Preliminary Results of MT-401 [multi-tumor-associated antigen(multiTAA)-specific T cells] in Post-Transplant MRD+ AML Patients

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Background

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 (multiTAA)-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 testing has become more prevalent in AML, and MRD positivity is associated with increased relapse risk and shorter survival in AML. Currently, there no approved therapies for these patients.

Objective

To determine whether MRD+ patients post-allogeneic transplant can be treated safely and effectively with multiTAA-specific T cells (MT-401/zedenoleucel).

Mechanism of Action

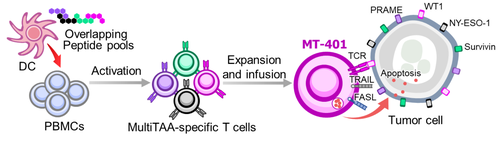


Figure 1. Mechanism of Action of MT-401 (zedenoleucel)

Methods

A multicenter Phase 2 study (ARTEMIS) evaluating the safety, tolerability and efficacy of zedenoleucel in patients with AML, including MRD+ patients, post-HSCT is ongoing. The study explores this therapy in patients with no active disease (in complete remission (CR) and MRD-) or in patients with active disease (frank relapse or MRD+). Patients may receive up to 3 consecutive infusions of zedenoleucel as a monotherapy (50-200 × 10^6 cells every 2 weeks) at weeks 0, 2 and 4 during the Intervention Period, and enter Follow-up at Week 8 for up to 5 years. Primary endpoints include various safety measurements. Efficacy evaluations occur at weeks 8, 12, 18, 24, 48 and yearly for 4 years using ELN recommendations for standard AML response criteria. MRD testing was done by flow cytometry or molecular testing (e.g. RT-PCR).

Clinical Study Design

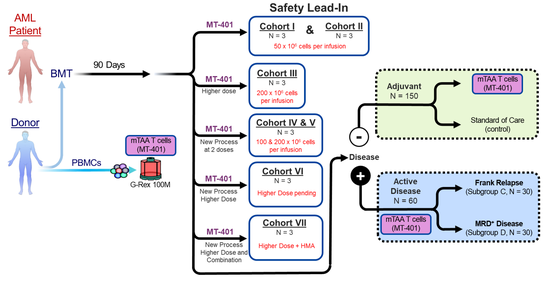


Figure 2. Clinical Study Design: Cohorts I-VII focus on active disease population post-transplant (frank relapse or MRD+ patients).

Main Outcome Measures

- The primary endpoint includes various safety measurements and incidence of dose-limiting toxicities (DLTs). The secondary endpoint was efficacy evaluations using ELN recommendations for standard AML response criteria.
- Two MRD+ AML patients (as determined by flow cytometry or molecular testing) were enrolled and treated in the ARTEMIS study.

Manufacturing & Product Profile

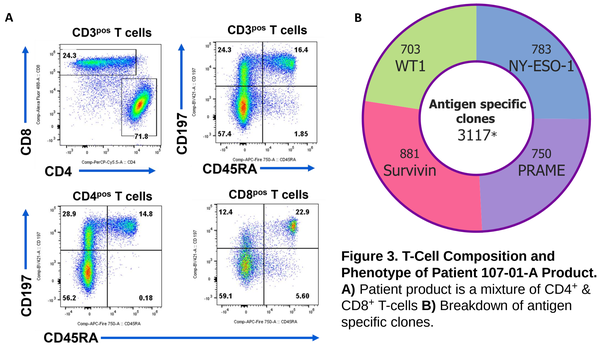


Figure 3. T-Cell Composition and Phenotype of Patient 107-01-A Product. **A)** Patient product is a mixture of CD4+ & CD8+ T-cells **B)** Breakdown of antigen specific clones.

Patient Background & Results

Patient #	Donor Type	Genetic mutations	Genetic abnormalities
107-01-1A	Haploidentical	c-KIT	t(8;21)(q22;q22.1) [RUNX1-RUNX1T1]
115-01	Matched-Related Donor	NPM, TET2	46,XY

Table 1: Two MRD+ patients have been enrolled into the study (patients 107-01-1A and 115-01). Patient 107-01-1A is a 43-year-old Hispanic male with 5 prior lines of therapy and received bridging therapy with azacitidine/decitabine, and patient 115-01 is a 47-year-old Asian female who received 1 prior line of therapy without any bridging therapy.

Patient #	MRD testing methodology	Baseline MRD testing	Post-treatment MRD status
107-01-1A	PCR (RUNX1)	0.809%	0.086% (at 1 year)
115-01	Immunostaining (NPM1)	Present	Absent at Week 8

Table 2: Two MRD+ patients have been enrolled into the study (patients 107-01-1A and 115-01). 107-01-1A showed MRD positivity of RUNX1 based on RT-PCR testing of BM aspirate samples with the exception of week 32 which was done by peripheral blood. 115-01 showed NPM1.

T-Cell Expansion

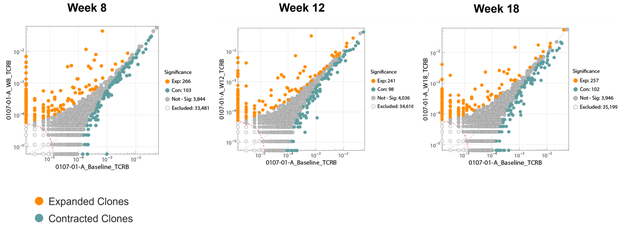


Figure 4. Peripheral T-Cell Clones in Patient 107-01-A Compared to Pre-infusion. Clonal expansion/contraction of T-cells can be observed throughout patient immune monitoring using TCR sequencing. A significant number of different T-cell clones expand in the patient after product infusion.

Post infusion Antigen Expression

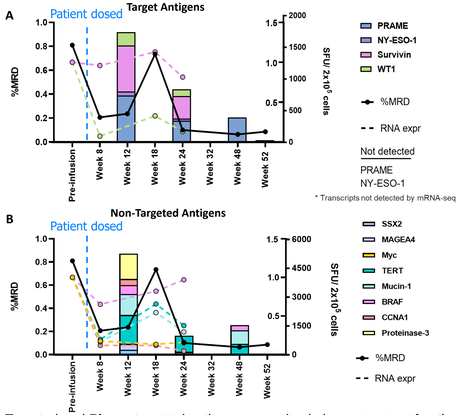


Figure 5. A) Targeted and **B)** non-targeted antigen expression in bone marrow of patient 107-01-A. Specificity as measured by ELISpot for IFNγ. %MRD is indicated by the black line.

Conclusions

Encouraging overall safety

- No DLTs, including cytokine release syndrome (CRS) or neurotoxicity were observed.
- 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.
- 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.

- **Overall:** The early ARTEMIS results showed that administration of MT-401 converted MRD+ patients to MRD- indicating that early intervention with MT-401 administration at MRD+ stage in post-transplant AML can be beneficial.

References

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