A clinical stage Engineered Toxin Body (ETB) targeting PD-L1 (MT-6402) induces peripheral pharmacodynamic responses unique from PD-L1 monoclonal antibodies

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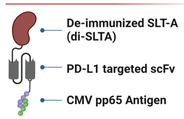
Abstract 736

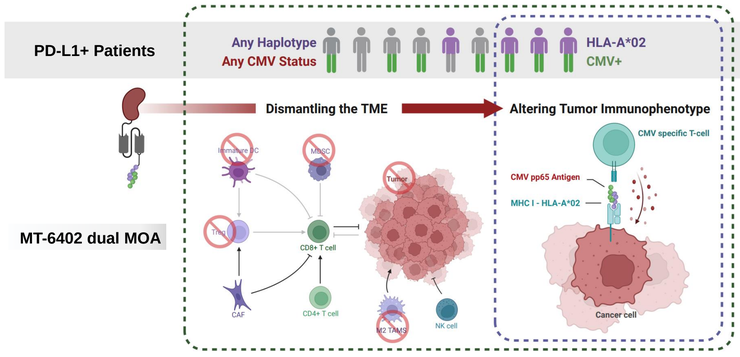
Targeting PD-L1 with MT-6402 represents a differentiated approach to Immunotherapy

MT-6402: PD-L1 Targeting ETB
De-immunized SLTA toxin with Antigen Seeding Technology (AST)



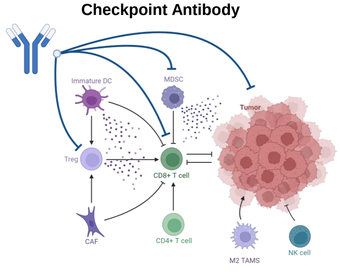
MT-6402 characteristics	
Binding affinity	Low nanomolar
Potency	Low picomolar
Size	110 kD
Half-life	~2.5 hrs

MT-6402: PD-L1 targeting ETB with dual I/O Mechanisms of action

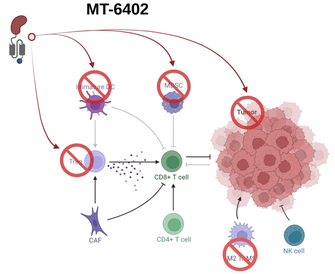


- **MT-6402 potently kills PD-L1+ tumor and immune cells (pM IC50) to dismantle the tumor microenvironment and restore T-cell biology**
- **MT-6402 can alter the tumor immunophenotype to redirect a CMV specific T-cell response to the tumor**

Checkpoint Antibody



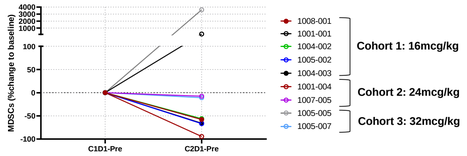
MT-6402



Antibody mediated checkpoint blockade	ETB-mediated PD-L1⁺ cell clearance
Steric hinderance of PD-1/PD-L1 checkpoint axis	Targeted removal of PD-L1⁺ tumor or immune cells for fundamental alteration of the TME's cellular content
Checkpoint positive immunosuppressive cells remain present	Removal of PD-L1+ suppressive immune cells
Potentiates activation of tumor targeting cytotoxic T cells	Potentiates activation of tumor targeting cytotoxic T cells
No direct effect on tumor cells	Direct cell kill of PD-L1+ tumor cells
No secondary mode of action	Delivers CMV antigen and redirects antigen specific cytotoxic T cells

Depletion of MDSCs restores T-cell biology in the periphery

MT-6402 drives depletion of myeloid-derived suppressor cells (MDSCs)



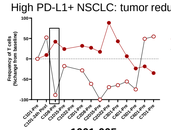
After cycle 1, MDSCs are depleted in the periphery in 7/9 patients. MDSCs return to the periphery only when VEGF levels are reduced (right)

Trafficking of NLVP-specific T cells is driven by Antigen Seeding Technology

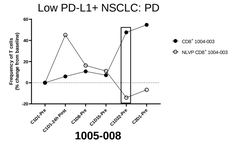
AST engaged patients (HLA-A*02 and CMV positive) show trafficking of NLVP specific T cells

- 4/19 patients enrolled to date were AST engagers. 1/4 of these patients had high tumor PD-L1 positivity.
- Each of the AST engaged patients show NLVP specific T cell movement after dosing.
- The total CD8+ T cell population increases, indicative of checkpoint break.

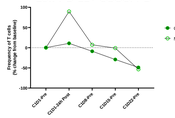
1008-001
High PD-L1+ NSCLC: tumor reduction



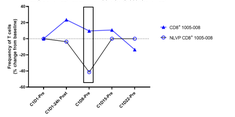
1004-003
Low PD-L1+ NSCLC: PD



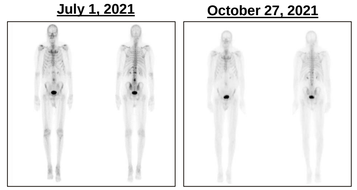
1001-005
Low PD-L1+ CSCC: PD



1005-008
Low PD-L1+ Pancreatic: PD



July 1, 2021 | **October 27, 2021**



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

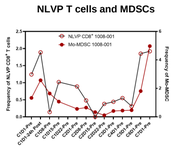
Interval decrease of T11 and L1 has mostly resolved. Left 5th rib and left 11th rib lesions have resolved.

This patient who had PD-L1 TPS 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.

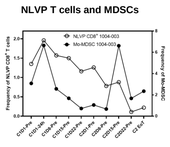
Trafficking of NLVP-specific T cells is driven by Antigen Seeding Technology but is dependent on MDSC clearance

- **Trafficking of NLVP specific T-cells correlates tightly with reduction in MDSCs**
  - Non-CMV-specific T-cells do not track with MDSCs
- **No trafficking observed in patients when peripheral MDSCs are high**
  - MDSCs are known to inhibit T-cell trafficking
  - MDSCs are key inhibitors of T-cell mediated therapies (i.e. CAR-T, bispecifics) in solid tumor
- **Trafficking of NLVP T-cells in patients observed when peripheral MDSCs are low**

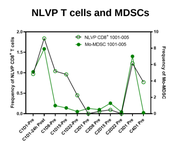
1008-001
High PD-L1 NSCLC: tumor reduction



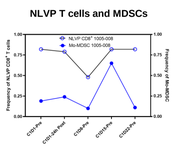
1004-003
Low PD-L1+ NSCLC: PD



1001-005
Low PD-L1+ CSCC: PD

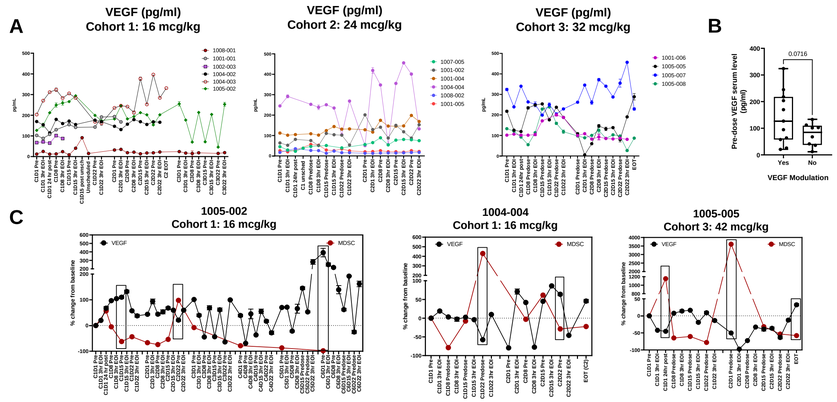


1005-008
Low PD-L1+ Pancreatic: PD



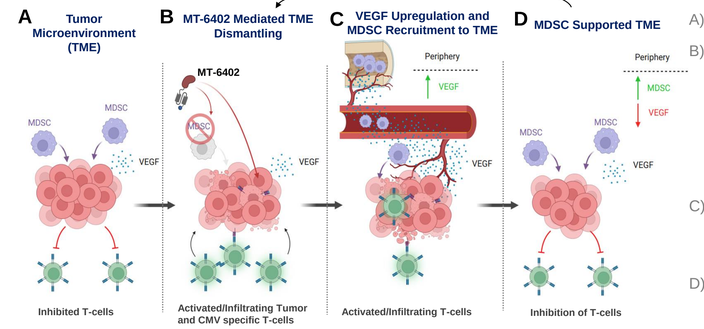
MT-6402 induces unique peripheral PD responses in patients

VEGF is released with MT-6402 dosing, and is inversely correlated to peripheral MDSCs



A) After multiple MT-6402 doses, a "sawtooth" pattern of VEGF secretion emerges subsequent to each MT-6402 dose. Increasing MT-6402 drives VEGF modulation earlier in treatment.
B) 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. There appears to be no functional consequence to ADA.
C) VEGF and MDSC levels in the periphery are inversely correlated

MT-6402 demonstrates unique pharmacodynamic responses indicative of tumor dismantling and remodeling



A) MDSC and inhibited T cell infiltrated TME (1).
B) MT-6402 removes immunosuppressive MDSCs, and PD-L1+ tumor cells to release checkpoint and allow tumor specific T cell infiltration. In AST engaged patients, CMV antigen is seeded to change tumor cell immunophenotype and attract CMV specific T cells.
C) Tumor damage results in VEGF release to attract MDSCs from blood and bone marrow, and suppress T cell function (2, 3).
D) Immunosuppressive TME returns, until patients are dosed again with MT-6402.

Conclusions

MT-6402 is a clinical stage PD-L1 targeted ETB with novel pharmacodynamic effects not seen with traditional monoclonal antibody-based checkpoint inhibitors

- Designed to directly kill PD-L1 expressing tumor cells, leverage existing CMV-specific cytotoxic T cell responses, and eliminate PD-L1⁺ immunosuppressive cell types in the tumor microenvironment (remodeling the TME)
- Elimination of peripheral myeloid-derived suppressor cells (MDSCs) observed, potentially licensing CMV T cells to traffic to antigen seeded tumor. MDSC loss coincides with rises in serum VEGF.
- Selective re-direction of CMV-specific T cells in HLA-A2/CMV⁺ subjects (likely extravasation to the tumor). Tumor biopsies from phase 1 dose expansion studies will confirm tumor targeting.
- MT-6402 is driving pharmacodynamic responses that are differentiated from those seen in the checkpoint inhibitor therapeutic landscape

MT-6402 is in phase 1 dose escalation (NCT04795713), for more information, see SITC 2022 Poster #764, or follow the QR code. **References**: (1) Chen and Mellman, *Immunity*, 2013 (2) Yang et al, *Frontiers in Immunology*, 2018 (3) Bourhis et al, *Frontiers in Immunology*, 2021. Figures made with Biorender (Biorender.com)

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