A First-in-Human Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of MT-0169, a CD38-targeting Engineered Toxin Body (ETB), in Relapsed or Refractory Multiple Myeloma

Dickran Kazandjian, MD[1]; Scott R. Solomon, MD[2]; Moshe Y. Levy, MD[3]; James E. Hoffman, MD[1]; Admasu Mamuye, MD, MSc[4]; Soratree Charoenthongtrakul, PhD[4]; Chris Moore, PhD[4]; Silvia Ferrati, PhD[4]; Kevin Kelly, MD[5]

[1]University of Miami; Miami, FL, USA; [2]Northside Hospital Cancer Institute, Atlanta, GA, USA; [3]Baylor University Medical Center, Dallas, TX, USA; [4]Molecular Templates, Inc., Austin, TX, USA; [5]Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

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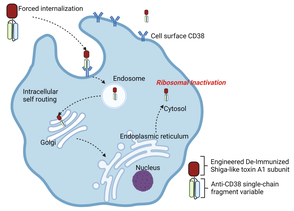
BACKGROUND: CD38 Targeted ETB with Novel Mechanisms of Action

- Engineered toxin bodies (ETBs) are comprised of a proprietarily engineered form of de-immunized Shiga-like Toxin-I A1 subunit genetically fused to antibody binding domains.
- ETBs force internalization, self-route through intracellular compartments to the cytosol, and induce potent cell-kill via the enzymatic and permanent inactivation of ribosomes.
- MT-0169 is a CD38-targeting next generation ETB with improved potency and reduced immunogenicity over first-generation ETBs targeting CD20 for hematological tumors (**Figure 1**).
- This novel mechanism of action provides potential activity of MT-0169 in patients who are refractory to antibodies or other therapies.
- MT-0169 may not be subject to resistance mechanisms that exist for other CD38-targeted therapies such as down-regulation of CD38 expression or high levels of complement inhibitory protein, CD59.

FIGURE 1: MT-0169 Mechanisms of Action



Compound Name	MT-0169
Description	Fusion Protein
Appearance	Colorless solution
Theoretical Molecular Weight	109,559 Daltons
Theoretical Isoelectric Point (pI)	8.59
Theoretical Extinction Coefficient	179040 $M^{-1}cm^{-1}$

METHODS: Phase 1 Dose Escalation and Expansion Trial

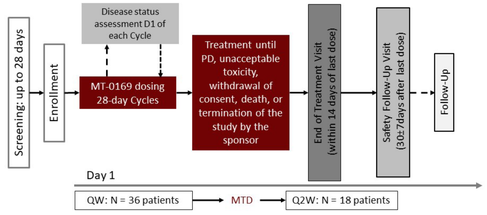
Primary Objectives: To evaluate the safety and tolerability of MT-0169 monotherapy in heavily pre-treated patients with RRMM, and establish the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D)

Secondary Objectives: Pharmacokinetics, efficacy (DoR, time to event), safety, immunogenicity, CD38 expression, and immunogenicity

Key Eligibility Criteria:
- RRMM patients ≥18 years old, refractory to at least 1 proteasome inhibitor (PI) and at least 1 immunomodulatory drug (IMiD), and at least 1 steroid.
- Patients must have received ≥3 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 therapy such as daratumumab and Isatuximab
- Patients must have normal baseline LVEF, cardiac troponin, NT-proBNP, and QTc interval.
- Patients must have a plasma cell percentage ≤ 50%

Treatment: IV infusion once weekly (QW) on Days 1, 8, 15, and 22 of each 28-day cycle

FIGURE 2: STUDY DESIGN FOR MT-0169-001



MTD: maximum tolerated dose; QW: once weekly; Q2W: once every 2 weeks; RP2D: recommended phase 2 dose; RR: relapsed or refractory; RRMM: relapsed or refractory multiple myeloma.

RESULTS: Patient Cohorts

As of 14 September 2023, 14 patients with RRMM have been treated (**Table 1**) in Part A (dose escalation): 5 patients at 50 µg/kg, 4 patients at 5µg/kg, 3 at 10µg/kg, and 2 at 15µg/kg.
- Median age: 68.5 years (range 52-87)
- 10 male (71.4%), 4 female (28.6%) patients

TABLE 1: Demographics (N = 14)

	Sex	Age	Race	ECOG	Disease
Cohort 1 (50µg/kg)	M	67	Black or AA	1	RRMM
	M	82	Not reported	1	RRMM
	F	52	White	1	RRMM
	M	73	Black or AA	1	RRMM
	F	73	White	1	RRMM
Cohort 2 (5µg/kg)	F	63	White	1	RRMM
	M	80	White	1	RRMM
	M	70	White	1	RRMM
	M	54	White	1	RRMM
Cohort 3 (10µg/kg)	M	62	White	0	RRMM
	M	55	White	0	RRMM
	M	58	White	1	RRMM
Cohort 4 (15µg/kg)	F	78	White	1	RRNHL
	M	76	White	1	RRMM

RESULTS: Safety

TABLE 2: Grade ≥ 2 Treatment Related AEs

	AE	Grade	Comment(s)
Cohort 1 (50µg/kg)	Increased AST	2	
	Myocarditis	2	SAE
	Cardiac troponin I increase	3	DLT
	Nausea	2	
	Worsening Myalgia	2	
	Worsening Anemia	2	
	Fatigue	2	
	Thrombocytopenia	2	
	Low ejection fraction	3	DLT
Cohort 2 (5µg/kg)	Neutrophil count decreased	2	
Cohort 3 (10µg/kg)	Anemia	2	
	Diarrhea	2	
Cohort 4 (15µg/kg)	*No Grade ≥ 2 Treatment Related AEs reported*		

Each AE has occurred in one (1) patient

TABLE 3: Overall Interim Summary of Treatment Related AEs

Category	Number of Subjects (%)
Safety Analysis Set	14
TEAEs[1]	13 (92.9%)
Related TEAEs[2]	7 (50.0%)
TEAEs Grade ≥ 3	5 (35.7%)
Related Serious TEAEs	2 (14.3%)
TEAEs Leading to the End of Treatment	0
Cytokine Release Syndrome (CRS)	1 (7.1%)
Infusion-Related Reaction (IRR)	0

1. Defined as an AE that occurs between the first dose and 30 days after the last dose
2. Includes the values Possibly Related, Probably Related, and Definitely Related

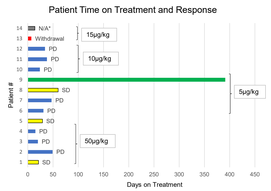
RESULTS: 14 patients treated, One Stringent Complete Response and 3 Stable Disease

TABLE 4: Prior Lines of Treatment (LoT) and Best Response to MT-0169

	Prior LoT	Best Response to MT-0169
Cohort 1 (50µg/kg)	5	PD
	9	PD
	13	PD
	6	Stable Disease
	6	Stable Disease
Cohort 2 (5µg/kg)	12	PD
	15	PD
	12	Stable Disease
	5	Stringent Complete Response
Cohort 3 (10µg/kg)	10	PD
	8	PD
	7	PD
Cohort 4 (15µg/kg)	7	PD
	7	N/A

- Heavily pre-treated population of patients
- Median prior lines of treatment: 7.5 (Range 5-15)

FIGURE 3: Response and Time on Treatment



Median number of cycles: 1.0 (range 1-14)

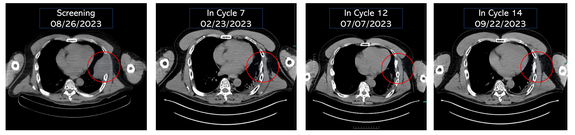
**Investigator assessment not currently available.*

Results: stringent Complete Response in 1 Patient with extramedullary disease

- Stringent Complete Response (sCR) in a 54-year-old male patient with RRMM of IgA lambda type diagnosed in July 2015.
- Patient had 5 previous LoT including SCT, Dara/Pom/Dex for about 2 years, and Carfilzomib/Pom/Dex for > 3 years and BCMA/CD3 BiTE (~4 mo)
- Patient had a left 5th rib plasmacytoma and minimal bone marrow disease.
- Palliative radiation therapy given 2 weeks before C1D1 to the left lateral fifth rib lesion.

Test	Screening	C1D1	C2D1	C3D1	C4-C12	C13D1
Serum M protein	Measurable	Detectable	None	None	None	None
Serum immunofixation	Positive - IgA lambda	Positive	Positive	Negative	Negative	Negative
Serum FLC ratio (k/l) (0.26 to 1.65)	<0.26	ND	ND	Normal	Normal	Normal
Serum IgA (mg/dL)	621.39	246.24	17.1	2.67	→	34.46
Hemoglobin (g/dL)	10.1	10.1	13.3	14.3	14 to 15	14.1

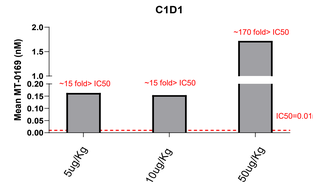
FIGURE 4: Baseline and Follow-up PET/CT scans in a patient with sCR



- The large left fifth rib plasmacytoma (red circle) that was present at Screening (baseline) was treated with palliative radiotherapy 2 weeks prior to first dose of MT-0169.
- The plasmacytoma disappeared completely after 3 cycles of treatment and that was maintained through 14 cycles.
- Patient remains on MT-0169 and is currently in Cycle 15.

RESULTS: Pharmacokinetics

FIGURE 5: Approximately dose proportional C_{max}



The observed clinical C_{max} at 50 µg/kg (N = 5) was a mean of 1.72 nM (190 ng/mL), ~170-fold greater than the IC_{50} demonstrated by the in vitro cytotoxicity studies in human multiple myeloma cells (MOLP-8, NCI-H929, ANBL-6 and RPMI-8226, IC_{50}= 0.00034 to 0.01 nM)

15 µg/Kg PK analysis is ongoing.

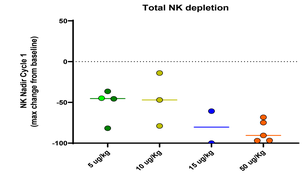
TABLE 4: Pharmacokinetic Parameters

Dose (µg/Kg)	N	C_{max} (nM)	Folds above IC_{50}	$t_{1/2}$ (hr)
5	3	0.16	16	NC
10	2	0.15	15	NC
50	5	1.72	172	1

Patients dosed at 5 and 10 µg/kg. Serum samples were collected for PK analysis but had limited quantifiable drug concentrations on Cycle 1 Day 1 due to the lower dose levels and the LLOQ of the assay limiting PK parameters calculations.

RESULTS: Pharmacodynamics

FIGURE 6: Dose Proportional Pharmacodynamic Response



- Profound depletion of the peripheral surrogate biomarker (NK cells, a majority of which expresses CD-38).
- Based on surrogate PD marker, expected efficient targeting of CD-38 positive MM cells

Note: highlighted in green the patient with stringent CR

CONCLUSIONS

- MT-0169 is a unique ETB with a novel and potent MOA targeting CD38 in hematological cancers.
- A stringent Complete Response (sCR) has been observed in a patient with extramedullary disease
- MT-0169 has an acceptable safety profile with 2 DLTs at 50 µg/kg (a Grade 2 myocarditis and a Grade 3 reduced ejection fraction) both asymptomatic. No similar adverse event observed at lower doses of 5, 10, and 15 µg/kg
- Enrollment is ongoing at 15 µg/kg at multiple US sites

DISCLOSURES

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Please contact Admasu Mamuye at admasu.mamuye@mtem.com for questions or comments.

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