A Phase 1 Study of MT-6402, a novel Engineered Toxin Body (ETB) targeting PD-L1, in patients with PD-L1 expressing advanced solid tumors

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

MT-6402 is a PD-L1 targeted engineered toxin body (ETB) composed of (Figure 1):

- De-immunized Shiga-like Toxin A subunit (SLTA) genetically fused to PD-L1 targeting antibody binding domain (scFv)
- HLA-A*02 restricted pp65 cytomegalovirus (CMV) antigen

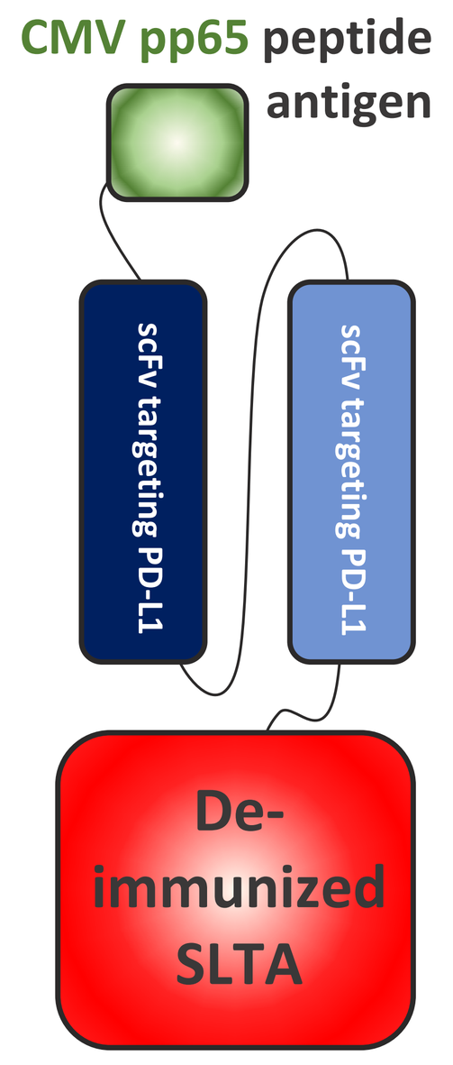
MT-6402 elicits novel dual anti-PD-L1 mechanisms of action

- 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+)

FIGURE 1: MT-6402 structure



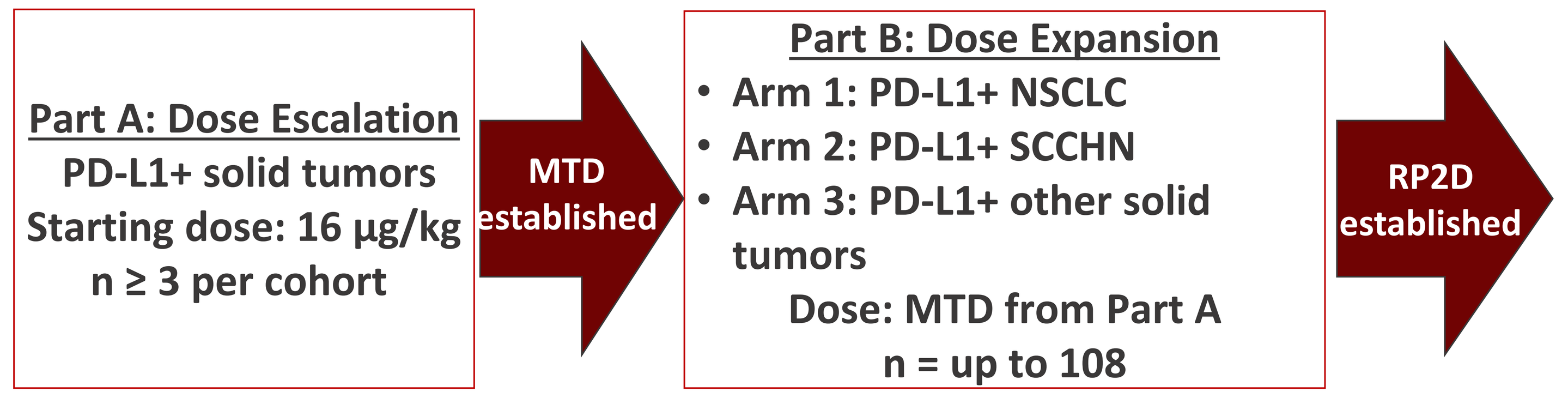
Currently approved PD-L1 targeting agents act through steric inhibition of PD-1/PD-L1 binding and are subject to the same mechanistic limitation: the inability to induce a sufficiently potent T-cell response to the existing tumor immunophenotype. MT-6402 may overcome this limitation through novel mechanisms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

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 (circulating cytokines and immune cells), efficacy (DoR, PFS, OS), and immunogenicity.
- **Exploratory endpoints:** Cytokine/chemokine profiles, overall 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
- **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: Study Schema



MTD=maximum tolerated dose; NSCLC=non-small cell lung carcinoma; PD-1=programmed cell death protein 1; PD-L1=programmed 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 (N = 12)

	Patient ID	Disease	Year of Birth	Sex	Prior CPI	HLA-A*02/CMV IgG positive	PD-L1 Assay	Result
Cohort 1 (16µg/kg)	1008-001	NSCLC	1945	M	Yes	Yes Yes	22C3	TPS 80%
	1004-002	NSCLC	1939	F	Yes	No	22C3	TPS 70%
	1001-001	Melanoma	1988	M	Yes	No	SP263	0.5% IC
	1002-003	Ovarian	1958	F	No	No	22C3	CPS > 1
	1005-002	Solid tumor	1974	M	No	No	22C3	TPS 10%
	1004-003	NSCLC	1958	M	Yes	Yes Yes	22C3	CPS > 1
Cohort 2 (24µg/kg)	1007-005	Esophageal	1951	M	Yes	Yes No	22C3	CPS 10
	1004-004	Solid tumor	1950	M	No	HLA TBD Yes	22C3	TPS 20%
	1001-002	NSCLC	1955	M	Yes	Yes No	22C3	TPS 10%
	1001-004	RCC	1971	F	Yes	Yes No	22C3	TPS 1%
	1008-002	Pancreatic	1960	M	No	No	SP142	5%
	1001-005	Skin SCC	1957	M	Yes	Yes Yes	22C3	CPS 3

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 prior Grade 2 IRR
	Anorexia	2	
	CRS (SAE)	2	Recovered within 2 days
	Fever	2	
	IRR	2	Recovered within 1 hour
	Pruritus	2	
	Nausea	2	
Cohort 2 (24µg/kg)	Rash	3	Improved within 1 day on systemic steroids
	Fever	2	

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

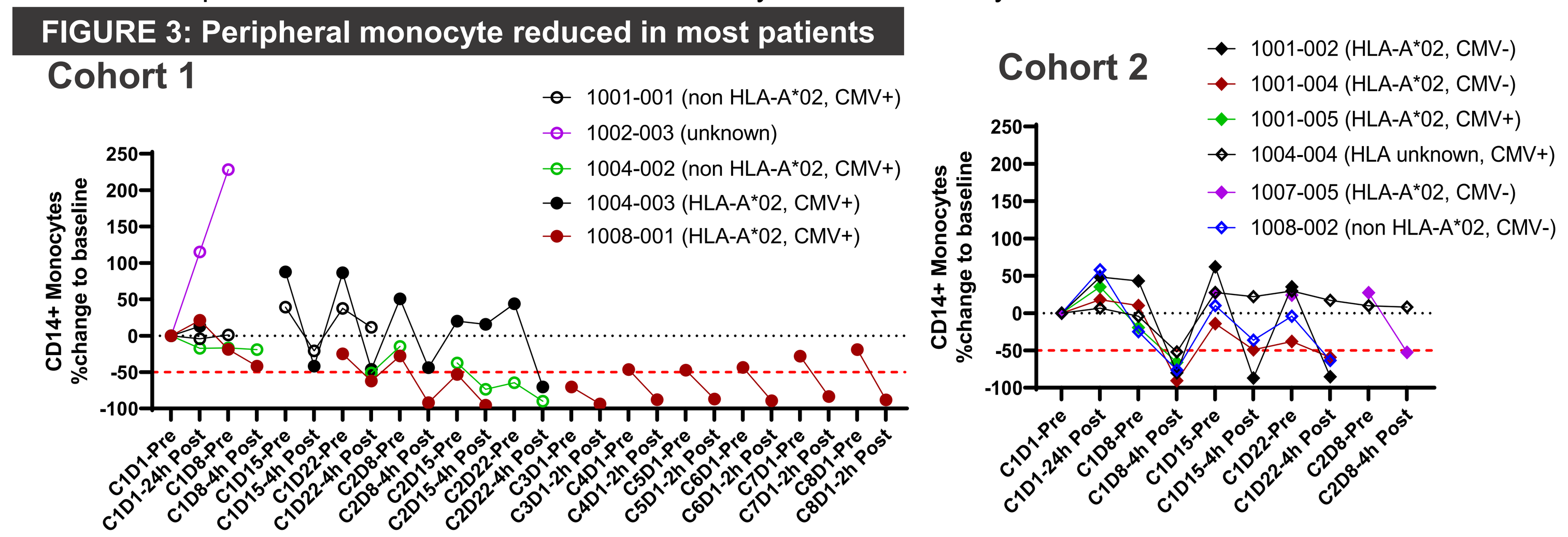
RESULTS: Pharmacokinetics (Cohort 1)

- C_{max}, AUC, and half-life was 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 neutralizing as pharmacodynamic effects post-ADA continue to be observed.

RESULTS: Pharmacodynamics (Cohort 1 and Cohort 2)

- CD14⁺ monocyte counts decreased by >50% in 3/6 patients (Cohort 1) and 6/6 patients (Cohort 2) regardless of AST engagement status (**Figure 3**)
  - The 3 patients with CD14⁺ monocyte counts that decreased by > 50% Cohort 1 achieved this in Cycle 2. 5/6 patients in Cohort 2 achieved this monocyte reduction in Cycle 1.

FIGURE 3: Peripheral monocyte reduced in most patients



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

RESULTS: Pharmacodynamics (Cohort 1)

FIGURE 4: Peripheral elimination of key immunosuppressive cell types

- Peripheral myeloid derived suppressor cells (MDSCs) and T regulatory cells (Tregs) reduced in all patients
- MDSCs are a key cell type linked with response to checkpoint therapy. This may represent a shift toward an immune active phenotype.
- **The effects on peripheral immunosuppressive cells appear unique to MT-6402 and have not been reported with traditional checkpoint therapy**

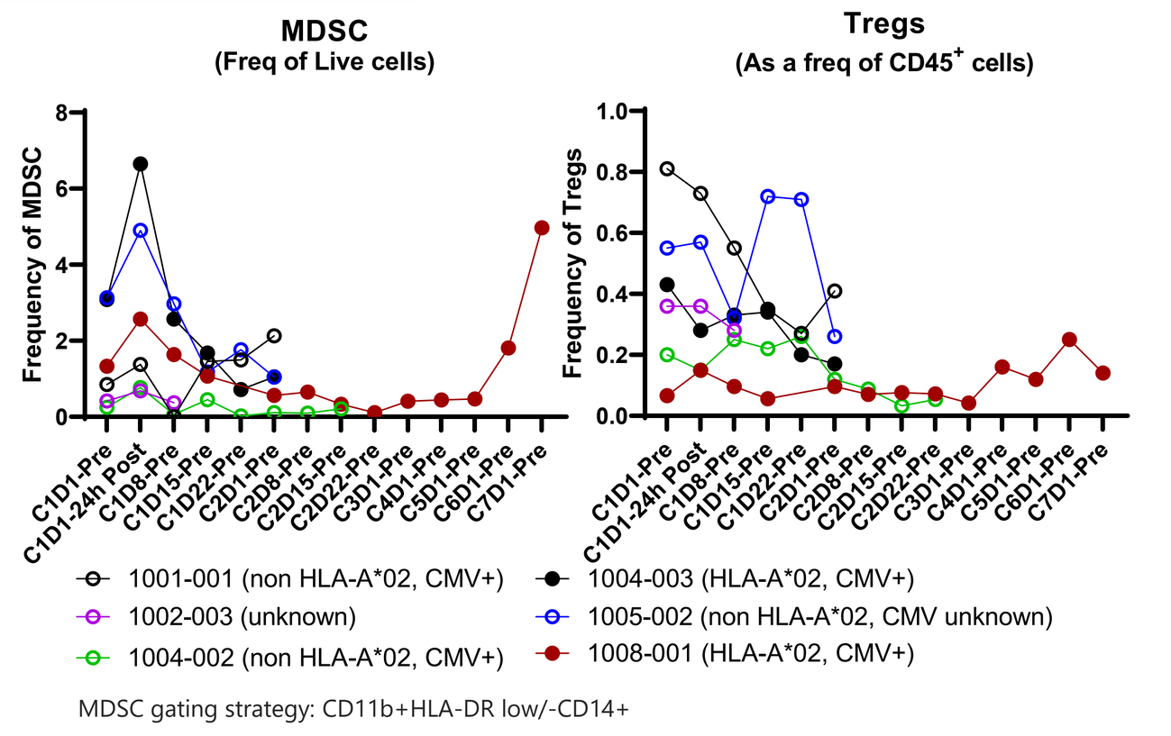
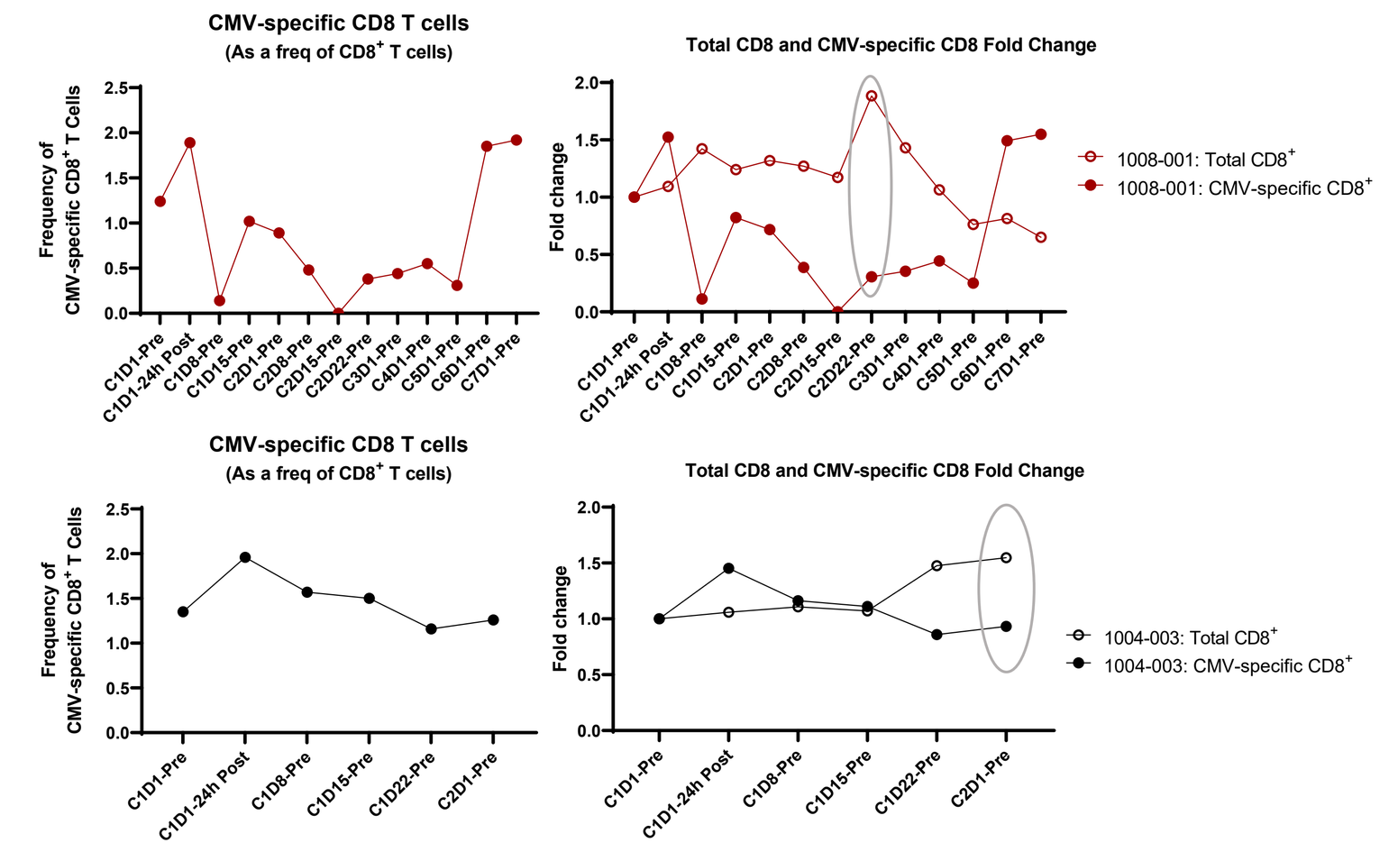


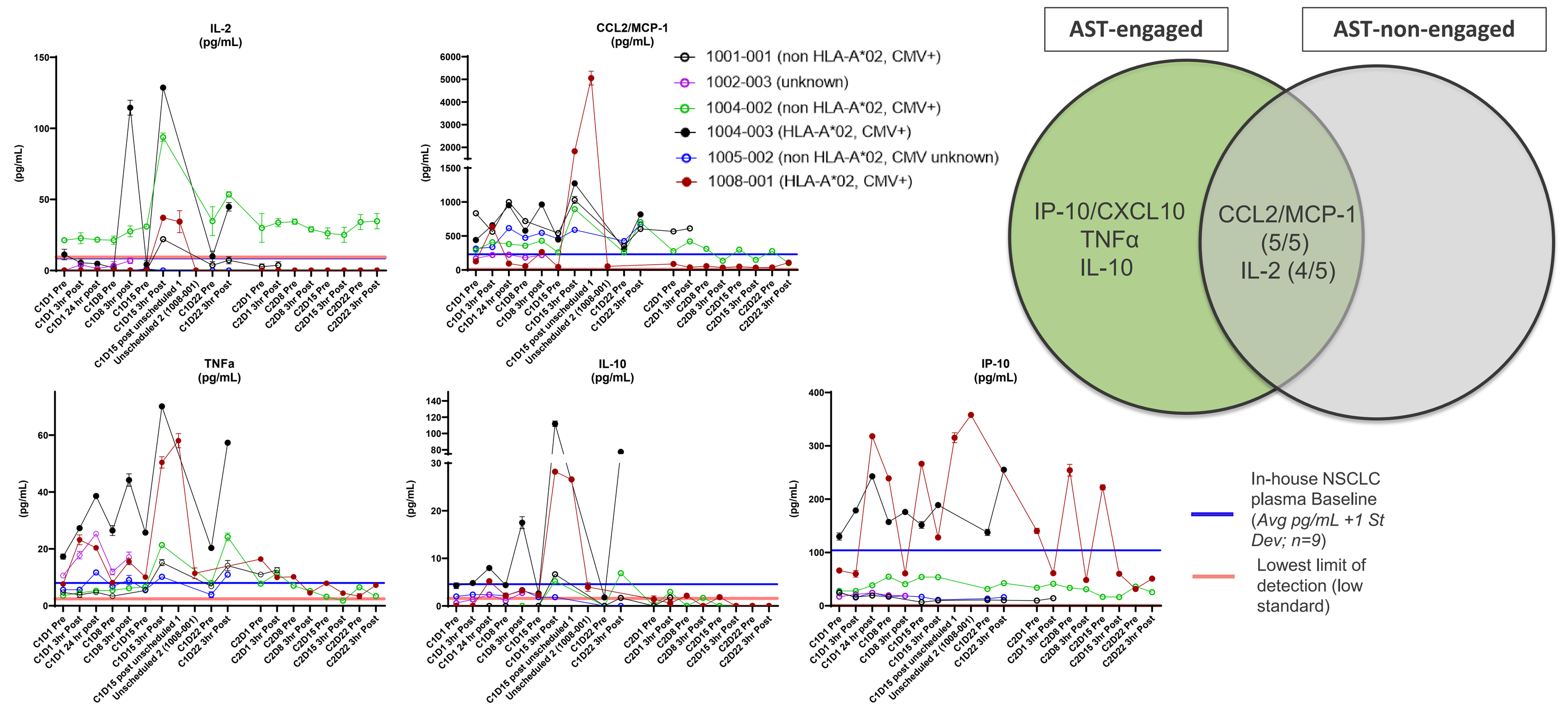
FIGURE 5: First evidence of antigen seeding technology engagement

- CMV-specific T cells appear to have extravasated in both AST-engaged patients (1008-001, 1004-003)
- Pre-dose PD-L1 expression higher in 1008-001, compared to 1004-003 (TPS 80% vs CPS 1), likely inducing more AST. Data not available for 1001-1005.
- **Effect is specific for CMV-T cells as antigen-independent peripheral CD8+ T cells do not change within same patient**



RESULTS: Cytokine comparison between AST-engaged and non-engaged patients

FIGURE 6: Elevated Cytokine Profiles for AST-engaged vs. non-engaged patients



- IP-10 upregulation occurs with each dosing **ONLY** in AST-engaged patients
- **Serum IP-10 may be used as a biomarker for AST-engagement**

TABLE 3: Clear differentiation in cytokine expression within AST-engaged patients

	Cytokines*	PBMC Changes	
All Patients (Irrespective of HLA or CMV status)	▲ CCL2/MCP-1	▼ Monocytes ▼ MDSCs	**Movement of myeloid cells to tissues and/or direct cell kill**
	▲ IL-2	▲ Tbet+ CD8 Tcells ▲ NK cells	**Global T cell activation due to checkpoint break**
AST-Engaged Only (HLA-A*02, CMV+)	▲ TNFa ▲ IL-10	▲ Peripheral CD8 T cells ▲ Peripheral CMV-specific T cells (initial expansion)	**Checkpoint break plus AST driven activation of CMV-specific T cells**
	▲ IP-10/CXCL10	▼ Peripheral CMV-specific T cells (after first dose) ▼ Peripheral dendritic cells	**Migration of dendritic cells and CMV-specific T cells from periphery**

** Listed cytokines are not comprehensive; panel contains 24 total cytokines, some of which were below limit of detection, some were unchanged, and others did not show trends*

RESULTS: Patient 1008-001: Correlation of pharmacodynamic markers with clinical outcome

- AST-engaged patient with osseous metastases from NSCLC (non-measurable lesions) with history of treated brain lesions (no CNS lesions evaluable at study entry)
- Demonstrated marked CMV-specific T-cell extravasation at C1D8 and serum cytokine signatures consistent with antigen dependent responses and T cell mobilizations, suggesting engagement of MT-6402 AST pathway (**Figure 5**)
- Grade 2 cytokine release syndrome (CRS) on C1D15 with complete recovery in two days. Resumed treatment at 50% reduced dose (8 µg/kg).

★ C4D15: reduction in number and uptake of bone lesions on bone scan
★ C6D15: appearance of sub-centimeter brain metastases. Further treatment approved due to lack of alternative local or systemic treatment options and good general health
☆ C8D1: withdrawal from treatment due to increased uptake in osseous metastases on bone scan

FIGURE 7: Patient 1008-001 CD14+ Monocytes, MDSCs, and CMV-specific T-cells on Treatment

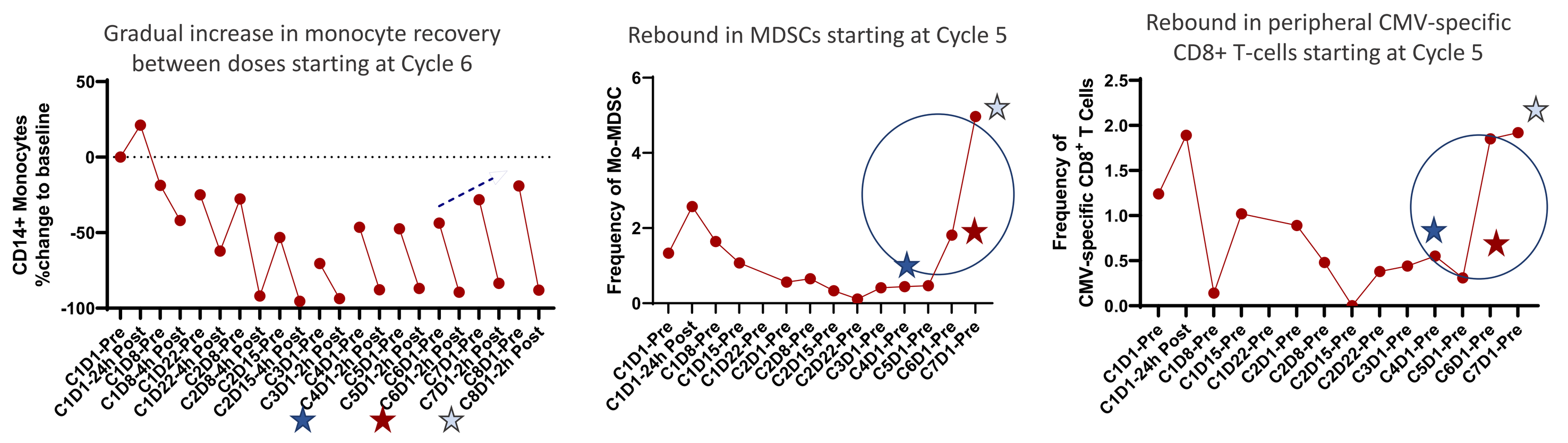
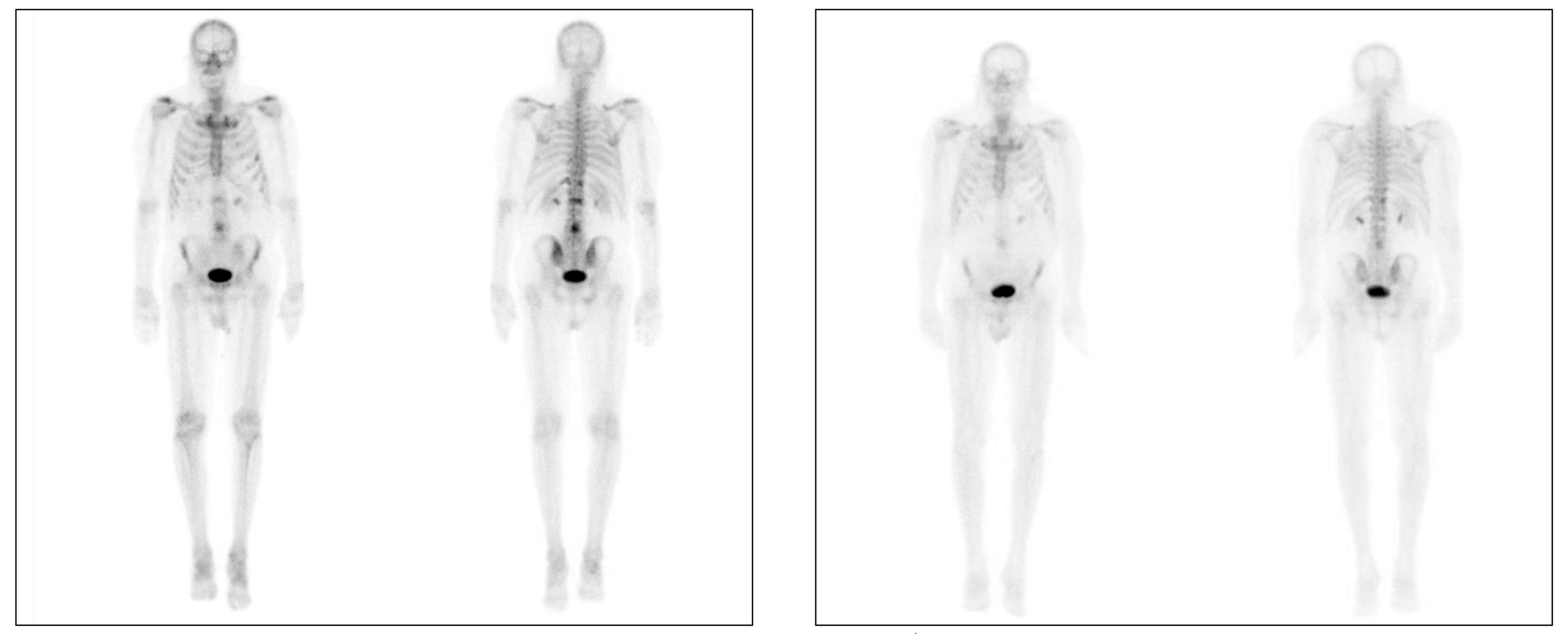


FIGURE 8: Qualitative reduction in non-measurable disease in Patient 1008-001



01JUL2021
Metastatic uptake: L1, T11, left 11th rib, left 5th rib, right ischial tuberosity.

★ **27OCT2021**
Interval decrease of T11, L1 has mostly resolved.
Left 5th rib resolved, left 11th rib resolved

Note: these images are untouched and are presented exactly as provided to MTEM.

CONCLUSIONS

- **MT-6402 represents a wholly unique approach to checkpoint modulation, demonstrating changes in peripheral immunophenotypes and cytokines/chemokines consistent with anti-tumor immunity.**
- **Unlike traditional immune checkpoint inhibitors, MT-6402 displays the potential to remodel patient immunity toward a more "checkpoint responsive" phenotype.**
- **These data provide rationale for potential combination of MT-6402 with traditional PD-1 inhibitors in patients whose tumors have been unresponsive to checkpoint inhibitors. Combination studies being considered.**
- **Dose escalation is ongoing.**

DISCLOSURES

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

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