First-In-human, Dose Escalation and Expansion Study of MT-6402, a Novel Engineered Toxin Body (ETB) Targeting PD-L1, in Patients with Relapsed/Refractory Advanced Solid Tumors: Interim Data

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Abstract CT191

BACKGROUND: Three Novel Mechanisms of Action

Engineered toxin bodies (ETBs) comprise a proprietary form of the Shiga-like Toxin A subunit (SLT-A) genetically fused to an antibody binding domain.

MT-6402, a first-in-class ETB that carries a CMV antigen payload and exploits the internalization and ribosomal toxicity of de-immunized SLT-A **(Figure 1).**

MT-6402 - Targeting PD-L1 via Differentiated MOA

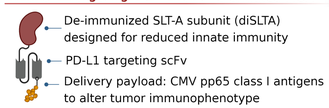
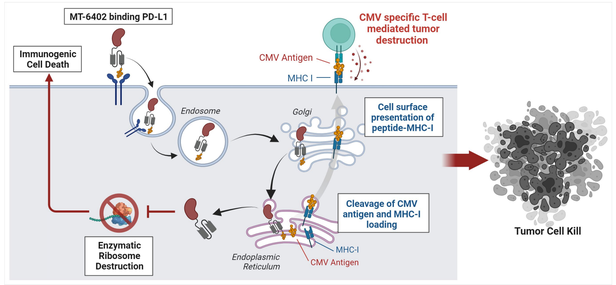


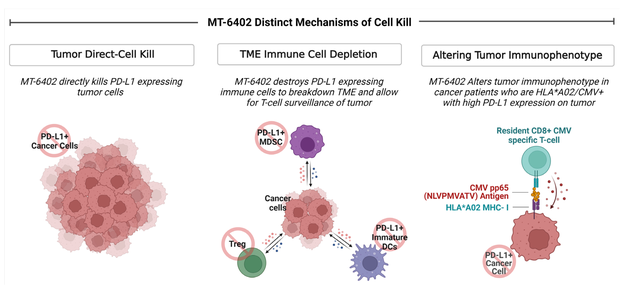
FIGURE 1: MT-6402 Mechanisms of Action

Internalization and Cellular Mechanism of Action



CMV: cytomegalovirus; MHC: major histocompatibility complex; PD-L1: programmed death ligand 1

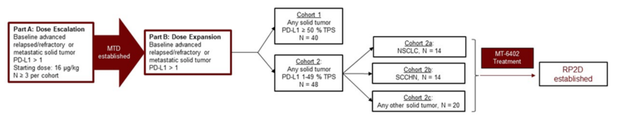
MT-6402 Activity Pathways



METHODS: Phase 1 Dose Escalation and Expansion Trial

- **Primary objectives** are to determine safety, tolerability, Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) of MT-6402, and efficacy (ORR)
- **Secondary objectives** are to determine pharmacokinetics, efficacy (DoR, PFS, DCR), and immunogenicity.
- **Key eligibility criteria** include any level of PD-L1 positivity on tumor and/or immune cells, as assessed by an FDA approved assay. Prior checkpoint inhibitor therapy is required if approved for the specific cancer type.
  - HLA-A*02 and CMV+ (AST-engaged) status is NOT required for study enrollment

FIGURE 2: Overall Study Design



CPS = combined positivity score, MTD = maximum tolerated dose; NSCLC = non-small cell lung carcinoma; PD-L1 = programmed death-ligand 1; RP2D = recommended Phase 2 dose; SCCHN = squamous cell carcinoma of the head and neck; TPS = tumor proportion score

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RESULTS: Patient Cohorts

56 patients have been treated (**Table 1**) as of 08March24: 48 in Part A, 8 in Part B

TABLE 1: Demographics (N = 56)

	Part A								Part B Total (PD-L1, TPS ≥ 50%)	Overall Total
	16 µg/kg	24 µg/kg	32 µg/kg	42 µg/kg	63 µg/kg	83 µg/kg	100 µg/kg	Part A Total		
Number of Subjects	6	6	4	3	11	15	3	48	8	56
Age (years)										
Mean	60.5	63.7	64.8	61.0	55.2	60.1	57.3	59.7	62.5	60.1
SD	18.0	7.7	9.5	14.0	14.0	9.6	15.8	12.0	13.2	12.1
Sex										
Male (%)	4 (66.7%)	5 (83.3%)	1 (25%)	3 (100%)	7 (63.6%)	9 (60.0%)	2 (66.7%)	31 (64.6%)	4 (50.0%)	35 (62.5%)
Female (%)	2 (33.3%)	1 (16.7%)	3 (75%)	0	4 (36.4%)	6 (40.0%)	1 (33.3%)	17 (35.4%)	4 (50.0%)	21 (37.5%)
Tumor Type										
Head and Neck (SCC)	0	0	0	0	2 (18.2%)	6 (40.0%)	1 (33.3%)	9 (18.8%)	3 (37.5%)	12 (21.4%)
Lung (NSCLC)	3 (50.0%)	1 (16.7%)	0	0	1 (9.1%)	2 (13.3%)	1 (33.3%)	8 (16.7%)	4 (50.0%)	12 (21.4%)
Gastrointestinal (Esophageal, Gastric/Gastroesophageal, Pancreatic, Colorectal)	0	3 (50%)	2 (50%)	2 (66.6%)	5 (45.5%)	1 (6.5%)	0	13 (27.1%)	1 (12.5%)	14 (25%)
Breast	0	0	1 (25.0%)	0	0	2 (13.3%)	1 (33.3%)	4 (8.3%)	0	4 (7.1%)
Melanoma	1 (16.7%)	1 (16.7%)	0	0	0	1 (6.7%)	0	3 (6.3%)	0	3 (5.4%)
RCC	0	1 (16.7%)	0	0	1 (9.1%)	0	0	2 (4.2%)	0	2 (3.6%)
Ovarian	1 (16.7%)	0	0	0	0	1 (6.7%)	0	2 (4.2%)	0	2 (3.6%)
Any other solid tumor	1 (16.7%)	0	1 (25.0%)	1 (33.3%)	2 (18.2%)	2 (13.4%)	0	7 (14.6%)	0	7 (12.5%)
Prior Lines of Therapy										
Mean	2.0	3.8	4.3	3.0	3.3	2.4	2.3	2.9	2.1	2.8
SD	0.9	1.8	2.9	1.0	1.4	1.4	1.5	1.6	0.8	1.5
AST Engagement Status*										
HLA-A*02/CMV+	2 (33.3%)	1 (16.7%)	1 (25.0%)	1 (33.3)	1 (9.1%)	3 (20.0%)	0	9 (18.6%)	2 (25%)	11 (19.6%)
AST Engaged: High PD-L1** / HLA-A*02 / CMV+	1 (16.7%)	0	0	0	0	0	0	1 (2.1%)	2 (25%)	3 (5.4%)

**AST engaged tumor: A tumor with high PD-L1 expression (TPS>/=50%) in a patient who has HLA-A*02 and a positive CMV serology.*
***Central lab PD-L1 testing failed to show high TPS scores in 2 of the 3 patients with high PD-L1 expression obtained from sites.*

- Patients are eligible with historical tumor biopsy evidence of PD-L1 expression by FDA-approved assays (22C3, 28-8, SP263, SP142) per local institution.
- Notably, most patients enrolled have low PD-L1 expression in tumor samples.

RESULTS: Safety

TABLE 2A: Treatment Related AEs Grades ≥3 by Preferred Term and Cohort

Group	Cohort	AE Preferred Term	Grade	Count
Part A	16µg/kg	Anaemia	3	1
		Back pain	3	1
	24µg/kg	Hypokalaemia	3	1
	32µg/kg	*None reported*		0
	42µg/kg	Amylase increased	3	1
		Lipase increased	3	1
	63µg/kg	Anaemia	3	1
		Infusion related reaction	3	1
	83µg/kg	Anaemia	3	1
		Gamma-glutamyltransferase increased	3	1
		Lymphocyte count decreased	3	1
	100µg/kg	Maculopapular rash	3	1
Part B	63µg/kg	*None reported*		0
	83µg/kg	*None reported*		0

- No Grade 4 or 5 treatment-related AE were reported.
- A Grade 5 pulmonary hemorrhage that occurred in a subject in the 100 µg/kg dose cohort was related to progression of cancer in the endobronchial location.

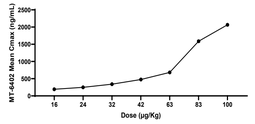
TABLE 2B: Dose Limiting Toxicities (DLT) by Preferred Term and Cohort

Part A Cohort	AE Preferred Term	Grade	Comment
24µg/kg	Maculopapular rash	2	DLT due to treatment interruption for > 2 weeks
63µg/kg	Infusion related reaction	3	Resolved within 90 minutes. Treated with IV Demerol and Solu-Medrol.
83µg/kg	Cardiac Troponin T increased	1	DLT due to treatment interruption for > 2 weeks.
100µg/kg	Cardiac Troponin T increased	1	DLT due to treatment interruption for > 2 weeks. Dose reduced to 50µg/kg. Considered resolved.
	Maculopapular rash	3	Improved within 1 day on systemic steroids.

High sensitivity troponin increases are common in patients receiving MT-6402. To date, all have been Grade 1 with no associated symptoms, ECG changes, or new echocardiogram findings. Onset occurred within Cycle 1 with peak troponin occurring around Day 22 and appearing to coincide with spikes in IL-2. The highest peak high sensitivity cardiac troponin-I observed was 335 ng/L. Similar troponin changes have been observed in patients treated with checkpoint inhibitors (CPIs).

RESULTS: Pharmacokinetics

FIGURE 3: MT-6402 exposure vs dose curve



For PK parameters from previous cohorts, please see previous presentations (Barve et al., 2023).

- Dose proportional exposure between 16 and 63 µg/kg. Greater than dose proportional increase in C_{max} at 83 and 100 µg/kg dose (*Figure 3*).
- C_{max} 25-fold above IC_{50} at 83 µg/kg and 36-fold above IC_{50} at 100 µg/kg (established *in vitro* in CHO cells) and $t_{1/2}$ is short.
- Anti-drug antibody (ADA) develops in all patients by Day 15 but pharmacodynamic effects post-ADA continue to be observed like with other approved immunotoxins.

RESULTS: MT-6402 shows dose dependent depletion of target positive cells

FIGURE 4: Reduction of Peripheral PD-L1+ MDSC in a dose-dependent manner

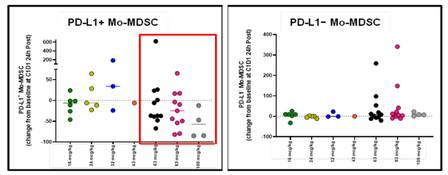


Figure 4: No depletion of target negative, PD-L1- MDSCs observed. Similar reduction noted for other PD-L1 expressing cells such as monocytes and dendritic cells.

RESULTS: MT-6402 offers a unique ability to dismantle the tumor microenvironment

FIGURE 5: Prolonged modulation of TME-associated markers and depletion of PD-L1+ MDSC in HNSCC patients

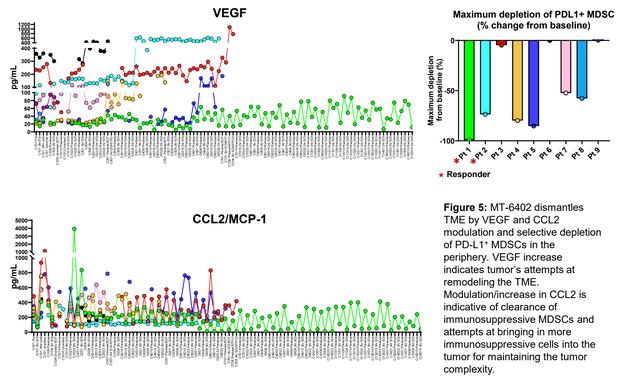


Figure 5: MT-6402 dismantles TME by VEGF and CCL2 modulation and selective depletion of PD-L1+ MDSCs in the periphery. VEGF increase indicates tumor's attempts at remodeling the TME. Modulation/increase in CCL2 is indicative of clearance of immunosuppressive MDSCs and attempts at bringing in more immunosuppressive cells into the tumor for maintaining the tumor complexity.

FIGURE 6: Dramatic increase in T cell associated cytokines and CD8:CD4 ratio

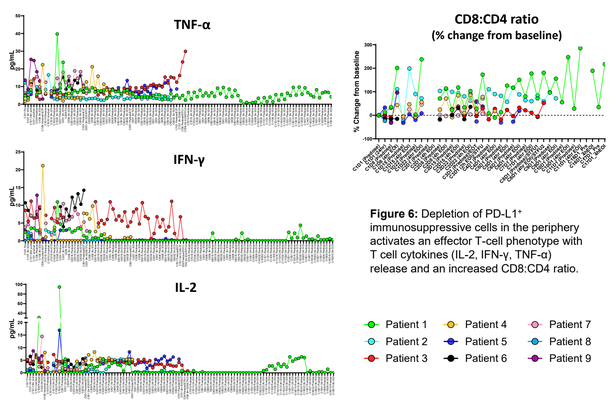


Figure 6: Depletion of PD-L1+ immunosuppressive cells in the periphery activates an effector T-cell phenotype with T cell cytokines (IL-2, IFN-γ, TNF-α) release and an increased CD8:CD4 ratio.

RESULTS: Objective Responses in Two Patients with HNSCC

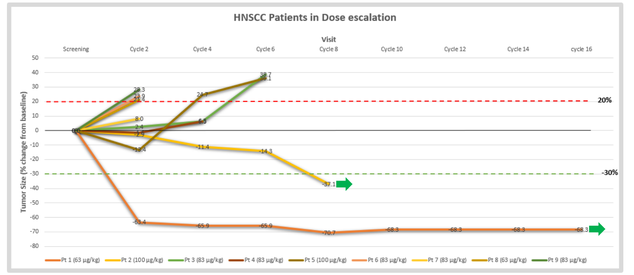
Confirmed PR in patient with Nasopharyngeal SCC and low PD-L1 expression

- A 49-year-old male patient with metastatic SCC of the nasopharynx treated at 63 µg/kg after progressing on 4 prior treatment regimens that included chemotherapy and pembrolizumab.
- The tumor was not AST engaged (not HLA-A*02, CMV positive), and PD-L1 expression of 2% by TPS.
- Achieved Partial Response (PR) with 63% reduction in index lesion after Cycle 2 and 70% reduction after 8 cycles (*Figure 7 – Patient 1*).
- Patient remains on study in Cycle 18

Unconfirmed PR in patient with multiple-CPI pre-treated Oral cavity SCC and low PD-L1 expression

- A 61-year-old male patient with metastatic SCC of oral cavity treated initially at 100µg/kg (reduced to 83µg/kg after Cycle 1 Day 8) after progressing on 4 prior treatment regimens that included ipilimumab, nivolumab, cetuximab, and pembrolizumab. Tumor was first refractory to ipilimumab and nivolumab, but later responded to pembrolizumab with chemotherapy.
- The tumor was not AST engaged (not HLA-A*02, CMV negative), and PD-L1 expression of 10% by CPS.
- Achieved unconfirmed Partial Response (uPR) with 37% reduction in index lesion after Cycle 8 (*Figure 7 – Patient 2*)
- Patient remains on study in Cycle 9

FIGURE 7: HNSCC Patients in Part A (Dose Escalation) (n=9*)



*One patient initially classified as an HNSCC was later determined to have a SCC of the auricular skin. The patient had a PD-L1 CPS of 5% and had progressed after six prior lines of therapy and was refractory to pembrolizumab. The patient received only two doses of MT-6402 at 83 µg/kg before discontinuing due to Grade 1 troponin increase. The site determined the patient to be in stable disease at the time of discontinuation; an external review of scans showed at 36% decrease in index tumor volume consistent with a marked size reduction on physical exam per treating physician description.

- Dose assignment is per first dose received. Three patients had dose reductions: Patient 2 to 83 µg/kg, Patient 3 to 42 µg/kg, and Patient 5 to 50 µg/kg.

DISCUSSION

- Overall, MT-6402 has been well tolerated. A total of 5 DLTs (one Grade 3 and one Grade 2 maculopapular rash, one Grade 3 IRR, and two Grade 1 asymptomatic high-sensitivity troponin increases) were observed. There was no evidence of capillary leak syndrome (CLS) or other payload-derived toxicity.
- The troponin increases were mild and asymptomatic with no ECG or echocardiogram changes. Similar troponin changes were observed in patients treated with checkpoint inhibitors (CPIs) (*Waliany et al, 2021*). This phenomenon appears to be an effect of checkpoint-mediated T-cell stimulation. These changes, albeit low grade, resulted in treatment interruptions and study-specific guidances have been developed based on patient evaluation and management.
- MT-6402 depletes immunosuppressive PD-L1+ immune cells and tumor cells, activates T-effector phenotype, and dismantles the TME by modulation of tumor-associated cytokines/chemokines. This differentiates MT-6402 from PD-L1 antibodies.
- An early efficacy signal in a subgroup of patients with recurrent and metastatic CPI-pretreated HNSCC has been identified, where there is still a large unmet need.

CONCLUSIONS

- **MT-6402 works via multiple novel MOAs and targets a well validated checkpoint target (PD-L1) with the potential to directly kill PD-L1+ tumors and deplete PD-L1+ immune cells to alter the TME.**
- **MT-6402 has an acceptable safety profile with no drug-related Grade 4 or Grade 5 toxicities.**
- **Pharmacodynamic effects observed with MT-6402 are distinct from PD-L1 monoclonal antibodies.**
- **Encouraging signs of monotherapy activity reported in 2 of the nine HNSCC patients treated in dose escalation phase**
  - Both patients were heavily pretreated (including checkpoint inhibitors) with PD-L1 low expression
  - Both patients remain on study and in responses at Cycles 18 and 9, respectively
- **Expansion monotherapy cohort with pre- and on-treatment biopsies is currently ongoing in high PD-L1 expressing tumor types exploring both the 63 and 83 µg/kg dose levels.**

REFERENCES

Barve, M., Van Tine, B.A., Redman, R.A. Powell, S.F., Edenfield, W.J., Peguero, J., et al. (2023, June 2-6). First-in-Human Study of MT-6402, an Engineered Toxin Body (ETB) Targeting PD-L1: Interim Data. ASCO 2023 Chicago, IL, USA.

Waliany et al. Myocarditis Surveillance With High-Sensitivity Troponin I During Cancer Treatment With Immune Checkpoint Inhibitors. JACC:Cardiooncology. 2021, 3:1; 137-139.

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