47P - Phase I Study to Assess the Safety and Efficacy of P-BCMA-ALLO1, a Fully Allogeneic CAR T Therapy, in Patients with Relapsed / Refractory Multiple Myeloma (RRMM)

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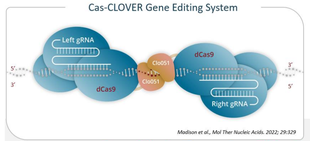
BACKGROUND

- Multiple myeloma (MM) is an incurable plasma cell malignancy with high expression of B-cell Maturation Antigen (BCMA)
- Autologous Chimeric Antigen Receptor T-cell (CAR T) therapies targeting BCMA have shown significant activity in MM
- Unfortunately, autologous CAR T poses several challenges including the need for apheresis, long manufacturing times, high manufacturing costs, costs and poor product quality because the T-cells are obtained from myeloma patients
- An allogeneic "off the shelf" CAR T could address these unmet needs by eliminating the need for apheresis, providing on demand therapy and better-quality T-cells from healthy donors for manufacturing
- P-BCMA-ALLO1 is an allogeneic CAR T targeting BCMA being investigated for the treatment of relapsed refractory multiple myeloma (RRMM)
- P-BCMA-ALLO1 utilizes non-viral transposon-based integration (piggyBac® DNA Delivery System) that introduces a humanized anti-BCMA VH-based CAR producing a highly enriched T stem cell memory (T_{SCM}) product
- The Cas-CLOVER™ Site-Specific Gene Editing System eliminates endogenous T cell receptor (TCR) expression via knockout of the *TCR beta chain 1* gene to prevent graft-vs-host disease and reduces MHC class I expression to eliminate host-vs-graft responses via *beta-2 microglobulin* gene knockout
- P-BCMA-ALLO1 demonstrated compelling activity in MM xenografts, providing rationale for this first-in-human phase I study

CAS-CLOVER: CLEAN GENE EDITING



- **Low-to-no off-target cutting**
- **High Editing Efficiency** in resting T-cells resulting in high % of T_{SCM} cells
- Ease of use/design
- Multiplexing ability
- High specificity
- Lower cost

Potentially the Cleanest Gene Editing Platform
with important ability to efficiently edit resting cells enables fully **Allogeneic CAR-T** products and **Gene Therapy** applications including ongoing development for non-viral in vivo gene editing

ALLOGENEIC PLATFORM

Unique allogeneic platform

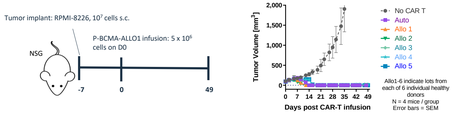
- Preserve/improve high T_{SCM}
- Optimized dosing regimens
- Healthy donor material
- Robust manufacturing
- Dramatic cost reductions – Up to 100s of doses

Booster molecule

Our patented technology is designed to overcome the "allo tax" and **significantly increase production yield** while **preserving desirable T_{SCM} attributes** of P-MUC1C-ALLO1

PRECLINICAL RESULTS

Efficacy in the RPMI-8226 Multiple Myeloma Model



CLINICAL STUDY METHODS AND DESIGN

Topic	Detail
Study information	Open label, multicenter, Phase 1, dose escalation study to assess the safety and efficacy of P-BCMA-ALLO1, which will be administered intravenously as a single dose. Dose levels will be tested in 3+3 escalation design in approximately 40 RRMM patients
Study design	**Dose escalation**: Standard 3+3 design is utilized in the dose-escalating cohorts to evaluate DLTs within 28 days post P-BCMA-ALLO1 administration. Adverse events (AE), Serious Adverse Events (SAE) and Treatment Emergent Adverse Events (TEAEs) will be evaluated throughout the study. If cohort 5 is completed without a Maximum Tolerated Dose (MTD), the Safety Committee may elect to assess further escalation cohorts in higher dose levels. P-BCMA-ALLO1 will be administered on D0 following lymphodepleting chemotherapy: Fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day on D-5, -4, -3
Study patient population	RRMM patients who have received greater than 3 lines of therapy, which must include a proteasome inhibitor (PI), immunomodulatory drug (IMiDs) and CD38 monoclonal antibody (mAb)
Evaluation criteria: efficacy, safety, and other variables	Safety/feasibility: AE, Cytokine Release Syndrome (CRS), neurotoxicity, Graft vs Host Disease (GVHD) Efficacy: IMWG criteria will be used for response. Overall Response Rate (ORR), Time to Response (TTR), Duration of Response (DOR), Progression Free Survival (PFS), Overall Survival (OS) will be analyzed.
Exploratory	P-BCMA-ALLO1 cellular kinetics; T cell composition in P-BCMA-ALLO1 drug product; immune response in the context of patient-donor match metrics; soluble BCMA levels; BCMA expression on MM cells; putative blood markers of safety and efficacy.

Major Inclusion Criteria

- Relapsed / Refractory Multiple Myeloma as defined by the IMWG
- Must have received at least three lines of therapy that must include a PI, IMiDs and CD38 mAb
- Have a measurable disease as defined by one of the following: 1) serum M-protein > 1.0g/dL; 2) Urine M-protein > 200mg/24hr; 3) FLC > 10 mg/dL; 4) Bone marrow plasma cells > 30%
- ANC ≥1000 /mL, platelets 50,000 /mL, Hb >8 g/dL
- Creatinine ≤1.5 mg/dL, SGOT < 3x ULN
- LVEF ≥45%

Major Exclusion Criteria

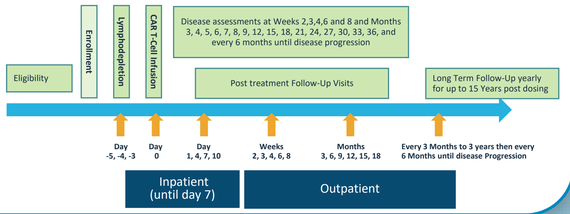
- Active hemolytic anemia; plasma cell leukemia, etc.
- Active second malignancies other than multiple myeloma
- Active autoimmune disease
- History of significant central nervous system disease
- Active systemic infections
- History of hepatitis; HTLV or HIV infection
- Has NYHA Class III or IV heart failure
- Received prior gene therapy

DOSE ESCALATION PLAN AND STUDY SCHEMATIC

Single infusion
Dose Levels (cells/kg/dose) include:

Cohort minus 2:	0.0625 x 10^6
Cohort minus 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

If cohort 5 is completed without concluding an MTD, the safety Committee may elect to assess further escalation cohorts in 5-10 X 10^6 P-BCMA-ALLO1 cells/kg increments.



PHASE 1 DOSE-ESCALATION CLINICAL RESULTS

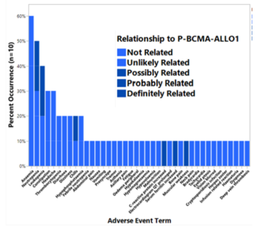
PATIENT DEMOGRAPHICS AND CHARACTERISTICS

CAR-T cells Administered: Cells/kg	Mean (Min/Max) x 10^6	Patients, n
Cohort 1: 0.75 x 10^6 single infusion	48 (37/ 64)	7
Cohort 2: 2.0 x 10^6 single infusion	162 (126/210)	3
Age / Gender/ Time since Diagnosis / Performance Status (n=10)		
Median (min, max) age, y		75 (33, 85)
Male, n (%)		3 (30)
Median (min, max) time since diagnosis, y		5.17 (1.48, 18.85)
Diagnosis Subtype, n (%)*		IgG, 7 (70)
		IgA, 2 (20)
		Kappa FLC, 5 (50)
		Lambda FLC, 5 (50)
Cytogenetic High-risk, n (%)		5 (50)
ECOG (Baseline) PS, 0 (%) /1 (%)		3 (30) / 7 (70)
Prior Therapy Exposure (n=10)		
Median (min, max) # prior regimens		6.5 (4, 10)
Prior anti-BCMA therapy, n (%)		3 (30)

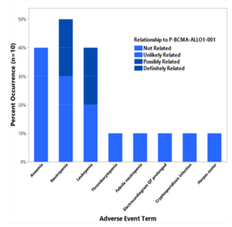
*No patients with IgM, IgE, IgD or Non-Secretory Diagnosis Subtypes

SAFETY RESULTS

Safety Population: All TEAEs



TEAEs Grade ≥ 3

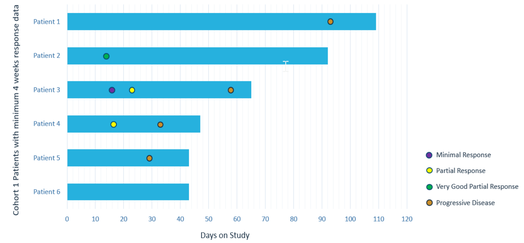


SUMMARY

- A total of 10 patients were treated with P-BCMA-ALLO1, 7 in cohort 1, and 3 in cohort 2
- Three SAE occurred in cohort 1 (G3 Febrile Neutropenia, G3 Disseminated Herpes Zoster, G3 Cryptosporidiosis infection)
- No SAE were related to P-BCMA-ALLO1
- **No CRS, GVHD, neurotoxicity, DLT or Adverse Events of Special Interest (AESI) have been observed as of the data cutoff**
- Six cohort 1 patients are available for response evaluation

EFFICACY RESULTS

Patient	Cohort	Age	Prior Lines of therapy	Cytogenetic Risk	Prior BCMA Targeting Therapy	Best Response
1	1	79	8	Standard	Yes (Belantamab)	SD
2	1	69	5	High	Yes (Belantamab)	VGPR
3	1	75	5	High	No	PR
4	1	33	10	Standard	Yes (Bispecific Ab)	PR
5	1	75	4	High	No	SD
6	1	66	4	High	No	SD



SUMMARY

- All enrolled patients are heavily treated having received 6.5 median prior lines of therapy
- 3 out of 6 evaluable cohort 1 patients had received prior BCMA targeted therapy
- 4 out of 6 evaluable cohort 1 patients had high risk cytogenetics
- ORR for Cohort 1 is 50%
- ORR in patients who have received prior BCMA targeting therapy is 66%
- ORR in patients with high-risk cytogenetics is 50%

CONCLUSION

- P-BCMA-ALLO1 is an allogeneic "off the shelf" BCMA targeting CAR T therapy that demonstrates compelling anti-myeloma activity, in a heavily pretreated patient population, at the lowest dose tested, while demonstrating excellent tolerability
- It is active in patients who have failed prior BCMA targeted therapy and in patients with high-risk myeloma
- The clinical activity is seen without CRS, GVHD or neurotoxicity
- P-BCMA-ALLO1 represents an important cellular therapy advance and could represent an attractive treatment option for multiple myeloma
- Dose escalation is ongoing
- Additional treatment regimens including cyclic dosing, repeat dosing, Rituximab combination and fixed (non-weight based) dosing will be explored

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