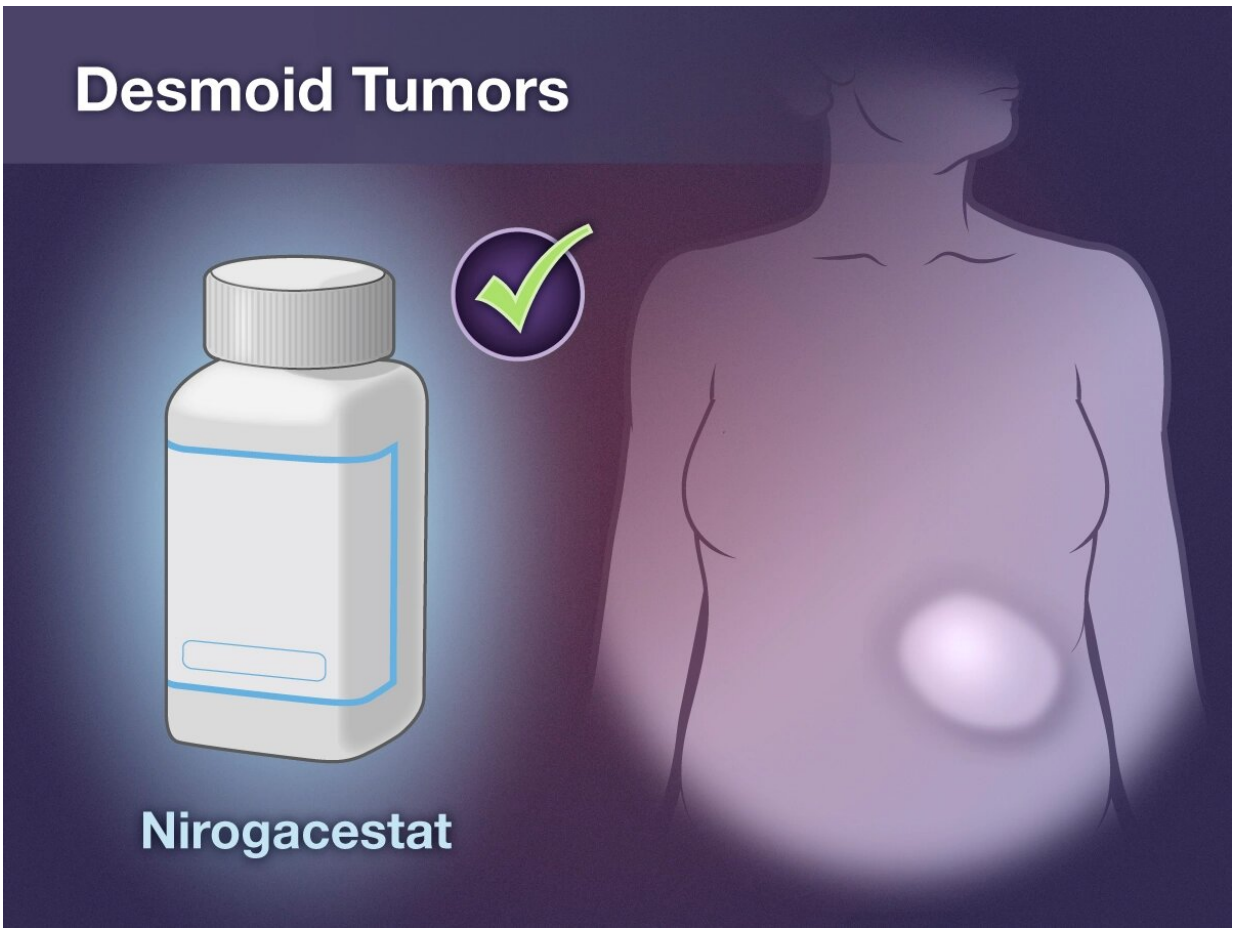
Nirogacestat, a new desmoid tumor treatment, found to improve outcomes for people with sarcoma

March 9 2023



Credit: *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2210140

When Dana Avellino, now 36, first noticed a lump near her groin in the summer of 2018, she thought it was related her recent cesarean section. Her younger daughter was only 2 months old at the time. When a biopsy revealed that the lump was a sarcoma, a type of tumor that affects the body's soft tissues, her doctors recommended that she go to Memorial Sloan Kettering Cancer Center (MSK), known worldwide for expertise in treating sarcomas.

After other treatments left her with severe side effects, Dana's MSK doctor, sarcoma expert Mrinal Gounder, MD, told her about a clinical trial testing an experimental targeted drug called nirogacestat. Dana has now been taking the drug for more than three years. Her tumor, a rare, noncancerous subtype of sarcoma called a desmoid tumor, has shrunk so much that she can hardly feel it anymore.

"When I agreed to participate in the trial, I didn't know what the end result would be," Dana says. "But the side effects from the drug have not been bad, and I'm not in any pain from the tumor. It's been amazing."

Phase 3 trial of nirogacestat for desmoid tumors has positive results

On March 9, results from an international, randomized phase 3 clinical trial of nirogacestat led by Dr. Gounder were published in *The New England Journal of Medicine*. Nirogacestat, which blocks a protein called Notch, is a new type of targeted drug called a gamma-secretase inhibitor. The paper reported that 41% of patients' tumors significantly shrank after they took nirogacestat.

After two years, tumors did not grow in more than 75% of patients on the targeted drug, compared with only 44% of patients in the placebo group. The most common side effects were fatigue (feeling tired), gastrointestinal problems, and skin rashes. Dana has experienced skin

problems but is otherwise feeling good.

Diagnosing desmoid tumors, a rare subtype of sarcoma

Dana's first doctor at MSK was world-renowned sarcoma surgeon Samuel Singer, MD. Dr. Singer performed a second biopsy, and MSK sarcoma pathologist Meera Hameed, MD, determined that Dana's soft tissue tumor was a type called a desmoid tumor (also known as aggressive fibromatosis).

Unlike most soft tissue sarcomas, desmoid tumors don't spread to distant parts of the body. But these tumors can grow quite large and lead to disfigurement, disability, and debilitating pain. In rare cases, they invade vital organs, resulting in severe complications and even death.

Dr. Singer told Dana that he could perform surgery to remove her tumor, but there was a high likelihood that it would grow back. He referred her to Dr. Gounder, who is one of the world's leading experts on desmoid tumors. Dr. Gounder has led a number of clinical trials studying drugs that target the defective proteins that cause these tumors to grow.

"Sarcoma itself is a rare disease, and desmoid tumors are a rare type of sarcoma," Dr. Gounder explains, adding that only about 900 people are diagnosed with them in the United States every year. "MSK doesn't only treat the major cancers," he says. "We have expertise across more than 400 different types."

Trying different desmoid tumor treatments before the nirogacestat clinical trial

Dr. Gounder first offered Dana treatment with sorafenib (Nexavar). He

had previously led studies that found this drug is effective in many people with desmoid tumors. But in Dana, the drug caused very high blood pressure. Another drug led to allergic reactions.

Meanwhile, the tumor in her lower abdomen continued to grow, to the point where she could no longer bend over to pick up her young daughters. Eventually, Dr. Gounder suggested that Dana consider the clinical trial for nirogacestat. In November 2019, she started taking the drug—three pills, twice a day.

MSK has a multidisciplinary team that specializes in treating desmoid tumors. Dr. Gounder; sarcoma surgeon Aimee Crago, MD, Ph.D., who also studies desmoid tumors in her lab; and interventional radiologist Joseph Erinjeri, MD, Ph.D., work together to determine the best, most personalized treatment for each patient. The treatments may include medications like nirogacestat and sorafenib, surgery, an interventional procedure, or a combination of these.

Dr. Erinjeri specializes in less-invasive, image-guided therapies. One of these is cryoablation, in which a specialized, chilled needle is used to create ice crystals within a tumor, destroying it. Another treatment uses microscopic beads loaded with chemotherapy drugs, which are injected directly into the arteries that feed the tumor.

"These treatments can be very effective in patients who don't respond to medications and who are not candidates for surgery," Dr. Erinjeri says. "We've found that in patients who have these procedures and who are considered low risk, the chances of the tumor coming back are low."

Radiologist Robert Lefkowitz, MD, who specializes in imaging sarcomas, is another important member of the team. He reviewed all the scans of the patients in the recent trial. "There were some very good responses," he notes. "Many of the tumors were measurably smaller,

including Dana's."

Better quality of life for younger patients with desmoid tumors

Most people diagnosed with a desmoid tumor are in their teens, 20s, or 30s. These growths are more common in women than in men, although experts don't know why. The trial was unique because it included surveys about patients' quality of life during treatment. "When developing new sarcoma drugs, we want to determine whether they actually make patients feel better, in addition to shrinking their tumors," Dr. Gounder says.

The tools to measure a patient's quality of life were first developed at MSK in collaboration with the Desmoid Tumor Research Foundation (DTRF), a nonprofit patient advocacy group.

Another side effect of nirogacestat was that in many female patients it caused temporary ovarian dysfunction, which was reversible in most patients. Because of this, the trial also included follow-up research to study reproductive function. "This tumor affects many people who may want to have children, so this is an important part of finding better treatments," Dr. Gounder adds.

Dana experienced these problems, but it was not a concern for her because she was not planning to have more children.

Desmoid tumor advocacy group helped make nirogacestat a success

Nirogacestat has an interesting history. It was originally developed to treat Alzheimer's disease, but ultimately was not effective. It was later

tested against several types of cancer with equally disappointing results.

Just when the company that makes the drug was about to abandon it, the leaders of the patient advocacy group DTRF saw results suggesting it might be successful in treating desmoid tumors. The group worked with the pharmaceutical company and the National Cancer Institute to develop clinical trials and recruit patients to participate in them.

"Our partnership with DTRF is really an important part of this success story," Dr. Gounder says. Drs. Gounder, Crago, and Lefkowitz all serve on DTRF's Medical and Scientific Advisory Boards.

In addition to desmoid tumors, nirogacestat is now being evaluated in clinical trials for other cancers, including multiple myeloma.

Dana continues to live a normal life with her family

Dana, who lives in Pelham, New York, and whose daughters are now 4 and 7, has been able to continue working during most of her treatment. She teaches third grade special education at a public school in the Bronx. Although she had to travel into Manhattan during the first part of the trial, she is now able to receive scans and other tests at MSK Westchester, closer to her home and her work.

"That makes it much easier, because I don't have to take the whole day off," Dana says. "Participating in a clinical trial is a huge commitment, but definitely it was worth it for me."

More information: Mrinal Gounder et al, Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2210140

Provided by Memorial Sloan Kettering Cancer Center