764 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 MT-6402 is a unique, potent PD-L1-targeted engineered toxin body capable of directly killing PD-L1 expressing tumor and immune cells by internalization of a de-immunized Shiga-like toxin A subunit (SLTA), which results in permanent SLTA-mediated ribosomal inactivation. Targeting PD-L1 expressing tumor cells may directly drive tumor regression, whereas targeting of PD-L1 expressing immune cells (IC) may release immunosuppression and drive immune recognition of the tumor. MT-6402 also delivers an HLA-A*02 restricted cytomegalovirus (CMV) class I antigen into PD-L1 expressing cells (antigen seeding) that can be recognized by existing CMV-specific cytotoxic T cells.

Methods A first-in-human dose escalation and expansion study (QW in 4-week cycles) was initiated in 2021.

Results 18 patients with PD-L1-expressing advanced solid tumors received $\geq$ 1 dose of MT-6402. 14 patients were eligible for Dose Limiting Toxicity (DLT) assessment in Cohorts 1 through 4. MT-6402 was well tolerated and no DLT was observed in Cohorts 1 and 3 (16 µg/kg and 32 µg/kg, respectively). 1 DLT of a Grade (G)2 maculopapular rash occurred in Cohort 2 (24 µg/kg). There was no G4 or G5 adverse events (AEs) or treatment-related discontinuations in the first 3 cohorts. Immune-related AEs of Infusion-related reaction (G1 and G2) and cytokine-release syndrome (G1 and G2) occurred, generally lasting 1-2 days.

2 patients in Cohort 1 had stable disease for 8 months. A significant reduction in CD14+ monocytes was observed after each administration, indicating HLA-independent pharmacodynamic effect. Dose dependent reduction of monocytes was observed across 3 cohorts and correlated with CCL2 and IL-8 modulation. PD-L1-negative peripheral monocytes and dendritic cell populations were spared, indicating on-target removal. Most patients display CD8 T cell expansion/activation and IL-2 and TNFα cytokine release, consistent with removal of PD-1/PD-L1 interaction.

One patient with high PD-L1 expression and osseous metastases who is HLA-A*02/CMV+ showed complete CMV-specific T-cell extravasation by C1D8, persisting until C6, and serum cytokine signatures consistent with antigen dependent responses and T cell mobilization. This patient had reduced tracer uptake of metastatic bone lesions with resolution of 3 lesions. 3 additional HLA-A*02/CMV+ patients with low PD-L1 expression followed a similar trend of extravasation of peripheral CMV-specific T cells.

Conclusions These results describe a novel approach to checkpoint modulation by MT-6402 with a potential to alter tumor immunophenotype particularly in patients with HLA-A*02/CMV positivity. Dose escalation is ongoing. These results provide compelling rationale for continued development of MT-6402, including in the R/R setting, possibly in combination with PD-1 inhibitors.

Trial Registration NCT04795713

Ethics Approval This study was conducted in compliance with current Good Clinical Practice (GCP) standards as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for GCP, all applicable national, state, and local laws and regulations, and the applicable Institutional Review Board/Independent Ethics Committee (IRB/IEC) and other institutional requirements.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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