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Interim results of a phase 1 study of the novel immunotoxin MT-5111 in patients with HER2+ tumors

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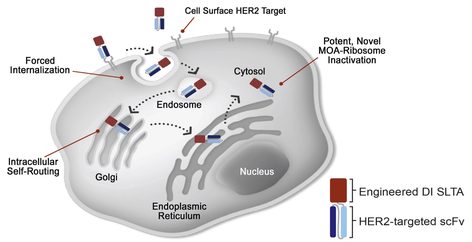
BACKGROUND

- Engineered toxin bodies (ETBs) are composed of a de-immunized Shiga-like Toxin A subunit genetically fused to an antibody-like binding domain
- ETBs can force receptor internalization, induce potent cell-kill via enzymatic and permanent inactivation of ribosomes, and may not be subject to resistance mechanisms of other therapeutics
- MT-5111 is a 55 kD ETB targeting HER2 that may demonstrate efficacy in patients resistant to other HER2-targeting agents, as its mechanism of action induces direct cell-kill via enzymatic and permanent ribosome destruction and does not rely on inhibition of kinase signaling or cytoskeletal/DNA damage
- MT-5111 binds to an epitope distinct from trastuzumab and pertuzumab, offering potential combination strategies with other HER2-targeting agents (**Figure 1**)

Figure 1. Mechanism of Action of MT-5111

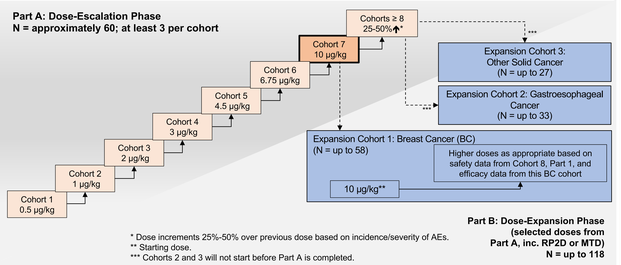


DI SLTA = de-immunized Shiga-like Toxin A subunit; HER2 = human epidermal growth factor receptor 2; MOA = mechanism of action; scFv = single-chain variable fragment.

Methods

- The primary objective of this phase 1 study is to determine the maximum tolerated dose (MTD) of MT-5111 monotherapy in adult patients with advanced HER2+ solid tumors
- Secondary objectives are pharmacokinetics (PK), efficacy, and immunogenicity
- Using a 3+3 design, patients with HER2+ tumors are enrolled into the dose-escalation part of the study into sequential cohorts: 0.5, 1, 2, 3, 4.5, 6.75, and 10 µg/kg/dose. No dose-limiting toxicities (DLTs) were observed at the 10 µg/kg/dose; higher doses will be explored using a modified toxicity probability interval (2nd version [mTPI-2]) design until the MTD has been determined (**Figure 2**).
- Three dose-expansion cohorts will follow for HER2+ breast cancer, gastroesophageal junction adenocarcinoma (GEA), and other HER2+ tumors. Since the 10 µg/kg/dose level has been declared safe, the breast cancer cohort will open at 10 µg/kg. The other 2 cohorts will follow once MTD has been identified.

Figure 2. Study Design



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

Results

- Per the data cut in September 2021, which contains preliminary data, 24 patients (mean age 64 years, range 34-78; 38% male) in 7 cohorts were treated (**Table 1**)

Table 1. Baseline Demographics and Tumor Characteristics Overall (N=24)

Dose (µg/kg/dose)	0.5	1.0	2.0	3.0	4.5	6.75	10.0	Total
Number of patients treated with MT-5111	4	3	3	3	3	5	3	24
Male, n (%)	1	1	0	1	3	2	1	9 (38)
Female, n (%)	3	2	3	2	0	3	2	15 (62)
Age, mean years (range)	69 (64-78)	49 (34-68)	69 (65-74)	63 (60-67)	62 (48-70)	67 (62-71)	65 (56-78)	64 (34, 78)
ECOG PS, grade, n (%)								
0	2 (50)	2 (67)	1 (33)	1 (33)	10 (0)	1 (20)	1 (33)	8 (33)
1	2 (50)	1 (33)	2 (67)	2 (67)	3 (100)	4 (80)	2 (67)	16 (67)
Prior lines of therapy								
Systemic therapies, median (range)	5 (3-8)	6 (3-7)	3 (3-6)	3 (1-6)	3 (2-4)	4 (2-8)	4 (3-6)	4 (1-8)
HER2 therapies, median	2.5	2	3	1	0	3	2	2
Number of patients with HER2 2+ by IHC	1	1	1	1	0	4	1	9
Number of patients with HER2 3+ by IHC	3	2	2	2	3	1	2	15

ECOG PS = Eastern Cooperative Oncology Group performance status; GEA = gastroesophageal junction adenocarcinoma; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry.

- Eight (33%) patients had breast cancer, three of whom had metastatic HER2 2+ and five of whom had metastatic HER2 3+ breast cancer (**Table 2**)
- Breast cancer patients had a median of 5.5 prior lines of systemic therapies and 4 prior lines of HER2-targeting treatments

Table 2. Selected Baseline Demographics and Tumor Characteristics for Breast Cancer Patients (n=8)

Dose (µg/kg/dose)	0.5	1.0	2.0	3.0	4.5	6.75	10.0	Total
Number of patients with breast cancer treated	2	1	1	2	-	1	1	8
HER2 status based on biopsy of metastasis								
Number of patients with HER2 2+ by IHC*	1	1	0	1	0	0	0	3
Corresponding ISH*	4-6	<2	0	NA	0	0	0	-
Number of patients with HER2 3+ by IHC*	1	0	1	1	0	1	1	5
Corresponding ISH*	>6	0	>10	NA	0	>10	NA	-
Prior lines of therapy								**Overall Median**
Systemic therapies, median (range)	6.5 (5, 8)	3	6	3.5 (1, 6)	-	6	4	5.5
HER2 therapies, median (range)	4	2	6	2.5 (0, 5)	-	6	4	4

IHC = immunohistochemistry; ISH = in situ hybridization; NA = not available.
*The ICH/ISH analyses were all performed at the local pathology lab.

Safety/Efficacy

- Treatment-related adverse events (AEs) occurred in 13 (54%) patients
- The most common treatment-related AEs were fatigue (n=7, 29%), nausea (n=4, 17%), chills, and headache (both n=3, 13%)
- No Grade 4 or 5 treatment-related AEs occurred

Results (cont.)

- 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 and monitoring (qualifying the event as an SAE); the patient had no clinical symptoms or ECG/ECHO abnormalities; the troponin returned to normal range within approximately 24 hours, without triggering a DLT
  - One patient with uterine carcinosarcoma (10 ug/kg) experienced Grade 1 troponin level increases (Troponin I or T) without any concurrent cardiac symptoms or ECG or ECHO changes; these 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
- Two patients (3 µg/kg and 4.5 µg/kg) had reversible Grade 2 infusion-related reactions that manifested with typical symptoms such as rigors, low grade fever, and myalgia in one case (4.5 µg/kg) and pruritus, facial swelling, and hypotension in the other case (3.0 µg/kg) within an hour of drug infusion; in both instances, administration of systemic antihistamines, NSAIDs, or steroids resulted in resolution of the infusion-related reactions
- Best response to date has been stable disease (SD) in five patients; one of these patients 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 without any DLTs, and the next cohort (Cohort 8) is open for recruitment; MTD has not yet been reached
- An expansion cohort for patients with breast cancer is open for enrollment

Pharmacokinetics

- 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 high HER2-expressing breast cancer cell lines (approximately 2-13 ng/mL) and approached the IC_{50} of moderately HER2-expressing cell lines
- **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=3) are approximately dose proportional compared to the 6.75 µg/kg dose cohort (n=5) (**Table 3**)
- No evidence has been seen of increased dose-normalized C_{max} and AUC_{last} for the higher dose group (10 µg/kg; n=3)

Table 3. Cycle 1 Day 1 C_{max} and AUC_{last} Summary Data (N=23)

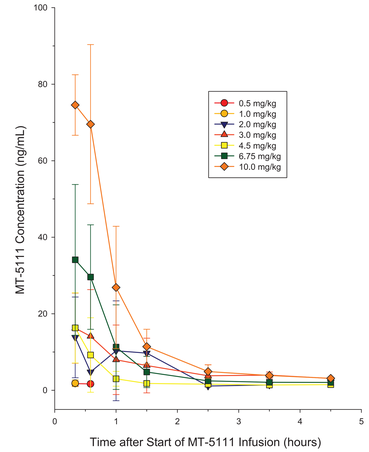
Dose (µg/kg)	N	C_{max} (ng/mL)	C_{max}/D	AUC_{last} (hr*ng/mL)	AUC_{last}/D
		Mean		Mean	
0.5	4	1.9	3.8	--	--
1	2*	1.8	1.8	--	--
2	2^	13.8	6.9	16.5	8.2
3	3	17.4	5.8	24.8	8.3
4.5	3	16.3	3.6	13.4	3.0
6.75	5	43.2	6.4	33.7	5.0
10	3	74.6	7.5	75.9	7.6

*One patient on C1D1 was <LLOQ and excluded.
^One patient on C1D1 was excluded due to pre-dose sample not being <LLOQ.
AUC_{last} = area under curve up to the last measurable concentration; C1D1 = Cycle 1 Day 1; C_{max} = maximum serum concentration; CV = coefficient of variation; D = dose; LLOQ = lower limit of quantification.

Results (cont.)

- The pharmacokinetic-based exposure was within the expected range at Cycle 1 Day 1 (**Figure 3**)

Figure 3. Cycle 1 Day 1 Pharmacokinetics



CONCLUSIONS

- MT-5111 was well tolerated with no clinically significant immuno- or cardiotoxicity
- Dose escalation is ongoing and nearing dose levels, starting at 10 ug/kg, expected to be required for efficacious exposure

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