Clinical Trials of BCMA-Targeted CAR-T Cells Utilizing a Novel Non-Viral Transposon System

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BACKGROUND

CAR-T (chimeric antigen receptor T cell) therapies have demonstrated impressive efficacy in the treatment of multiple myeloma. However, toxicities, such as cytokine release syndrome (CRS) and CAR-T related encephalopathy syndrome (CRES), can be severe and even fatal.

P-BCMA-101 is a novel CAR-T cell therapy targeting BCMA for multiple myeloma (MM), designed to increase efficacy while minimizing toxicity through: Lack of tonic signaling, a safety switch, high purity (>95% CAR+), and high T stem cell memory (T_{SCM}) phenotype, which has correlated with efficacy for P-BCMA-101 and other CAR-T cell products.

A Phase 1/2 clinical trial is currently being conducted with P-BCMA-101 in patients with relapsed/refractory MM (PRIME; NCT03288493).

Fig. 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 Delivery System, which is a transposon-based system requiring only transposase mRNA and transposon plasmid DNA. PB eliminates the need for virus and cytokines in production, preferentially producing a final product with a high percentage of 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.

The PRIME trial is a Phase 1/2, 3+3 single dose escalation from 0.75 to 15 x 10^6 P-BCMA-101 CAR-T cells/kg. We have previously reported on the safety and efficacy of P-BCMA-101 alone at ASH. After 43 patients were enrolled, the manufacturing process was changed to a nanoplasmid (NP)-based system. Single dose escalation was then repeated using this product (SA-NP), as well as with P-BCMA-101 CAR-T cells in combination with rituximab (RIT) and with lenalidomide (R/RP). Here we report updated data, including results with the lenalidomide and rituximab combinations.

Also, presented is the first report on a clinical trial with P-BCMA-ALLO1, an allogeneic CAR-T cell product utilizing the same transposon CAR-T template and nanoplasmid, but an improved CAR binding domain, as well as next-generation allogeneic-enabling gene editing methods and booster molecules. Thus, P-BCMA-ALLO1 is expected to carry and improve up on the favorable attributes of P-BCMA-101.

OBJECTIVES AND ENDPOINTS

Primary Objective
To determine the safety and maximum tolerated dose (MTD) of P-BCMA-101 based on dose limiting toxicities (DLT)

Key Secondary Objectives
- Safety and feasibility of P-BCMA-101
- Anti-myeloma effect of P-BCMA-101
- Effect of cell dose to guide dose selection of doses for further assessment in Phase 2/ 3

Primary Endpoint
Number of subjects with DLT at each dose level to define maximal tolerated dose (MTD)

Secondary Endpoints
- Safety and tolerability based on adverse events (AEs), examinations, and standard laboratory studies
- Overall response rate (ORR) and duration of response (DOR) by International Myeloma Working Group Criteria (Kumar, 2016)

KEY INCLUSION/EXCLUSION CRITERIA AND TREATMENT SCHEDULE

- Patients must be >=18 years old, have signed informed consent, measurable disease by International Myeloma Working Group criteria (IMWG; Kumar 2016), adequate vital organ function and without significant autoimmune, CNS and infectious diseases
- Patients with r/r MM and ≥3 prior lines of therapy, including a proteasome inhibitor and immunomodulatory agent (IMiD) or double-refractory
- Open Label, 3+3 dose escalation with up to 6 dose levels in up to 120 patients
- Patients undergo leukapheresis and T cell purification followed by electroporation of the P-BCMA-101 plasmid and transposase to manufacture CAR-T cells
- Standard cyclophosphamide (300 mg/m^2) and fludarabine (30 mg/m^2) conditioning on Days -5 to -3 before P-BCMA-101 infusion on day 0
- No hospitalization required (fully outpatient administration allowed)
- Cohort SA: single administration of P-BCMA-101 with non-nanoplasmid manufacturing method
- Cohort SA-NP: single administration of P-BCMA-101 with standard nanoplasmid-based manufacturing
- Cohort R: lenalidomide 10 mg orally daily for 21 of every 28 days beginning 1 week before P-BCMA-101 infusion
- Cohort RP: lenalidomide 10 mg orally daily for 7 days beginning 1 week before apheresis and for 21 of every 28 days beginning 1 week before P-BCMA-101 infusion
- Cohort RIT: 375 mg/m2 via intravenous infusion, 12 and 5 days before P-BCMA-101 infusion, then every 8 weeks until disease progression

Dose Levels (P-BCMA-101 cells/kg/dose) include:
Cohort -1: 0.25 x 10^6
Cohort 1: 0.75 x 10^6
Cohort 2: 2 x 10^6
Cohort 3: 6 x 10^6
Cohort 4: 10 x 10^6
Cohort 5: 15 x 10^6

BASELINE CHARACTERISTICS

Patients Dosed, n	98
Median (min, max) age, y	62 (28, 80)
Male, n (%)	63 (64)
Median (min, max) time since diagnosis, y	5.8 (0.5, 29.1)
ECOG PS, n (%)	
0	31 (32)
1	67 (68)
Median (min, max) prior regimens	7 (2, 18)

	Exposed	Refractory
proteasome inhibitor, n (%)	98 (100)	52 (53)
bortezomib	92 (94)	33 (34)
carfilzomib	80 (82)	38 (39)
ixazomib	34 (35)	12 (12)
IMiD, n (%)	98 (100)	57 (58)
lenalidomide	96 (98)	47 (48)
pomalidomide	94 (96)	43 (44)
thalidomide	22 (22)	4 (4)
daratumumab, n (%)	92 (94)	46 (47)
Prior autologous SCT	73 (74)	

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Poseida has licensed certain rights to the Centyrin™ technology platform from Janssen Pharmaceuticals, Inc. for use in autologous T cell therapeutics

SAFETY

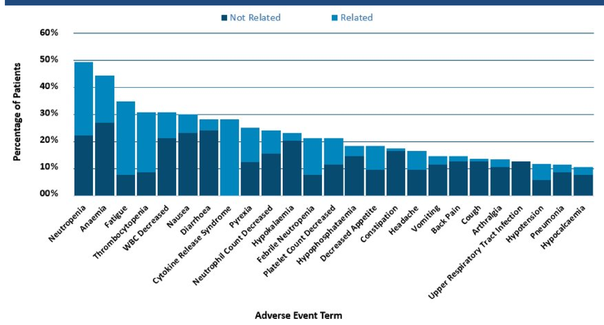
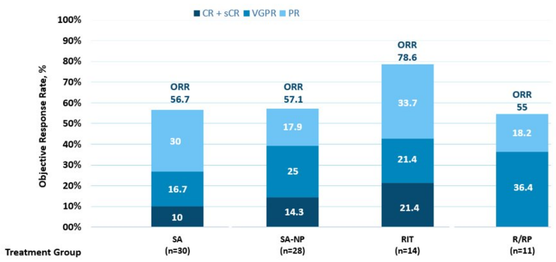


Fig.2: Safety Population: TEAEs with Incidence Rates > 10% (n = 103). As of this data cut, 98 unique patients have been treated. Five patients were retreated with P-BCMA-101 and are included in the safety cohort. The second administration was not counted in the ORR analysis. Three patients were treated in the phase 2 portion of the study undertaken with the original plasmid. No DLTs were observed in the study and there were no treatment related deaths. CRS occurred in 28% of patients. There were no cases of G3/4 CRS. Neurotoxicity (NT) occurred in 7% of patients (2% G3). There were no CAR-T related toxicities that led to ICU admissions. We treated patients in five dose cohorts with the original plasmid, three dose cohorts with the nanoplasmid, two dose cohorts with the rituximab combination and one cohort with the lenalidomide combination. Twenty-eight patients were treated fully outpatient.

RESPONSES IN EVALUABLE PATIENTS BY TREATMENT GROUP



Data cutoff: October 15th, 2021. ORR Objective Response Rate, attaining sCR, CR, VGPR or PR, including confirmed and unconfirmed responses. Evaluable patients: Obtained first response assessment by IMWG m-protein criteria or PD/death.

Fig. 3: ORR by treatment group

ANTI DRUG ANTIBODIES

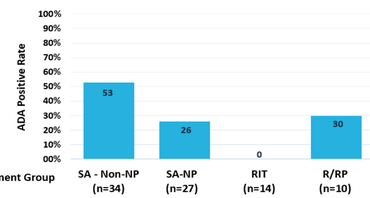


Fig. 4: Percent of patients developing anti-drug (anti-CAR) antibodies, assessed in serum using MSD, by treatment group

OVERALL SURVIVAL

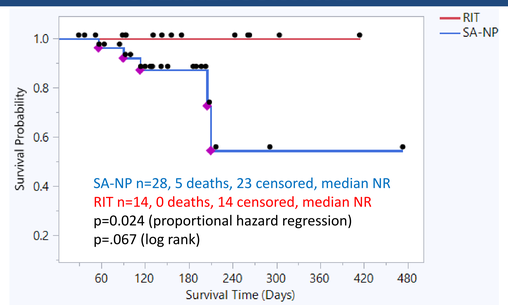


Fig. 5: Kaplan-Meier curves for overall survival for SA-NP and RIT treatment groups

P-BCMA-ALLO1

- Based on the success of P-BCMA-101 we have developed P-BCMA-ALLO1, an allogeneic CAR-T cell therapy that leverages piggyBac™ transposon technology to introduce an improved V_H BCMA binder
- P-BCMA-ALLO1 utilizes the proprietary Cas-CLOVER™ Site-specific Gene Editing System to knock out beta-2 microglobulin and the T-cell Receptor (TCR) beta chain to prevent GVHD and HVG, creating an allogeneic product
- Cas-CLOVER™ is a clean, efficient and versatile gene editing platform that is highly specific with low-to-no off-target cutting, and can be used in quiescent T-cells, maintaining a high percentage of Tscm cells.
- Proprietary "booster molecule" is used during manufacturing to create up to hundreds of doses.
- P-BCMA-ALLO1 cells were highly effective at controlling a human myeloma model in mice (Fig. 9)
- P-BCMA-ALLO1 investigational new drug (IND) was given a "safe to proceed" by the US Food and Drug Administration earlier this year
- We have launched a first in human phase I dose escalation study to assess the safety and maximum tolerated dose (MTD) of P-BCMA-ALLO1 based on dose limiting toxicities (DLT) (NCT04960579)

Fig. 6. P-BCMA-ALLO1 transposon transgene: a three-in-one CAR-T therapy

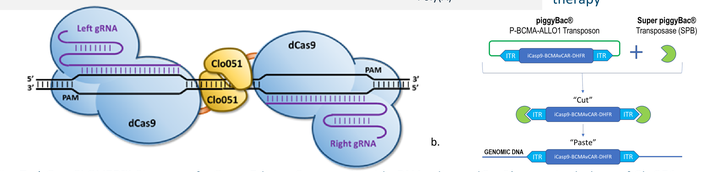


Fig. 7 a) Cas-CLOVER™ Site-specific Gene Editing System: 2 guide RNAs direct dCas9's to unite halves of Clo051 endonuclease to cut DNA b) piggyBac™ transposase removes transgene from plasmid and inserts into genome. Abbreviations: DHFR = dihydrofolate reductase; VCAR = variable human heavy-chain domain (VH)-based CAR; iCasp 9 = inducible caspase 9; ITR = inverted terminal repeats; BCMA = B cell maturation antigen

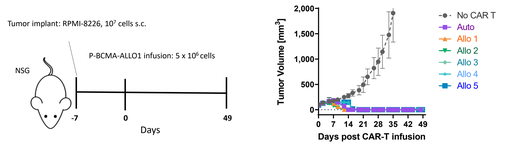


Fig. 8: Efficacy in the RPMI-8226 Multiple Myeloma Model

Single infusion
Dose Levels (cells/kg/dose) include:
Cohort minus 2: 0.0625 x 10e6
Cohort minus 1: 0.25 x 10e6
Cohort 1: 0.75 x 10e6
Cohort 2: 2 x 10e6
Cohort 3: 6 x 10e6
Cohort 4: 10 x 10e6
Cohort 5: 15 x 10e6

P-BCMA-ALLO1-001 OBJECTIVES AND ENDPOINTS

Primary Objective
- To assess the safety and maximum tolerated dose (MTD) of P-BCMA-ALLO1 based on dose limiting toxicities (DLT)

Key Secondary Objectives
- The safety of P-BCMA-ALLO1
- The anti-myeloma effect of P-BCMA-ALLO1

Primary Endpoint
- Number of subjects with DLT at each dose level to define an MTD

Key Secondary Endpoints
- Safety and tolerability based on adverse events , examinations, and standard lab assessments
- Efficacy based on International Myeloma Working Group (IMWG) Uniform Response Criteria (Rajkumar 2011, Kumar 2016, Cavo 2017)

CONCLUSIONS

- P-BCMA-101, a non-viral transposon-based autologous CAR-T demonstrates is well tolerated and demonstrates strong anti-tumor activity in an advanced late line RRMM patient. It can be safely administered fully outpatient.
- P-BCMA-101 produces little CRS (no Gr3+) or NT, and can be safely combined with lenalidomide or rituximab
- There is a moderate incidence of ADA in patients treated with P-BCMA-101 (legacy plasmid), which is decreased in patients that received P-BCMA-101 manufactured using the nanoplasmid.
- Rituximab completely prevented the development of ADA.
- There is a trend towards improved RR and OS in P-BCMA-101 combined with rituximab compared to P-BCMA-101 alone. The rituximab arm showed a 100% overall survival rate as of October 15, 2021. This combination could likewise be used with P-BCMA-ALLO1
- This data indicates that the PB transposon-based platform is an attractive option for allogeneic CAR-T cells.
- P-BCMA-ALLO1, an allogeneic CAR-T product that leverages this transposon technology and the unique Cas-CLOVER™ Site-specific Gene Editing System, produced marked anti-tumor activity in a myeloma mouse model.
- We have launched a first in human phase I study to assess the safety and tolerability of P-BCMA-ALLO1 in RRMM.