A First-in-Human study of CT0590, a triple knock-out, allogeneic CAR T-cell therapy targeting BCMA and NKG2A, in patients with Relapsed/ Refractory Multiple Myeloma

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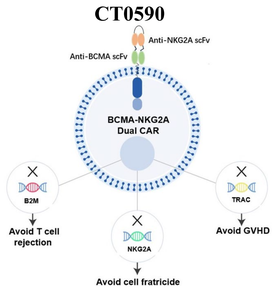
INTRODUCTION

Allogeneic CAR T-cell therapy has the potential to mitigate the high cost, time-consuming personalized manufacturing and the risk of manufacturing failure associated with autologous CAR T-cell therapies.[1,2]



CT0590 is an allogeneic dual CAR T-cell therapy targeting B-cell maturation antigen (BCMA) and NKG2A (a membrane protein expressed in NK and T cells), with a triple gene knockout for T-cell receptor (TRAC)/β2-microglobulin (B2M)/NKG2A to prevent graft-versus-host disease, host immune rejection and cell fratricide.

AIM

To evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy of CT0590 in a first-in-human (FIH), open-label, single center, phase I study in patients with relapsed refractory multiple myeloma (RRMM) (NCT05066022).

METHODS

Eligibility: Age: 18-75 years; Treated with at least 3 prior regimens including at least one proteasome inhibitor (PI) and one immunomodulatory agent (IMiD) OR stable disease, relapse, or progression following treatment with at least one PI or one IMID; relapse within 12 months after the most recent therapy OR failed to achieve at least Minimal Response OR had progression within 60 days after the most recent therapy; an ECOG score 0-1.

Dose levels (i3+3 escalating scheme): 50×10^6, 150×10^6, 300×10^6, 450×10^6 CT0590 cells.

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RESULTS

Safety Summary

	N (%)
TEAE	5 (100.0)
SAEs	1 (20.0)
≥Grade 3 AEs	5 (100.0)
Treatment related TEAEs	4 (80.0)
SAE	0
≥Grade 3	3 (60.0)
≥Grade 3 Cytopenias	3 (60.0)
≥Grade 3 Neurotoxicities	0
≥Grade 3 Infections	1 (20.0)
CRS	2 (40.0)
ICANS	0
GvHD	0
AEs leading to withdrawal	0
AEs leading to death	0
DLT	0

Abbreviations: AEs = adverse events; CRS = cytokine release syndrome; DLT = dose limiting toxicity; GvHD= graft-vs-host disease; ICANS = immune-cell associated neurotoxicity syndrome; SAEs = serious adverse events; TEAE = treatment emergent adverse events.

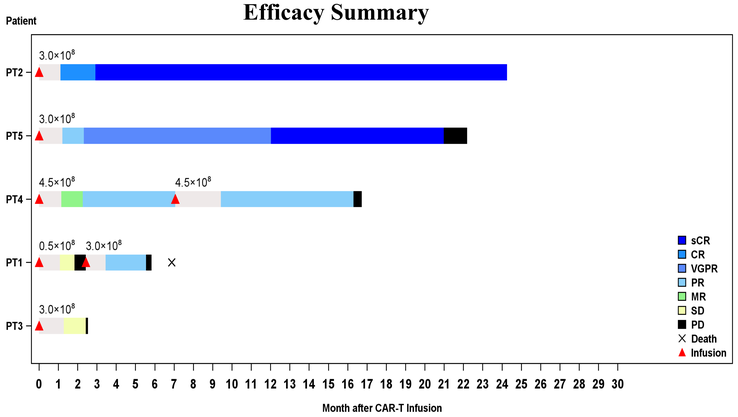
- Data cut off: 22-Apr-2024
- 5 patients were infused: 4 had RRMM and 1 had primary plasma cell leukemia (pPCL) treated under compassionate use; 2 patients were re-infused.
- 2 patients experienced CRS: 1 patient each at Grade 1 and Grade 2. Time to CRS onset: 8-10 days post infusion; CRS duration: 3-4 days.
- The majority of Grade 4 TEAEs were cytopenias reported in all patients. 3 patients had treatment-related Grade 4 cytopenias (Lymphocyte count decreased [2 patients], Platelet count decreased [3 patients], Neutrophil count decreased [2 patients], White blood cell count decreased [1 patient])
- Treatment-related Infections: 2 patients (1 Grade 1 neutropenic infection and 1 Grade 3 pneumonia)

Patient Characteristics and Outcomes

Patient (Diagnosis)	Dose (*10^6 cells)	Age (year)	Sex	ECOG	High risk cyto-genetics Y/N	ISS stage	# of prior lines	Refract-oriness to PI/ IMiD*	% Bone marrow smear plasma cell at baseline	% Baseline NKG2A expression NK cells	Best overall response	DOR (mo)	TTR (mo)	Peak CAR copy number (copies/ug gDNA)	Time to peak CAR copy number (days)
PT 1 (MM)	50	54	F	1	Y	I	2	1	8	23	SD	NA	NA	BLQ	NA
PT 1-reinf (MM)	300								NA					5102	11
PT 2 (MM)	300	71	M	1	Y	I	2	2	94.5	38	sCR	23	1.1	482749	19
PT 3 (MM)	300	50	F	1	Y	III	3	2	6	12	SD	NA	NA	BLQ	NA
PT 4 (MM)	450	71	M	1	Y	III	3	2	6	NA	PR	4	2.3	BLQ	NA
PT 4-reinf (MM)	450								25		PR	6.9	2.4		
PT 5 (pPCL)	300	51	M	1	N	NA	3	2	80	46	sCR	20	1.2	280863	15

Abbreviations: BLQ= below limit of quantification; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; gDNA = genomic DNA; IMiD = immuno-modulatory drug; ISS = International Scoring System; MM = multiple myeloma; mo = months; NA = not available or Not applicable in the case of DOR and TTR; PI = proteasome inhibitor; pPCL = primary plasma cell leukemia; PR = partial response; re-inf = re-infusion; sCR = stringent complete response; SD =stable disease; TTR = time to response. *2 indicates double class refractoriness (to a PI and an IMiD), 1 indicates patient refractory to a PI.

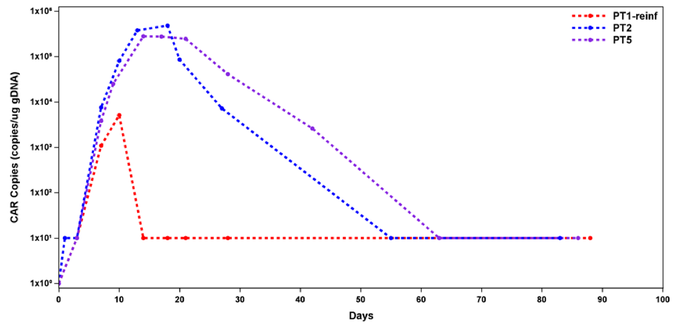
Efficacy Summary



Abbreviations: CR =complete response; DOR = duration of response; MR= minimal response; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD =stable disease; VGPR = very good partial response

- Median follow-up time: 16.6 (range: 5.1, 24.2) months
- 3 patients achieved confirmed responses:
  - Patient 2 with RRMM: sCR ongoing as of data cut-off; DOR >23 months
  - Patient 5 with pPCL: sCR with DOR of 20 months
  - Patient 4 with RRMM: PR with DOR of 4 and 6.9 months, after 1st and 2nd infusion, respectively

CT0590 copy number



- Both patients with sCR had peak CAR copy number of **482749 and 280863 copies/μg** and time to peak copy number of **19 days** and **15 days**, respectively.
- CAR copy number in other patients was low or below limit of quantification

Baseline NKG2A expression on NK cells

- Both patients who attained sCR had relatively higher NKG2A expression compared to the 2 patients who achieved SD. This may explain the discrepancies observed in the expansion of CT590 as well as clinical response.

CONCLUSIONS

Preliminary results of this FIH study of CT0590, an allogeneic dual CAR T-cell therapy targeting BCMA and NKG2A for the treatment of RRMM and RRpPCL, demonstrate a manageable safety profile while achieving durable clinical responses. Additional clinical studies are warranted to further evaluate the clinical utility of CT0590.

ACKNOWLEDGEMENTS

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