

## **Lay abstract**

When breast cancer spreads beyond the breast and nearby lymph nodes to other parts of the body, it is called stage IV or metastatic breast cancer. For some people, this spread includes the brain. Unfortunately, brain metastases are common in patients with triple-negative breast cancer (TNBC) and are often very difficult to treat. Current medicines rarely work well in the brain, and many clinical trials exclude patients with active brain metastases that have not been surgically removed or treated with radiation therapy. As a result, this group of patients has fewer treatment options and worse survival. In recent years, a new type of cancer treatment called an antibody–drug conjugate (ADC), which is a more cancer cells–guided chemotherapy than the conventional chemotherapies, has shown promise. ADCs are designed to deliver powerful cancer-killing drugs directly to tumor cells while limiting harm to healthy cells. Sacituzumab tirumotecan is one of these new ADCs. It has been effective against TNBC in other parts of the body, but we still do not know how well it works in the brain or how to predict which patients will benefit. Our study will test sacituzumab tirumotecan in patients with TNBC and active brain metastases. The goal is to see whether the drug can shrink a patient’s brain metastatic tumors, control the disease, and improve quality of life. We will also study tumor samples from the body (when available), including from tumor, from spinal fluid and from blood using advanced techniques that can examine each cell individually to understand why some tumors respond and others resist treatment. This will help us design better treatments in the future. Our study also includes a patient support program that offers small stipends to help with costs related to clinic visits, making it easier for people from diverse backgrounds and financial restraints to participate. This approach aims to make the trial more inclusive and ensure that the results benefit all communities affected by metastatic breast cancer. If successful, this research could lead to a much-needed treatment option for patients with breast cancer brain metastases and set the stage for new combinations that work better in the brain. It will also generate knowledge that can guide future drug development, bringing hope to patients facing one of the most challenging forms of stage IV breast cancer.