STAT+ [1]

# Natural killer cells, primed with an antibody, induce remissions in patients with advanced blood cancer

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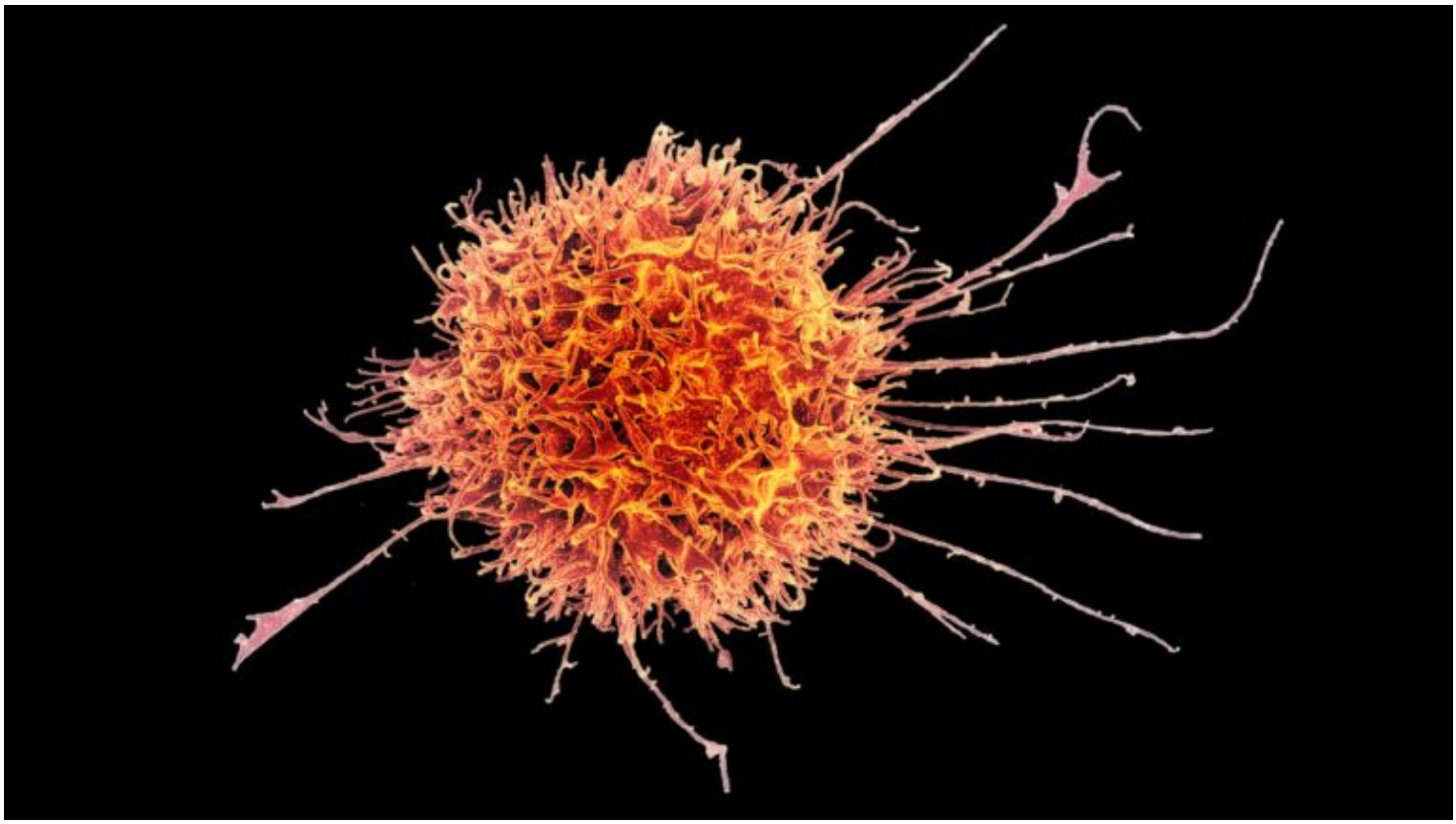
*By* Adam Feuerstein[2] [3] April 9, 2021



A colorized scanning electron micrograph of a natural killer cell. *NIAID/NIH*

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Two patients with advanced Hodgkin lymphoma were told their tumors were so resistant to treatment that hospice was their best option. Then, they were enrolled in a clinical trial of a novel immunotherapy involving so-called natural killer cells. After treatment, they saw complete remission.

Researchers say the results, detailed in data released Friday, are a hopeful if preliminary sign of the potential of immunotherapies harnessing natural killer,

or NK, cells — innate immune system cells that have certain advantages over the more commonly recognized adaptive T cell cancer therapies.

The treatment in the study, developed by the University of Texas MD Anderson Cancer Center and the German drug maker Affimed, combined off-the-shelf NK cells with a separate antibody that primes the cells to recognize a specific protein signature of the tumors. Two additional patients administered the same treatment have shown ongoing partial responses.

“These results show you just how powerful NK cells are,” said Katy Rezvani, a stem-cell transplant physician and NK cell researcher at MD Anderson, who is spearheading the development of this new treatment.

“It’s amazing when you see these responses for patients who have so few options, patients who’ve been told that they should go to hospice,” Rezvani told STAT.“I cannot begin to tell you how satisfying this is for clinicians.”

Data from the study is to be presented at the annual meeting of the American Association for Cancer Research (AACR) on Friday.

A lot still needs to be learned about dosing of the treatment and whether it can produce long-term benefits for patients with cancer. Still, Rezvani said the data add to a growing body of clinical evidence supporting a new type of tumor-killing immunotherapy centered around NK cells.

Academic, industry, and investor interest in development of NK cell-based cancer treatments has skyrocketed in recent years. Biotechs including Fate Therapeutics and Nkarta are adding armaments and embellishments to “naked” NK cells to boost their tumor-killing potency and make the cell persist longer in the body. It’s not unlike CAR-T therapy, except the engineered T cell is actually an engineered NK cell — and they can be mass-produced and ready for infusion into patients on demand.

Last year, Rezvani and colleagues published a widely cited paper in the New England Journal of Medicine[7], demonstrating so-called CAR-NK cells engineered to target a protein called CD19 on tumor cells induced a 73% response rate in 11 patients with two types of advanced lymphoma. All but one of the patients had a complete remission. Equally important: The CAR-NK cells did not cause cytokine release syndrome or neurotoxicity — manageable, but serious and potentially fatal immune side effects commonly seen with CAR-T treatments.

The more recent research — and the focus of Rezvani's AACR presentation — started with a question: Is it possible to endow NK cells with CAR-like potency but without genetically engineering the cells?

To find out, Rezvani and her team started with NK cells harvested from banked donor cord blood. In the lab over two weeks, these NK cells were expanded and activated to promote persistence, but were otherwise not genetically manipulated — no armaments or enhancements were made.

Then, while still in the lab, the culture containing the NK cells was infused with an "engager" antibody from Affimed called AFM13. Essentially, the NK cells and AFM13 sat together in the same bath for an hour, and during that time, a CD16 protein arm on the AFM13 engager mated with a complimentary CD16 receptor on the NK cells, forming a strong bond between the two.

Affimed's AFM13 engager is a matchmaker. It's designed with a second protein arm that recognizes and attaches to a receptor called CD30 found on the surface of lymphoma cells. When infused into a patient, the NK cells — mated to the engager via that CD16 bond — are introduced to tumor cells by the CD30 connection. When that happens, cancer cells die.

The clinical trial enrolled three patients with the blood cancer Hodgkin lymphoma, which originates in lymphocytes, a type of white blood cell. The three patients entered the study with lymphoma that was no longer responsive

to an average of seven prior treatments, including Adcetris and PD-1 checkpoint inhibitors.

After a single infusion of 1 million engaged NK cells per kilogram, the lowest dose tested, all three patients achieved a partial response, assessed at one month. One of the patients received a second cycle of the NK cells, after which she went into complete remission. All of the patients also received three additional infusions of AFM13 alone, as a way to amplify efficacy and promote durability.

”She was being sent to hospice and we gave the cells to her and she goes into remission and she’s now home with a fantastic performance status,” Rezvani told STAT, referring to the patient who received two treatments.

One of the first three patients has moved ahead to receive a stem cell transplant, which is potentially curative. Doctors are also planning a stem cell transplant for a second patient.

A fourth patient, also with advanced Hodgkin lymphoma, was treated with a higher dose of 10 million engaged NK cells per kilogram. This patient achieved a complete remission and will likely receive a second treatment cycle with the engaged NK cell therapy.

None of the patients reported any serious, treatment-related side effects. There were no cases of cytokine release syndrome or neurotoxicity.

Andreas Harstrick, Affimed’s chief medical officer, said the collaboration with Rezvani and MD Anderson will continue, with additional patients enrolled at the 10 million cell dose and a higher 100 million cell dose.

“For us to see these very meaningful responses in patients who had very few treatment options left, to see tumors just shrinking, it’s extremely exciting,” he said.

Affimed is exploring broad uses for its AFM13 NK cell engager. In some studies, it is being administered to patients on its own, seeking to recruit patients' native NK cells. It's also being studied in combination with Keytruda, Merck's checkpoint inhibitor. The German company is developing other types of NK cell engagers that bind to different tumor-causing proteins.

For Rezvani, the research into NK cells continues. While highly encouraged by the early responses seen with the engaged NK cells, she cautions that patients have not been followed long enough to determine if responses can be durable. Enhancing the potency of NK cells and getting them to persist longer in patients is still a technical challenge that needs to be overcome. How best to preserve and store NK cells so that they can be a truly "off the shelf" product is a work in progress.

"I have called NK cells the step-cousins of T cells, but hopefully now they're going to be siblings," she said.

## About the Author

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