Clinical trial of P-BCMA-101 T stem cell memory (Tscm) CAR-T cells in relapsed/refractory multiple myeloma

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ABSTRACT

CAR-T cell therapies have demonstrated impressive efficacy in a number of indications, including multiple myeloma (MM) by targeting BCMA. However, toxicities, such as cytokine release syndrome (CRS), can be severe and even fatal.

P-BCMA-101 is a novel chimeric antigen receptor (CAR)-T cell therapy targeting BCMA designed to increase efficacy while minimizing toxicity through reduced immunogenicity, lack of tonic signaling, a safety switch, high purity (>95% CAR+) and a T stem cell memory (Tscm) phenotype (gradual and prolonged activity).

The P-BCMA-101 CAR utilizes an anti-BCMA Centyrin™ fused to a second-generation CAR scaffold (a CARTyrin) rather than scFv antibody fragments. Centyrins, like antibody fragments, have high binding affinities and are target-specific. However, Centyrins are fully human making them potentially less immunogenic, are more stable at the cell surface, and do not form multimers effectively rendering them resistant to antigen/ligand-independent tonic signaling.

Figure 1. P-BCMA-101 transposon transgene: a three-in-one CAR-T therapy

P-BCMA-101 (Fig. 1) is manufactured using the non-viral piggyBac™ (PB) DNA modification system, which is a transposon-based system requiring only mRNA and plasmid DNA. PB eliminates the need for virus and cytokines in production, preferentially producing the desirable Tscm phenotype and reducing manufacturing costs. Also, higher cargo capacity of PB permits the incorporation of additional genes, such as a safety switch and a selection gene, in P-BCMA-101.

- **The selection gene allows enrichment of CAR⁺ cells for high purity to improve therapeutic index (i.e. minimizes potential toxicity from non-CAR-T⁺ cells)**
- **Tscm are lymphocyte stem cells that are long-lived, self-renewing, and multi-potent. They appear to gradually differentiate into effectors, likely reducing CRS while increasing efficacy and durability**
- **The safety switch allows for rapid, dose-dependent *in vivo* depletion of P-BCMA-101 if severe adverse events were to occur**

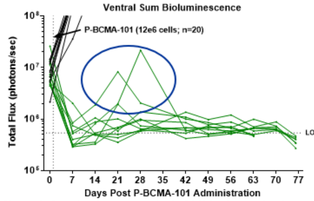


Figure 2. Spontaneous re-control of MM relapses *in vivo*

Efficacy of P-BCMA-101 in NSG mice bearing human MM.1S or p53 -/- MM.1S MM cell lines was reported (Hermanson, AACR 2016). Whereas control animals died early, tumor burden was reduced to the limit of detection after P-BCMA-101 treatment, and **recurrences were spontaneously re-controlled (Fig. 2)**.

This 3+3 dose escalation Phase 1 clinical trial (**P-BCMA-101-001; NCT03288493**) was initiated in patients with relapsed/refractory MM to assess the safety and efficacy of P-BCMA-101. Three patients have been treated at a dose of **0.75 × 10⁶ P-BCMA-101+ CAR-T cells/kg.** Safety/efficacy exceeded what has been reported on BCMA targeted CAR-T cells at this dose level, consistent with the preclinical hypotheses & findings.

Historical MM Clinical Results with ~0.75 x 10⁶ CAR-T cells/kg (~50 x 10⁶ CAR-T cells Total)				
Product	Dose	Patient #	Responses	CRS
bb2121[A]	50 x 10⁶ cells	3	33% (1 PR)	33% (100% of PR)
CART-BCMA[B]	0.3-1 X 10⁶ cells/kg	6	17% (1 PR)	83% (Gr2+)(100% of PR)
CART-BCMA[C]	10-50 X 10⁶ cells	5	20% (1 PR)	60%

Table 1. Published Historical Multiple Myeloma Clinical Trial Results with ~0.75 x 10⁶ BCMA-Targeted CAR-T cells/kg
PR: Partial Response. All responses lasted ≤ 8 weeks; A) Berdeja et al. ASH 2017 Corporate Presentation, B) Ali et al. ASH 2017, C) Cohen et al. ASH 2017; (*Doses and product details not published for LCAR-B38M, Zhao et al.*)

OBJECTIVES

Primary: Determine safety and maximum tolerated dose (MTD)
Secondary/Exploratory:
- Assess the anti-myeloma effect of P-BCMA-101
- Evaluate the relationship between BCMA expression and clinical response
- Characterize the expansion and functional persistence of the P-BCMA-101 cells
- Evaluate the relationship between putative CRS markers and efficacy or safety

METHODS

- **Single Dose of P-BCMA-101 on Day 0**
- Patients with relapsed and/or refractory MM: ≥3 prior lines of therapy, including a proteasome inhibitor and immunomodulatory agent (IMiD) or double-refractory, and who meet other protocol entry criteria based on vital organ function, concomitant medical conditions and prior therapies, may be enrolled
- Patient leukapheresis followed by electroporation of the P-BCMA-101 plasmid and transposase to manufacture autologous CAR-T cells
- Standard cyclophosphamide (300 mg/m²) and fludarabine (30 mg/m²) conditioning on Days -5 to -3
- Open Label, 3+3 dose escalation with up to 6 dose levels and 40 subjects
- Escalating dose levels administered intravenously starting at **0.75 × 10⁶ P-BCMA-101 cells/kg**

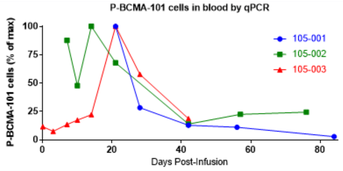
PATIENT DEMOGRAPHICS AND BACKGROUND

Table 2. Patient demographics. As of April 3rd, 2018, three patients had been treated with P-BCMA-101 at 0.75 × 10⁶ P-BCMA-101 cells/kg with data presented here. On April 9th, the first patient was treated with 2 × 10⁶ P-BCMA-101+ CAR-T cells/kg; sufficient data has not yet been reported for publication, however, no P-BCMA-101-related adverse events were reported after administration in this patient to date.

	Results	Comments
Age (range)	50-65 years	
Time since diagnosis (mean)	6.7 years	
Prior therapies (range)	6-9	
High risk (% patients)	100%	Del17p (TP53): 33%

P-BCMA-101 CAR-T CELLS IN BLOOD

Figure 3. Expansion of P-BCMA-101 CAR-T cells in blood. After injection, P-BCMA-101 gradually expanded in patients' peripheral blood, correlating with tumor regression. At peak, up to 40% of all circulating T cells were seen to be P-BCMA-101 CAR-T cells (initial results from RUO assay; missing data points due to unavailable samples).



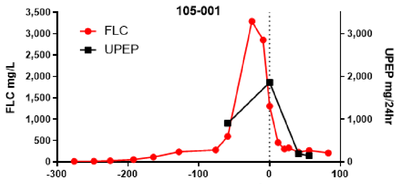
CLINICAL RESULTS

Patient 105-001: 54 yo female with lambda light chain myeloma
Cytogenetics: t(11;14), del13q14, 11q23(x3)
Prior Therapies:

- bortezomib/dexamethasone HD melphalan with ASCT
- lenalidomide/dexamethasone
- lenalidomide/dexamethasone/ixazomib
- lenalidomide/dexamethasone/daratumumab
- pomalidomide/dexamethasone/carfilzomib

Free Light Chains (FLC) escalated to 3,290 mg/L immediately before P-BCMA-101 treatment, causing renal failure (Fig. 4). Being immediately life-threatening, she was urgently treated with cyclophosphamide/prednisone & plasmapheresis bridging therapy. After treatment with P-BCMA-101, FLC and M-protein on UPEP markedly decreased to a strong partial response (PR), and she has remained in good condition since.

Figure 4. FLC and UPEP in 105-001



Adverse Events (≥ Possibly Related)
None

CRS: no

Cytokines (peak)
CRP: 3.5 mg/dL
Ferritin: 776 ng/ml
IL-6: 35 pg/ml
TNFa: 25 pg/ml

24-hour Urine M-protein decreased by 92% (PR), and involved FLC by 79% by 2 months after P-BCMA-101 administration.

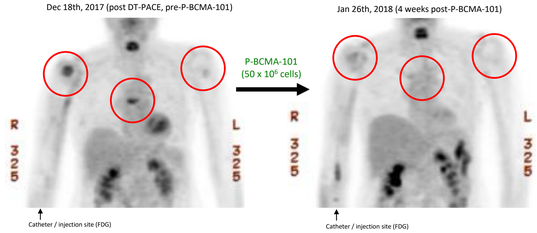
CLINICAL RESULTS (cont'd)

Patient 105-002: 50 yo female with oligosecretory kappa light chain myeloma and plasmacytomas
Cytogenetics: **del17p(TP53)**, 11q13(x3)
Prior Therapies:

- lenalidomide/dexamethasone/bortezomib HD melphalan with ASCT
- pomalidomide/dexamethasone/carfilzomib
- carfilzomib/dexamethasone/ibrutinib
- pomalidomide/dexamethasone/daratumumab
- pomalidomide/dexamethasone/elotuzumab

Plasmacytomas were painfully enlarging, and the patient was treated with DT-PACE bridging therapy (Fig. 5). After P-BCMA-101, bone plasmacytomas resolved to below background, with one new non-bone lesion appearing months later.

Figure 5. PET imaging in 105-002



Adverse Events (≥ Possibly Rel.) **Grade**
Neutropenia **2,3,4**
Thrombocytopenia **3,4**

CRS: no

Cytokines (peak)
CRP: 1.6 mg/dL
Ferritin: 413 ng/ml
IL-6: 8 pg/ml
TNFa: 7pg/ml

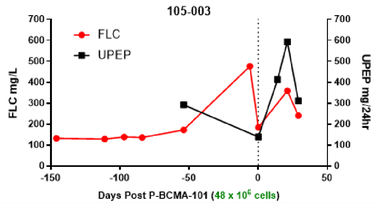
Oligosecretory disease, M-protein, SPEP, UPEP, FLC not measurable/within normal limits.

Patient 105-003: 65 yo female with lambda light chain myeloma
Cytogenetics: del13q14
Prior Therapies:

- thalidomide/dexamethasone HD melphalan with ASCT
- lenalidomide/dexamethasone
- bortezomib
- carfilzomib
- pomalidomide/dexamethasone
- ACP-196/pembrolizumab
- cyclophosphamide
- daratumumab
- elotuzumab/lenalidomide/dexamethasone

FLC had increased to 172 mg/L, then to 476 mg/L on lenalidomide/dexamethasone bridging therapy, rose then decreased after P-BCMA-101 (Fig. 6).

Figure 6. FLC and UPEP in 105-003



Adverse Events (≥ Possibly Related) **Grade**
Easy bruising **1**
Fatigue **2**
Febrile neutropenia **3**
Hypogammaglobinemia **2**
Neutropenia **2,3**
Thrombocytopenia **3,4**

CRS: no

Cytokines (peak)
CRP: 1.5 mg/dL **IL-6: 5 pg/ml**
Ferritin: 245 ng/ml **TNFa: 6 pg/ml**

CONCLUSIONS

- Favorable safety profile with no clear CRS symptoms or significant increase in CRS biomarkers seen in any patient despite marked anti-myeloma activity in all patients
- P-BCMA-101 is a nearly pure CAR-T⁺ product, which may improve therapeutic index
- Tscm CAR-T gradually increase in blood and circulate at high levels for a prolonged period, putatively explaining the unique safety and efficacy findings with P-BCMA-101

This poster and past publications on Poseida's products are available at Poseida.com/publications
Multiple positions are currently available and listed at Poseida.com/Careers
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