147 MEMORY PHENOTYPE IN ALLOGENEIC ANTI-BCMA CAR-T CELL THERAPY (P-BCMA-ALLO1) CORRELATES WITH IN VIVO TUMOR CONTROL

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Background The emergence of CAR-T cell therapy has transformed the treatment of refractory/relapsed multiple myeloma (MM). Yet, autologous CAR-T cells suffer from many manufacturing challenges including mainly consistency, toxicity, and cost. To address these issues, we engineered a fully allogeneic anti-BCMA CAR-T cell candidate for MM from healthy donors (P-BCMA-ALLO1). Herein, we demonstrate that this therapy maintains a stem cell memory T cell (TSCM) phenotype through editing which correlates with in vivo antitumor efficacy.

Methods Using Poseida's non-viral piggyBac® (PB) DNA Delivery System in combination with the high-fidelity Cas-CLOVER™ (CC) Site-Specific Gene Editing System and a proprietary 'booster molecule', we generated P-BCMA-ALLO1 from healthy donor T cells. We used CC to eliminate surface expression of both the TCR and MHC class I to make fully allogeneic CAR-T cells. In addition to the CAR molecule, PB enables the delivery of a selectable marker allowing the generation of a final cell product that is >95% CAR-positive. The inclusion of the 'booster molecule' in the manufacturing process improves the expansion of gene-edited cells without compromising memory phenotype or function. This process can produce up to hundreds of patient doses from a single manufacturing run which significantly reduces manufacturing cost per dose. We characterized the memory phenotype of P-BCMA-ALLO1 by assessing the mRNA and protein expression profiles of rested and activated CAR-T cells by flow cytometry and Nanostring analysis. We also assessed the antitumor capabilities of these cells using cytotoxicity assays and performed serial in vitro restimulation to assess the ability of P-BCMA-ALLO1 to undergo multiple rounds of activation and expansion. We then evaluated the relationship of these characteristics with in vivo efficacy, as defined by control of tumor in an immunodeficient RPMI-8226 subcutaneous murine tumor model.

Results P-BCMA-ALLO1 is comprised of a high frequency of TSCM. It has potent in vivo antitumor activity, which is comparable to non-edited autologous anti-BCMA CAR-T cell therapy. Expression of memory markers at both mRNA and protein levels across individual lots significantly correlates with in vivo tumor control. Conversely, suboptimal research products with worse in vivo outcomes expressed an exhausted gene expression profile. Moreover, CAR-T products that are more effective in vivo are also more viable, cytotoxic, and proliferative following multiple rounds of restimulation in vitro.

Conclusions P-BCMA-ALLO1 is a highly potent and safe allogeneic anti-BCMA CAR with a manufacturing process that consistently maintains a TSCM phenotype, which correlates with antitumor efficacy. P-BCMA-ALLO1 is advancing rapidly towards the clinic (NCT04960579).

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