Abstract #4095: Phase I trial of Chimeric Anti-GPC3 scFv-CD3ε Engineered T Cells (CT0180) in Patients with Advanced Hepatocellular Carcinoma

Yi Zheng[3], Qihan Fu[3], Qingwei Zhao[4], Lulu Liu[3], Zhou Tong[3], Hangyu Zhang[3], Xudong Zhu[3], Peng Zhao[3], Weijia Fang[3], Wanwan Gao[2], Yumeng Wang[2], Daijing Yuan[2], Huamao Wang[2], Zonghai Li[2]*,Tingbo Liang[1]*

[1]Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [2]CARsgen Therapeutics Ltd., Shanghai, China; [3]Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China; [4]Department of Clinical Pharmacy, The First Affiliated Hospital, Zhejiang University; *Corresponding author

Background

- Glypican-3 (GPC3) is considered a potential immunotherapeutic target for hepatocellular carcinoma (HCC), since it's barely expressed in normal tissues and highly expressed in 70-80% of HCC [1-2].
- CT0180 is a chimeric anti-GPC3 scFv-CD3ε engineered T-cell therapy intended for the treatment of patients with GPC3-positive advanced HCC.
- Preclinical studies showed competitive antitumor activity, but lower cytokine release compared to 28ζ or BBζ chimeric antigen receptor T cells [3].

Methods

- This is an open-label, first-in-human, dose-escalation phase I study to investigate the safety, preliminary efficacy, and cellular pharmacokinetics of CT0180 in patients with GPC3-positive advanced HCC (CT0180-CG1203, NCT04756648).
- Patients who met the inclusions/exclusions criteria underwent apheresis, lymphodepletion, and cell infusion in sequence. The study process is shown in **Figure 1**.
- Five dose levels (DLs, ranging 10×10^6 - 600×10^6 cells) with up to 3 cycles were explored using i3 + 3 design, and intra-patient dose-escalation was allowed.
- Fludarabine 25 mg/m^2 and cyclophosphamide 300 mg/m^2 daily for 3 days were used as the lymphodepletion regimen prior to CT0180 infusion.

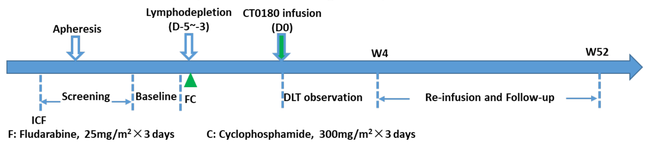


Figure 1. Schedule of activities of CT0180 study

Results

Patients and Treatments

- From Feb-2021 to Jul-2022, 7 male patients with hepatitis B virus-related HCC were enrolled. All patients had extrahepatic spread and the most common metastatic organ was lung.
- All patients had prior surgery and had received 2 or more prior lines of systemic therapy, including at least one antiangiogenic tyrosine kinase inhibitor/bevacizumab and one anti-PD-1/PD-L1 immunotherapy. Five patients had received locoregional therapies as well (**Table 1**).
- All patients received at least one CT0180 infusion (one patient each at 10×10^6 and 30×10^6 DLs, three at 100×10^6 DL, and two at 300×10^6 DL). Two patients received 2 infusions and 3 patients received 3 infusions (**Table 1**).

Safety

- The most common grade 3-4 adverse events (AEs) were hematologic toxicities, including lymphocyte count decreased and neutrophil count decreased, which were considered to be related to lymphodepletion (**Table 3**).
- No dose-limiting toxicities (DLTs), immune effector cell-associated neurotoxicity syndrome (ICANS), or AEs leading to deaths/withdrawal were reported. One treatment-related serious adverse event (SAE) occurred (**Table 2**).
- Grade 1 cytokine release syndrome (CRS) occurred in 6 patients, most of whom recovered within 3 days. No grade ≥2 CRS occurred. Tocilizumab was used in only 1 patient and no corticosteroids were used.

Efficacy

- As of the data cutoff date (Mar 31, 2023), the median follow-up time was 17.8 months.
- All 7 patients were evaluable for efficacy. Two patients (30×10^6 and 300×10^6 DL) achieved partial response (PR), and 3 patients (10×10^6, 100×10^6 and 300×10^6 DLs) achieved stable disease (SD) according to RECIST v1.1. One patient had sustained PR for 6.7 months, and 2 patients had sustained SD for more than 5 months (**Table 1**).
- The median progression-free survival (mPFS) and median overall survival (mOS) was 7.6 months (95% CI, 0.8, NE) and 11.6 months (95% CI, 4.3, NE), respectively. Three patients were still alive at last follow-up. (**Figure 2, Figure 3**).

Pharmacokinetics

- After each infusion of CT0180, the peak values were observed on either day 3 or day 7 post-infusion, the C_{max} of CT0180 transgene copy number ranged 51–4487 copies/μg genomic DNA.
- No significant difference in pharmacokinetics was found among the different DLs, possibly limited by the small sample size in this trial.

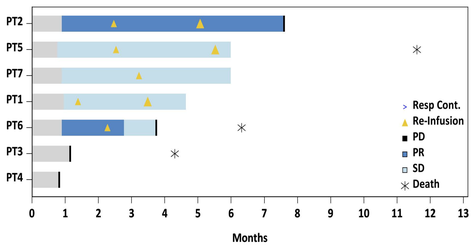


Figure 2. Tumor response after CT0180 infusion

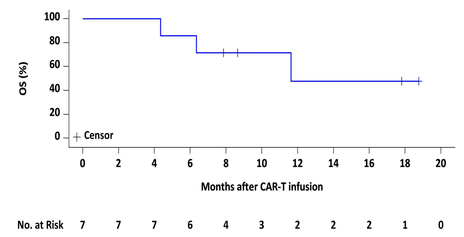
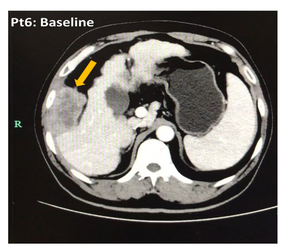


Figure 3. Kaplan-Meier Curve of OS



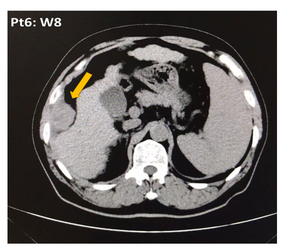


Figure 4: Best response of target lesion in Pt6

Pt6 achieved PR since week 4, and one of the target lesions significantly decreased from 70.5 mm (baseline) to 39.8 mm (week 8).

Note : Baseline (enhanced CT scan). Week 8 (CT plain scan, due to allergic reaction to iodinated contrast media)

Table 1. Baseline characteristics and treatment

Subject	Age (years)	Gender	HCC history (years)	HBV infection	ECOG	Child-Pugh score	GPC3 expression (IHC)	BCLC stage	EHS/ metastatic organ number	Baseline AFP (ng/mL)	Prior anticancer treatments					Dose level / cycles	C_{max} (copies/μg gDNA)	Best overall response	DDC (months)	PFS (months)	OS (months)
											Surgery	Locoregional therapies*	Systemic therapies								
													Prior lines	PD-(L)1 inhibitor	TKI/ Bevacizumab						
Pt1	28	Male	2.0	Yes	0	5	3+	C	Yes/1	>80000	Yes	Yes	2	Yes	Yes	10×10^6/3	204	SD	3.7#	4.7#	18.8&
Pt2	41	Male	5.9	Yes	0	5	3+	C	Yes/3	1286.4	Yes	No	≥3	Yes	Yes	30×10^6/3	255	PR	6.7	7.6	17.8&
Pt3	46	Male	1.5	Yes	0	5	3+	C	Yes/2	1399.8	Yes	Yes	2	Yes	Yes	100×10^6/1	93	PD	/	1.1	4.3
Pt4	50	Male	0.7	Yes	0	5	3+	C	Yes/2	5675	Yes	Yes	≥3	Yes	Yes	100×10^6/1	< LLOQ	PD	/	0.8	7.9&&
Pt5	74	Male	3.8	Yes	0	5	3+	C	Yes/1	1047	Yes	Yes	2	Yes	Yes	100×10^6/3	51	SD	5.3#	6.0#	11.6
Pt6	59	Male	1.4	Yes	0	5	3+	C	Yes/1	5844.8	Yes	No	≥3	Yes	Yes	300×10^6/2	4487	PR	2.9	3.7	6.3
Pt7	37	Male	3.5	Yes	0	5	3+	C	Yes/1	1429.8	Yes	Yes	2	Yes	Yes	300×10^6/2	222	SD	5.1#	6.0#	8.6&

*Radiofrequency ablation, transcatheter arterial chemoembolization, and/or portal vein embolization; # censored; & survival follow-up; && lost to follow-up; EHS: Extrahepatic spread; DDC: Duration of disease control; LLOQ: lower limit of quantification

Table 2. Summary of AEs

Adverse event, n (%)	10×10^6 DL (N=1)	30×10^6 DL (N=1)	100×10^6 DL (N=3)	300×10^6 DL (N=2)	Total (N=7)
All AEs	1 (100)	1 (100)	3 (100)	2 (100)	7 (100)
Treatment-emergent AEs	1 (100)	1 (100)	3 (100)	2 (100)	7 (100)
Treatment-related AEs	1 (100)	1 (100)	3 (100)	2 (100)	7 (100)
Lymphodepletion-related	1 (100)	1 (100)	3 (100)	2 (100)	7 (100)
CT0180-related	1 (100)	1 (100)	2 (66.7)	2 (100)	6 (85.7)
Treatment-emergent SAE	0	0	0	1 (50.0)	1 (14.3)
Treatment-related SAE	0	0	0	1 (50.0)	1 (14.3)
Lymphodepletion-related	0	0	0	1 (50.0)	1 (14.3)
CT0180-related	0	0	0	1 (50.0)	1 (14.3)
Dose-limiting toxicity	0	0	0	0	0
AE leading to death/withdrawal	0	0	0	0	0
Grade ≥3 hematologic toxicity	1 (100)	1 (100)	3 (100)	2 (100)	7 (100)
Grade 3	0	0	0	0	0
Grade 4	1 (100)	1 (100)	3 (100)	2 (100)	7 (100)
Grade ≥3 nonhematologic toxicity	0	0	0	1 (50.0)	1 (14.3)
Grade 3	0	0	0	1 (50.0)	1 (14.3)
Grade 4	0	0	0	0	0
Cytokine release syndrome	1 (100)	1 (100)	2 (66.7)	2 (100)	6 (85.7)
Grade 1	1 (100)	1 (100)	2 (66.7)	2 (100)	6 (85.7)
Grade ≥2	0	0	0	0	0
ICANS	0	0	0	0	0
Liver function abnormal	0	0	1 (33.3)	0	1 (14.3)
HBV reactivation	0	0	0	1 (50.0)	1 (14.3)

Table 3. Most Common TRAEs (any grade ≥25%) and Grade 3-4

Preferred term, n (%)	Grade 3 or 4	Any grade
Any AE	7 (100)	7 (100)
Hematologic toxicity	7 (100)	7 (100)
Lymphocyte count decreased	7 (100)	7 (100)
Neutrophil count decreased	4 (57.1)	7 (100)
White blood cell count decreased	5 (71.4)	7 (100)
Platelet count decreased	3 (42.9)	5 (71.4)
Nonhematologic toxicity	0	6 (85.7)
Pyrexia	0	6 (85.7)
Asthenia	0	2 (28.6)
Cytokine release syndrome	0	6 (85.7)
Nausea	0	4 (57.1)
Vomiting	0	2 (28.6)
Rash	0	2 (28.6)
Myalgia	1 (14.3)	1 (14.3)

Conclusion

These preliminary results showed that CT0180 had manageable safety profile and promising efficacy in patients with heavily treated advanced HCC. Further exploration of CT0180 in HCC is needed.

References

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E-mail: liangtingbo@zju.edu.cn