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

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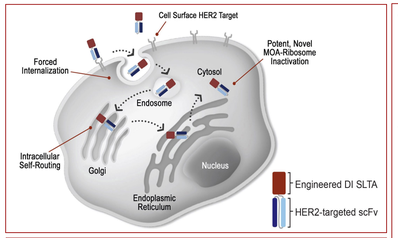
BACKGROUND: Novel De-immunized Direct Cell Killing ETB

- **MT-5111** is a first in class de-immunized ETB targeting HER2 for treatment of solid tumors. By virtue of the novel MoA, MT-5111 may not be subject to resistance mechanisms that exist for TKI, ADC, 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.

FIGURE 1: Mechanism of Action of MT-5111



DI SLTA = de-immunized Shiga-like Toxin A subunit; HER2 = human epidermal growth factor receptor 2; MOA = mechanism of action; scFv = single-chain variable fragment.

- **Engineered toxin bodies** (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 mechanisms of action** (MoA) 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

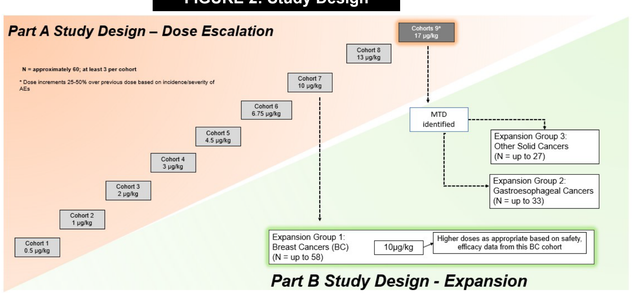
METHODS: Novel De-immunized Direct Cell Killing ETB

•**The primary objective** of this Phase 1a/b study is to determine the maximum tolerated dose (MTD) or Recommended Phase 2 Dose (RP2D) of MT-5111 monotherapy in adult patients with previously treated advanced HER2+ solid tumors. **Secondary objectives** include pharmacokinetics (PK), efficacy, and immunogenicity.

•In Part A (dose-escalation) of the study, patients with HER2+ tumors are enrolled into sequential dose cohorts. Cohorts 1 to 8 at doses of 0.5, 1, 2, 3, 4.5, 6.75, 10 and 13 µg/kg/dose have been completed without Dose Limiting Toxicities (DLTs). Cohort 9 (17 µg/kg) is currently recruiting (**Figure 2, Part A**). Prior use of anthracyclines is not allowed in Part A.

•In Part B (dose-expansion) of the study, three separate groups of patients with HER2+ tumors are enrolled to collect additional safety and efficacy data for HER2+ breast cancer, gastric or gastroesophageal junction adenocarcinoma (GEA), and other HER2+ tumors, respectively (**Figure 2, 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. Prior exposure to anthracyclines is allowed in Part B.

FIGURE 2: Study Design



All patients receive MT-5111 weekly as 30min 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: 35 Patients

Per the data cut on 18 April 2022, which includes preliminary data, 35 patients with various types of HER2 positive advanced solid tumors have been treated with MT-5111. Thirty-one patients were enrolled in Part A (dose escalation) and 4 patients in Part B1 (Breast Cancer expansion) (**Table 1**).

TABLE 1: Baseline Demographics and Tumor Characteristics Overall (N = 35)

		Part A (Dose-escalation)	Part B1 (Breast Cancer expansion)
N (patients treated)		31	4
Female, n (%)		21 (67.7)	4 (100)
Age, Median (range)		67 (34-78)	53 (38-71)
ECOG PS			
	ECOG 0, n (%)	12 (38.7)	2 (50)
	ECOG 1, n (%)	19 (61.3)	2 (50)
Prior Lines of Therapy			
	Systemic Therapy, median (range)	4 (1-9)	6.5 (4-18)
	HER2 targeted therapy, median (range)	2 (0-6)	4 (3-11)
HER2 IHC Status			
	HER2 2+, n (%)	12 (38.7)	0 (0)
	HER2 3+, n (%)	19 (61.3)	4 (100)
Primary Tumor Locations			
	Breast Cancer, n (%)	11 (35.5%)	4 (100%)
	Biliary Tract*, n (%)	6 (19.4%)	NA
	Gastric/GEJ, n (%)	5 (16.1%)	NA
	Other Solid^, n (%)	9 (29%)	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.

SAFETY: No DLTs, 3 mild CV-related AEs, no innate immune response related AEs to date

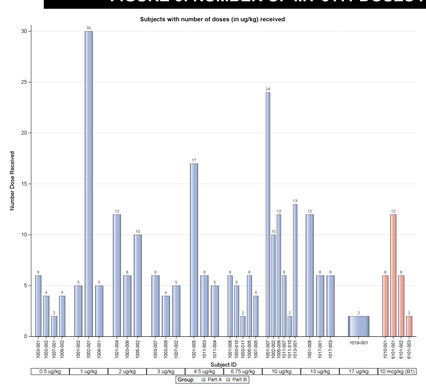
•No Grade 4 or 5 treatment-emergent adverse events (AEs) or DLTs occurred. Treatment-related AEs occurred in 19 (54%) patients, most commonly Grade 1 or 2 fatigue (n = 13, 37%).

•Three (3) patients (1 patient at 6.75 µg/kg/dose, 2 patients at 10 µg/kg/dose) had Grade 1 troponin elevations without clinical signs or symptoms of cardiac disease.

•Two (2) patients (1 patient at 3 µg/kg and 1 patient at 4.5 µg/kg) had reversible Grade 2 and Grade 1, respectively, infusion-related reactions (IRR)s . Both instances resolved the same day with only saline administered. A comparison of cytokines from baseline to on-treatment timepoints reveals no evidence of significant changes, even in patients with IRR.

•Cohort 9 (17 µg/kg) is open for recruitment. MTD has not yet been reached.

FIGURE 3: NUMBER OF MT-5111 DOSES RECEIVED



- A total of 269 doses of MT-5111 have been administered to the 35 patients enrolled in the study.
- The median (min, max) number of doses was 6 (2,30).
- Two patients received MT-5111 for more than 6 months without development of treatment-limiting AEs.

EFFICACY: 15 Stable Disease, 1 non-CR/non-PD

- Best response per RECIST 1.1 thus far was stable disease (SD) in 15 patients or non-complete response/non-progressive disease in 1 patient.
- Of those 16 patients with best response of SD or non-CR/non-PD, 6 patients had radiological SD at the time of their discontinuation from treatment due to Clinical Progression, Patient or Physician decision.
- One patient (10 µg/kg, pancreatic cancer, HER2 IHC 3+) had SD for 24 weeks; 1 patient (1 µg/kg/dose, breast cancer, HER2 IHC 2+) had non-CR/non-PD for 30 weeks.

PHARMACOKINETICS: Dose Proportional MT-5111 Exposure Observed

- The mean serum concentration of MT-5111 increases in a dose-proportional manner at higher doses starting from 6.75µg/kg (**Table 2**).
- The variability and low C_{max} values at the lower doses may be due to the binding of MT-5111 by soluble HER2 (sHER2) receptors in circulation. As the dose of MT-5111 increases, more sHER2 receptors may be saturated, leading to more measurable and predictable serum concentrations (**Figure 4**).

TABLE 2: C1D1 Pharmacokinetics

Dose (µg/kg)	N	C_{max} (ng/mL)	$t_{1/2}$ (hr)
0.5	4	0.72 (± 0.28)	4.8*
1.0	3	0.63 (± 0.60)	9.3 (± 5.0)#
2.0	3	13 (± 9.1)	7.0 (± 3.1)
3.0	3	12 (± 7.0)	4.5 (± 3.1)
4.5	3	10 (± 5.2)	3.1 (± 0.24)
6.75	5	33 (± 12)	3.7 (± 1.8)
10.0	10	54 (± 25)	6.4 (± 6.0)^
13.0	3	81 (± 46)	5.3 (± 4.1)

*Data available for one patient; #Data available for two patients ^Data available for 9 patients.
C_{max} = maximum serum concentration; C_{max} and $t_{1/2}$ values are mean (± SD).

FIGURE 4: C1D1 MT-5111 Concentration

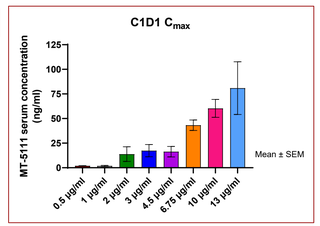
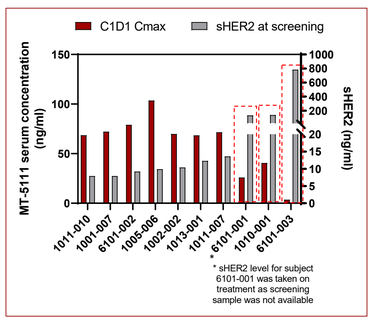


FIGURE 5: C1D1 MT-5111 Concentration and Baseline sHER2 at 10µg/kg Dose



- The variability in C_{max} values seems to be related to the baseline sHER2 levels as illustrated here using patients dosed at 10 µg/kg.
- Patients with relatively high baseline sHER2 levels have markedly lower C_{max} values compared to the other patients in the cohort (red dotted boxes in **Figure 5**).
- This suggests that by further increasing the dose, the binding effects of sHER2 in the circulation can be overcome allowing for MT-5111 to engage with HER2 in the tumor[3].

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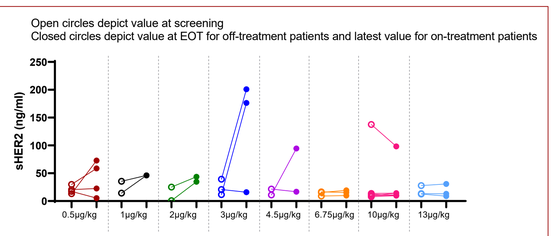
PHARMACODYNAMICS: sHER2 Levels Stable or Decreasing with Higher Doses

FIGURE 6: Soluble HER2 Levels in Serum



- Compared to baseline, the sHER2 levels at end of treatment were generally higher in cohorts that received ≤ 4.5µg/kg of MT-5111, whereas the levels were similar or lower in those cohorts that received ≥ 6.75µg/kg of MT-5111 (**Figure 6**). This may indicate increasing sHER2 receptor saturation at higher doses (rendering them unmeasurable) or fewer tumor cells shedding sHER2 or a combination of both[4].
- No correlation was observed between baseline sHER2 and last received HER2-targeted therapy before MT-5111 administration (Data not shown).

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 this Phase 1b trial, no Grade 4 or 5 treatment emergent AEs or DLTs have been identified in 35 patients, including 2 patients who were treated for 6 months or longer.
- The best response per RECIST thus far was stable disease including one patient maintaining that status for 24 weeks.
- Serum concentration of MT-5111 showed predictable and dose-proportional increasing exposure in the last three dose cohorts.
- Higher MT-5111 doses and exposures have been well tolerated and appear to saturate circulating sHER2, allowing more MT-5111 to reach the tumor.
- Dose escalation is ongoing at 17µg/kg and breast cancer expansion cohort is open at 10 µg/kg.

Disclosures and Acknowledgements

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

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