ADI-002: AN IL-15 ARMORED ALLOGENEIC 'OFF-THE-SHELF' V δ 1 GAMMA DELTA CAR T CELL THERAPY FOR SOLID TUMORS TARGETING GLYPICAN-3 (GPC3)

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Background Glypican-3 (GPC-3) is an oncofetal protein that is highly expressed in various solid tumors including hepatocellular carcinoma (HCC) but is rarely expressed in healthy adult tissues and serves as a therapeutic target of interest. Autologous $\alpha\beta$ chimeric antigen receptor (CAR) T cell therapy has established clinical benefit in hematologic malignancies but limited success in solid tumors due to numerous challenges including poor T cell homing, heterogeneous antigen expression, and hostile tumor microenvironments.¹ These challenges may be overcome by the V δ 1 subset of gamma delta T cells due to their natural peripheral tissue tropism and ability to recognize and kill tumor cells through MHC-independent antigens upregulated under stress.² Allogeneic V δ 1 T cells engineered with CARs can have enhanced intrinsic antitumor activity and overcome challenges of allogeneic $\alpha\beta$ T cells, including graft-versus-host disease (GvHD). Here, we describe the first preclinical evaluation of ADI-002, a next-generation allogeneic CAR V δ 1 T cell therapy targeting GPC-3 and armored with IL-15, for the treatment of solid tumors.

Methods V δ 1 T cells were expanded from healthy donor PBMCs and transduced to express a 4-1BB/CD3z CAR against GPC-3 that encodes constitutively-secreted IL-15 (sIL-15), which we hypothesized could sustain proliferation and antitumor activity of intratumoral GPC-3.CAR V δ 1 T cells. In vitro characterization included co-culture with HCC targets expressing high (HepG2) and low (PLC/PRF/5) GPC-3, phenotypic analysis by flow cytometry, and cytokine production by multiplexed immunoassay. For in vivo assessment, immunodeficient NSG mice were subcutaneously injected with HepG2 tumor cells and treated with a single dose of GPC-3.CAR V δ 1 T cells. Tissues were harvested 7 days post transfer and analyzed for V δ 1 T cell tissue homing and proliferation, or at study end and analyzed for GvHD by immunohistochemistry.

Abstract 119 Figure 1 In vivo antitumor efficacy in a subcutaneous HepG2 tumor model in NSG mice

Results GPC-3.sIL-15.CAR V δ 1 T cells expanded over 10,000-fold and routinely reached >80% purity. Expanded V δ 1 T cells showed a primarily naïve-like phenotype (CD45RA⁺CD27⁺) with minimal exhaustion receptor expression and

displayed robust proliferation, cytokine production, and cytotoxic activity against HCC cell lines in vitro. In vivo, GPC-3.sIL-15.CAR V δ 1 T cells primarily accumulated and proliferated in tumors, and a single dose could efficiently control tumor burden without causing GvHD. When compared to GPC-3.CAR V δ 1 T cells lacking sIL-15, GPC-3.sIL-15.CAR V δ 1 T cells displayed greater tumor-specific proliferation that resulted in enhanced tumor control (figure 1).

Conclusions Expanded V δ 1 T cells engineered with GPC-3.CAR and sIL-15 represent a promising approach for safe and effective off-the-shelf treatment of HCC and support further investigation in the clinical setting.

REFERENCES

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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 and after appropriate approvals.

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