

# Real-world efficacy and safety of cabozantinib in Korean patients with advanced hepatocellular carcinoma: a multicenter retrospective analysis

Yeong Hak Bang<sup>\*</sup> , Choong-kun Lee<sup>\*</sup>, Changhoon Yoo<sup>†</sup> , Hong Jae Chon , Moonki Hong, Beodeul Kang, Hyung-Don Kim, Sook Ryun Park, Won-Mook Choi, Jonggi Choi, Danbi Lee, Ju Hyun Shim, Kang Mo Kim, Young-Suk Lim, Han Chu Lee, Min-Hee Ryu and Baek-Yeol Ryoo<sup>†</sup>

## Abstract

**Background:** Cabozantinib, a multiple kinase inhibitor, was recently approved for patients with previously treated unresectable hepatocellular carcinoma (uHCC). We investigated the real-world safety and efficacy profiles of cabozantinib.

**Methods:** This multicenter retrospective study included 110 patients with uHCC who received cabozantinib after progression on other systemic treatments between October 2019 and May 2021.

**Results:** The median age was 58 (range, 20–77) years, and 98 (89.1%) were male. Prior to cabozantinib, all patients were treated with other systemic therapies: sorafenib ( $n = 104$ , 94.5%) and regorafenib ( $n = 91$ , 82.7%) were the most commonly used agents. Immune checkpoint inhibitors were previously used in 93 patients (84.5%). Cabozantinib was used beyond the third-line of therapy in most patients ( $n = 90$ , 81.8%). With a median follow-up duration of 11.9 months [95% confidence interval (CI), 10.8–17.2], the median progression-free survival (PFS) was 3.7 months (95% CI, 3.1–4.9), and the median overall survival (OS) was 7.5 months (95% CI, 5.5–9.5). The disease control rate and overall response rate (ORR) were 66.3% and 3.6%, respectively. In the Child–Pugh A cohort ( $n = 88$ ), the ORR was 4.5%, and the median PFS and OS were 4.3 months (95% CI, 3.6–5.8) and 9.0 months (95% CI, 7.5–11.7), respectively.

**Conclusion:** Cabozantinib showed consistent efficacy outcomes with a prior phase III trial, although in this study, it was used as later-line therapy for patients who were refractory to multiple systemic treatments, including immune checkpoint inhibitors.

**Keywords:** cabozantinib, hepatocellular carcinoma

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## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the fourth most common cause of cancer-related death worldwide.<sup>1</sup> For patients with advanced HCC, systemic therapy is the mainstay of treatment. Although sorafenib was the only agent approved for unresectable HCC (uHCC),<sup>2</sup> multiple agents have recently acquired approval for the management of patients

with uHCC based on positive results in the prospective phase II and III trials.<sup>3–8</sup> While sorafenib and lenvatinib have been the standard first-line therapy,<sup>2,3</sup> the landscape of first-line therapy for uHCC is rapidly changing as atezolizumab–bevacizumab and tremelimumab–durvalumab demonstrated significant improvements in overall survival (OS) compared to sorafenib in the phase III IMbrave150 and HIMALAYA trials.<sup>8,9</sup>

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Correspondence to:

**Changhoon Yoo**  
Department of Oncology,  
Asan Medical Center,  
University of Ulsan College  
of Medicine, 88 Olympic-ro  
43-gil, Songpa-gu, Seoul  
05505, Korea.

[yooc@amc.seoul.kr](mailto:yooc@amc.seoul.kr)

**Baek-Yeol Ryoo**  
Department of Oncology,  
Asan Medical Center,  
University of Ulsan College  
of Medicine, 88 Olympic-ro  
43-gil, Songpa-gu, Seoul  
05505, Korea.

[ryooby@amc.seoul.kr](mailto:ryooby@amc.seoul.kr)

**Yeong Hak Bang**  
**Hyung-Don Kim**  
**Sook Ryun Park**  
**Min-Hee Ryu** Department  
of Oncology, Asan Medical  
Center, University of Ulsan  
College of Medicine, Seoul,  
Korea

**Choong-kun Lee**  
**Moonki Hong**  
Division of Medical  
Oncology, Department of  
Internal Medicine, Yonsei  
University College of  
Medicine, Seoul, Korea

**Hong Jae Chon**  
**Beodeul Kang**  
Department of Medical  
Oncology CHA Bundang  
Medical Center, CHA  
University, Seongnam,  
Korea

**Won-Mook Choi**  
**Jonggi Choi**  
**Danbi Lee**  
**Ju Hyun Shim**  
**Kang Mo Kim**  
**Young-Suk Lim**  
**Han Chu Lee**  
Department of  
Gastroenterology, Asan  
Medical Center, University  
of Ulsan College of  
Medicine, Seoul, Korea

\*Yeong Hak Bang  
and Choong-kun Lee  
contributed equally as co-  
first authors.

†Changhoon Yoo  
and Baek-Yeol Ryoo  
contributed equally as co-  
corresponding authors.

Atezolizumab plus cabozantinib showed significantly improved progression-free survival (PFS) compared to sorafenib in the phase III COSMIC-312 trial, but it failed to demonstrate its superiority in terms of OS.<sup>10</sup>

As salvage therapies, regorafenib, cabozantinib, and ramucirumab have demonstrated survival benefits for patients who progressed on first-line sorafenib in randomized phase III trials.<sup>4,5,11</sup> Despite a lack of positive data in the phase III trials, immune checkpoint inhibitors (ICIs), including nivolumab, pembrolizumab, and an ipilimumab–nivolumab combination, were approved in some countries for patients who progressed on sorafenib based on the promising results in the phase II trials.<sup>6,12,13</sup>

Cabozantinib is an oral multiple kinase inhibitor (MKI) targeting vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3, MET, and the TAM kinase family (TYRO-3, AXL, and MER).<sup>14</sup> In the CELESTIAL trial, cabozantinib showed significant improvement in terms of a median PFS of 3.3 months and a median OS of 2.2 months compared to placebo for patients with uHCC who are intolerant of or progressed on sorafenib.<sup>5</sup> In contrast to ramucirumab, which has only been approved for patients with alpha-feto-protein (AFP) levels  $\geq 400$  ng/ml<sup>11</sup> and the pivotal trial for regorafenib<sup>4</sup> was limited to sorafenib-tolerant patients, cabozantinib demonstrated a clinical benefit in a more general patient population. Cabozantinib was investigated as second- or third-line therapy in the CELESTIAL trial, while other agents were tested as only second-line therapy.<sup>5</sup>

Given that the characteristics of patients with uHCC in daily practice are often different from those in the prospective clinical trials in terms of liver function or tumor burden, and the rapidly changing landscape of the management of uHCC, particularly the widespread incorporation of ICIs in first- or later-line therapy,<sup>15</sup> there is an unmet need for real-world efficacy and safety assessments of cabozantinib. We, therefore, performed a multicenter retrospective analysis of cabozantinib as subsequent therapy after progression on any prior systemic therapy for patients with uHCC.

### Patients and methods

This was a multicenter, retrospective, open-label, non-comparative observational study. Patient

data were retrospectively collected and reviewed using electronic medical records from three tertiary referral hospitals in Korea. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of each participating center. Informed consent from the patients was waived by the IRB because of the retrospective nature of this study.

Between October 2019 and May 2021, a total of 110 uHCC patients who received cabozantinib as a subsequent therapy after failure of other systemic therapy were identified. The dosing schedule and modification per adverse events (AEs) of cabozantinib were based on the protocol of the CELESTIAL trial in general.<sup>5</sup> However, doses could be adjusted at the discretion of the attending physicians with the consideration of toxicities on prior therapy or comorbidities. Laboratory tests, including a complete blood count, chemistry and coagulation battery, and a physical examination, were performed every 4 weeks. Tumor response evaluation was performed using computed tomography (CT) or magnetic resonance imaging (MRI) scans every 8–12 weeks and was graded per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Liver functions were classified according to the Child–Pugh score and albumin–bilirubin (ALBI) grade as previously described.<sup>16,17</sup>

PFS was defined as the time from the initiation of cabozantinib to the date of disease progression determined by the RECIST v1.1 criteria or death. OS was defined as the time interval between the date of the initiation of cabozantinib and the date of death from any cause. The safety profile was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.

The survival curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses of PFS and OS were performed using log-rank tests and Cox proportional hazards models. In the multivariate analysis, variables with a potential relationship ( $p < 0.1$ ) in the univariate analyses were included. A  $p$  value of less than 0.05 was considered statistically significant. Statistical analyses were performed using R software (version 4.5.1, R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Baseline characteristics

The baseline characteristics of the patients are summarized in Table 1. The median age was 58 (range, 20–77) years, and 98 (89.1%) were male. Hepatitis B virus (HBV) infection ( $n=99$ , 90.0%) was the most frequent etiology of HCC. Most patients ( $n=88$ , 80.0%) had Child–Pugh A, whereas 22 (20.0%) had Child–Pugh B liver function at the time of initiating cabozantinib. All patients had Barcelona Clinic Liver Cancer (BCLC) C stage; 51 (46.4%) patients had macrovascular invasion, and 104 (94.5%) had extrahepatic metastasis.

All patients received other types of systemic therapy prior to the administration of cabozantinib. Most patients ( $n=90$ , 81.8%) received cabozantinib as the fourth or greater line of therapy followed by third line ( $n=18$ , 16.4%). Sorafenib was the most frequently used agent prior to cabozantinib ( $n=104$ , 94.5%), followed by regorafenib ( $n=91$ , 82.7%); the median time to progression (TTP) on prior sorafenib and regorafenib was 2.7 (range, 0.5–28.9) months and 3.4 (range, 0.9–23.0) months, respectively. ICIs were previously given to 93 patients [84.5%; nivolumab ( $n=82$ , 74.5%), atezolizumab–bevacizumab ( $n=10$ , 9.1%), pembrolizumab ( $n=3$ , 2.7%), and durvalumab ( $n=2$ , 1.8%)]. A sorafenib–regorafenib sequence was previously used in 79 patients (71.8%). The starting dose of cabozantinib was 60 and 40 mg daily in 65 (59.1%) and 43 (39.1%) patients, respectively. The remaining two (1.8%) patients received 60 mg every other day at the discretion of the attending physician with the consideration of financial constraints as the cost of cabozantinib was not reimbursed. In patients with Child–Pugh A and B liver function, a starting dose of 60 mg daily was used in 57 (64.8%) and 8 patients (36.4%), respectively.

### Efficacy outcomes

With a median follow-up of 11.9 months [95% confidence interval (CI), 10.8–17.2], the median PFS was 3.7 months (95% CI, 3.1–4.9) and the median OS was 7.5 months (95% CI, 5.5–9.5) among all patients (Figure 1). The overall response rate (ORR) was 3.6%, with 4 (3.6%), 69 (62.7%), and 20 (18.2%) patients showing partial responses, stable disease, and progressive disease, respectively, and a response evaluation was not

available for 17 patients (15.5%). In the Child–Pugh A cohort ( $n=88$ ), the ORR was 4.5%, and the median PFS and OS were 4.3 months (95% CI, 3.6–5.8) and 9.0 months (95% CI, 7.5–11.7), respectively (Table 2). Among the 79 patients who received the sorafenib–regorafenib sequence prior to cabozantinib, the median OS from the start of first-line sorafenib was 28.3 months (95% CI, 26.3–33.1) (Supplementary Figure 1).

Because of the heterogeneous nature of the population included in this study, the efficacy outcomes were analyzed after stratification according to the treatment line of cabozantinib and the Child–Pugh class when cabozantinib was initiated (Table 2). Compared with patients with Child–Pugh A, patients with Child–Pugh B had worse PFS (median 4.3 *versus* 2.2 months,  $p<0.001$ ), OS (9.0 *versus* 3.8 months,  $p<0.001$ ), and lower disease control rates (DCRs; 71.5% *versus* 45.5%,  $p=0.021$ ). Patients with ALBI grade 3 showed significantly worse PFS (3.5 *versus* 6.2 months,  $p=0.009$ ) and OS (5.6 *versus* 13 months,  $p<0.001$ ) compared to patients of ALBI grade 1 or 2 (Figure 2). Patients with AFP levels  $\geq 400$  ng/ml showed significantly worse OS (5.3 *versus* 9.5 months,  $p=0.014$ ), while there was a trend toward worse PFS (3.1 *versus* 4.6 months,  $p=0.14$ ). Prior administration of ICIs was not associated with PFS ( $p=0.43$ ) or OS ( $p=0.64$ ) (Figure 3).

Multivariate analysis revealed that Child–Pugh B was an independent negative prognostic factor for both PFS [*versus* Child–Pugh A, hazard ratio (HR), 3.38 (95% CI, 1.50–4.60);  $p=0.001$ ] and OS [HR, 4.95 (95% CI, 2.81–10.2);  $p<0.001$ ] (Table 3). There were marginal significances for the association between OS and baseline serum AFP levels [ $\geq 400$  *versus*  $<400$  ng/ml; HR, 1.89 (0.98–2.74);  $p=0.059$ ] and TTP on prior sorafenib [ $\geq$ median *versus*  $<$ median; HR, 0.61 (0.37–1.04);  $p=0.069$ ]. Multivariate analysis including ALBI grade was conducted separately, considering the potential high collinearity between the ALBI score and the Child–Pugh score (Supplementary Table 1). ALBI grade 3 was significantly associated with a worse PFS [HR, 2.07 (95% CI, 1.13–3.79);  $p=0.018$ ] and OS [HR, 2.85 (95% CI, 1.43–5.70);  $p=0.003$ ] compared to ALBI grade 1 or 2. In this analysis set, baseline AFP level was significantly associated with OS [ $\geq 400$  *versus*  $<400$  ng/ml; HR, 1.68 (1.02–2.76);  $p=0.042$ ].

**Table 1.** Baseline patient characteristics.

	N = 110 (%)
Age (years)	58 (20–77)
Male gender	98 (89.1)
Etiology	
HBV	99 (90.0)
HCV	2 (1.8)
Alcohol	4 (3.6)
Unknown	5 (4.5)
ECOG PS	
0–1	96 (87.3)
2	14 (12.7)
BCLC stage	
C	110 (100.0)
Child–Pugh class	
A	88 (80.0)
B	22 (20.0)
ALBI grade	
1	24 (21.8)
2	69 (62.7)
3	17 (15.5)
Macrovascular invasion	
Yes	51 (46.4)
No	59 (53.6)
Extrahepatic metastasis	
Yes	104 (94.5)
No	6 (5.5)
AFP, median (range), ng/ml	475.6 (1.6–503,168)
<400	52 (47.3)
≥400	54 (49.1)
Unknown	4 (3.6)
Previous systemic treatment lines	
1	2 (1.8)
2	18 (16.4)

(Continued)

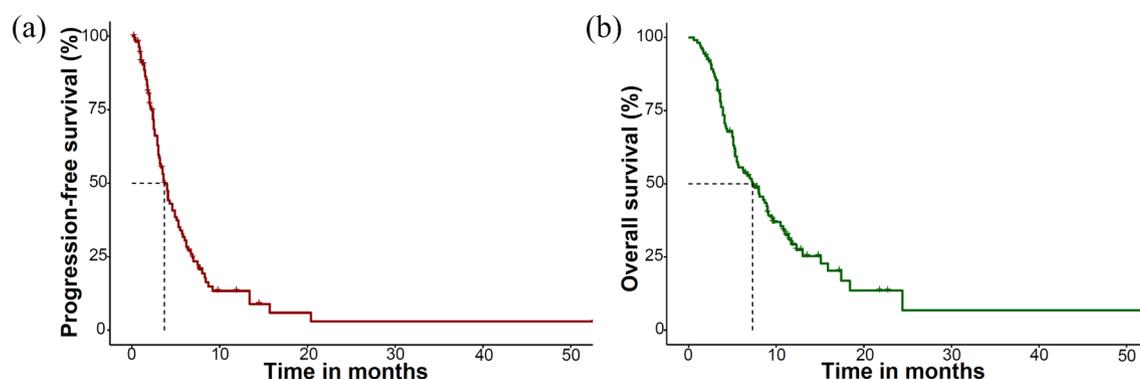
**Table 1.** (Continued)

	N = 110 (%)
≥3	90 (81.8)
Previous treatments	
Liver transplantation	9 (8.2)
Surgical resection	47 (42.7)
TACE	85 (77.3)
RFA	9 (8.2)
SBRT	46 (41.8)
Previous systemic treatment	
Sorafenib	104 (94.5)
Lenvatinib	26 (23.6)
Regorafenib	91 (82.7)
Ramucirumab	2 (1.8)
Nivolumab	82 (74.5)
Atezolizumab + bevacizumab	10 (9.1)
Durvalumab	2 (1.8)
Pembrolizumab	3 (2.7)
Doxorubicin + cisplatin	3 (2.7)

ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; PS, performance status; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization.  
Data are presented as *n* (%) or median (range).

### Safety outcomes

The AEs associated with cabozantinib are summarized in Table 4. Any grade AEs were noted in 83 (75.5%) patients, while grade 3–4 AEs were present in 18 (16.4%) patients. The most common toxicity was hand-foot skin reaction; any grade in 35 patients (31.8%) and grade 3–4 in 5 patients (4.5%). Thrombocytopenia (*n* = 28, 25.5%), diarrhea (*n* = 23, 20.9%), and anorexia (*n* = 18, 16.4%) were also frequently reported toxicities. The dose of cabozantinib was reduced in 18 (16.4%) patients because of the toxicities. Hand-foot skin reaction (*n* = 5, 4.5%) and thrombocytopenia (*n* = 5, 4.5%) were the most common cause of dose reduction, followed by



**Figure 1.** Kaplan–Meier curves of the survival outcomes of the study cohort: (a) PFS and (b) OS.

**Table 2.** Efficacy parameters of cabozantinib.

Response according to RECIST version 1.1	Overall ( <i>n</i> = 110)	Child–Pugh A			Child–Pugh B ( <i>n</i> = 22)
		All ( <i>n</i> = 88)	Second and third line ( <i>n</i> = 16)	Fourth line ( <i>n</i> = 72)	
Complete response, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Partial response, <i>n</i> (%)	4 (3.6)	4 (4.5)	1 (6.3)	3 (4.2)	0 (0)
Stable disease, <i>n</i> (%)	69 (62.7)	59 (67.0)	11 (68.8)	48 (66.7)	10 (45.5)
Progressive disease, <i>n</i> (%)	20 (18.2)	13 (14.8)	2 (12.5)	11 (15.3)	7 (31.8)
Not evaluable, <i>n</i> (%)	17 (15.5)	12 (13.6)	2 (12.5)	10 (13.9)	5 (22.7)
ORR, %	3.6	4.5	6.3	4.2	0
Disease control rate, %	66.3	71.5	75.1	70.9	45.5
Median OS, month (95% CI)	7.5 (5.5–9.5)	9.0 (7.5–11.7)	24.4 (11.7–NR)	8.5 (7.0–10.8)	3.8 (2.9–5.0)
Median PFS, months (95% CI)	3.7 (3.1–4.9)	4.3 (3.6–5.8)	5.3 (4.0–NR)	4.1 (3.1–6)	2.2 (1.4–3.3)

CI, confidence interval; NR, not reached; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

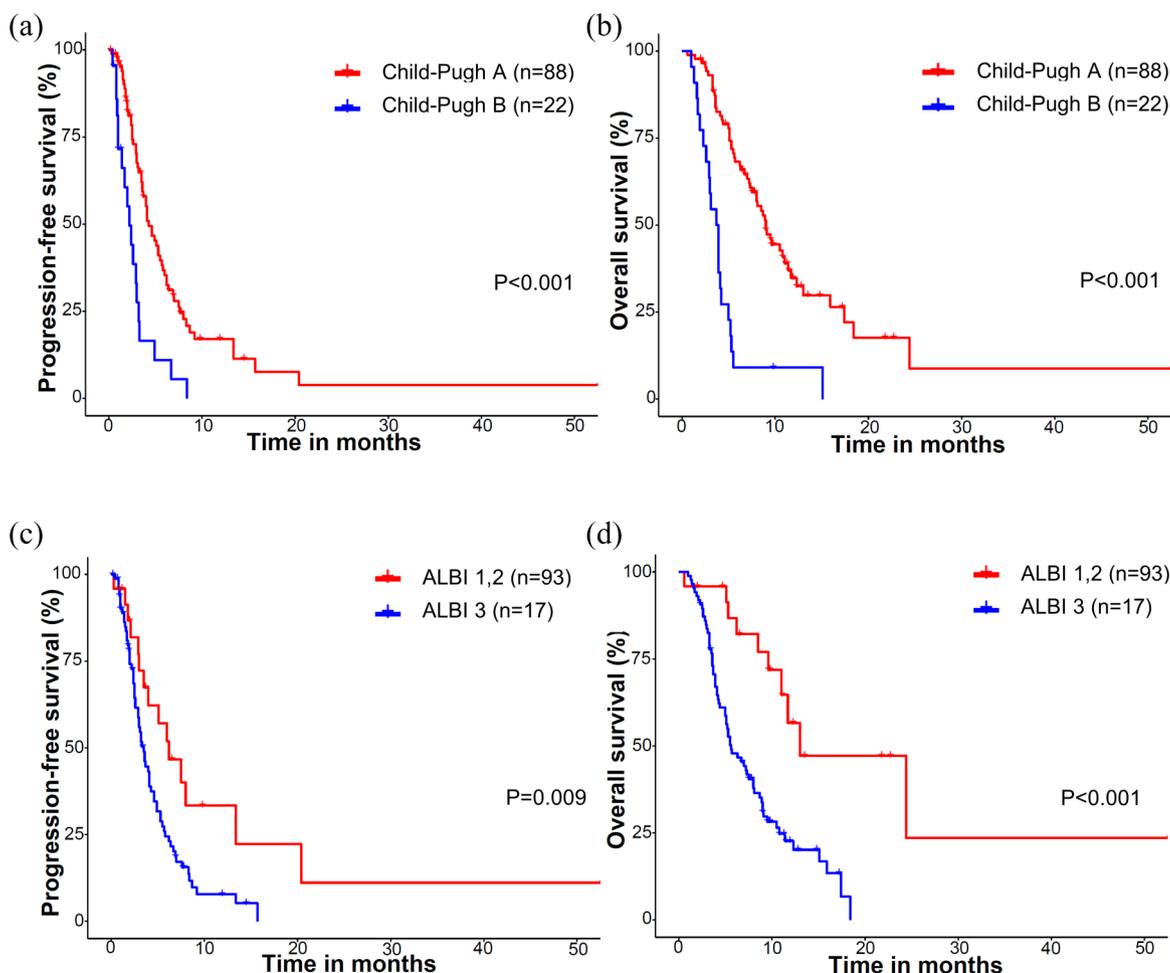
stomatitis (*n* = 2, 1.8%), fatigue (*n* = 2, 1.8%), nausea (*n* = 2, 1.8%), diarrhea (*n* = 1, 0.9%), and elevated aspartate aminotransferase (*n* = 1, 0.9%). Compared to patients with Child–Pugh A, an increased bilirubin level was more frequently noted in patients with Child–Pugh B (2.3% *versus* 13.6%, *p* = 0.054 for any grade and 0% *versus* 9.1%, *p* = 0.039 for grade 3–4).

## Discussion

This multicenter retrospective study, which included uHCC patients who were refractory to at least one prior systemic chemotherapy, showed that the efficacy outcomes of

cabozantinib were consistent with the results of the CELESTIAL trial, even though the current study included a broader patient population.<sup>5</sup> The median PFS and OS with cabozantinib were 3.7 and 7.5 months, respectively, and the ORR per RECIST v1.1 was 3.6%. Our findings were also in line with the results of recent European multicenter retrospective studies (median PFS, 3.2–5.1 months; and median OS, 6.8–12.1 months).<sup>18,19</sup>

In this study, cabozantinib was administered to heavily pretreated patients, as 81.8% of the study population received cabozantinib as the fourth or greater line of therapy and 20.0% of the patients

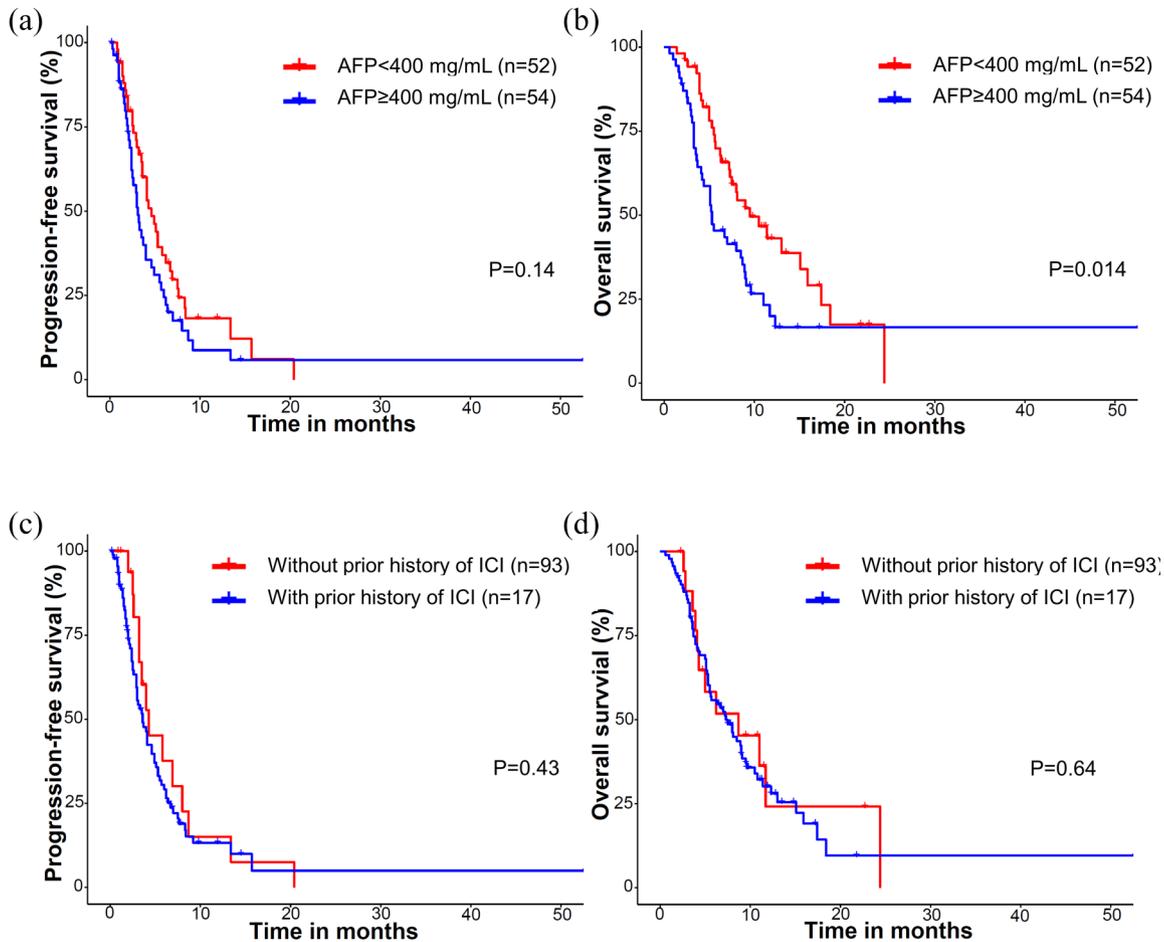


**Figure 2.** Survival outcomes according to the Child–Pugh score and ALBI grade: (a) PFS and (b) OS according to the Child–Pugh score. (c) PFS and (d) OS according to ALBI grade.

had Child–Pugh B liver function. Cabozantinib was investigated as second- or third-line therapy for Child–Pugh A patients after failure on first-line sorafenib in the pivotal CELESTIAL trial.<sup>5</sup> In the previous real-life studies, cabozantinib was mainly used as third-line therapy (79.1% of 96 patients) in the Italian analysis (all patients were Child–Pugh A), and 20.4% of 88 patients in Austria, Switzerland, and Germany received cabozantinib as fourth or greater lines of therapy (25% of patients were Child–Pugh B).<sup>18,19</sup> Consistent efficacy outcomes even in the later-line setting in the current analysis suggest that cabozantinib may maintain its clinical benefit even in heavily pretreated HCC patients and reinforce the importance of sequential treatments in patients with advanced HCC.

The current study showed that patients with Child–Pugh B and ALBI grade 3 were significantly

associated with a worse OS with cabozantinib in the multivariate analyses. Considering the potential deterioration of liver function related to tumor progression, and the risk of mortality from liver decompensation, Child–Pugh, and ALBI grades, indicators of liver function were the significant prognostic factors in patients with advanced HCC treated with targeted agents including cabozantinib, sorafenib, lenvatinib, regorafenib, and ramucirumab.<sup>5,7,20–23</sup> Lower starting doses in Child–Pugh B patients could also be associated with worse DCR and PFS compared to Child–Pugh A patients in the current study. Given the poor clinical outcomes and increased frequency of AEs in patients with poor liver function, the use of cabozantinib should be decided based on shared decision-making with consideration of the potential clinical benefits and risks for each individual patient. In addition, high baseline AFP levels  $\geq 400$  mg/ml were associated with a worse OS in



**Figure 3.** Survival outcomes according to the AFP level and prior exposure to ICIs: (a) PFS and (b) OS according to AFP ( $\geq 400$  and  $< 400$  ng/mL). (c) PFS and (d) OS according to prior exposure to ICIs.

our patient population. This is in line with the results of prior prospective and real-world studies of cabozantinib, sorafenib, and regorafenib, which have all identified high serum AFP levels as a negative prognostic factor.<sup>4,24–28</sup>

As cabozantinib, regorafenib, and ramucirumab have only been investigated among patients previously treated with sorafenib, and there is no head-to-head comparison among these agents, selection of the appropriate drug for each individual patient is a key issue for the management of patients who failed on first-line sorafenib. Recent *post hoc* analysis studies, which used data from the pivotal trials of cabozantinib,<sup>5</sup> regorafenib,<sup>4</sup> and ramucirumab,<sup>7</sup> showed that cabozantinib was associated with a prolonged median PFS compared with ramucirumab in patients with AFP  $\geq 400$  ng/mL (median 5.5 *versus* 2.8 months,  $p=0.016$ )<sup>29</sup> and regorafenib in second-line treatment (median 5.6 *versus* 3.1 months,  $p<0.001$ ).<sup>30</sup> In addition, while a previous

retrospective study of 440 patients showed that the efficacy of regorafenib was poor in patients with a shorter TTP on prior sorafenib,<sup>31</sup> the efficacy of cabozantinib was not significantly associated with TTP on prior sorafenib in the current study. Recent multinational retrospective analysis using matching-adjusted indirect comparison analysis also suggested that cabozantinib may provide a better OS than regorafenib in patients with early progression on prior sorafenib.<sup>32</sup> This may suggest that cabozantinib could be considered as a priority option, particularly for patients who progressed rapidly with sorafenib. In addition, as there is no established biomarker for the selection of therapeutic agents in HCC except AFP for ramucirumab, further efforts are required to define additional specific biomarkers for the prediction of each agent's efficacy or toxicity.<sup>33</sup>

A combination of atezolizumab, an anti-PD-L1 antibody, and bevacizumab, an anti-VEGF

**Table 3.** Multivariate analyses for PFS and OS.

Variables	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p value						
Age ( $\geq 60$ versus $< 60$ years)	0.89 (0.58–1.38)	0.606			0.80 (0.51–1.26)	0.341		
Sex (Male versus female)	0.89 (0.41–1.94)	0.766			0.68 (0.30–1.58)	0.373		
Etiology (HBV versus others)	1.16 (0.58–2.33)	0.678			1.80 (0.77–4.20)	0.177		
Child–Pugh class (B versus A)	2.84 (1.67–4.81)	<0.001	3.38 (1.50–4.60)	0.001	4.10 (2.40–6.95)	<0.001	4.95 (2.81–10.2)	<0.001
Presence of macrovascular invasion (Yes versus no)	1.48 (0.96–2.30)	0.076	0.80 (0.76–1.92)	0.421	2.03 (1.29–3.21)	0.002	1.14 (0.63–1.97)	0.715
Baseline serum AFP levels ( $\geq 400$ ng/ml versus $< 400$ $\mu$ g/mL)	1.39 (0.90–2.15)	0.142			2.43 (1.12–2.85)	0.015	1.89 (0.98–2.74)	0.059
Presence of prior history of ICI (Yes versus no)	1.26 (0.71–2.25)	0.431			1.16 (0.62–2.16)	0.642		
TTP of sorafenib ( $\geq$ median versus $<$ median)	0.95 (0.60–1.49)	0.816			0.53 (0.33–0.84)	0.007	0.61 (0.37–1.04)	0.069
Treatment lines ( $> 3$ versus $\leq 3$ )	1.35 (0.79–2.31)	0.271			2.12 (1.05–4.27)	0.035	1.23 (0.55–2.95)	0.574

AFP, alpha-fetoprotein; CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; ICI, immune checkpoint inhibitor; TTP, time to progression.

antibody, is the new standard first-line therapy based on the results of the pivotal IMbrave 150 trial, which demonstrated significantly improved ORR, PFS, and OS compared to sorafenib.<sup>8,34</sup> Recently, the HIMALAYA trial demonstrated that a priming dose of tremelimumab and a regular dose of durvalumab was superior to sorafenib in terms of OS, and this regimen will become one of the standard first-line regimens.<sup>9</sup> When the CELESTIAL trial was conducted, ICIs were not available in daily practice for the management of unresectable HCC, and the clinical outcomes of cabozantinib in patients previously treated with ICIs have not been sufficiently demonstrated, although a *post hoc* analysis of the CELESTIAL trial showed that the outcomes of 14 patients previously treated with ICIs prior to cabozantinib were similar to the other patients.<sup>35</sup> In our study, ICIs were previously given to 93 patients (84.5%) and there was no significant impact of prior

exposure to ICIs on the clinical outcomes of cabozantinib, implying that cabozantinib might provide consistent efficacy after progression on an atezolizumab–bevacizumab combination. In future studies, the clinical relevance of cabozantinib should be further investigated among patients after failure of these new combination treatments. Currently, a multinational prospective trial is ongoing to assess the efficacy and safety of cabozantinib after progression on ICIs, including atezolizumab–bevacizumab (ClinicalTrials.gov identifier NCT04588051).

The safety profiles of cabozantinib in this study were in line with the results of the CELESTIAL trial and previous retrospective studies of uHCC patients.<sup>5</sup> Most AEs were of grade 1 or 2, although there might be underestimation of the toxicity profile considering the retrospective nature of the current study. The toxicities noted in this study

**Table 4.** AEs.

NCI-CTCAE v5	All (n = 110)		Child-Pugh A (n = 88)		Child-Pugh B (n = 22)		p value	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any AEs	83 (75.5)	18 (16.4)	67 (76.1)	13 (14.8)	16 (72.7)	5 (22.7)	0.466	0.272
Hand-foot skin reaction	35 (31.8)	5 (4.5)	31 (35.2)	4 (4.5)	4 (13.6)	1 (4.5)	0.098	0.739
Anorexia	18 (16.4)	1 (0.9)	15 (17.0)	1 (1.1)	3 (13.6)	0 (0)	0.492	0.800
Nausea/vomiting	5 (4.5)	1 (0.9)	3 (3.4)	0 (0)	2 (9.1)	1 (4.5)	0.261	0.492
Diarrhea	23 (20.9)	3 (2.7)	18 (20.5)	2 (2.3)	5 (22.7)	1 (4.5)	0.509	0.492
Hypertension	17 (19.8)	4 (3.6)	12 (13.6)	3 (3.4)	5 (22.7)	1 (4.5)	0.228	0.596
Fatigue	5 (4.5)	0 (0)	3 (3.4)	0 (0)	2 (9.1)	0 (0)	0.261	NE
Increased blood bilirubin	5 (2.7)	2 (0.9)	2 (2.3)	0 (0)	3 (13.6)	2 (9.1)	0.054	0.039
Elevated AST/ALT	22 (20)	1 (0.9)	16 (18.2)	1 (1.1)	6 (27.3)	0 (0)	0.250	0.800
Anemia	14 (12.7)	2 (1.8)	12 (13.6)	1 (1.1)	2 (9.1)	1 (4.5)	0.437	0.361
Thrombocytopenia	28 (25.5)	4 (3.6)	21 (23.9)	3 (3.4)	7 (31.8)	1 (4.5)	0.304	0.596
Neutropenia	6 (5.5)	1 (0.9)	4 (4.5)	1 (1.1)	2 (9.1)	0 (0)	0.345	0.800
Skin rash	4 (3.6)	1 (0.9)	3 (3.4)	0 (0)	1 (4.5)	1 (4.5)	0.596	0.200

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NE, not evaluable.

were mostly well manageable with appropriate supportive care, which may lead to improved treatment outcomes.<sup>36</sup> Although the overall incidence of AEs was comparable between Child-Pugh A and Child-Pugh B patients, grade 3–4 increased blood bilirubin was more frequently observed in Child-Pugh B patients, and this indicates that close monitoring of AEs is warranted for Child-Pugh B patients during the administration of cabozantinib.

This study has limitations, the most prominent of which is its retrospective design since this introduces unintentional biases. Although our study was based on multiple tertiary referral institutions, this study included only Korean patients and the study population was relatively small. This may limit the interpretation and generalizability of our data. Nevertheless, given the limited reports on clinical outcomes of cabozantinib treatment in the real world and among patients who progressed on prior ICIs, our results may be

helpful for the management of uHCC and can be used to guide clinical decisions.

### Conclusion

In this real-world analysis of Korean patients with uHCC, cabozantinib showed consistent efficacy and safety outcomes compared to the pivotal phase III CELESTIAL trial. Further investigations into the role of cabozantinib after failure of the new standard first-line treatment, atezolizumab–bevacizumab, are required.

### Ethical approval and patient consent statement

The ethical review boards of each participating site approved the study protocol (Asan Medical Center, 2021-1199; Yonsei Cancer center, 4-2021-1302; CHA Bundang Medical Center, 2021-10-024) and waived the need for informed consent for this study given the non-requirement of consent in retrospective analyses according to the regulations in Korea.

### Consent for publication

All data are reported in an anonymized, aggregate manner.

### Author contribution(s)

**Yeong Hak Bang:** Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

**Choong-kun Lee:** Conceptualization; Formal analysis; Resources; Writing – original draft; Writing – review & editing.

**Changhoon Yoo:** Conceptualization; Resources; Supervision; Writing – original draft; Writing – review & editing.

**Hong Jae Chon:** Conceptualization; Resources; Writing – review & editing.

**Moonki Hong:** Conceptualization; Data curation; Writing – review & editing.

**Beodeul Kang:** Conceptualization; Resources; Writing – review & editing.

**Hyung-Don Kim:** Conceptualization; Resources; Writing – review & editing.

**Sook Ryun Park:** Conceptualization; Resources; Writing – review & editing.

**Won-Mook Choi:** Conceptualization; Resources; Writing – review & editing.

**Jonggi Choi:** Conceptualization; Resources; Writing – review & editing.

**Danbi Lee:** Conceptualization; Resources; Writing – review & editing.

**Ju Hyun Shim:** Conceptualization; Resources; Writing – review & editing.

**Kang Mo Kim:** Conceptualization; Resources; Writing – review & editing.

**Young-Suk Lim:** Conceptualization; Resources; Writing – review & editing.

**Han Chu Lee:** Conceptualization; Resources; Writing – review & editing.

**Min-Hee Ryu:** Conceptualization; Resources; Writing – review & editing.

**Baek-Yeol Ryoo:** Conceptualization; Resources; Supervision; Writing – original draft; Writing – review & editing.

### ORCID iDs

Yeong Hak Bang  <https://orcid.org/0000-0001-6544-6431>

Changhoon Yoo  <https://orcid.org/0000-0002-1451-8455>

Hong Jae Chon  <https://orcid.org/0000-0002-6979-5812>

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Supplemental material for this article is available online.

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