CT130

Phase 1 study of the novel immunotoxin MT-5111 in patients with HER-2+ tumors

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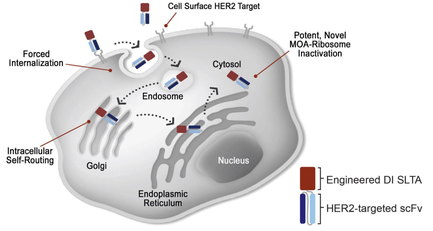
Background

- Engineered toxin bodies (ETBs) are comprised of a proprietarily engineered form of Shiga-like Toxin A subunit genetically fused to antibody-like binding domains
- MT-5111 is a de-immunized ETB targeting human epidermal growth factor receptor 2 positive (HER2+) solid tumors
- Its novel mechanism of action, via enzymatic ribosome inactivation, may not be subject to resistance mechanisms that exist for tyrosine kinase inhibitors, antibody-drug conjugates, or antibody modalities (**Figure 1**)

Figure 1. MT-5111 Mechanism of Action



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.

- MT-5111 binds an epitope on HER2, distinct from trastuzumab or pertuzumab, that may provide for combination potential with other HER2-targeting agents
- Half maximal inhibitory concentrations (IC_{50}) were observed at 3.1 ng/mL and below (**Table 1**)[1]

Table 1. MT-5111 and T-DM1 IC_{50} for High and Moderate HER2 Expressing Cell Lines

Indication	Cell Line	IC_{50} (ng/mL) T-DM1	IC_{50} (ng/mL) MT-5111	HER2 Spec/Iso Ratio
Stomach	NCI-N87	17.0	0.6	264.2
Breast	EFM-192A	8.0	2.0	220.6
Ovary	SK-OV3	7.1	0.4	163.9
Breast	SK.BR-3	3.4	2.6	162.0
Breast	HCC1569	39.0	0.3	138.3
Breast	HCC202	7.1	0.8	95.5
Breast	MDA-MB-453	170.0	>10,000.0	34.9
Breast	JIMT-1	3,000.0	3.1	25.3
Stomach	SNU-216	>10,000.0	0.9	24.8
Breast	MCF-7	5,000.0	>10,000.0	4.2
Breast	MDA MB 231	>10,000.0	>10,000.0	3.2
Breast	MDA MB 468	2,800.0	>10,000.0	1.2
Breast	BT-20	>10,000.0	>10,000.0	1.0

HER2 = human epidermal growth factor receptor 2; IC_{50} = half maximal inhibitory concentration; iso = isotype; spec = specific; T-DM1 = ado-trastuzumab emtansine.

Background

- This is a Phase 1 first in human, open-label dose escalation and expansion study of MT-5111 monotherapy to evaluate safety and tolerability in patients with HER2+ solid tumors (NCT04029922)

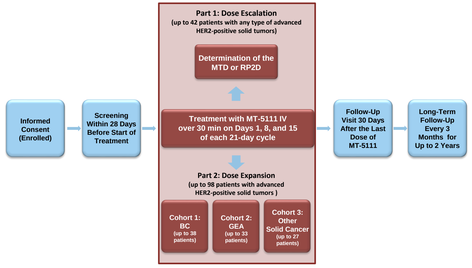
Objectives

- The primary objective is to determine the maximum tolerated dose (MTD) of MT-5111 monotherapy in adult patients with advanced HER2+ solid tumors
- Secondary objectives include characterization of the pharmacokinetic (PK) profile and evaluation of efficacy and immunogenicity for MT-5111 in this patient population

Methods

- Using a modified 3+3 design, the dose escalation part of the study includes the following 7 cohorts: 0.5, 1, 2, 3, 4.5, 6.75, and 10 µg/kg
- If Cohort 7 (10 µg/kg) is tolerated, additional dose escalation cohorts may be added
- Three dose expansion cohorts will follow for HER2+ breast cancer, gastroesophageal cancer, and any other HER2+ tumors (**Figure 2**)

Figure 2. Phase 1 Study Design



BC = breast cancer; GEA = gastroesophageal cancer; HER2 = human epidermal growth factor receptor 2; IV = intravenously; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose.

- The breast cancer dose expansion cohort is anticipated to open first based on achieving a reasonable multiple of the IC_{50} for high HER2+ expressing cell lines; doses will begin at 10 µg/kg or lower depending upon dose escalation findings
- Enrollment in the gastroesophageal and other HER2+ tumor cohorts will begin after the MTD is determined through dose escalation
- All patients will receive MT-5111 weekly on Days 1, 8, and 15 as a 30-min IV infusion in each 21-day treatment cycle until progressive disease (PD), unacceptable toxicity, death, or withdrawal of consent

Results

- As of the data cut in December 2020, 16 pts were treated; cancer types included biliary tract (n=6), breast (n=6), pancreatic (n=2), gastric (n=1), and colon (n=1)
- As of the data cut in December 2020, no patients had been enrolled in the 6.75 and 10 µg/kg cohorts
- The mean age was 63 years (range, 34-78), and 38% of patients were male (**Table 2**)

Table 2. Patient Baseline Demographics and Tumor Characteristics

	0.5 µg/kg (n=4)	1.0 µg/kg (n=3)	2.0 µg/kg (n=3)	3.0 µg/kg (n=3)	4.5 µg/kg (n=3)	Total (N=16)
Male, n (%)	1 (25)	1 (33)	0	1 (33)	3 (100)	6 (38)
Age, years (range)	69 (64-78)	49 (34-68)	69 (65-74)	63 (60-67)	62 (48-70)	63 (34-78)
Primary tumor location, n (%)						
Biliary tract carcinomas	2 (50)	1 (33)	2 (67)	--	1 (33)	6 (38)
Breast cancer	2 (50)	1 (33)	1 (33)	2 (67)	--	6 (38)
Pancreatic carcinomas	--	--	--	--	2 (67)	2 (13)
Gastric/gastroesophageal junction	--	1 (33)	--	--	--	1 (6)
Colon	--	--	--	1 (33)	--	1 (6)
ECOG performance status grade, n (%)						
0	2 (50)	1 (33)	1 (33)	1 (33)	1 (33)	6 (38)
1	2 (50)	2 (67)	2 (67)	2 (67)	2 (67)	10 (63)
Prior lines of systemic therapy, median (range)						
Systemic therapies	5 (3-8)	6 (3-7)	3 (3-6)	3 (1-6)	3 (2-4)	4 (1-8)
HER2 therapies	2.5 (0-5)	2 (2-3)	3 (0-4)	1 (0-5)	0 (0-1)	2 (0-5)

ECOG = Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

- Patients received a median of 4 prior lines of systemic therapies (range, 1-8)
- Patients who did not receive prior HER2-targeting therapy were either ineligible due to tumor indication or were immunohistochemistry (IHC) 2+ without gene amplification
- Three patients experienced stable disease as best response per RECIST 1.1
  - One additional patient in Cohort 2 (1 µg/kg) with breast cancer had non-PD/non-complete response over 8 treatment cycles. This patient had resolution of 3 hepatic lesions (sub-centimeter lesions pre-therapy) at the end of Cycle 8; however, the patient came off study due to clinical progression/symptomatic deterioration at the end of Cycle 10.
  - One patient with pancreatic cancer experienced PD by the end of Cycle 6, two patients with breast and biliary cancer, respectively, by the end of Cycle 4, and all other patients by the end of Cycle 2
- No grade 4 or grade 5 treatment-emergent adverse events (TEAEs) occurred
- Six patients had 11 grade 3 TEAEs; the most common were increased aspartate aminotransferase (n=2 at 0.5 µg/kg, both unrelated, both patients had large liver metastases) and dyspnea (n=2 at 3.0 µg/kg and 4.5 µg/kg, both patients with pulmonary disease). In one of these patients (4.5 µg/kg dose) with histologically confirmed pulmonary lymphangitis carcinomatosis, the AE of dyspnea was deemed possibly related and serious (hospitalization).
- Another patient had an unrelated serious AE of abdominal distension
- Treatment-related TEAEs occurred in 8 (50%) patients; the most common was fatigue (n=5, 31%) and all were ≤ grade 2 in nature, except for one grade 3 event of dyspnea (**Table 3**)

Table 3. Treatment-Related TEAEs for All Cohorts

	0.5 µg/kg (n=4)	1.0 µg/kg (n=3)	2.0 µg/kg (n=3)	3.0 µg/kg (n=3)	4.5 µg/kg (n=3)	Total (N=16)
Treatment-Related TEAEs, n (%)						
Fatigue	--	1 (33)	1 (33)	1 (33)	2 (67)	5 (31)
Nausea	--	1 (33)	--	--	2 (67)	3 (19)
Chills	1 (25)	--	1 (33)	--	--	2 (13)
Headache	--	1 (33)	--	--	1 (33)	2 (13)
AST increased	1 (25)	1 (33)	--	--	--	2 (13)
ALP increased	--	1 (33)	--	--	--	1 (6)
ALT increased	--	1 (33)	--	--	--	1 (6)
Anemia	--	1 (33)	--	--	--	1 (6)
Dizziness	--	--	--	--	1 (33)	1 (6)
Dyspnea	--	--	--	--	1 (33)	1 (6)
Fever	--	--	1 (33)	--	--	1 (6)
Hypophosphatemia	--	1 (33)	--	--	--	1 (6)
Hypertension	--	--	--	--	1 (33)	1 (6)
Hypotension	--	--	--	1 (33)	--	1 (6)
Infusion-related reaction	--	--	--	1 (33)	--	1 (6)
Pain in extremity	--	--	--	--	1 (33)	1 (6)
Rash	--	--	--	--	1 (33)	1 (6)
Rigors	--	--	--	--	1 (33)	1 (6)
Stomatitis	--	--	--	1 (33)	--	1 (6)
Vomiting	--	--	--	--	1 (33)	1 (6)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse events.

- Post-infusion reactions (grade 1 chills, grade 2 rash, grade 2 infusion-related reaction, grade 2 rigors) indicative of potential innate immune response to study drug were observed in 5 patients
- No cardiac TEAEs, clinically significant changes in cardiac biomarkers (troponin, electrocardiogram, left ventricular ejection fraction, N-terminal-pro hormone BNP [NT-proBNP]), or cases of capillary leak syndrome were observed
- C_{max} values up to 4.5 µg/kg match simulations based on non-human primate toxicokinetic data (**Table 4**)
- The C_{max} for dose groups >2 µg/kg were approximately 5-fold higher than the IC_{50} of moderate-high HER2-expressing cell lines (see **Table 1**)

Table 4. MT-5111 C_{max}, Dose-Normalized C_{max}, and Simulated C_{max} by Cohort

Dose (µg/kg)	N	C_{max} Mean & Range (ng/mL)	Mean C_{max}/Dose	Simulated C_{max} (ng/mL)
0.5	4	1.9 (1.1-2.3)	3.8	1.8
1.0	2*	1.8 (1.2-2.5)	1.8	3.6
2.0	2†	13.8 (6.4-21.3)	6.9	7.1
3.0	3	17.4 (6.4-27.9)	5.8	10.7
4.5	3	16.3 (7.3-25.6)	3.6	16.0

*One patient in C1D1 was <LLOQ and excluded.
†One patient in C1D1 was excluded due to pre-dose sample not being <LLOQ.
C_{max} = maximum observed plasma concentration; LLOQ = lower limit of quantification.

Conclusions

- MT-5111 has been well tolerated at escalated doses up to Cohort 5 (4.5 µg/kg)
- There have not been any dose-limiting toxicities nor clinically significant cardiotoxicity to date, and the MTD has not been reached
- Pharmacokinetic data for the first 5 cohorts matched simulations based on non-human primate studies
- Exposures at 4.5 µg/kg have reached approximately 5x the IC_{50} of HER2-expressing cell lines. Dose escalation continues and no dose-limiting toxicities have been observed to date at 6.75 µg/kg.

References

1. Waltzman RJ, et al. *J Clin Oncol.* 2020;38(4 suppl):433-433.

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