MT-401 (multi-tumor-associated antigen-specific T cells) utilized for treatment of MRD+ AML patients

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Introduction

Acute myeloid leukemia (AML) has been proven to be sensitive to immune-based intervention. The graft-versus-leukemia (GVL) effect mediated by adoptively transferred unmanipulated donor T-cells following allogeneic hematopoietic stem cell transplant (HSCT) is one of the most striking examples illustrating the benefit of harnessing the power of the immune system. Using multi-tumor-associated antigen (multi-TAA)-specific T-cells can potentially enhance the GVL effect while simultaneously mitigating the risk of inducing graft-versus-host disease (GVHD). MT-401 (zedenoleucel) is a non-genetically modified allogeneic multi-tumor associated antigen (mTAA)-specific T-cell therapy with selectivity to multiple tumor antigens, specifically PRAME, WT1, NY-ESO-1 and Survivin.

A Phase 2 trial with a safety lead-in is being conducted to study the efficacy of MT-401 in AML patients in post-transplant setting for use as an adjuvant therapy and for relapsed disease, including patients with measurable residual disease (MRD). MRD positivity is associated with increased relapse risk and shorter survival in AML. We enrolled 6 patients in the safety lead-in portion (5 patients with frank relapse, 1 patient with MRD+ disease) to test the safety of a new vendor for a reagent in the manufacturing process. Three patients were treated with product manufactured using a legacy reagent, and 3 other patients were treated with product manufactured using a new reagent.

Methods

- Six patients were enrolled and treated in the safety lead-in portion of Phase 2 study (5 patients with frank relapse, and 1 MRD+ patient). No dose limiting toxicities (DLTs) were observed.
- Patients received up to 3 consecutive intravenous infusions of zedenoleucel as a monotherapy (50 × 10^6 cells every 2 weeks).
- Efficacy evaluations completed using ELN recommendations for standard AML response criteria.
- mRNA-Seq was used to detect target and non-target antigen mRNA expression in patient bone marrow samples.
- IFNγ ELISpot was used as a readout for antigen specific T-cells.

Clinical Study Design

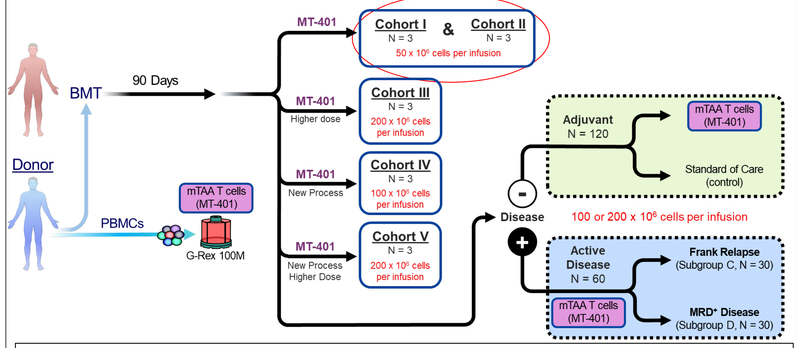


Figure 1. Study design. A Phase 2 Study of Donor-Derived Multi-Tumor-Associated Antigen-(MTAA)-Specific T cells (MT-401) Administered to Patients with Acute Myeloid Leukemia (AML) following Hematopoietic Stem Cell Transplantation (ARTEMIS, NCT04511130). SOC = standard of care.
Note: Cohort I is testing a product using vendor 1 reagent and Cohort II is testing a product using vendor 2 reagent.

Safety Lead-In Patient Summary

A

Patient Demographics	Total (N = 6)
Age	
Median (Min, Max)	52 (42, 66)
≥ 65	2
Male	2
Disease Status	
MRD+	1
Frank Relapse	5
Number of Prior Lines of Therapy (Prior to Transplant)	
1	1
2	2
3	1
4	0
≥ 5	2

B

Patient #	Donor Type	Genetic Mutations	Genetic Abnormalities
1) **107-01-A**	Haplo	c-KIT	t(8;21)(q22;q22.1) [RUNX1-RUNX1T1]
2) **103-01-A**	MUD	NPM1, TET2	46XX
3) **101-01-A**	Haplo	NRAS, U2AFQ Mutation	Normal karyotype
4) **114-01-B**	Haplo	NRAS, ETV6, RBM-15, MLLT10	46XY, wt NPM1 without or with FLT3-ITD
5) **108-01-B**	MRD	Monosomy 7, Inversion 3	46,XX, INV(3)(Q21Q26.2)[4]/45, IDEM, -7[2]/46,XX[14]
6) **103-02-B**	Haplo	NRAS, TP53	ASXL1, SETBP1, SRSF2, APC

Figure 2. Safety Lead-In Cohort Characteristics. A) Patient demographics. **B)** Patient specific characteristics. [Note: Patient numbers ending in A were administered product using vendor 1 reagent (Cohort I) and those ending in B were administered product from vendor 2 reagent (Cohort II)]

Safety and Efficacy Summary

Safety (1° endpoint):

- No dose-limiting toxicities (DLTs) observed in any of the 6 patients
- No cytokine release syndrome (CRS) or neurotoxicity noted

Efficacy (2° endpoint):

- MRD+ patient converted to MRD- (Patient 107-01-A) post-MT-401 infusion
- No objective responses noted in the 5 frank relapsed patients

Patient 107-01-A Profile

- 43 yo Hispanic male w/ AML (recurrent genetic abnormalities)
- 5 prior lines of therapy (I+C, FLAG-IDA+ IC chemo, MEC +IC chemo, azacitidine, decitabine)
- Haploidentical donor
- Genetic mutations: c-KIT
- Genetic abnormalities: t(8;21)(q22;q22.1) [RUNX1-RUNX1T1]

Patient 107-01-A T cell Product

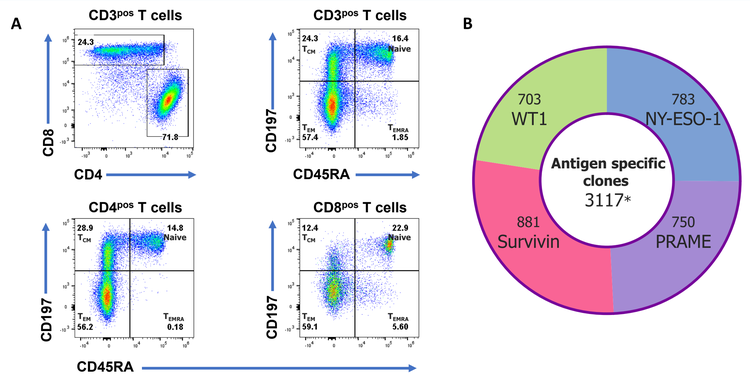


Figure 3. T-Cell Composition and Phenotype of Patient 107-01-A Product. A) Patient product is a mixture of CD4+ & CD8+ T-cells that are predominantly effector memory cells comprised of more than 3,000 different antigen-specific T-cell clones – unlike a single T cell receptor (TCR) transgenic clone. **B)** Breakdown of antigen specific clones.

T-Cell Expansion

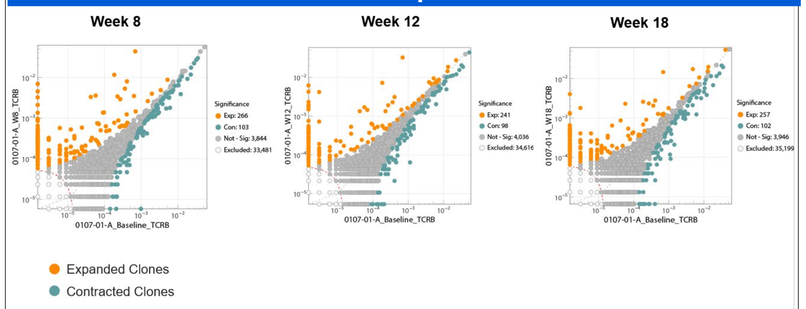


Figure 4. Peripheral T-Cell Clones in Patient 107-01-A Compared to Pre-infusion. Clonal expansion/contraction of T-cells can be observed throughout patient immune monitoring using TCR sequencing. A significant number of different T-cell clones expand in the patient after product infusion.

Tumor Antigen Expression

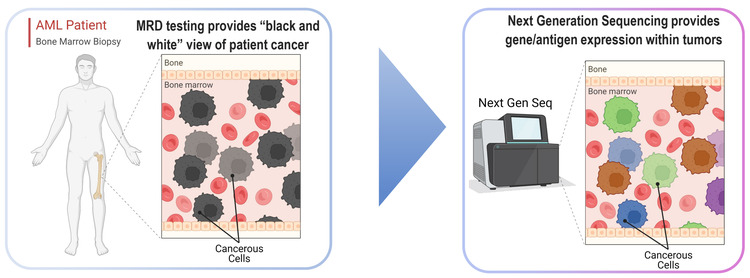
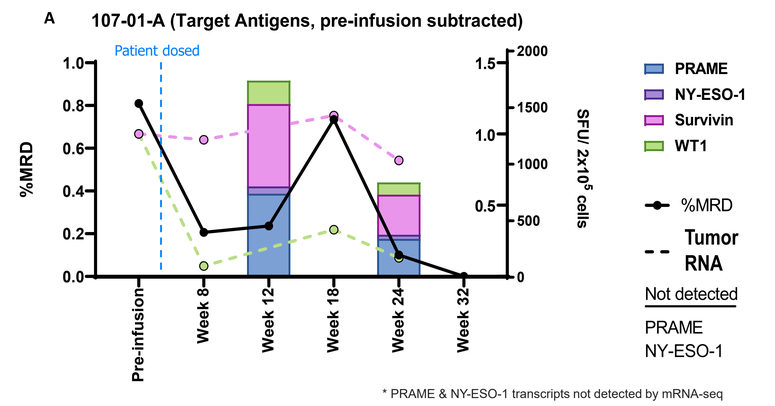


Figure 5. Details of Patient Tumor Dynamics are Revealed Through Next Generation Sequencing

MRD, Target and non-Target Antigen Expression, and T-cell specificity



* PRAME & NY-ESO-1 transcripts not detected by mRNA-seq

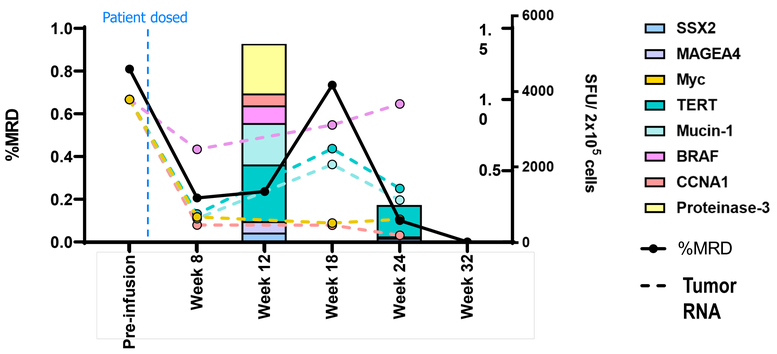


Figure 6. Antigen Expression in Bone Marrow of Patient 107-01-A. A) Targeted antigen expression in bone marrow of Patient 107-01-A vs T-Cell Specificity as measured by ELISpot for IFNγ. **B)** Antigen Expression in Bone Marrow of Patient 107-01-A vs T-Cell Specificity – Non-target Antigens.

Conclusions

- **Encouraging overall safety**
  - No DLTs, CRS or neurotoxicity
  - Safety data consistent with safety results from Phase 1/2 trials at Baylor College of Medicine across over 150 patients[1-4]
- Provides clinical support that MT-401 is effective in treating MRD+ AML patients
- MT-401 generated additional evidence of epitope spreading
- Marker's T-cells are protected from exhaustion and have been shown to expand and persist in the patient
- A significant number of T-cell clones expanded after product infusion
- A total of 27,369 individual T-cell clones were in the final product as determined by TCR sequencing
- Patient product is a mixture of CD4 & CD8 T-cells that are predominantly effector memory cells comprised of more than 3,000 different antigen-specific T-cell clones – unlike a single TCR transgenic clone
- Expression of targeted tumor antigens, Survivin and WT1, directly correlates with MRD
- Decreases in Survivin and WT1 expression on the tumor correlate with increases in target antigen-specific T-cells detected in the peripheral blood
- Additional non-targeted tumor antigens significantly decrease after product infusion and trends with MRD

Future Directions

- Complete all cohorts (III-IV) exploring high doses and accelerated manufacturing process
- Begin the main phase 2 portion of the study, including both adjuvant and active disease groups

References

[1] Lulla P, Naik S, Vasileiou S, et al. Clinical effects of administering leukemia-specific donor T cells to patients with AML/MDS post-allogeneic transplant. Blood. 2020a:blood.2020009471. doi: 10.1182/blood.2020009471.
[2] Naik S, Vasileiou S, Tzannou I, et al. Donor-Derived Multiple Leukemia Antigen Specific T-cell Therapy to Prevent Relapse Post-Transplant in Patients with ALL. Blood. 2022 Feb 8:blood.2021014648. Epub ahead of print.
[3] Vasileiou S, Lulla PD, Tzannou I, et al. T-Cell Therapy for Lymphoma Using Nonengineered Multiantigen-Targeted T Cells Is Safe and Produces Durable Clinical Effects. J Clin Oncol. 2021:JCO2002224.
[4] Lulla PD, Tzannou I, Vasileiou S, et al. The safety and clinical effects of administering a multiantigen-targeted T cell therapy to patients with multiple myeloma. Sci Transl Med. 2020b;12(554):eaaz3339.