CT071

Clinical Activity of P-BCMA-ALLO1, a B-cell Maturation Antigen (BCMA) Targeted Allogeneic Chimeric Antigen Receptor T-cell (CAR-T) Therapy, in Relapsed Refractory Multiple Myeloma (RRMM) Patients Following Progression on Prior BCMA Targeting Therapy

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BACKGROUND

Despite therapeutic advances, multiple myeloma remains incurable. B-cell Maturation Antigen (BCMA) is a well validated myeloma antigen for which multiple targeted therapies are now approved. BCMA targeting immunotherapies, such as bispecific T-cell engagers (TCE) and autologous CAR-T provide high response rates, but relapses are common. Autologous CAR-T are logistically challenging due to the need for apheresis, prolonged manufacturing times and occasional manufacturing failures. Many patients suffer disease progression and require bridging therapy while awaiting autologous CAR-T manufacturing. Some patients die from disease progression while waiting for autologous CAR-T to be manufactured. TCE are hampered by the need for chronic dosing that is logistically challenging. Emerging data also indicate that autologous CAR-T have lower clinical activity in patients who have progressed on TCE. Lastly, patients who have progressed after a prior BCMA targeting immunotherapy are an emerging area of high unmet need for whom there are few commercially available therapies.

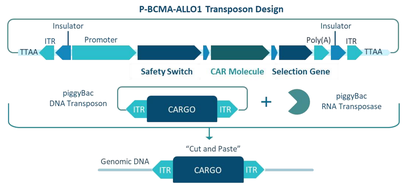
P-BCMA-ALLO1 is an allogeneic CAR-T therapy manufactured from healthy donor T-cells, that is available "off-the-shelf", and is being evaluated in a phase 1 clinical trial (P-BCMA-ALLO1-001; NCT04960579) in RRMM patients. This primary objective is to determine the maximum tolerated dose of P-BCMA-ALLO1, and the key secondary objective is to investigate the anti-myeloma activity. The patients must have progressed on a prior proteasome inhibitor, immunomodulatory drug and anti-CD38 monoclonal antibody. The study allows enrollment of patients who have received prior BCMA targeting therapy. The study is exploring escalating P-BCMA-ALLO1 doses and several different lymphodepletion chemotherapy (LD) regimens. Here we report the safety and early efficacy results for the 5 patients who were treated with P-BCMA-ALLO1 after having progressed on BCMA targeting CAR-T, TCE or both. These patients were treated in arms P1 (LD: cyclophosphamide (cy) 500 mg/m^2 + fludarabine (flu) 30 mg/m^2 × 3 days) or arm P2 (LD: cy 1000 mg/m^2 + flu 30 mg/m^2 × 3 days) at a P-BCMA-ALLO1 dose of $\geq 2 \times 10^6$ to $<6 \times 10^6$ cells/kg.

Here we demonstrate that P-BCMA-ALLO1 has clinical activity in the post BCMA immunotherapy setting including in patients who have received multiple prior BCMA targeting immunotherapies.

Proprietary, non-viral approach to produce T_{SCM}-rich, fully allogeneic P-BCMA-ALLO1 CAR-T from healthy donors

piggyBac® Gene Insertion

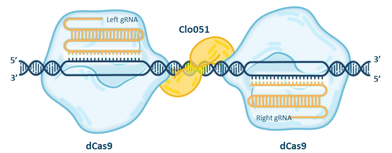
PiggyBac transposon system inserts transgene encoding BCMA-directed CAR



- Preferentially transposes naïve T cells resulting in T_{SCM} rich product
- Large cargo capacity delivers CAR, inducible safety switch, and selectable marker in single step

Cas-CLOVER™ Gene Editing

High fidelity gene editing system used to address graft vs. host and host vs. graft alloreactivity

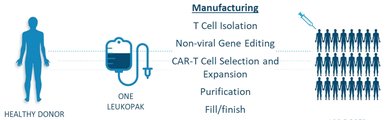


Madison et al., Molecular Therapy – Nucleic Acids, 2022. (https://www.sciencedirect.com/science/article/pii/S2162253122001558)

- High editing efficiency in resting T cells results in high % of T_{SCM}
- Low to no off target cutting
- Edits include TCR and B2M (MHC I) knockouts

High-yield Clinical Manufacturing

Allogeneic manufacturing process enhanced with Booster Molecule technology

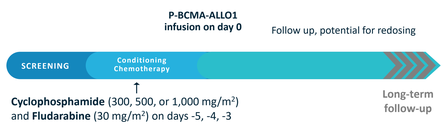


Manufacturing

T Cell Isolation
Non-viral Gene Editing
CAR-T Cell Selection and Expansion
Purification
Fill/finish
Storage in inventory

- Production process preserves T_{SCM} phenotype
- Nearly all CAR-carrying cells
- "On demand" Delivery

Study P-BCMA-ALLO1-001: open-label, multicenter, phase 1 study to assess the safety of P-BCMA-ALLO1 in patients with RRMM



Key Inclusion Criteria:

- RRMM as defined by the IMWG
- Must have received PI, IMiDs & CD38 mAb or triple refractory
- ECOG 0 or 1

PRIMARY OBJECTIVE

- Assess safety and MTD based on DLT

SECONDARY OBJECTIVES

- Evaluate the anti-myeloma effect of P-BCMA-ALLO1
- Study effect of cell dose & LD regimen selection to guide dose selection for pivotal studies

Presented are patients that have received and progressed on BCMA targeted therapies

P-BCMA-ALLO1 dose and LD arms evaluated, and no. of patients* infused at each cohort:

DL2† — Arm P1 (Cy 500); N = 2
— Arm P2 (Cy 1,000); N = 3

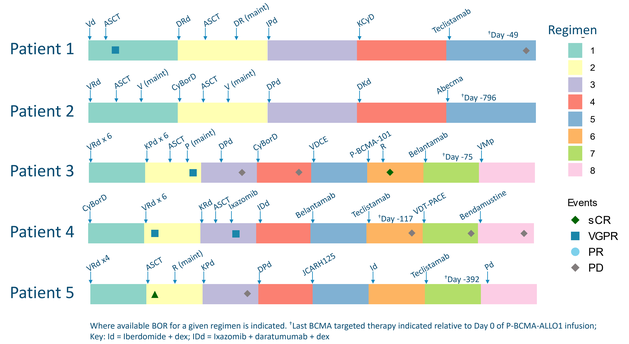
*minimum of 4 weeks follow-up; †DL2 = 2 x 10^6 – 6 x 10^6 cells/kg

Patient characteristics

Characteristics	Patient 1	2	3	4	5
Demographics	57-year-old white Male	62-year-old white female	64-year-old white female	45-year-old African American male	73-year-old white female
Year Dx / # prior regimens	2015; 5 priors	2014; 5 priors	2015; 8 priors	2019; 8 priors	2013; 8 priors
Myeloma Diagnosis Subtype	IgG; Kappa free light chain	IgG; Lambda free light chain	IgA; Kappa free light chain	IgG; Kappa free light chain	IgG; Kappa free light chain
Target or Measurable Plasmacytoma	Extramedullary disease present	Absent	Absent	Absent	Absent
Cytogenetics	Standard risk	Standard risk	Standard risk	High-risk MM (t(14:20))	Standard risk
Prior anti-BCMA CAR-T and anti-BCMA therapy	Teclistamab	Abecma	P-BCMA-101 (AUTO), Belantamab	Belantamab, Teclistamab	JCARH125, Teclistamab
BCMA MESF BCMA % +	4341; 40%	NR	2432; 37%	2703; 19%	6705; 26%
P-BCMA-ALLO1 Response (BOR)*	Arm P2 → SD	Arm P2 → VGPR	Arm P2 → VGPR	Arm P1 → SD	Arm P1 → VGPR
P-BCMA-ALLO1 Related SAEs	None	CRS Gr 2 (D10-12) ICANS G1/2 (D14-17)	CRS Gr 1(D5 -8)	CRS Gr 2 (D14-16)	Febrile neutropenia (D13-15)

*BOR includes confirmed and unconfirmed responses. Data cutoff: March 18th, 2024

Heavily pretreated patients with prior PD on BCMA targeted agents



Where available BOR for a given regimen is indicated. †Last BCMA targeted therapy indicated relative to Day 0 of P-BCMA-ALLO1 infusion;
Key: Id = Iberdomide + dex; IDd = Ixazomib + daratumumab + dex

Patient cellular kinetics (CK) and cytokine profiles

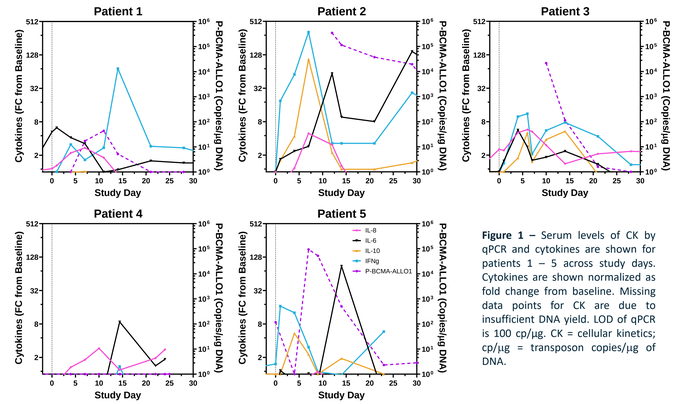


Figure 1 – Serum levels of CK by qPCR and cytokines are shown for patients 1 – 5 across study days. Cytokines are shown normalized as fold change from baseline. Missing data points for CK are due to insufficient DNA yield. LOD of qPCR is 100 cp/µg. CK = cellular kinetics; cp/µg = transposon copies/µg of DNA.

Responding patients showed higher max IL-15 and IL-7 and lower day 4 CD3+ lymphocytes

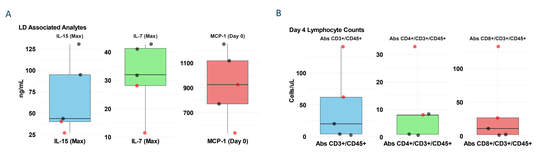


Figure 2 – A) Serum levels of LD associated cytokines IL-15 and IL-7 and chemokine MCP-1 (Day 0) are shown for patients 1 – 5 across study days. IL-15 and IL-7 shown as max values over D0 – D14. **B)** Absolute lymphocytes (total), CD4 or CD8 at Day 4. Non-responding patients (1 & 4) are highlighted in RED.

Preliminary clinical activity in heavily pre-treated and previously BCMA exposed patients

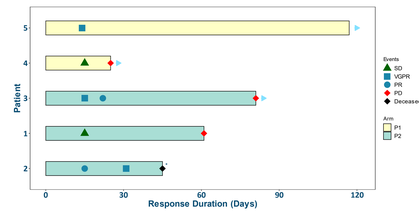


Figure 3 – Duration of response for patients dosed with P-BCMA-ALLO1 at DL2 with LD containing 500 mg/m^2 (P1) or 1000 mg/m^2 (P2) cyclophosphamide. Events shown include both confirmed and unconfirmed responses. Arrow indicates patients still in follow up.

*G5 AE aspiration pneumonia (assessed as unrelated) at day +45
†Data cut date: March 18th, 2024

CONCLUSIONS

- P-BCMA-ALLO1 is a T_{SCM}-rich allogeneic CAR-T manufactured from healthy donor cells that is rapidly available for dosing without the need for bridging chemotherapy.
- We have previously reported that P-BCMA-ALLO1 demonstrates high response rates in multiple myeloma patients who have received PI, IMiDs and CD38 mAb (Dholaria et al. ASH 2023, abstract 3479). Here we demonstrate that P-BCMA-ALLO1 has promising clinical activity in patients who have received all currently available BCMA directed therapies including antibody drug conjugates, CAR-T and TCE.
- P-BCMA-ALLO1 was well tolerated with no cases of DLTs or GvHD, and no instances of >Gr2 CRS or ICANS.
- These early promising results suggest that P-BCMA-ALLO1 can fulfil the unmet medical need in a wide variety of multiple myeloma patients.
- Further enrollment in the study is ongoing, with extensive biomarkers and correlative analysis to understand drivers of response and mechanisms of resistance.

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ABBREVIATIONS: Allo = Allogeneic; Auto = Autologous; BCMA = B-cell maturation antigen; B2M = β2 microglobulin; BMA = Bone marrow aspirate; CK = Cellular kinetics; CRS = Cytokine release syndrome; Cy = Cyclophosphamide; DLT = Dose limiting toxicity; ECOG = Eastern Cooperative Oncology Group; FLC = Free light chains; Flu = Fludarabine; GvHD = Graft-versus-host disease; IMiD = Immunomodulatory imide drugs; IMWG = International Myeloma Working Group; ITR = inverted terminal repeats; ITT = Intention-to-treat; LD = Lymphodepletion; LOD = Limit of detection; MESF = Molecules of Equivalent Soluble Fluorochrome; MHC = Major histocompatibility complex; MM = Multiple myeloma; MTD = Maximum tolerated dose; PI = proteosome inhibitors; PR = Partial response; RRMM = Relapsed and Refractory Multiple Myeloma; sCR = Stringent Complete Response; TCE = T cell engager; T_{SCM} = Stem cell memory T cells; VGPR = Very Good Partial Response

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