ADI-270: An Armored Allogeneic Anti-CD70 CAR γδ T cell Therapy Designed for Multiple Solid and Hematological Cancer Indications

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Background

CD70 is a compelling target for CAR T cell therapy, given its elevated expression across multiple solid and hematologic malignancies, with expression in normal tissues limited to a subset of activated lymphocytes. γδ T cells combine innate and adaptive immunity and their capability to infiltrate solid tumors significantly correlates with clinical benefit[1,2]. We have previously described ADI-270, an allogeneic CAR γδ T cell product engineered with a next-generation CAR to target CD70 using its natural receptor (CD27) as the binding moiety and armored with a dominant negative form of the TGFβ receptor (dnTGFβRII) that provides functional resilience to the immunosuppressive tumor microenvironment (TME) found in many solid tumors. We have shown that the design of ADI-270 provides enhanced functionality and potency in CD70+ expressing tumors such as clear cell renal cell carcinoma (ccRCC) models, where we observed robust infiltration and persistence, resulting in significant preclinical efficacy. Here we expand on previous data, evaluating the kinetics of ADI-270 activity in the ccRCC model and its efficacy against additional tumor indications and models designed to mimic the low and/or heterogeneous antigen expression profile expected in most cancers.

Methods

CD70 expression profiling by flow cytometry and immunohistochemistry (IHC) on tumor microarrays (TMAs) was used to identify tumor indications for which ADI-270 represents a potential therapeutic. Healthy donor PBMCs were used to activate, expand, and engineer Vδ1 T cells to express the armored anti-CD70 CAR construct. Functional characterization of ADI-270 against cancer cells with varying levels of CD70 expression was determined using cell-based cytotoxicity assays. Human tumor xenografts in NSG mice were used to evaluate the in vivo efficacy of ADI-270 against solid and hematological cancers including ccRCC, NSCLC, and T cell lymphoma. Tumors and blood were collected from A498 xenograft models for pharmacodynamic analyses using IHC, multiplex IF, and Luminex. In addition, cytotoxicity assays against mixed CD70 +/- expressing cells were used to inform functional comparisons between ADI-270 and multiple clinically relevant benchmarks representing scFV-based anti-CD70 CAR approaches.

Results

Elevated CD70 expression was confirmed in various solid and hematological tumor indications, with frequency being highest in ccRCC samples. ADI-270 exhibited potent in vitro cytotoxicity against a range of cancer cell lines expressing various levels of CD70. CAR-mediated killing of CD70(+) tumor cell lines by ADI-270 promoted enhanced $\gamma\delta$ T cell activity, including innate and adaptive activity against CD70(-) tumor cells. ADI-270 significantly inhibited tumor growth in CD70+ ccRCC (A498), NSCLC (H1975) and T cell lymphoma (Hut78) human tumor xenograft models in NSG mice. In A498 tumor xenografts, robust ADI-270 tumor infiltration, proliferation,

and effector function were observed at the earliest assessment time point (Day 3), leading to potent efficacy and eradication of CD70+ tumor cells.

Conclusion

These results demonstrate the activity of ADI-270 in multiple cancers, which includes innate anti-tumor immunity, potent next-generation CAR targeting, and resilience to attenuation by TGFβ. Based on the functional characterization demonstrated to date, further clinical evaluation of ADI-270 is warranted in ccRCC and additional CD70+ indications.

1. Gentles AJ, et al. *Nat Med* 2015 Aug;21(8):938-945.
2. Rancan C, et al. *Nat Im* 2023 Apr;24(4):612-624.