TITLE PAGE

PROTOCOL TITLE:	A Phase 2 Study of Donor-Derived Multi-Tumor-Associated Antigen-Specific T Cells (MT-401) Administered to Patients with Acute Myeloid Leukemia (AML) following Hematopoietic Stem Cell Transplantation (ARTEMIS)
Short Title:	Efficacy of MT-401 in patients with AML following stem cell transplant
ARTEMIS:	AML: Treatment of Relapse after Transplant or Extended Maintenance of Remission – Investigational Study (ARTEMIS)
Protocol Number:	MRKR-19-401-01
Protocol Version:	6.1
Replaces:	**Version 5.0 dated 24 September 2021**
Approval Date:	22 November 2022
Amendment Number:	5
Investigational Product:	MT-401, zedenoleucel
Study Phase:	2
Sponsor Name:	Marker Therapeutics, Inc.
Address:	4551 Kennedy Commerce Dr, Houston, TX, 77032

Regulatory Agency Identifier Numbers:

Health Authority	Identifying #
US Food and Drug Administration	IND 19147
National Cancer Institute	NCT04511130

Sponsor Signatory:

Mythili Koneru, MD, PhD Chief Medical Officer	Date: 29 November 2022

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Confidentiality Notice

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Phase 2 Study of Donor-Derived Multi-Tumor-Associated Antigen-Specific T Cells (MT-401) Administered to Patients with Acute Myeloid Leukemia (AML) following Hematopoietic Stem Cell Transplantation (ARTEMIS)

Protocol Version: 6.1

Protocol Date: 22 November 2022

I have read the protocol specified above. In my formal capacity as investigator, my duties include ensuring the safety of the study patients enrolled under my supervision and providing Marker Therapeutics with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice (GCP) principles and to abide by the terms of this protocol.

Investigator Signature: _____

Printed Name of Investigator: _____

Date: _____

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADSPAM	**A**dministration of **D**onor-Derived Multi-Tumor-Associated Antigen-**SP**ecific T Cells to Patients with **A**ML or **M**DS
AE	adverse event
AML	acute myeloid leukemia
APC	antigen-presenting cell
BOR	best overall response
CAR	chimeric antigen receptor
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CI	confidence interval
CR	complete remission
CR2	second complete remission
CRi	complete remission with incomplete recovery
CR_{MRD-}	complete remission without minimal residual disease
CRS	cytokine release syndrome
CSR	clinical study report
CTA	cancer testis antigen
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DL	Dose Level
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOCR	duration of complete remission
$DOCR_{MRD-}$	duration of complete remission without minimal residual disease
DOR	duration of response
eCRF	electronic case report form
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRFS	graft-versus-host disease relapse-free survival
GVHD	graft-versus-host disease
GVL	graft versus leukemia
HL	Hodgkin lymphoma
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IERC	Independent Efficacy Review Committee
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous(ly)
KM	Kaplan-Meier
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MRD	minimal residual disease
MRD^{+}	patients with minimal residual disease

MRD^-	patients without minimal residual disease
mRNA	messenger ribonucleic acid
multiTAA	multi-tumor-associated antigen
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NMDP	National Marrow Donor Program
NYESO	New York esophageal 1
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PET	positron-emission tomography
PFS	progression-free survival
PR	partial remission
PRAME	Preferentially Expressed Antigen in Melanoma
PRO	patient-reported outcome
RFS	relapse-free survival
RT-qPCR	quantitative reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SoC	standard of care
SRC	Sponsor Review Committee
TAA	tumor-associated antigen
TCR	T cell receptor
WT1	Wilms Tumor-1

1. PROTOCOL SUMMARY

1.1. Synopsis

Introduction	Multi-tumor-associated antigen (multiTAA)-specific T cell product (hereafter referred to as MT-401 and also known as zedenoleucel) is a non-genetically modified allogeneic T cell therapy that is being developed for the treatment of patients with acute myeloid leukemia (AML) after receiving allogeneic stem-cell transplant. MT-401 is composed primarily of multi-antigen specific CD4+ and CD8+ T cells that have been manufactured under current Good Manufacturing Practices (cGMPs) by in vitro stimulation of T cells with antigen-presenting cells (APCs), which were cultured with overlapping peptide pools. Briefly, donor T cells are cultured with APCs presenting peptides spanning the primary sequence of four tumor-associated antigens (TAAs), namely Preferentially Expressed Antigen in Melanoma (PRAME), New York esophageal 1 (NYESO-1), Survivin, and Wilms Tumor-1 (WT1) in the presence of recombinant cytokines. A Phase 1 study is being conducted at Baylor College of Medicine under an investigator-sponsored study to evaluate the safety and efficacy of multiTAA-specific T cells in patients with AML entitled "**A**dministration of **D**onor-Derived MultiTAA-**SP**ecific T Cells to Patients with **A**ML or **M**yelodysplastic syndromes (MDS) (ADSPAM)".
Protocol Title	A Phase 2 Study of Donor-Derived Multi-Tumor-Associated Antigen-Specific T Cells (MT-401) Administered to Patients with Acute Myeloid Leukemia (AML) following Hematopoietic Stem Cell Transplantation (ARTEMIS)
Short Title	Efficacy of MT-401 in patients with AML following stem cell transplant
Investigational Product	The investigational product used in this study is MT-401. Patient-specific MT-401 is an allogeneic multiTAA-specific T cell product manufactured under Good Manufacturing Practice (GMP) using donor-derived T cells obtained from apheresed peripheral blood mononuclear cells (PBMCs), which are stimulated with donor-derived APCs presenting overlapping peptides spanning the four TAAs: PRAME, NYESO-1, Survivin, and WT1. MT-401 final product is cryopreserved until the patient is ready for the product to be administered. This study was initiated with MT-401 using a manufacturing process that took >2 weeks, however, recently the manufacturing process has been shortened to about one week, which is referred to as an accelerated process (being tested in Cohorts IV and V). MT-401 manufacturing process and dosing regimens for each study cohort and Phase 2 (Group 1 and 2) are as follows: • Cohort I: MT-401 manufactured with JPT peptides (50×10^6 cells) • Cohort II: MT-401 manufactured with Almac peptides (50×10^6 cells) • Cohort III: MT-401 manufactured with Almac peptides (200×10^6 cells) • Cohort IV: MT-401 manufactured with an accelerated manufacturing process and Almac peptides (100×10^6 cells) • Cohort V: MT-401 manufactured with an accelerated manufacturing process and Almac peptides (200×10^6 cells) • Phase 2 (Groups 1 and 2): Following completion of Cohorts I and II, the peptide manufacturer to be used in Phase 2 will be identified based on review of the safety data. At any time, following completion of Cohort III, the Sponsor may change the Phase 2 dosing regimen to that evaluated in Cohort III. At the conclusion of Cohorts IV and V, which evaluate the safety of the product manufactured using an accelerated process at two different doses, the Sponsor may change the Phase 2 dose to the dose deemed to be safe for MT-401 manufactured using the accelerated process.
Study Location	Approximately 20-25 centers
Sponsor	Marker Therapeutics, Inc.

<table>
<tr><td>Number of Patients</td><td>A total of approximately 225-240 patients will be randomized/treated in this study as follows:
• Safety Lead-in: 6-12 patients
• Cohorts III, IV and V: 9-18 patients
• Phase 2: approximately 210 patients
  • ~150 patients in Group 1 (adjuvant therapy)
  • ~60 patients in Group 2 (active disease)
Enrollment will continue in Phase 2 to achieve approximately 210 evaluable patients randomized/treated with the final MT-401 dose and manufacturing process, thereby replacing any patients that have not been randomized/treated with the final Phase 2 product and dose, as determined by the Sponsor.</td></tr>
<tr><td>Length of Study</td><td>Approximately 5 years
Planned 1st patient to enroll on study (sign informed consent form [ICF]): October 2020</td></tr>
<tr><td>Study Objectives</td><td>
<table>
<tr><th>Phase</th><th>Objectives</th><th>Endpoint</th></tr>
<tr><td></td><td colspan="2">Primary</td></tr>
<tr><td>Safety Lead-in (Cohort I and II) & Cohorts III-V</td><td>To assess safety and tolerability of MT-401:
• Manufactured using peptides produced by two different vendors (Safety Lead-in: Cohorts I and II).
• At a higher dose than the dose used in the Phase 2 portion of the study (Cohort III).
• Manufactured using an accelerated manufacturing process at two dose levels (Cohort IV and V)</td><td>• DLTs
• Safety (including but not limited to): TEAEs, SAEs, deaths and clinical laboratory abnormalities per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0)</td></tr>
<tr><td>Phase 2 - Adjuvant (Group 1)</td><td>To compare relapse-free survival (RFS) for MT-401 (Arm A) vs standard of care (SoC; Arm B)</td><td>RFS</td></tr>
<tr><td>Phase 2 – Active Disease (Group 2):</td><td>• Subgroup C (frank relapse): to estimate complete remission (CR) rate and duration of CR (DOCR)
• Subgroup D (MRD+): to estimate complete remission (CR_{MRD}-) rate and duration of CR without minimal residual disease (DOCR_{MRD}-)</td><td>• Subgroup C:
  ○ CR rate
  ○ DOCR
• Subgroup D:
  ○ CR_{MRD}- rate
  ○ DOCR_{MRD}-</td></tr>
<tr><td></td><td colspan="2">Secondary (Efficacy)</td></tr>
</table>
</td></tr>
</table>

	Safety Lead-in (Cohorts I and II) & Cohorts III-V	To assess efficacy of MT-401: • Manufactured using peptides produced by two different vendors (Safety Lead-in: Cohorts I and II). • At a higher dose than the dose used in the Phase 2 portion of the study (Cohort III). • Manufactured using an accelerated manufacturing process at two dose levels (Cohort IV and V)	CR rate and DOCR (Active disease patients)
	Phase 2 (Adjuvant-Group 1)	• To analyze overall survival (OS) for MT-401 (Arm A) and SoC (Arm B) • To compare graft-versus-host disease RFS (GRFS) for MT-401 (Arm A) vs SoC (Arm B)	• OS • GRFS
	Phase 2 (Active Disease-Group 2: Subgroups C and D)	• To evaluate overall response rate (ORR), duration of response (DOR), progression-free survival (PFS) and OS for MT-401 alone • To evaluate RFS, OS, and GRFS for patients who achieve CR following bridging therapy	• ORR • DOR • PFS • OS • RFS • GRFS
		Secondary (*Safety)*	
	Phase 2 (Adjuvant- Group 1 and Active Disease-Group 2)	To evaluate the safety and tolerability of administering donor-derived MT-401 to patients with AML post-HSCT	• GVHD Assessments • Vital signs • Clinical laboratory assessments • Physical examination • AEs
		Exploratory	

	Safety Lead-in, Cohort III-V, & Phase 2	• To examine the expansion, persistence, clonality and anti-tumor immune effects of the adoptively-transferred, donor-derived, MT-401, as well as the presence of epitope spreading in all groups • Time to minimal residual disease (MRD) positivity in patients without MRD (MRD$^-$) • Clearance of MRD from MT-401 infusion in patients with CR but persistent evidence of MRD • Phase 2 (Group 2 Subgroup C only): to explore patient reported outcomes (PROs)	• Markers of immune function, cell targeting, signaling pathways and disease status, including MRD • PRO questionnaire
Study Design	This study is a Phase 2 multicenter study evaluating the safety and efficacy of MT-401 administered to patients with AML, who received their first allogeneic hematopoietic stem cell transplant (HSCT). Part 1 of the study includes a Safety Lead-in portion prior to the Phase 2 study which includes two cohorts (Cohort I and Cohort II) that will evaluate the safety and tolerability of three consecutive MT-401 doses of 50 x 10^6 cells manufactured with peptide pools obtained from two different vendors. Once Cohorts I and II in the Safety Lead-in are complete, the Phase 2 portion will open. Phase 2 will initially evaluate the efficacy and safety of MT-401 at a flat dose of 100 x 10^6 cells either as adjuvant therapy in patients (Group 1) with no active disease (in CR and MRD$^-$) or in patients with active disease (Group 2, frank relapse or MRD$^+$). Part 2 of the study includes Cohorts III, IV, and V which will run in parallel with Phase 2. Cohort III will evaluate MT-401 at a higher dose (200 x 10^6 million cells) than the dose used in the Phase 2 portion using the initial (>2 weeks) manufacturing process. If Cohort III data determines the 200 x 10^6 cell dose to be safe, the Phase 2 patients may be switched to receive the 200 x 10^6 cell dose, infused three times at intervals of at least 2 weeks. Cohorts IV and V will evaluate MT-401 manufactured using an accelerated process; patients will receive three consecutive doses of MT-401 at fixed doses of 100 x 10^6 cells and 200 x 10^6 cells, respectively. Following completion of Cohorts IV and V, the Sponsor may change the Phase 2 dose to the dose deemed to be safe for MT-401 manufactured using the accelerated process.		
Study Population	Patients aged ≥18 years old undergoing or having relapse after their first allogeneic HSCT (matched sibling, matched unrelated donor, or haploidentical transplants) for AML are eligible. Potential patients for the study may be screened/enrolled: • Prior to their first allogeneic HSCT. Leukapheresis material, from the HSCT donor, for the production of MT-401 will be obtained as a separate collection from the HSCT or ~30 days after, based on donor status at time of collection. or • When experiencing their first relapse post-allogeneic transplant. The same HSCT donor must be available and agree to undergo leukapheresis for production of MT-401. Patients eligible for the study will be placed into one of two groups:		

	• **Adjuvant (Group 1)**: Patients screened prior to their HSCT with CR without minimal residual disease (CR_{MRD}-) at 80 days post-transplant based on central testing will be randomized (1:1) in an unblinded fashion to: – MT-401 (Arm A) – SoC – observation (Arm B) Randomization will be stratified by pre-transplant status (MRD^+ vs MRD^-/Unknown) and cytogenetic risk (Unfavorable vs. Other). However, randomization will be performed only if MRD testing performed centrally at Baseline visit (80 days post-transplant) is negative. Note: Patients whose product includes fewer cells or does not meet specifications may be treated with MT-401. • **Active Disease: (Group 2)**: Patients meeting the following criteria will be assigned to Subgroup C (frank relapse) or Subgroup D (MRD^+) in Group 2 and will receive MT-401: – Patients in Group 1 who experience relapse (patients with MRD [MRD^+] or frank relapse) prior to randomization – Patients in Arm B of Group 1 (SoC) who experience relapse (MRD^+ or frank relapse) after randomization (crossover patients) – Patients who do not consent prior to HSCT but are experiencing their first relapse (MRD^+ or frank relapse) and have the same donor available for manufacturing Note: Patients in Group 2 may receive bridging chemotherapy for ≤6 months prior to receiving MT-401. Additionally, patients that meet the eligibility criteria for Group 2 only can be used for the Safety Lead-in portion of the study. Those patients who enter the study prior to HSCT must meet applicable inclusion/exclusion criteria prior to and following HSCT for study entry and must agree to provide bone marrow aspirate sample(s) to be held for testing. Relapse is defined as bone marrow blasts ≥5%, or reappearance of blasts in the blood, or development of extramedullary disease, or development of MRD positivity after having a post-treatment MRD negative status. Disease assessments will be performed by local and central laboratory facilities. MRD status will be monitored as outlined in Section 1.3 of the full protocol (Schedule of Activities) by central testing. MRD^+ will be defined as CR (including normalization of counts) with detection in blood, bone marrow or any other tissues by flow cytometry and/or molecular testing (eg, PCR, next generation sequencing). The study will evaluate safety and efficacy endpoints in post-HSCT patients after the infusion of MT-401 using standard methods of assessment (peripheral blood and bone marrow evaluation, positron-emission tomography (PET) scan, etc.). Response will be evaluated using the European LeukemiaNet (ELN) recommendations. Historical data will inform the clinical relevance of the magnitude and durability of response in Group 2 and will supplement data from the concurrently randomized control arm in Group 1 (Arm B).
Diagnosis and Main Entry Criteria	All applicable inclusion and exclusion criteria must be met at Screening (up to 28 days before allogeneic HSCT for Group 1 patients, and prior to the start of manufacturing for Group 2 patients, or at the time of consideration for study) and at Baseline (re-assessment of eligibility within 14 days prior to group assignment for Group 1). **Patient Inclusion Criteria:** Patients are eligible to be included in the study only if all of the following criteria apply and the patient, in the judgment of the investigator, is an appropriate candidate for experimental therapy:

	1. Eligible to receive donor-derived MT-401 following first allogeneic HSCT, are in ≤ third complete remission (CR3) prior to transplant (including matched sibling, matched unrelated donor with at least 6 of 8 HLA markers, or haploidentical with at least 5 of 10 HLA markers) as: • Adjuvant therapy for AML (**Group 1**) at 85-130 days post-HSCT defined as: – patients with CR_{MRD-} by central testing for purposes of randomization (if optional local MRD testing performed and results are positive, the patient will be moved to Group 2 subgroup D); – and are considered intermediate/high risk (e.g., pre-transplant MRD^+, intermediate/adverse risk cytogenetics or received non-myeloablative or reduced intensity conditioning); or • Treatment for relapsed AML (first relapse post-HSCT) when disease occurs after transplant (**Group 2**) defined as ◦ First relapse (MRD^+ or frank relapse) post-HSCT ◦ Patients in Group 1 who are randomized to Arm B (SoC) and experience first relapse (MRD^+ or frank relapse) post-HSCT or experience relapse prior to randomization ◦ Patients with frank relapse will enter into Subgroup C while patients with MRD^+ disease will enter into Subgroup D • Safety Lead-in (Cohorts I and II) and Cohorts III-V defined as patients whose prior treatment course does not meet precise eligibility criteria but may still be approved upon review by the Sponsor as described above for Group 2 only Note: Engraftment must be confirmed post-transplant (absolute neutrophil count >1000/m^3 without granulocyte colony-stimulating factor for 7 days, donor chimerism ≥50%). 1. Are ≥18 years of age prior to administration of MT-401 2. Patients must have donor-derived cells available to make MT-401 3. Karnofsky/Lansky score of ≥60 4. Life expectancy ≥12 weeks 5. Adequate blood, liver, and renal function • Blood: Hemoglobin ≥7.0 g/dL (can be transfused) • Liver: Bilirubin ≤1.5X upper limit of normal; aspartate aminotransferase ≤3X upper limit of normal • Renal: Serum creatinine ≤2X upper limit of normal or measured or calculated creatinine clearance ≥45mL/min 6. Sexually active patients must be willing to utilize one of the highly effective birth control methods or practice complete abstinence starting from Screening for T cell infusion until 6 months after the last T cell infusion. Male patients who are sexually active must agree to use a condom during this period. 7. Patients are allowed to be on experimental conditioning regimens prior to transplant if no planned maintenance therapy post-transplant. 8. In Group 2, patients may receive bridging therapy at the investigators' discretion in situations where MT-401 is not ready for administration or the treating physician

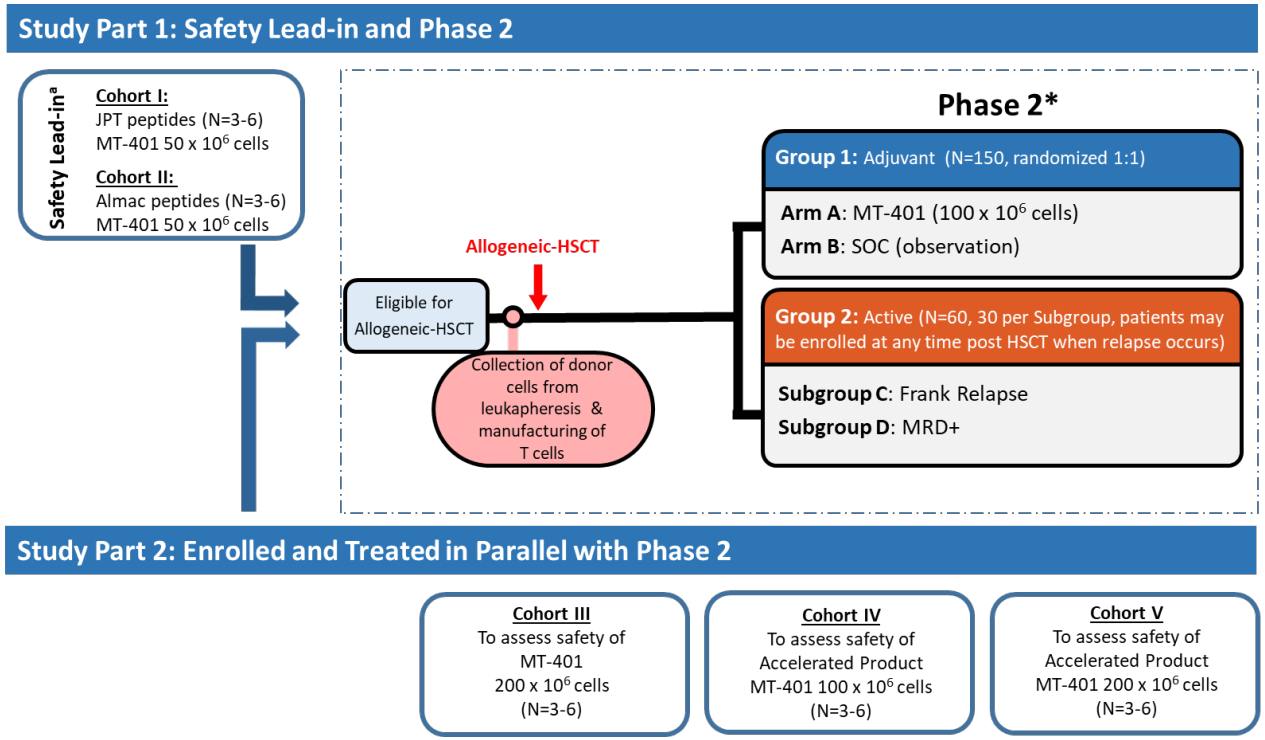
	believes the patient would benefit (particularly in cases of high tumor burden) for ≤6 months as long as the following criteria are met: • Disease assessment including bone marrow biopsy to be performed within 14 days prior to administration of MT-401 (patients may receive MT-401 even if CR is achieved post-bridging therapy but will be analyzed separately; additionally, patients must have ≤30% bone marrow blasts) • At least 4 half-lives or 1 week has passed after administration of bridging therapy whichever is shorter **Patient Exclusion Criteria:** Patients are excluded from the study if any of the following criteria apply: 1. Clinically significant or severely symptomatic intercurrent infection 2. Pregnant or lactating 3. Any other issue which, in the opinion of the treating physician, would make the patient ineligible for the study 4. For Group 1, anti-neoplastic therapy after HSCT and prior to or during dosing of MT-401 5. For Group 2, concomitant anti-neoplastic therapy during or after dosing of MT-401 6. Evidence of acute or chronic GVHD ≥Grade 2 (exception: acute or chronic Grade 2 GVHD of skin allowed if stable) within one week prior to receiving MT-401 7. Taking systemic corticosteroids (exception: physiological doses of steroids allowed) 8. On other investigational therapy post-HSCT 9. Anti-thymocyte globulin or Campath within 28 days of MT-401 infusion **Donor Inclusion Criteria:** Donors for allogeneic stem cell transplants must be considered suitable for and consent to stem cell donation, as per the standard operating procedures of the stem cell transplant program. If a donor has been chosen for the transplant, that same donor will also be used to manufacture the T cell product provided that there are no new reasons for ineligibility since the stem cell collection. The donors will be evaluated as per standard institutional guidelines. The donor clearance by the National Marrow Donor Program (NMDP) is also acceptable. Leukapheresis material will be collected from the same HSCT donor to manufacture MT-401 for the patient.
Dosage and Route of Administration	A dose of 50 x 10^6 cells (flat dosing) will be the dose explored in the Safety Lead-in portion for this study with a minus 1 (-1) dose level of 25 x 10^6 cells (flat dosing), should the need arise to de-escalate. For the Phase 2 portion of the study, the dose administered is 100 x 10^6 cells (flat dosing). Cohort III will evaluate a higher dose (200 x 10^6 cells [flat dosing]) of MT-401 than that used in the Phase 2 portion of the study. Initially, following the completion of Cohorts I and II, patients in Groups 1 and 2 of the Phase 2 portion of the study will receive three consecutive flat doses of 100 x 10^6 cells each, at intervals of at least 2 weeks. MT-401 will be given by IV infusion through either a peripheral or central line. The patients will be monitored for 1 hour post -infusion as outpatients. If Cohort III data determines the 200 x 10^6 cell dose to be safe, the Phase 2 patients may be switched to receive the 200 x 10^6 cell dose, infused three times at intervals of at least 2 weeks. In Cohorts IV and V, patients will receive three consecutive doses of MT-401, manufactured using the accelerated process, at a fixed dose of 100 x 10^6 cells and 200 x 10^6 cells, respectively, infused at intervals of at least 2 weeks. The dose determined to be safe at the conclusion of Cohorts IV and V will determine the final Phase 2 dose.

Statistical Methods	**Analysis Populations**: **All enrolled patients**: All patients who sign the ICF and donor undergoes leukapheresis.. **All randomized patients in Phase 2 (Adjuvant - Group 1 only):** All patients in Group 1 who are randomized with the final dose and manufacturing process and are MRD^- prior to randomization by central testing and local testing (if a local test was also performed). Efficacy analyses for Group 1 will be conducted in this population. A patient randomized based on negative MRD result per central test but confirmed to be MRD^+ will be excluded from Group 1 analyses. The patient will be included in Group 2 Subgroup D analyses if treated with MT-401. **All treated patients:** All patients who receive at least one dose of MT-401 or were randomized to SOC. Patients whose product includes fewer cells or does not meet specifications may still be treated, but will be summarized separately from patients whose product meets specifications. For Group 1 (adjuvant therapy), safety analyses will be conducted in this population, and safety data for patients randomized to SOC will also be shown for reference. For Group 2 (active disease), the primary and secondary efficacy analyses and safety analyses will be conducted in this population. For the Safety Lead-in (Cohorts I and II) and Cohorts III-V, all efficacy and safety analyses will be conducted in this population. **DLT-evaluable:** All patients in the Safety Lead-in (Cohorts I and II) and Cohorts III-V who receive at least one dose of MT-401 and have had the opportunity to be followed for 28 days from the initial MT-401 infusion or have experienced a DLT. **Per-protocol in Phase 2:** All treated patients, as defined above, who have no major protocol deviations. Select efficacy analyses for Group 1 and Group 2 will be conducted in this population for sensitivity analysis.
	Planned Analysis: Safety Lead-in (Cohorts I and II) and Cohorts III-V: Safety data will be reviewed at the end of the Safety Lead-in to determine if it is appropriate to move forward with the specific peptide manufacturer in the Phase 2 portion of the study. The evaluation of DLTs will be conducted in the DLT-evaluable set. Safety data will also be reviewed at the end of Cohort III to determine if it is appropriate to switch to a higher dose in the Phase 2 portion of the study. Additionally, safety data will also be reviewed at the end of Cohorts IV-V to determine if it is appropriate to switch to a dosing regimen with the MT-401 product manufactured using the accelerated process in the Phase 2 portion of the study. This decision will be made by the Sponsor based on multiple parameters, including the safety and biomarker data available. One interim and 1 primary analysis are planned for Phase 2 Group 1. These analyses will be event driven and will occur when approximately 45 and 90 RFS events have been observed, respectively. The Data Monitoring Committee (DMC) will review safety and efficacy data at the interim analyses. One interim analysis and 1 primary analysis is planned for Phase 2 Group 2. The interim analysis will occur after the first 10 patients per subgroup in Group 2 have completed their efficacy assessments and have had the opportunity to be followed for 6 months. The primary analysis will occur after all patients treated have been followed for 6 months. The primary analysis of the study will occur when 90 RFS events have occurred in Phase 2 Group 1. The clinical study report will be written based on this analysis. If the primary analysis of either Group 1 or 2 occurs after the primary analysis of the other group, an addendum to the CSR will be written to describe the results of the other group. **General Methods of Analysis:**

	Categorical variables will be summarized as counts and percentages. Continuous variables will be summarized with univariate statistics, including mean, median, range, and standard deviation. Confidence intervals (CIs) will be calculated for summary statistics, addressing the primary and secondary efficacy outcomes. ***Safety Lead-In (Cohorts I and II) and Cohorts III-V:*** For both the Safety Lead-in, which includes Cohorts I and II, and Cohorts III-V, the number of DLTs per cohort will be identified. The confirmed dose and peptide manufacturer will be identified based on the procedures of the standard 3+3 design. Safety analyses described below for the Phase 2 portion of the study will also be conducted for the Safety Lead-in portion of the study and Cohorts III-V. **Secondary analyses (efficacy):** ***Phase 2:*** **Primary efficacy analyses**: RFS curves will be estimated using the Kaplan-Meier (KM) product limit method. For Group 1, the hazard ratio and corresponding 95% CI will be estimated using a Cox proportional hazards model using randomized arm as a single factor. The KM estimate of the medians will be reported, and the corresponding 95% CI will be computed. KM estimates of RFS rates at milestone time points will be reported along with two-sided 95% CIs using Greenwood's formula, provided the minimum follow-up in patients exceeds the time point to support stable estimation of the rate. In addition to the Cox model, a log-rank test will be used to compare the treatment arms stratified by pre-transplant MRD status (MRD^+ vs. MRD^-/Unknown) and cytogenetic risk (Unfavorable vs. Other). For Group 2, the CR rate and the corresponding 95% exact CI will be calculated. The DOCR will be estimated using the KM product limit method. The DOCR will be estimated using the KM product limit method. The KM estimate of the median DOCR and the DOCR rates at milestone timepoints will be reported along with the two-sided 95% CI. Best overall response will be summarized by response category. **Safety Analysis:** Safety and toxicity outcomes including treatment-emergent AEs, cytokine release syndrome (CRS), GVHD, neurological findings, and laboratory evaluations will be summarized using descriptive statistics for all patients in the All treated population by group. Safety evaluations will be based on the incidence, intensity, and type of AEs or serious adverse events (SAEs), as well as changes in the patient's physical examination findings, vital signs, and clinical laboratory results. AEs will be assessed for severity according to the U.S. NCI CTCAE, Version 5.0,

1.2. Study Schematic

Figure 1 Study Schematic



Abbreviations: CR=complete remission; HSCT=hematopoietic stem cell transplant; SoC=standard of care

[a] Safety Lead-in (Cohorts I and II) and Cohorts III-V defined as patients who fit a majority of the criteria for Group 2 only (as determined by the Sponsor).

*Patients in Groups 1 and 2 will receive 100 x 10^6 cells, but the Sponsor may change the Phase 2 dose regimen to either a higher dose (Cohort III) and/or to the product manufactured using the accelerated process (Cohorts IV and V).

Notes:

- Disease assessment and group assignment occur at Day 80 post-HSCT (±5 days) for Group 1 patients.
- Patients in Group 1 – Arm B who relapse after randomization may cross over to Group 2 to receive MT-401 if the particular subgroup is open and/or Sponsor agreement.
- Patients may be identified post-HSCT and enter Group 2 if the same donor cell is available to provide cells for manufacturing MT-401 and eligibility is fulfilled.
- If relapse occurs less than 80 days post-HSCT and T cells have been manufactured and stored, the patient may receive MT-401 and be included in a subgroup analysis of Group 2.
- Group 2 patients may receive MT-401 even if CR_{MRD^-} is achieved post-bridging therapy but will be analyzed separately.

1.3. MT-401 Schedule of Activities

Table 1: Schedule of Activities

Procedure	Screening [a]	Baseline [b]	Intervention Period and Follow-up [Weeks] [c]						
			0 [d]	2 [d]	4 [d]	Follow-up Visits [e]			
						12 (±1 week)	24 (±1 week)	52 (±4 weeks)	Yearly (±4 weeks)
Informed consent	X	X							
Inclusion and exclusion criteria	X	X							
Demography	X								
Medical History and Complete Physical Exam (includes performance status)	X	X							
Brief Physical Exam [f]			X	X	X	X	X	X	X
Pregnancy test (WOCBP only) (serum or urine) [g]	X	X							
Laboratory assessments [h]	X	X	X	X	X	X	X	X	X
Vital signs [i]	X	X	X	X	X	X	X	X	X
Randomization for Group 1 patients [b]		X							
Disease Assessment [j]	X	X	X [k]			X	X	X	X
GVHD Assessments		X	X	X	X	X	X	X	X
Study treatment [l]			X	X	X				
AE, SAE, and concomitant medication review		X	X	X	X	←═══════════════════════════→			
Biomarkers [n]			X			X	X	X	X
PRO questionnaire (Group 2 Subgroup C only) [o]	X	X				X	X	X	X

Abbreviations: AE=adverse event; CBC=complete blood count; eCRF=electronic case report form; GVHD=graft-versus-host disease; HSCT=hematopoietic stem cell transplant; MRD=minimal residual disease; PRO = patient-reported outcome; SAE=serious adverse event; SoA=Schedule of Activities; SoC=standard of care; WOCBP=women of childbearing potential

Note: Additionally, treatment visits may be modified for 1 week due to inclement weather, vacation, etc., but any longer durations need to be discussed with the Sponsor. Any unscheduled visit, including discontinuation visits, will follow the assessments shown for Week 24.

[a] Screening is to be performed up to 45 days before allogeneic-HSCT or at the time of consideration for study.

[b] Baseline for Group 2 patients should be performed within 14 days prior to first infusion. Disease assessment occurs at Day 80 (±5 days) post-HCST, prior to randomization for Group 1 patients.

[c] Intervention Period includes study treatment and Active Follow-up and Survival Follow-up as defined in Section 4.4 (including for Safety Lead-in portion of the study). Day 0/Week 0 is considered the day of the first infusion of MT-401 (which differs from the Day 1 used for allogeneic HSCT). Each infusion and visit must be at least 2 weeks apart. Active Follow-up Period as defined in Section 4.4: occurs after the last dose of MT-401 has been administered until patient relapses/progresses or declines additional study visits. Timing of Follow-up Visits are in relation to the timing of the Day 0 visit. Sponsor will schedule Day 0 timing for all patients in all groups, including Group 1 SoC arm.

[d] SoC patients do not need to perform visit Weeks 2 or 4, unless clinically indicated. Week 0 visit for SoC patients may occur between days 85-130 post-HSCT, as instructed by Sponsor.

[e] Survival follow-up begins after relapse/progression or active follow-up is completed and occurs every 3 months for 3 years, every 6 months for the remainder of the study (which can be phone contact to collect patient survival status [if alive, last date known alive, and if dead, date of death], and collect any additional anticancer therapy post-MT-401 or SoC received during study.

[f] Brief physical exam, to include at a minimum, assessments of the Cardiovascular, Respiratory, and Gastrointestinal systems (height and weight will be needed at screening at minimum and any changes recorded if >10%).
[g] Pregnancy testing is required unless a patient has no possibility of being pregnant (for example post-hysterectomy). Perform as clinically indicated during intervention period for WOCBP. See Section 8.3.5 for details.
[h] On day of MT-401 administration, laboratory assessments and/or disease assessments are completed prior to infusion (see Section 8.2.3 for additional details of laboratory assessments to be performed).
[i] Vital signs obtained within 1 hour pre- and post-infusion (window ±15 min).
[j] Disease assessment will be performed on blood, bone marrow samples, and/or other tissue samples at these time-points. For Group 1 and Group 2, the screening disease assessment may be performed as part of SoC (prior to consent if it was already completed). For Group 1, pre-transplant testing of MRD should be performed locally by any testing methodology and results recorded in the eCRF. Post-transplant baseline MRD testing will be performed centrally, and results must be available prior to randomization. If any additional disease assessments, such as additional time points or additional testing (e.g., imaging for extramedullary disease), or visits occur due to clinical necessity, information will be recorded on eCRF. Includes central testing for MRD status for all samples collected as per SoC and as per standard institutional guidelines at other time points by methods outlined in protocol in Section 4.1 (samples stored for central confirmation at later date). If imaging is performed on a patient, the Sponsor may request imaging to be sent to a central vendor along with any disease assessment reports.
[k] Disease assessment at Day 0 for Group 1 only (disease assessment does not need to be repeated if within 3 weeks of prior disease assessment and results can be pending prior to treatment).
[l] Study treatment is administered for all patients (except SoC - Group 1- Arm B) on Day 0 and every 2 weeks for a planned maximum of 3 doses. Patients randomized to SoC (Group 1B) at 80 days post-transplant may crossover to the relapse group (Group 2) if the patient is found to have relapse of disease (MRD^{+} or frank relapse) and the subgroup is open and/or Sponsor agreement. After relapse and prior to bridging chemotherapy, the patient should perform assessments associated with the Screening visit if not already completed. The patient should perform the assessments associated with Baseline following bridging chemotherapy and prior to MT-401 administration. The patient will have their visits reset and have their MT-401 administered on Day 0 and follow the schedule of events from that point forward. Group 1- Arm B (SoC) patients will continue to follow the SoA minus administration of MT-401. Refer to Section 6 for additional dosing details. Administration of MT-401 can be delayed due to management of AEs or other toxicities, but patients should resume T cell infusions within 2 weeks of their scheduled dose. If greater than 2 weeks is needed, Sponsor will determine if patient can resume T cells infusions.
[m] All AEs and SAEs, from Day 0 and Baseline, respectively, to the Week 12 Visit will be collected; after Week 12, only treatment-related AEs and SAEs will be collected.
[n] Detailed studies outlined in Section 8.8.
[o] Additional details regarding the PRO questionnaire and associated instructions will be provided in a separate document.

2. INTRODUCTION

2.1. Study Rationale

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. Unfortunately, these benefits must be weighed against the coincident risk of inducing acute or chronic graft-versus-host disease (GVHD). In the current study, enhancing the GVL effect is proposed, while simultaneously mitigating the risk of inducing GVHD by using multi-tumor-associated antigen (multiTAA)-specific T cells.

MultiTAA-specific T cells are produced by selectively amplifying patient or donor-derived tumor-targeted precursors ex vivo using stimulation with antigen presenting cells (APCs) expressing a range of antigens that are selectively overexpressed on malignant cells. The multiTAA-specific T cell therapy differentiates from some other T cell therapies in that it uses non-genetically modified, tumor-specific T cells that recognize a defined set of tumor-associated antigenic targets. For this study, donor-derived T cells obtained from apheresed peripheral blood mononuclear cells (PBMCs) will be utilized to manufacture multiTAA-specific T cells (hereafter referred to as MT-401 and also known as zedenoleucel). In addition, rather than targeting an individual antigen, the multiTAA-specific T cell therapy is composed of multi-antigen specific $CD4^+$ and $CD8^+$ T cells that can attack four or five different tumor-associated antigens (TAAs), with potential to add more targets to the platform.

Seven Phase 1 or Phase 1/2 studies in various tumor types (acute lymphocytic leukemia, AML, multiple myeloma, Hodgkin lymphoma/non-Hodgkin lymphoma (HL/NHL), pancreatic, breast, and sarcoma) are ongoing with safety and efficacy data available from more than 130 patients over the various indications. MultiTAA-specific T cells are shown to be clinically safe without cytokine release syndrome (CRS) or neurotoxicity, which are typically associated with chimeric antigen receptor (CAR) T cell therapies. Additionally, since MT-401 is not genetically engineered, there is no risk of insertional mutagenesis. More importantly, despite the lack of lymphodepletion, multiTAA-specific T cell therapy has shown results in patients with more durable responses in lymphoma compared to CAR T cell approaches, and enhancement of response through epitope spreading, thereby preventing antigen-negative or antigen-low tumor escape (Lulla et al, 2019; Carrum et al, 2019; Naik et al, 2018; Lulla et al, 2018; Carrum et al, 2018).

The study rationale is supported by the tolerable safety profile and anti-tumor activity noted in the Baylor Phase 1 dose-escalation study entitled the **A**dministration of **D**onor-Derived multi-Tumor-Associated Antigen (multiTAA)-**SP**ecific T Cells to Patients with **A**ML or **m**yelodysplastic syndromes (**M**DS) (ADSPAM). In addition, the study rationale is supported by the high unmet medical need in AML post-HSCT, where few therapies are available to patients.

2.2. Background

2.2.1. Acute Myeloid Leukemia

AML is a malignant neoplasm of myeloid lineage cells arising within the bone marrow and outgrowing normal hematopoietic elements. Although AML can present at all ages, it has a bimodal age distribution, with one peak within the first 10 years of life and a much larger peak beyond age 60. In 2019, there was an estimated 61,780 new cases of leukemia in the United States and 22,840 deaths from leukemia (all types), and 21,450 new cases of AML with 10,920 deaths (Key Statistics for AML, 2019).

Adult patients with AML are stratified based on cytogenetics and molecular features into low-, intermediate- and high-risk disease groups, in order to identify those who would benefit from allogeneic HSCT in first remission. The standard first-line treatment approach for the past 4 decades, regardless of risk stratification, has been combination chemotherapy using cytarabine and an anthracycline, which has produced initial complete remission (CR) rates in 50-80% of patients; however, approximately half of these patients eventually relapse. Eligible patients subsequently proceed to allogeneic HSCT, but disease relapse is frequent (~60%) and is a major cause of death in these patients (Estey and Döhner, 2006). Overall, patients who are not cured with front- or second-line therapy have an estimated median survival of <1 year (Estey and Döhner, 2006) highlighting the need for novel therapies. Pediatric patients are similarly risk stratified with disease response, as well as molecular features and cytogenetics being critical to assessment of prognosis. With improved therapy as well as supportive care, pediatric patients have ~70% chance of survival at 5 years from diagnosis; however, patients with refractory or relapsed disease (~35%) have a very poor prognosis. This subset is generally offered re-induction chemotherapy followed by allogeneic HSCT. Outcomes are improved with disease remission at the time of transplant, but overall survival in this group remains < 30% (Rubnitz, 2012).

There have been recent advances in the landscape of treatment for patients with AML. Since 2017, the Food and Drug Administration has approved 6 drugs for the treatment of AML. Three products have been approved for newly diagnosed patients (glasdegib, liposomal combination of daunorubicin + cytarabine, and midostaurin), and 3 products for patients who have relapsed or are refractory to prior interventions (gilteritinib, ivosidenib, and enasidenib). The therapies targeting specific mutations – FLT3, IDH1, and IDH2- have approved companion diagnostics for the targeted therapy. Importantly, the recent approvals, which are not specific to the treatment of patients in the HSCT setting, highlights the need for more effective therapeutic options in a broader patient population, post-HSCT. Patients ineligible, unwilling or unable to be treated with other FDA approved targeted options would be able to enroll in the current study.

2.2.2. Targeting TAAs in Acute Myeloid Leukemia

AML blasts express several T cell immunogenic tumor antigens that fall into two categories: (i) minor histocompatibility antigens, and (ii) TAAs overexpressed by leukemic cells and with limited expression on normal cells. For purposes of this study, TAAs will be the focus.

2.2.2.1. Tumor-associated antigens

TAAs that are overexpressed on malignant cells (e.g., Wilms Tumor-1 [WT1]; Survivin; and the cancer testis antigens [CTAs] Preferentially Expressed Antigen in Melanoma [PRAME] and NY-ESO-1) have been targeted using a range of immunotherapeutic strategies in both the preclinical and clinical setting, including antibody-based therapies, peptide vaccines and adoptive T cell transfer. Table 2 shows the frequency of expression of select TAAs in AML based on published reports (Carter et al, 2012; Almstedt et al, 2010; Cilloni et al, 2002).

Table 2: Frequency of TAAs expressed in AML

	WT1	SURVIVIN	PRAME	NY-ESO-1
AML	70-90%	72-100%	30-60%	0-7%

Abbreviations: AML=Acute Myeloid Leukemia; TAA=tumor-associated antigens; WT1=Wilms Tumor-1

WT1: WT1 is a nuclear zinc finger transcription factor that is essential during embryonic development of the urogenital system. Post-natally, WT1 expression in healthy tissues is limited to the ovary, testis, podocytes of the kidney and the mesothelial linings of the peritoneum and pleura. Additionally, WT1 is expressed at low levels in hematopoietic progenitor cells where it normally acts to induce quiescence of $CD34^+$ Lin^- cells and promote differentiation of precursors at later stages of development (Harris, et al, 2016; Hohenstein and Hastie, 2006). In contrast, WT1 is highly expressed in several solid tumors, and >70% of AMLs affecting children and adults; high levels of WT1 expression are associated with poor prognosis (Hou et al, 2010).WT1 is also aberrantly expressed in chronic myeloid leukemia and in advanced forms of myelodysplasia (Rosenfeld et al, 2003). In leukemic blasts, the balance of WT1 isoforms expressed appears to promote proliferation and resistance to apoptosis, while inhibition of WT1 expression (e.g., using short hairpin ribonucleic acid) reverses these effects, thereby eliminating leukemic cells with clonogenic potential (Yang et al, 2007; Yamagami et al, 1996).

Survivin: Survivin is a member of the inhibitor of apoptosis protein family and is overexpressed in the majority of tumors including esophageal, lung, ovarian, breast, and colorectal cancer, as well as most hematologic malignancies (Andersen et al, 2007). Elevated Survivin expression is commonly associated with resistance to chemotherapy, enhanced proliferative capacity and, in the case of AML, it is an independent unfavorable prognostic factor (Carter et al, 2012).

PRAME: PRAME was initially identified as a tumor antigen in melanoma but has since been found to be overexpressed in many hematologic malignancies and solid tumors, while its expression is low or absent in normal tissues (vanBaren et al, 1998). PRAME may significantly contribute to maintaining the tumor phenotype, because its expression can strongly inhibit cell differentiation induced by the retinoic acid receptor-α ligand all-*trans* retinoic acid, a crucial pathway for the proliferation and differentiation of both normal and malignant hematopoietic cells. PRAME overexpression has been demonstrated to contribute to leukemogenesis by inhibiting myeloid differentiation through blockage of the retinoic acid receptor-α-signaling pathway (Epping et al, 2005).

NY-ESO-1: NY-ESO-1 is a highly immunogenic CTA aberrantly expressed in a variety of malignancies including melanoma, lung cancer, sarcoma, multiple myeloma, and leukemia, while normal tissue expression is limited to germ line tissues, which lack major histocompatibility complex molecules. It was

first discovered as an immunogenic CTA based on the detection of specific antibodies in the sera of patients with esophageal carcinoma (Simpson et al, 2005). Later, it was also shown to induce $CD8^+$ and $CD4^+$ T-cell responses in patients with NY-ESO-1 positive tumors (Jagasia et al, 2015; Jager et al, 2000). Wolchock and colleagues noted a clear association between clinical benefit and the detection of NY-ESO-1- specific antibodies in melanoma patients treated with ipilimumab, suggesting its immunotherapeutic importance (Yuan et al, 2011).

2.2.3. MultiTAA-specific T cells (MT-401)

MT-401 is a non-genetically modified allogeneic multiTAA-specific T cell therapy that is being developed for the treatment of patients with AML after receiving allogeneic stem-cell transplant. MT-401 is composed primarily of multi-antigen specific $CD4^+$ and $CD8^+$ T cells that have been manufactured under current Good Manufacturing Practices (cGMP) by *in vitro* stimulation of T cells with APCs, which were cultured with overlapping peptide pools. Briefly, donor T cells are cultured with APCs presenting peptides spanning the primary sequence of four TAAs, namely, PRAME, NY-ESO-1, Survivin, and WT1 in the presence of recombinant cytokines.

This study was initiated with MT-401 using a manufacturing process that took >2 weeks; however, recently the manufacturing process has been shortened to about one week which is referred to as an accelerated process in the study protocol.

2.2.4. Choosing the Optimal TAA Targets

The CTAs NY-ESO-1 and PRAME are expressed to varying degrees in leukemic stem cells and blasts (Table 2). In addition, WT1 is expressed in 70-90% of AML cells, while Survivin is ubiquitously expressed on malignant cells. The expression of these tumor antigens in AML and their apparent immunogenicity make them potential targets for T cell therapy (Carter et al, 2012; Almstedt et al, 2010; Cilloni et al, 2002). Although most tumor cells express one or more of these antigens, there may be differences in levels of antigen expression from patient to patient, as well as between individual tumor cells. Thus, in order to provide potential clinical benefit to the majority of patients, T cell lines with simultaneous activity against NY-ESO-1, PRAME, Survivin, and WT1 were generated and the safety of these cells was tested in a dose escalation Phase 1 study. Additionally, the expression frequency of these antigens on tumor cells was assessed, though antigen expression was not an eligibility criterion.

As a means of stimulating T cells, APCs that had been incubated with GMP grade overlapping peptide pools that span the primary sequences of NY-ESO-1, Survivin, WT1 and PRAME are used. These peptide libraries encompass all possible human leukocyte antigen (HLA) class I epitopes and the majority of HLA class II epitopes of each protein. Using this approach T cell lines with specificity for up to four antigens will be generated, as has been the experience in pre-clinical validation studies (Weber et al, 2013) and the ongoing Phase 1 clinical study at Baylor College of Medicine (NCT02494167). Since the individual peptides are at least 15 amino acids in length, activation of both $CD4^+$ and $CD8^+$ T cells is anticipated.

2.2.5. Risks of Administering Tumor-Specific T Cells

It is possible that the infusion of T cells targeting self-antigens expressed in normal tissues may induce an inflammatory response post-infusion, as reported by Warren and colleagues (Warren et al, 2010). These investigators evaluated the safety of adoptively transferring donor-derived $CD8^+$ T-cell clones recognizing minor histocompatibility antigens to patients with relapse of acute leukemia after myeloablative allogeneic HSCT. The highest doses administered to each patient ranged from 2.25-6.6 x 10^9 cells. Pulmonary toxicity was seen in three of the seven treated patients, and was severe in one, and correlated with the level of expression of the mHAg-encoding genes in lung tissue. However, the administration of steroids resulted in a rapid reversal of pulmonary symptoms. Thus, the associated toxicity could be rapidly and effectively controlled. We do not anticipate such problems with the current protocol due to the following:

- Our proposed infused cell doses are similar to those being used in the current Phase 1 AML study (NCT02494167), which has proven safe to date and these doses are 2-3 logs lower than the Warren study and a log lower than our previous latent membrane protein (from Epstein-Barr virus)-specific T-cell study in which no toxicity was observed.
- The T cells are polyclonal, directed against multiple rather than single epitopes/antigens.
- NY-ESO-1 and PRAME are not expressed on normal tissue, except for germ line tissues.
- WT1 is only present at low levels in nephrons and hematopoietic cells. There have been 2 WT1 vaccine studies and 2 studies involving the infusion of WT1-specific T-cells with nearly 10 patients with MDS, without the development of myelosuppression and there have been no reports of nephritis following immunotherapeutic approaches targeting WT1 (Tsuboi et al, 2012; Keilholz et al, 2009).
- Survivin is expressed only at low levels in some normal cell types, such as thymocytes, T cells, basal colonic epithelial cells and $CD34^+$ bone marrow-derived stem cells. High Survivin expression has been reported in tumors of lung, breast, colon, stomach, esophagus, pancreas, liver, uterus ovaries, as well as in HL, NHL, leukemias, neuroblastoma, soft-tissue sarcomas, gliomas and melanoma while the normal tissues from these same organs did not express Survivin (Fukuda et al, 2006). Survivin-directed therapies in animal models and a variety of human clinical studies targeting metastatic melanoma, advanced or recurrent urothelial cancer, metastatic renal cell carcinoma, advanced or recurrent breast cancer, prostate cancer, pancreatic cancer, and non-small cell lung cancer using peptides, peptide-loaded dendritic cells, messenger ribonucleic acid (mRNA) vaccines or oncolytic viruses to induce Survivin-specific T cells have revealed no major systemic toxicities (Friedrichs et al, 2006; Saito et al, 2006; Altieri, 2008; Mita et al, 2008; Rapoport et al, 2011) .
- In studies at Baylor College of Medicine targeting NY-ESO-1, PRAME, and Survivin expressed in lymphoma, there was no evidence of in vivo toxicities including in individuals with high frequencies of circulating reactive T cells (unpublished results).

Another reported potential risk in patients who receive T cells (Lee et al, 2014a) or bispecific T-cell engagers (Teachey et al, 2013) are serious adverse events (SAEs) associated with CRS. The majority of CRS cases have been reported after the infusion of CAR T cells (Davila et al, 2014; Lee et al, 2014b; Maude et al, 2014a), but CRS can also occur after the infusion of conventional antigen-specific T cells

(Papadopoulou et al, 2014) or tumor infiltrating lymphocytes (Stevanovic et al, 2015). Several published guidelines for the management of CRS exist (Lee et al, 2014a; Maude et al, 2014b; Neelapu et al, 2018), and includes treatment options based on the clinical severity of the symptoms, such as oxygen, inotropic agents, anti-IL-6 receptor antibody (4-8 mg/kg), anti-tumor necrosis factor-α antibody (5-10 mg/kg), and/or steroids (1-2 mg/kg/day of methylprednisolone or equivalent).

Unlike CAR- or TCR-engineered T cells, MT-401 consists of donor-derived T cells that have not been genetically modified or enhanced. As a result, the endogenous TCRs expressed by these T cells have undergone thymic selection in the donor that ensures deletion of auto-reactive T cells (central tolerance) and have been subjected to all mechanisms that ensure peripheral tolerance in the body. The MT-401 manufacturing process does not generate novel TCRs that may pose threat to the patient, but only amplifies existing TAA-specific T cells that were present in the donor.

2.2.6. Phase 1 Clinical Study Results in Acute Myeloid Leukemia

Results from the ongoing Baylor Phase 1 dose-escalation study (ADSPAM), administered post-HSCT in the adjuvant, as well as relapsed/refractory setting has shown acceptable safety and tolerability and promising preliminary clinical results. The objectives of the study are to determine the following: the safety of an intravenous (IV) infusion of donor-derived multiTAA-specific T cells, administered as prophylaxis (i.e., adjuvant) or treatment of AML or MDS post-allogeneic HSCT; to obtain information on the expansion, persistence and anti-tumor effects of the adoptively transferred donor-derived multiTAA-specific T cells, and to determine whether multiTAA-specific T cells can increase the spectrum of epitopes/antigens targeted by endogenous T cells (i.e., epitope spreading). Five dose cohorts have been evaluated to date – 5 x 10^6 cells/m^2 (Dose Level [DL] 1), 10 x 10^6 cells/m^2 (DL2) 20 x 10^6 cells/m^2 (DL3), 50 x 10^6 cells/m^2 (DL4) and 100 x 10^6 cells/m^2 (DL5) with repeat dosing to date on DL1 and DL2.

As of January 2021, 20 patients have completed treatment and initial follow-up on the study (13 in Arm A – Adjuvant; 7 in Arm B – Active disease). Three of the patients (ID 12428, 17553, and 18900) were re-enrolled to the study. One patient did not complete treatment and initial follow-up. Patient ID 17553 progressed at week 2 after his re-enrollment, received chemotherapy and was unevaluable. There was 1 patient from Group A with two transient Grade 3 liver transaminase elevations within the toxicity evaluation period at DL1, which were thought to be possibly related to the multiTAA-specific T cell therapy. No patient had a Grade 3-4 GVHD for protocols in which GVHD is a risk, and there were no treatment-related dose-limiting toxicities among the evaluable patients who finished their safety follow-up. No stopping rule has been triggered. Since a maximum tolerated dose level has not been reached (no dose-limiting toxicities [DLTs] at DL3), two additional dose levels (DL4: 50 x 10^6 cells/m^2 and DL5: 100 x 10^6 cells/m^2) are being studied in Phase 1. DL4 and DL5 have completed evaluation with 2 patients each, and none of the patients had any DLTs noted.

One death has occurred on Arm A while the patient was in complete remission (CR) due to complications from the flu. All patients on Arm B have died while in relapse (ranging from 4 months to 21 months, including one patient who had initially been enrolled on Arm A and was 30 months out at the time of death from the initial multiTAA-specific T cell infusion received on Arm A), but all deaths were unrelated to the multiTAA-specific T cell product.

Preliminary evidence of anti-tumor activity on ADSPAM has been observed. Ten of the 12 remaining patients on Arm A are alive in CR (ranging from 6 weeks to 2.5 years), one is alive in relapse (relapse at 8 months after multiTAA-specific T cells, still alive at 1.5 years), and one died in CR at 1 year, due to complications from the flu. Of the 7 patients on Arm B (relapsed/refractory), all have subsequently died in relapse (ranging from 7 months to 21 months). There was one CR in patient 12428, who relapsed at month 13 and died in relapse at month 21 (although out to month 30 from the time of multiTAA-specific T cells on Arm A), 1 PR in subject 17355 who went through a second allogeneic HSCT and subsequently died in relapse at month 12.

A more detailed description of the chemistry, pharmacology, efficacy, and safety of MT-401 is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

When taken together, the unmet need for patients with AML and the potential benefits of MT-401 administration outweigh the risks and support further development of this treatment. More detailed information about the known and expected benefits and risks and reasonably expected AEs of MT-401 may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Phase	Objectives	Endpoint
	Primary	
Safety Lead-in (Cohort I and II) & Cohorts III-V	To assess safety and tolerability of MT-401: • Manufactured using peptides produced by two different vendors (Safety Lead-in: Cohorts I and II). • At a higher dose than the dose used in the Phase 2 portion of the study (Cohort III). • Manufactured using an accelerated manufacturing process at two dose levels (Cohort IV and V)	• DLTs • Safety (including but not limited to): TEAEs, SAEs, deaths and clinical laboratory abnormalities per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0)
Phase 2 - Adjuvant (Group 1)	To compare relapse-free survival (RFS) for MT-401 (Arm A) vs standard of care (SoC; Arm B)	RFS

Phase	Objectives	Endpoint
Phase 2 – Active Disease (Group 2):	• Subgroup C (frank relapse): to estimate complete remission (CR) rate and duration of CR (DOCR) • Subgroup D (MRD^+): to estimate complete remission (CR_{MRD}-) rate and duration of CR without minimal residual disease ($DOCR_{MRD}$-)	• Subgroup C: ○ CR rate ○ DOCR • Subgroup D: ○ CR_{MRD}- rate ○ $DOCR_{MRD}$-
	Secondary *(Efficacy)*	
Safety Lead-in (Cohorts I and II) & Cohorts III-V	• To assess efficacy of MT-401: • Manufactured using peptides produced by two different vendors (Safety Lead-in: Cohorts I and II). • At a higher dose than the dose used in the Phase 2 portion of the study (Cohort III). • Manufactured using an accelerated manufacturing process at two dose levels (Cohort IV and V)	CR rate and DOCR (Active disease patients)
Phase 2 (Adjuvant- Group 1)	• To analyze overall survival (OS) for MT-401 (Arm A) and SoC (Arm B) • To compare graft-versus-host disease RFS (GRFS) for MT-401 (Arm A) vs SoC (Arm B)	• OS • GRFS
Phase 2 (Active Disease- Group 2: Subgroups C and D)	• To evaluate overall response rate (ORR), duration of response (DOR), progression-free survival (PFS) and OS for MT-401 alone • To evaluate RFS, OS, and GRFS for patients who achieve CR following bridging therapy	• ORR • DOR • PFS • OS • RFS • GRFS
	Secondary (*Safety)*	
Phase 2 (Adjuvant- Group 1 and Active Disease- Group 2)	To evaluate the safety and tolerability of administering donor-derived MT-401 to patients with AML post-HSCT	• GVHD Assessments • Vital signs • Clinical laboratory assessments • Physical examination • AEs
	Exploratory	
Safety Lead-in, Cohort III-V, & Phase 2	• To examine the expansion, persistence, clonality and anti-tumor immune effects of the adoptively-transferred, donor-derived, MT-401, as well as the presence of epitope spreading in all groups • Time to minimal residual disease (MRD) positivity in patients without MRD (MRD^-) • Clearance of MRD from MT-401 infusion in patients with CR but persistent evidence of MRD • Phase 2 (Group 2 Subgroup C only): to explore patient reported outcomes (PROs)	• Markers of immune function, cell targeting, signaling pathways and disease status, including MRD • PRO questionnaire

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 2 multicenter study evaluating the safety and efficacy of MT-401 administered to patients with AML, who received their first allogeneic hematopoietic stem cell transplant (HSCT). Part 1 of the study includes a Safety Lead-in portion prior to the Phase 2 study and includes two cohorts (Cohort I and Cohort II) that will evaluate the safety and tolerability of three consecutive MT-401 doses of 50 x 10^6 cells manufactured with peptide pools obtained from two different vendors. Once Cohorts I and II in the Safety Lead-in are complete, the Phase 2 portion will open.

Phase 2 will initially evaluate the efficacy and safety of MT-401 at a flat dose of 100 x 10^6 cells either as adjuvant therapy in patients (Group 1) with no active disease (in CR and MRD^-) or in patients with active disease (Group 2, frank relapse or MRD^+).

Part 2 of the study includes Cohorts III, IV, and V which will run in parallel with Phase 2. Cohort III will evaluate MT-401 at a higher dose (200 x 10^6 million cells) than the dose used in the Phase 2 portion using the initial (>2 weeks) manufacturing process. If Cohort III data determines the 200 x 10^6 cell dose to be safe, the Phase 2 patients may be switched to receive the 200 x 10^6 cell dose, infused three times at intervals of at least 2 weeks.

Cohorts IV and V will evaluate MT-401 manufactured using an accelerated process; patients will receive three consecutive doses of MT-401 at fixed doses of 100 x 10^6 cells and 200 x 10^6 cells, respectively. Following completion of Cohorts IV and V, the Sponsor may change the Phase 2 dose to the dose deemed to be safe for MT-401 manufactured using the accelerated process.

Please refer to Section 4.3 for additional details regarding the dosing schema.

A total of approximately 225-240 patients will be randomized/treated in this study as follows:

- Safety Lead-in: 6-12 patients
- Cohorts III, IV and V: 9-18 patients
- Phase 2: approximately 210 patients
    - ~150 patients in Group 1 (adjuvant therapy)
    - ~60 patients in Group 2 (active disease)

Enrollment will continue in Phase 2 to achieve approximately 210 evaluable patients randomized/treated with the final MT-401 dose and manufacturing process, thereby replacing any patients that have not been randomized/treated with the final Phase 2 product and dose, as determined by the Sponsor. Patients aged ≥18 years old undergoing or having relapse after their first allogeneic HSCT (matched sibling, matched unrelated donor, or haploidentical transplants) for AML are eligible.

Potential patients for the study may be screened/enrolled:

- Prior to their first allogeneic HSCT. Leukapheresis material, from the HSCT donor, for the production of MT-401 will be obtained as a separate collection from the HSCT or ~30 days after, based on donor status at time of collection.

or

- When experiencing their first relapse post-allogeneic transplant. The same HSCT donor must be available and agree to undergo leukapheresis for production of MT-401.

Patients eligible for the study will be placed into one of two groups:

- **Adjuvant (Group 1)**: Patients screened prior to their HSCT with CR without minimal residual disease (CR_{MRD}-) at 80 days post-transplant based on central testing will be randomized (1:1) in an unblinded fashion to:

  - MT-401 (Arm A)
  - SoC - observation (Arm B)

  Randomization will be stratified by pre-transplant MRD status (MRD^+ vs. MRD^-/Unknown) and cytogenetic risk (Unfavorable vs. Other).

  Note: Patients whose product includes fewer cells or does not meet specifications may be treated with MT-401.

- **Active Disease: (Group 2**): Patients meeting the following criteria will be assigned to Subgroup C (frank relapse) or Subgroup D (MRD^+) in Group 2 and will receive MT-401:

  - Patients in Group 1 who experience relapse (patients with MRD [MRD^+] or frank relapse) prior to randomization
  - Patients in Arm B of Group 1 (SoC) who experience relapse (MRD^+ or frank relapse) after randomization (crossover patients)
  - Patients who do not consent prior to HSCT but are experiencing their first relapse (MRD^+ or frank relapse) and have the same donor available for manufacturing

  Note: Patients in Group 2 may receive bridging chemotherapy for ≤6 months prior to receiving MT-401. Additionally, patients that meet the eligibility criteria for Group 2 only can be used for the Safety Lead-in portion of the study.

Those patients who enter the study prior to HSCT must meet applicable inclusion/exclusion criteria prior to and following HSCT for study entry and must agree to provide bone marrow aspirate sample(s) to be held for testing.

Relapse is defined as bone marrow blasts ≥5%, or reappearance of blasts in the blood, or development of extramedullary disease, or development of MRD positivity after having a post-treatment MRD negative status.

Disease assessments, as outlined in the Schedule of Activities (SoA) (Table 1), will be performed by local and central laboratory facilities. Screening assessment for Group 1 patients can be a prior disease assessment completed within 45 days of screening as per SoC. For Group 1, pre-transplant testing of MRD should be performed locally by any testing methodology and results recorded in the eCRF. Post-transplant baseline MRD testing will be performed centrally and results must be available prior to randomization. MRD^+ will be defined as CR (including normalization of counts) with detection in blood, bone marrow or any other tissues by flow cytometry and/or molecular testing (eg, PCR, next generation sequencing).

The study will evaluate safety and efficacy endpoints in post-HSCT patients after the infusion of MT-401 using standard methods of assessment (peripheral blood and bone marrow evaluation, positron-emission tomography [PET] scan, etc.). Response will be evaluated using the European LeukemiaNet (ELN) recommendations (Döhner et al, 2017). Historical data will inform the clinical relevance of the magnitude and durability of response in Group 2 and will supplement data from the concurrently randomized control arm in Group 1 (Arm B).

The Data Monitoring Committee (DMC; described in Section 9.4) will review data after the first 45 RFS events in Group 1 have been observed (as described in Section 9.4) to assess safety and evaluate estimates of RFS for future study planning. Additionally, the Sponsor will review safety and efficacy data in Group 2 after approximately the first 10 patients per subgroup have progressed or have had the opportunity to be followed for 6 months.

4.2. Scientific Rationale for Study Design

The general rationale for the study design is described in Section 2.1.

4.3. Doses and Justification for Doses

The Phase 1 study (ADSPAM) conducted by Baylor College of Medicine has cleared five dose cohorts to date: 5 x 10^6 cells/m^2 (DL1); 10 x 10^6 cells/m^2 (DL2); 20 x 10^6 cells/m^2 (DL3); 50 x 10^6 cells/m^2 (DL4) and 100 x 10^6 cells/m^2 (DL5) (see Section 2.2.6 for a detailed description). Based on data gathered by Baylor, Marker has considered DL3, DL4 and DL5 safe to proceed with and has proposed the dosing schema for the Phase 2 study that is described in detail under the respective sections below.

In summary, for the Safety Lead-in portion, which was included for the purpose of comparing MT-401 manufactured with peptides produced from two different vendors, Marker proposed a flat dose of 50 x 10^6 cells, which is equivalent to 20 x 10^6 cells/m^2 (DL3 of the Phase 1 study) for ease of comparison. For the main portion of the Phase 2 study, Marker proposed a flat dose of 100 x 10^6 million cells, which is equivalent to 50 x 10^6 cells/m^2 (DL4 of Phase 1 study).

Part 2 of the study includes Cohorts III, IV and V which will run in parallel with Phase 2. Cohort III will evaluate MT-401 at a higher dose (200 x 10^6 million cells) than the dose used in the Phase 2 portion using the current manufacturing process. If Cohort III data determines the 200 x 10^6 cell dose to be safe, the Phase 2 patients may be switched to receive 200 x 10^6 cell dose, infused three times at intervals of at least 2 weeks. Cohorts IV and V will evaluate MT-401 manufactured using an accelerated manufacturing process at 100 and 200 x 10^6 cell doses, respectively. Following completion of Cohorts IV and V, the

Sponsor may change the Phase 2 dose to the dose deemed to be safe for MT-401 manufactured using the accelerated process.

A total of 15-30 patients (3-6 patients per cohort) will be treated in Cohorts I-V. The dosing schemes are shown in Table 4.

Table 4: Dosing Scheme

Cohort	Dose Level	MT-401 dose	Number of Patients	Peptide Manufacturer
-I	-1	25 x 10^6 cells flat dose	3-6 patients	JPT
-II	-1	25 x 10^6 cells flat dose	3-6 patients	Almac
I	1	50 x 10^6 cells flat dose	3-6 patients	JPT
II	1	50 x 10^6 cells flat dose	3-6 patients	Almac
III	3	200 x 10^6 cells flat dose	3-6 patients	Almac [a]
-IV	1	50 x 10^6 cells flat dose	3-6 patients	Almac
IV[b]	2	100 x 10^6 cells flat dose	3-6 patients	Almac [a]
V[b]	3	200 x 10^6 cells flat dose	3-6 patients	Almac [a]

[a] Almac is the preferred manufacturer if both JPT and Almac are deemed to be safe during evaluation of Cohorts I and II of the Safety Lead-in portion.
[b] MT-401 product manufactured using an accelerated process

4.3.1. Safety Lead-in Portion of the Phase 2 Study

The Safety Lead-in portion includes two cohorts (Cohort I and Cohort II) that will evaluate the safety profiles of MT-401 manufactured with peptide pools obtained from two different vendors (JPT versus Almac). Therefore, Cohorts I and II may be enrolled in parallel. Approximately 3-6 patients closely fitting the eligibility criteria of active disease (Group 2) will be infused with MT-401 in each of Cohorts I and II to determine the safety of patient-specific product consisting of 50 x 10^6 cells (flat dosing) every 2 weeks for a total of 3 doses using the standard 3+3 design (Section 4.5). A minus 1 (-1) dose level of 25 x 10^6 cells (flat dosing) may be used should the need arise to de-escalate (Section 4.3). All patients treated will be observed for 28 days from the day of the initial MT-401 infusion before safety is established. If no differences in the safety are noted between the peptide vendors, then it will be concluded that the change in peptide manufacturer is not relevant to dosing and the main portion of the Phase 2 study will be initiated with the product utilizing Almac peptides.

4.3.2. Main Portion of the Phase 2 Study

Following completion of the Safety Lead-in portion the study will proceed to open Groups 1 and/or 2 of the Phase 2 study at the highest cleared dose of 100 x 10^6 cells (DL4 – 50 x 10^6 cells/m^2) from the Phase 1 trial. Briefly, in the dose escalation portion of the Phase 1 ADSPAM study, 50 x 10^6 cells/m^2 cohort (DL4 – 100 x 10^6 cells) completed evaluation with 2 patients, and neither patient had any DLTs noted. A 100 x 10^6 cells/m^2 dose cohort (DL5 – 200 x 10^6 cells) has completed the DLT period for 1 patient without any DLTs noted. Therefore, patients in Groups 1 and 2 will receive three consecutive flat doses of 100 x 10^6 cells every 2 weeks. MT-401 will be given by IV infusion through either a peripheral or central line. The patients will be monitored for any safety concerns for 1 hour after infusion as outpatients.

In total, approximately 210 patients will be treated in the Phase 2 portion of the study. The Phase 2 portion includes two groups of patients who will be treated with product as adjuvant therapy (Group 1) or

with active disease (Group 2). Approximately 150 patients will be randomized 1:1 to either MT-401 product or standard of care therapy in Group 1 (adjuvant) and 60 patients with active disease will be treated in Group 2.

Following completion of Cohorts I and II, the confirmed peptide manufacturer to be used in Phase 2 will be identified based on review of the safety data. At any time, following completion of Cohort III the Sponsor may change the Phase 2 dosing regimen to that evaluated in Cohort III. At the conclusion of Cohorts IV and V, which evaluate the safety of the product manufactured using an accelerated process at two different doses, the Sponsor may change the Phase 2 dose to the dose deemed to be safe for MT-401 manufactured using the accelerated process.

4.3.3. Cohort III: 200 x 10^6 cells

In parallel to the opening of Groups 1 and/or 2, a separate cohort (Cohort III) will test DL5 being studied in the Phase 1 trial, which is the flat dose equivalent of 200 x 10^6 cells. Three to 6 patients will be dosed to determine the safety of this dose level using the standard 3+3 design (see Section 4.5). If the 200 x 10^6 cells dose being tested in Cohort III is noted to be safe, then the patients enrolled, but not yet treated, in Groups 1 and 2 may be treated at the 200 x 10^6 cells dose, unless the Sponsor decides to remain at the current dose of 100 x 10^6 cells.

4.3.4. Cohorts IV and V

Cohorts IV and V will evaluate the safety of MT-401 manufactured using the accelerated method at doses of 100 x 10^6 and 200 x 10^6 cells, respectively. A lower dose level of 50 x 10^6 cells (flat dosing) may be used should the need arise to de-escalate (Section 4.3). Three to 6 patients will be dosed in each cohort to determine the safety and tolerability using the standard 3+3 design (Section 4.5). Patients enrolled, but not yet treated, in Groups 1 and 2 may be treated with this MT-401 product at the initial Phase 2 dose of 100 x 10^6 cells or higher at 200 x 10^6 cells.

For additional details on administration, please refer to the Investigational Product Manual.

For allowable dose modifications, please refer to Section 6.6.

4.4. Study Period and End of Study Definitions

Screening: begins when the informed consent form (ICF) is first signed. The patient is enrolled once Screening tests have been completed successfully and prior to HSCT for Group 1 patients, and prior to the start of manufacturing for Group 2 patients.

Baseline: A re-assessment of eligibility will occur within 14 days prior to group assignment for Group 1 to confirm eligibility has been met.

Randomization: Randomization to MT-401 or SoC for patients in Group 1 will occur once eligibility has been reconfirmed post-HSCT and groups have been assigned.

Study Period: begins the day of the first patient's first dose of MT-401 and ends at End of Study.

- Study Treatment Period: begins with the day of the patient's first study treatment and ends the day the patient and investigator agree that the patient will discontinue study treatment or after all doses of MT-401 have been administered (whichever is earlier) (including for the Safety Lead-in portion of the study).
- Follow-up Period: begins the day after the study treatment period ends and is complete the day of the patient's death, withdrawal of consent, loss-to-follow-up or End of Study (whichever is earlier). It includes safety follow-up visits and additional long-term follow-up visits, as outlined in the SoA (Table 1):

  – Active Follow-up: occurs after the last dose of MT-401 has been administered until patient relapses/progresses or declines any additional study visits (but patient may continue with survival follow-up).
  – Survival Follow-up: begins the day a patient relapses as determined by investigator or declines any additional study visits and ends with the End of Study.

End of Study: A patient is considered to have completed the study if he/she has completed the planned study treatment and follow-up periods of the study as per SoA, withdrawn, patient's death or lost to follow-up.

No intervention following the End of Study is planned, and patients will return to their physician for further management.

4.5. 3+3 Design (Safety Lead-in and Cohorts III-V)

A minimum of 3 patients each will be treated in Cohorts I and II; if 1 patient experiences a DLT related to MT-401, 3 additional patients will be treated in the cohort (see Section 5.6). If overall, 0 out of 3 patients or 1 out of 6 patients experience a DLT in the specific cohort, this dose will be established as safe for the Phase 2 portion of the study (see Section 5.6). Additional patients may be treated to acquire data such as biomarkers as long as no safety issues arise. In the event that > 1 patient, experiences a DLT (see Section 5.6) related to MT-401, then no further patients will be treated in that cohort. A new cohort of patients will be treated at a lower dose level (DL1) with a flat dose of 25 x 10^6 cells (Cohorts -I or -II). Dose Level 1 will be repeated with an additional 3-6 patients once new peptides are synthesized for use during manufacturing (Cohort II). If Cohort II is deemed safe for patients, this dose and peptide manufacturer will be used in the Phase 2 portion of the study. In parallel to opening the Phase 2 portion of the study, Cohorts III-V will open to enroll patients using the same standard 3+3 design described above for Cohorts I and II.

Patients who initially receive any dose of MT-401, but are subsequently deemed unevaluable (e.g., important protocol deviation, starting investigational drugs not approved by the Sponsor) and removed from the study will not count as DLTs in the Safety Lead-in and Cohorts III-V and may need to be replaced.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Patient Inclusion Criteria

All applicable inclusion and exclusion criteria must be met at Screening (up to 28 days before allogeneic HSCT for Group 1 patients, and prior to the start of manufacturing for Group 2 patients, or at the time of consideration for study) and at Baseline (re-assessment of eligibility within 14 days prior to group assignment for Group 1).

Patients are eligible to be included in the study only if all of the following criteria apply and the patient, in the judgement of the investigator, is an appropriate candidate for experimental therapy:

2. Eligible to receive donor-derived MT-401 following first allogeneic HSCT, are in ≤ third complete remission (CR3) prior to transplant (including matched sibling, matched unrelated donor with at least 6 of 8 HLA markers, or haploidentical with at least 5 of 10 HLA markers) as:

    - Adjuvant therapy for AML (**Group 1)** at 85-130 days post-HSCT defined as:

        – patients with CR_{MRD}- by central testing for purposes of randomization (if optional local MRD testing performed and results are positive, the patient will be moved to Group 2 subgroup D);
        – and are considered intermediate/high risk (e.g., pre-transplant MRD^+, intermediate/adverse risk cytogenetics or received non-myeloablative or reduced intensity conditioning); or

    - Treatment for relapsed AML (first relapse post-HSCT) when disease occurs after transplant **(Group 2**) defined as

        ◦ First relapse (MRD^+ or frank relapse) post-HSCT
        ◦ Patients in Group 1 who are randomized to Arm B (SoC) and experience first relapse (MRD^+ or frank relapse) post-HSCT or experience relapse prior to randomization
        ◦ Patients with frank relapse will enter into Subgroup C while patients with MRD^+ disease will enter into Subgroup D
    - Safety Lead-in (Cohorts I and II) and Cohorts III-V defined as patients whose prior treatment course does not meet precise eligibility criteria but may still be approved upon review by the Sponsor as described above for Group 2 only

Note: Engraftment must be confirmed post-transplant (absolute neutrophil count >1000/m^3 without granulocyte colony-stimulating factor for 7 days, donor chimerism ≥50%).

2. Are ≥18 years of age prior to administration of MT-401

3. Patients must have donor-derived cells available to make MT-401

4. Karnofsky/Lansky score of ≥60

5. Life expectancy ≥12 weeks

6. Adequate blood, liver, and renal function

   - Blood: Hemoglobin ≥7.0 g/dL (can be transfused)
   - Liver: Bilirubin ≤1.5X upper limit of normal; aspartate aminotransferase ≤3X upper limit of normal
   - Renal: Serum creatinine ≤2X upper limit of normal or measured or calculated creatinine clearance ≥45mL/min

7. Sexually active patients must be willing to utilize one of the highly effective birth control methods or practice complete abstinence starting from Screening for T cell infusion until 6 months after the last T cell infusion (see details in Section 8.3.5). Male patients who are sexually active must agree to use a condom during this period.

8. Patients are allowed to be on experimental conditioning regimens prior to transplant if no planned maintenance therapy post-transplant.

9. In Group 2, patients may receive bridging therapy at the investigators' discretion in situations where MT-401 is not ready for administration or the treating physician believes the patient would benefit (particularly in cases of high tumor burden) for ≤6 months as long as the following criteria are met:

   - Disease assessment including bone marrow biopsy to be performed within 14 days prior to administration of MT-401 (patients may receive MT-401 even if CR MRD^- is achieved post-bridging therapy but will be analyzed separately; additionally, patients must have ≤30% bone marrow blasts)
   - At least 4 half-lives or 1 week has passed after administration of bridging therapy whichever is shorter

5.2. Patient Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Clinically significant or severely symptomatic intercurrent infection

2. Pregnant or lactating

3. Any other issue which, in the opinion of the treating physician, would make the patient ineligible for the study

4. For Group 1, anti-neoplastic therapy after HSCT and prior to or during dosing of MT-401

5. For Group 2, concomitant anti-neoplastic therapy during or after dosing of MT-401

6. Evidence of acute or chronic GVHD ≥Grade 2 (exception: acute or chronic Grade 2 GVHD of skin allowed if stable) within one week prior to receiving MT-401

7. Taking systemic corticosteroids (exception: physiological doses of steroids allowed)

8. On other investigational therapy post-HSCT

9. Anti-thymocyte globulin or Campath within 28 days of MT-401 infusion

5.3. Donor Inclusion Criteria

Donors for allogeneic stem cell transplants must be considered suitable for and consent to stem cell donation, as per the standard operating procedures of the stem cell transplant program. If a donor has been chosen for the transplant, that same donor will also be used for to manufacture the T cell product provided that there are no new reasons for ineligibility since the stem cell collection. The donors will be evaluated as per standard institutional guidelines. The donor clearance by the National Marrow Donor Program (NMDP) is also acceptable.

Leukapheresis material will be collected from the same HSCT donor to manufacture MT-401 for the patient.

5.4. Lifestyle Considerations

No restrictions for diet; caffeine, alcohol, and tobacco; or activity are required during this study.

5.5. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to MT-401 (Groups 1) or fail to receive at least one dose of MT-401 (Group 2). Minimal data will be collected for screen failures, which will include demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened patients should be assigned the same patient number as for the initial screening. Repeating laboratory tests that did not meet eligibility criteria during the 28-day screening period does not constitute rescreening. If a repeated laboratory value meets eligibility criteria, that test must be repeated again to confirm eligibility.

Patients may be rescreened up to 2 times after the initial screening. The interval between rescreenings should be at least 1 week. Any laboratory tests and procedures falling outside original 28-day period need to be repeated. Local laboratories will be used to assess eligibility.

5.6. Dose-Limiting Toxicity Determination

A DLT is defined as one of the following AEs reported during the observation period (28 days from the day of the initial MT-401 infusion), if considered to be definitely, probably, or possibly related to MT-

401 and deemed clinically significant by the investigator; and fulfills any of the following criterion using NCI CTCAE (Version 5.0) with the exceptions as noted below:

1. Grade 3-4 GVHD

2. Grade 3-4 toxicity felt to be related to, or resulting from CRS

    - Exception: Grade 3 and 4 expected reactions seen with the use of T cell-based immunotherapy, such as (but not limited to) fever and hypotension not requiring pressor support, will not be considered DLTs

3. Grade 3-4 infusion reactions that are persistent beyond 72 hours despite optimal medical management

4. Any other Grade 3-4 toxicity that is ***not*** pre-existing and/or ***not*** due to the underlying malignancy or infection or treatment of disease lasting for extended period of time despite optimal supportive care (for example, nausea, vomiting, and diarrhea lasting > 3 days; fatigue lasting > 7 days)

    - Exception: Laboratory abnormality deemed not to be clinically significant

5. Grade 5 toxicity (that is, death)

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

6.1. Study Intervention Administered

Table 5 presents a summary of the study interventions administered for each of the treatment arms. Details regarding study intervention administration are described in Section 6.1.1 through Section 6.1.4.

Table 5: Study Interventions Administered

Group	**1 (Arm A)**	**1 (Arm B)[a]**	**2[b]**	**Safety Lead-in (Cohorts I and II) and Cohorts III-V**
Arm Name	**A**	**B**	**NA**	**NA**
Intervention Name	MT-401	SoC (Observation)	MT-401	MT-401
Type	Investigational Product	NA	Investigational Product	Investigational Product
Dose Formulation	Multi-antigen specific $CD4^+$ and $CD8^+$ T cells	NA	Multi-antigen specific $CD4^+$ and $CD8^+$ T cells	Multi-antigen specific $CD4^+$ and $CD8^+$ T cells
Unit Dose Strength[c]	100 x 10^6 cells flat dose (or 200 x 10^6 cells flat dose as	NA	100 x 10^6 cells flat dose (or 200 x 10^6 cells flat dose as	Safety Lead-in (Cohorts I & II): 50 x 10^6 cells flat dose

Group	1 (Arm A)	1 (Arm B)[a]	2[b]	Safety Lead-in (Cohorts I and II) and Cohorts III-V
Arm Name	**A**	**B**	**NA**	**NA**
	determined by Sponsor)		determined by Sponsor)	Cohort III: 200 x 10^6 cells flat dose Cohort IV: 100 x 10^6 cells flat dose Cohort V: 200 x 10^6 cells flat dose
Dosage Level[d]	Up to 3 doses total, with each dose at least 2 weeks apart	NA	Up to 3 doses total, with each dose at least 2 weeks apart	Up to 3 doses total, with each dose at least 2 weeks apart
Route of Administration	IV infusion through either a peripheral or a central line	NA	IV infusion through either a peripheral or a central line	IV infusion through either a peripheral or a central line
Use	Experimental	Comparator	Experimental	Experimental
Sourcing	Provided centrally by the Sponsor	Locally by the study site, subsidiary, or designee.	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Abbreviations: AE=adverse event; HSCT=hematopoietic stem cell transplant; IV=intravenous; NA=not applicable; SoC=standard of care
[a] Patients in Group 1 – Arm B who relapse after randomization may cross over to Group 2 to receive MT-401, if the subgroup is open and/or Sponsor agreement.
[b] If relapse occurs less than 80 days post-HSCT and T cells have been manufactured and stored, the patient may receive T cells and be included in a subgroup analysis of Group 2 (study intervention details for the subgroup will be the same as those presented for Group 2 in the table).
[c] Manufacturing maximum will also dictate the dose. As a result, patients may receive doses different to those listed; these patients will complete the study but will be unevaluable.
[d] Timing of MT-401 administration (at least every 2 weeks) may be modified for 1 week due to inclement weather, vacation, etc., but any longer durations need to be discussed with the Sponsor. Administration of MT-401 can be delayed due to management of AEs or other toxicities, but patients should resume T cell infusions within 2 weeks of their scheduled dose. If greater than 2 weeks is needed, Sponsor will determine if patient can resume T cells infusions.

6.1.1. Pre-Medication

Patients are recommended to be pre-medicated before MT-401 with diphenhydramine (Benadryl) up to 1 mg/kg IV (max 50 mg) and acetaminophen (Tylenol) up to 10 mg/kg orally (max 650 mg), and/or as per institutional guidelines.

6.1.2. Cell Administration

MT-401 will be given by IV infusion through either a peripheral or central line. Further details are provided in the Investigational Product Manual.

6.1.3. Monitoring of Infusion

Monitoring will be undertaken according to institutional standards for administration of blood products with the exception that the infusion will be given by a physician or trained professional. The patients will be monitored for any safety concerns for 1 hour post-infusion as outpatients.

6.1.4. Supportive Care

Patients will receive supportive care for acute or chronic toxicity, including blood components or antibiotics, and other intervention as appropriate and as per institutional guidelines.

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate conditions have been maintained for all MT-401 received and any discrepancies are reported and resolved before use of the MT-401.

Only patients enrolled in the study may receive MT-401. All MT-401 must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions.

The investigator or designee is responsible for MT-401 accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study investigational product are provided in the Investigational Product Manual.

6.3. Randomization

Disease assessment and group assignment occur at Day 80 (±5 days) post-HCST, prior to randomization for Group 1 patients. Post-transplant baseline MRD testing will be performed centrally, and results must be available prior to randomization.

For Group 1, randomization codes will be prepared to allow the clinical study sites to enroll patients by using an interactive response technology (IRT) system. Treatment group assignments will be known to site personnel (i.e., investigator, pharmacist, and study staff) and patients. After completion of required screening procedures, patients will be assigned, using the randomization schedule, to MT-401 vs observation (SoC) with a 1:1 allocation. The randomization schedule will be created with two stratification factors as specified in Section 4.1 using random block sizes. SoC patients in Group 1-Arm B who relapse after randomization may cross over to Group 2 to receive MT-401, if the subgroup is open and/or Sponsor agreement.

For Group 2, after the patient's eligibility is established and informed consent has been obtained, the patient will be enrolled, and a number will be assigned through the IRT. Since this is a single-arm cohort, all enrolled patients who meet eligibility criteria will be treated with MT-401.

Due to the nature of the administration of MT-401 along with the fact that the endpoints are objectively evaluated without the concern for bias, the study is not blinded.

Patients in the Safety Lead-in (Cohorts I and II) and Cohorts III-V will not be randomized.

6.4. Study Intervention Compliance

When patients are dosed at the site, they will receive MT-401 directly from the physician or trained personnel, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of MT-401 and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the MT-401.

6.5. Concomitant Medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Concomitant Medications

Patients should not receive other antineoplastic agents or systemic steroids. Physiologic doses of systemic steroids (e.g., for adrenocortical insufficiency) are allowed before or after MT-401. For patients in Group 2, bridging therapy prior to MT-401 infusion is permitted as described in eligibility.

If steroids are received outside parameters specified in protocol, the patient may be considered unevaluable.

Patients should not be administered any live vaccines while on study unless prior approval from Sponsor is obtained.

6.5.2. Toxicity Management

The study site will supply rescue medication that will be obtained locally. The following rescue medications may be used to manage toxicity, as explained in Section 11.1.2:

1. Corticosteroids (oral or IV)
2. Tocilizumab

Although the use of rescue medications is allowable, the use of rescue medications should be delayed, if no safety concerns related to study drug are present, for at least 6 months following the administration of MT-401. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6. Dose Modification

No dose modifications will be allowed except in rare instances of manufacturing constraints, and any other issues specifically discussed with the Sponsor. As a result, patients may receive either lower or higher than the intended doses; these patients will complete the study but will be evaluable in a separate sub-group.

Timing of MT-401 administration (at least 2 weeks apart) may be modified for 1 week due to inclement weather, vacation, etc., but any longer durations need to be discussed with the Sponsor. Administration of MT-401 can also be delayed due to management of AEs or other toxicities, but patients should resume T cell infusions within 2 weeks of their scheduled dose. If greater than 2 weeks is needed, Sponsor will determine if patient can resume T cells infusions. All dose modifications should be documented, including the approach taken and a clear rationale for the need for modification. Additionally, the investigator must assess if a toxicity is considered attributable to T cells. If MT-401 is available for a patient, a patient may be re-dosed if requested by the investigator and approved by the Sponsor on a case-by-case basis.

7. DISCONTINUATION OF MT-401 AND PARTICIPANT DISCONTINUATION/ WITHDRAWAL

7.1. Discontinuation of MT-401

If it becomes necessary for a patient to permanently discontinue MT-401, the patient will remain in the study to be evaluated for safety, response, and survival. See the SoA (Table 1) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

The following criteria will result in the patient being ineligible for further treatment on the protocol, although safety and response data will continue to be collected as applicable:

- Any patient who develops a DLT. In such patients, the toxicity will be followed until resolution or until their off-study date.
- Any patient who receives any other hematopoietic cell product (e.g., donor leukocyte infusion) except for routine blood product transfusions such as platelets and packed red blood cells. In such patients, AE data collection will cease.
- Any patient who enrolls in another clinical study involving investigational product or other type of medical research judged not to be scientifically/medically compatible with this study or receives antineoplastic treatment for relapse of their primary malignancy within 4 weeks after the T cell infusion. In such patients, adverse event data collection will cease.
- Refusal of the patient to continue treatment or observations.
- Decision by the investigator that discontinuation of treatment is in the patient's best medical interest.
- Unrelated medical illness or complication deemed significant by the investigator.
- Death.

- Progressive Disease.
- Lost to follow-up.
- At the request of Marker Therapeutics, Inc.
- Any patient who becomes pregnant.

Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation or Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Patient may agree to be followed for safety, efficacy, and survival after discontinuation from the study.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted (as described in the SoA [Table 1]). The patient will be permanently discontinued both from MT-401 and from the study at that time (see Section 7.1 for details on MT-401 discontinuation).

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

A patient will be considered off study when one of the following has occurred:

- The patient reaches End of Study, as defined in Section 4.4.
- If the patient desires to withdraw from the study or if the physician feels that it is in the best interest of the patient.
- Lost to follow-up (see Section 7.3 for details).
- Death.

7.3. Lost to Follow up

A patient will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Methods to account for missing data resulting for patients who were lost to follow up is described in the statistical analysis plan (SAP).

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or the referring physician and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible 3 attempts via at least 2 modalities [i.e., telephone call,

e-mail, or a certified letter to the patient's last known mailing address or local equivalent methods]). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable after 3 attempts, the investigator may consider the patient withdrawn from the study.

Discontinuation of specific sites or of the study are handled as part of Section 10.6.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.

Safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue MT-401.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

Disease will be assessed by standard criteria as indicated in Section 8.1.1. Evaluations of response will be performed at the time points listed in SoA (Table 1). Additional studies will evaluate leukemic involvement (e.g., imaging/blood/bone marrow, or other tissue samples that are obtained from the patient) as part of SoC. Patient long-term overall survival and PFS will also be evaluated. Efficacy assessments, including CT scans used to assess extramedullary disease may be collected and sent to a central imaging facility for assessment along with any disease assessment reports.

This study will use the ELN recommendations for AML response criteria (Döhner et al, 2017) as well as the FDA guidance for developing AML treatments (FDA, 2020). In addition, levels of any molecular marker or mRNA expression of a protein known to represent minimal residual disease or early relapse (e.g., WT1) may be performed. The response criteria are defined in the following section.

8.1.1. Disease Assessment - Response Criteria in AML

The response criteria in AML (Döhner et al, 2017) are as follows in Table 6Relapse includes either hematologic and/or molecular relapse as defined in Table 6 at any disease assessment.

Table 6. Response Criteria in AML

Category	Definition
CR without minimal residual disease (CR_{MRD}-)	If studied pretreatment, CR with negativity for a genetic marker by quantitative reverse transcription polymerase chain reaction (RT-qPCR), or CR with negativity by multiparameter flow cytometry (MFC) and/or molecular testing
Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count ≥1.0 x 10^9/L (1000/µL); platelet count ≥100 x 10^9/L (100,000/µL) Note: MRD^+ or unknown
CR with incomplete recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 x 10^9/L [1000/µL]) or thrombocytopenia (<100 x 10^9/L [100,000/µL])
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent
Treatment failure	
Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Response criteria for clinical trials only	
Stable disease[a]	Absence of CR_{MRD}-, CR, CR_i, PR, MLFS; and criteria for PD not met
Progressive disease (PD)	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (>0.5 x 10^9/L [500/µL], and/or platelet count to >50 x 10^9/L [50,000/µL] nontransfused); or >50% increase in peripheral blasts (WBC X % blasts) to >25 X 10^9/L (>25,000/µL) (in the absence of differentiation syndrome); or New extramedullary disease
Relapse	
Hematologic relapse (after CR_{MRD}-, Cr, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease
Molecular relapse (after CR_{MRD}-)	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC

[a] The period of stable disease should be at least 3 months to be considered SD.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1. GVHD Assessments

A potential toxicity for patients receiving allogeneic T cells is GVHD. The risk that adoptively transferred leukemia-targeted T cells will cause GVHD is very low. GVHD will be assessed as per SoA (Table 1) and as per acute and chronic GVHD guidelines (Harris et al 2016; Jagasia et al, 2015).

8.2.2. Vital Signs

Vital signs will be evaluated at specified time points as indicated in SoA (Table 1).

Temperature, pulse rate, and blood pressure will be assessed, and if clinically indicated, respiratory rate will also be assessed.

8.2.3. Clinical Laboratory Assessments

See the SoA (Table 1) for the timing and frequency of clinical laboratory tests to be performed. Laboratory tests to be collected (on days of MT-401 administration, labs should be performed prior to MT-401 administration): complete blood count and differential, glucose, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, bilirubin (total and direct), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, sodium, potassium, chloride, carbon dioxide, albumin, and total protein. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of MT-401. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF with assistance of site personnel. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of MT-401 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.4. History and Physical Examinations

History and physical examinations will be performed at specified time points as indicated in the SoA (Table 1). A complete physical examination will be performed as per institutional guidelines but at baseline will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems, and height (at Screening) and weight will also be measured and recorded.

- A brief physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, and Gastrointestinal systems (height and weight will be needed at screening at minimum and any changes recorded if >10%).

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3. Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of MT-401, whether or not considered related to MT-401. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of MT-401. The NCI CTCAE (Version 5.0) for Adverse Events will be utilized for AE reporting. The criteria listed in the Cancer Therapy Evaluation Program (CTEP) NCI Common Toxicity Criteria Scale will be used in grading toxicity, with the exception of CRS toxicity and neurotoxicity that are related to T-cell infusions. CRS toxicity will be graded according to Table 13 (as per Lee et al, 2019 which also contains assessment of neurotoxicity). The CTEP CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative). In addition, the investigator (or designee) is responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to MT-401 or study procedures, or that caused the patient to discontinue treatment or the study (see Section 7).

If an event is not an AE, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease or planned procedures/surgeries).

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening (that is, immediate risk of dying)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is considered significant by the investigator based on appropriate medical judgement

8.3.1. Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from Day 0 until the Week 12 Visit at the time points specified in the SoA (Table 1), after which only treatment-related AEs and SAEs will be noted.

All SAEs from Baseline Visit to Week 12 Visit will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Appendix 1, Section 11.1. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. Additionally, any patient with any grade CRS or neurotoxicity will be reported in an expedited fashion within 24 hours of learning of event.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be at least possibly related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports, are provided in Appendix 1, Section 11.1 .

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences. The investigator (or designee) is responsible for detecting, documenting, and recording events in addition to any reported by patients.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 1, Section 11.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators, as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Pregnancy testing will be conducted as shown in the SoA (Table 1). Per the exclusion criteria, patients must not be pregnant or lactating, and per the inclusion criteria, sexually active patients must be willing to utilize one of the more effective birth control methods for 6 months after the T cell infusion. If a patient becomes pregnant during the study, they are to be discontinued from MT-401, but will continue follow-up (Section 7.1).

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of MT-401 and until the Follow-up Visit.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined below.

Pregnancy outcomes will be collected and abnormal pregnancies (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

No AEs of special interest are noted.

8.4. Treatment of Overdose

The dose of MT-401 is carefully monitored and administered by health care personnel. No overdose of MT-401 has been reported. In the event of an overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study, with the exception of biomarkers, as described in Section 8.8.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Collection of samples for other biomarker research is also part of this study including but not limited to blood and bone marrow biopsies/aspirate as noted in the Laboratory Manual. Samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA (Table 1).

Samples will be tested for immune phenotype, repertoire and function, cell targeting, signaling pathways and disease status, including MRD to evaluate their association with the observed clinical responses to MT-401. If any previous local MRD testing has been completed, the results may be collected.

In addition, samples will be stored and analysis may be performed on biomarker variants thought to play a role in immune surveillance and function including, but not limited to, serum/plasma analytes, or tissue biomarkers to evaluate their association with observed clinical responses to MT-401.

Other samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to immune pathways, disease process and/or mechanism of action of MT-401.

Samples may be stored for a maximum of 10 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to MT-401.

Other Tissue: If the patient dies, an autopsy may be requested. If granted, tissue may be requested to assess presence of infused cells and assess tumor antigen expression profile.

Bilateral bone marrow aspirations and other biopsies: Samples of a previous bone marrow biopsy (or other aspirates or biopsies of tissues suspected to be infiltrated with tumor cells) or of additional biopsies performed while the patient is on study will be used to assess disease status, as well as specificity and functionality of bone marrow infiltrating T cells. For any additional bone marrow biopsy (any performed in addition to the protocol specified bone marrow biopsies) the patient has had performed while he/she is on study, an extra 5-20cc of bone marrow aspirate and/or core biopsy will be obtained for the testing described above and provided to the Sponsor.

8.9. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.10. Patient-reported Outcomes

As an exploratory endpoint (For Phase 2, Group 2 Subgroup C only), a PRO questionnaire will be completed. Additional details regarding the PRO questionnaire and associated instructions will be provided in a separate document.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

9.1.1. Adjuvant Population (Group 1)

A total of approximately 150 Group 1 patients will be randomized with a 1:1 allocation to receive MT-401 or to be under observation (SoC arm). Median RFS for the SoC arm is expected to be approximately 8 months (Rashidi et al, 2016; Goyal, 2016). A clinically meaningful increase in median RFS for the MT-401 arm over SoC is thought to be 2 months or more. The primary analysis will be conducted when 90 RFS events have been observed. Ninety (90) RFS events provides 80% power with alpha=0.05 to detect a median RFS improvement of 6.5 months over the assumed SoC median RFS of 8 months (hazard ratio=0.55). Ninety RFS will be observed assuming uniform accrual of 150 patients (75 per arm) over a 50-month period and an additional 12-month minimum follow-up period. The DMC and Sponsor will review data from Phase 2 based on the planned interim analyses described in Section 9.5.

If the decision is made to dose patients in Phase 2 with any of the MT-401 dosing regimens evaluated in Cohorts III-V, enrollment will continue in Phase 2 Group 1 to achieve 150 evaluable patients randomized and approximately 75 patients treated with the final MT-401 dose and the intended manufacturing process, thereby replacing any patients that have not been treated with the final Phase 2 product, as determined by the Sponsor.

9.1.2. Active Disease and Late Relapse Population (Group 2)

A total of approximately 60 Group 2 patients are planned to be enrolled and treated with MT-401, 30 patients in Subgroup C (frank relapse patients) and 30 patients in Subgroup D (MRD^+). After approximately the first 10 patients in each subgroup have progressed or have had the opportunity to be followed for 6 months, clinical safety and efficacy will be reviewed comprehensively. Patients who develop CR_{MRD-} after bridging therapy and patients who relapse early (defined < 90 days ± 10 days post-transplant and termed Group 2 Early Relapse patients) will be analyzed separately, and not be counted as part of the 60 patients in Group 2.

Overall response rates in the literature vary widely and range from 10% to 60% (Loren and Porter, 2008; Porter et al, 2010). Complete remission rates would be expected to be lower than ORR rates. The sample size of 30 per subgroup is not based on a formal power calculation. An increase in the CR rate of greater than 10-15% compared to historical rates for standard of care would be considered clinically meaningful.

If the decision is made to dose patients in Phase 2 with any of the MT-401 dosing regimens evaluated in Cohorts III-V, enrollment will continue in Phase 2 Group 2 to achieve 60 evaluable patients treated with the final MT-401 dose and manufacturing process, thereby replacing any patients that have not been treated with the final Phase 2 product as determined by the Sponsor.

For historical control response rates ranging from 5% to 40%, the observed treatment effects (and associated 95% confidence intervals) needed to attain 80% and 90% power with a sample size of 30 patients per subgroup are provided in Table 7.

Table 7. Power[a] and 95% Confidence Intervals Relative to Historical Control Rates

Historical Control CR Rate	Observed Treatment Effect (80% Power) (95% CI)	Observed Treatment Effect (90% Power) (95% CI)
5%	21% (9%, 40%)	25% (11%, 44%)
10%	29% (14%, 48%)	32% (17%, 52%)
15%	36% (19%, 55%)	40% (22%, 59%)
20%	43% (25%, 62%)	47% (28%, 66%)
25%	50% (31%, 68%)	53% (34%, 72%)
30%	53% (34%, 71%)	57% (37%, 75%)
35%	60% (40%, 77%)	63% (44%, 80%)
40%	63% (43%, 79%)	66% (47%, 82%)

[a] based on a 1-sided exact test at the 0.05 alpha level.

9.1.3. Safety Lead-in (Cohorts I and II) and Cohorts III-V

Approximately 6-12 patients are expected to be treated in the Safety Lead-in portion of this study per a standard 3+3 design with 2 planned cohorts. In addition, approximately 9-18 patients (3-6 patients per cohort) are expected to be treated in the Cohorts III-V portion of this study as per a standard 3+3 design.

9.2. Populations for Analyses

Populations for analyses are defined in Table 8.

Table 8. Populations for Analysis

Population	Description
All enrolled patients	All patients who sign the ICF and donor undergoes leukapheresis
All randomized patients in Phase 2 (Adjuvant - Group 1 only)	All patients in Group 1 who are randomized with final dose and manufacturing process, and are MRD^- prior to randomization by central testing and local testing (if a local test was also performed). Efficacy analyses for Group 1 will be conducted in this population. A patient randomized based on negative MRD result per central test but confirmed to be MRD^+ will be excluded from Group 1 analyses. The patient will be included in Group 2 Subgroup D analyses if treated with MT-401.
All treated patients	All patients who receive at least one dose of MT-401 or were randomized to SoC. Patients whose product includes fewer cells or does not meet specifications may still be treated, but will be summarized separately from patients whose product meets specifications. For - Group 1, safety analyses will be conducted in this population, and safety data for patients randomized to SoC will also be shown for reference. For - Group 2, all efficacy analyses and safety analyses will be conducted in this population. For the Safety Lead-in (Cohorts I and II) and Cohorts III-V, all efficacy and safety analyses will be conducted in this population
DLT-evaluable	All patients in the Safety Lead-in (Cohorts I and II) and Cohorts III-V who receive at least one dose of MT-401 and have had the opportunity to be followed for 28 days from the initial MT-401 infusion or have experienced a DLT.
Per-protocol in Phase 2	All treated patients, as defined above, who have no major protocol deviations. Select efficacy analyses for Group 1 and Group 2 will be conducted in this population for sensitivity analysis.

Abbreviations: DLT=dose-limiting toxicity; ICF=informed consent form; MRD=minimal residual disease; SoC=standard of care

9.3. Statistical Analyses

The SAP will be finalized before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

The primary analysis of the study will occur when 90 RFS events have occurred in Phase 2 Group 1. The clinical study report will be written based on this analysis. If the primary analysis of either Group 1 or 2 occurs after the primary analysis of the other group, an addendum to the CSR will be written to describe the results of the other group.

Categorical variables will be summarized as counts and percentages. Continuous variables will be summarized with univariate statistics, including mean, median, range, and standard deviation. Confidence intervals (CIs) will be calculated for summary statistics, addressing the primary and secondary efficacy outcomes.

The primary analysis will include disease assessments associated with the first treatment regimen of MT-401 only. Any disease outcomes collected subsequent to re-treatment (i.e. re-dosing) will be analyzed separately.

9.3.1. Primary Safety Analysis: Safety Lead-In (Cohorts I and II) and Cohort III-V

The primary objectives for the Safety Lead-in are to assess safety and tolerability of MT-401 manufactured using peptides produced by two different vendors, including identifying DLTs. The primary objective for Cohort III is to assess the safety and tolerability of a higher dose than the dose used in the Phase 2 portion of the study. The primary objective for Cohorts IV-V is to assess the safety and tolerability of the accelerated MT-401 product. For both the Safety Lead-in, which includes Cohorts I and II, and Cohorts III-V, the number of DLTs per cohort will be identified as defined in Section 5.6. The confirmed dose and peptide manufacturer will be identified based on the procedures of the standard 3+3 design described in Section 4.5 and review of entirety of the safety data. Safety endpoints will be analyzed as discussed in Section 9.3.5.

9.3.2. Primary Efficacy Analysis: Group 1

The primary endpoint for Group 1 is RFS, defined as the time between the date of randomization and the date of first relapse per ELN recommendations or death by any cause, whichever occurs first. For patients who remain alive and whose disease has not relapsed, RFS will be censored on the date of last evaluable disease assessment. For patients who remain alive and have no recorded post-randomization disease assessment, RFS will be censored on the date of randomization. Censoring rules for the primary analysis of RFS in Group 1 are presented in Table 9.

Relapse includes either hematologic and/or molecular relapse as defined in Table 6 at any disease assessment.

For the interim analysis, RFS as determined by the investigator will be used.

Table 9: Censoring Scheme for Primary definition of RFS

Situation	Date of Event or Censoring	Outcome
Relapse per ELN recommendations	Date of first relapse	Event
Death without relapse	Date of death	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No relapse and no death	Date of last evaluable disease assessment	Censored
New anti-cancer therapy received without relapse reported prior to or on the same day as disease assessment	Date of last evaluable disease assessment on or prior to the date of initiation of subsequent therapy	Censored
Two or more consecutive missed scheduled disease assessments	Date of last evaluable disease assessment prior to the missed disease assessments	Censored

Abbreviations: AML=acute myeloid leukemia; RFS=relapse-free survival

RFS curves will be estimated using the Kaplan-Meier (KM) product limit method. For Group 1, the hazard ratio and corresponding 95% confidence interval (CI) will be estimated using a Cox proportional hazards model using randomized arm and two stratification factors as covariates. The KM estimate of the medians will be reported, and the corresponding 95% CI will be computed. KM estimates of RFS rates at milestone time points will be reported along with two-sided 95% CIs using Greenwood's formula, provided the minimum follow-up in patients exceeds the time point to support stable estimation of the rate. In addition to the Cox model, a stratified log-rank test will be used to compare the treatment arms, stratified by pre-transplant MRD status (MRD^+ vs. MRD^-/Unknown) and cytogenetic risk (Unfavorable vs. Other).

RFS is defined as the time between the date of first dose and the date of first relapse per ELN recommendations or death by any cause for Group 2 patients, and will be summarized for Group 2 Subgroup D patients and those in Group 2 who are in CR_{MRD-} prior to administration of MT-401.

9.3.3. Primary Efficacy Analysis: Group 2

The primary endpoints for Group 2 are CR rate and duration of complete response. For Group 2 Subgroup C, CR rate is defined as the proportion of treated patients who achieve a best response of CR_{MRD-} or CR using the ELN recommendations. For Group 2 Subgroup D, CR rate is defined as the proportion of treated patients who achieve a best response of CR_{MRD-}. Best overall response (BOR) is defined as the best response designation recorded between the date of first dose and the date of objectively documented progression or relapse per ELN recommendations or the date of subsequent therapy, whichever occurs first. For patients without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.

The primary analysis will occur after all patients treated have been followed for 6 months.

For Group 2 Subgroup C, duration of complete response is defined as the time between the date of first documented response of CR_{MRD-} or CR to the date of the first documented relapse per ELN recommendations or death due to any cause, whichever occurs first. For Group 2 Subgroup D, duration of

complete response is defined as the time between the date of first documented response of CR_{MRD-} to the date of the first documented relapse per ELN recommendations or death due to any cause, whichever occurs first.

The CR rate from Group 2 Subgroup C will be evaluated in the context of results from an ongoing retrospective study of AML patients who are similar to the inclusion/exclusion criteria of Group 2 Subgroup C patients. Any comparison of Group 2 data to results from the retrospective study will be described in a separate SAP.

Censoring rules for DOCR are provided in Table 10.

Table 10: Censoring Scheme for Primary Definition of DOCR

Situation	Date of Event or Censoring	Outcome
Relapse per ELN recommendations	Date of first relapse	Event
Death without relapse	Date of death	Event
No relapse and no death	Date of last evaluable disease assessment	Censored
New anti-cancer therapy received without relapse reported prior to or on the same day as disease assessment	Date of last evaluable disease assessment on or prior to the date of initiation of subsequent therapy	Censored
Two or more consecutive missed scheduled disease assessments	Date of last evaluable disease assessment prior to the missed disease assessments	Censored

Abbreviations: AML=acute myeloid leukemia; RFS=relapse-free survival
Relapse includes either hematologic and/or molecular relapse as defined in Table 6 at any disease assessment.

The CR rate and the corresponding 95% exact CI will be calculated. The DOCR will be estimated using the KM product limit method. The KM estimate of the median DOCR and the DOCR rates at milestone timepoints will be reported along with the two-sided 95% CI.

9.3.4. Secondary Analyses

9.3.4.1. Overall Survival (Groups 1 and 2)

Overall survival is defined as the time from randomization (Group 1) or first dose (Group 2) to the date of death. A patient who has not died will be censored on their last contact date ("last known alive date").

The statistical methods for analyzing OS are identical to those described for RFS.

Patients in Group 2 who achieve CR_{MRD-} post-bridging therapy will be summarized separately for OS.

9.3.4.2. Graft-versus-host Disease- and Relapse-free Survival (Groups 1 and 2)

Graft-versus-host disease- and relapse-free survival (GRFS) is defined as the time from randomization (Group 1) or first dose (Group 2) to date of GVHD, relapse, or death, whichever occurs first. GVHD events are defined as any grade 3-4 acute GVHD or chronic GVHD requiring systemic therapy. A patient who has not experienced any of these events will be censored on the date of their last evaluable disease

assessment. For patients who remain alive and have no recorded post-baseline disease assessment, GRFS will be censored on the date of randomization (Group 1) or first dose (Group 2). Censoring rules for the analysis of GRFS in Group 1 are presented in Table 11.

Table 11. Censoring Scheme for Primary Definition of GRFS

Situation	Date of Event or Censoring	Outcome
GVHD or relapse	Date of first event type	Event
Death without GVHD or relapse	Date of death	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No GVHD, no relapse, and no death	Date of last evaluable disease assessment	Censored
New anti-cancer therapy received without relapse reported prior to or on the same day as disease assessment	Date of last evaluable disease assessment on or prior to the date of initiation of subsequent therapy	Censored
Two or more consecutive missed scheduled disease assessments	Date of last evaluable disease assessment prior to the missed disease assessments	Censored

Abbreviations: AML=acute myeloid leukemia; GRFS=graft-versus-host disease relapse-free survival

The statistical methods for analyzing GRFS are identical to those described for RFS.

GRFS will be summarized for Group 1 and Group 2 Subgroup D, respectively.

9.3.4.3. Overall Response Rate (Group 2 Subgroup C)

Overall response rate (ORR) is defined as the proportion of treated patients who achieve a best response of CR_{MRD}-, CR, CRi, MLFS or PR using the ELN recommendations. The statistical methods for analyzing ORR are identical to those described for CR.

Duration of response is defined as the time between the date of first documented response of CR_{MRD}-, CR, CRi, MLFS or PR to the date of the first documented progression. The statistical methods for analyzing ORR are identical to those described for DOCR.

9.3.4.4. Progression-free Survival (Group 2 Subgroup C)

Progression-free survival is defined as the time between the date of first dose and the date of documented progression or death by any cause, whichever occurs first. For patients who remain alive and whose disease has not progressed, PFS will be censored on the date of last evaluable disease assessment. For patients who remain alive and have no recorded post-baseline disease assessment, PFS will be censored on the date of first dose. Censoring rules for the analysis of PFS in Group 2 Subgroup C are presented in Table 12.

Table 12: Censoring Scheme for Primary Definition of PFS

Situation	Date of Event or Censoring	Outcome
Progression	Date of progression	Event

Death without progression	Date of death	Event
No baseline disease assessment	Date of first dose	Censored
No on-study disease assessments and no death	Date of first dose	Censored
No progression and no death	Date of last evaluable disease assessment	Censored
New anti-cancer therapy received without progression reported prior to or on the same day as disease assessment	Date of last evaluable disease assessment on or prior to the date of initiation of subsequent therapy	Censored
Two or more consecutive missed scheduled disease assessments	Date of last evaluable disease assessment prior to the missed disease assessments	Censored

Abbreviations: AML=acute myeloid leukemia; PFS=progression-free survival

The statistical methods for analyzing PFS are identical to those described for RFS.

9.3.4.5. Safety Lead-in (Cohorts I and II) and Cohorts III-V

Secondary efficacy endpoints (i.e., CR rate and DOCR) will be summarized for patients in the Safety Lead-in (Cohorts I and II) and Cohorts III-V portion of the study by cohort.

9.3.5. Safety Analyses

Safety and toxicity outcomes including treatment-emergent AEs, CRS, GVHD, neurological findings, and laboratory evaluations will be summarized using descriptive statistics for all patients in the All treated population by group. Safety evaluations will be based on the incidence, intensity, and type of AEs or SAEs, as well as changes in the patient's physical examination findings, vital signs, and clinical laboratory results.

AEs will be assessed for severity according to the U.S. NCI CTCAE, Version 5.0, and the verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 25 or higher) for purposes of summarization.

The safety analysis will be performed in all treated patients. Descriptive statistics of safety will be presented by dose cohort or by treatment arm. All on-treatment AEs, drug-related AEs, late-emergent drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE Version 5.0 criteria by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE Version 5.0 criteria.

All deaths within 30 and 60 days of the last dose of MT-401 will be summarized. For Group 1 SoC arm, deaths within 30 days and 60 days of randomization date plus average time from randomization to last dose in the MT-401 arm will also be summarized as reference.

9.3.6. Other Analyses

A summary of the PRO data will be presented using descriptive statistics for Group 2 Subgroup C only.

Other analyses will be detailed in the SAP for the clinical study report (CSR). Some exploratory analyses may not be presented in the CSR.

9.4. Monitoring and Oversight Committees

A Sponsor review committee (SRC) will be convened to review the toxicities and endpoints related to the Safety Lead-in (Cohorts I and II), meet separately once Cohort III is complete and again once Cohorts IV-V are complete. The SRC will consist of at least 1-2 clinicians that includes the Medical Monitor and/or the Medical Director, along with 1 statistician. The SRC will convene at the end of the Safety Lead-in to determine if it is appropriate to move forward with the Phase 2 portion of the study and after Cohort III to determine if the dose should be increased. The SRC will also convene after Cohorts IV-V have been completed to determine if a particular dose of the MT-401 product manufactured with the accelerated process should be used to treat patients in Groups 1 and 2 of the Phase 2 portions of the study.

A DMC will be formed for the Phase 2 portion of the study. Briefly, an independent DMC will review safety and efficacy data from this study. The DMC will make recommendations on ongoing study conduct, including the accrual of additional patients to Group 1 based on the futility and efficacy criteria that are established in the DMC charter. In addition, an Independent Efficacy Review Committee (IERC) may be formed to provide independent disease assessment. Separate charters will outline the details, including roles and responsibilities of these two committees.

9.5. Interim Analyses

Safety Lead-in (Cohorts I and II) and Cohorts III-V: Safety data will be reviewed at the end of the Safety Lead-in to determine if it is appropriate to move forward with the specific peptide manufacturer in the Phase 2 portion of the study. The evaluation of DLTs will be conducted in the DLT-evaluable set. Safety data will also be reviewed at the end of Cohort III to determine if it is appropriate to switch to a higher dose in the Phase 2 portion of the study. Additionally, safety data will also be reviewed at the end of Cohorts IV and V to determine if it is appropriate to switch to a dosing regimen with the MT-401 product manufactured using the accelerated process in the Phase 2 portion of the study. This decision will be made by the Sponsor based on multiple parameters, including the safety and biomarker data available.

9.5.1. Phase 2 Group 1: One interim analysis is planned for Group 1.

The first interim analysis of Group 1 will occur when 45 RFS events have occurred in Group 1. It is anticipated that this will occur approximately 30 months after the first patient randomized. At this analysis, the DMC will assess safety, futility, and potential expansion of study accrual according to the criteria defined in the DMC charter. At the time of this analysis, enrollment of the remaining patients will continue, unless any safety concerns are identified.

9.5.2. Phase 2 Group 2:

After the first approximately 10 patients in each subgroup in Group 2 have progressed or had the opportunity to be followed for 6 months, clinical safety and efficacy will be reviewed comprehensively. Further enrollment for a subgroup may be terminated due to futility based on totality of the data. Patients

treated in cohorts IV-V with the same manufacturing process as Group 2 may be included in Group 2 Subgroup C or Subgroup D analyses for decision making.

Details of the interim analysis will be described in the SAP, including pre-specified rules for futility and potential expansion of Group 1 enrollment and methods for control of the overall type I error rate.

Upon review of this interim analysis, the DMC may recommend adding additional patients to Group 2 based on the emerging data from the historical control study and the observed response rate at the interim analysis.

10. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) good clinical practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative as defined by institutional guidelines will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. Additionally, a second ICF at the Baseline Visit may be required.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date. A second ICF will be signed at Baseline within 14 days prior to group assignment (as shown in the SoA; Table 1)

Enrollment of eligible patient/donor pairs will commence prior to stem cell transplant. The NMDP will have an NMDP IRB protocol and consent form that will be used when obtaining blood for cell line preparation from an unrelated donor.

Patients in SoC (Group 1-Arm B) will have to re-sign the ICF and confirm eligibility prior to entering into Group 2 for receiving MT-401.

10.3. Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.4. Data Quality Assurance

All patient data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.5. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.6. Study and Site Closure

The Sponsor (or designee) reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further MT-401 development

10.7. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Adverse Events: Procedures for Recording, Evaluating, Follow-up, Reporting, and Management

11.1.1. Grading of Toxicity Events

Cytokine release syndrome toxicities will be graded according to Table 13 (as per Lee et al, 2019).

11.1.2. Management of Toxicities Related to Cellular Therapy

Based on the mechanism of action of MT-401, AEs of immune related etiology may occur shortly after the first dose or several months after the last dose of treatment. MT-401 must be withheld for drug-related toxicities or severe life-threatening AEs. Use the following references for instructions on management of adverse events, including CRS, neurotoxicity, and immune-related AEs: National Comprehensive Cancer Network (Management of immunotherapy-related toxicities) and Lee et al, 2019.

Table 13. Grading of Cytokine Release Syndrome Toxicity Events

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

11.2. Appendix 2: Protocol Amendment History

11.2.1. Amendment 1 Version 2

Protocol Amendment 1, dated 24 October 2019, included the changes noted below, as well as clarifications and minor editorial changes. The revisions listed below were made to Version 1 of the protocol (dated 08 July 2019) in Protocol Amendment 1, and a full detailed summary of changes is available in Protocol Amendment 1.

- The Group 2 primary objective was changed from ORR to CR rate and added the maximum windows of time between marrow sampling and peripheral blood tests to establish CR, which is more indicative of efficacy of a treatment in this disease population than ORR.
- MRD status was changed from local testing to central testing to create uniformity in testing.
- GVHD assessments were changed from institutional guidelines to acute and chronic GVHD guidelines to provide more updated standards used by investigators.
- The SRC, DMC, and IERC were added and defined to provide safety and efficacy oversight for the study.
- The Safety Lead-in was added, including definitions of DLT and dose levels to evaluate safety.
- The statistical analyses were updated to provide detailed rationale for study size and analysis plan of safety and efficacy data during and at the end of the study.

11.2.2. Amendment 2 Version 3

Protocol Amendment 2, dated 22 Jun 2020, included the changes noted below, as well as clarifications and minor editorial changes.

Summary of Changes: The revisions listed below were made to Version 2 of the protocol (dated 24 Oct 2019) in Protocol Amendment 2. (Note: Deletions are stricken and additions are indicated in bold font; minor grammatical changes [e.g., capitalization, punctuation] are not detailed unless included with other changes.)

- The dose was updated globally to 50 x 10^6 cells (flat dosing), and the dose justification and rationale was updated throughout the protocol to support this change.
- Response criteria were updated to the European LeukemiaNet (ELN) recommendations and edits were made globally throughout the protocol to be in alignment with these recommendations.
- Additional detail was provided throughout the synopsis and protocol regarding the Safety Lead-in portion of the study. In addition, a DLT-evaluable population was included in the analysis populations, and was defined as all patients in the Safety Lead-in who receive at least one dose of

MT-401 and have had the opportunity to be followed for 28 days from the initial MT-401 infusion or have experienced a DLT.

11.2.3. Amendment 3 Version 4

Protocol Amendment 3, dated 08 Feb 2021, included the changes noted below, as well as clarifications and minor editorial/non-substantive changes that are not explicitly indicated in the table below.

Summary of Changes: The revisions listed below were made to Version 3 of the protocol (dated 22 Jun 2020) in Protocol Amendment 3. (Note: Deletions are stricken and additions are indicated in bold font; minor grammatical changes [e.g., capitalization, punctuation] are not detailed unless included with other changes.)

- The dose in Groups 1 and 2 in the Phase 2 portion of the study was updated to 100 x 10^6 cells (flat dosing) from the 50 x 10^6 cells (flat dosing) included in the previous version of the protocol.

- Cohort III was added to the study with the objective to test a higher dose (200 x 10^6 cells) than the dose used in the Phase 2 portion of the study, and information was added globally throughout the protocol regarding this cohort.

- The dose and justification for dose text was revised to provide rationale for inclusion of Cohort III and the higher dose.

- The study FDA guidance for developing AML treatments (FDA, 2020) was included in the protocol as a reference and was included as part of the definition for the CR rate assessed during the study.

- Text was added where appropriate to explicitly state that patients who were treated with product not meeting specifications will be excluded from analyses and potentially replaced.

11.2.4. Amendment 4 Version 5.0

Protocol Amendment 4, dated 24 September 2021, included the changes noted below, as well as clarifications and minor editorial/non-substantive changes that are not explicitly indicated in the table below.

Summary of Changes: The key revisions listed below were made to Version 4 of the protocol (dated 06 April 2021) in Protocol Amendment 4. (Note: deletions are indicated with a strikethrough, additions are indicated in bold font, and explanatory text is provided in italics; minor grammatical changes [e.g., capitalization, punctuation] are not detailed unless included with other changes.)

- Group 2 of the Phase 2 portion of the study is updated to split the patient population into two subgroups as follows:
  - Subgroup C: includes patients with frank relapse
  - Subgroup D: includes patients who are MRD^+
- Objectives and endpoints are added for the Phase 2 Group 2 subgroups.
- Cohorts IV and V were added to the study. Initially, patients were treated in Cohorts I-III with MT-401 using a manufacturing process that took >2 weeks, however, recently the manufacturing process has been shortened to about one week which is referred to as an accelerated process (being tested in Cohorts IV and V). The primary objectives of Cohorts IV and V are to test the safety and tolerability of MT-401 manufactured with the accelerated process. Information regarding objectives, endpoints, study design, etc. was added globally throughout the protocol for these cohorts.

- The Investigational Product section was revised to provide a complete list of MT-401 manufacturing process and dosing regimens used for Cohorts I-V and Phase 2.

- Sample sizes and justifications were added to include Cohorts IV-V, and for Phase 2 Group 2 portion (Active Disease) sample size was increased from 60 to 80 total patients, including 40 subjects per subgroup.
  - An explanation was added to ensure enrollment will continue in Phase 2 to achieve approximately 180 evaluable patients treated with the final MT-401 dose and manufacturing process, thereby replacing any patients that have not been treated with the final Phase 2 product and dose, as determined by the Sponsor.

- Text was added where appropriate to explicitly state that patients who were treated with product not meeting specifications will be excluded from analyses and potentially replaced.

- Molecular testing (eg. PCR, next generation sequencing etc.) was added as an acceptable method for confirmation of MRD^+.

- Patient inclusion criteria were updated to reflect the two subgroups in Phase 2 Group 2 and reduce the waiting time for inclusion of patients requiring bridging therapy prior to inclusion in the study.

- Clarified that donors will be evaluated as per standard institutional guidelines.

- For the per-protocol analysis population added that Phase 2 Group 1 will also be analyzed.

- Revised the interim analysis data cut-off threshold to occur after the first 15 patients per subgroup in Group 2 Phase 2 portion of the study.

- Revised the background section with updated Phase 1 clinical study results for the Baylor study in AML indicating that five dose levels have been evaluated including 100 x 10^6 cells (DL5).

- Deleted the biomarker sample at Screening since the Baseline sample is sufficient for biomarker status prior to MT-401 treatment.

11.2.5. Amendment 5 Version 6.0 and 6.1

Protocol Amendment 5, dated 22 Nov 2022 included the changes noted below, as well as clarifications and minor editorial changes.

Summary of Changes: The key revisions listed below were made to Version 5 of the protocol (dated 24 Sep 2021) in Protocol Amendment 4. (Note: deletions are indicated with strikethrough, additions are indicated in bold font; minor grammatical changes [e.g., capitalization, punctuation] are not detailed unless included with other changes.)

- The total number of patients randomized/treated in this study was updated from 195-220 patients to **225-240 patients**.
  - The numbers of patients in Phase 2 and Phase 2, Group 1 were updated from approximately 180 patients to **210 patients** and from approximately 120 patients to **150 evaluable patients randomized (75 patients per arm)**, respectively.
- Electrocardiogram measurements were removed from the Secondary Safety endpoints and from the Schedule of Assessments.
- Eligible patients:
  - Adjuvant (Group 1) was updated to randomize patients without minimal residual disease **80 days** ~~90 days~~ post-transplant **based on central testing** and to allow accrual of patients over a **50-month** ~~24 month~~ period. **Randomization will be stratified by pre-transplant MRD status (MRD+ vs. MRD-/Unknown) and cytogenetic risk (Unfavorable vs. Other).**
  - Active Disease (Group 2) was updated to include patients **in Group 1** who experience relapse (patients MRD^+ or frank relapse) prior to **randomization** ~~at or prior to post-transplant Day 90~~ and patients in Group 1 – Arm B (SoC) who relapse **after randomization** ~~90 days post-HSCT~~ (crossover patients).
- Disease assessment was updated to specify that for **Group 1, pre-transplant testing of MRD should be performed locally by any testing methodology and results recorded in the eCRF and post-transplant baseline MRD testing will be performed centrally, and results must be available prior to randomization**.
- Sponsor and DMC review of safety and efficacy data in Group 2 was updated to occur after approximately the first **10 patients** ~~15 patients~~ per subgroup **have progressed or have** had the opportunity to be followed for 6 months.
- Patients whose product includes fewer cells or does not meet specifications was updated such that these patients "**may be treated with MT-401**" replaced "will not be randomized"
- Inclusion Criterion #1 was updated to define eligible patients as patients who had received adjuvant therapy for AML (Group 1) at 85-**130 days** ~~90 days (±10 days)~~ post-HSCT. In addition, "and are MRD negative pre-transplant by local or central testing" was replaced with:

  - patients with CR_{MRD-} by central testing **for purposes of randomization (if optional local MRD testing performed and results are positive, the patient will be moved to subgroup D);**
  - **and are considered intermediate/high risk (e.g., pre-transplant MRD^+, intermediate/adverse risk cytogenetics or received non-myeloablative or reduced intensity conditioning)**

- The Follow-up Period was updated as follows:

  - Active Follow-up was updated to include patients who **decline any additional study visits (but patient may continue with survival follow up**)
  - Survival Follow-up was updated to include patients who **decline any additional study visits and ends with the End of Study**

- End of Study was updated such that a patient is considered to have completed the study if he/she **has completed the planned study treatment and follow-up periods of the study as per SoA, withdrawn, patient's death or lost to follow-up** replaced "if he/she has completed all phases of the study follow up"
- Analysis Populations were updated to define All enrolled patients as all patients who sign the ICF **and donor undergoes leukapheresis**
- The period and frequency of collection AE and SAE information was updated to specify that all AEs and SAEs, from Day 0 and Baseline, respectively, to the Week 12 Visit will be collected; after which, only treatment-related AEs and SAEs will be collected
- For Group 1, the log-rank test was updated to include **two** stratification factors as covariates to compare the treatment arms: **pre-transplant MRD status (MRD^+ vs. MRD^-/Unknown) and cytogenetic risk (Unfavorable vs. Other)**.
- "Second non-AML cancer reported to or on the same day as disease assessment" was removed from all censoring schemes.
- Overall survival was updated to specify that patients in **Group 2** who achieve CR_{MRD-} post-bridging therapy will be summarized separately.
- Censoring of GVHS and GRFS and PFS was updated from post-randomization and randomization for patients who remain alive and have no recorded **post-baseline** disease assessment and updated the date of censoring to the date of **first dose** for Group 2.
- GVHD and GRFS were clarified as time from randomization **for Group 1** or time **from first dose for Group 2**. In addition, GVHD events were defined as **any grade 3-4 acute GVHD or chronic GVHD requiring systemic therapy**.
- Overall response rate was updated to include treated patients who achieve best response of **MLFS** in addition to CR_{MRD-}, CR, CRi, or PR using ELN recommendations and removed "repeated MRD assessment to determine ORR."
- Group 2 **Subgroup C** was specified for efficacy and PRO analyses as applicable.
- Summary of deaths was updated as follows: All deaths within 30 and 60 days of the first dose of MT-401 (Group 2) will be summarized. **For Group 1 SOC arm, deaths within 30 days**

and 60 days of randomization date plus average time from randomization to first dose in the MT-401 arm will also be summarized as reference.

- The SoA was updated as follows:

  - Follow-up Visits 8 and 18 for biomarker samples were removed. The decision to remove these timepoints was taken after noticing that 1) the patients were not compliant as they were being inconvenienced, and 2) data gathered to date showed that these timepoints did not show any meaningful signal towards clinical safety and efficacy outcomes.
  - Footnote a and globally: Screening was updated to be performed up to **45 days** ~~28 days~~ before allogenic-HSCT
  - Footnote b: **Baseline for Group 2 patients should be performed within 14 days prior to first infusion. Disease assessment occurs at Day 80 (±5 days) post-HCST, prior to randomization for Group 1 patients** ~~(including a re-assessment of eligibility for Group 1) is to be performed within 14 days prior to group assignment~~.
  - Footnote d: Removed Week 0 from the list of visits SOC patients do not need to perform
  - Footnote e: Added that Survival Follow-up **begins after relapse/progression or active follow-up is completed and occurs** every 3 months for 3 years…
  - Footnote h: Added that on day of MT-401 administration, laboratory assessments **and/or disease assessments** are completed prior to infusion…
  - Footnote j: Added the statement that **For Group 1 and Group 2, the screening disease assessment may be performed as part of SoC (prior to consent if it was already completed).**
  - Added Footnote k: **Disease assessment at Day 0 for Group 1 only.**
  - Added Footnote m: **All AEs and SAEs, from Day 0 and Baseline, respectively, to the Week 12 Visit will be collected; after Week 12, only treatment-related AEs and SAEs will be collected.**
  - Added Footnote o: **Biomarkers at screening are required only for Group 2 patients; Screening biomarker samples are not required for Group 1 patients, but biomarkers at Week 0 are needed if visit performed.**
  - Version 6.**1 had administrative changes prior to submission to health authorities and IRBs**

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