Cover Page for **Stratum 1 - Informed Consent Form** for:

PBTC-058: Phase 2 Study of Intraventricular Omburtamab-based Radioimmunotherapy for Pediatric Patients with Recurrent Medulloblastoma and Ependymoma

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Research Study Informed Consent Document – Stratum 1

Study Title for Participants:
Testing the addition of a new anti-cancer drug, ^{131}I-Omburtamab, to usual chemotherapy in recurrent medulloblastoma

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
PBTC-058: Phase 2 Study of Intraventricular Omburtamab-based Radioimmunotherapy for Pediatric Patients with Recurrent Medulloblastoma and Ependymoma

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent, we mean you or your child; "we" means the doctors and other staff.

Overview and Key Information

You are being asked to take part in a research study because you have a brain tumor called medulloblastoma that has come back after other treatment. We are asking if you want to participate in this study because there is not a proven treatment for your brain tumor. This consent document gives you information about this study. Please read it carefully and take time to make the decision about whether to participate. You may discuss this decision with your family and friends.

Taking part in this study is voluntary. If you decide to take part in this study, you may change your mind and stop anytime. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled.

This research is studying an investigational drug called ^{131}I-omburtamab to see if it is safe and tolerated without severe side effects in children when added to standard chemotherapy (anti-cancer therapy) which includes irinotecan, temozolomide, and bevacizumab. The research is also studying whether the addition of ^{131}I-omburtamab improves survival compared to patients in the past who only received chemotherapy. ^{131}I-omburtamab works by binding to cancer cells in the body to kill them. Early studies have shown that ^{131}I-omburtamab might strengthen the anti-tumor effects of chemotherapy.

Because of your cancer diagnosis, you will be asked to enroll on Stratum 1 of this study. The treatment for Stratum 1 on this study will be given in three parts called (1) Induction Chemotherapy, (2) Radioimmunotherapy, and (3) Maintenance Chemotherapy, which are described in detail in this document. The treatment on this study may take up to 2 years. During your time on this study, you will need to see your study doctor every week for the first 3–6 months, then every other week thereafter for up to 1 year. During your study visits, you will have exams, tests and procedures to help your doctor closely monitor your safety and health.

All people who receive cancer treatment are at risk of having side effects. The common side effects for ^{131}I-omburtamab are infection, especially when white blood cell count is low, headache, vomiting, fever, and abnormal lab results. You can ask your study doctor questions about side effects at any time.

We hope this investigational drug will help you personally, but we do not know if it will. It is unlikely to cure your disease. However, this study will help doctors learn more about brain tumors and conditions like yours, and it is hoped that this information will help in the treatment of future patients with conditions like yours.

If you decide not to participate in this research, your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

The rest of this form provides detailed information about the study and what to expect if you decide to participate.

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to treat diseases like cancer

We are asking you to take part in this research study because you have medulloblastoma that has grown or come back after receiving chemotherapy (anti-cancer therapy) and radiation therapy.

Taking part in this study is your choice.

You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Can we lower the chance of your brain tumor growing or spreading by adding a new drug called ^{131}I-omburtamab to the usual combination of chemotherapy drugs?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your recurrent medulloblastoma. The usual approach is defined as care most people get for recurrent medulloblastoma.

What is the usual approach to recurrent medulloblastoma?

The usual approach for patients who are not in a study is treatment with surgery, radiation, or drugs. Sometimes, combinations of these treatments are used. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer. Radiation therapy involving the entire brain or spine (called craniospinal irradiation or CSI) can be curative in some patients. There are also cases when CSI therapy may not be preferred, such as in very young patients, those with certain genetic or medical conditions which may prevent them from receiving CSI therapy, or patients who have already received prior radiation therapy. Your doctor can explain which treatment may be best for you.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will receive treatment in three parts called (1) Induction Chemotherapy, (2) Radioimmunotherapy, and (3) Maintenance Chemotherapy. Treatment on this study is expected to last up to 2 years.

After you finish your study treatment, your doctor and study team will continue to follow your condition for 30 days and watch you for side effects for up to 5 years following your first dose of study treatment. They will see you in clinic during the follow-up every 3 months during Year 1, every 4 months during Year 2, and every 6 months during Years 3–5. This means you will keep seeing your doctor for 5 years after treatment.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study treatment may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the study treatment. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Infection, especially when white blood cell count is low
- Headache
- Nausea
- Vomiting
- Fever
- Abnormal lab results

There may be some risks that the study doctors do not yet know about.

Benefits

^{131}I-omburtamab has stabilized your type of cancer in a limited number of people with your cancer and in animals. It is unlikely that it will work in everyone with your cancer or help you live longer. This study may help the study doctors learn things that may help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It is important that you stop safely. This may mean slowly stopping the study drugs so that there is not a sudden unsafe change, risk to your health, etc. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- If you become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (the Pediatric Brain Tumor Consortium (PBTC)). The study sponsor (PBTC) is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to test the good and bad effects of the drug called ^{131}I-omburtamab. ^{131}I-omburtamab, when added to chemotherapy that includes irinotecan, temozolomide, and bevacizumab, could shrink your cancer, but it could also cause side effects which are described in the risks section below. The study doctors hope to learn if the study drug will help in stabilizing or stopping your cancer from growing.

There will be about 40 people taking part on Stratum 1 in this study.

What are the study groups?

In this study, you will get the usual chemotherapy of irinotecan, temozolomide, and bevacizumab. You will also get the study drug ^{131}I-omburtamab. Omburtamab is a type of drug called a monoclonal antibody. A monoclonal antibody is a type of protein made in a laboratory that can bind to things in the body, including cancer cells. The omburtamab is bound to a radioisotope called 131-Iodine (or ^{131}I) to make ^{131}I-omburtamab. A radioisotope is an unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. ^{131}I-omburtamab works by binding to cancer cells and releasing radiation as it breaks down, which can kill cancer cells. ^{131}I-omburtamab is considered investigational because it has not been approved by the FDA for the treatment of your disease.

The study treatment will be conducted in three parts called (1) Induction Chemotherapy, (2) Radioimmunotherapy, and (3) Maintenance Chemotherapy.

Induction Chemotherapy & Observation Period
The first part of the study treatment is called Induction Chemotherapy. During Induction Chemotherapy, you will receive the drugs irinotecan, temozolomide, and bevacizumab for 2 courses. A course/cycle is a length of time that you will receive study treatment. One course of

chemotherapy on this study is 28 days. Irinotecan will be given on Days 1–5 of each course through a vein in your arm over 90 minutes. Temozolomide will be given on Days 1–5 of each course by mouth. Bevacizumab will be given on Days 1 and 15 of Course 1, and on Day 1 only of Course 2 (or Course 4 if you receive 4 courses of chemotherapy) through a vein in your arm over 90 minutes or less.

After 2 courses of chemotherapy, your doctor will perform tests to see if your tumor is stable or growing. If your tumor is stable, you will proceed to the observation period. Most patients are expected to complete 2 courses of Induction Chemotherapy. If there is any delay before you can move on to the observation period, you may receive up to 2 additional courses of chemotherapy. These 2 additional courses will consist of the drugs irinotecan, temozolomide, and bevacizumab given on the same schedule as your first 2 courses. Before proceeding to the observation period, your doctor will again perform tests to see if your tumor is stable or growing. If your tumor is stable, you will proceed to the observation period.

The observation period is 4–6 weeks long. During the observation period, the study doctors will monitor your health to see if you are ready to move to the next part of the study treatment. You will also undergo a minor surgery to have an indwelling catheter device (sometimes called programmable VP shunt or Ommaya reservoir) placed in your head under your scalp if you do not already have one. An indwelling catheter device is a small, soft, plastic device that is connected to a tube. It will be used to deliver drugs directly into your brain and the fluid-filled space surrounding it (called intraventricular space or cerebrospinal fluid [CSF]).

Radioimmunotherapy
Radioimmunotherapy is 56 days. After the observation period and placement of the indwelling catheter device (if applicable), you will have an additional test done to check if the CSF in your body is flowing adequately. This test, called a CSF flow test, is to make sure that you can receive the drug ^{131}I-omburtamab.

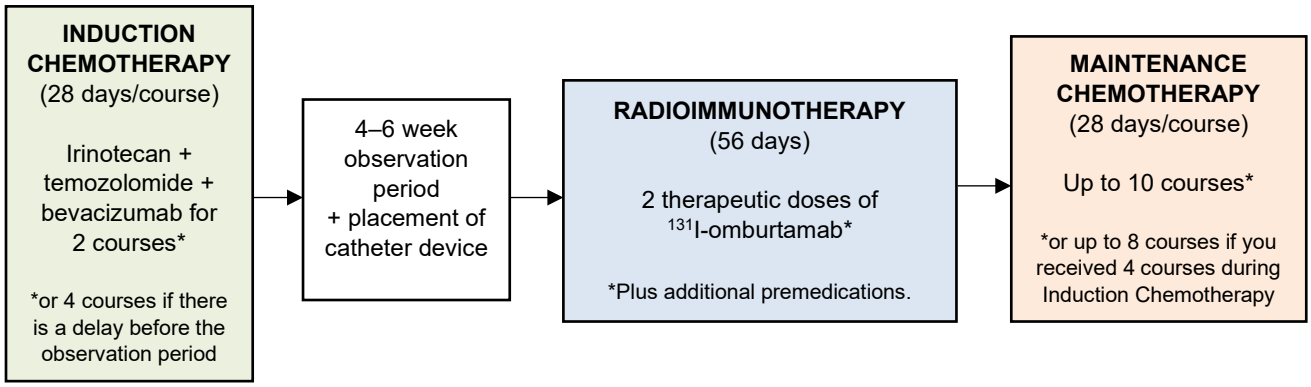
You may start Radioimmunotherapy with the premedications for the drug ^{131}I-omburtamab while you wait for the placement of your indwelling catheter device and the results from your CSF flow test, but you cannot receive the drug ^{131}I-omburtamab until the device is placed and your CSF flow results are known.

Before you receive the drug ^{131}I-omburtamab, you will be given a few extra premedications. You will receive two drugs called liothyronine and super saturated potassium iodide (SSKI) which are used to protect the thyroid against radiation. These will start on Day 1 of Radioimmunotherapy and will continue for at least 7 days pre- and 14 days post- each ^{131}I-omburtamab injection. Another premedication drug is called dexamethasone, which is used to prevent or reduce the side effects of swelling. Dexamethasone will be given in 6 doses starting within 24 hours of each ^{131}I-omburtamab injection. You will also be given 3 additional drugs to help with any potential side effects you might experience like nausea or dizziness, pain, fever, allergies, and an upset stomach. These will be given within 1 to 3 hours before your ^{131}I-omburtamab injections and then as needed after the injection.

You will receive two doses of the study drug ^{131}I-omburtamab on Days 8 and 36, at least 1 week after the start of your premedications liothyronine and SSKI through the indwelling catheter device in your head.

Maintenance Chemotherapy
After Radioimmunotherapy, you will go on to the last part of the study treatment called Maintenance Chemotherapy. During Maintenance Chemotherapy, you will receive the drugs irinotecan, temozolomide, and bevacizumab. One course of chemotherapy is 28 days. You will repeat these 28-day courses for up to 10 courses (or up to 8 courses if you received 4 courses of Induction Chemotherapy) unless your disease gets worse or the side effects become too severe. Irinotecan will be given on Days 1–5 of each course through a vein in your arm over 90 minutes. Temozolomide will be given on Days 1–5 of each course by mouth. Bevacizumab will be given on Days 1 and 15 of each course through a vein in your arm over 90 minutes or less.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are extra exams, tests, and procedures that need to be done as part of this study to monitor your safety and health but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- You will need to have an indwelling catheter device (sometimes called a programmable VP shunt or Ommaya reservoir) placed in your head under your scalp by a neurosurgeon if you do not already have one. This device is quarter-sized, soft, and plastic. It is connected to a small tube that can deliver drug directly into your brain and the fluid-filled space around it (called intraventricular space or cerebrospinal fluid [CSF]). The study drug will be given to you through this tube, which will remain in place as long as it's needed.

- A test will be done to confirm that your CSF (the fluid around your brain and spinal cord) is flowing adequately and can move the study drug to your brain and spinal canal. For this test, a special dye (called an isotope) is injected into the indwelling catheter device that was placed in your head. Pictures are taken after the injection and the day following to make sure the dye has cleared from the device and that your CSF is flowing adequately.
- Thyroid testing done before each cycle of Radioimmunotherapy.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 6 months after you have completed the study.

Side Effect Risks

The study treatment used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study treatment.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away quickly, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus the study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of ^{131}I-Omburtamab

COMMON, SOME MAY BE SERIOUS In 100 people receiving ^{131}I-omburtamab, more than 20 and up to 100 may have:
• Headache • Vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ^{131}I-omburtamab, from 4 to 20 may have:
• Swelling of the brain • Development of other cancers (acute myeloid leukemia, myelodysplastic syndrome) • Infection, especially when white blood cell count is low • Anemia, which may cause tiredness or may require a blood transfusion • Low platelet count, which may cause bruising, bleeding, or may require a blood transfusion

RARE, AND SERIOUS In 100 people receiving ^{131}I-omburtamab, from 3 or fewer may have:
• None known

Possible Side Effects of Dexamethasone (Table Version Date: September 22, 2017)

Because you will receive a low dose of dexamethasone for only a short time, we do not think that you will experience any side effects. However, risks and side effects related to dexamethasone include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, more than 20 and up to 100 may have:
• High blood pressure which may cause headaches, dizziness • Pain in belly • Infection • Diabetes • Loss of bone tissue

COMMON, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, more than 20 and up to 100 may have:
• Damage to the bone which may cause joint pain or loss of motion • Mood swings • In children and adolescents: decreased height • Swelling of the body, tiredness, bruising • Increased appetite and weight gain in belly, face, back and shoulders • Difficulty sleeping • Skin changes, rash, acne

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, from 4 to 20 may have:
• Blood clot which may cause swelling, pain, shortness of breath • Kidney stones • Glaucoma • Cloudiness of the eye, visual disturbances, blurred vision • A tear or a hole in the bowels which may cause pain or that may require surgery • Heartburn • Numbness and tingling of the arms, legs and upper body • Muscle weakness • Non-healing wound

RARE, AND SERIOUS In 100 people receiving dexamethasone, 3 or fewer may have:
• Bleeding from sores in stomach • Broken bones

Possible Side Effects of Liothyronine

COMMON, SOME MAY BE SERIOUS In 100 people receiving liothyronine, more than 20 and up to 100 may have:
• None known

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving liothyronine, from 4 to 20 or fewer may have:
• None known

RARE, AND SERIOUS In 100 people receiving liothyronine, 3 or fewer may have:
• Fast heart rate • Abnormal heartbeat • Chest pain

RARE, AND SERIOUS In 100 people receiving liothyronine, 3 or fewer may have:
• Increased blood pressure, which may cause headaches, dizziness, or blurred vision

Possible Side Effects of Super Saturated Potassium Iodide (SSKI)

COMMON, SOME MAY BE SERIOUS In 100 people receiving potassium iodide, more than 20 and up to 100 may have:
• None known

OCCASSIONAL, SOME MAY BE SERIOUS In 100 people receiving potassium iodide, from 4 to 20 may have:
• Nausea, vomiting • Diarrhea • Stomach pain • Abnormal heart rate • Confusion • Tiredness • Fever • Burning of the mouth or throat • Metallic taste • Rashes, hives or other allergic reactions • Flare up of acne • Hyper or Hypothyroid where the thyroid produces too little or too much thyroid hormone

RARE, AND SERIOUS In 100 people receiving potassium iodide, from 3 or fewer may have:
• An allergic reaction in the blood vessels of the skin which turn the skin red, inflamed and bumpy and which may lead to skin breakdown • Severe rashes • A condition called “Iodism” which occurs when large doses are given over a very long time and can lead to skin rashes and blisters, burning in the mouth, runny nose, eye irritation, puffy eyelids, headache, fluid accumulation in the lungs which could lead to shortness of breath, upset stomach, swelling and pain in the tonsils, throat, and the glands in the throat • A non-cancerous thyroid tumor

Possible Side Effects of Famotidine

COMMON, SOME MAY BE SERIOUS In 100 people receiving famotidine, more than 20 and up to 100 may have:
• Agitation

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving famotidine, from 4 to 20 may have:
• Headache

RARE, AND SERIOUS In 100 people receiving famotidine, 3 or fewer may have:
• Diarrhea • Constipation

Possible Side Effects of Diphenhydramine

COMMON, SOME MAY BE SERIOUS In 100 people receiving diphenhydramine, more than 20 and up to 100 may have:
• Dry mouth, nose, or throat • Dizziness • Tiredness • Irritable

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving diphenhydramine, from 4 to 20 may have:
• Restlessness • Nervousness • Increased heart rate • Lower blood pressure • Constipation • Headache • Blurry vision • Difficulty urinating • Confusion • Shaking

RARE, AND SERIOUS In 100 people receiving diphenhydramine, 3 or fewer may have:
• Skin rash • Seizures • QT prolongation • Lower platelets • Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Possible Side Effects of Acetaminophen

COMMON, SOME MAY BE SERIOUS In 100 people receiving acetaminophen, more than 20 and up to 100 may have:
• None
OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving acetaminophen, from 4 to 20 may have:
• Itching • Constipation • Nausea and vomiting • Agitation

RARE, AND SERIOUS In 100 people receiving acetaminophen, 3 or fewer may have:
• Increased blood level of liver tests which may mean there has been damage to the liver • Liver damage which may cause yellowing of eyes and skin, swelling • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Possible Side Effects of Irinotecan, Temozolomide (Table Version Date: March 11, 2020)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Irinotecan, Temozolomide, more than 20 and up to 100 may have:
• Headache, seizure • Cough, shortness of breath • Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Severe diarrhea • Constipation, nausea, vomiting • Sores in mouth • Loss of appetite, weight loss • Trouble with memory • Difficulty sleeping • Muscle weakness, paralysis, difficulty walking • Fever, pain • Dizziness, • Tiredness • Rash • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Irinotecan, Temozolomide, from 4 to 20 may have:
• Scarring of the lungs • Blood clot which may cause swelling, pain, shortness of breath • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Severe skin rash with blisters and can involve inside of mouth and other parts of the body

RARE, AND SERIOUS In 100 people receiving Irinotecan, Temozolomide, 3 or fewer may have:
• Cough, damage to the lungs which may cause shortness of breath • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require blood transfusions • Liver damage which may cause yellowing of eyes and skin, swelling • A new cancer including leukemia resulting from treatment of a prior cancer

Possible Side Effects of Bevacizumab

COMMON, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, more than 20 and up to 100 may have:
• High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, from 4 to 20 may have:
• Anemia which may require blood transfusion • Low white cell count that may increase the risk of infection • Infection, including collection of pus in the belly or rectum • Abnormal heartbeat which may cause palpitations or fainting • Pain in the belly, rectum, chest, joints, muscles, or tumor • Low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration • Bleeding from multiple sites including the vagina or nose • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine • Blockage of internal organs which may cause vomiting or inability to pass stool • Sores in the mouth • Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Delay in healing of wounds or spontaneous opening of wounds • Weight loss, tiredness, or dizziness • Muscle weakness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab, from 4 to 20 may have:
• Damage to the jawbone which may cause loss of teeth • Headache • Numbness, tingling or pain in the fingers or toes • Hoarseness, stuffy nose, or cough • Dry skin • Swelling and redness of the skin • Blood clot in limbs or lungs which may cause swelling, pain, shortness of breath • Leakage of protein in the urine, which can rarely lead to damage to the kidney

RARE, AND SERIOUS In 100 people receiving bevacizumab, 3 or fewer may have:
• Clots in the arteries, causing stroke (which may cause paralysis or weakness) or heart attack (which may cause chest pain or shortness of breath). This risk is significantly increased in patients who are elderly or with history of diabetes • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Bowel perforation (a tear in the bowel) that can cause pain or bleeding and require surgery to repair • A tear or hole (fistula) in internal organs such as the nose, throat, lungs, esophagus, rectum, or vagina. These conditions may cause serious infections or bleeding and require surgery to repair • Sores in the throat • Flesh-eating bacteria syndrome, an infection in the deep layers of skin • Damage to organs (bone, lungs, others) which may cause loss of motion • Bleeding in the tumor, brain, belly or lungs which may cause confusion, blood in stool or coughing up blood • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Kidney damage which may require dialysis • Redness, pain or peeling of palms and soles

Additional Notes on Possible Side Effects for Bevacizumab:

- Risk in children or adolescents: abnormal bone changes which may interfere with growth.
- Risk in pre-menopausal women: more likely to develop menopause when taking bevacizumab.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time,

Additional Drug Risks

Some drugs or supplements may interact with your treatment plan. Talk to your doctor, pharmacist, or study team before starting any new prescription drugs, over-the-counter drugs, herbals, or

supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

Rarely, there are problems with getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Additional Risks for Study-Related Procedures
The following study-related procedure risks, though rare, may also occur:

- Spinal taps: Risks include swelling of the spinal cord, discomfort from the needle stick, small risk of infection, scarring, bleeding, or headache.
- Intraventricular access device placement: Risk for bleeding or infection
- CSF flow study: Risk for bleeding or infection

What are my responsibilities in this study?

If you choose to take part in this study, you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.
- Write down in your medication diary when you take/use temozolomide at home.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 6 months after your last dose of study drug.

For post-^{131}I-omburtamab care at home:
This study will include a type of treatment called radioimmunotherapy. The radiation that is given off by the drug may help kill the cancer cells but may also be harmful to others around you. Because of this, you must take special precautions for up to a week after treatment like:

- Keeping your distance from others
- Limiting your contact with people
- Avoiding public spaces
- Avoiding using public transportation
- Practicing good hygiene

Your doctor will give you additional handouts about post-treatment care that you will need to practice while at home. Please review these carefully and ask your doctor or the study staff if you have any questions.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for other costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety and prevent and treat side effects.
- the costs of getting ^{131}I-omburtamab ready and giving it to you.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- Optional studies, including: Exosomes study and cfDNA study

You or your insurance provider will not have to pay for the ^{131}I-omburtamab while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work and school.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study treatment now or in the future. This would include any organization helping the sponsor with the study, including Y-mAbs Therapeutics, Inc. and SpectronRx.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The PBTC who oversees this study and Memorial Sloan Kettering Cancer Center (MSKCC) who provides regulatory support for this study.
- Similar regulatory agencies in other countries who review research.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor *insert name of study doctor* at *insert telephone number, and email address if appropriate*.

For questions about your rights while in this study, call the *insert name of organization or center* Institutional Review Board at *insert telephone number*.

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with your condition in the future. The results will not be added to your medical records and you or your study doctor will/will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for but cannot complete any of these studies for any reason, you can still take part in the main study.

Optional sample collections for known laboratory studies and/or storage for possible future studies.

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Known future studies

a. **cfDNA Study (optional, for research purpose only):**

If you choose to take part in this optional study, researchers will collect blood and cerebrospinal fluid (CSF) to perform research on the nature of medulloblastoma and how it might respond to future therapies. Recent advances in technology have allowed for the detection of cell-free DNA (cfDNA). cfDNA is small fragments of tumor DNA that can shed into body fluids, like blood in CSF, in patients with brain tumors. The detection of cfDNA in blood and CSF is known as a "liquid biopsy" and is non-invasive. Multiple studies in other cancer types have shown that cfDNA can be used for diagnosis, to monitor disease response, and to track the evolution of disease. The genetic test used in this study will study the cfDNA that your tumor sheds to look for any relationship between cfDNA and response to treatment with ^{131}I-omburtamab. It will also help the researchers to understand the genetic changes that occur in medulloblastomas over time.

Samples of your blood and CSF will be taken at 3 different timepoints. This test will require 12–23 mL of blood per timepoint (about 36–69 mL or 1–4.5 tablespoons of blood total) and 2–3 mL of CSF per timepoint (about 6–9 mL or 2 teaspoons of CSF total). Blood will be collected from your central line or arm. CSF will be collected through your indwelling catheter device or through a needle inserted into the lower part of your spine (known as a spinal tap or lumbar puncture). Sample collection will occur at the following timepoints during Radioimmunotherapy: Before the 1st ^{131}I-omburtamab injection, 4 weeks after the 1st ^{131}I-omburtamab injection, and 4 weeks after the 2nd ^{131}I-omburtamab injection.

b. **Exosomes Study (optional, for research purpose only):**

If you choose to take part in this optional study, researchers will collect blood and cerebrospinal fluid (CSF) to perform research on ways to detect medulloblastoma in its early stages. Exosomes are tiny sac-like structures that are formed inside a cell and contain some of the cell's proteins, DNA, and RNA. Exosomes get released into the body by many types of cells, including cancer cells. They can travel through the blood to other parts of the body. While traveling through the body, exosomes can transfer some of the proteins, DNA, and RNA they contain into other cells. Research has shown that exosomes may play a role in the spread of cancer and may keep immune cells from killing cancer cells. They are being studied in the laboratory to develop new ways of diagnosing and treating cancer.

This test will require 2–3 mL of blood per timepoint (about 6–9 mL or 2 teaspoons total) and 2–3 mL of CSF per timepoint (about 6–9 mL or 2 teaspoons of CSF total). Blood will be collected from your central line or arm. CSF will be collected through your indwelling catheter device or through a needle inserted into the lower part of your spine (known as a lumbar puncture). Sample collection will occur at the following timepoints during Radioimmunotherapy: Before the 1st ^{131}I-omburtamab injection, 4 weeks after the 1st ^{131}I-omburtamab injection, and 4 weeks after the 2nd ^{131}I-omburtamab injection.

Unknown future studies

c. **Pathology Central Review and Biorepository (optional):**

If you choose to take part in this optional study, a blood sample (5 mL, approximately 1 teaspoon) and some of your stored tumor tissue which was removed during a previous surgery will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Pediatric Brain Tumor Consortium and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who the researchers are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your blood and/or tissue. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes. If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. About 1 teaspoon of blood (5 mL) will be collected from a vein in your arm before you start the study. A sample from the tissue that was collected at the time of your previous surgery will be sent to the biobank.
2. Your sample will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, Dr. Matthias Karajannis, at 212-639-6410, who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, Dr. Matthias Karajannis, at 212-639-6410.

Please circle your answer below to show if you would or would not like to take part in each optional study:

a. cfDNA Study (optional, for research purpose only)

I agree that my samples and related information may be used for the laboratory study described above.

YES NO

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b. Exosomes Study (optional, for research purpose only)

I agree that my samples and related information may be used for the laboratory study described above.

YES NO

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c. Pathology Central Review and Biorepository (optional, samples for unknown future studies):

I agree that my samples and related health information may be kept in a biobank for use in future health research.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form, or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

_____
Participant's signature

_____
Date of signature

_____
Parent or Legal Guardian Signature

_____
Date of Signature

_____
2nd Parent or Legal Guardian (if required)
If permission by both parents is required, both signatures should be completed unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for the care and custody of the child.

_____
Date of Signature

_____
Signature of person(s) conducting the informed consent discussion

_____
Date of signature

Appendix A: Study Calendar for Stratum 1

Lab/Assessment	Frequency
Medical history and Physical exam which includes height, weight, vital signs and how you are doing.	Prior to Induction Chemotherapy, Days 1 & 15 during each course of Induction Chemotherapy, weekly during Radioimmunotherapy, Days 1 & 15 of Maintenance Chemotherapy (for 8–10 courses depending on the number of Induction courses received), and at the end or discontinuation of treatment. Before you start treatment, you will be asked whether or not you currently smoke or have smoked in the past.
Performance status and Neurological exam	Prior to each course of Induction Chemotherapy, during Radioimmunotherapy, Days 1 & 15 of Maintenance Chemotherapy (for 8–10 courses depending on the number of Induction courses received), and at the end or discontinuation of treatment.
Blood & CSF Tests	**Frequency**
CBC	Prior to Induction Chemotherapy, weekly during Induction Chemotherapy and Radioimmunotherapy, prior to each course of Maintenance Chemotherapy (8–10 courses depending on the number of Induction courses received), and at the end or discontinuation of treatment. Your doctor may require additional blood tests if you are having side effects.
Blood chemistry	Prior to each course of Induction Chemotherapy, weekly during Radioimmunotherapy, prior to each course of Maintenance Chemotherapy (8–10 courses depending on the number of induction course received), then at the end or discontinuation of treatment. Your doctor may require additional blood tests if you are having side effects.
Blood tests for thyroid function	Prior to Induction Chemotherapy, then prior to each injection in Radioimmunotherapy.
Blood test to test how your blood clots	Prior to Induction Chemotherapy.
Pregnancy testing (urine or blood)	Prior to each course of Induction Chemotherapy, prior to each injection in Radioimmunotherapy, and prior to each course of Maintenance Chemotherapy.
CSF cytology if your doctor thinks it is needed to collect cerebrospinal fluid (CSF) to determine disease status	Prior to Induction Chemotherapy Course 1, prior to injection in Radioimmunotherapy, then prior to every other course of Maintenance Chemotherapy at the time of MRI (if positive prior to the start of chemotherapy).
CSF Flow Study to makes sure your spinal fluid moves appropriately through your brain and spinal column	Prior to the first injection in Radioimmunotherapy.
Imaging	**Frequency**
Brain MRI with diffusion	Prior to Induction Chemotherapy, then after Course 2 and 4 (if applicable) of Induction Chemotherapy, during Radioimmunotherapy and Maintenance Chemotherapy, then at the end or discontinuation of treatment.
Spine MRI, if your doctor thinks you need it	Prior to Induction Chemotherapy, then after Course 2 and 4 (if applicable) of Induction Chemotherapy, during Radioimmunotherapy

	and Maintenance Chemotherapy, then at the end or discontinuation of treatment.
Optional Research Laboratory Studies for patients in Stratum 1	**Frequency**
Blood samples for biology studies	Before the 1st ^{131}I-omburtamab injection, 4 weeks after the 1st ^{131}I-omburtamab injection, and 4 weeks after the 2nd ^{131}I-omburtamab injection in Radioimmunotherapy.
CSF samples for biology studies	Before the 1st ^{131}I-omburtamab injection, 4 weeks after the 1st ^{131}I-omburtamab injection, and 4 weeks after the 2nd ^{131}I-omburtamab injection in Radioimmunotherapy.