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A phase I study of GPRC5D targeting CAR T-cell therapy CT071 for high-risk newly diagnosed multiple myeloma

J Du[1], H He[1], L Jin[1], X Fan[1], J Lu[1], W Qiang[1],G Pei[1], L He[2], N Rajakumaraswamy[2], Y Luo[2] ,D Chen[2], and Z Li[2]
[1] Department of Hematology, Myeloma & Lymphoma Center, Shanghai Changzheng Hospital, Naval Medical University, Shanghai, China.
[2] CARsgen Therapeutics Co. Ltd., Shanghai, China.

INTRODUCTION

Despite significant improvement in the outcomes of patients with newly diagnosed multiple myeloma (NDMM) with novel therapies. However, the prognosis of high-risk patients remains extremely poor [1]. G protein-coupled receptor, class C, group 5, member D (GPRC5D) is an emerging target for the treatment of MM[2]. CT071 is a GPRC5D-targeted autologous second-generation CAR T-cell therapy with expedited manufacturing.

AIM

In this single-arm, single center, open-label exploratory clinical trial, we evaluated the safety and preliminary efficacy of CT071 in patients with high-risk (HR) NDMM (NCT06407947)

METHOD

Patients with NDMM with at least one high-risk feature and ECOG score 0-2 were enrolled. High risk was defined as the presence of any of the following cytogenetic abnormalities: del(17p), t(4;14), t(14;16),t(14;20) or 1q21 amplification with ≥4 copies or R-ISS stage III or R2-ISS stages III or IV or presence of extramedullary disease (EMD) or 2-5% peripheral plasma cells. Upon diagnosis, all patients received 2 cycles of VRd (bortezomib, lenalidomide and dexamethasone) prior to study enrollment. Following apheresis and lymphodepletion with fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day for 3 days, CT071 was administered as a single infusion. Lenalidomide maintenance was started 4 months after CT071 infusion.

REFERENCES

1. Rees MJ, et al. 2024 Jun;44(3):e433520. doi: 10.1200/EDBK_433520. PMID: 38772002.
2. Mailankody S, et al. N Engl J Med. 2022;387(13):1196-1206.

RESULTS

Patient Characteristics

Baseline characteristic	3.0×10^5/kg (N=10)
Age, median (range), y	54.0 (34, 68)
Male, n(%)	7 (70)
R2-ISS Stage, n(%)	
I	1 (10)
II	2 (20)
III	4 (40)
IV	3 (30)
Extramedullary Disease, n(%)	3 (30)
ECOG PS, n (%)	
0	0
1	10 (100)
2	0
High-risk Cytogenetics, (%)	6 (60)
Cytogenetic Features, (%)	
del(17p13.1)	1 (10)
t(4;14)	4 (40)
t(14;16)	0
t(14;20)	0
1q21 with ≥4 copies	1 (10)
GPRC5D (%), n (%)	
<50%	2 (20)
≥50%	8 (80)

Note: y, years; D,days
Note: Baseline value is defined as the last nonmissing value taken prior to lymphodepletion chemotherapy.
Note: Bridging therapy was not required for any of the patients.
Note:Flow cytometry was used for the detection of GPRC5D in plasma cells. Baseline GPRC5D exp ression within the abnormal bone marrow (BM) plasma cell subset was quantified at baseline bu t not required for enrollment.

Safety Summary

Characteristic, n (%)	3.0×10^5/kg (N=10)
TEAE	10 (100)
Treatment-emergent SAE	1 (10)
Treatment-related SAE	1 (10)
CRS, any grade	7 (70)
Grade 1	7 (70)
≥Grade 2	0
ICANS, any grade	0
≥Grade 3 Infections	0
≥Grade 3 hematologic TRAE	10 (100)
Neutropenia	8 (80)
Thrombocytopenia	2 (20)
Anemia	1 (10)
Death due to TEAE	0

Note: AE, Adverse Events; TEAE, Treatment-emergent AE; TRAE, Treatment-related AE; CRS, Cytokine Release Syndrome; SAE, Serious Adverse Events; ICANS, Immune Effector Cell–associated Neurologic Syndrome.

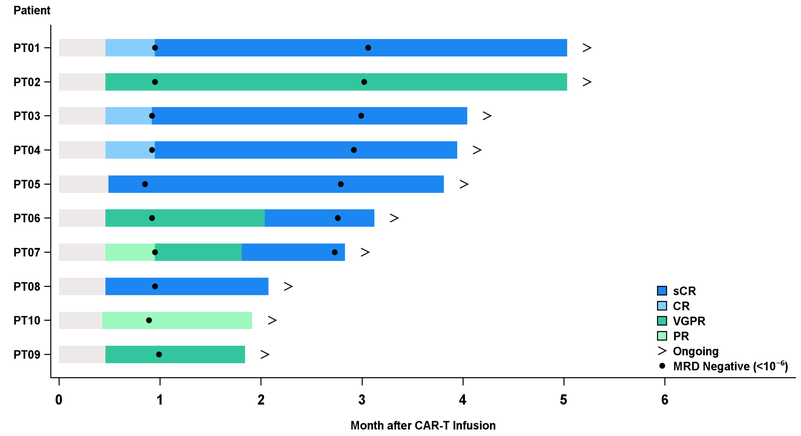
- As of Jan 02, 2025, 10 patients were apheresed and infused with CT071 at 3 ×10^5 cells/kg.
- All 10 infused patients experienced Grade 3 or higher hematologic toxicities.
- Seven patients (70%) had CRS, all at Grade 1 and resolved.
- One patient experienced treatment-related SAE of Grade 3 hemophagocytic lymphohistiocytosis, which recovered within 10 days.
- No dose limiting toxicity, ICANS, or death due to TRAE occurred.

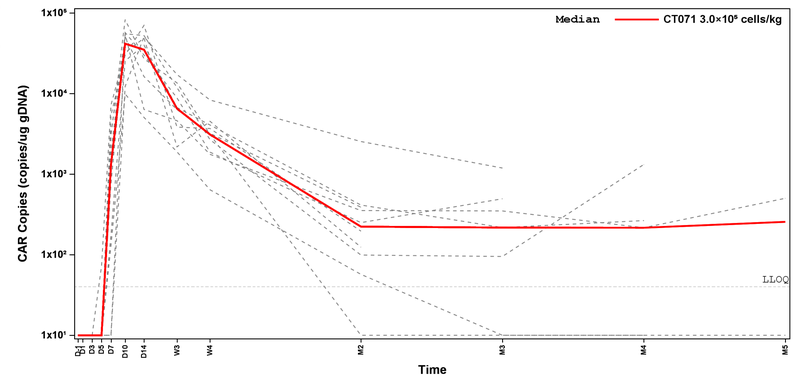
Efficacy and Pharmacokinetics Summary

	VRd (N=10)	3.0×10^5/kg (N=10)
Best Overall Response, n(%)		
sCR	1 (10)	7 (70)
CR	0	0
VGPR	6 (60)	2 (20)
PR	3 (30)	1 (10)
MR	0	0
SD	0	0
ORR, n(%) (95% CI)	10 (100)	10 (100) (69.2, 100)
CR/sCR rate, n(%)	1 (10)	7 (70)
VGPR or better rate, n(%)	7 (70)	9 (90)
Time to Response, Median (range), Month	--	0.5 (0.5, 0.5)
Time to VGPR or better, Median (range), Month	--	0.5 (0.5, 1.0)
Time to CR or better, Median (range), Month	--	0.5 (0.5, 2.1)
MRD Negativity (<10^{-6}) at Week 4, n (%)	2 (20)*	10 (100)
MRD negativity (<10^{-6}) within CR/sCR patients, n(%)	0	7(100)

Note: CI, Confidence Interval; CR, Complete Response; ORR, Objective Response Rate; PR, Partial Response; sCR, Stringent Complete Response; MR,Minimal Response;SD, Stable Disease; VGPR, Very Good Partial Response.
*The results are after two cycles of VRD treatment, and prior to cell infusion.

- As of Jan 02, 2025, the median follow-up time was 3.4 months (range 1.8 to 5.9).
- All 10 patients received two cycles of VRd therapy.
- The median vein-to-vein time (from leukapheresis to infusion) was 23 days (range: 20 to 33).
- The ORR assessed by investigator was 100% (95 CI, 69.2%, 100%).
- Five patients achieved sCR by week 4.
- All 10 patients achieved MRD negativity at 10^{-6} threshold.





Note: LLOQ, lower limit of quantitation (40 copies/μg gDNA); Concentrations below the limit of quantitation are imputed as ½ of the LLOQ.

- As of Jan 02, 2025, the pharmacokinetic results of these 10 patients received CT071 infusion showed robust cell expansion and persistence.
- Median T_{max}: 10 days (range: 10 to 14).
- Median C_{max}: 54812.0 copies/μg gDNA (range: 9885 to 82600).
- Median $AUC_{0\text{-}t}$: 459089.50 day*copies/μg gDNA (range: 89279.0, 668235.0).
- Median T_{last}: 71.5 days (range: 29 to 150).

CONCLUSIONS

Preliminary results indicate that CT071 induces deep responses in HR NDMM with a favorable safety profile. Further research is warranted to fully evaluate the potential of GPRC5D targeting CAR T-cell therapy in HR NDMM.

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CONTACT INFORMATION

Corresponding author: Juan Du, M.D., Ph.D, Shanghai Changzheng Hospital; No.415 Fengyang Road, Huangpu Area, Shanghai, 200003, China. Tel.: +86-21-81885423; Email: juan_du@live.com