CAT-248 (ENGINEERED NK CELLS EXPRESSING CD70 CAR, IL15, AND TGFβ DNR) DEMONSTRATES IN VIVO EXPANSION, TUMOR INFILTRATION, AND DURABLE REGRESSION OF MULTIPLE CD70-EXPRESSING XENOGRAFT TUMORS

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Background Durable and effective therapies are needed for solid tumors despite recent advances with targeted therapies and immunotherapies as many patients relapse or are refractory to these agents. Engineered immune cell therapies can be effective options given their potency, specificity, and durability. However, solid tumors present unique challenges for cell therapies due to heterogenous antigen expression, poor infiltration of immune cells, and an immunosuppressive tumor microenvironment.

CAT-248 is an allogeneic, engineered peripheral blood derived natural killer (NK) cell product with four modifications: (1) a chimeric antigen receptor (CAR) targeting CD70, an antigen frequently overexpressed in many solid tumors as well as hematological malignancies, (2) Interleukin 15 (IL15) to enhance expansion and persistence of engineered NK cells, (3) TGFβ dominant negative receptor (TGFβDNR) to maintain activity in TGFβ rich tumor microenvironment of solid tumors, and (4) knockout of endogenous CD70 using CRISPR/Cas9 to prevent fratricide by CD70 CAR.

Methods We evaluated in vitro and in vivo efficacy of CAT-248 in renal cell carcinoma (RCC) and EGFR inhibitor resistant non-small cell lung cancer (NSCLC) models as both these malignancies are associated with high CD70 expression. We tested CAT-248 in the context CD70 high (A498 and 786-O), CD70 medium (Caki-2), and CD70 low NCI-H1975 NSCLC xenografts. CAT-248 was dosed intravenously (IV) to established subcutaneous xenografts in NOD/SCID/IL2Rγnull (NSG) mice, and tumor volumes were quantified over time until control groups reached humane end points.

Results CAT-248 demonstrated high in vitro cytotoxicity (>90% at 10:1 effector:target ratio after 24 hrs, p <0.05) upon co-culture with RCC and NSCLC cell lines expressing CD70 at various levels. Cytotoxicity was dependent on the CD70 CAR expression on CAT-248 NK cells and CD70 (ligand) expression on target tumor cells. Following IV administration in mice with or without implanted tumors, CAT-248 cells rapidly expanded and persisted for over 40 days. Expanding CAT-248 cells led to durable, rapid regression of established A498, NCI-H1975 and Caki-2 xenografts and substantial reduction (>75%, p<0.05) in 786-O xenograft volumes relative to control groups dosed with either mock NK cells or saline. Immunohistochemistry of 786-O xenografts two weeks post start of treatment revealed extensive infiltration of CAT-248 NK cells into the tumor and significant reduction of CD70-expressing tumor cells.

Conclusions CAT-248 infiltrates and durably regresses tumor xenografts expressing CD70 at high, medium or low antigen densities. CAT-248 has the potential to be a potent and durably effective allogeneic NK cell therapy for CD70 expressing solid tumors.

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