A phase 1 study of the novel immunotoxin MT-5111 in patients with HER2+ tumors: interim results

MOLECULAR TEMPLATES

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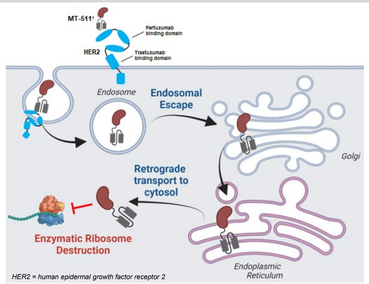
BACKGROUND: Novel De-immunized Direct Cell Killing

- **MT-5111** is a first in class de-immunized engineered toxin body (ETB) targeting HER2 for treatment of solid tumors. By virtue of the novel mechanism of action (MoA), MT-5111 may not be subject to resistance mechanisms that exist for tyrosine kinase inhibitors, antibody drug conjugates (ADCs), or antibody modalities and thus, demonstrate efficacy in patients resistant to other HER2-targeting agents[1,2].
- MT-5111 binds an epitope on HER2, distinct from trastuzumab or pertuzumab, that may provide for combination potential with other HER2 targeting agents.
- MT-5111 is a 55 kilodalton protein and may have improved tumor penetration capability in the solid tumor settings as compared to monoclonal antibodies.

TABLE 1: ETBs vs. ADCs - Biology and MoAs

	ETBs	Antibody Drug Conjugates (ADC)
Amenable Targets	Internalizing or non-internalizing	Targets must be readily internalized
Intracellular Routing	Endosomal escape and self-routing to cytosol	No escape from endosome, shuttle to lysosome
MoA	Enzymatic ribosomal inactivation	Chemo
Cytosolic/ER Delivery	Yes	No

FIGURE 1: Mechanism of Action of MT-5111

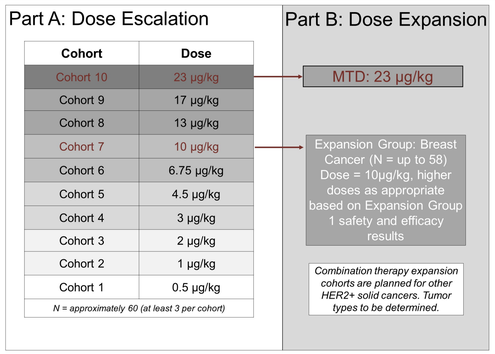


- ETBs are comprised of a proprietarily engineered form of Shiga-like Toxin A subunit (SLT-A) genetically fused to antibody-like binding domains (**Figure 1**)
- ETBs work through **novel MoAs** and are capable of forcing internalization, self-routing through intracellular compartments to the cytosol, and inducing potent cell-kill via the enzymatic and permanent inactivation of ribosomes

METHODS: Novel De-immunized Direct Cell Killing ETB

Primary objective:	To determine the maximum tolerated dose (MTD) or Recommended Phase 2 Dose (RP2D) of MT-5111 monotherapy in patients with previously treated advanced HER2+ solid tumors
Secondary objectives:	Pharmacokinetics (PK), efficacy, and immunogenicity
Part A (dose-escalation):	Patients with HER2+ tumors enroll into sequential dose cohorts: Cohorts 1 to 10 at doses of 0.5, 1, 2, 3, 4.5, 6.75, 10,13, 17, and 23 µg/kg/dose have been completed. One Dose Limiting Toxicity (DLT) of reversible Grade 3 acneiform rash was observed at 23 µg/kg/dose. (**Figure 2, Part A**).
Part B (dose-expansion):	Patients with HER2+ breast cancer will enroll to collect safety and efficacy data (**Figure 2, Part B**). Part B1 is recruiting a minimum of 6 evaluable patients at the 10 µg/kg/dose, followed by planned enrollment of ≥ 6 breast cancer patients to higher doses cleared during Part A. Additional dose expansion cohorts will open after a protocol amendment.
	Prior exposure to anthracyclines is allowed in Part B

FIGURE 2: MT-5111-001 Study Design



All patients receive MT-5111 weekly as 30 min IV infusions on Days 1, 8, and 15 of each 21-day treatment cycle (C) until disease progression (PD), unacceptable toxicity, death, or withdrawn consent (NCT04029922).

RESULTS: 48 Patients Enrolled To Date

Per the most recent data cut on 07 Oct 2022, 48 patients with HER2 positive advanced solid tumors have been treated with MT-5111. Forty-two patients were enrolled in Part A (dose escalation) and 6 patients in Part B1 (Breast Cancer expansion) (**Table 2**).

TABLE 2: Baseline Demographics and Tumor Characteristics Overall (N = 48)

	Part A (Dose-Escalation)	Part B1 (Breast Cancer expansion)
N (patients treated)	42	6
Female, n (%)	26 (62%)	6 (100%)
Age, Median (range)	67 (34-78)	51.5 (38-71)
ECOG PS		
ECOG 0, n (%)	19 (45%)	2 (33%)
ECOG 1, n (%)	23 (55%)	4 (67%)
Prior anti-Cancer Therapy		
Number of Lines of Therapy (LoT)# median (range)	4 (1-9)	8 (4-18)
Number of LoT containing HER2-targeted therapy, median (range)	3 (1-9)	6 (4-18)
Received T-DXd, n (%)	13 (30%)	3 (50%)
HER2 IHC Status		
HER2 2+, n (%)	15 (36%)	2 (33%)
HER2 3+, n (%)	27 (64%)	4 (67%)
Primary Tumor Locations		
Breast Cancer, n (%)	11 (26%)	6 (100%)
Biliary Tract*, n (%)	6 (14%)	NA
Gastric/GEJ, n (%)	11 (26%)	NA
Other Solid^, n (%)	14 (33%)	NA

ECOG PS = Eastern Cooperative Oncology Group performance status; IHC = immunohistochemistry; N/A = not applicable; *Biliary tract cancers include gallbladder cancer and cholangiocarcinoma; ^Other solid cancers include colon, ampullary, pancreas, lung, rectal, and uterine cancers. # LoT= total number of prior anticancer therapy received in early and advanced disease setting. T-DXd= trastuzumab deruxtecan.

RESULTS: Safety

TABLE 3: Grade ≥ 2 and Important Grade 1 Treatment-Related Adverse Events

Dose (µg/kg)	# of Patients	Adverse Events, Grade
23	1	Acneiform rash, G3 (DLT)
	7	Troponin increase, G1 *
	1	LFT Abnormal, G4 (SAE, alternative causality of disease progression in liver)
17	1	Rash, G2 Pruritus, G2
	2	Fatigue, G2
10	1	Lymphopenia, G2
	1	Rash maculopapular, G2 Pruritus, G2
	2	Troponin increase, G1
	1	Fatigue, G2
	1	Rash maculopapular, G1
	1	Chills, G2
	1	Vomiting, G2
	1	Nausea, G2
6.75	1	Back pain, G2
	1	Troponin increase, G1 (SAE)
	2	Fatigue, G2
	1	Nausea, G2
	1	Vomiting, G2
4.5	1	IRR, G1 (2 episodes in one patient, 3 weeks apart)
	1	Hypoxia, G3
	1	Dyspnea, G3 (SAE, alternative causality of disease progression)
	1	Rash, G2
3.0	1	IRR, G2
	1	Hypotension, G2
1.0	1	Anemia, G2
0.5	1	AST increase, G2

*4 reported as AEs, remaining 3 are laboratory abnormalities.

- **SAE**: 1 patient experienced a G1 troponin elevation possibly related to study drug and was hospitalized for observation qualifying the event as an SAE. No clinical sequelae were noted in this patient.
- **1 DLT**: G3 acneiform rash that was controlled with topical steroid treatment.

PHARMACOKINETICS

- Following 0.5 hour IV infusion, MT-5111 plasma exposure increased with dose, with Cmax increasing dose proportionally from 6.75 ug/kg to 17 ug/kg (**Table 4**). Elimination was multiphasic. The variability and low C_{max} values at the lower doses may be due to the binding of MT-5111 by soluble HER2 receptors in circulation.
- C_{max} in C1D1 was 22-170 fold above IC_{50} (established *in vitro* in HER2 expressing cells) at doses between 6.75 and 23 µg/kg (**Figure 4**).
- Like other approved immunotoxins, anti-drug antibody (ADA) develops in most of the patients by C2D1 (first assessment after treatment initiation).

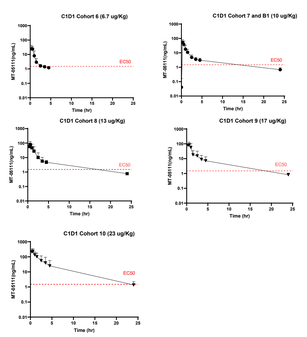
TABLE 4: C1D1 PK PARAMETERS

Dose (ug/kg)	# of Patients	C_{max} (ng/mL)	$T_{1/2}$ (hr)
0.5	4	0.71(±0.28)	NC#
1.0	3	0.62(±0.59)	NC#
2.0	3	8.52(±6.68)	7.67(±3.9)*
3.0	3	11.5(±6.9)	6.9(±1.2)*
4.5	3	10.2(±5.2)	NC#
6.75	5	32.8(±11.5)	5.2(±0.5)*
10	12	55.7(±23.7)	11.7(±5.5)**
13	3	80.8(±46.2)	NC#
17	4	93.44(±27.2)	9.0(±2.6)*
23	8	255(±98.1)**	6.46^

 # Non calculable
***Data available for 2 patients**
**** Data available for 5 patients**
^ data available for 1
C_{max} = maximum serum concentration; $T_{1/2}$ = terminal half life
C_{max} and $t_{1/2}$ values are mean (± SD)

Note: One subject (1005-002) was excluded due to elevated pre-dose concentrations, two subjects (1001-002 and 1003-001) were excluded due to less than 3 quantifiable samples.

FIGURE 4: C1D1 PK PROFILES



EFFICACY: Evaluable Metastatic Breast Cancer Patients

Metastatic breast cancer expansion cohort with 5 evaluable patients treated at 10 µg/kg (Table 5)

- 6-month disease control rate of 60%
- Two of these patients are still on treatment
  - One has completed 13 cycles
  - One has a 14% reduction in tumor size

TABLE 5: Responses Per RECIST 1.1 in 5 Patients

HER2 Status	Last Dose Received	Best Response	Prior Rx (# of lines)	Prior HER2-targeting Rx (duration)
IHC 3+	C2D15 (5wk)	PD	18	TRA, LAP, PER, T-DM1, TUC, MARG, T-DXd (10mo)
IHC 3+	C2D15 (5wk)	PD	4	PER (7mo), TRA (7mo), T-DM1
IHC 3+	C8D15 (24wk) Off-Rx	SD (+3.4%)	9	TRA, PER, TUC, DHES0815A, T-DXd (3mo)
IHC 3+	C14D15 (40wk) ON TX	SD (+5.7%)	4	TRA, PER, T-DM1 (8mo)
IHC 2+	C8D15 (23wk) ON TX	SD (-14%)	10	TRA, PER, T-DM1 (5mo), T-DXd (21mo), TUC (10mo)

Abbreviations: TRA = Trastuzumab; LAP = Lapatinib; PER = Pertuzumab; T-DM1 = Trastuzumab emtansine; MARG = Margetuximab; T-DXd = trastuzumab deruxtecan; TUC = Tucatinib; DHES0815A = Investigational HER2-directed ADC

One Breast Cancer Patient at 10µg/kg has a 14% Reduction in Tumor Size

- Female patient diagnosed with metastatic breast cancer in October 2015.
- At enrollment, diseased assessed as HER2 IHC 2+, ISH amplified, Stage IV, moderately differentiated invasive ductal carcinoma of the right breast with multiple metastases to the lung and mediastinal lymphadenopathy including left infra-hilar, subcarinal and right paratracheal nodes.
- **10 prior lines of systemic therapy**
  - Multiple rounds of HER2-targeted therapy including trastuzumab, pertuzumab, trastuzumab emtansine, lapatinib, trastuzumab deruxtecan, and tucatinib.
- **MT-5111 treatment course**:
  - Receiving 10 µg/kg IV infusion QW
  - C1D1 on 01 June 22. Received C7D1 on 05 Oct 22.
  - Developed maculopapular rash (Grade 2) with pruritus (Grade 2) 2 days after dosing
  - Rash needed treatment with high dose systemic steroids. Both rash and pruritus improved to Grade 1 after 8-9 weeks.

Tumor Reduction in Pre-treated Breast Cancer Patient with MT-5111

Response to MT-5111 treatment (Figure 5A, 5B)

- The total target tumor size has progressively decreased by 14% after 6 cycles of treatment.
- *The two nodal lesions* (i.e., left infra-hilar node and subcarinal node) have significantly decreased in size (approximately 43%).
- *The non-nodal lesions* (i.e., necrotic LUL and RLL masses) have remained stable in size. Per the treating physician, these lesions grew in the past and the patient had pulmonary symptoms.

Figure 5A:Left infra-hilar node

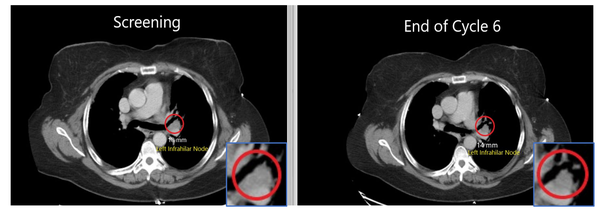
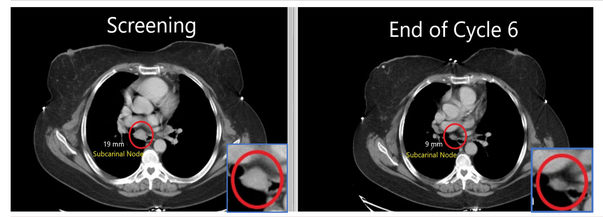


Figure 5B: Subcarinal node



CONCLUSIONS

- **MT-5111 is a HER2-targeted ETB with a novel MoA and is being studied in patients with previously treated, advanced HER2 positive solid tumors.**
  - **In Phase 1, MTD has been declared as 23 µg/kg**
- **In this Phase 1b trial, 1 DLT of Grade 3 skin rash has been identified at 23 µg/kg (MTD); several Grade 1 troponin increases that were asymptomatic and without EKG or LVEF changes were noted, which contributed to the decision to declare the MTD.**
- **The best response per RECIST thus far was stable disease, including one patient with a 14% reduction in index lesions (comprised of a 43% reduction in lymphadenopathy and stabilized pulmonary lesions that had been previously enlarging)**
- **Reduction in size of metastatic lymph nodes demonstrates that ETBs can penetrate solid tumors**
- **Among the 12 patients treated at 10 µg/kg and higher, 4 received MT-5111 for at least 6 cycles of treatment with one patient actively on treatment through Cycle 13, demonstrating no cumulative toxicity.**
  - **Three breast cancer patients on treatment through 8 cycles at a dose of 10 µg/kg**
- **Dose proportionality of MT-5111 exposure occurred consistently between 6.75-17 µg/kg.**
- **First breast cancer expansion cohort is completing enrollment at 10 µg/kg and will open enrollment to a second cohort at a higher dose.**
- **Combination expansion cohorts are planned for 1 or more HER2+ solid cancers.**

Disclosures

This study is sponsored and funded by Molecular Templates, Inc.

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

References

1. Investigator's Brochure: MT-5111 (2020). Molecular Templates. Austin, TX.
2. Hubbard JM, Van Tine BA, Mita MM, Barve MA, Hamilton EP, Brenner AJ, et al. (2022). A phase 1 study of the novel immunotoxin MT-5111 in patients with HER2+tumors: Interim results. *J Clin Oncol*: 40:4_suppl, 297.

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