Second Edition
UNDERSTANDING BRAIN TUMORS
A TREATMENT GUIDE FOR PATIENTS AND THEIR FAMILIES

WHERE INFORMATION EQUALS HOPE

Pineal gland tumors
Pituitary adenomas
Meningiomas
Glioblastoma
Schwannomas
Germ cell tumors

PATIENT RESOURCE
A Study for Management of Eye Side Effects in Patients with EGFR-Amplified Glioblastoma Receiving Depatuxizumab Mafodotin (ABT-414)

Glioblastoma (GBM) Research Study

Do you or someone you know have a glioblastoma?

This study evaluates the effect of several eye treatments for the management of eye side effects in patients treated with depatuxizumab mafodotin (Depatux-M). All participants will receive Depatux-M along with 1 of 3 eye treatments.

Patients must meet the following criteria:

- Be ages 18 or older
- Newly diagnosed GBM and have not already started treatment
- GBM tumor tested positive for EGFR amplification (about half of people with GBM tumors have EGFR amplification)
- Not pregnant or breastfeeding
- Other criteria must also be met

For more information, ask your doctor about the Ocular Side Effect Study or visit www.clinicaltrials.gov (NCT03419403) to see if you qualify.

Depatuxizumab Mafodotin is an investigational medicine that is not approved by the FDA. Safety and efficacy have not been established.
Overview

Diagnosing Brain Tumors

Pathology & Grading

The Power of Positivity: Scott Hamilton

Types of Brain Tumors

Exploring Brain Tumors in Children

Survivor Story: Richie Johnson

From the Physician’s Desk: Dr. Andrew B. Lassman and Dr. Tony J. C. Wang

Treatment Options

Understanding Clinical Trials

Side Effects

After Treatment Ends

The Role of a Caregiver

Assistance & Support Resources

I don’t let cancer take every second of every day. I won’t let it diminish me like that.

~ Scott Hamilton, page 6
Receiving a brain tumor diagnosis can lead to many emotions, questions and concerns. Your diagnosis may bring challenges you hadn’t planned on, but the promising news is that you are not alone. Surrounding yourself with a skilled medical team you trust and supportive family and friends will enable you to face this experience head on. The more you know about your diagnosis, the more prepared you will be to make decisions about your treatment.

When doctors refer to brain tumors, they include the spine and spinal cord in addition to the brain. These three areas make up the central nervous system (CNS), which controls our personality, senses, movements and many basic bodily functions. A mass of abnormal cells that develops in or near to the brain or spinal cord is commonly referred to as a CNS tumor.

Brain tumors can affect adults and children, but they may require different diagnostic and treatment approaches. This guide focuses mostly on adult brain tumors that originate in the brain or spinal cord.

UNDERSTANDING BRAIN TUMORS

Brain tumors are categorized as either primary or metastatic. Primary brain tumors begin in the brain tissue and rarely spread to other parts of the body. Metastatic brain tumors (also known as secondary tumors) are cancer that has spread to the brain from another site. In addition to where tumors start, it’s important to know how fast they are metastasizing, how readily they are spreading through the rest of the brain or spinal cord, and if they can be removed or treated to minimize the chance they will return (recur).

The brain and spinal cord are composed of multiple types of tissues and cells. Primary brain tumors can start in any of these tissues or cells. Tumors may be one type of cell or a mixture. As a result, tumors are divided into groups by specific cell type, and a measurement known as the grade is assigned.

Primary brain tumors may be considered benign (noncancerous) or malignant (cancerous). However, a benign tumor can be just as dangerous or life-threatening as a malignant tumor if it’s located in or near an area of the brain that controls crucial functions, or has a tendency to keep returning.

Benign tumors are slow-growing, appear to have mostly normal cells when examined with a microscope, and have distinct borders, meaning they’re less likely to spread into surrounding tissues. Malignant brain tumors grow rapidly and are invasive. They may have “roots” that extend into surrounding tissue, making the tumor borders less defined and more difficult to remove surgically. Although brain tumors rarely spread to distant organs, malignant tumors may spread to other areas of the brain or spine through the cerebrospinal fluid.

BRAIN ANATOMY

To begin to understand your diagnosis, it’s helpful to know the anatomy of the brain. The main areas of the brain include the cerebrum, cerebellum and brain stem.

The cerebrum is the large outer part of the brain. It is made up of two hemispheres (halves) and is further divided into four lobes. Frontal lobes are located behind the forehead. Parietal lobes are located just behind the frontal lobes. Temporal lobes are responsible for memory and hearing; they are located under the frontal and parietal lobes. Occipital lobes are located at the back of the brain and process visual images from your eyes.

The cerebellum lies under the cerebrum at the back part of the brain. It helps coordinate movement and balance.

The brain stem is the lower part of the brain that is connected to the spinal cord. It controls the nerves and muscles that are responsible for involuntary functions, such as breathing, heartbeat, blood pressure and body temperature.

The spinal cord is made up of nerve fibers that are protected by membranes and the bones of the spine. The spinal cord allows the brain to send and receive signals from the rest of the body to control muscles, sensation and feeling.

The cranial nerves emerge directly out of the base of the brain. These nerves allow direct communication to occur between the brain and the face, eyes, ears, tongue, mouth, neck and other areas.

The brain and spinal cord are surrounded by three protective membranes (layers of tissue) collectively known as the meninges. Cerebrospinal fluid, which also protects the CNS, flows through a network of cavities in the brain called ventricles.
To diagnose the type of brain tumor you have, your doctor will perform a thorough exam that will include questions about your medical history and symptoms, as well as a neurologic exam to assess your vision, hearing, strength and reflexes. In addition, your doctor may add any of the following tests to diagnose the tumor and determine how advanced it may be.

**IMAGING TESTS**

*Angiogram* uses X-rays to map out blood flow in the brain. You will be given a special dye (called a “contrast”) before the scan. The X-ray images map how the dye moves through the arteries and into the blood vessels of the brain. Movement of the dye helps identify the network of blood vessels that supply the tumor.

*Computed tomography (CT)* produces three-dimensional, cross-sectional X-ray images, enabling it to provide more details than a standard X-ray.

*Electroencephalography (EEG)* measures and records the electrical activity that is produced when brain cells communicate with each other. Special sensors, called electrodes, are attached to the outside of your head and are connected to a computer, which displays the activity in wavy lines.

*Hemodynamic imaging* measures the brain’s blood supply and flow. The photos taken are used to create images of the blood flow into the tumor, allowing the doctor to see the tumor’s blood supply.

*Magnetic resonance imaging (MRI)* uses magnetic fields instead of X-rays to create visual images of internal structures of the body. Magnetic resonance spectroscopy (MRS) measures metabolites (substances produced by living tissue) to produce images that represent patterns of activity in the brain. These patterns can be helpful in diagnosing specific types of brain tumors or to help determine whether a tumor is malignant.

*Magnetoencephalography (MEG)* measures the magnetic fields emitted when nerve cells produce electrical currents during neurotransmission. This type of scan creates computer-generated images that help gauge the function of certain areas of the brain.

*Positron emission tomography (PET)* images are not as finely detailed as those from CT or MRI but can provide helpful information to supplement those results and determine tumor grade. Single photon emission computed tomography (SPECT) is similar to PET. SPECT uses a special camera to detect radioactive material that has been injected into the body. It is rarely used to diagnose brain tumors but may help the doctor distinguish between low- and high-grade tumors.

**LUMBAR PUNCTURE (SPINAL TAP)**

A spinal tap is used to collect a sample of cerebrospinal fluid, which is examined for the presence of tumor cells, blood infection and proteins. This procedure may be used to help diagnose pineal region or meningeal tumors or central nervous system lymphoma, as well as tumors that have spread after surgery. The sample may be studied for the presence of biomarkers.

**BIOPSY**

A biopsy is the removal of tissue from a suspected tumor or removal of the entire tumor during surgery. Three types of biopsy procedures are generally used for brain tumors.

1. **Needle biopsy** is a procedure in which a small hole is drilled into the skull, and a hollow needle is inserted into the tumor. A sample of tissue from the tumor is collected in the hollow part of the needle. Even if a tumor is considered inoperable, it may be possible for the surgeon to perform a needle biopsy.

2. **Open biopsy** is the removal of a tumor sample during a surgical procedure in which the tumor is exposed.

3. **Stereotactic biopsy** is a computer-assisted needle biopsy that uses a guidance system to identify the precise location of the tumor.
A pathology report provides you and your health care team with essential information about the specific characteristics of your tumor. This information serves as a guide to plan the treatment most likely to be effective for your tumor based on its features. A final diagnosis is usually made based on these findings.

The pathology report is compiled by a pathologist, a doctor with specialized training in determining the nature and cause of disease. The pathologist conducts an examination of cells or tissue samples obtained during biopsy of the tumor or of the entire tumor after definitive surgery (removal of the tumor). The specimen is examined with and without a microscope, and its size, shape and appearance are documented and special tests may be performed. Cerebrospinal fluid (fluid around the brain and spinal cord) also may be collected for examination to help determine the grade of cancer by looking for the presence of tumor cells.

A neuropathologist, a pathologist who specializes in the examination and diagnosis of diseases of the brain and central nervous system, may also contribute by examining the tumor sample to determine the specific tumor type, test for tumor markers (biomarkers) and genetic abnormalities, and classify the tumor according to a grading system.

CLASSIFYING & GRADING BRAIN TUMORS

Brain and spinal cord tumors are given a grade based on how the tumor cells look and behave under a microscope. A tumor grade is different from the stage of a cancer. Cancer staging is based upon the size of a primary tumor and the location of cancer cells in the body. A tumor grade indicates how closely cancer cells resemble normal healthy cells. Cancer cells that resemble normal cells are called “well-differentiated,” and they grow and spread at a slower rate than “undifferentiated” and “poorly differentiated” cells, which look very abnormal when compared to normal cells. In some cases, a single tumor may consist of several different cell types. The tumor is graded overall based on the highest grade cells within the tumor.

The most commonly used grading system for brain tumors is the World Health Organization (WHO) Classification and Grading system for central nervous system tumors (see Table 1). This grading system helps doctors develop an appropriate treatment plan.

OTHER BRAIN TUMORS

The four-grade classification system is used for many brain tumor types, but others, such as germ cell tumors and medulloblastomas, are classified using different methods.

Germ cell tumors are typically evaluated using magnetic resonance imaging (MRI) and tests done on cerebrospinal fluid because there is no universally accepted system to classify them. In general, doctors classify a germ cell tumor into one of two groups: M0 (metastatic-negative) or M+ (metastatic-positive).

Instead of using a classification system to determine a treatment plan for medulloblastomas, doctors develop a treatment plan based on factors that indicate the risk of tumor recurrence (returning after treatment). In general, doctors may classify medulloblastomas in children into one of two risk groups depending on the child’s age, how much of the tumor remains after surgery and whether the tumor has spread.

- **Standard-risk**: A standard or “average-risk” tumor is located in the very back portion of the brain and has not spread to other areas of the brain and spinal cord. This classification is assigned when almost all of the tumor is removed during surgery.
- **High-risk**: A high-risk tumor has either spread to other parts of the brain or the spine, or has not spread, but more than 1.5 cc of the tumor remains after surgery. A high-risk classification may also be assigned to a tumor that initially appears to be a standard-risk tumor after biomarker testing is completed.

### TABLE 1: BRAIN TUMOR GRADES

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>The slowest growing and least malignant (cancerous) tumors, these tumors are often referred to as nonmalignant tumors. They consist of cells that look mostly normal when examined with the use of a microscope. These tumors rarely recur (come back) as a higher grade tumor.</td>
</tr>
<tr>
<td>Grade II</td>
<td>These tumors grow relatively slowly and consist of cells that look only slightly abnormal when examined with the use of a microscope. They can spread into nearby normal tissue and may recur later as a higher grade tumor.</td>
</tr>
<tr>
<td>Grade III</td>
<td>These malignant tumors quickly reproduce abnormal cells that are likely to spread to nearby normal tissue. They have a higher risk of recurrence and may return as a higher grade tumor. It can sometimes be difficult to differentiate between Grade II and Grade III tumors.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>The most rapidly growing type of brain tumor, these malignant tumors reproduce cells that appear completely abnormal and can easily spread into surrounding tissue.</td>
</tr>
</tbody>
</table>


### ADDITIONAL RESOURCES

- American Brain Tumor Association: [www.abta.org](http://www.abta.org)
- American Society of Clinical Oncology: [www.cancer.net](http://www.cancer.net)
- National Cancer Institute: [www.cancer.gov](http://www.cancer.gov)

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**HOW BRAIN TUMOR CELLS EVOLVE**

<table>
<thead>
<tr>
<th>Benign Tumor</th>
<th>Grade I Tumor</th>
<th>Grade II Tumor</th>
<th>Grade III Tumor</th>
<th>Grade IV Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cells with a healthy appearance.</td>
<td>Slow-growing cells that appear almost normal.</td>
<td>Relatively slow-growing cells with a slightly abnormal appearance, capable of invading adjacent normal tissue.</td>
<td>Actively reproducing abnormal cells that move into adjacent normal brain tissue.</td>
<td>Rapidly reproducing, abnormally shaped cells that contain dead tissue and invade nearby areas.</td>
</tr>
</tbody>
</table>
Pediatric High Grade Gliomas (HGG) Research Study

Do you or someone you know have a child with a high grade glioma that is EGFR Amplified?

The INTELLANCE2 sub-study is a research study evaluating the pharmacokinetics, safety and tolerability of a novel therapy for children with a high grade glioma that is EGFR amplified.

Patients must meet the following criteria:

- Less than 18 years of age
- Newly diagnosed or recurrent high grade glioma (grade III glioma, grade IV glioma or diffuse intrinsic pontine glioma (DIPG))
- Sufficiently recovered from previous therapy
- No current or recent treatment with another investigational drug
- Other criteria apply

For more information, ask your doctor about the INTELLANCE2 Pediatric Sub-Study or visit www.clinicaltrials.gov (NCT02343406) to see if you qualify.
Scott Hamilton is many things — a husband and father, figure skating champion and Olympic gold medalist, broadcaster, author, motivational speaker, and testicular cancer and brain tumor survivor. His unwavering optimism in all aspects of his life has enabled him to help others who are enduring the challenges of cancer.

In 1977, Scott Hamilton lost his mother to breast cancer. At the time, not many treatment resources were available at their local hospital, and he realized much more research was needed to fight cancer. Twenty years later, he found himself facing the need for himself.

“I was on tour and hadn’t been feeling well,” Scott explained. “I was having abdominal pain, and it was hard for me to stand up straight. I assumed it was an ulcer, so I had it checked out. The doctor told me it was a mass. I thought that was kind of funny. At just more than five feet tall, no one had ever used ‘mass’ to describe anything about me.”

Scott has always had that level of positivity. In fact, when doctors diagnosed him with testicular cancer, he told them, “That seems kind of personal. Can I have something else? After all, my audience is 70 percent female, and I really don’t want to be talking about testicular cancer for the rest of my life.” They told Scott that he needed to take it seriously, and he told them he needed to deal with it however he could.

“I decided to use humor and levity because I wanted to be able to look back one day and think ‘There was a lot of laughter in my hospital room,’ instead of thinking about all of the physical descriptions of my cancer.”
His treatment included chemotherapy and surgery. It was rough, but he was determined to “own” his cancer, so he set a goal for his recovery to skate in a national show four months after surgery. He accomplished that goal, and his first words at the microphone were “I win!”

Scott felt good until 2004, when he noticed changes with his vision. “At first, my doctor told me vision issues happen when you’re in your forties, but I persisted. I told him my peripheral vision was super blurry. He sent me for a CT, which showed I had a brain tumor. When I told my wife, Tracie, the first thing she did was take my hand and we prayed. It was both powerful and empowering. I felt peace and knew we’d be okay.”

To learn more, doctors performed a biopsy by cutting a hole in the top of Scott’s head and inserting a needle. “The doctors told me that with this type of biopsy, a lot of bad things could happen. When I woke up after it, I looked at the clock, decided I knew who I was and where I was, and said ‘test’ out loud to make sure I could speak.”

The brain tumor was diagnosed as a craniopharyngioma, a benign tumor that is typically detected early in a child’s life. “I had growth issues as a very young child and was in and out of the hospital. My parents were never given a definitive reason, but now I know this type of brain tumor can stunt growth,” Scott explained. “I’d probably had it all of my life, but it never did its mischief while I was skating, so I didn’t know it was there.”

Scott’s treatment consisted of gamma knife radiation. His pituitary gland was damaged, resulting in hormonal issues that were treated with steroids.

Life went on until six years later when he began feeling symptomatic while he was traveling. He remembered that after having the tumor removed, his doctors told him, “By the way, these things like to come back.” It had, indeed, come back. Scott had transphenoidal surgery to remove the tumor.

“When I woke up from surgery, my leg, of all things, was in a brace,” he laughed. “My ophthalmic artery was nicked during surgery, and an aneurism formed. I had angiogram after angiogram with a catheter in my leg, which explained the brace. A specialist who focused only on aneurysms was brought in, and he coiled the aneurysm from the inside. That was a tough one!”

Once more, normal life resumed, with Scott continuing to get follow-up scans. During a routine cerebroangiogram in 2016, his doctor noticed a black spot. A scan showed the very tip of the brain tumor coming back.

“We caught it early, and my doctor allowed me to try something. I wanted to go home, get fit and get stronger before having more surgery. I also wanted to research my options, including a new targeted therapy and proton therapy.”

That was August. When Scott returned for more scans in February 2017, they discovered the tumor had shrunk. “These tumors just don’t shrink,” he explained, “My doctors couldn’t explain it medically. Whatever I was doing – getting fit, praying and being positive – it all worked. It was an absolute miracle.”

That infectious attitude especially comes through when Scott describes how he handles his cancer challenges with his four children. “Your kids depend on you for guidance and information, and they follow your lead. I set the tone with a little bit of humor. When my youngest son asked me if my brain tumor was back and if I was scared, I said, ‘It is! Do I look scared?’ He said I didn’t, so I told him he shouldn’t be either. I don’t let cancer take every second of every day. I won’t let it diminish me like that.”

As a patient, Scott identified many things that would have improved his own experiences, and he felt compelled to take action. “I remember asking my doctor how sick I’d be with chemotherapy for the testicular cancer, and he told me ‘moderate to severe.’ What does that mean? And, I know now that the depression and anger I felt during chemotherapy were emotional side effects, but I didn’t realize it at the time. I wanted to provide information to patients so they weren’t flying blind.”

With the goal of improving patient survivorship by creating world-class cancer research and the highest quality patient treatment and care, Scott created the Scott Hamilton CARES Foundation (Cancer Alliance for Research, Education and Survivorship). From that came several other resources, including Chemocare.com, Radcare.org and the 4th Angel Mentoring Program.

“4th Angel came from the idea that when you have cancer, the first angel is your oncologist. The second is your oncology nurse. The third is your friends and family, and the fourth is someone you can talk to who has ‘been there, done that.’”

“Your kids depend on you for guidance and information, and they follow your lead. I set the tone with a little bit of humor.”
The brain is made up of many different types of cells, and primary tumors may originate in any of them. These cells may be in the brain tissue or in any of the membranes, nerves or glands in and around the brain. As a result, many different types of primary central nervous system (CNS) tumors can occur in any of these areas. Some estimates say there are more than 120 types.

The tumor types are named according to the tissue or cell type involved, the location of the tumor, whether it is benign (noncancerous) or malignant (cancerous), and whether it is fast-growing (aggressive) or slow-growing. Although brain tumors may contain one type of cell, they may also be a mixture of cell types.

Some of the most common types include gliomas, meningiomas, schwannomas, pituitary tumors, pineal gland tumors and primary germ cell tumors of the brain. The following includes information about each of these types, where they are located and some of their notable characteristics.

Gliomas

Gliomas, which develop from glial cells, are the most common type of brain tumors. Any cancer that develops from the glial cells is referred to as a glioma. Glial cells are the most common and abundant cell type within the CNS, and they have many functions, including surrounding, protecting and supporting neuron cells with nutrients and oxygen. There are multiple types of glial cells: astrocytes, oligodendrocytes and ependymal cells. Tumors of these glial cells are known as astrocytomas, oligodendrogliomas and ependymomas.

Gliomas are graded based on how aggressive the tumor is. They can range from Grade I (noncancerous, slow-growing) to Grade IV (cancerous, fast-growing) (see Pathology & Grading, page 4). More information about the three types of gliomas is listed below.

Astrocytomas

Astrocytomas begin in astrocytes, which are star-shaped cells that comprise the supportive tissue of the brain. Astrocytomas make up the majority of all gliomas. Astrocytomas can develop in various parts of the brain and CNS, including the cerebellum (back part of the brain), the cerebrum (large front portion of the brain), and central areas of the brain, brain stem and spinal cord.

Astrocytomas may be difficult to remove surgically because they spread widely throughout the brain and blend with normal brain tissue. In some cases, they spread along the cerebrospinal fluid (CSF) pathways, but they rarely spread outside of the brain or spinal cord.

Astrocytomas are graded on a scale from I to IV based on how abnormal the cells look under a microscope. They range from low-grade astrocytomas to high-grade astrocytomas. Low-grade astrocytomas are typically contained in one location and grow slowly. High-grade astrocytomas grow rapidly and spread into surrounding tissues. Astrocytomas are typically high grade in adults.

Following are the most common types of astrocytomas, from low grade to high grade.

- **Pilocytic astrocytomas** are typically classified as Grade I astrocytomas. They are considered the most benign (noncancerous) of all the astrocytomas. They typically stay in the location where they begin and do not spread. Although they are usually slow-growing, these tumors can become very large.

- **Low-grade astrocytomas** are also known as diffuse astrocytoma or astrocytoma Grade II. With Grade II, more cells look abnormal when examined under a microscope than with Grade I. The tumors usually do not spread to nearby tissues but are more likely to invade surrounding tissue than a Grade I tumor. They tend to grow at a relatively slow pace. They also typically contain the IDH+ and 1p19q- molecular markers.

- **Anaplastic astrocytomas** are considered Grade III tumors and are fairly rare. These tumors are malignant and often require more aggressive treatment than pilocytic astrocytomas. Anaplastic astrocytomas may develop in any area of the CNS. They are more likely to begin in the cerebrum, including any of the lobes (frontal, temporal, parietal or occipital). Other common sites for anaplastic astrocytomas include the part of the brain that controls the thalamus and hypothalamus, the lower area of the brain near the back of the neck that controls movement and balance (cerebellum), and the spinal cord. These tumors tend to have tentacle-like projections that grow into surrounding tissue, making them difficult to completely remove during surgery.

- **Glioblastomas (GBMs)** are considered high-grade tumors (Grade IV). They may also be known as astrocytoma Grade IV or glioblastoma multiforme because the cells may take a variety of appearances under the microscope. There are two types of glioblastoma — primary (or de novo) and secondary. Primary tumors are very aggressive and are the most common form of astrocytoma Grade IV. Secondary tumors begin as lower-grade tumors and evolve into Grade IV tumors.

GBMs usually contain a mix of cell types along with cystic mineral, calcium deposits, blood vessels or a mixed grade of cells. They increase in frequency with age and affect more men than women. GBMs have finger-like tentacles and are difficult to completely remove, particularly when they are near parts of the brain that control functions such as language and coordination (see Figure 1).

Although GBMs can be found anywhere in the brain or spinal cord, they are generally found in the cerebral hemispheres of the brain.

GBMs are usually highly malignant (cancerous) because the cells reproduce quickly and migrate into the brain substance, and they are supported by a large network of blood vessels. These cells are able to easily invade and live within normal brain tissue. However, they rarely spread elsewhere in the body.

Oligodendroglialomas

Oligodendroglialomas are tumors that develop from fried egg-shaped cells called oligodendrocytes, which are a type of glial cell. Oligodendroglialomas, which contain the IDH+ and 1p19q+ molecular markers, are classified as oligodendrogliomas and anaplastic oligodendrogliomas.

Oligodendrogliomas are considered low grade (Grade II), and anaplastic oligodendroglialomas are malignant and more aggres-
MENINGIOMAS

Unlike gliomas that form in the cells that make up the brain’s tissues, meningiomas develop in the meninges. The meninges consist of three layers of tissue that cover the outer part of the brain inside the skull and spinal cord. Because the meninges surround the brain, these tumors are usually found in the layers on the top of the brain and the outer curve (see Figure 2). However, these tumors may form at the base of the skull as well. Meningiomas are the most common primary brain tumor in adults.

Meningiomas sometimes occur in families who have neurofibromatosis, a genetic syndrome in which many benign tumors of nerve tissue develop. These tumors are more likely to be found in adults older than 60, and the incidence appears to increase with age.

The majority of meningiomas are benign, but some may be classified as malignant. Although rare, malignant meningiomas may be highly aggressive. Even if the meningioma is benign, it can cause problems if it grows into nearby areas of the brain. These tumors typically grow slowly and inward, putting pressure on the brain or spinal cord, which can interfere with normal brain function. However, they also can grow outward toward the skull and cause it to thicken. Some contain sacs of fluid (cysts), mineral deposits (calcifications), or tightly packed bunches of blood vessels.

These tumors are graded from Grade I to Grade III. Grade I meningiomas are benign and look mostly normal under a microscope. Grade II meningiomas may be considered anaplastic or malignant and look mostly abnormal under a microscope. Grade III meningiomas may be considered anaplastic or malignant and look mostly abnormal under a microscope. These grow quickly, can grow into other parts of the brain and bone, and can return after treatment.

It is estimated that a majority of meningiomas contain an abnormal chromosome 22 that typically suppresses tumor growth. The exact cause of this abnormality is unknown. Research has found that meningiomas typically have extra copies of the platelet-derived growth factor (PDGF) and its receptor (PDGFR) and epidermal growth factor receptor (EGFR) genes, which may cause these tumors to grow. This may be the subject of further research in clinical trials.

Anaplastic ependymomas can be either Grade I or II, are less aggressive and typically grow slowly with mostly normal cells when viewed under a microscope. Ependymomas usually are located along, within or next to the ventricular system. Grade I ependymomas can be either myxopapillary ependymomas or subependymomas. Grade II ependymomas grow into the ventricles.

Anaplastic ependymomas grow quickly and may spread into surrounding tissues. When viewed under a microscope, the cells look different than normal cells. This type is rarely found in the spinal cord.

Because ependymomas form in the cells that line the ventricles, they most often spread along the cerebrospinal fluid pathways but rarely spread outside the brain or spinal cord. They are typically soft and grayish or red.

Ependymomas develop from ependymal cells, which line the ventricles of the brain and the middle of the spinal cord. The ventricles are the passageways where cerebrospinal fluid is made and stored. Ependymomas may prevent cerebrospinal fluid from leaving the ventricles, which causes the ventricles to enlarge. These tumors range from low grade, which are less aggressive, to high grade, which are more aggressive.

Ependymomas or spinal cord. They are typically soft and grayish or red. Ependymomas may prevent cerebrospinal fluid from leaving the ventricles, which causes the ventricles to enlarge. These tumors range from low grade, which are less aggressive, to high grade, which are more aggressive.

Ependymomas

Ependymomas develop from ependymal cells, which line the ventricles of the brain and the middle of the spinal cord. The ventricles are the passageways where cerebrospinal fluid is made and stored. Ependymomas may prevent cerebrospinal fluid from leaving the ventricles, which causes the ventricles to enlarge. These tumors range from low grade, which are less aggressive, to high grade, which are more aggressive.

Ependymomas are relatively common tumors and have only recently been recognized by the World Health Organization. These do not develop within the pineal gland but, instead, may grow from regions or structures around the pineal gland. Grades have yet to be determined for this group, but it is believed they are close to Grade II or III. (continued on page 10)

There are several common types.

• **Pineocytomas** are considered Grade I or II, are less aggressive and typically grow slowly with mostly normal cells when viewed under a microscope. They can be relatively benign.

• **Pineal parenchymal tumors of intermediate differentiation** are considered Grade II or III and fall between pineocytomas and pineoblastomas, which are Grade IV. Parenchymal cells (pineocytes) are the cells that make up most of the pineal gland. The tumor cells may spread into nearby tissue or the cerebral spinal fluid. These cells look very different under a microscope.

• **Papillary tumors of the pineal region** are relatively uncommon tumors and have...
A cancer diagnosis for a child is much rarer than for an adult. If your child is diagnosed with a brain tumor, your medical team will provide you with detailed, personal information about your child’s unique situation.

ABOUT PEDIATRIC BRAIN TUMORS
The cause of most childhood brain and spinal cord tumors is unknown. The tumors may be high-grade or low-grade. When a tumor grows into or presses on an area of the brain, it may stop that part of the brain from working the way it should. Although low-grade brain tumors grow and press on nearby areas of the brain, they rarely spread to other parts. Both types of brain tumors need treatment.

The signs and symptoms of childhood brain and spinal cord tumors differ in every child, depending on the following:

• Where the tumor arises — in the brain or spinal cord
• The size of the tumor
• How fast the tumor grows
• The child’s age and development

A variety of tests and procedures may be used to diagnose brain and spinal cord tumors (see Diagnosing Brain Tumors, page 3).

If doctors suspect a brain tumor, a biopsy may be done to remove a sample of tissue. Most childhood brain tumors are diagnosed conclusively through a biopsy or resection. The biopsy is often done through a small needle while a resection is achieved by removing part of the skull to identify and remove some or all of the tissue. A pathologist views the tissue under a microscope to look for the type of cancer cells present. This will help guide the neurosurgeon in the type of resection needed. The pathologist will also allow for a better definition of the type and grade of the brain tumor. The grade of the tumor is based on how abnormal the cancer cells look under a microscope and how many of the tumor cells are actively dividing.

Many factors affect the way a brain tumor is treated and the child’s chance of recovery, including the type of tumor, the child’s age and overall health, how fast the tumor is growing, where the tumor has formed and if it has spread to nearby tissue or to other parts of the body.

As you discuss treatment options with your medical team, ask about potential side effects and late effects, which are side effects that can occur months or even years after treatment ends (see Side Effects, page 17).

• Pilocytic astrocytomas are Grade IV, malignant (cancerous) and the most aggressive. They may resemble medulloblastomas and retinoblastomas. Their cells look very different under a microscope, and their cells may even contain dead regions.

PITUITARY TUMORS
The pituitary is a small gland located inside the brain. It sits above the nasal passages, which are above the fleshy back part of the roof of the mouth (known as the soft palate). The pituitary gland is responsible for releasing multiple types of hormones that affect many bodily functions. Sometimes referred to as the “master endocrine gland,” it produces hormones for the thyroid, adrenal gland, testicles, ovaries and breasts, as well as melanin, oxytocin and growth hormones.

Tumors that start in the pituitary gland are categorized into two groups.

• Pituitary adenomas are divided into benign pituitary adenomas and invasive pituitary adenomas. Benign pituitary adenomas are not considered cancerous, grow very slowly and do not spread outside of the pituitary gland. However, invasive pituitary adenomas may spread to the skull or the sinus cavity below the pituitary gland.

• Pituitary carcinomas, also known as pituitary cancer, are malignant (cancerous) and are very rare. They can grow into other areas of the brain and spinal cord or outside of the CNS.

Almost all pituitary tumors are pituitary adenomas, which are benign. However, they still can cause problems if they grow large enough to press on nearby structures or if they make too much of any kind of hormone (see Figure 3, page 9). For example, optic nerves that send visual information from the eyes to the brain are near the pituitary gland and may be affected by a tumor in this region.

Pituitary tumors can occur at any age, but they are most often found in older adults. The majority of pituitary adenomas are Grade I, benign. They grow slowly and do not spread outside the pituitary gland. These tumors can be fast or slow growing, and many require no treatment. However, the tumor can press on the optic nerves that send visual information from the eyes to the brain, the optic chiasm, the hypothalamus, the thalamus and the brainstem (see Understanding Clinical Trials, page 16).

Childhood Central Nervous System Embryonal Tumors
Central nervous system (CNS) embryonal tumors may begin in embryonic (fetal) cells that remain in the brain after birth. CNS embryonal tumors tend to spread through the cerebrospinal fluid (CSF) to other parts of the brain and spinal cord. There are different types of CNS embryonal tumors.

Medulloblastomas
These fast-growing tumors that form in brain cells of the cerebellum are the most common CNS embryonal tumors. The cerebellum controls movement, balance and posture. The tumor can spread through the spinal fluid to other parts of the brain and spine. In rare cases, medulloblastomas can spread to the bone, bone marrow, lung or other parts of the body.

Non-medulloblastoma embryonal tumors
Non-medulloblastoma embryonal tumors are fast-growing tumors that usually form in brain cells outside of the cerebellum (in the cerebrum). The cerebrum controls thinking, learning, problem-solving, emotions, speech, reading, writing and voluntary movement. Non-medulloblastoma embryonal tumors may also form in the brain stem or spinal cord. There are four types of non-medulloblastoma embryonal tumors.

• Embryonal tumors with multilayered rosettes (ETMR) are rare tumors that form in the brain and spinal cord. ETMRs most commonly occur in young children and are fast-growing tumors.

• Medullopitheliomas are fast-growing tumors that usually form in the brain, spinal cord or nerves just outside the spinal column. They occur most often in infants and young children.

• CNS neuroblastomas are very rare tumors that form in the nerve tissue of the cerebrum or the layers of tissue that cover the brain and spinal cord. CNS neuroblastomas may be large and spread to other parts of the brain or spinal cord.

• CNS ganglieneuroblastomas are rare tumors that form in the nerve tissue of the brain and spinal cord. They may form in one area and be fast-growing or form in more than one area and be slow-growing.

CNS embryonal tumors, including medulloblastoma, are typically treated with surgery, radiation therapy and/or chemotherapy.
develop in the front two-thirds of the pituitary gland.

In addition to dividing these tumors by whether they are benign or malignant, the tumors may be classified as “functioning” or “non-functioning” because the pituitary gland connects the brain with the endocrine system, which is responsible for directing the body to make hormones. Most pituitary tumors are the “functioning” type, producing larger than normal amounts of one or more hormones.

When pituitary tumors grow outside of the gland, there is very little room to grow in this part of the skull. Therefore, if the tumor becomes larger than about 1 cm (about half an inch) across, it may grow upward, where it can compress and damage nearby parts of the brain and the nerves that arise from it.

**Schwannomas**

Schwannomas are tumors that form in the Schwann cells that primarily cover and protect cranial nerves but can include other nerves, as well. When these tumors develop on the nerve that controls hearing and balance (known as the acoustic or vestibulocochlear nerve), they are also known as vestibular schwannomas or acoustic neuromas. Although they can form on any cranial nerve, they typically develop on the acoustic or vestibulocochlear nerve, which is near the cerebellum. In addition to cranial nerves, schwannomas can begin on spinal nerves where they extend from the spinal cord. When schwannomas press on the spinal cord, they can cause weakness, sensory loss, and bowel and bladder problems.

Schwannomas are almost always benign and usually very slow growing. They are considered Grade I tumors. The vast majority of schwannomas occur spontaneously and as a single tumor. Multiple schwannomas may develop in a small percentage of people. In these cases, the person may have an inherited condition that can be passed from parent to child. (continued on page 12)
OTHER TYPES OF BRAIN TUMORS*

**Types of Brain Tumors**

**Diffuse astrocytic and oligodendroglial tumors**
- Diffuse astrocytoma
- Gemistocytic astrocytoma
- Giant cell glioblastoma
- Gliosarcoma
- Epithelioid glioblastoma
- Diffuse midline glioma

**Other astrocytic tumors**
- Pilomyxoid astrocytoma
- Pleomorphic xanthoastrocytoma
- Anaplastic pleomorphic xanthoastrocytoma

**Ependymal tumors**
- Papillary ependymoma
- Clear cell ependymoma
- Tanyctytic ependymoma

**Other gliomas**
- Astroblastoma

**Choroid plexus tumors**
- Choroid plexus carcinoma

**Neuronal and mixed neuronal-glial tumors**
- Anaplastic ganglioglioma

**Embryonal tumors**
- Embryonal tumor with multilayered rosettes
- CNS embryonal tumor
- Atypical teratoid/rhabdoid tumor
- CNS embryonal tumor with rhabdoid features

**Tumors of the cranial and paraspinal nerves**
- Malignant peripheral nerve sheath tumor (MPNST)
- Epithelioid MPNST
- MPNST with perineural differentiation

**Meningiomas**
- Papillary meningioma
- Rhabdoid meningioma
- Anaplastic (malignant) meningioma

**Mesenchymal, nonmeningothelial tumors**
- Solitary fibrous tumor/hemangiopericytoma
- Epithelial hemangioblastoma
- Angiosarcoma
- Kaposi sarcoma
- Ewing sarcoma/peripheral primitive neuroectodermal tumor
- Liposarcoma
- Fibrosarcoma
- Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Chondrosarcoma
- Osteosarcoma

**Melanocytic lesions**
- Meningeal melanoma
- Meningeal melanomatosis

**Lymphomas**
- Diffuse large B-cell lymphoma of the CNS
- Anaplastic large cell lymphoma
- Intravascular large B-cell lymphoma
- MALT lymphoma of the dura

**Histiocytic tumors**
- Langerhans cell histiocytosis
- Erdheim-Chester disease
- Histiocytic sarcoma

**Germ cell tumors**
- Embryonal carcinoma
- Yolk sac tumor
- Choriocarcinoma
- Immature teratoma
- Teratoma with malignant transformation
- Mixed germ cell tumor

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*Source: American Joint Committee on Cancer (AJCC), Eighth Edition (2017)
There are two conceptual classes of brain tumors: primary brain tumors, which begin in the brain and rarely move outside the brain, and metastatic tumors, those that have spread to the brain from a different type of primary cancer, such as lung cancer or breast cancer. Although they can have similar effects on a person, the treatments used are typically different. In this article, Dr. Lassman and Dr. Wang, colleagues at Columbia University and co-chairs on an international brain tumor clinical trial, discuss treating primary brain tumors.

According to Dr. Lassman, when people learn they have a brain tumor, the first thing they typically want is information.

“Sometimes people request an appointment before we have all of the details available,” he said, “but that’s understandable. They are distressed about their diagnosis, and they want to know what they have, what it means and what they should do. My goal is to answer those questions for them.”

As part of that initial meeting, Dr. Lassman talks about the standard, or first-line, therapy available. He also often introduces clinical trials as a treatment option.

“Glioblastomas are the most common type of primary brain tumors in adults, and they are also the most aggressive. Although the standard treatment we have can be very effective, it isn’t always as effective as we want it to be. Therefore, we often consider clinical trials.”

When he introduces the concept of a trial to patients, he explains that, by definition, a clinical trial is experimental.

“It may be better, it may be worse, or it may be the same with more side effects. If we knew it were better, it would already be the standard treatment. If we knew it were worse, we wouldn’t do it. But, simply doing a clinical trial gives us hope that we will find a better treatment.”

“It’s important to explain that clinical trials come in different types and different flavors,” he said. “Because of the aggressive nature of glioblastomas, most clinical trials for newly diagnosed disease include the standard therapy as well as the experimental therapy — not one or the other. Ensuring patients understand this helps clear up the common misconception that a patient would be receiving something that is instead of an established effective therapy.”

When meeting with patients, Dr. Lassman also discusses the benefits of participating in a trial, such as receiving a higher level of care. More monitoring by a larger medical team, which includes the research team as well as a neuro-oncologist, medical oncologist, radiation oncologist, neurosurgeons, pathologists, radiologists and more, takes place because of the protocols that must be followed in every clinical trial. Studies suggest that participants of a clinical trial are associated with better outcomes regardless of the type of treatment they receive because of that more intense care.

“There are more eyes on the patient,” he said, “which means side effects or other problems can be noticed and addressed earlier.”

Because radiation therapy is one of the main pillars of treatment for glioblastoma in standard treatments as well as clinical trials, Dr. Lassman recommends that patients set up a consultation with Dr. Wang and his radio-oncology team during the initial visit. To make it easier for patients, the doctors often try to coordinate so both appointments can be on the same day.

“Glioblastoma patients will almost always see a radiation oncologist for an opinion about radiotherapy,” Dr. Wang explained. “And, almost all patients, with some exceptions, will be offered radiotherapy.”

According to Dr. Wang, radiotherapy for glioblastoma typically comes in the form of external beam radiotherapy. When explaining the recommended therapy to patients, he discusses the pros and cons of the treatment and the data on outcomes. He also discusses the potential side effects, which are usually a concern for patients.

A brain tumor diagnosis is alarming, and patients generally feel that “time is of the essence” and want to begin treatment right away. Although timing is very important, recent research shows there is actually an optimal window to begin each aspect of therapy. For example, it’s important for the patient to have recovered from surgery before beginning radiotherapy, which may take a few weeks.

As leaders in the industry who are involved in both the clinical and research aspects of treating brain tumors, both physicians are optimistic about the potential for advances through clinical trials.

“Trials are becoming more personalized and focused on individual disease characteristics, including biomarkers and mutations,” Dr. Wang said. “Drugs are developed for personalized treatment that may increase the therapeutic ratio for our glioblastoma patients. There has been a great interest in personalized treatment based on individual biomarkers and genetic mutations. Additionally, there have been lots of developments in immunotherapy trials for glioblastoma. I feel that this will continue to grow for years to come.”

“Clinical trials are incredibly important to improve outcomes for not just individuals, but all patients,” Dr. Lassman added. “I think people feel empowered that they’re contributing to society and making the world a better place.”

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Tony J. C. Wang, MD, is the Co-Director of the Center for Radiosurgery and an Associate Professor of Radiation Oncology (in Neurological Surgery) at New York Presbyterian/ Columbia University Medical Center. Dr. Wang cares for patients with all types of cancer, with extensive expertise in malignant and benign brain tumors. His research interests are in Gamma Knife stereotactic radiosurgery and brain tumors.
Multiple treatment options are available for brain tumors. Often, more than one type of treatment is used. Once your doctor has chosen your treatment plan based on your tumor type, you will work closely with a multidisciplinary care team, including a neurologist, radiologist, surgeon, nurse, financial counselor and others.

It is important to talk openly with your health care team and ask questions about your treatment options, including clinical trials, and their potential side effects (see Side Effects, page 17). Understanding as much about your diagnosis and possible risks and benefits will help you make more informed decisions. Following are the most common treatment options.

**SURGERY**

Typically, surgery is the first treatment option for a brain tumor, whether it’s considered benign (noncancerous) or malignant (cancerous). Surgery may be performed to remove as much of the tumor as possible (as primary treatment or before chemotherapy or radiation therapy); to take a biopsy sample for testing; to place an implant for brain tumor treatment; or to help alleviate symptoms, such as seizures or pressure inside the skull.

A tumor is considered operable when the doctor believes it can be surgically removed with minimal risk of neurologic damage. A tumor is considered inoperable when the risk of brain damage is high due to the location of the tumor within the brain or central nervous system, or in relation to other structures responsible for important functions, such as language, vision or movement. Advancements in imaging techniques and neurosurgery have helped make it possible to surgically remove tumors that were once considered inoperable. For example, a new optical imaging agent has been approved for malignant gliomas. The agent helps neurosurgeons to distinguish tumor tissue from normal tissue.

Several surgical procedures may be used to remove a brain tumor.

- **Craniotomy** is the most common brain surgery used to treat brain tumors. A piece of the skull is removed to expose the brain so the surgeon can find and remove as much of the tumor as possible. The piece of skull is then replaced.
- **Craniectomy** is almost the same as a craniotomy; however, the piece of skull removed at the beginning of the procedure is not replaced at the end. The surgeon may do a craniectomy in situations where the piece of skull was damaged by the tumor or if the brain is expected to swell after surgery. In cases of expected swelling, the piece of skull may be saved and replaced at a later time, but this rarely happens.

  - **Complete removal or gross total resection** is when the surgeon removes the entire tumor. After surgery, diagnostic imaging tests may be performed to look for any remaining tumor. Even if it appears that the entire tumor was removed, there may still be microscopic tumor cells that are too small to see using current imaging methods. Additional treatment may be recommended to destroy any remaining tumor cells.
  - **Partial removal** is when the surgeon chooses to remove only part of the tumor because of a risk of brain damage. Additional therapy, such as radiation therapy or drug therapy, is often recommended to treat the remaining tumor.
  - **Debulking surgery** is removal of as much of a tumor as possible when it’s unlikely that the entire tumor or multiple tumors can be completely removed. This is typically done to reduce the pressure the tumor is placing on the brain or surrounding structures.
  - **Neuroendoscopy** involves the use of a long, narrow tube with a camera and light that is inserted into the hollow pathways of the brain through a small hole drilled in the skull. A laser may also be attached to the endoscope, allowing the surgeon to perform biopsies and remove small tumors, cysts or blockages within the ventricles.
  - **Laser interstitial thermal therapy (LITT)** involves the use of a laser to heat and destroy brain tissue while being monitored by magnetic resonance imaging (MRI). The laser is directed at the tumor through one or more small holes drilled into the skull. This procedure may be used for tumors that pose a health risk or are unreachable with a craniotomy.
  - **Photodynamic therapy (PDT)** is a procedure in which a “sensitizing” drug, or a drug that will be absorbed by the tumor, is injected into a vein or artery shortly before surgery. The drug contains a compound that allows the cells to glow a fluorescent color. These cells can then be viewed with the use of special microscopic filters. During the procedure, the surgeon aims a laser at the glowing cells, which activates the drug and kills the tumor cells.

**COMMONLY USED MEDICATIONS**

**CHEMOTHERAPY**

- carmustine (BCNU)
- carmustine implant (Gliadel Wafer or polifeprosan 20 with carmustine implant)
- cyclophosphamide
- lomustine (CCNU, Gleostine)
- temozolomide (Temodar)
- vincristine sulfate PFS

**COMBINATION THERAPY**

- PCV: procarbazine hydrochloride (Matulane), lomustine (CCNU, Gleostine) and vincristine sulfate PFS

**CORTICOSTEROIDS**

- dexamethasone

**TARGETED THERAPY**

- bevacizumab (Avastin)
- bevacizumab (Mvasi)
- dinutuximab (Unituxin)
- everolimus (Afinitor)

**Skull base surgery** involves the use of specialized techniques, including neuroendoscopy. This surgery is very difficult because the skull base is a delicate area containing several nerves and blood vessels that are crucial for sensory and motor functions.

**Transsphenoidal surgery** is done by going through the nostril to reach the pituitary gland, or by making an incision in the upper lip above the teeth to access the tumor through the sphenoid sinus. It is most often used to treat pituitary adenomas and craniopharyngiomas.

**Embolization** is used to stop the flow of blood to tumors that have a large number of surrounding blood vessels. This procedure is done to prevent excessive bleeding during surgery. Before surgery, an angiogram is performed to map the blood vessels around the tumor. The neurosurgeon or interventional radiologist then inserts a plug in the blood vessels feeding the tumor to stop blood flow to the tumor. Surgery to remove the tumor is typically done within a few days.

**Shunt placement** involves placing a shunt, or catheter, into one of the four ventricles of the brain or a cyst to drain fluid that may be causing increased pressure inside the skull. The pressure is often caused by excess fluid buildup or blocked fluid pathways as a result of the tumor itself, or swelling caused by the tumor. The shunt drains cerebrospinal fluid or tumor fluid away from the brain and into the body, where it can be absorbed through normal processes. A shunt can be permanent or temporary.

**Ultrasonic aspiration** involves the use of vibrations caused by ultrasonic waves to break apart the brain tumor, which is then aspirated (removed with suction).
**CHEMOTHERAPY**

Chemotherapy is the use of drugs to destroy cancer cells. Chemotherapy may be used as the primary treatment for certain tumors, before surgery to help shrink the tumor, or, more commonly, after surgery to destroy any remaining cells. Chemotherapy is sometimes given with radiation therapy (known as chemoradiation) to make the radiation more effective.

Using chemotherapy for brain tumors is different from treating any other type of tumor because of the blood-brain barrier. Only certain chemotherapy drugs are capable of passing through the barrier to treat the tumor. A process known as blood-brain barrier disruption may be used to temporarily disable the brain’s protective barrier. A drug is used to expand the blood vessels in the brain, during which time powerful doses of chemotherapy are injected into an artery or vein. The expanded blood vessels disrupt the barrier and allow the drugs to reach the tumor. As the drug wears off, the barrier is restored.

Other additional methods of delivering chemotherapy directly to the brain tumor are available.

- **Ommaya reservoir** is a small container attached to a tube that is surgically implanted underneath the scalp. The tube leads into a ventricle or fluid-filled cyst within the brain, where chemotherapy may be delivered or fluid may be removed when needed.

- **Convection-enhanced delivery (CED)** involves a catheter that is surgically inserted into the tumor. The other end is connected to a device that pumps chemotherapy drugs (or other therapeutic substances) into the catheter, allowing the drugs to flow directly into the tumor. CED is currently being studied in clinical trials for use in delivering additional therapies and tracers, which are injected past the blood-brain barrier to improve CT and MRI images of brain tumors that may be otherwise difficult to see.

- **Polymer wafer implants** contain a chemotherapy drug that may be inserted into the tumor site after surgery to treat any remaining tumor cells that may have spread into surrounding tissue. Up to eight of these nickel-sized wafers may be placed into the cavity during the procedure and remain in place until they dissolve and release the drug, which usually occurs over two to three weeks. Wafer implants are most commonly used to treat malignant gliomas.

**RECURRENT**

Brain tumors have the potential to recur (return) even after successful treatment. As part of your follow-up care, you’ll continue to receive imaging scans to monitor for this. Recurrent brain tumors often return near where the first tumor was found, but can show up in another location. If a tumor returns, a new cycle of diagnostic testing will be done to determine the best treatment because your treatment for a recurrent tumor may be different than the treatment you received with the first one. Ask your doctor for more information about your risk of recurrence, as it is critical to contact your doctor at the first sign of the return of cancer.

**RADIATION THERAPY**

Radiation therapy is the use of high-energy X-rays or particles to destroy cancer. It may be given as primary treatment for certain brain tumors or when surgery is not an option. It may be given before surgery to shrink the tumor or after surgery to destroy any remaining cancer cells. Radiation therapy may be given in combination with some chemotherapy drugs (chemoradiation) to improve the effectiveness of radiation therapy. Radiation therapy may also be used to relieve symptoms caused by the brain tumor.

Different types of radiation therapy used to treat brain tumors include three-dimensional conformal radiation therapy (3D-CRT), conventional radiation therapy, intensity-modulated radiation therapy (IMRT), volumetric arc-based therapy (VMAT), craniospinal radiation, stereotactic radiosurgery and proton therapy.

To ensure the radiation is delivered to the same place each time, you may be fitted with a radiation mask to help hold your head in place during the treatment session. The mask is made with a mesh material and will be shaped to your face. Marks made on the mask or tattooed onto your skin (if a mask is not used) will indicate exactly where treatment needs to be delivered.

Different brain tumors require different amounts of radiation therapy. Just like any other tissue in the body, the brain can only withstand a certain amount of radiation. To increase the effectiveness of radiation therapy, a radiation boost (a type of local radiation) may be used in addition to conventional radiation. Drugs called radiosensitizers may also be given to increase the sensitivity of tumor cells to radiation; that is, to make the cells more likely to be destroyed by radiation.

**IMMUNOTHERAPY**

Immunotherapy uses the body’s own immune system to fight cancer cells. Although no immunotherapies have been approved to treat brain tumors, success in treating other cancers has encouraged researchers to evaluate its effectiveness through clinical trials.

**ADDITIONAL RESOURCES**

- **American Brain Tumor Association:** www.abta.org
- **American Cancer Society:** www.cancer.org
- **American Society of Clinical Oncology:** www.cancer.net
Currently, scientists and doctors are working to learn more about how brain tumors begin, how to quickly diagnose them, how they can be prevented and the best ways to treat them. Much of this research is conducted in clinical trials, which are essential for evaluating new treatments for people with brain tumors.

There are many reasons to consider clinical trials. They could offer you access to new treatments that aren’t yet available to the general public. You may have a rare type of brain tumor that hasn’t been studied as much as other types, or your current treatment may not be working as well as expected. By simply participating, you are helping refine and improve the way millions of people with all types and stages of cancer are treated.

In addition to asking your doctor about available clinical trials, you are encouraged to do your own research. Learn more by talking with other people who have participated in a clinical trial. Keep in mind that everyone has a different treatment experience, so you cannot expect to have an identical response to treatment or the same side effects. You can, however, find out what it’s like to receive care within a trial. Regardless of the information you gather, participating in a clinical trial is your decision.

PARTICIPATING IN A CLINICAL TRIAL
Clinical trial participants must meet certain eligibility criteria, such as type and stage of disease, conditions specific to what the trial will study, age and overall health. Sometimes the results from diagnostic tests can be used to determine if you are a candidate for a certain trial. Your medical team may use existing tissue samples, blood test results and scan reports to avoid repeating procedures.

Once you are accepted into a trial, your medical research team will include doctors, nurses, social workers and other health care professionals. You will have regular visits with this team, as well as visits with your regular doctor. You will be carefully monitored throughout your care. Clinical trials are carefully thought out, planned and performed in an extremely consistent manner so that all patients are treated exactly the same, from medication dosage and schedule to the frequency of follow-up appointments. Whether you’re at a small rural hospital or a large facility in a metropolitan area, your medical team is responsible for diligently following all of the same protocols and safety measures for your treatment plan. Even after the treatment ends, you will continue to be in close contact with the medical team managing your trial.

FINANCIAL CONSIDERATIONS
Cost is a common concern when you consider participating in a clinical trial. Routine patient care costs typically include those related to doctor visits, hospital stays and some testing procedures that are part of standard care and may be covered by your insurance. Research costs, which are directly related to the clinical trial and include drugs and procedures, are typically covered by the trial sponsor. Sponsors of clinical trials include government agencies (such as the National Cancer Institute), independent groups of doctors and health care institutions, or the pharmaceutical or biotechnology industries. Before dismissing the idea of participating because of the cost, research available resources and explore your insurance plan benefits. You may find that you can have access to an innovative treatment and be an integral part of cancer research without incurring a great deal of additional expense.

MYTH VS FACT

MYTH ➔ Clinical trials are only for people who have no other options for treatment (a “last resort”).

FACT ➔ Clinical trials of cancer treatment may be available for individuals with cancer of all types and stages.

MYTH ➔ Clinical trials only take place at large hospitals or cancer centers.

FACT ➔ Clinical trials occur in all parts of the country, in both rural and urban areas.

MYTH ➔Signing the Informed Consent form “locks” you into staying in a trial.

FACT ➔ You are free to change your mind at any time, even after signing the Informed Consent form. You can drop out of a trial at any time for any reason.

MYTH ➔ A clinical trial must be recommended by a doctor for a person to participate.

FACT ➔ If your doctor does not talk to you about clinical trials, raise the topic yourself. You may also search for clinical trials online.

MYTH ➔ Some participants in a clinical trial will get a placebo (sugar pill) instead of treatment.

FACT ➔ Participants in cancer clinical trials receive, at minimum, the current standard of care, and will never receive a placebo instead of cancer treatment.

Before volunteering for a clinical trial, you will receive detailed information about the clinical trial in an Informed Consent form. This form details the purpose of the research, including what your role will be in the trial and how the trial will work, as well as benefits, risks and other pertinent information. The form will include how you will be monitored and what side effects to expect, the best standard of care for your stage of disease (regardless of the doctor or institution), the safeguards in place and how to withdraw from the trial at any time. To ensure you fully understand what you are agreeing to, you are required to review the form during the Informed Consent process.

Before signing the form, check with your insurance providers to determine what procedures are covered and what you will be expected or required to pay out of pocket. Although many trials cover the costs of certain treatments, other expenses may be the responsibility of the participants, which is best to know before you begin a trial.

You are encouraged to ask questions about anything you don’t fully understand. To help you make a more informed decision, talk with your medical team about the many falsehoods that persist about clinical trials. For example, although there is fear to the contrary, participants are guaranteed to receive, at minimum, the current standard of care treatment during the trial, meaning you never jeopardize your care by choosing to participate. Rest assured, you can continue to ask questions and share your concerns with your medical team throughout the trial. And, although you sign the Informed Consent form, you are not locked in. You may change your mind at any time during the trial and choose to receive standard of care.

ADDITIONAL RESOURCES

- American Brain Tumor Association: www.abta.org/secure/clinical-trials.pdf
- Clinical Trials and Me: www.clinicaltrialsandme.com
When treating a brain tumor, healthy tissues may be affected, resulting in side effects. Some treatments are more likely to cause side effects than others. Side effects vary from person to person, even among those who receive the same treatment.

Some side effects may be prevented, and others may be managed by you and your doctor. Ask your doctor what to expect before beginning treatment. Tell your medical team when a new side effect begins, even if you consider it trivial. The sooner side effects are addressed, the sooner your medical team will be able to help you manage them. Following are some of the common side effects of brain tumors and their treatment and ways to manage them.

**ALOPECIA (HAIR LOSS)**
Some treatments may cause loss of hair on the head, face and other parts of the body. Radiation therapy may cause hair loss in the area being treated. Not every person treated for cancer will lose his or her hair, even when they receive the same treatment.

Be gentle with your hair to reduce the amount of hair loss. Use a soft-bristle brush or wide-toothed comb, and avoid shampoos with strong detergents. Ask your oncologist for a prescription for a wig. Using certain phrasing on the prescription, such as “cranial (or skull) prosthesis due to alopecia caused by treatment for cancer,” may make the wig eligible for insurance coverage.

**DIARRHEA**
Certain types of treatment may cause diarrhea. When mild, diarrhea is an inconvenience. If left untreated, it can lead to serious problems, such as dehydration, loss of important nutrients, weight loss and fatigue.

Over-the-counter medicines and supplements are available to control diarrhea, but ask your doctor before taking anything. If diarrhea is severe, your doctor may prescribe other medications or choose to stop your cancer treatment temporarily until it is controlled.

**MEMORY AND COGNITIVE CHANGES**
A brain tumor and its treatments may affect your ability to think, reason, concentrate, process and remember information. Fatigue can zap the energy you need for thinking and remembering. These changes may make it difficult for you to focus on tasks or follow conversations, plan or organize your thoughts, learn new things or remember names and dates.

Let friends and family know you’re having trouble remembering things, and ask them to help you by repeating information. A daily planner may help you keep track of events and appointments. Don’t multitask; instead, focus on one thing at a time.

If you experience these types of side effects, talk with your doctor about your concerns. He or she likely will schedule an evaluation to help determine the best ways to train or retrain the cognitive skills that may have been lost or affected during treatment.

**EMOTIONAL CHANGES**
An interference with brain function may cause unexpected changes in personality and feelings. Your moods may differ, and you may deal with anxiety, anger or stress differently.

A brain tumor diagnosis is often accompanied by depression. It may be caused by the tumor, its treatments or by the diagnosis. Depression is more complex than just feeling sad or hopeless and can result from low hormones, a chemical imbalance in the brain, uncontrolled pain or other unrelied symptoms.

Spend time with family and friends who can help you cope better with daily life and perhaps reduce the risk of depression. Join an online or in-person cancer support group to meet people who are going through a similar situation. Consider speaking with a counselor or exploring psychological treatment, which may include individual psychotherapy (counseling to explore emotional issues that contribute to depression) and cognitive-behavioral therapy (counseling to help a person change his or her negative thought patterns and behaviors). If you have thoughts of hurting yourself or others, talk with your doctor immediately.

**PHYSICAL CHALLENGES**
Brain tumor treatment may cause muscle weakness, changes in motor skills and difficulty with speech.

Physical therapy is a form of rehabilitation that aims to improve the ability to move and function. A physical therapist helps identify and correct any issues with mobility that occur as a result of brain tumor treatment.

Speech pathology is a form of rehabilitation that focuses on issues with speech and swallowing. A speech pathologist may offer ways to regain the ability to speak or to improve speech impairment.

**FINANCIAL ANXIETY**
Treatment and related items, such as additional care, can be expensive, which can add to the stress you may feel already. Some people may even let the cost prevent them from seeking or continuing treatment. You are encouraged to learn more about the costs related to treating your brain tumor, as well as resources that are available to help reduce or manage the expense. Ask your treatment team or your health insurance provider to refer you to someone who is familiar with your case and can provide more information.
SIDE EFFECTS

HEADACHES
Headaches may be a side effect from treatment, as well as a symptom of the pressure caused by the tumor itself. People who have surgery or receive radiation therapy or drug therapy may have headaches.

Try over-the-counter pain relievers and get plenty of rest. If your headache is severe, keep track of the characteristics of your headache. Include the time of day it starts, how often it happens, how long it lasts and where it occurs (forehead, temples, side of head, back of head, etc.). This information may be helpful to your doctor, who may prescribe medication to relieve the pain.

MOUTH SORES
Mouth sores may form in the lining of the inside of the mouth and can affect the gums, tongue, roof of mouth or lips. Mouth sores can develop into white patches that may become large red lesions. Pain may range from mild to severe, making it difficult to talk, eat or swallow. Mouth sores are most often related to drug therapy.

If mouth sores develop, try to keep your mouth and lips moist and avoid spicy, acidic or rough-textured foods. Your doctor may suggest rinsing your mouth with special solutions, or may prescribe a medication that coats the lining of your mouth or a pain medication that can be applied topically. Over-the-counter medications may help relieve discomfort.

NAUSEA AND VOMITING
Nausea is feeling sick to your stomach and may be accompanied by vomiting (throwing up). Severe vomiting can lead to dehydration and interrupt treatment. Nausea and vomiting are much easier to prevent than to control once they’ve started. People who have drug therapy or radiation therapy may experience nausea and vomiting.

Talk to your doctor about lowering your medication doses, adding antiemetics (anti-nausea drugs) or other suggestions to help keep you comfortable.

ADDITIONAL RESOURCES
- American Brain Tumor Association: www.abta.org
  Depression and Mood Changes
  Memory and Cognitive Changes
  Side Effects and their Management
- American Society of Clinical Oncology: www.cancer.net
  Attention, Thinking, or Memory Problems

AFTER TREATMENT ENDS

At the end of your treatment period, your doctor will discuss your follow-up care schedule. This details the need for future appointments, lab work, scans and/or any ongoing maintenance therapy. Follow-up care is an important step in monitoring for recurrence (cancer that has come back). It’s also an opportunity to talk with your doctor about any long-term side effects you’re having or any late effects that arise. Late effects may begin weeks, months or even years after treatment ends.

Additionally, as you resume some of your daily activities, you may face the following challenges. Talk with a member of your health care team for resources that can help you manage them.

- Cognitive issues. Memory, motor skills, learning and behavior can be affected. Children who experience these issues may have learning disabilities.
- Dental concerns. Increased risk for cavities, thinning of tooth enamel and problems with roots are likely. Visit your dentist regularly.
- Emotional changes. Changes in mood and behavior can occur. It is important to watch for these types of changes and report them to your doctor immediately so you can be evaluated right away.
- Fertility issues. Your fertility may be affected, impairing your ability to have a child or to maintain a pregnancy. If having children is part of your life plan, ask your doctor to check your hormone levels annually. An endocrinologist is recommended to monitor the progress of puberty and hormone levels in children after receiving treatment for a brain tumor.
- Hearing loss and tinnitus (ringing in the ears). You should have regular audiology testing after treatment. Hearing aids may help, if necessary.
- Hormonal issues. Growth and reproductive issues and osteoporosis may occur. Hormone levels should be checked regularly. Children should be monitored closely throughout puberty.
- Language and speech impairment. Many problems can occur regarding your ability to express yourself and your ability to comprehend others. Rehabilitation with a speech pathologist can help you find ways to improve these communication skills.
- Rehabilitation. Health care professionals work as a team to provide rehabilitation care, which helps patients improve their physical strength, including function and movement and their ability to care for themselves and assist in the management of pain and other symptoms.
- Resuming your career. You may have taken time off from work during treatment and are now exploring the idea of re-entering the workforce. Before you jump right back into work, it’s important to re-evaluate your career goals and abilities. You may be dealing with difficult side effects that might require temporary adjustments at work. Talk to your supervisor about your workload and be realistic about what you can manage. Also, talk to your doctor about how your follow-up treatment schedule and long-term side effects might affect your ability to perform the same job you had before cancer.
- Vision problems. The risk of vision loss or cataracts is increased. Be sure to have your eyes checked regularly.

- Maintain dental checkups.
- Monitor hormone levels.
- Have your ears tested.
- Get rehabilitative care.
- Discuss your workload.
- Schedule an eye exam.
As you manage your own emotions and fears caused by this diagnosis, you are faced with the responsibility of caring for and assisting your loved one who has a brain tumor. The job of a caregiver requires commitment, hard work and flexibility.

You will face a unique set of challenges because of the types of changes that can occur in your loved one as a result of a brain tumor and its treatment. Your loved one may encounter emotional, cognitive and psychological changes that could include frequent mood swings, memory problems or difficulty communicating. As you provide care, you can expect to draw from your many strengths. You may be pleasantly surprised to discover some strengths you didn’t even know you had. Learn as much as you can about your loved one’s type of brain tumor so you can provide both physical and emotional support.

Your typical caregiver duties may include managing side effects, administering medications, scheduling appointments and organizing paperwork, cooking and cleaning, among other things.

Attending medical appointments is an important function. In addition to driving your loved one to appointments, listen carefully and ask questions. Take notes to help remember key information, and report progress and problems to the medical team during the visits. Share updates by group e-mail or social media to relieve you and your loved one of having to repeat the same story multiple times.

Consider your loved one’s special dietary needs and preferences when preparing meals. By shopping for and preparing the right foods, you can help your loved one get the right nutrition during treatment. Choose foods that nourish the body and help manage the symptoms and side effects of medications.

You may also be caring for your loved one’s children. Help your loved one enjoy some downtime by taking the kids out. Entertaining kids doesn’t have to be costly — an afternoon at the park or in the library is fine. If your loved one prefers not to be left alone, plan an at-home activity, such as making posters or get well cards for the parent who is undergoing treatment.

Along with advocating for your child to get the best treatment available and taking on the typical duties of a caregiver, you are confronted with the extraordinary task of continuing to parent as you did before your child was diagnosed. You may feel overwhelmed at times. Keep in mind that patience and flexibility will be important. Here are a few suggestions that may help make your day-to-day life easier:

- **Follow a schedule.** Although you may feel overwhelmed at times, it helps to have a normal routine as much as possible. It may not be your old routine, but sticking to a regular schedule adds structure and reduces anxiety.
- **Be creative with food.** Loss of appetite is a common challenge. Traditional meals and mealtimes may go by the wayside for the time being, and that’s okay. Let your child eat whenever he or she feels hungry, and offer high-calorie, high-protein snacks throughout the day.
- **Help your child stay connected.** Phone calls, texts, video chats and social media platforms make it easier for your child to stay in touch with friends, especially when an in-person visit may not be possible.
- **Pay attention to siblings.** Your child’s siblings may feel a variety of emotions, from fear and guilt to anger. It’s important to address their concerns. Set aside time for each child, and involve siblings in caregiving, as appropriate.
- **Boost your child’s spirits.** Explore new hobbies that can be done during hospital stays or at home when visitors aren’t recommended. If you notice your child is frequently sad or appears to be depressed, call the doctor.
- **Be positive.** Show your child that you’re optimistic about the road ahead. Most important, trust your instincts. After all, you know your child best. And, remember, you’re not alone. Your child’s medical team is available to assist or recommend others who can.

### ADDITIONAL RESOURCES
- **American Cancer Society:**
  - [www.cancer.org/Children and Cancer](www.cancer.org/Children and Cancer)
- **American Brain Tumor Association:**
  - [www.abta.org/Caregiver Resource Center](www.abta.org/Caregiver Resource Center)
- **American Society of Clinical Oncology:**
  - [www.asco.org/Children and Cancer](www.asco.org/Children and Cancer)
  - [www.cancer.net/Siblings and Cancer](www.cancer.net/Siblings and Cancer)
FINANCIAL ASSISTANCE
Bringing Hope Home ........................................ www.bringinghopehome.org
CancerCare ...........................................................www.cancercare.org
Cancer Financial Assistance Coalition ...................... www.cancerfac.org
HealthWell Foundation ........................................www.healthwellfoundation.org
Hope Lodge .................................................... www.cancer.org/treatment/supportprogramservices/hopelodge
Medicare.gov ..................................................... www.medicare.gov
Patient Access Network Foundation ........................... www.paf.org
Patient Advocate Foundation .............................................www.patientadvocate.org
Patient Services, Inc. .............................................www.patientservicesinc.org
Social Security Administration ......................................www.ssa.gov
Social Security Disability Resource Center ................. www.ssdrc.com
State Health Insurance Assistance Programs ............. www.shiptacenter.org

MENTAL HEALTH SERVICES
American Psychosocial Oncology Society Helpline ....... www.apos.org, 888-276-7443

PEDIATRIC BRAIN CANCER
A Kid’s Brain Tumor Cure ........................................www.akidsbraintumor.org
Children’s Brain Tumor Foundation .........................www.cbtf.org
Children’s Neuroblastoma Cancer Foundation ..............www.cnccf.org
Jessie Rees Foundation ...........................................www.jessierees.org
Making Headway Foundation ......................................www.makingheadway.org
The Neuroblastoma Children’s Cancer Society ..............www.neuroblastomacancer.org
Pediatric Brain Tumor Foundation ............................www.cure4kids.org

PRESCRIPTION EXPENSES
CancerCare Co-Payment Assistance Foundation ............www.cancercare.org, 866-552-6729
Cancer Financial Assistance Coalition ...................... www.cancerfac.org
Foundation for Health Coverage Education ..................www.coverageforall.org
Good Days .................................................... 972-806-7141
HealthWell Foundation ..........................................www.healthwellfoundation.org
Mission4Maureen (brain cancer) ........... www.mission4maureen.org, 440-640-6497
NeedyMed ...................................................... 800-503-8997
Partnership for Prescription Assistance .......................www.ppparx.org
Patient Access Network Foundation ....................... www.paf.org, 866-316-7263
Patient Advocate Foundation Co-Pay Relief .......... www.patientadvocate.org, 888-512-3861
Patient Services, Inc. .............................................www.patientadvocate.org, 800-366-7263
Rise Above It (youth, young adults) ........................... www.ralsa.org
RxAssist ....................................................... www.rxassist.org
RxHope ..........................................................www.rxhope.com
Rx Outreach ......................................................www.rxoutreach.com, 888-796-1234
Stupid Cancer ....................................................www.stupidcancer.org, 877-735-4673
Together Rx Access ...........................................www.togetherrxaccess.org, 844-404-1106

REIMBURSEMENT & PATIENT ASSISTANCE PROGRAMS
AbbieVie Patient Assistance Foundation ...........www.abbievie.com, 800-222-8885
Amen Assist 360 ............................................ www.amenassist360.com, 888-642-7478
Amen First Step ................................................888-687-8371
ActiZaneca Access 360 ......................................... www.myaccess360.com, 844-275-2360
AstraZeneca Prescription Savings Program (AZ&ME) ...........www.astrazeneca.com, 800-292-8363
Avastin Access Solutions ...................................www.avastin.com, 888-422-2377
Eisa Reimbursement Resources ............................www.eisa.com
Genentech Access Solutions ....................................www.genentech.com, 888-422-2377
Genentech BioOncology Co-pay Card .......................www.copayassistancecancernow.com, 865-692-6729
Glaidel Wafer Arbor Assistance Program ............www.gladel.com/patient/reimbursement.php, 866-516-4950
Helsin Cars ..............................................................www.helsinreimbursement.com, 844-357-4688
Janssen CarePath .............................................www.janssencarepath.com, 877-227-3728
Janssen Prescription Assistance ...............................www.janssensprescriptionassistance.com
Merek Access Program ........................................www.merckaccessprogram.com, 855-257-3932
Merk Helps ......................................................www.merkhelps.com, 800-727-5400
Novartis Oncology Patient Support .................www.novartis Oncology.com, 800-268-7630
Novartis Patient Assistance NOW ......................www.patientoncology.com, 800-659-6562
Patient ReSolutions .............................................www.patientreSolutions.com, 888-676-5884
Pfizer Oncology Together ............................................www.pfizeroncology.com, 877-744-5675
Pfizer RePathways .............................................www.pfizerrePathways.com, 898-928-7284
Sanoz Patient Assistance ........................................www.sanoz.com/patient/patient-assistance, 800-676-5884
Sandoz One Source ................................................www.sandozsource.com, 844-726-3691
Temodar Patient Assistance Programs ..................www.merckhelps.com/temodor, 800-727-5400
Teva Cares Foundation Patient Assistance Programs ....www.tevapatientcare.com, 877-237-4881
Teva Oncology Care Reimbursement Assistance & Support ..................www.tevapatientcare.com, 888-827-3256
Together with Tesaro ..............................................www.togethertwotlesaro.com, 844-283-7276
Zano Sandoz One Source ...........................................www.zanos.com/patient/support, 844-726-3691
A Study for Management of Eye Side Effects in Patients with EGFR-Amplified Glioblastoma Receiving Depatuxizumab Mafodotin (ABT-414)

Glioblastoma (GBM) Research Study

Do you or someone you know have a glioblastoma?

This study evaluates the effect of several eye treatments for the management of eye side effects in patients treated with depatuxizumab mafodotin (Depatux-M). All participants will receive Depatux-M along with 1 of 3 eye treatments.

Patients must meet the following criteria:

• Be ages 18 or older
• Newly diagnosed GBM and have not already started treatment
• GBM tumor tested positive for EGFR amplification (about half of people with GBM tumors have EGFR amplification)
• Not pregnant or breastfeeding
• Other criteria must also be met

For more information, ask your doctor about the Ocular Side Effect Study or visit www.clinicaltrials.gov (NCT03419403) to see if you qualify.

Depatuxizumab Mafodotin is an investigational medicine that is not approved by the FDA. Safety and efficacy have not been established.
Pediatric High Grade Gliomas (HGG) Research Study

Do you or someone you know have a child with a high grade glioma that is EGFR Amplified?

The INTELLANCE2 sub-study is a research study evaluating the pharmacokinetics, safety and tolerability of a novel therapy for children with a high grade glioma that is EGFR amplified.

Patients must meet the following criteria:

- Less than 18 years of age
- Newly diagnosed or recurrent high grade glioma (grade III glioma, grade IV glioma or diffuse intrinsic pontine glioma (DIPG))
- Sufficiently recovered from previous therapy
- No current or recent treatment with another investigational drug
- Other criteria apply

For more information, ask your doctor about the INTELLANCE2 Pediatric Sub-Study or visit www.clinicaltrials.gov (NCT02343406) to see if you qualify.