

ALLOGENEIC NATURAL KILLER CELLS ENGINEERED TO EXPRESS HER2-DIRECTED CAR, INTERLEUKIN-15 AND TGF β DOMINANT NEGATIVE RECEPTOR EFFECTIVELY CONTROL HER2+ TUMORS<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0264>

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Background The remarkable clinical responses of chimeric antigen receptor (CAR)-engineered immune cell therapies in hematological malignancies have not been replicated in solid tumors. Engineered, off-the-shelf, allogeneic natural killer (NK) cells are particularly attractive as a chassis for effective cell therapies for solid tumors given their clinical safety, efficacy, and ability to reduce tumor escape through inherent multimodal recognition of tumor cells.

We describe here preclinical efficacy and pharmacodynamics of CAT-179, a novel CAR-NK cell therapy, in multiple models of HER2-amplified ovarian and gastric cancer. CAT-179 cells are engineered to express three transgenes: a HER2-directed CAR to effectively target tumor cells, a transforming growth factor β (TGF β) dominant negative receptor (DNR) for resistance to TGF β -mediated immune suppression in the tumor microenvironment, and interleukin-15 (IL15) to enhance NK cell persistence and activity for durable response.

Methods PBMC-derived NK cells were engineered with a tricistronic construct expressing HER2-directed CAR, TGF β DNR, and IL15 under the control of a MND promoter using TcBuster™ transposase. CAT-179 activity was assessed in vitro by quantifying cytotoxicity and cytokine production upon coculture with HER2-expressing cell lines. TGF β DNR activity was assayed by quantifying TGF β -induced SMAD phosphorylation and DNAM1 receptor expression. In vivo persistence and anti-tumor efficacy was evaluated in NSG mice. Anti-tumor efficacy was tested against luciferase-engineered SKOV-3 ovarian cancer cells (SKOV-3-luc) and N87 gastric carcinoma xenografts.

Results CAT-179 demonstrates both CAR-dependent and innate NK receptor-dependent tumor cell killing in vitro, reducing the likelihood of tumor escape through antigen loss. CAT-179 demonstrated high CAR-dependent cytotoxicity as well as TNF α and IFN γ production when co-incubated with multiple HER2-expressing cell lines. Engineered NK cells demonstrated 75% reduction (relative to control NK cells) in TGF β -induced SMAD2 phosphorylation, prevented TGF β -induced downregulation of NK cell activating receptors, and restored NK cell cytotoxic activity. Furthermore, TGF β DNR protected bystander cells from TGF β -induced phenotypic changes. After a single IV dose, CAT-179 cells persisted for more than two months and retained cytotoxic activity. CAT-179 effectively reduced SKOV-3-luc tumor burden in NSG mice (95% AUC, $p < 0.0001$ for survival).

Conclusions CAT-179 is a promising demonstration of the Catamaran CAR-NK platform, as a novel off-the-shelf cell therapy to overcome the challenges associated with solid tumors.

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Ethics Approval We confirm that legal and ethical requirements have been met with regards to the humane treatment of mice described in this work, according to regulations within IACUC.