HER2-SPECIFIC HIGHLY SCALABLE CAR NK CELL (ANTI-
HER2-CAR SNK02) EXHIBITS A SIGNIFICANTLY
ENHANCED ANTITUMOR ACTIVITY AGAINST HER2-
EXPRESSING TUMORS AS AN OFF-THE-SHELF
ALLOGENEIC IMMUNE CELL THERAPY

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Background Although anti-HER2 monoclonal antibodies (e.g., trastuzumab) are currently recognized as effective therapeutics in patients with HER2-overexpressing tumors, a significant number of patients demonstrate resistance to this treatment. Genetic modification of NK cells to express a HER2-specific chimeric antigen receptor (CAR) is likely a better therapeutic approach against HER2-positive solid tumors. SNK02 is a highly scalable, off-the-shelf allogeneic NK cell product in clinical development with high purity, cytotoxicity, and tumor site migration potential. In this study, we aimed to develop allogeneic anti-HER2-CAR NK cells (CAR-SNK02) using the SNK02 manufacturing platform and to test their antitumor activity against HER2-expressing cancers.

Methods The CAR-SNK02 cells were generated by ex vivo feeder-stimulated expansion of peripheral blood NK cells along with transduction of retrovirus expressing anti-HER2 CAR and membrane-bound IL-15 using the SNK02 manufacturing platform. The CAR-SNK02 cells were characterized for their CAR expression, cytotoxicity, degranulation, and cytokine production in response to ER2-positive cancer cells. The stability of CAR expression and cytotoxicity were also examined after freezing and thawing.

Results The CAR-SNK02 cells underwent a billion-fold expansion over a 45–46 day culture period, through feeder cell and cytokine stimulation, while maintaining persistent high expression of the CAR in over 80% of the cells during expansion. Upon target cell stimulation, the expanded CAR-SNK02 cells exhibited potent anti-cancer activity against HER2-positive cancer cells, as well as increased cytokine production and high levels of degranulation. Moreover, the CAR-SNK02 cells maintained key phenotypic features of NK cells, including high expression of NK cell activating and chemokine receptors without signs of exhaustion, indicating their preserved functionality. The CAR-SNK02 cells showed enhanced survival under IL-2-deprived conditions, confirming activity of IL-15. Furthermore, the NK cells maintained CAR expression and enhanced cytotoxicity against HE2-expressing cancer cells even after freezing and thawing. Importantly, they effectively eliminated cancer cells with low HER2 expression levels, surpassing limitations of trastuzumab-induced antibody-dependent cellular cytotoxicity (ADCC) of NK cells.

Conclusions High expandability of the CAR-SNK02 cells, coupled with their enhanced antitumor activity against HER2-expressing cancer cells, even after freezing and thawing, highlights their promising potential as an off-the-shelf immune cell therapy. In addition, the SNK02 platform serves as a valuable foundation for further exploration and advancement of genetically engineered NK cell therapies. We are currently testing the antitumor activity of the CAR-SNK02 cells in a xenograft mouse model of cancer expressing HER2 for future translation into human trials.

Ethics Approval This study was approved by the Institutional Review Board (IRB) approval of Asan Medical Center (IRB No. 2021–0354).

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0296