First-in-human, dose escalation and expansion study of MT-6402, a novel engineered toxin body (ETB) targeting PD-L1, in patients with PD-L1 expressing relapsed/refractory advanced solid tumors: Interim Data

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BACKGROUND: PD-L1 targeted ETB with Novel Mechanisms of Action

MT-6402 is a PD-L1 targeted engineered toxin body (ETB) (Figure 1A).

- **Engineered toxin bodies** (ETBs) are comprised of a proprietarily engineered form of Shiga-like Toxin A subunit (SLTA) genetically fused to antibody-like binding domains.
- 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.
- MT-6402 carries a de-immunized SLTA that is genetically fused to PD-L1 targeting antibody binding domain (scFv) and an HLA-A*02 restricted pp65 cytomegalovirus (CMV) antigen.

MT-6402 elicits novel dual anti-PD-L1 mechanisms of action (Figure 1B):

- Direct cell kill of PD-L1 expressing tumor and immune cell types
- Delivery and presentation of a fused CMV (pp65) antigen in complex with MHC class I on the surface of the tumor also called antigen seeding technology (AST)

Patient effects can be separated into two biological responses to MT-6402

- HLA/CMV-*independent* (**AST-non-engaged**) direct PD-L1-targeted cell kill via SLTA-mediated permanent inactivation of ribosomes resulting in cellular apoptosis (relevant for all patients)
- HLA/CMV-*dependent* (**AST-engaged**) cell kill via antiviral (CMV) cytotoxic T-cells. (relevant for patients with HLA-A*02 genotype who are CMV+)

Currently approved PD-L1 targeting agents act through steric inhibition of PD-1/PD-L1 binding and are subject to the same mechanistic limitation: the inability to induce a sufficiently potent T-cell response to the existing tumor immunophenotype. MT-6402 may overcome this limitation through novel mechanisms of action: direct tumor/immunotolerant cell kill and re-direction of host antiviral immunity.

MT-6402 represents a wholly novel approach to checkpoint inhibition with the potential to result in direct tumor regression and remodeling of tumor and systemic immunophenotypes in favor of anti-tumor immune responses.

Epidemiological information: ***AST-engaged pathway is relevant to ~20-40% of population, but cell death activity is engaged regardless of HLA status.***

FIGURE 1A: MT-6402 Structure

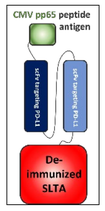
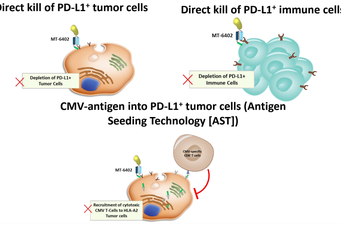


FIGURE 1B: MT-6402 Mechanisms of Action



METHODS: Phase 1 Dose Escalation and Expansion Trial

Primary objectives: Safety, Tolerability, and Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) of MT-6402

Secondary objectives: Pharmacokinetics, Pharmacodynamics (peripheral PD-L1+ immune cells), Efficacy (DoR, PFS, OS), and Immunogenicity.

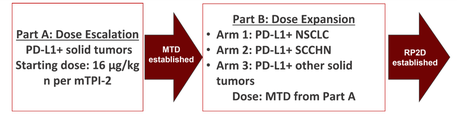
Exploratory endpoints: Cytokine/chemokine profiles, Alterations in non-PD-L1+ peripheral immune cell subsets, circulating CMV-specific T cells (AST PD effects); in dose expansion cohorts: pre/on-treatment tumor biopsy to assess tumor microenvironment (TME)

Key eligibility criteria:

- Any level of PD-L1 positivity on tumor and/or immune cells, as assessed by an FDA approved IHC assay
- HLA-A*02 and CMV+ (AST-engaged) status is NOT required for study enrollment
- Prior checkpoint inhibitor therapy is required if any is approved for the specific cancer type

Treatment: MT-6402 IV over 30 minutes QW in each 28-day treatment cycle until disease progression (PD), unacceptable toxicity, death, or withdrawn consent (NCT04795713)

FIGURE 2: mTPI-2 Design for Dose Escalation and Simon's Two-Stage Design for Dose Expansion



MTD=maximum tolerated dose; mTPI-2=modified toxicity probability interval-2; NSCLC=non-small cell lung carcinoma; PD-L1=programmed cell death-ligand 1; RP2D=recommended phase 2 dose; SCCHN=squamous cell carcinoma of the head and neck.

RESULTS: Patient Cohorts

12 patients have been treated (**Table 1**) in Part A (dose escalation): 6 in cohort 1 (16 µg/kg/dose) and 6 in cohort 2 (24 µg/kg/dose)

TABLE 1: Baseline Demographics and Tumor Characteristics Overall (N = 12)

	Patient ID	Disease	Year of Birth	Sex	Prior CPI	HLA-A*02 positive	CMV IgG positive
Cohort 1 (16µg/kg)	1008-001	NSCLC	1945	M	Yes	Yes	Yes
	1004-002	NSCLC	1939	F	Yes	No	Yes
	1001-001	Melanoma	1988	M	Yes	No	No
	1002-003	Ovarian	1958	F	No	Unknown	Unknown
	1005-002	Solid tumor	1974	M	No	No	Yes
	1004-003	NSCLC	1958	M	Yes	Yes	Yes
Cohort 2 (24µg/kg)	1007-005	Esophageal	1951	M	Yes	Yes	No
	1004-004	Solid tumor	1950	M	Yes	HLA not done	Yes
	1001-002	NSCLC	1955	M	Yes	Yes	No
	1001-004	RCC	1971	F	Yes	Yes	No
	1008-002	Pancreatic	1960	M	No	No	No
	1001-005	Cutaneous squamous cell carcinoma	1957	M	Yes	Yes	Yes

***Highlighted** patients are able to leverage AST mechanism of action in addition to PD-L1 targeted ETB-mediated cell death*

RESULTS: Safety

TABLE 2: Grade ≥ 2 Treatment Related AEs

	AE*	Grade	Comment
Cohort 1 (16µg/kg)	Anemia	3	Patient entered study with Grade 2 anemia
	Back pain	**3**	**During infusion; treatment restarted within 30min after event resolved on Demerol and Phenergan; same patient had a prior Grade 2 IRR**
	Anorexia	2	
	CRS (SAE)	**2**	**Recovered within 2 days**
	Fever	**2**	
	IRR	**2**	**Recovered within 1 hour**
	Nausea	2	
	Pruritus	2	
Cohort 2 (24µg/kg)	Cough	2	
	Dyspnea	2	
	Fever	**2**	
	Nausea	2	
	Rash	**2**	**Improved within 1 day on systemic steroids**

Immune-related AEs are bolded.
**Each AE incidence has occurred in one (1) patient.*

RESULTS: PD-L1 expression in patient tumor samples

TABLE 3: PD-L1 IHC Staining Harmonized with SP263

Cohort 1	1008-001	1004-002	1001-001	1002-003	1005-002	1004-003
Historical PD-L1 staining positivity	TPS 80% (22C3)	TPS 70% (22C3)	N/A**	CPS >1 (22C3)	TPS 10% (22C3)	CPS >1 (22C3)
vCPS% using SP263	N/A*	90	0	0	1	5
Cohort 2	**1007-005**	**1004-004**	**1001-002**	**1001-004**	**1008-002**	**1001-005**
Historical PD-L1 staining positivity	CPS 10 (22C3)	TPS 20% (22C3)	TPS 10% (22C3)	TPS 1% (22C3)	5% (SP142)	CPS 3 (22C3)
vCPS% using SP263	2	20	2	3	0.5	3

** Patient 1008-001 tissue biopsy was a bone sample and could not be performed using the SP263 IHC assay*
*** Patient 1001-001 was enrolled based on SP263 IHC staining results: 0.5% IC PD-L1 positivity*

- Patients are eligible for enrollment on the basis of historical tumor biopsy evidence of PD-L1 expression as determined by any one of the following FDA-approved assays (22C3, 28-8, SP263, SP142). These historical PD-L1 data were generated per local institution.
- Visually estimated combined positivity score (vCPS) results were generated with the Ventana PD-L1 (SP263) IHC assay using the archived material from patients. vCPS is scored from 0-100%, and is a measure of PD-L1 positivity represented by the total % of the tumor area (tumor and stroma) covered by PD-L1+ tumor cells (TC) and tumor associated immune cells (IC) at any intensity.
- **Notably, most patients enrolled have low PD-L1 expression in their tumor samples**

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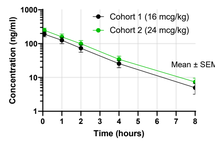
RESULTS: Pharmacokinetics

C_{max}, AUC, and half-life are consistent with results from non-human primate studies. Anti-drug antibody (ADA) develops in all patients by Day 22 but does not appear to be functionally neutralizing as pharmacodynamic effects post-ADA continue to be observed.

Cohort	N	$t_{½}$ (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)
1 (16 µg/kg)	6	1.42 (± 0.10)	192.4 (± 73.7)	449.5 (± 214.0)
2 (24 µg/kg)	6	1.41 (± 0.16)	248.0 (± 91.0)	608.1 (± 309.6)

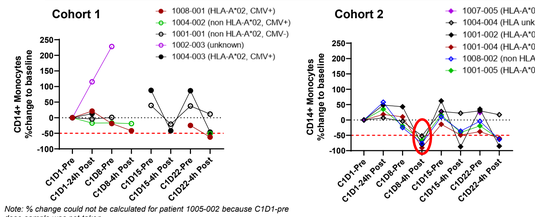
C_{max} = maximum serum concentration
All values (± SD)

FIGURE 3: C1D1 Serum Concentration



RESULTS: Pharmacodynamics (Cohort 1 and Cohort 2)

FIGURE 4: Peripheral Monocytes Reduced in Most Patients

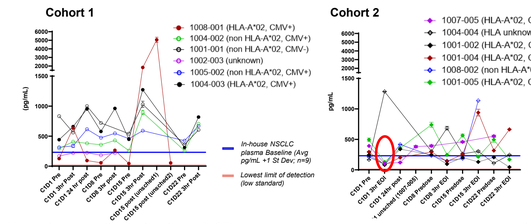


Note: % change could not be calculated for patient 1005-002 because C1D1-pre dose sample was not taken.

CD14+ monocyte counts decreased by >50% in 3/6 patients (cohort 1) and in 6/6 patients (cohort 2) regardless of AST engagement status (**Figure 4**)

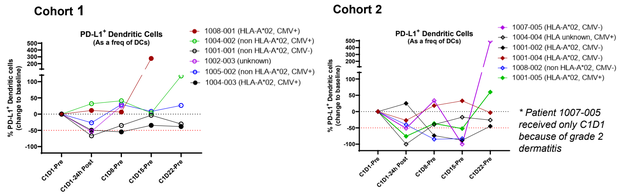
- The 3 patients with CD14+ monocyte counts that decreased by > 50% in cohort 1 achieved this in Cycle 2. 6/6 patients in cohort 2 achieved this monocyte reduction in Cycle 1. This is evidence of dose response in ETB induced cell death.
- ***Peripheral CD14+ mediated monocyte depletion in the higher dose cohort is likely driven by potent MT-6402 cell death effects on cells expressing even low levels of PD-L1****

FIGURE 5: Peripheral MCP-1 patterns of expression between cohorts may reflect dose increased ETB effects on CD14+ monocytes



- Monocyte chemoattractant protein 1 (MCP-1) is a chemokine produced by macrophages and endothelial cells which recruits monocytes, memory T cells, and dendritic cells to sites of inflammation produced by either tissue injury or infection.
- **Rapid drop in resting MCP-1 observed in 5/6 patients in cohort 2, but not in cohort 1; this is likely linked to the dose escalation of MT-6402 cell death effects.**
- Cohort 1 does not exhibit MT-6402 cell death as potently as does cohort 2. Immunomodulation is occurring as evidenced by marked upregulation of MCP-1 at C1D15.
- MCP-1 is also modulated in cohort 2 after recovery from initial effects on resting MCP-1 observed at 3hr post C1D1.

FIGURE 6: PD-L1 Dendritic Cells Decreased in Cohort 2 (24µg/kg)

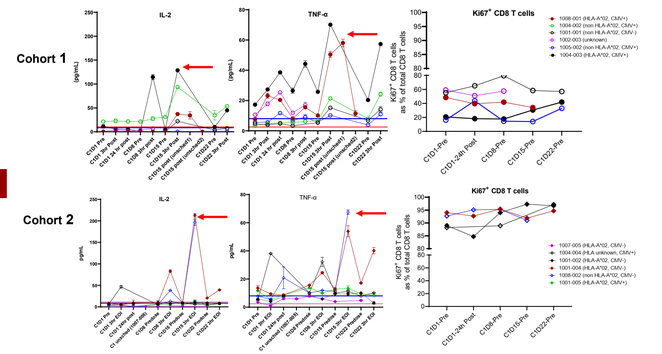


** Patient 1007-005 received only C1D1 because of grade 2 dermatitis*

- Peripheral PD-L1+ dendritic cells are markedly depleted in cohort 2 emphasizing the increased MT-6402 target mediated cell death in this higher dose (24µg/kg) (**Figure 6**)
- 2/6 patients in cohort 1 and 4/6 patients in cohort 2 experienced a decline in PD-L1+ dendritic cells.

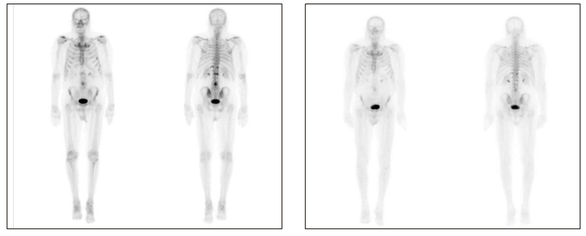
RESULTS: Pharmacodynamics (Cohort 1 and Cohort 2)

FIGURE 7: Peripheral T-Cell Proliferative Markers Are Upregulated in Cohort 2



- IL-2 and TNF-α are peripheral cytokines that drive T cells toward an activated/proliferative phenotype. Two patients within both cohorts exhibit elevations in serum IL-2/TNF-α (**Figure 7**).
- Elevations in T cell proliferative cytokines are concomitant with increased ki-67 proliferation marker in CD8/CD4 T cell subsets in 2/4 subjects from cohort 2.
- These data support a conclusion of an immune augmenting effect on T cell effector and memory phenotypes. These peripheral effects are *not* typical of current PD-(L)1 monoclonal antibodies that function only by steric hindrance of the PD-1/PD-L1 immune axis.

FIGURE 8: Qualitative reduction in non-measurable disease in Patient 1008-001



01JUL2021
Metastatic uptake: T11 and L1 vertebral bodies. Left 5th and 11th rib, right ischial tuberosity.

27OCT2021
Interval decrease of T11, L1 has mostly resolved. Left 5th rib and left 11th rib lesions have resolved.

This patient was treated at 50% reduced dose (8µg/kg) starting on C2D1 due to Grade 2 CRS on C1D15.

CONCLUSIONS

- **MT-6402 represents a wholly unique approach to checkpoint modulation, demonstrating changes in peripheral immunophenotypes and cytokines/chemokines consistent with anti-tumor immunity. This effect appears to be dose proportional and is not dependent on HLA-A*02 status.**
- **Safety assessments reveal mostly grade 1-2 AEs consistent with the immunostimulatory mechanism of action.**
- **Unlike traditional immune checkpoint inhibitors, MT-6402 displays the potential to remodel patient immunity by removing tolerogenic immune cells.**
- **MT-6402 has the potential for more robust activity in highly-expressed PD-L1 positive settings and possibly in patients with AST-engaged status.**
- **Dose escalation is ongoing given an adequate tolerability profile and enhanced PD effects.**
- **These data provide rationale for the combination of MT-6402 with traditional PD-1 inhibitors in patients whose tumors have been unresponsive to checkpoint inhibitors. Combination studies are being considered.**

DISCLOSURES

This study is sponsored and funded by Molecular Templates, Inc.

Please contact Agnes Rethy at agnes.rethy@mtem.com for questions or comments.

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