ENHANCEMENT OF TCR-ENGINEERED T-CELLS TARGETING MAGE-A4 ANTIGEN BY CO-EXPRESSION OF CD8α AND INHIBITION OF AKT SIGNALING DURING EX VIVO T-CELL EXPANSION

Emily Schmidt, Katerina Mardilovich, Natalie Bath, Gareth Betts, William Spinnere, Kathryn Sun, Ian Donaldson, Cheryl McAlpine, Raymond Luke, Jean-Marc Navenot, Joseph Sanderson, Phil Bassett, Chris Evans, Karen Miller, Quan Lin, Mark Dudley, Alex Tipping*. Adaptimmune, Abingdon, UK

Background Autologous Specific Peptide Enhanced Affinity Receptor (SPEAR) T-cells targeting MAGE-A4 can be effective treatment for solid tumors.1–3 To improve efficacy, we developed a next-generation SPEAR-T cell targeting MAGE-A4 co-expressing CD8α (ADP-A2M4CD8). ADP-A2M4CD8 is under investigation in the Phase 1 SURPASS trial (NCT04044859). Enhancements have also been made to the manufacturing process with an AKT inhibitor (AKTi) during ex vivo expansion to provide a greater proliferative potential and enhanced memory phenotype.4

Methods SPEAR-T cells were manufactured using a Lentiviral vector with CD8α and MAGE-A4 targeted TCR genes. AKTi was added during ex vivo expansion. T-cell attributes were evaluated, including markers of differentiation (flow cytometry), capacity for in vitro tumor lysis (Incucyte) and changes to gene expression (scRNASeq) initially assessed with the first-gen product. Post-infusion, the presence of transduced T-cells in the peripheral circulation (PCR) and levels of inflammatory cytokines in serum (MesoScale Discovery Assay [MSD]) were evaluated.

Results As of May 24, 2021, 18 patients with 9 different primary tumor types were evaluable. Twelve pts received product that had AKTi during manufacture. Five patients had objective responses (RECIST), and 10 had stable disease. Responses occurred at lower MAGE-A4 expression levels and lower transduced T-cell doses relative to the first-gen product targeting MAGE-A4.1 CD4 T-cells from manufactured ADP-A2M4CD8 demonstrated direct in vitro tumor cell killing similar to CD8+ T-cells (Incucyte). scRNASeq gene expression profiles of first-gen ADP-A2M4 product manufactured with AKTi revealed the AKTi-expanded T-cells had a greater proliferation or an enhanced memory phenotype; scRNASeq analyses are ongoing for the ADP-A2M4CD8 product. An increase in IL-12 levels (MSD) in serum post-infusion suggests that endogenous immune cells are being activated, further resulting in increased levels of IFN gamma (MSD) secretion relative to patients who received first-gen product. Manufacturing with AKTi resulted in T-cells with a less differentiated phenotype (flow cytometry), and post-infusion was associated with enhanced antigen-specific serum cytokine responses, increased proliferative state (i.e., elevated levels of IL-2), and higher persistence of T-cells in peripheral blood by PCR.

Conclusions SPEAR T-cells targeting MAGE-A4 expressing cancers have been enhanced by co-expressing CD8α and adding AKTi during manufacture. These enhanced products improve CD4+ T-cell killing, release more inflammatory cytokines, proliferate more robustly with an early memory phenotype, and better engage the patient’s endogenous immune system when compared to first-gen products or next-gen manufactured without AKTi.

Trial Registration NCT04044859

REFERENCES

http://dx.doi.org/10.1136/jitc-2021-SITC2021.373