Modifying a Chemotherapy Drug Offers Hope to People with Rare Brain and Spine Tumors

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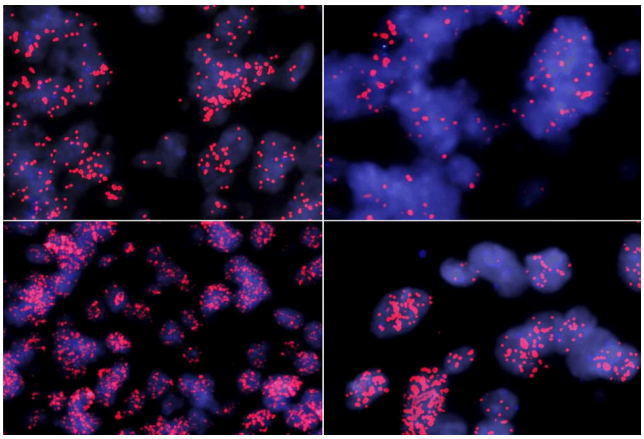
> A phase 1/2 clinical trial is testing an investigational drug called PLX038 on hard-to-treat central nervous system tumors containing extra copies of the *MYC* and *MYCN* genes.



Microscopy images of four different MYCN amplified ependymomas. The bright spots indicate extra copies of the MYCN gene.
Credit: Raffeld et al. Acta Neuropathologica Communications. 2020 Dec; 8(1):1-1.

Nearly 100,000 new cases of primary brain and spine tumors are diagnosed each year in the United States. Roughly 30 percent of these central nervous system (CNS) tumors are malignant (cancerous). Some of these tumors—including a new subtype of ependymoma and some medulloblastomas—contain changes in genes called *MYC* and *MYCN*. Tumors with these genetic alterations were once considered "undruggable." However, a chemotherapy called PLX038 may be able to damage the DNA inside cancer cells to control or prevent their growth.

A new phase 1/2 clinical trial led by NCI-CONNECT is testing whether PLX038 can treat adults with primary CNS cancers with extra copies of *MYC* and *MYCN* (called *MYC* and *MYCN* "amplified" tumors). PLX038 has been tested in other early clinical trials in solid tumors outside of the CNS, including ovarian and lung cancer. However, NCI-CONNECT's clinical trial will be the first to test this chemotherapy in people with CNS tumors.

PLX038 is an intravenous drug. This means it is injected directly into the bloodstream through a vein. It gets slowly broken down by the body into its active ingredient: a molecule known as SN-38 that damages tumor cells' DNA. SN-38 is the active ingredient in two other FDA-approved chemotherapies (irinotecan and sacituzumab govitecan). PLX038 is based on these chemotherapies, but it has been developed to be more effective and longer lasting. It may also have fewer side effects.

Many types of CNS tumors may respond to PLX038, says Marta Penas-Prado, M.D., the study's principal investigator and a senior clinician at the NCI Center for Cancer Research (CCR) Neuro-Oncology Branch. However, Dr. Penas-Prado anticipates that CNS tumors containing *MYC* and *MYCN* amplifications may be especially sensitive, because they rely heavily on an enzyme called topoisomerase 1 (TOP1) to fix their DNA. PLX038 is a TOP1 inhibitor, meaning it prevents the TOP1 enzyme from fixing damaged DNA inside cancer cells—causing the cancer cells to die.

People with *MYCN* amplified ependymomas have particularly limited treatment options. They often receive surgery followed by radiation, but soon develop resistance to this treatment. Dr. Penas-Prado hopes PLX038 will prove to be another viable approach. "All CNS tumors are rare, so many patients do not have access to clinical trials," she says. "The goal of this phase 1/2 trial—and our NCI-CONNECT program in general—is to break down some of these barriers to care."

Phase 1 is open to adults with any type of recurrent primary and malignant CNS tumor. The goal is to establish the recommended dose of PLX038, which provides the most benefit with the least side effects. This dose will then be used in phase 2 of the trial. Previous clinical trials have already determined the appropriate dose for other solid tumors. But, as Dr. Penas-Prado explains, people with CNS tumors who have received brain and spine radiation may require a lower dose to decrease potential side effects, such as low blood counts.

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>
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Clinical trial participants will receive PLX038 every 21 days at the Neuro-Oncology Clinic in Bethesda, Maryland. They will be monitored for side effects to help the researchers determine whether to increase or decrease the dose. Participants will also fill out questionnaires to report and grade their own symptoms, both during and after treatment.

This aspect of the clinical trial is overseen by CCR's Office of Patient-Centered Outcomes Research (OPCORe). "Occurrence and changes in both disease- and treatment-related symptoms often serve as early indicators of treatment benefit and tolerability," says Terri Armstrong, Ph.D., head of OPCORe and senior investigator at the Neuro-Oncology Branch. "This information also helps evaluate the clinical benefit of the disease response."

Once the researchers have identified the recommended dose of PLX038, phase 2 of the trial can begin. This phase is open to adults with primary CNS tumors containing *MYC* and *MYCN* amplifications, such as *MYCN* amplified ependymoma or recurrent medulloblastoma with *MYC* or *MYCN* amplifications. The goal is to assess the effectiveness of PLX038 in these participants and slow tumor progression.

A Care Partner's Perspective on Brain Tumor Support

Liz shares how she works together with her husband to navigate his ependymoma diagnosis.

Participants will receive PLX038 for up to seven months. After that, they will continue to return to the Neuro-Oncology Clinic for follow-up visits. The study also includes an opportunity for participants to have a tumor biopsy while they receive treatment. This component of the study may provide important insights so researchers can better understand how well the chemotherapy is working. The molecular analyses will also reveal whether tumors develop resistance to PLX038, informing future treatment strategies.

"We often lack investigational drugs to offer people with rare CNS tumors," Dr. Penas-Prado says. "Our phase 1/2 trial fills an unmet need and offers hope to treat the trickiest and rarest tumors."

For questions or to enroll in this study, the patient's treating physician can contact the Neuro-Oncology Clinic.