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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Background PD-L1 targeting mAbs have had success in the clinic for a variety of solid tumors and specific patient subsets. To date, all PD-L1 mAbs rely on blocking the PD-1/PD-L1 axis through steric hindrance for their activity. MT-6402 is a clinical stage ETB that binds to PD-L1, triggers receptor internalization, and induces cell death of PD-L1+ cells through ribosomal destruction. MT-6402 represents a wholly novel approach to targeting PD-L1 expressing immune and tumor cells built upon the clinical hypothesis that elimination rather than blocking of PD-L1+ tumor and immune cells could transform immune tolerant tumor microenvironments (TME) to immune augmenting phenotypes. To this end, MT-6402 also carries a CMVpp65 peptide capable of HLA-A*02 restricted antigen presentation designed to redirect CMV-specific cytotoxic T cells to tumor tissue. Thus far, MT-6402 has completed three dosage cohorts (n=16) in a phase 1 dose escalation trial. Here we show changes in serum vascular endothelial growth factor (VEGF) correlate with peripheral reductions in monocyte derived suppressor cells (MDSCs), both biomarkers of potential TME alterations and a unique peripheral effect not seen with PD-L1 blocking mAbs.

Methods Peripheral blood mononuclear cells (PBMC) from MT-6402-dosed patients were stained with surface antibodies and acquired on a flow cytometer to identify CD11b+CD14+HLA-DR-/low Monocytic MDSCs. Luminex was used to quantify VEGF concentrations in patient matched serum.

Results A sawtooth pattern of peripheral VEGF levels emerged in 5/7 patients with higher pre-dose VEGF levels (>125pg/ml) following multiple doses of MT-6402 and indicative of a tumor remodeling response. A gradual VEGF increase in cohort 1 cycle 1 correlated with peripheral MDSC extravasation into tissue or TME. For cohorts 2 and 3, an inverse relationship between VEGF concentrations and MDSC frequencies emerged, where spikes in MDSCs correlated to sharp reductions in serum VEGF levels. Overall, PBMC phenotyping and cytokine data demonstrated an inverse correlation of MDSC frequencies and VEGF concentrations across dosage cohorts.

Conclusions PD-L1 expression on tumor and immune cells have non-redundant contributions to the maintenance of the TME and disease progression. Current PD-L1 antibodies physically inhibit PD-L1 and PD-1 interaction but do not fully inhibit PD-L1+ immune cell functions that contribute to TME maintenance (i.e., cytokine/chemokine secretion). Unlike PD-L1 antibodies, MT-6402 was designed to destroy PD-L1+ immune cells in a target-specific manner. We demonstrate here that MDSCs are depleted in the periphery of patients treated with MT-6402 and that this depletion appears related to peripheral changes in VEGF and alterations of the TME.

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 Harmonization 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.