Abstract #4017

Safety, Tolerability and Preliminary Efficacy Results in Patients with Advanced Gastric/Gastroesophageal Junction Adenocarcinoma from a Phase Ib/II Study of CLDN18.2 CAR T-cell therapy (CT041)

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BACKGROUND

- Claudin18.2 (CLDN18.2) has emerged as a promising therapeutic target, which is often highly expressed in gastric/gastroesophageal junction (G/GEJ) cancers [1-2].
- Although chimeric antigen receptor (CAR) T therapy has been a success in hematological malignancies, its value in solid tumors has not been proven [3-4].
- CT041, a CLDN18.2-redirected CAR T-cell, showed promising anti-tumor activity in preclinical studies [5]. The CAR structure of CT041 is comprised of a humanized anti-CLDN18.2 single-chain variable fragment (anti-CLDN18.2 scFv), linked to the intracellular CD28 costimulatory domain and CD3ζ signaling domain, via the CD8α hinge region and CD28 transmembrane (CD28 TM) region.
- Recently reported results of a phase I study [6] demonstrated that CT041 was well tolerated and had encouraging efficacy in previously treated, CLDN18.2-positive advanced G/GEJ adenocarcinoma (G/GEJA).
- Here we report the preliminary data in Chinese patients with G/GEA from an ongoing phase Ib/II study (CT041-ST-01, NCT04581473).

METHODS

- This open-label, multicenter, phase Ib/II study consisted of a dose-escalation/ dose-expansion phase (phase Ib) and a confirmatory phase (phase II).
- In the dose-escalation/dose-expansion phase, CT041 dose levels of 2.5×10^8 and 3.75×10^8 cells with up to 3 doses were investigated using 3 + 3 design.
- The primary objective of phase Ib is to evaluate the safety, tolerability within 4 weeks after initial infusion of CT041, and determine the recommended phase 2 dose (RP2D) of CT041. The second objectives include the overall safety profile, preliminary efficacy and PK characteristics of CT041.

Key eligibility criteria (phase Ib)

- Patients aged 18 to 75 years with pathologically diagnosed advanced G/GEJA;
- Refractory to or intolerant of at least 2 prior lines of treatment; HER2-positive patients should have received standard anti-HER2 therapy;
- Confirmed positive expression of CLDN18.2 by immunohistochemistry (IHC) staining (2+/3+ in ≥40% tumor cells);
- At least one measurable lesion per RECIST v1.1.

RESULTS

Patients

- From November 2020 to May 2021, 14 eligible patients with G/GEJA were enrolled in phase Ib. As of the data cut-off date (December 22, 2021), the median (range) follow-up time was 8.8 (3.0 - 13.6) months.
- 78.6% were Lauren diffuse/mixed type, 64.3% were signet ring cell carcinoma.
- 57.1% had ≥ 3 metastatic organs, and 92.9% had peritoneal dissemination.
- Most of the patients (85.7% [12/14]) had received 2 prior treatments or a triple combination of fluoropyrimidine, oxaliplatin, and paclitaxel.

Treatment

- All 14 patients received 1 cycle of bridging chemotherapy determined by the investigators, including 13 patients (92.9%) received FOLFIRI, and only 1 received 5-FU plus intraperitoneal nab-paclitaxel.
- Lymphodepletion treatment (fludarabine 25mg/m^2 d1-2, cyclophosphamide 250mg/m^2 d1-3 and nab-paclitaxel 100mg d2) was administrated in all patients before CT041 infusion, except 2 patients received reduced dose of cyclophosphamide before second infusion due to hematological toxicity.
- All patients had at least one CT041 infusion (11 in 2.5×10^8 and 3 in 3.75×10^8). The median duration from apheresis to the first infusion was 28 (26-35) days.
- 7 patients received two infusions (6 in 2.5×10^8 and 1 in 3.75×10^8) , and the median interval between the first and second infusion was 132 (49-252) days.

- **These preliminary results suggest that CT041 had a manageable safety / tolerability profile and promising efficacy in patients with previously treated advanced G/GEJ adenocarcinoma.**
- **This study is ongoing with further investigation of CT041 in confirmatory phase II phase underway.**

Table 1. Demographics and Baseline Characteristics

Demographics and Baseline Characteristics	Total (N = 14)
Median age (range), year	44.5 (23-71)
Male, n (%)	6 (42.9%)
ECOG PS=1, n (%)	12 (85.7%)
Lauren classification, n (%)	
Intestinal type	3 (21.4%)
Diffuse type	9 (64.3%)
Mixed type	2 (14.3%)
Signet ring cell carcinoma, n (%)	9 (64.3%)
Claudin18.2 staining, n (%)	
2+	2 (14.3%)
3+	12 (85.7%)
HER2 expression, n (%)	
Positive	1 (7.1%)
Negative	12 (85.7%)
Unknown	1 (7.1%)
Numbers of metastatic organs, n (%)	
<3	6 (42.9%)
≥3	8 (57.1%)
Peritoneal metastasis, n (%)	13 (92.9%)
Liver metastasis, n (%)	3 (21.4%)
Numbers of prior lines, n (%)	
2*	12 (85.7%)
≥ 3	2 (14.3%)
Prior systemic therapies, n (%)	
Fluorouracil	14 (100%)
Platinum	14 (100%)
Paclitaxel / nab-paclitaxel	13 (92.9%)
PD-(L)1 inhibitor	5 (35.7%)
Tyrosine-kinase inhibitor	2 (14.3%)

* 5 patients received a triple combination of fluoropyrimidine, oxaliplatin, and paclitaxel as first line treatment.

Safety

- Treatment-related adverse events (TRAEs) of ≥ Grade 3 were reported in 100% patients (Table 2), most of which were lymphopenia related to lymphodepletion.
- 3 serious TRAEs were observed in 2 patients. No patients had dose-limiting toxicities (DLTs) or AE leading to death.
- Cytokine release syndrome (CRS) was reported in all patients after the first infusion and in 85.7% (6/7) after the second .
- Most CRS were grade 1 or 2; Only one patient had grade 4 CRS, which was related to the investigational disease and fully recovered after corticosteroids treatment.
- The median (range) onset time of CRS occurred after the first infusion and second infusion was 2 (1-4) days and 1 (1-2) day.
- Tocilizumab and corticosteroids were administered in 71.4% (10/14) and 7.1% (1/14) of patients as the treatment for CRS. The median (range) recovery time of CRS was 7 (1-22) days.
- No immune effector cell-associated neurotoxicity syndrome (ICANS) or gastrointestinal mucosal injury were reported.

Table 2. Summary of AEs

n (%)	Total (N=14)
TRAEs	14 (100%)
≥ Grade 3	14 (100%)
Serious AEs	3 (21.4%)
≥ Grade 3	3 (21.4%)
Serious TRAEs [a]	2 (14.3%)
DLTs	0 (0)
AE leading to CT041 discontinuation [b]	1 (7.1%)
AE leading to death	0 (0)
CRS	14 (100%)
Grade 1	0 (0)
Grade 2	13 (92.9%)
≥ Grade 3	1 (7.1%)
ICANS	0 (0)
Gastrointestinal mucosal injury	0 (0)

a. One patient experienced anaphylactic shock. One patient experienced pneumonitis and CRS.
b. One patient discontinued CT041 infusion after experiencing anaphylactic shock.
AE, adverse events; TRAEs, treatment-related adverse events; DLTs, dose-limiting toxicities; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

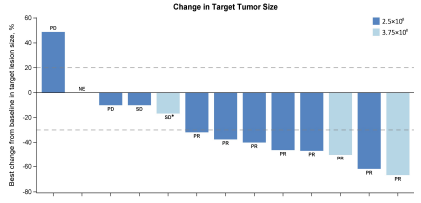
Table 3. Most Common TRAEs of Any Grade and Grade 3/4

Preferred term, n (%)	2.5×10^8 cells (N=11)		3.75×10^8 cells (N=3)		Total (N=14)	
	Any	Gr3/4	Any	Gr3/4	Any	Gr3/4
Hematological toxicity						
Lymphopenia	11 (100)	11 (100)	3 (100)	3 (100)	14 (100)	14 (100)
Leukopenia	11 (100)	9 (81.8)	3 (100)	2 (66.7)	14 (100)	11 (78.6)
Neutropenia	11 (100)	6 (54.4)	3 (100)	1 (33.3)	14 (100)	7 (50)
Anemia	8 (72.7)	1 (9.1)	2 (66.7)	1 (33.3)	10 (71.4)	2 (14.3)
Thrombocytopenia	3 (27.3)	1 (9.1)	2 (66.7)	0	5 (35.7)	1 (7.1)
Nonhematological toxicity						
CRS	11 (100)	1 (9.1)	3 (100)	0	14 (100)	1 (7.1)
Fever	11 (100)	1 (9.1)	3 (100)	0	14 (100)	1 (7.1)
ALT elevation	7 (63.6)	1 (9.1)	1 (33.3)	0	8 (57.1)	1 (7.1)
Bilirubin elevation	6 (54.5)	1 (9.1)	1 (33.3)	0	7 (50)	1 (7.1)
Lipase elevation	6 (54.5)	2 (18.2)	0	0	6 (42.9)	2 (14.3)
AST elevation	4 (36.4)	1 (9.1)	1 (33.3)	0	5 (35.7)	1 (7.1)
Pneumonitis	0	1 (9.1)	0	0	0	1 (7.1)
Anaphylactic shock	0	1 (9.1)	0	0	0	1 (7.1)

Efficacy

- 13 patients were evaluable and 1 patient withdrew from the study before any tumor assessment was performed.
- 8 of 14 patients (57.1%) achieved partial response (PR) at the first assessment after the first infusion. The objective response rate (ORR) per investigators' assessment was 57.1% (95%CI 28.9, 82.3).
- 3 of 14 patients (21.4%) showed stable disease (SD) and the disease control rate (DCR) was 78.6% (95%CI 49.2, 95.3).
- The m PFS and mOS was 5.6 months (95%CI 1.9, 7.4) and 10.8 months (95%CI 5.1, NE), respectively. 7 patients were still alive by the cut-off date.

Figure 1. Best Change from Baseline in Target Lesions



* Assessed as SD at W4 and PD at W8

Figure 2. Swimmer Plot of Patients

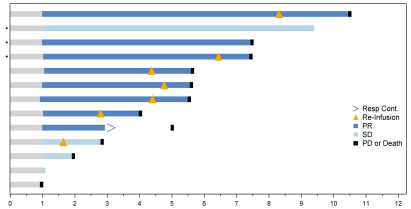


Figure 3. Kaplan-Meier Analysis of PFS

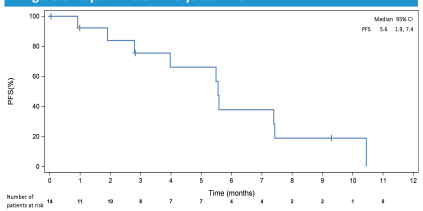
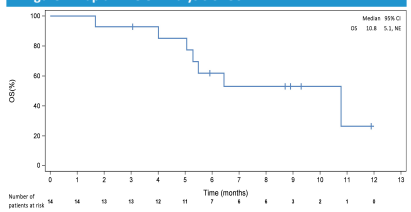


Figure 4. Kaplan-Meier Analysis of OS



Pharmacokinetics

- After the first CT041 infusion, the median (range) Cmax and Tmax value of CAR copies was 1,736 (466-10,151) copies/μg of genomic DNA (gDNA) and 7 (7-10) days, respectively. The median (range) persistence time was 27 (14-189) days.
- After the second infusion, obvious decreases in Cmax were observed after the second infusion compared with the first infusion, with a median (range) value of 254 (75-2,232) copies/μg of gDNA. The median (range) Tmax and persistence time were 3 (3-7) days and 26 (5-68) days, respectively.

Figure 5. CT041 Expansion and Persistence

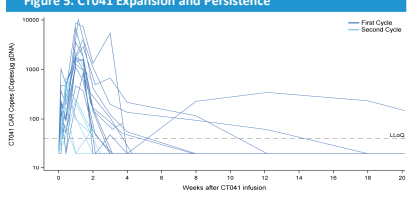


Table 4. Analysis of Tumor Response per RECIST v1.1 Based

	Total N=14
ORR, % (95% CI)	57.1 (28.9, 82.3)
Best overall response, n (%)	
Complete response	0 (0)
Partial response	8 (57.1)
Stable disease	3 (21.4)
Progressive disease	2 (14.3)
Not evaluable*	1 (7.1)
DCR, % (95% CI)	78.6 (49.2, 95.3)

* One patient was not evaluated due to early withdrawal before the first tumor assessment. CI, confidence interval; ORR, objective response rate; DCR, disease control rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

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