

# Cancer Immunotherapy: Make Way for CAR NK

First clinical results for CD19-targeting CAR NK cells indicate a high response rate, excellent safety profile

Nearly 3 years after showing, preclinically, that natural killer (NK) cells outfitted with a chimeric antigen receptor (CAR) could be a promising alternative to CAR-bearing T cells, the first clinical data are in from researchers at The University of Texas MD Anderson Cancer Center (MDACC) in Houston.

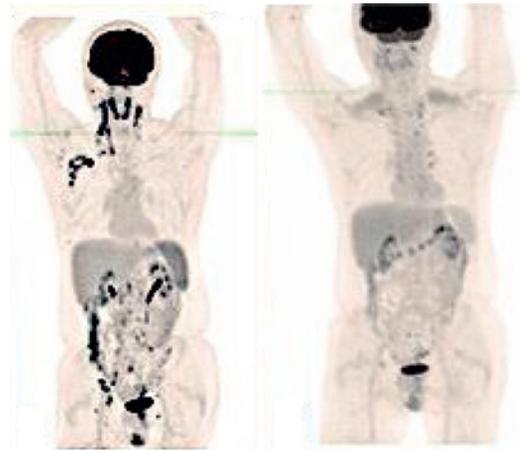
It's early days, but "that we've seen responses even during phase I is very encouraging," said senior author Katy Rezvani, MD, PhD. She and her team published results from 11 patients with relapsed/refractory non-Hodgkin lymphoma or chronic lymphocytic leukemia who received CAR NK cells targeting CD19 (N Engl J Med 2020;382:545–53). These cells, also equipped with the IL15 gene to improve proliferation and survival, were derived from MDACC's umbilical cord blood bank—unlike T cells, NK cells do not cause graft-versus-host disease, and a donor-generic product can be safely administered.

The objective response rate was 73%, including seven complete responses. Notably, none of the participants developed cytokine release syndrome or neurotoxicity, two common complications with CAR T-cell therapy. "I believed we'd see efficacy," Rezvani observed, "but the safety profile is really beyond what we could have expected." Phase II of the trial is under way; a global study is also being planned with Takeda.

To Jeffrey Miller, MD, of the University of Minnesota in Minneapolis, "the great thing is that a clinical signal has now been seen, which will motivate the field to say CAR NK cells are worth assessing." However, he noted that because the study protocol allowed responders to receive subsequent treatments for remission consolidation, response durability to CAR NK-cell therapy could not be accurately evaluated.

Another CD19-targeting CAR NK-cell therapy, albeit still preclinical, is Fate Therapeutics' FT596. Derived from human induced pluripotent stem cells (iPSC) rather than cord blood, FT596 is "engineered with three active antitumor modalities," said chief development officer Bob Valamehr, MD, PhD: It contains not only the appropriate CAR construct and IL15, but CD16 as well. With CD16 added, FT596 can be combined with drugs such as rituximab "to augment a key killing mode of NK cells," antibody-dependent cellular cytotoxicity (Blood 2020;135:399–410). During the 2019 American Society of Hematology Annual Meeting, Valamehr reported that in a mouse model of leukemia, FT596 was "highly efficacious" as monotherapy. It also proved effective alongside rituximab in mice with lymphoma, "where rituximab alone failed to control tumor burden."

With current CAR T-cell therapies, "not every cell gets engineered, and not every engineered cell is pristine," Valamehr noted, touting Fate's iPSC strategy for generating "master banks with uniform composition of cell material, extensively characterized so clonal cell lines and homogeneous products



Before-and-after PET scans of a complete responder from the MDACC trial.

can be made." Miller, too, appreciates this platform "because of its unlimited manufacturing potential," but added that the best NK-cell source remains to be determined.

"The field is very much in its infancy—perhaps the source doesn't really matter, but we won't know that until there's clinical data," Rezvani agreed. For now, the cord blood-derived CAR NK cells are freshly made for each patient on her study, but "we're working hard to develop a cryopreserved bank that can be readily thawed and infused. NK cells are trickier to freeze than T cells; no one quite knows why."

Rezvani is also interested in investigating the therapeutic utility of donor NK cells in which the expressed killer immunoglobulin-like receptor (KIR) does not match the recipient's HLA ligand. "We've known for 20 years now, from the bone marrow transplantation field, that such a mismatch results in unfettered NK cells with even better antitumor activity; it's a phenomenon we'd like to exploit," she explained. When possible, the team now selects KIR–ligand mismatched cord blood units for CAR NK-cell production, but Rezvani acknowledged that "we'd need to treat at least several hundred patients to see if there's a real effect."

Meanwhile, Miller has been working with GT Biopharma to develop a different NK-cell therapy, TriKE, which is short for "trispesific killer engager." Similar in design to blinatumomab (Blinicyto; Amgen)—which deploys T cells instead—this product brings NK cells and tumor cells together by binding CD16 and CD33, respectively; it also features an IL15 linker. A phase I trial evaluating TriKE in relapsed/refractory acute myeloid leukemia is enrolling patients.

"Our goal is to stimulate endogenous NK cells with both IL15 and antigen specificity," Miller said. The trial will reveal how healthy one's NK cells have to be for therapeutic efficacy, he added: "We anticipate identifying certain patients who may benefit from an additional infusion of [donor] NK cells, for which we'd want off-the-shelf availability."

Miller expects "there'll be a place for both" CAR NK-cell therapies and NK-cell engagers. As to whether NK or T cells will cross that finish line first, "I think we'll have an answer in the next couple of years—the proof, as always, will be in clinical responses and durability." —Alissa Poh ■

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