CTX-009(ABL001), a bispecific antibody targeting DLL4 and VEGF A, in combination with paclitaxel in patients with advanced biliary tract cancer (BTC): A Phase 2 study

Abstract #540
NCT04492033

Do-Youn Oh[1], Joon Oh Park[2], Jin Won Kim[3], Kyu-Pyo Kim[4], Jeesun Yoon[1], Tae-Yong Kim[1], Seung Tae Kim[2], Young Suk Park[2], Jeeyun Lee[2], Ji-Won Kim[3], Keun Wook Lee[3], Baek-Yeol Ryoo[4], Changhoon Yoo[4], BokJin Hyun[5], HyunJoo Son[5], SunYoung Kim[5], SangMi Lee[6], Jooyeon Park[6], Eunsin Ha[6]
[1]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; [2]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [3]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; [4]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [5]Handok Inc., Seoul, South Korea; [6]ABL Bio, Inc., Seongnam, South Korea
Contact information: ohdoyoun@snu.ac.kr

Background

- CTX-009 is a novel bispecific antibody that simultaneously inhibits Delta-like ligand 4/Notch-1 (DLL4) and VEGF A, two signaling molecules which play an important role in angiogenesis in the tumor microenvironment.[1, 2]
- Encouraging results in phase 1b in BTC pts, CTX-009 in combination with paclitaxel, including two durable Partial Responses (PRs) out of 3 pts, prompted the expansion of the study to a Phase 2 cohort which includes BTC pts treated in 2L or 3L setting. We present preliminary results of the Phase 2 study.

Methods

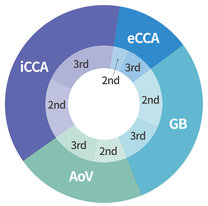
- This is a open-label, multi-center, single-arm Phase 2 study in pts with unresectable advanced, metastatic or recurrent BTC in 2L or 3L setting. Eligible pts were treated with CTX-009 (10 mg/kg IV biweekly) in combination with paclitaxel (80 mg/m^2 IV on Day 1, 8, 15 q4-weekly).
- The primary objective was to assess the objective response rate (ORR) based on RECIST v1.1. Secondary endpoints included time to treatment failure (TTF), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results

- As of the data cut-off date (Nov 09, 2022), 24 pts have been enrolled and 1 pt remained on treatment. The median follow-up duration was 12.1 months (m; range, 1.6-19.1) and 11 pts were treated in 2L and 13 pts in 3L.

Table 1. Baseline characteristics

	Total (n = 24)
Age (Years)	
Median (range)	61.5 (39-73)
Sex, n (%)	
Male/Female	14 (58.3) / 10 (41.7)
Time from diagnosis to randomization (year)	
Median (range)	2.2 (0.4-8.4)
ECOG performance Status, n (%)	
0	13 (54.2)
1	11 (45.8)
Number of previous systemic therapies, n (%)	
1	11 (45.8)
2	13 (54.2)
Previous therapy	
Surgery	18 (75.0)
Radiotherapy	8 (33.3)



BTC sub-type	n (2L/3L)
Intrahepatic cholangiocarcinoma	9 (4/5)
Extrahepatic cholangiocarcinoma	3 (1/2)
Gallbladder cancer	7 (4/3)
Ampullary carcinoma	5 (2/3)

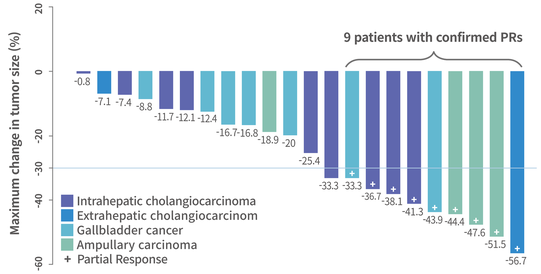
- There were 9 confirmed PRs with ORR 37.5% (95% CI, 18.8-59.4; 2L: 63.6%, 3L: 15.4%) by investigator's assessment.

Table 2. Response rate

Response rate (n=24)	Investigator's assessment		
	Total (n=24)	2L (n=11)	3L (n=13)
ORR	9 (37.5%)	7 (63.6%)	2 (15.4%)
CR	0	0	0
PR	9 (37.5%)	7 (63.6%)	2 (15.4%)
SD	13 (54.2%)	4 (36.4%)	9 (69.2%)
PD	0	0	0
NE*	2 (8.3%)	0	2 (15.4%)

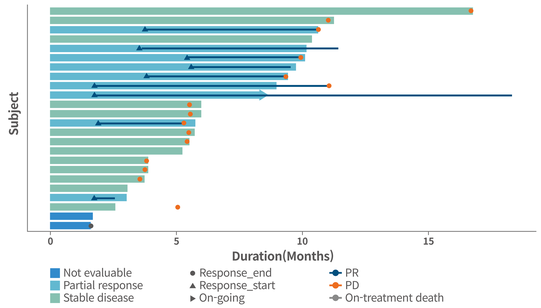
* One participant with no post-baseline tumor scan and the other with tumor assessment scan before the scheduled first assessment. Objective response rate: ORR; Complete Response: CR; Partial Response: PR; Progressive Disease: PD; Not evaluable: NE

Figure 1. Waterfall plot of maximum change in tumor size by investigator's assessment (n=23)†



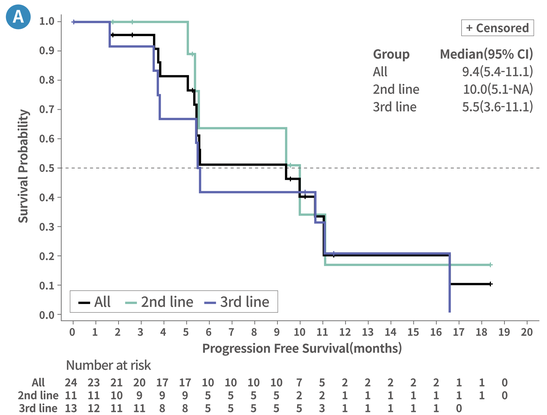
† One participant was not included due to absence of post-baseline tumor scan.

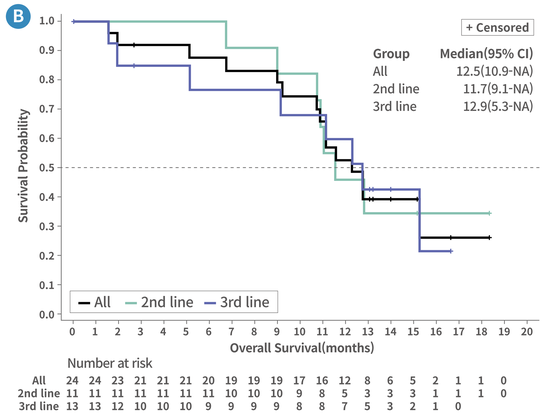
Figure 2. Swimmer plot by investigator's assessment (n=24)



- Median PFS and OS were 9.4 m (95% CI, 5.4-11.1) and 12.5 m (95% CI, 10.9-NA), respectively; the OS rate at 12 m was 52.4% (95% CI, 30.7-70.2). Median DOR was 6.9 m (95% CI, 3.5-NA) and median TTF 5.9 m (95% CI, 3.9-9.8).

Figure 3. Progression free survival (A) and Overall survival (B)





Safety

- TEAEs of ≥ Grade (Gr) 3 were reported in 95.8% (including one grade 5 pneumonia), regardless of relationship to CTX-009 or paclitaxel. Six pts (25.0%) experienced TEAEs that led to discontinuation of the study treatment: confusional state, embolism, pneumonia, biliary fistula, large intestine perforation, blood creatinine increased, and blood urea nitrogen increased.
- The AEs of special interest (AESIs) were reported in 41.7% of pts and AESIs of ≥ Gr 3 in 12.5% of pts.

Table 3. Adverse events

Overall AE, n (%) [case]**	CTX-009 + Paclitaxel	
Any TEAE (Treatment Emergent AE)	24 (100) [485]	
CTX-009 related AE	24 (100) [208]	
Serious AE	11 (45.8) [18]	
AE leading to discontinuation	6 (25.0) [8]	
TEAEs*, n (%) [case]**	**Any Grade**	**Grade≥3**
Neutrophil count decreased	22 (91.7) [82]	20 (83.3) [58]
Hypertension	12 (50.0) [27]	4 (16.7) [10]
Platelet count decreased	9 (37.5) [28]	3 (12.5) [5]
Anaemia	5 (20.8) [9]	5 (20.8) [8]
Ascites	4 (16.7) [18]	2 (8.3) [12]
Decreased appetite	4 (16.7) [8]	2 (8.3) [2]
Neutropenia	2 (8.3) [8]	2 (8.3) [5]
Liver abscess	2 (8.3) [7]	2 (8.3) [4]
Hepatic infection	2 (8.3) [6]	2 (8.3) [3]
Cholangitis	2 (8.3) [2]	2 (8.3) [2]
Embolism	2 (8.3) [2]	2 (8.3) [2]
AESIs, n (%) [case]**	**Any Grade**	**Grade ≥3**
Haemoptysis or haemorrhage	10 (41.7) [21]	3 (12.5) [5]
Pulmonary hypertension	4 (16.7) [4]	0 [0]
GI or tumor perforation	2 (8.3) [3]	2(8.3) [2]
Wound healing complication	0 [0]	0 [0]
Cardiac failure	0 [0]	0 [0]

** When Gr changed, the same AE was considered as separate cases and counted in duplicate.
*** Only TEAEs with 2 or more adverse events with Gr≥3 were presented.

Conclusion

The Phase 2 study has shown promising efficacy in BTC pts treated in 2L or 3L setting. TRAEs based on mode of action was high, but DLL4/VEGF targeting in BTC has a potential of development. Further investigation of safety and efficacy of this regimen is warranted.

References and Acknowledgement

1. Kuhnert F, et al. Vasc Cell. 2011 Sep 18;3(1):20.
2. Li JL, et al. Cancer Res. 2011;71(18):6073-83.

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