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

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Background

- Cabozantinib, an oral MKI targeting vascular endothelial growth factor receptors (VEGFRs) 1, 2 and 3, MET, and AXL, was investigated as 2nd or 3rd line therapy for the patients with unresectable hepatocellular carcinoma (uHCC) in the CELESTIAL trial.

- Given that the characteristics of patients with unresectable HCC in daily practice are often different from those in the prospective clinical trials, and the rapidly changing landscape of the management of uHCC, particularly the wide-spread incorporation of immune checkpoint inhibitors (ICIs), there is unmet need for real-world efficacy and safety assessment of cabozantinib.

- We, therefore, performed a retrospective analysis of cabozantinib as subsequent therapy after progression on any prior systemic therapy for patients with uHCC.

Methods

- 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 at Asan Medical Center, Severance hospital and CHA Bundang medical center, Korea. The dosing schedule and modification per adverse events of cabozantinib were based on the protocol of the CELESTIAL trial.

- Statistical analysis
  - Overall survival (OS) was defined from the date of initiation of cabozantinib to the date of death from any cause
  - Progression-free survival (PFS) was defined from the initiation of cabozantinib to the date of progression or death
  - OS and PFS curves were estimated by the Kaplan-Meier method and compared by log-rank tests.
  - Univariate and multivariate analysis were performed by the Cox proportional hazards regression to explore prognostic factors for OS and PFS

Baseline characteristics

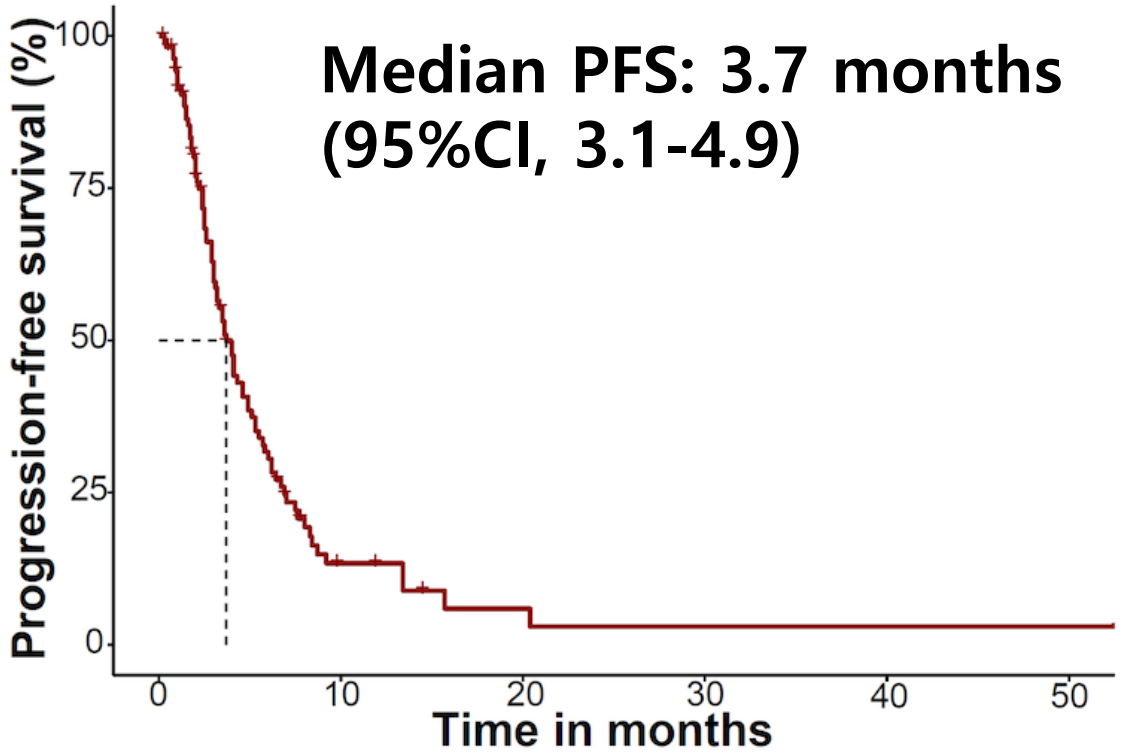
	N(%)
Age	58 (20-77)
Male gender	98 (89.1%)
Etiology	
HBV	99 (90.0%)
HCV	2 (1.8%)
Alcohol	4 (3.6%)
Unknown	5 (4.5%)
ECOG PS	
0-1	96 (87.3%)
2	14 (12.7%)
BCLC stage	
C	110 (100%)
Child-Pugh class	
A	88 (80.0%)
B	22(20.0%)
ALBI grade	
1	24 (21.8%)
2	69 (62.7%)
3	17 (15.5%)
Macrovascular invasion	
Yes	51 (46.4%)
No	59 (53.6%)
Extrahepatic metastasis	
Yes	104 (94.5%)
No	6 (5.5%)
Alpha-fetoprotein	475.6 (1.6-503168)
<400 ng/ml	52 (47.3%)
≥400 ng/ml	54 (49.1%)
Unknown	4 (3.6%)

Previous systemic treatment lines	
1	2 (1.8%)
2	18 (16.4%)
≥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 plus cisplatin	8 (10.8%)

HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; PS, performance status; BCLC, Barcelona Clinic Liver Cancer; ALBI Grade, Albumin-Bilirubin Grade; TACE, Transarterial Chemoembolization; RFA, Radiofrequency Ablation; SBRT, Stereotactic Body Radiation therapy

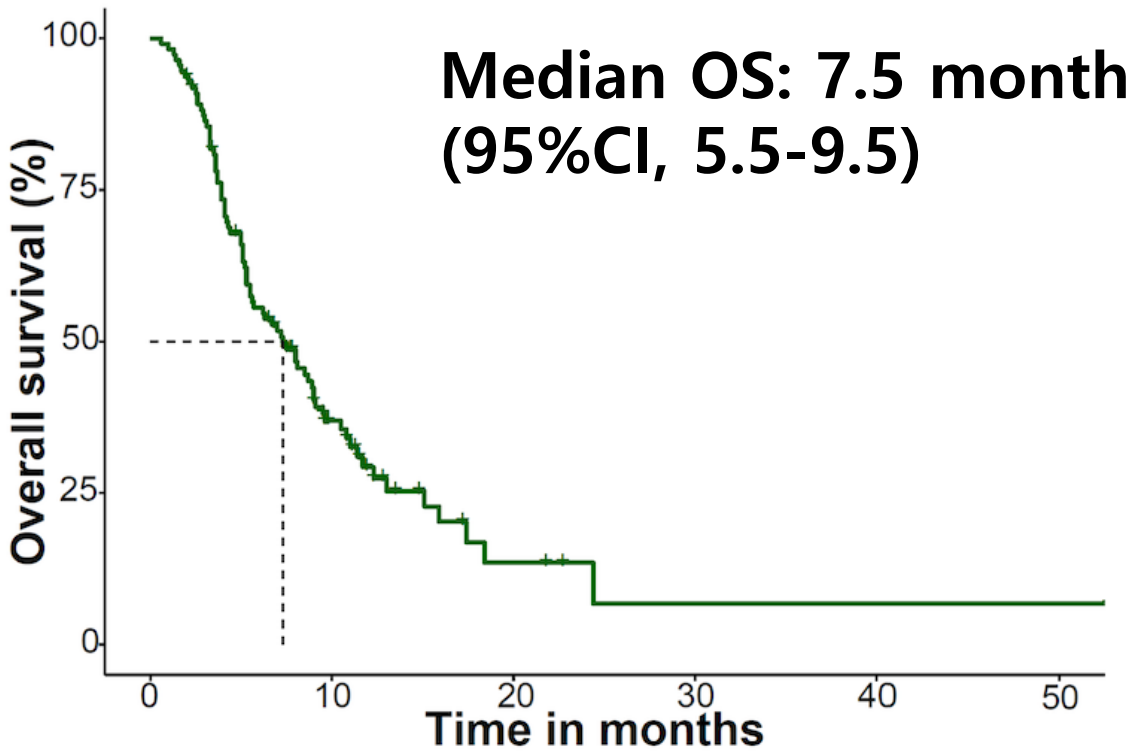
Survival outcomes

(A)



Median PFS: 3.7 months (95%CI, 3.1-4.9)

(B)



Median OS: 7.5 months (95%CI, 5.5-9.5)

Multivariate analysis

Variables	Progression-free survival				Overall survival			
	univariate		multivariate		univariate		multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (≥ 60 years vs. < 60 years)	0.89 (0.58-1.38)	0.606			0.80 (0.51-1.26)	0.341		
Sex (Male vs. Female)	0.89 (0.41-1.94)	0.766			0.68 (0.30-1.58)	0.373		
Etiology (HBV vs others)	1.16 (0.58-2.33)	0.678			1.80 (0.77-4.20)	0.177		
ALBI grade (3 vs 1, 2)	2.13 (1.19-3.82)	0.011	2.07 (1.13-3.79)	0.018	3.61 (1.78-7.35)	<0.001	2.85 (1.43-5.70)	0.003
Presence of macrovascular invasion (Yes vs. No)	1.48 (0.96-2.30)	0.076	1.41 (0.91-2.19)	0.124	2.03 (1.29-3.21)	0.002	1.64 (0.97-2.78)	0.067
Baseline serum AFP levels (≥400 ng/mL vs. <400 μg/mL)	1.39 (0.90-2.15)	0.142			2.43 (1.12-2.85)	0.015	1.68 (1.02-2.76)	0.042
Presence of prior history of ICI (Yes vs. No)	1.26 (0.71-2.25)	0.431			1.16 (0.62-2.16)	0.642		
TTP of sorafenib (≥ median vs. <median)	0.95 (0.60-1.49)	0.816			0.53 (0.33-0.84)	0.007	0.72 (0.44-1.20)	0.209
Treatment lines (>3 vs. ≤3)	1.35 (0.79-2.31)	0.271			2.12 (1.05-4.27)	0.035	1.18 (0.51-2.74)	0.703
Age (≥ 60 years vs. < 60 years)	0.89 (0.58-1.38)	0.606			0.80 (0.51-1.26)	0.341		

Toxicity profile

	All (n=110)		Child-Pugh A (n=88)		Child-Pugh B (n=22)		P-value	
NCI-CTCAE v5	**Any**	**Grade 3-4**	**Any**	**Grade 3-4**	**Any**	**Grade 3-4**	**Any**	**Grade 3-4**
Any adverse events	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

Conclusion

- The current study, which included uHCC patients who were refractory to at least one prior systemic chemotherapy, showed that the efficacy and safety outcomes of cabozantinib were consistent with the results of the CELESTIAL trial, even though current study patient population included patients with cabozantinib as 4th or later line treatment or Child Pugh Class B.

- The combination of atezolizumab, anti-PD-L1 antibody, and bevacizumab, an anti-VEGF antibody, is the new standard first-line therapy based on the results of the pivotal IMBrave 150 trial. 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 with prior ICIs has not been demonstrated before.

- Our study showed that there is 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. Further investigations are needed into the role of cabozantinib after failure of the new standard, atezolizumab-bevacizumab.