First-in-Human, Dose Escalation and Expansion Study of MT-6402, an Engineered Toxin Body (ETB) Targeting PD-L1, in Patients with PD-L1 Expressing Relapsed or Refractory Advanced Solid Tumors: Interim Data

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MOLECULAR TEMPLATES

Abstract 764

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

- **Engineered toxin bodies (ETBs) comprise a proprietarily engineered form of Shiga-like Toxin A subunit (SLTA) genetically fused to an antibody-like binding domain**
- **MT-6402 is a first-in-class PD-L1 targeted ETB that carries a CMV antigen payload**
- **MT-6402 has novel dual MoAs (Figure 1):**
  - Direct cell kill via enzymatic and permanent ribosomal inactivation against PD-L1+ tumor and immune cells to dismantle the tumor microenvironment (TME)
  - In a subset of patients who are HLA-A*02/CMV+, MT-6402 alters the tumor immunophenotype by delivering a CMV (pp65) antigen to PD-L1+ tumors which is processed and presented on the tumor cell surface in context with MHC class I. CMV-specific T-cells are redirected to the tumor with altered immunophenotype.

Engineered Toxin Body (ETB)
MT-6402

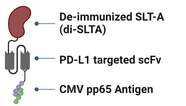
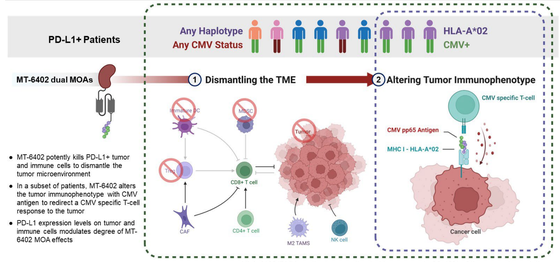


FIGURE 1: MT-6402 Mechanisms of Action



*HLA-A*02/CMV+ patients are estimated to represent ~20-40% of the general population*

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

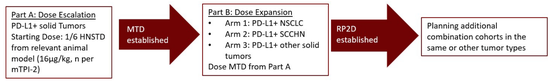
Secondary Objectives: Pharmacokinetics, pharmacodynamics (peripheral PD-L1+ immune cells), efficacy (ORR, DoR, PFS, OS), and immunogenicity

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 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



HNSTD = highest non severely toxic dose; 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.

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RESULTS: Patient Cohorts

19 patients have been treated (**Table 1**) in Part A (dose escalation): 6 in Cohort 1 (16 µg/kg/dose), 6 in Cohort 2 (24 µg/kg/dose), 4 in Cohort 3 (32 µg/kg/dose), and 2 in Cohort 4 (42 µg/kg/dose).

TABLE 1: Demographics (N = 19)

	Patient ID	Disease	Prior CPI	Lines of Treatment	Best Overall Response to CPI/Duration	HLA-A*02/CMV IgG	Historical PD-L1 Positivity and IHC
Cohort 1 (16µg/kg)	*1008-001	NSCLC	Nivolumab + Ipilimumab 1L	1	UNK (1Y)	+/+	TPS 80% (22C3)
	1004-002	NSCLC	Pembrolizumab 1L	3	UNK	-/+	TPS 70% (22C3)
	1001-001	Melanoma	Nivolumab Adjuvant Pembrolizumab 1L	3	Adjuvant	-/-	0.5% IC (SP263)
	1002-003	Ovarian	No	2	N/A	UNK	CPS > 1 (22C3)
Cohort 2 (24µg/kg)	1005-002	Solid tumor	No	4	N/A	-/+	TPS 10% (22C3)
	1004-003	NSCLC	Pembrolizumab 1L & PD-1 + TIM-3	2	UNK (2mo)/PD (3wks)	+/+	CPS > 1 (22C3)
	1007-005	Esophageal	Pembrolizumab 2L	2	UNK (7mo)	+/-	CPS 10 (22C3)
	1004-004	Solid tumor	Nivolumab 2L	4	SD (4mo)	HLA UNK/+	TPS 20% (22C3)
	1001-002	NSCLC	Pembrolizumab 1L	2	PD (3mo)	+/-	TPS 10% (22C3)
	1001-004	RCC	Nivolumab + Ipilimumab 1L	4	PD (5mo)	+/-	TPS 1% (22C3)
	1008-002	Pancreatic	No	4	N/A	-/-	TC 5% (SP142)
	1001-005	Cutaneous squamous cell carcinoma	Cemiplimab, 4&5L	7	PD (2mo)	+/+	CPS 3 (22C3)
Cohort 3 (32µg/kg)	1005-005	Solid tumor	No	4	N/A	-/-	5% IC (22C3)
	1005-007	Esophageal	Nivolumab + Ipilimumab, maintenance	1	UNK	-/NA	TPS 10% (22C3)
	1001-006	Breast	Pembrolizumab 7L	8	UNK (7mo)	-/-	CPS 15 (22C3)
	1005-008	Pancreatic	Anti-CD47 ab 3L	5	PD (2mo)	+/+	TPS 1-20% (22C3)
Cohort 4 (42µg/kg)	1017-001	Peritoneal mesothelioma	Pembrolizumab 2L	4	PD (3wks)	+/-	10% (SP263)
	1024-001	Colon	No	3	N/A	+/+	IC 20% (22C3)
	1017-002	Gastroesophageal junction	Nivolumab 2L	2	SD (7mo)	-/+	CPS 20-35 (22C3)

Highlighted patients in yellow or green are able to leverage AST mechanism of action (MoA) in addition to PD-L1 targeted ETB-mediated cell death.
*Patient is able to leverage antigen seeding MOA because of being HLA-A*02/CMV+ and patient has high PD-L1 expression*
Historical tumor biopsy evidence of PD-L1 by FDA-approved assays (22C3, 28-8, SP263, SP142) per local institution.

- Median age: 63 years (min 33, max 81); 13 male (72.0%), 6 female (28.0%)
- 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 their tumor samples**

RESULTS: Safety

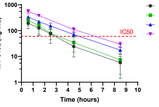
TABLE 2: Grade ≥ 2 Treatment Related AEs

Cohort	AE*	Grade	Comment
Cohort 1 (16µg/kg)	Anemia	2	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	
	Dehydration	3	
	Pruritus	2	
Cohort 2 (24µg/kg)	Cough	2	
	Dyspnea	2	
	Fever	2	
	Nausea	2	
	Hyperbilirubinemia		
	Rash	2	Improved within 1 day on systemic steroids
Cohort 3 (32µg/kg)	No Treatment Related AEs Grade 2 or higher		
Cohort 4 (42µg/kg)	Amylase, lipase, ALT, AST increased	3	Patient's gastric tumor progressed and compressed the biliary tree.
	Low back pain	2	
	Pruritus	2	

**Each AE incidence has occurred in one (1) patient.*

RESULTS: Pharmacokinetics

FIGURE 3: C1D1 Serum Concentration

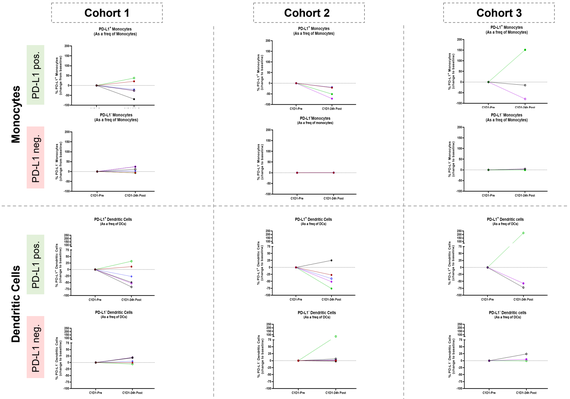


C_{max}, AUC, and half-life ($t_{1/2}$) from C1D1 are consistent with results from non-human primate studies, dose proportional exposure, no accumulation after repeat dosing, and C_{max} 3-9 fold above IC_{50} (established *in vitro* in CHO cells). Anti-drug antibody (ADA) develops in all patients by Day 15 but like other approved immunotoxins, pharmacodynamic effects post-ADA continue to be observed.

Cohort	N	T1/2	Cmax (ng/mL)	AUClast (hr*ng/mL)
1	6	1.6 (± 0.17)	192.5 (± 73.6)	446.6 (± 205.4)
2	6	1.6 (± 0.14)	248.0 (± 90.9)	610.3 (± 317.4)
3	4	2.3 (± 0.84)	340.0 (± 26.3)	1027.8 (± 194.3)
4	2	1.9 (± 0.10)	555.0 (± 107.5)	1609.4 (± 249.1)

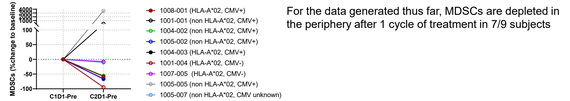
RESULTS: Pharmacodynamics

FIGURE 5: MT-6402 is selective for PD-L1 positive monocytes and dendritic cells



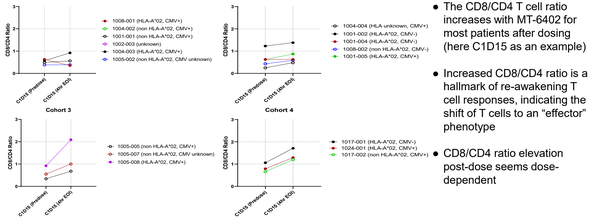
Most patients see a decrease in PD-L1-positive peripheral monocytes and dendritic cells 24hrs following first dose of MT-6402. PD-L1 negative monocytes and dendritic cells are largely unchanged (Figure 5)

FIGURE 6: MT-6402 depletes myeloid-derived suppressor cells (MDSCs)



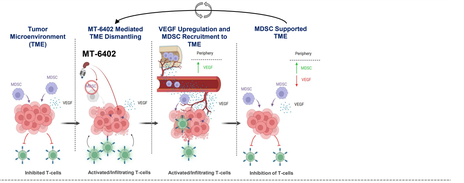
For the data generated thus far, MDSCs are depleted in the periphery after 1 cycle of treatment in 7/9 subjects

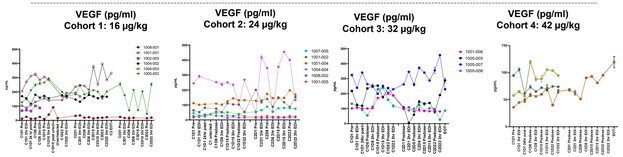
FIGURE 7: MT-6402 drives shift toward T cell effector phenotypes: increased CD8/CD4



- The CD8/CD4 T cell ratio increases with MT-6402 for most patients after dosing (here C1D15 as an example)
- Increased CD8/CD4 ratio is a hallmark of re-awakening T cell responses, indicating the shift of T cells to an "effector" phenotype
- CD8/CD4 ratio elevation post-dose seems dose-dependent

FIGURE 8: MT-6402 offers a unique ability to dismantle the tumor microenvironment





- After multiple MT-6402 doses, a "sawtooth" pattern of VEGF secretion emerges subsequent with each MT-6402
- Lack of VEGF modulation in some subjects appears driven by resting VEGF levels and not the emergence of ADA, as there is persistence of PD responses well beyond the ADA
- Onset of VEGF modulation appears to be dose-dependent

For additional details on these unique MT-6402 pharmacodynamic responses indicative of tumor dismantling, remodeling, and delivery of antigen please refer to ***SITC Poster #736.***

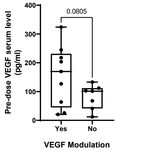
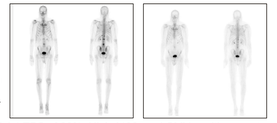


FIGURE 9 Reduction in Metastases in Patient 1008-001



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.

Patient 1008-001 who had PD-L1 TPS of 80%, HLA-A*02, and CMV positive was treated at 50% reduced dose (8µg/kg) starting on C2D1 due to Grade 2 CRS on C1D15.

CONCLUSIONS

- **MT-6402 represents a novel MOA and approach to targeting a well validated checkpoint target (PD-L1) with the potential to directly kill PD-L1+ tumors and deplete PD-L1+ immune cells to dismantle the TME**
- **In certain patients (HLA-A*02/CMV+), MT-6402 can altering the tumor immunophenotype with a highly immunogenic CMV antigen to redirect a pre-existing antigen specific T-cell response against the tumor**
- **MT-6402 uses a unique MoA that differs from traditional PD-(L)1 inhibitors and ADCs**
- **MT-6402 has an acceptable safety profile with only one DLT – a Grade 2 DLT of maculopapular rash - and may be combinable with other agents**
- **Expansion monotherapy cohorts are planned in select populations due to evidence of efficacy**
  - Combination expansion cohorts with PD-1 inhibitor planned
  - One or more expansion cohorts will specifically evaluate patients with high PD-L1 tumoral expression
  - All expansion cohorts will mandate pre- and on-treatment biopsies to evaluate changes in the TME
  - Post-dose collections of PBMCs will study response of PD-L1 specific immune cell populations to MT-6402

DISCLOSURES

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

Please contact Karen Stein at karen.stein@mtem.com for questions or comments.