First-in-Human Study of MT-6402, an Engineered Toxin Body (ETB) Targeting PD-L1: Interim Data

MOLECULAR TEMPLATES

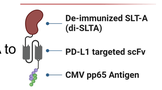
Abstract #2552

Minal Barve, MD[1]; Brian A. Van Tine, MD[2]; Rebecca A. Redman, MD[3]; Steven F. Powell, MD[4]; William J. Edenfield, MD[5]; Julio Peguero, MD[6]; Victoria M. Villaflor, MD[7]; Drew M. Rasco, MD[8]; Konstantin H. Dragnev, MD[9]; Admasu Mamuye, MD, MSc[10]; Chris B. Moore, PhD[10]; Rachael M. Orlandella, PhD[10], Swati Khanna, PhD[10]; Silvia Ferrati, PhD[10]; Soratree Charoenthongtrakul, PhD[10]; Kristina Dabovic, PharmD[10]; David R. Spigel, MD[11]

[1]*Mary Crowley Cancer Research Center, Dallas, TX, USA;* [2]*Washington University in St. Louis School of Medicine, St Louis, MO, USA;* [3]*University of Louisville, Louisville, KY, USA;* [4]*Sanford Cancer Center, Sioux Falls, SD, USA;* [5]*Prisma Health, Greenville, SC, USA;* [6]*Oncology Consultants, Houston, TX, USA;* [7]*City of Hope, Duarte, CA, USA,*[8]*START, San Antonio, TX, USA;* [10]*Dartmouth Cancer Center, Lebanon, NH, USA;* [10]*Molecular Templates, Austin, TX, USA;* [11]*Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA*

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-like binding domain.



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

1. **Directly kill PD-L1+ tumor and immunosuppressive cells**
2. **Remodel the tumor microenvironment by eliminating** PD-L1+ immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs).
3. Elicit cytomegalovirus (CMV) **CD8 T-cell response to tumor cells** by delivering HLA-A*02 restricted CMV peptide pp65 to the cell surface of PD-L1 expressing cells for recognition by cytotoxic cells.

FIGURE 1: MT-6402 Mechanisms of Action

Figure 1A: Internalization and Cellular Mechanism of Action

Figure 1B: MT-6402 Activity Pathways

CMV: cytomegalovirus, ETB: Engineered Toxin Body; MHC: major histocompatibility complex; PD-L1: programmed death ligand 1

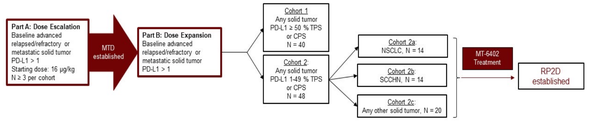
TABLE 1: ADCs vs. ETBs - Biology and MoAs

Antibody drug conjugate (ADC)	Engineered Toxin Bodies (ETB)
Off-target payload/drug release	Targeted removal of cells without off-target effects
Chemotherapy-based MOA	Novel MOA that allows for immunogenic cell death and potential to alter tumor immunophenotype
Payload/drug cannot internalize if receptor is non-internalizing	Self internalizing, can internalize even non-internalizing receptors

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

43 patients have been treated (**Table 2**) in Part A (dose escalation):

TABLE 2: Demographics (N = 43)

		16µg/kg	24µg/kg	32µg/kg	42µg/kg	63µg/kg	83µg/kg	Total
Number of Subjects		6	6	4	3	11	13	43
Age (years)								
	Mean	60.5	63.7	64.8	61	55.2	59	59.6
	SD	16.7	7.7	9.5	14	14	9.9	12.1
Sex								
	Male (%)	4 (66.7%)	5 (83.3%)	1 (25.0%)	3 (100%)	7 (63.6%)	7 (53.8%)	27 (62.8%)
	Female (%)	2 (33.3%)	1 (16.7%)	3 (75.0%)	0	4 (36.4%)	6 (46.2%)	16 (37.2%)
Disease								
	NSCLC	3 (50.0%)	1 (16.7%)	0	0	1 (9.1%)	2 (15.4%)	7 (16.2%)
	Melanoma	1 (16.7%)	1 (16.7%)	0	0	0	1 (7.6%)	3 (7.0%)
	Ovarian	1 (16.7%)	0	0	0	0	0	1 (2.3%)
	RCC	0	1 (16.7%)	0	0	1 (9.1%)	0	2 (4.7%)
	Pancreatic	0	1 (16.7%)	1 (25.0%)	0	2 (18.2%)	0	4 (9.3%)
	Breast	0	0	1 (25.0%)	0	0	2 (15.4%)	3 (7.0%)
	Colon, Rectum	0	0	1 (25.0%)	1 (33.3%)	3 (27.3%)	0	5 (11.6%)
	Gastric/Gastroesophageal	0	1 (16.7%)	0	1 (33.3%)	1 (9.1%)	0	3 (7.0%)
	Squamous Cell Head and Neck	1 (16.7%)	1 (16.7%)	0	0	2 (18.2%)	5 (38.5%)	9 (20.9%)
	Any other solid tumor	0	0	1 (25.0%)	1 (33.3%)	1 (9.1%)	3 (23.1%)	6 (14.0%)
Lines of Prior Treatment								
	Mean	2.3	4.7	5.5	4.0	3.6	3.0	3.6
	SD	0.8	2.4	2.5	1.0	1.4	1.6	1.8
HLA/CMV Status								
	HLA-A*02/CMV+	2 (33.3%)**	0	1 (25.0%)**	0	1 (9.1%)**	3 (23.1%)	7 (16.3%)

**Patient 1004-004 is HLA in-evaluable*
***Patients 1002-003, 1005-007, 1005-010 are CMV in-evaluable*

TABLE 3: PD-L1 Expression

	Patient ID	Historical PD-L1 Positivity and IHC
16µg/kg	1008-001	TPS 80%
	1004-002	TPS 70%
	1001-001	0.5% IC
	1002-003	CPS > 1
	1005-002	TPS 10%
	1004-003	CPS > 1
24µg/kg	1007-005	CPS 10
	1004-004	TPS 20%
	1001-002	TPS 10%
	1001-004	TPS 1%
	1008-002	TC 5%
	1001-005	CPS 3
	1005-005	5% IC
32µg/kg	1005-007	TPS 10%
	1001-006	CPS 15
	1005-008	TPS 1-20%
42µg/kg	1017-001	10% IC
	1024-001	20% IC
	1017-002	CPS 20-35
63µg/kg	1020-002	CPS 10
	1021-001	CPS 60
	1005-010	CPS < 10
	1005-011	CPS 10/TPS 9%
	1005-013	CPS 70
	1033-001	CPS 2
	1004-006	CPS 90
	1005-012	TPS 3-5%
	1022-003	CPS 70
	1017-003	CPS 50
	1020-004	CPS 30
83µg/kg	1017-004	CPS 20
	1033-003	CPS 90
	1020-006	TPS 50%
	1020-007	CPS 10
	1022-004	CPS 60
	1033-004	TPS 70%
	1021-002	CPS 3
	1022-005	CPS 20
	1023-002	CPS > 50
	1001-007	CPS 10
	1024-004	CPS 7
	1002-005	CPS 15
	1008-004	CPS 4/TPS2%

- Average age: 59.6 years (±12.1 years); 27 male (62.8%), 12 female (37.2%)
- 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 (Table 3)**

RESULTS: Safety

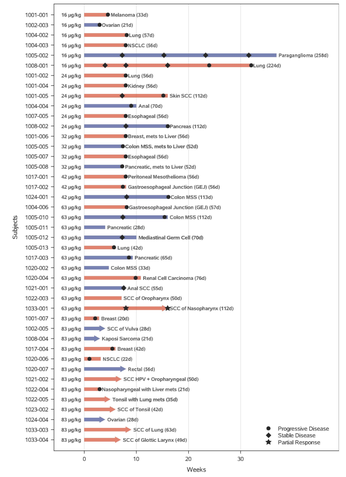
TABLE 4: Treatment Related AEs Grade ≥ 2 by Preferred Term and Cohort

All Treatment-Related AEs listed below have occurred in one patient unless otherwise noted.

Cohort	AE*	Grade	Comment
16µg/kg	Anemia	3	Patient entered study with Grade 2 anemia
	Anemia	2	
	Back pain	3	During infusion; treatment restarted within 30min after event resolved on Demerol and Phenergan; same patient had a prior Grade 2 IRR
	CRS (SAE)	2	Recovered within 2 days
	Decreased appetite	2	
	IRR	2	Recovered within 1 hour
	Pruritus	2	
	Pyrexia	2	
	Stomatitis	2	
24µg/kg	Cough	2	
	Dyspnea	2	
	Hypokalemia	3	
	Nausea	2	
	Pyrexia	2	
	Maculopapular Rash (DLT)	2	Improved within 1 day on systemic steroids
	Transaminases increased	2	
32µg/kg	No Treatment Related AEs Grade 2 or higher		
42µg/kg	Amylase Increased	3	Patient's gastric tumor progressed and compressed the biliary tree.
	Back pain	2	
	Lipase increased	3	
	Pruritus	2	
63µg/kg	Anemia	2	*Has occurred in 2 patients*
	Anemia	3	
	Back pain	3	
	IRR	2	*Has occurred in 2 patients* Both recovered within one hour
	IRR (DLT)	3	Resolved with 25mg Demerol and 40mg Solu-Medrol IV within 1.5 hours
83µg/kg	Muscle weakness	2	
	Fatigue	2	*Has occurred in 4 patients*
	IRR	2	Recovered within 1 day
	Pyrexia	2	
	Insomnia	2	

RESULTS: Responses in Two Patients

FIGURE 2: MT-6402 Time on Treatment



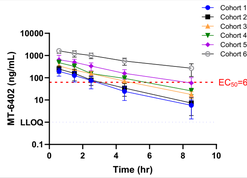
*** Patient 1008-001: Clinical, non-RECIST, response*

Immunotherapy non-responsive tumor type

Immunotherapy responsive tumor type

RESULTS: Pharmacokinetics

FIGURE 4: C1D1 Serum Concentration

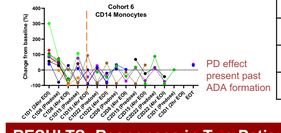


C_{max}, AUC, and half-life ($t_{1/2}$) from C1D1 are consistent with results from non-human primate studies, dose proportional exposure between 16 and 63 µg/kg, no accumulation after repeat dosing, and C_{max} 25-fold above IC_{50} at 83 µg/kg (established *in vitro* in CHO cells). Anti-drug antibody (ADA) develops in all patients by Day 15 but like other approved immunotoxins, pharmacodynamic effects post-ADA continue to be observed (**Figure 5**).

Cohort Dose (µg/kg)	N	$t_{1/2}$	Cmax (ng/mL)	C_{max}/EC_{50}	AUC_{last} (hr*ng/mL)
16	6	1.6 (± 0.17)	192.5 (± 73.6)	3	446 (± 205.4)
24	6	2.3 (± 0.14)	248.0 (± 90.9)	4	610 (± 317.4)
32	4	1.9 (± 0.84)	340.0 (± 26.3)	5	1028 (± 194.3)
42	3	2.1 (± 0.10)	476 (± 155.5)	8	1373 (± 445)
63	11	2.6 (± 0.4)	683 (± 318)	11	2254 (± 1275)
83	13	2.6 (± 0.4)*	1589 (± 371)*	25	7185 (± 2655)*

** PK data currently available for 9 patients*

FIGURE 5: Persistent PD response



PD effect present past ADA formation

RESULTS: Responses in Two Patients

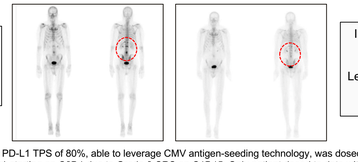
Altering tumor immunophenotype to redirect CMV specific T cells

PD-L1 targeted ETB provides distinct benefits for overcoming clinical challenges of checkpoint non-responsive tumors

- Fundamentally alters the tumor microenvironment (TME) through direct depletion, rather than inhibition, of PD-L1+ immunosuppressive cellular infiltrates (e.g., MDSCs)
- Direct killing of PD-L1 expressing tumor cells through irreversible ribosomal inhibition
- Delivery of CMV antigen to PD-L1 expressing tumor and immunosuppressive cells to HLA compatible patients, thereby leveraging host anti-viral immunity through redirection and expansion of circulating memory cytotoxic T-cells to the TME

FIGURE 6: Resolution of Majority of Osseous Metastases in High PD-L1+ NSCLC (HLA-A*02/CMV+)

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



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

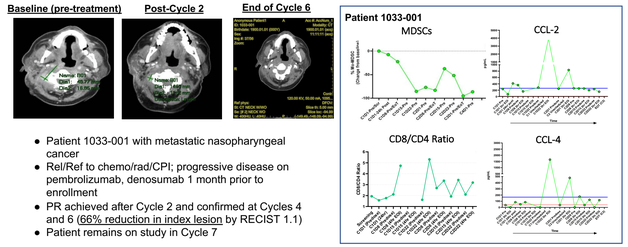
Patient 1008-001 (NSCLC) with PD-L1 TPS of 80%, able to leverage CMV antigen-seeding technology, was dosed at 16 µg/kg and then at a 50% reduction (8 µg/kg) starting on C2D1 due to Grade 2 CRS on C1D15. Only patient dosed to date with high PD-L1 expression able to leverage antigen seeding technology (HLA-A*02/CMV+).

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

MT-6402 depletes PD-L1+ immune cells and activates CD8 T-cells; Cytokines associated with TME disruption upregulated

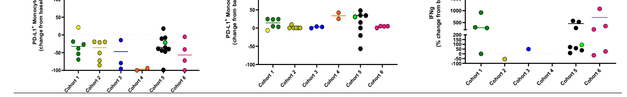
Metastatic nasopharyngeal cancer (NPC) patient treated at 63 µg/kg after progression on chemotherapy, radiation, and pembrolizumab. Tumor had PD-L1 expression of CPS 2% and patient is not HLA-A*02 (not AST engaged). RECIST Partial Response observed, suggesting altering of immunosuppressive cells in the TME by MT-6402. Clearance of immune cells may result in tumors increasing secretion of CCL2 and CCL4 to recruit immunosuppressive cells.

FIGURE 7: Confirmed PR in patient with CPI-refractory NPC and low PD-L1 expression at C2, confirmed at C4 and C6

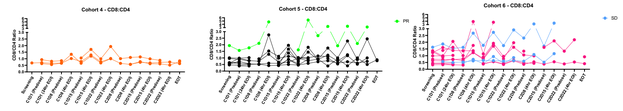


- Patient 1033-001 with metastatic nasopharyngeal cancer
- Rel/Ref to chemo/rad/CPI; progressive disease on pembrolizumab, denosumab 1 month prior to enrollment
- PR achieved after Cycle 2 and confirmed at Cycles 4 and 6 (66% reduction in index lesion by RECIST 1.1)
- Patient remains on study in Cycle 7

PD-L1+ immune cells are selectively depleted in the periphery of patients with MT-6402, removing immunosuppression and activating an effector T-cell profile (increased CD8/CD4 ratio). MT-6402 has no effect on target negative (PD-L1-negative) cells. Tumor data will be collected in Part B expansion.



CD8:CD4 T cell ratio



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.**
- **A long-lasting PR has been observed in one patient with CPI-refractory NPC (PD-L1 CPS 2%) indicating that clearance of immune cells may drive a response**
- **Regression of osseous metastases in a patient with NSCLC (PD-L1 TPS 80%, HLA-A*02/CMV positive) following disease progression on checkpoint inhibitors was observed in one patient, indicating that alteration of tumor immunophenotype may drive activity.**
- **MT-6402 has an acceptable safety profile:**
  - One Grade 2 dermatitis, one Grade 3 IRR, one Grade 1 asymptomatic high-sensitivity troponin were DLTs
  - No evidence of Capillary Leak Syndrome or other payload-derived toxicity
- **Six dose cohorts have completed with dosing continuing at 100 µg/kg**
- **Expansion monotherapy cohorts with pre- and on-treatment biopsies are planned in both high and low PD-L1 expressing tumor types due to evidence of activity in both high and low-PD-L1 expressing tumors.**

DISCLOSURES

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

Please contact Admasu Mamuye at admasu.mamuye@mtem.com for questions or comments.