# Experimental CAR T-Cell Therapy Shrinks Tumors in Children with Deadly Brain Cancer

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In a small clinical trial, a CAR T-cell therapy—a type of immunotherapy that uses a patient's own immune cells to fight cancer—shrank tumors in several children and young adults with diffuse midline gliomas. This fast-growing form of brain and spinal cord cancer typically causes death within a year of diagnosis.

In the trial, several participants were still alive two years or more after receiving the treatment.

Patients in the trial had a type of diffuse midline gliomas known as H3K27M mutant, a genetic change that is found in about 80% of younger patients with these cancers. Researchers at Stanford University, who led the study, designed the experimental CAR T-cell therapy to target a molecule called GD2 that is produced in large amounts by H3K27M-mutant diffuse midline gliomas.

Findings from the ongoing clinical trial were published November 13 in Nature.

"This study breaks new ground," said study co-investigator Crystal L. Mackall, M.D., of Stanford Medicine. "It demonstrates that CAR T cells can have real, meaningful benefit for solid cancers, something that many people have not believed [was possible]."

In the trial, 9 of 11 patients who received the GD2 CAR T-cell therapy had neurological improvement. Of those, 7 had tumor shrinkage and in some cases the effects were quite dramatic. As patients' tumors shrank, their symptoms improved and many regained physical functions they had lost from the disease, such as hearing, walking, and taste sensation.

Participants lived a median of nearly two years after treatment, with two patients still alive past the study's 2.5-year follow-up period. One of these patients had a complete disappearance of his tumor and remains cancer free four years after his diagnosis.

"It's really remarkable," said Rosandra N. Kaplan, M.D., of NCI's Center for Cancer Research, who

is also running a GD2 CAR T-cell therapy clinical trial but was not involved in this study. “This is a tumor for which nothing has ever worked. I think this is the start of a revolution in understanding how to treat these patients.”

## A serendipitous collaboration

Diffuse midline gliomas, which include a type of cancer in the brainstem called diffuse intrinsic pontine glioma, or DIPG, are difficult to remove by surgery because they are located in areas of the brain that control vital functions, such as breathing and heart rate. Chemotherapy and radiation provide only temporary relief from symptoms. H3K27M-mutant diffuse midline glioma tumors are extremely rare and almost uniformly fatal.

“We have made such little progress against these tumors,” Dr. Mackall said. The only standard therapy is radiation to help control symptoms, she explained.

“Not only do these patients have a short lifespan, but they progressively lose so much of their critical functioning that it’s just downhill from the day of diagnosis,” she said.

CAR T-cell therapy involves collecting the patients’ immune cells and engineering them to produce a receptor on their surface (the CAR) that allows them to latch on to and attack cancer cells. These cancer-fighting T cells are expanded into the millions and then returned to the patient in hopes that this army of immune cells will seek out and kill the cancer cells.

Several CAR T-cell therapies have been approved to treat blood cancers, but this approach is more challenging in solid tumors like brain cancers, in part because potential target molecules on the surface of solid tumors are also found on healthy cells.

However, an earlier study led by Michelle Monje, M.D., Ph.D., also of Stanford Medicine, found that diffuse midline glioma cells make high levels of GD2, a molecule that is produced at very low levels in normal brain cells. At the same time, Dr. Mackall had started testing a CAR T-cell therapy she had developed that targets GD2, based on studies showing it was abundant in tumors of people with two other cancers, neuroblastoma and osteosarcoma.

“It was truly one of those moments in science that was serendipitous,” Dr. Mackall said of their collaboration.

They and their Stanford colleagues then went on to show that the GD2 CAR T-cell therapy could successfully get into the brain and completely eliminate tumors in a mouse model of diffuse midline glioma.

## Small trial with surprising results

For this first human study of the GD2-targeted CAR T-cell therapy, 11 children and young adults

with either DIPG or spinal diffuse midline glioma were given an intravenous infusion of one of two different doses of GD2 CAR T cells. The lower dose caused less inflammation, they found, and will be used in a future, larger clinical trial.

The CAR T-cell therapies approved for blood cancers are a one-time treatment, but the Stanford team took a different approach in this trial.

All 9 patients who benefited from their first treatment went on to receive additional infusions of GD2 CAR T cells. And instead of giving the treatment via an infusion in the vein, it was administered directly into the brain through a special catheter. Patients got the treatments every one to three months, as long as their disease remained stable.

The trial investigators opted for giving the additional doses in this way, they explained, because previous studies in mice had shown that delivering the treatment directly to the brain caused less inflammation and was more potent at killing cancer cells than when delivered through the bloodstream.

After a follow-up period of 2.5 years after the first treatment, tumors shrank by more than half in four of the nine patients who had initially responded to the treatment, including one patient whose tumor disappeared entirely (a complete response) and has not returned.

All nine patients had improvement in their neurological disabilities, and some even regained the ability to walk, hear, and taste.

“We had a patient who was unable to walk, who was fully wheelchair-bound when she arrived. [After treatment,] she ended up using a cane for long walks,” Dr. Mackall said. “Her cancer eventually recurred, but she had a good year and a half where she was much more ambulatory. That’s priceless. It gives us hope that we can really turn things around.”

Side effects from the treatment included neurological issues—such as headaches, fever, and fluid buildup in the brain—which is commonly seen with inflammation of tumors in the brainstem and spinal cord. These and other side effects could be managed using standard treatments and approaches, the researchers explained.

## Improving responses to treatment

Dr. Kaplan said it’s important to understand why some patients responded better to the treatment than others.

“These patients all had the same [GD2] target, but not all of them responded. So [the response is about] more than just the target,” Dr. Kaplan said. The next steps are to understand how other components of the microenvironment around the tumor affect how the treatment works and to use that information to find ways to improve the overall immune response to the treatment and the length of response.

The Stanford clinical trial is ongoing, with additional groups of patients receiving all treatments directly into the brain, with no treatments given by IV. Some patients will not get chemotherapy prior to receiving the CAR T-cell treatment. Typically, this “lymphodepleting” chemotherapy is given to eliminate white blood cells that could try to attack the infused T cells.

Dr. Mackall and her colleagues ultimately plan to launch a larger phase two trial next that will enroll patients from centers besides Stanford.

Meanwhile, Dr. Kaplan is running a clinical trial evaluating the same CAR T-cell therapy in patients with neuroblastoma and osteosarcoma that express high levels of GD2.

The insights gained from these studies will help improve other CAR T-cell therapies for solid tumors, Dr. Kaplan said, several of which are already being tested in clinical trials. For example, one trial is currently testing a CAR T-cell therapy that targets a molecule called B7-H3 in children with diffuse midline gliomas and another is testing a B7-H3 targeted CAR T-cell therapy in adults with the brain cancer glioblastoma.

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