136 ATA3271: AN ARMORED, NEXT-GENERATION OFF-THE-SHELF, ALLOGENEIC, MESOTHELIN-CAR T CELL THERAPY FOR SOLID TUMORS

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Background Mesothelin (MSLN) is a GPI-anchored membrane protein with high expression levels in an array of malignancies including mesothelioma and is an attractive target antigen for tumor surface antigen-targeting therapies. Regional administration of autologous, 2nd generation MSLN-targeted CAR-T cells for malignant pleural mesothelioma has shown promise in early clinical evaluation.[1 2] More recently, a next-generation MSLN-targeted, autologous CAR T therapy leveraging 1XX CAR signaling and PD1DNR is currently under investigation for advanced mesothelioma [NCT04577326]. Although autologous MSLN CAR-T holds promise, an allogeneic approach may have more widespread application. EBV T-cells represent a unique, non-gene edited approach for allogeneic T-cell therapy. EBV-specific T-cells are currently in a phase 3 trial for EBV-positive post-transplant lymphoproliferative disease [NCT03394365] and, to-date, have demonstrated a favorable safety profile with no evidence for GvHD and cytokine release syndrome attributable to EBV T-cells. Clinical proof-of-principle studies for CAR transduced CD19-targeted allogeneic EBV T-cell therapies have shown acceptable safety and durable response.[3] The first preclinical evaluation of ATA3271 was reported last year.[4] Here, we describe updated preclinical data for this potential off-the-shelf, allogeneic cell therapy.

Methods We engineered MSLN CAR+ EBV T-cells (ATA3271) with a novel 1XX signaling domain that is associated with strong effector function and favorable persistence, as well as armored with PD1DNR to provide intrinsic checkpoint blockade.[5] Anti-tumor effect of ATA3271 was assessed using a MSTO-211H-derived tumor cell line overexpressing MSLN and PDL1.

Results Upon MSLN engagement, ATA3271 showed proliferation, efficient tumor cell lysis in the presence of high-level cell-surface PD-L1 expression and secretion of effector cytokines [IL-2, TNF-α, granzyme B]. In a 16-day serial stimulation assay, with PD-L1+ tumor cells added every 2–3 days, ATA3271 expanded 4 to 45-fold without the need for external cytokines, and retained comparable antitumor function as CD3/CD28-stimulated 'autologous' CAR-T cells. In an orthotopic mouse model of pleural mesothelioma, ATA3271 demonstrated anti-tumor efficacy without toxicities. Memory markers [CD62L, CCR7] play a key role for T-cell persistence in vivo. We identified donor-to-donor variability in memory marker expression on ATA3271 and optimized our process to maximize their expression. Memory marker expression impact on ATA3271 potency, both in vitro and in vivo, will be presented.

Conclusions Overall, these in vitro and in vivo data show potent anti-tumor activity without evidence of toxicity, suggesting that ATA3271 may be a promising approach for the treatment of MSLN-positive cancers that warrants further clinical investigation.

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