Abstract ID: 352662

A Phase 1 Study of the Novel Immunotoxin MT-5111 in Patients with HER2+ Tumors: Interim Results

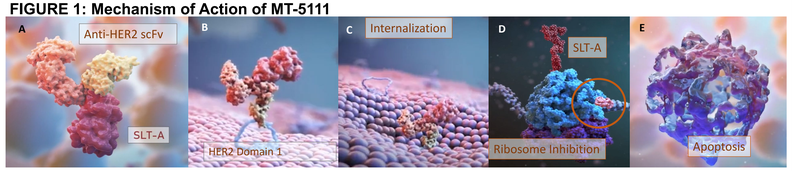
Joleen M. Hubbard, MD[1]; Brian A. Van Tine, MD, PhD[2]; Monica M. Mita, MD[3]; Minal A. Barve, MD[4]; Erika P. Hamilton, MD[5]; Andrew J. Brenner, MD, PhD[6]; Frances Valdes, MD[7]; Daniel Ahn, DO[8]; Jason Starr, DO[9]; Joshua Pelham[10]; Thomas Strack, MD[10]; Amy Yuet, PhD[11]; Angela Georgy, PharmD[10];Taunya Smith, MPH[12]; Andrés Machado Sandri, MD[13]; Zev A. Wainberg, MD[14]

[1]Mayo Clinic, Rochester, MN, USA; [2]Washington University School of Medicine, Saint Louis, MO, USA; [3]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [4]Mary Crowley Cancer Research Center, Dallas, TX; [5]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [6]University of Texas Health San Antonio Cancer Center, San Antonio, TX, USA; [7]University of Miami, Miami, FL, USA; [8]Mayo Clinic Arizona, Phoenix, AZ, USA; [9]Mayo Clinic, Jacksonville, FL, USA; [10]Molecular Templates, Inc., Jersey City, NJ, USA; [11]Molecular Templates, Inc., Austin, TX, USA; [12]Translational Research in Oncology, Edmonton, Alberta, Canada; [13]Translational Research in Oncology, Montevideo, Uruguay; [14]UCLA David Geffen School of Medicine, Los Angeles, CA, USA

BACKGROUND: Novel De-Immunized Direct Cell-Killing ETB

- Engineered toxin bodies (ETBs) are composed of a de-immunized Shiga-like Toxin A subunit genetically fused to an antibody-like binding domain (scFv) (**Figure 1A**)
- MT-5111 binds to an epitope distinct from trastuzumab and pertuzumab, offering potential combination strategies with other HER2-targeting agents (**Figure 1B**)
- ETBs can force receptor internalization (**Figure 1C**) to induce potent, direct cell killing via enzymatic and permanent inactivation of ribosomes(**Figure 1D**) and apoptosis (**Figure 1E**), and may not be subject to resistance mechanisms of other therapeutics

FIGURE 1: Mechanism of Action of MT-5111



HER2 = human epidermal growth factor receptor 2; scFv= single-chain variable fragment; SLTA = (de-immunized) Shiga-like Toxin A subunit

- MT-5111 is a 55 kDa ETB targeting HER2 that may demonstrate efficacy in patients resistant to other HER2-targeting agents, as its mechanism of action induces direct cell death via enzymatic and permanent ribosome destruction and does not rely on inhibition of kinase signaling or cytoskeletal/DNA damage.

METHODS: Ongoing Phase 1 Dose Escalation, Expansion Started without DLTs

- The primary objective of this phase 1 study is to determine the maximum tolerated dose (MTD) or Right Phase 2 Dose (RP2D) of MT-5111 monotherapy in adult patients with advanced HER2+ solid tumors
  - Secondary objectives include pharmacokinetics (PK), efficacy, and immunogenicity
- Patients with HER2+ tumors are enrolled into the dose-escalation part A of the study into sequential dose cohorts. Dose cohorts 0.5, 1, 2, 3, 4.5, 6.75, and 10 µg/kg/dose have been completed without DLTs, **cohort 8** (13 µg/kg) is currently recruiting (**Figure 2A**). Prior use of anthracyclines is not allowed in Part A.
- Three dose-expansion groups in Part B of the study are to collect additional safety and efficacy data for HER2+ breast cancer, gastroesophageal junction adenocarcinoma (GEA), and other HER2+ tumors, respectively (**Figure 2B**). Prior exposure to anthracyclines is allowed in Part B; the breast cancer expansion group B1 has started to recruit patients at the 10 µg/kg/dose. The other 2 expansion groups will follow once the MTD has been identified.

FIGURE 2A: Part A Study Design – Dose Escalation

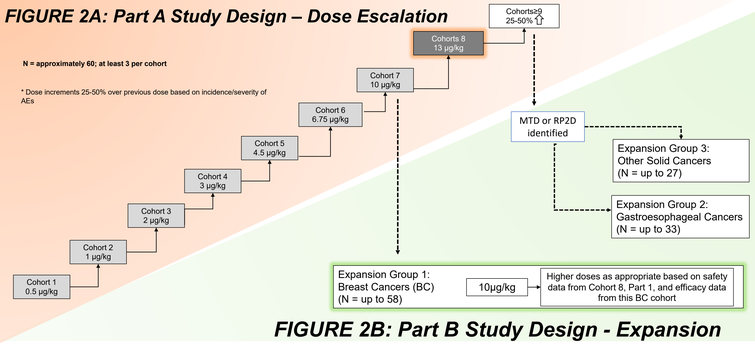


FIGURE 2B: Part B Study Design - Expansion

Treatment with MT-5111: 30 min IV infusion on Days 1, 8, and 15 of each 21-day cycle

- All patients receive MT-5111 weekly as 30min IV infusions in each 21-day treatment cycle (C) until disease progression (PD), unacceptable toxicity, death, or withdrawn consent (NCT04029922)

RESULTS: 30 Heavily Pretreated Patients on Treatment,16 GI tumors

- Per the data cut in January 2022, which includes preliminary data, 29 patients in 8 cohorts were treated in Part A (dose escalation) and 1 patient in 1 cohort in Part B (**Table 1**)

TABLE 1: Baseline Demographics and Tumor Characteristics Overall (N = 30)

		Part A									Part B1
Dose (µg/kg)		0.5	1.0	2.0	3.0	4.5	6.75	10.0	13.0*	***Total***	10.0
Number of patients treated		4	3	3	3	3	5	6	2	***29***	1
Male, n (%)		1 (25)	1 (33.3)	0 (0)	1 (33.3)	3 (100)	2 (40)	1 (17)	1 (50)	***10 (34.5)***	0
Female, n (%)		3 (75)	2 (66.7)	3 (100)	2 (66.7)	0 (0)	3 (60)	5 (83)	1 (50)	***19 (65.5)***	1(100)
Age, mean years (range)		69 (64-78)	49 (34-68)	69 (65-74)	63 (60-67)	62 (48-70)	67 (62-71)	64 (49-78)	67.5 (62-73)	***67 (34-78)***	71
ECOG PS, grade, n (%)											
0		2 (50)	2 (67)	1 (33)	1 (33)	0 (0)	1 (20)	2 (33)	2 (100)	***11***	0
1		2 (50)	1 (33)	2 (67)	2 (67)	3 (100)	4 (80)	4 (67)	0 (0)	***18***	1
Prior lines of therapy											
Systemic therapies, median (range)		4.5 (3-8)	6 (3-7)	3 (3-6)	3 (1-6)	3 (2-4)	4 (2-8)	3.5 (2-6)	4.5 (4-5)	***4 (1-8)***	18
HER2 therapies, median		2.5	2	3	1	0	3	2	2.5	***2 (0-6)***	18
HER2 Expression Status per IHC											
HER 2 **2+**	No of patients	1	1	2	1	0	4	3	1	***14***	0
	Concurrent ISH if available	4-6x	>6x	N/A	N/A	0	2-4x (n=1) >6x (n=2) N/A (n=1)	<2x (n=1) N/A (n=2)	N/A	***<2 (n=1) 2-4(n=1) 4-6 (n=1) >6 (n=3)***	0
HER2 **3+**	No of patients	3	2	1	2	3	1	3	1	***15***	1
Primary tumor locations, n (%)											
Biliary tract carcinomas		2	1	2	0	1	0	0	0	***6***	0
Colorectal		0	0	0	1	0	0	2	0	***3***	0
Pancreatic carcinomas		0	0	0	0	2	0	0	0	***2***	0
Gastric/gastroesophageal junction		0	1	0	0	0	2	1	0	***4***	0
Breast cancer		2	1	1	2	0	1	2	1	***10***	1
NSCLC		0	0	0	0	0	2	0	1	***3***	0
Uterine		0	0	0	0	0	0	1	0	***1***	0

ECOG PS = Eastern Cooperative Oncology Group performance status; IHC = immunohistochemistry; N/A = not available

* 13 µ/kg cohort still recruiting

FIGURE 3: Cycle 1 Day 1 Pharmacokinetics

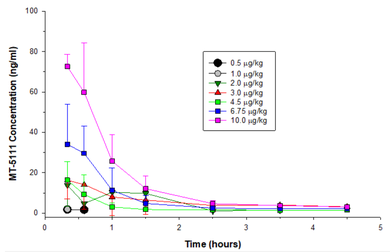


TABLE 2: Cycle Day 1 Pharmacokinetics

Dose (µg/kg)	N	C_{max} (ng/mL)	C_{max}/D	AUC_{last} (hr× ng/ml)	AUC_{last}/D
0.5	4	1.9	3.8	--	--
1.0	2*	1.8	1.8	--	--
2.0	2^	13.8	6.9	16.5	8.2
3.0	3	17.4	5.8	24.8	8.3
4.5	3	16.3	3.6	13.4	3.0
6.75	5	43.2	6.4	33.7	5.0
10.0	7	75.7	7.6	71.4	7.1

*one patient's drug concentrations on C1D1 were <LLQ

^One patient's pK data on C1D1 were excluded due to pre-dose sample values not being <LLQ

AUC_{last} = area under the curve up to the last measurable MT-5111 concentration; C1D1=Cycle Day 1; C_{max} = maximum serum concentration

Safety and Efficacy: No DLTs to-date, no innate immune response related AEs, 2 mild CV-related AEs; several patients with SD (3 in 10 µg cohort)

- Treatment-related adverse events (AEs) occurred in 16 (53%) of patients
- The most common treatment-related AEs were fatigue (n = 8, 12%), increased AST (n = 6, 9%), anemia, fever, headache and nausea (n = 4, 6%).
- **No Grade 4 or Grade 5 treatment-related AEs occurred**
- One patient with biliary cancer and concurrent lymphangitic carcinomatosis and *H. influenzae* infection (4.5 µg/kg) had a possibly (per principal investigator) related Grade 3 serious AE (SAE) of dyspnea, which resolved 9 days after the start of the SAE
- All other treatment-related AEs were ≤ Grade 2
- Two patients experienced troponin increase:
  - One patient with GEA (6.75 µg/kg) had a Grade 1 transient troponin increase (Troponin I); the patient was hospitalized for observation/monitoring (qualifying the events as an SAE); the patient had no clinical symptoms or ECG/ECHO abnormalities; the troponin returned to normal range within approximately 24hours without triggering a DLT.
  - One patient with uterine carcinosarcoma (10 µg/kg) experienced a Grade 1 troponin level increase (Troponin I or T) without any concurrent cardiac symptoms or ECG/ECHO changes; elevations occurred with the first administration of study drug.
- There were no other clinically significant changes in cardiac biomarkers (troponin, ECG, left ventricular ejection fraction), nor were there any cases of capillary leak syndrome
- No myocarditis or cardiomyopathy DLTs reported
- Two patients (3 µg/kg and 4.5 µg/kg) had reversible Grade 2 infusion-related reactions (IRRs) which manifested with typical symptoms (rigor, low grade pyrexia, myalgia) in one case (4.5 µg/kg) and pruritis, facial swelling, and hypotension in other case (3 µg/kg) within 1hr of drug infusion; in both instances, administration of systemic antihistamines, NSAIDs, or steroids resulted in resolution of IRRs.
- Best response to date has been stable disease (SD) in 5 patients; one of these had SD for 12 weeks (4.5 µg/kg, pancreatic cancer), and one patient had SD for 30 weeks (1 µg/kg, breast cancer).
- The 10 µg/kg dose cohort has completed evaluation with no DLTs and the next cohort (Cohort 8) is open for recruitment. MTD has not yet been reached.
- An expansion group for patients with breast cancer is open for enrollment.

Pharmacokinetics: Dose-Responsive Effect Observed

- **AUC_{last} and C_{max} data matched PK simulations based on non-human primate studies**
- C_{max} data at 10 µg/kg indicated that current in-patient exposure was at least 5 times the IC_{50} values of a high HER2-expressing gastric cancer cell line (NCI-N87: 3.8 ng/mL) and approached the IC_{50} of a moderately HER2-expressing liver cancer cell line (CFPAC-1: 88.6 ng/ml).
- **Thus a dose of at least 10 µg/kg may be required to achieve effective exposure.**
- C_{max} and AUC_{last} for the 10 µg/kg dose cohort (n=6) are approximately dose proportional compared to the 6.75 µg/kg dose cohort (n=5).
- The pharmacokinetic-based exposure was within the expected range at Cycle 1 Day 1 (**Figure 3, Table 3**).

CONCLUSIONS

•MT-5111 was well tolerated with no clinically significant immuno- or cardiotoxicity
•Dose escalation is ongoing and at a dose level of 13 µg/kg, expected to be required for efficacious exposure

ACKNOWLEDGEMENTS & DISCLOSURES

This study is sponsored by Molecular Templates, Inc. Editorial support was provided by Rebecca Miles, PhD, of MedValScientific Information Services, LLC (Princeton, NJ) and was funded by Molecular Templates.

JMH: Bayer, Merck, Boston Biomedical, TreosBio, Taiho, SenhwaPharmaceuticals, Bayer, Incyte, TriOncology, Seattle Genetics, Hutchison MediPharma **BAVT:**AdaptimmuneLimited, ApexigenINc, Cytokinetics Inc., DiiachiSankyo, DeciphereParmaceuticals, Epizyme, GSK, ADRx, Bayer (Consulting). Novartis, GSK, Adaptimune, Lilly. Health Advances, Intellisphere(Lecturres/Speaker). Polaris (Board Member/Leadership). Patent on the use of ME1 as a biomarker. Patent on ALEXT3102. AdvenchenLaboratories (Travel for research purposes). **MMM:**Seattle Genetics. **MAB:**None. **EPH:**Research funding (payable to institution only, no personal funds) from: OncoMed, Genentech/Roche, Zymeworks, Rgenix, ArQule, Clovis, Silverback Therapeutics, Millenium, AcertaPharma, SermonixPharmaceuticals, Torque, Black Diamond, Karyopharm, Infinity Pharmaceuticals, Curis, Syndax, Novartis, Boehringer Ingelheim, Immunomedics, FujiFilm, Taiho, Deciphera, Fochon, Molecular Templates, OnconovaTherapeutics, Dana Farber Cancer Hospital, Hutchinson MediPharma, Medimmune, SeaGen, Puma Biotechnology, Compugen, TapImmune, Lilly, Pfizer, H3 Biomedicine, Takeda, Merus, Regeneron, Arvinas, StemCentRx, Verastem, eFFECTORTherapeutics, CytomX, InventisBio, Lycera, Mersana, Radius Health, Abbvie, Nucana, Leap Therapeutics, Zenith Epigenetics, Harpoon, Orinove, AstraZeneca, Tesaro, Macrogenics, EMD Serono, Daiichi Sankyo, Syros, Sutro, G1 Therapeutics, Merck, PharmaMar, Olema, Polyphor, Immunogen, Plexxicon, Amgen, AkesobioAustralia, Shattuck Labs. Consulting/advisory role payments (to institution only, no personal funds accepted) from: Genentech/Roche, Boehringer Ingelheim, Novartis, Dantari, Lilly, Merck, Puma Biotechnology, Silverback Therapeutics, CytomX, Pfizer, Mersana, Black Diamond, H3 Biomedicine, Daiichi Sankyo, AstraZeneca, Arvinas, DecipheraPharmaceuticals, Eisai, Seagen. **AJB:**NanoTX; Travel accommodations; Vascular Biogenics.; Threshold.; miRNA. **FV:**Merck, Roche/Genentech. **DA:**Exelixis, Genentech, Eisai, Astra Zeneca, Bayer. **JS:**Pfizer, Natera, Ipsen, Pfizer, Rafael, Natera, Ipsen, Rafael, Incyte, Aprea, Xencor, Cardiff, Vedanta, Molecular Templates, Macrogenics, Merus, Daiichi **JP:**Salary: Molecular Templates. **TS:**Salary: Molecular Templates. **TS:** None **AMS:**None. **ZAW:**Merck, Bayer, Lilly, Five Prime, Daiichi, Molecular Templates, Inc.

Please contact Thomas Strack at thomas.strack@mtem.com for questions or comments.

Presented at the American Society of Clinical Oncology – Gastrointestinal Cancer Symposium; San Francisco, CA; January 20-22, 2022