC patients treated with cabozantinib as second- or later therapy reported a PR rate of 6.8% and a DCR of 38.6% [13]. Other retrospective studies have also shown similar efficacy of cabozantinib in treating patients with unresectable HCC [14,15]

As ICIs have become the recommended first-line treatment, Chan et al. conducted a phase II trial showing that cabozantinib retains efficacy after prior ICI treatment. In this trial, 47 patients who had received ICI-based regimens as first-line treatment showed an ORR of 6.4%, DCR of 83.0%, median PFS of 4.1 months, and OS of 9.9 months [16]. In our study, approximately half of the patients received cabozantinib after fifth-line treatment, with around 60% classified as CPS B or CPS C. Despite this, cabozantinib demonstrated a comparable DCR of 42.2% to other studies. Overall, cabozantinib has consistently shown clinical benefits after prior treatment with multiple kinase inhibitors or ICIs, as observed in both clinical trials and real-world data.

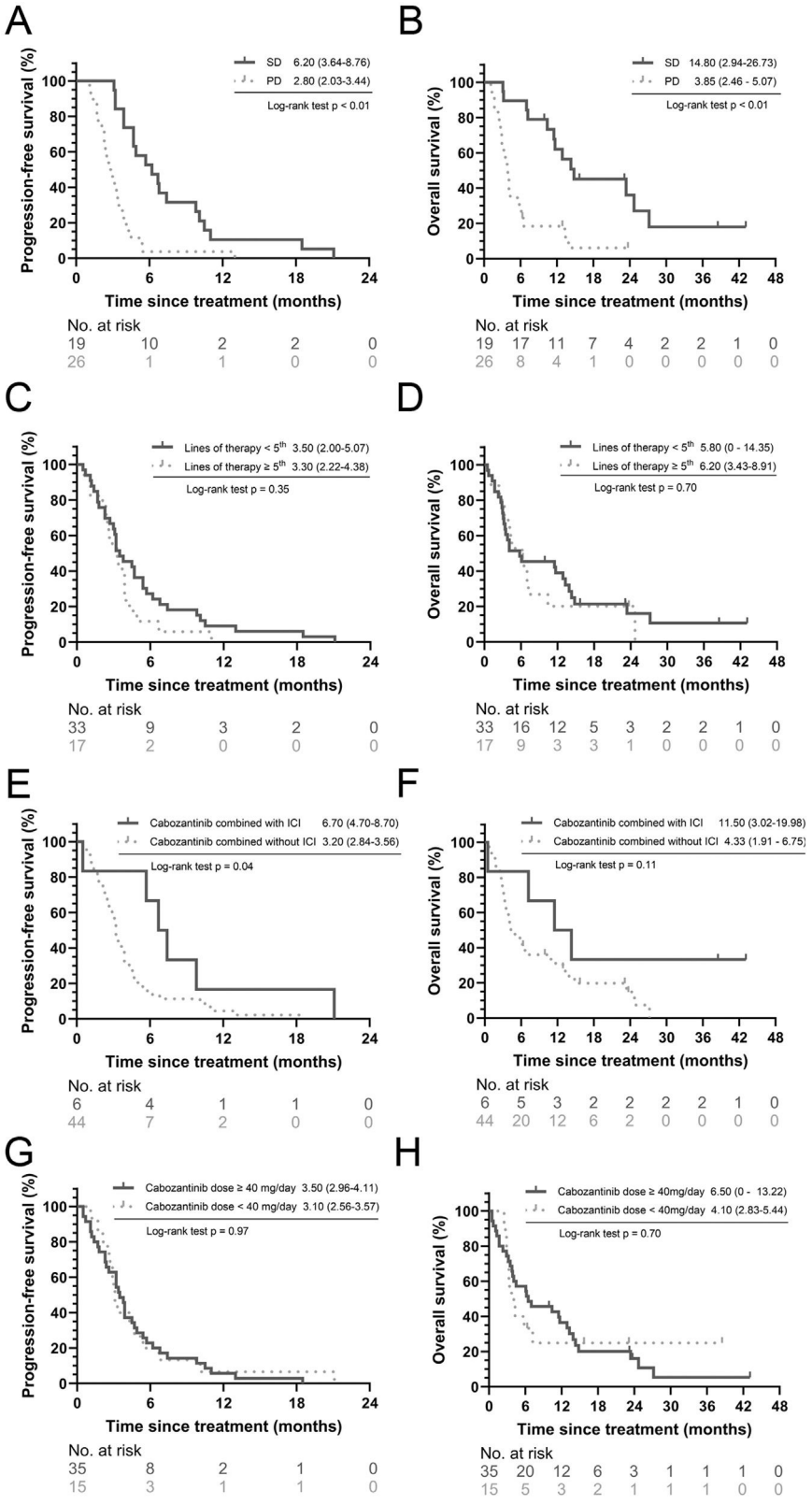

Fig. 1. Impact of treatment regimens and cabozantinib combination on progression-free survival and overall survival

Patients with stable disease exhibited (A) significantly longer PFS (6.2 vs. 2.8 months, $p < 0.01$) and (B) OS (14.8 vs. 3.9 months, $p < 0.01$) compared to those with progressive disease. No significant difference in (C) PFS or (D) OS was observed between patients who received five or more lines of treatment and those who received fewer than five lines. Patients treated with cabozantinib combined with ICIs showed significantly longer (E) PFS (6.7 vs. 3.2 months, $p = 0.04$) and (F) a trend toward longer OS compared to those not receiving the combination with ICIs. On the other hand, the dose of cabozantinib was not associated with clinical outcomes in terms of (G) PFS or (H) OS.

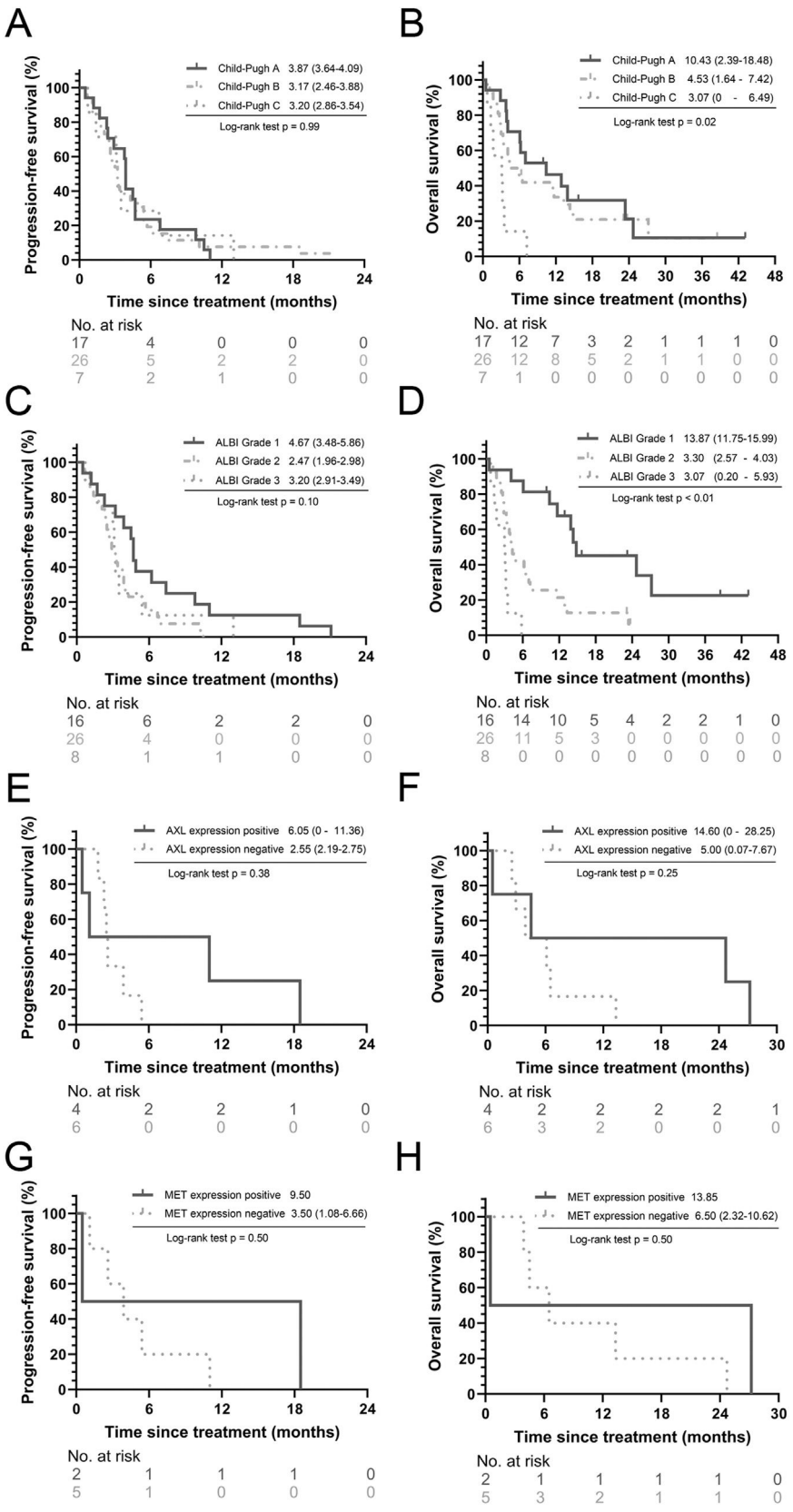

Fig. 2. Association of CPS Class, ALBI Grade, and AXL/MET expression with progression-free survival and overall survival

Both CPS class and ALBI grade were not significantly associated with (A, C) PFS, but were significantly associated with (B, D) OS, respectively. The presence of AXL expression demonstrated a significantly longer (E) PFS and a trend toward longer (F) OS. The presence of MET expression was not associated with (G) PFS and (H) OS.

Table 3
Risk factors for progression.

Variables		Univariate			Multivariate		
General factors		HR (95% CI)		*p* value	HR (95% CI)		*p* value
Age	≥ 65 vs. < 65	1.47	(0.76–2.84)	0.26			
Sex	Male vs. female	1.35	(0.68–2.67)	0.39			
HBsAg-positive	Yes vs. no	0.82	(0.41–1.62)	0.56			
Anti-HCV-positive	Yes vs. no	3.16	(1.25–7.99)	0.02	2.15	(0.79–5.90)	0.14
CPS class	Class B, C vs. A	1.03	(0.57–1.88)	0.92			
Cirrhosis	Yes vs. no	1.95	(1.09–3.49)	0.02	1.12	(0.58–2.16)	0.74
Macrovascular invasion	Yes vs. no	1.42	(0.81–2.52)	0.22			
Laboratory data							
AFP (ng/ml)	≥ 400 vs < 400	2.59	(1.35–4.95)	<0.01	2.39	(1.21–4.71)	0.01
Serum albumin (mg/dl)	< 3.5 vs ≥ 3.5	2.25	(1.26–4.05)	<0.01	1.94	(1.02–3.71)	0.04
Total bilirubin (mg/dl)	≥ 1.20 vs < 1.20	1.62	(0.91–2.88)	0.10			
Previous TKIs	≥ 2 TKIs vs < 2 TKIs	1.04	(0.55–1.95)	0.91			
Regimens with cabozantinib	with ICIs vs without ICIs	0.40	(0.16-1.03)	0.06	0.50	(0.19-1.34)	0.17
Dosage of cabozantinib (mg/day)	< 40 vs ≥ 40	1.04	(0.56–1.95)	0.89			
Treatment lines for cabozantinib	≥ 5^{th} vs < 5^{th}	1.60	(0.90–2.86)	0.11			

CPS class: Child-Pugh Score class; AFP: Alpha-Fetoprotein; TKIs: Tyrosine Kinase Inhibitors; ICIs: Immune Checkpoint Inhibitors

Table 4
Risk factors for death

Variables		Univariate			Multivariate		
General factors		HR (95% CI)		*p* value	HR (95% CI)		*p* value
Age	≥ 65 vs. < 65	1.52	(0.73–3.17)	0.26			
Sex	Male vs. female	1.72	(0.79–3.73)	0.17			
HBsAg-positive	Yes vs. no	0.78	(0.37–1.66)	0.52			
Anti-HCV-positive	Yes vs. no	2.26	(0.85–6.01)	0.10			
CPS class	Class B, C vs. A	1.52	(0.79–2.95)	0.21			
Cirrhosis	Yes vs. no	2.34	(1.24–4.43)	<0.01	1.16	(0.51–2.68)	0.72
Macrovascular invasion	Yes vs. no	1.46	(0.79–2.72)	0.23			
Laboratory data							
AFP (ng/ml)	≥ 400 vs < 400	1.67	(0.88–3.18)	0.12			
Serum albumin (mg/dl)	< 3.5 vs ≥ 3.5	8.52	(3.61–20.10)	< 0.01	10.66	(3.70-30.71)	< 0.01
Total bilirubin (mg/dl)	≥ 1.20 vs < 1.20	3.07	(1.61–5.82)	< 0.01	1.68	(0.70–4.03)	0.24
Previous TKIs	≥ 2 TKIs vs < 2 TKIs	0.99	(0.51–1.92)	0.98			
Regimens with cabozantinib	with ICIs vs without ICIs	0.44	(0.15-1.28)	0.11			
Dosage of cabozantinib (mg/day)	< 40 vs ≥ 40	0.99	(0.49–1.98)	0.97			
Treatment lines for cabozantinib	≥ 5^{th} vs < 5^{th}	1.33	(0.71–2.50)	0.37			

CPS class: Child-Pugh Score class; AFP: Alpha-Fetoprotein; TKIs: Tyrosine Kinase Inhibitors; ICIs: Immune Checkpoint Inhibitors

The benefits of combining cabozantinib with immunotherapy are not yet well established. In preclinical models, the combination of cabozantinib with antiprogrammed cell death protein-1 (anti-PD-1) therapy has shown enhanced tumor response rates, reduced viability, and increased necrosis compared to those of monotherapy. Additionally, neutrophil infiltration in tumors was significantly increased, enhancing the innate neutrophil-driven immune response. This combination also offers potential to overcome tumor resistance [17]. However, in the COSMIC-312 trial, cabozantinib combined with atezolizumab failed to demonstrate a survival benefit over sorafenib in the first-line setting [18]. In contrast, cabozantinib combined with nivolumab has shown superior efficacy compared to sunitinib in renal cell carcinoma (RCC), establishing it as a successful first-line regimen for RCC [7]. In our study, the combination of cabozantinib with ICI demonstrated a higher DCR and longer PFS, although no OS benefit was observed. Despite the heavily pretreated population and poor liver function in our cohort, the combination of cabozantinib with ICIs still showed potential for providing clinical benefit.

The role of AXL expression in HCC requires further investigation. AXL upregulation impacts the immune system, contributing to a suppressive tumor microenvironment that impairs the immune response against cancer cells [19,20] Additionally, high AXL expression has been linked to resistance to targeted therapies and anti-PD-1 treatments in various cancers. In HCC, AXL signaling upregulation has been associated with resistance to sorafenib and lenvatinib. Pharmacological inhibition of AXL may enhance tumor-intrinsic immunogenic responses in TKI-resistant HCC tumors [21,22] Overall, according to the literature, AXL expression is considered a poor prognostic factor in HCC patients who have not received AXL inhibitor treatment [23,24]

The correlation between AXL expression and the efficacy of cabozantinib across different cancer types remains unclear, and current evidence is inconclusive. In metastatic renal cell carcinoma, a post hoc analysis of 278 tumor tissue samples from the METEOR trial demonstrated that high levels of AXL expression was associated with better antitumor activity of cabozantinib and longer PFS compared to everolimus [25]. Our study is the first to observe a trend suggesting that AXL expression may predict better clinical efficacy of cabozantinib in HCC. Although the difference was not statistically significant due to the limited availability of tissue samples, this finding provides valuable insight for future research on the potential role of AXL as a predictive biomarker for cabozantinib in HCC.

This study has several limitations. First, as a retrospective analysis, it may be subject to information bias and selection bias. However, our data provide valuable insights, as this is the real-world study demonstrating the consistent efficacy of cabozantinib. Second, the limited sample size and non-randomized design raise questions about the reliability of the efficacy of the combination of cabozantinib and ICIs. A well-designed clinical trial or matched study is recommended to

address this. Lastly, the definition of AXL positivity is not well established, and further data are needed to validate its utility as a biomarker.

5. Conclusions

This real-world data demonstrated that cabozantinib is effective, well-tolerated, and feasible in patients with HCC refractory to multiple lines of systemic therapies. Additionally, we highlighted the potential for cabozantinib to be combined with immunotherapy in heavily pretreated HCC. The AXL expression may also serve as a predictive biomarker for cabozantinib efficacy in HCC.

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Data availability statement

Data are available by requesting.

Declaration of interests

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.aohep.2025.101917.

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