**INTRODUCTION**

C-funded represents a compelling target for developing CAR T cell therapies due to its high expression on multiple solid and hematologic malignancies, while also retaining a homologous expression by a subset of activated lymphocytes. CAR T cells in solid tumors have been a key challenge in the field, given emerging strategies to modulate allogeneic activity, especially with CAR T cell clinical trials emphasizing the development of CAR- T cell therapies that do not elicit cytokine-release syndromes. However, it is essential to improve CAR T cell efficacy and reduce CAR T cell dysfunction, including those expressing CD103, significantly contributes to survival. Strategies targeting CD103 by engineering CAR T cell receptors (CD103-CD3 zeta) may have demonstrated superior antitumor activity compared to activated allogeneic CAR T cells. The aim of this study was to evaluate the combined effect of CAR T cell resistance to immunosuppressive effects of TGF- β and adoptive transfer of ADI-270, an allogeneic T cell product expressing a CD103/CD3-zeta receptor third-generation CAR construct with a dominant-negative TGF- β functionality to modulate the potential of reduced CD103 susceptibility in targeting CD103+ cancers.

**METHODS**

Healthy donor PBMCs were used to isolate CD4+ or CD8+ T cells to express CAR T cells. In vivo phenotypes, cytokine profiles, and effector functionality were compared to ADI-270 and ADI-270-derived CAR T cells. ADI-270 was generated using a lentiviral delivery system to transduce ADI-270 with a CAR targeting CD103 and a dominant-negative TGF- β functionality. ADI-270 was evaluated in a syngeneic xenograft model and compared to ADI-270-derived CAR T cells in the tumor microenvironment.

**ADI-270 expresses a less differentiated T cell memory phenotype with minimal activation/exhaustion-associated markers**

ADI-270 is organized against immunosuppressive effects of TGF- β with a dominant-negative receptor (dnTGF- β) "bolt-on" similar to an activated CAR T cell phenotype. ADI-270 is expressed CAR T cell with a CAR targeting CD103 and a dominant-negative TGF- β functionality. ADI-270 was generated using a lentiviral delivery system to transduce ADI-270 with a CAR targeting CD103 and a dominant-negative TGF- β functionality. ADI-270 was evaluated in a syngeneic xenograft model and compared to ADI-270-derived CAR T cells in the tumor microenvironment.

**ADI-270 significantly inhibits tumor growth in a renal cell carcinoma xenograft model in NGS mice**


**SUMMARY & CONCLUSIONS**

- ADI-270 (VSi T cells modified to express an armed CD70 CAR) were successfully generated and expanded, demonstrating product expansion without indications of fracture.
- ADI-270 expressed a less differentiated T cell memory phenotype with low expression of exhaustion markers, exhibited potent in vitro cytotoxicity, and was associated with a favorable cytokine and chemokine profile.
- Highly potent tumor growth inhibition was observed with ADI-270 targeting tumor xenografts in immunodeficient mice with evidence of selective T cell infiltration, proliferation, and activation within the tumor.
- We observed a decrease in TgVβ5 T cells targeting ADI-270 compared to VSi T cells expressing an irrelevant CAR suggesting that ADI-270 can dampen TgVβ5 rejection to better support antitumor function.
- In summary, ADI-270 demonstrates preclinical proof-of-concept of an allogeneic CD70 + T cell therapy utilizing the CD27 natural receptor CAR format for targeting CD70+ cancers. These data support continued development and further investigation of ADI-270 in the clinic.