265 ADI-925: AN ALLOGENEIC OFF-THE-SHELF CHIMERIC ADAPTER (CAD) γδ T CELL THERAPY TARGETING NKG2D LIGAND-EXPRESSING CANCERS

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Background γδ T cells are a clinically active cytotoxic effector subtype that are correlated to improved survival in a broad range of solid and hematologic malignancies. γδ T cells target tumors through innate and adaptive mechanisms and can be further enhanced by cell engineering. NKG2D is an innate receptor highly expressed on γδ T cells which recognizes a family of target proteins commonly upregulated on tumors. NKG2D specifically associates with intracellular DAP10, a binding partner necessary for signal transduction and activation. We have previously described a novel form of cell engineering incorporating an enhanced intracellular DAP10 chimeric adaptor (CAd) protein, comprising DAP10 domain modifications and inclusion of 41BB and modified CD3z co-stimulation, designed to amplify potency for tumor targeting via endogenous NKG2D receptors. Here we report the development and functional characterization of ADI-925, an allogeneic Vδ1 γδ T cell product expressing a DAP10 CAd with broad tumor targeting across varied patterns of NKG2D ligand expression.

Methods ADI-925 was expanded from healthy donor PBMCs and transduced to express an enhanced DAP10 CAd. An initial expansion process was developed into a scaled process suitable for clinical development. *In vitro* characterization of activity included co-culture assays, flow cytometric phenotyping, and cytokine production by multiplexed immunoassay. Anti-tumor activity of ADI-925 was evaluated in human tumor xenograft models.

Results We evaluated the performance and extended characterization of ADI-925, including lots derived from a scaled clinical manufacturing process. ADI-925 showed robust expansion and transduction of Vδ1 γδ T cells. Extended characterization was performed in at least 8 donors and across multiple scales and processes. ADI-925 consistently exhibited high expression of NKG2D (>90%) that was maintained after five days of tumor cell coculture. ADI-925 displayed broad, NKG2D-dependent, cytotoxic activity within a panel of cancer cell lines exhibiting a range of antigen expression patterns across the eight NKG2D ligands.

Conclusions ADI-925, an allogeneic Vδ1 T cell product engineered with the recently-described chimeric adaptor technology, demonstrates preclinical proof-of-concept across an array of NKG2D ligand expressing tumors. A clinically suitable manufacturing process has been developed and generates cells that maintain potent tumor targeting. These data support continued development and further investigation of ADI-925 in the clinic.

Ethics Approval All mouse experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals and followed all institutional and national guidelines with appropriate protocol review and approval.

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