ADI-212: A next-generation gene-edited and armored allogeneic CAR γδ T cell therapy targeting PSMA for prostate cancer

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Background:

Metastatic castration-resistant prostate cancer (mCRPC) remains a challenging disease with poor prognosis and reduced survival. Prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein highly expressed in prostate cancer cells, particularly in advanced CRPC, is an attractive therapeutic tumor target. Strategies targeting PSMA, such as radioligand therapy, represent promising advances in the evolving landscape of mCRPC treatment options. However, a significant unmet need remains for PSMA-directed therapies. To address these limitations, we developed ADI-212, an allogeneic CAR-T cell product comprised of gamma delta (γδ) T cells to leverage their natural antitumor immunity and tissue tropism. ADI-212 is an optimized next-generation gene-edited and armored clinical candidate designed to enhance potency in solid tumors and to deliver multiple anti-tumor mechanisms of action to the tumor microenvironment. ADI-212 is engineered to express a novel CAR binder that targets a membrane-distal conformational PSMA epitope to support tolerability and specific tumor recognition. Additionally, we have integrated an oprimized combination of armoring and gene-editing, each providing enhanced cell tumor killing, proliferation, and survival function to ADI-212 while also conveying the potential to reshape the immunosuppressive microenvironment.

Methods:

Healthy donor PBMCs were used to activate, gene edit, expand, and engineer Vδ1 γδ T cells. The in vitro phenotype and antitumor functionality of ADI-212 were assessed using flow cytometry and cell-based cytotoxicity assays against PSMA-expressing cell lines. Human tumor xenograft models in immunodeficient mice were used to evaluate in vivo efficacy.

Results:

A novel anti-PSMA scFv with enhanced specificity compared to relevant benchmarks, such as J591, was selected for incorporation into the ADI-212 CAR. Enhanced cellular proliferation and overall growth of γδ T cells during manufacture was achieved through robust editing and protein knockout. Despite increased expansion, ADI-212 maintained a highly naïve phenotype compared to unedited controls. The synergistic combination of gene editing and CAR armoring technologies in ADI-212 substantially enhanced potency and rechallenge capacity in prostate cancer tumor models while maintaining a favorable cytokine profile associated with γδ T cells. CAR-dependent activation resulted in increased expression of the armoring component on ADI-212. Transcriptional profiling of ADI-212 demonstrated upregulation of genes within metabolic pathways suitable for a hypoxic environment. With the combination of gene-edit and armoring modifications, ADI-212 proliferation and cytotoxic activity were unaffected by coculture with immunosuppressive cells such as Tregs. In xenograft models, ADI-212 demonstrated potent, persistent anti-tumor efficacy against primary and secondary tumors.

Conclusion:

These preclinical results highlight the enhanced potency, efficacy, safety, and manufacturability of ADI-212. The innovative combination of gene editing and armoring integrated into ADI-212 has the potential to overcome challenges of reduced CAR-T efficacy and persistence associated with solid tumors and immunosuppressive microenvironments by promoting increased cell-intrinsic cytotoxic activity and recruitment of endogenous effectors.

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