Improving the Treatment of Glioblastoma and Diffuse Intrinsic Pontine Glioma at Memorial Sloan Kettering Cancer Center

Gliomas are one of the most common primary brain tumors. They originate in stem cells that give rise to glial cells, which surround and support neurons in the brain, spinal cord, and other parts of the nervous system. Glioblastoma multiforme (GBM) is the most aggressive type of glioma and is challenging to treat. The standard of care often includes surgery and radiation coupled with chemotherapy. Despite advances in therapies, GBM ultimately resists all treatments and is almost always fatal.

Neuro-oncologist Ingo Mellinghoff, MD, Evnin Family Chair in Neuro-Oncology, Chair of the Department of Neurology, and Chief of the Brain Tumor Service at MSK, is leading an innovative multiarm clinical trial of three investigational drugs—paxalisib, VAL-083, and regorafenib (Stivarga®)—to treat people with newly diagnosed or recurrent GBM. Participants in the study are randomly assigned to receive one of the three drugs. Dr. Mellinghoff's team at MSK is part of an exciting trial model that tests experimental drugs simultaneously at research institutions throughout the United States and abroad. This format gives physicians and researchers the flexibility to add promising drugs to clinical trials as they become available, bringing experimental therapies to more people with cancer and shortening the timeline for approval by the FDA.

This clinical trial is one of many elements within Dr. Mellinghoff's leading research portfolio investigating new targeted therapies to advance brain cancer research at MSK and bring new hope to people with GBM throughout the world.

GBM AGILE Clinical Trial: A New Way to Advance Therapies

In this pioneering endeavor, Dr. Mellinghoff and neuro-oncologist and neurologist Thomas Kaley, MD, are leading the clinical trial at MSK as part of an international cohort in collaboration with the Global Coalition for Adaptive Research, Kazia Therapeutics, and Kintara Therapeutics. This multiarm trial aims to more rapidly identify and confirm effective therapies for people with GBM.

Dr. Mellinghoff and Dr. Kaley have identified paxalisib, VAL-083, and regorafenib as promising drugs that each have the potential to improve outcomes for people with GBM who currently lack treatment options. All participants with newly diagnosed GBM also receive radiation and temozolomide (Temodar®), a standard chemotherapy drug, before any experimental therapy is administered. People with cancer whose disease returns following standard treatment receive either paxalisib, VAL-083, or regorafenib.

How It Works: Paxalisib

Through next-generation genome sequencing methods, researchers have discovered that the PI3K pathway, which controls cell metabolism and cell division, is overactive in more than 85% of glioblastomas. They found that the PI3K pathway is altered in GBM cells, causing the safety controls to be switched off, which leads to tumor growth. Paxalisib is a targeted therapy that inhibits this altered PI3K pathway, essentially halting tumor growth and promoting cell death. Paxalisib is effective against GBM because it can cross the blood-brain barrier, a major hurdle that other treatments, such as traditional chemotherapies, have been unable to accomplish.

A previous phase II study led by Kazia Therapeutics demonstrated that paxalisib increased patients' median overall survival by five months to 17.7 months, compared with 12.7 months for the current gold standard treatment. That study also reported no major adverse health effects—a goal when designing and testing new targeted therapies.

How It Works: VAL-083

Radiation inflicts damage on DNA in cancer cells, often resulting in cell death. Although radiation is standard for newly diagnosed GBM, these tumor cells are more resistant to DNA damage. A specific DNA repair enzyme rushes in to attend to injured cells, so the cancer can continue to multiply.

As the first drug of its kind, VAL-083 uniquely targets cancer cells by crossing the blood-brain barrier to stop DNA repair enzymes in their tracks. Since the drug inhibits these enzymes in GBM cells, other treatments such as radiation and chemotherapy can damage cancer cells beyond repair. What's more, VAL-083 can successfully target cancer cells that have become resistant to standard chemotherapy drugs, such as temozolomide, providing a new treatment for advanced GBM.

How It Works: Regorafenib

Cancer cells need a steady flow of oxygen and nutrients to grow and divide. Tumors accomplish this by signaling the body to create new blood vessels to provide them with the resources they need to survive. Regorafenib is a targeted therapy that inhibits the growth of new blood vessels, effectively starving tumors. The drug has been previously approved by the FDA to treat metastatic colorectal cancer, gastrointestinal stromal tumors, and liver cancer. Physicians and researchers hope to demonstrate the drug's effectiveness against recurrent GBM.

The GBM AGILE expanded trial model hopes to not only provide more life-changing treatment options for people with newly diagnosed or recurrent GBM but also to drastically shorten the length of time between trial and approval by the FDA.

Organoids: Understanding Tumor Evolution

Dr. Mellinghoff and neuro-oncologist and neurologist Maya Graham, MD, PhD, are studying a type of pediatric brain tumor that forms in the brain stem called diffuse intrinsic pontine glioma (DIPG). Like other glial tumors, DIPG is an aggressive disease and difficult to treat. To better understand the behavior of these tumors, Dr. Mellinghoff and Dr. Graham are growing organoids —miniature versions of the developing brain—to study their evolution and response to experimental drugs. Using organoids grown in a lab, researchers can induce the same mutations they have found in patients with these cancers and study the disease progression.

Dr. Mellinghoff and Dr. Graham are employing a new laboratory technique called single-cell sequencing to take snapshots of individual cells' gene expression profiles. Sequencing reveals which genes have been turned on or off, and researchers can then track how the tumors grow and change over time. This glimpse into the diversity of cells that make up a tumor helps doctors identify potential targeted treatments with greater accuracy than ever before.

Looking Ahead

Memorial Sloan Kettering is an established leader in targeted and immune-based therapies to treat brain cancer. With our physicians and scientists generating some of the field's most noteworthy

breakthroughs, we are poised to continue this momentum into the future. Continued investment in these research initiatives will allow us to achieve our goal of developing more treatment options for people with brain cancer—both at MSK and beyond.