SUMMARY OF CHANGES – INFORMED CONSENT DOCUMENT

For Protocol Amendment v10 to:

NCI Protocol #: PBTC-049
Local Protocol #: PBTC-049

NCI Version Date: November 14, 2024
Version Date: November 14, 2024

I. COMPANY COMMENTS REQUIRING A RESPONSE – DATED 11/02/2023

#	Section	Change
1.	Unknown Future Studies	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 (5 mL) of blood will be collected from a vein in your arm. A sample from the tissue that was collected at the time of your previous surgery will be sent to the biobank. Suggest to add the following text to the above section **HLA Subtypes** If you agree to take part in this optional sample collection, blood samples may be collected for germline DNA assessment at Cycle 1, Day 1, for exploration of the role of HLA alleles on clinical efficacy and in development of drug-related toxicity (such as but not limited to hypersensitivity) **PI Response:** **We do not think this level of detail regarding HLA subtypes is needed in the informed consent form. The language is deliberately vague as it pertains to unknown future research. We find that the mention of genomic sequencing including somatic and germline sequencing in consenting patients already encompasses HLA subtypes that were specifically requested to be added.**

II. INVESTIGATOR INITIATED CHANGES:

#	Section	Change
1.	General	• Updated version date of document • Minor administrative updates including corrections of typos and formatting changes have been updated throughout.
2.	What extra exams, tests, and procedures are involved in this study?	• Removed reference to study calendar as genomic analysis samples are only collected once after enrollment. • Clarified that 1 teaspoon (5 mL) of blood will also need to be collected. This is in alignment with Section 9.1.5.1 of the protocol.
3.	Appendix A: Study Calendar	Updated study calendar to match updated protocol with exception of references to the protocol. Patients will not have access to the protocol. Therefore, references to the protocol in the study calendar have been removed.

Research Study Informed Consent Document

Study Title for Participants: Testing Savolitinib in Patients with Recurrent, Progressive, or Refractory Medulloblastoma, High-Grade Glioma, Diffuse Intrinsic Pontine Glioma, and CNS Tumors Harboring MET Aberrations

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
PBTC-049: A Phase I Study of Savolitinib in Recurrent, Progressive or Refractory Medulloblastoma, High-Grade Glioma, Diffuse Intrinsic Pontine Glioma, and CNS Tumors Harboring MET Aberrations

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 of an experimental drug for brain tumors that have come back after other treatment. Research studies only include people who choose to take part. We are asking if you want to participate in this study because there is not a proven treatment for your brain tumor. This consent form gives you information about this study. Please read the consent form carefully and take time to make the decision about whether to participate. You may discuss this decision with your family and friends. If there are any questions, ask your study doctor *Physician's name* at *Physician's telephone number* or health care team for more explanation. No study procedure will be done until after you sign this form. You will be given a copy of it to keep if you decide to participate in this study.

This research is studying a drug called savolitinib. This trial is being conducted to see if savolitinib is safe and tolerated without severe side effects in children. Savolitinib is considered research because it has not been proven to work in a brain tumor like yours. There is evidence to believe it may work against brain tumors. However, we have not yet found the safe dose for children or proven that the drug works for brain tumors.

If you decide to participate in this study, you could continue for as long as 3 years. During that time, you would need to see your study doctor every week for the first course (28 days) and then at least every 4 weeks. During your study visits, you will have exams, tests and procedures to help your doctor closely monitor your safety and health. If you experience bad effects, you might have to return more frequently or even be in the hospital. The most common risks for this study are nausea, vomiting and feeling tired. Some patients on other studies using savolitinib in adults have experienced rashes, some swelling of their arms or legs and fever.

We do not know if there will be direct benefit to you from participating in this study. It is unlikely savolitinib will cure your disease. However, this study will help doctors learn more about brain

tumors, 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

This study is being done by the [redacted].

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 a brain cancer that has grown or come back. Patients with medulloblastoma must have failed prior radiation therapy and chemotherapy. Patients with high grade glioma (HGG), diffuse intrinsic pontine glioma (DIPG), and other brain tumor types with a specific genetic marker must have failed prior 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:

Is savolitinib safe in children? We determine safety by testing different doses of the drug in small groups to find out what effects, if any, it has on children in that group.

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 or progressive brain tumor. The usual approach is defined as care people get for a recurrent or progressive brain tumor.

What is the usual approach to my brain cancer that has grown or recurred?

The usual approach for patients who are not in a study is treatment with surgery, chemotherapy, radiation, or other investigational agents which may or may not be Food and Drug Administration (FDA) approved. Sometimes, combinations of these treatments are used. Your doctor can explain which treatment may be best for you. There are no treatments that are proven to help patients with your health condition live longer.

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 get the study drug savolitinib for up to 39 courses (approximately 3 years). If your doctor determines that there is evidence the drug may be helping you, you may remain on treatment until all other participants on this study are done with treatment. At that time, you will be notified that the study will be closed for treatment after your next scheduled MRI.

After you finish with savolitinib treatment, your doctor and study team will follow your condition and watch you for side effects for 30 days after your last dose of savolitinib. If side effects are continuing at the end of day 30, the study doctor may still follow you until they are resolved. The follow up period may continue for 2 years from your last dose of savolitinib, until you start another cancer therapy, or until your tumor grows.

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 approach may not be as good as the usual approach for your brain cancer.

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

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

- Nausea, vomiting, diarrhea
- Tiredness
- Swelling of your arms and/or legs
- Liver damage which may cause yellowing of the eyes and skin
- Loss of appetite
- Rash

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

Benefits
There is some evidence in animals, and in people with another cancer that this treatment can shrink or stabilize cancer, but we do not know if this will happen in children. It is unlikely that savolitinib will 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's important that you stop safely. 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 Institutional Review Board (IRB), Food and Drug Administration (FDA), Pediatric Brain Tumor Consortium (PBTC), or the study sponsor (National Cancer Institute). The study sponsor 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 safety of a drug called savolitinib. This drug has been tested in animals and adults, but it has not been tested in children. This study tests different doses of the drug to see which dose is safer for children.

There will be about 36 people taking part in this study. Patients who take part in this study must be greater than 5 years but less than or equal to 21 years of age.

Another purpose of this study is for study doctors to learn if there is a relationship between response to treatment and a specific genetic change, which can abnormally stimulate cells to grow and cause cancer. Patients in this portion of the study will require testing of tumor tissue from a previous surgery.

What are the study groups?

There are three parts in this study: A dose escalation/de-escalation group, a pharmacokinetics (PK) expansion group, and an efficacy expansion group. Your doctor will tell you which group you are in.

- Dose Escalation Group

Different people taking part in this study will get different doses of the study drug savolitinib. Savolitinib is a tablet you take by mouth once a day for a course. Each course lasts 28 days. This study has 39 courses.

The first 2–12 people taking part in this study will get the dose that we think is suitable for the pediatric population. If people have serious side effects, the dose will be lowered. The study doctor will watch each group carefully. Once the highest dose with manageable side effects is found, the dose escalation will be stopped and the PK expansion group will be open.

With the release of study version 3.0, patients who have completed the first course of treatment, do not have any side effect that is too serious, and are currently receiving study drug at the lowest dose level may have their dose increased back to the starting dose for this study.

With the release of study version 7.0 (version date October 6, 2022), enrollment to this group is closed.

- Pharmacokinetics (PK) Expansion Group

The PK testing measures the amount of study drug in the blood at different time points. The PK expansion part of this study will have 2 different sub-groups based on the age of the study participants (i.e., patients below 12 years old and equal or above 12 years old). In this part, the highest dose found safe in the first group will be given to at least 6 patients in each sub-group. This will help study doctors better understand the side effects that may happen with this drug based on age. Savolitinib will continue on the same schedule given during the dose escalation part of the study. If your doctor determines that there is evidence the drug may be helping you, you may

remain on treatment until all other participants on this study are done with treatment. At that time, you will be notified that the study will be closed for treatment after your next scheduled MRI.

- Efficacy Expansion Group

The next part of the study will look for a suggestion that certain tumor types might respond better to treatment with savolitinib. These patients must be tested to confirm they have tumors that show a specific marker before they can be enrolled. A total of 8 patients whose tumors have a specific marker will be enrolled in the efficacy expansion group.

You will not be able to get additional doses of the drug when the study ends. This drug is not approved by the FDA for treatment of your disease.

What extra 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 exams, tests, and procedures that need to be done as part of this study to monitor your safety and health but these 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 medical history, exams, tests, and procedures to monitor your safety and health include:

- You will be asked about your smoking status.
- An Electrocardiogram (EKG) will be done prior to starting treatment, 1–3 hours after the first dose of each week in Course 1, prior to Course 2 until Course 39, then every 3 courses (prior to course) for Courses 40+ until the end of treatment, and at the end of treatment.
- Right knee X-ray will be done prior to starting treatment then every 12 weeks during the remainder of treatment and at the end of treatment.
- MRI of both knees if unusual changes are seen on routine knee X-rays
- Blood counts to monitor your liver which are done weekly in Courses 1, 2, and 3
- If you are included in the efficacy expansion study group, you must have a recurrent, progressive or refractory primary CNS tumor that has been shown to have a specific genetic marker called c-MET.

Some exams, tests, and procedures are a necessary part of the research study but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

- **Pharmacokinetics (PK) blood specimen collection**

All patients (including the efficacy expansion study group) are required to take part in this study because determining how the body handles this drug is an important part of the study. The researchers would like to learn how much savolitinib stays in the blood at specific time points. You can either choose to have multiple sticks, or have a temporary line placed in your arm to get these PK blood samples.

Less than ½ teaspoon (about 2 mL) of blood will be collected before you start savolitinib, then 30 minutes, 1, 2, 4, 8 and 24 hours after your first dose of savolitinib on Day 1 of Course 1. Then, the same amount of blood will also be collected on Day 8 of Course 1 before you take savolitinib and 30 minutes, 1, 2, 4, 8 and 24 hours after you take savolitinib. Less than 2 tablespoons (about 28 mL) of blood will be collected during the study. Neither you nor your study doctor will get the results of this testing.

- **Test c-MET abnormality using existing tumor tissues**

Your study doctor will need to use some of the tissue left over from a previous surgery or biopsy. This sample is a required part of the study. Your study doctor would like to find out whether a marker called c-MET is present in your tumor cells and if present, is it related to your response to treatment. Neither you nor your study doctor will get the results of these tests.

- **Genomic analysis**

Your study doctor will need to use some of the tissue leftover from a previous surgery or biopsy. You will also need to provide about 1 teaspoon (5 mL) of blood. Your tissue and blood samples contain genes, which are made up of DNA and which serve as the "instruction book" for the cells that make up our bodies. Studying genes may help us understand how different patients respond to treatment with savolitinib. You and your study doctor will not get the results of this testing

During each part of the study, patients will keep a medication diary. This helps you keep track of when you take your pills. The study doctor will show you how to use this diary. Each time you visit the clinic, you must bring the medication diary, any remaining tablets, and the medication bottle(s).

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 savolitinib (AZD6094) 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.

Pregnancy risks (risks to an unborn child)

Savolitinib 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 after you have completed the study.

Genetic Testing Risks

- **Test c-MET abnormality using existing tumor tissues**

Genetic testing that is used for research purposes in this study will test your tumor tissue for the markers called c-MET. Since this study is only testing tumor tissue, we will not know if a genetic change in your tumor is also in your normal tissue. You and your study doctor will not get the results of this testing.

- **Genomic Analysis**

The genetic test used in this study will test your tumor and normal tissue for a relationship between response to savolitinib treatment and the presence of specific genomic changes or disease subgroups. You and your study doctor will not get the results of this testing.

It is possible that information from analyses of your samples and your medical information will be shared with other investigators or put into an access controlled online database. One example of such a database is the maintained by the National Institutes of Health. Only researchers who have received approval from a National Institutes of Health Data Access Committee will be allowed to access the NIH database. We expect that other databases will have the same kinds of procedures.

These databases will not contain any identifying information about you, such as your name, address, telephone number, or social security number. Your personal identifying information will not be shared with other investigators. Your privacy is very important to us and we use many safety procedures to protect your privacy. However, we cannot guarantee that no one will ever be able to use your genetic information to identify you.

Side Effect Risks

The savolitinib (AZD6094) 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 will 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 drug.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- 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.

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 for Savolitinib (CAEPR Version 2.5, July 25, 2020)

COMMON, SOME MAY BE SERIOUS In 100 people receiving savolitinib (AZD6094), more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Swelling of the body • Tiredness, fever • Liver damage which may cause yellowing of the eyes and skin

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving savolitinib (AZD6094), from 4 to 20 may have:
• Anemia which may require blood transfusion • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Bruising, bleeding • Infection, especially when white blood cell count is low • Loss of appetite • Cough

RARE, AND SERIOUS In 100 people receiving savolitinib (AZD6094), 3 or fewer may have:
• Change in the heart rhythm • Pain • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Low blood pressure which may cause feeling faint

Additional Drug Risks

Changes in electrical activities in the heart (detected by electrocardiogram)
The study drug may cause changes in the electrical activity of the heart called QTc prolongation on your EKG. Most of the time, these changes do not cause symptoms. However, in some patients, such changes may cause rapid or irregular heart beating, dizziness, light-headedness, chest discomfort, shortness of breath, losing consciousness and sudden death. These or other symptoms should be reported immediately to your doctor. Your study doctor will monitor your EKGs frequently.

Drug-Drug Interactions

Drugs that interact with certain specific enzymes in the liver known as CYP3A4 and CYP1A2 may also cause interaction when used with savolitinib. Your study doctor will review all medications that you are taking and tell you which ones to avoid. Your study doctor will also give you a drug information handout and wallet card that lists these possible drug interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.

The use of herbal preparations including cannabis products is not allowed during the study.

Testicular and Bone Growth Risks
A change in the bone was observed in a rat study. The significance of this for humans is not known. Effects on testes have been observed in animal studies. It is not known if these effects are reversible.

UV Exposures
During savolitinib therapy and for 4 weeks after the last dose your skin is very sensitive to the sun. You should avoid prolonged exposure to the sun, wear protective clothing and a hat, and seek shade from the sun. You should also use a sunscreen with SPF30+. Exposure to sunbeds and tanning booths should be avoided.

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

Risks of blood draw
The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.

MRI and Knee X-ray Risks
Risks of an MRI may include feeling closed in, discomfort due to lying still for a prolonged period of time, and other factors which will be described to you and discussed with you in the MRI Imaging clinic. The amount of radiation from an X-ray is minimal but does carry very small risk of causing cancer many years or decades later.

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 the study drug 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 savolitinib.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your brain 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 savolitinib 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 need to pay for exams, tests, and procedures done for toxicity monitoring during treatment, which include:

- The liver function tests done every week during Courses 1, 2, and 3
- The EKGs done 1–3 hours after the first dose of each week for Course 1, prior to Course 2 through Course 39, then every 3 courses (prior to course) for Courses 40+, and at the end of your treatment on the study.
    - Since EKGs are done 3 times at each time point, only 1 EKG of the 3 will be billed to your insurance.
- The extra right knee X-ray done every 3 months throughout the study.
- Knee MRI for both knees if abnormalities are detected on routine knee X-rays prior to and throughout treatment

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:

- The 3 EKGs done prior to treatment and the 2nd and 3rd EKGs done at each required time point
- The right knee X-ray done prior to treatment
- Sample collection and preparation for pharmacokinetics, biology studies and storage of samples for future research.

You or your insurance provider will not have to pay for the savolitinib 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.
- 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 agent now or in the future. This would include any organization helping the company with the study.
- 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.
- Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. governmental regulatory agencies involved in overseeing research.
- The PBTC who oversees this study and research partners, such as the PBTC Central Review and Biorepository (CRB) and Neuroimaging Center (NIC), and additional researchers who may need access to information to conduct approved research.
- St. Jude Children’s Research Hospital who provides support for this study.
- Similar regulatory agencies in other countries who review research.

- Researchers at Cincinnati Children's Hospital and Medical Center (CCHMC) and Nationwide Children's Hospital who will be analyzing correlative samples on this study.
- Your insurance company or other health benefits plan (if charges are billed to these plans).

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*

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 this optional study hope the results will help other people with brain cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

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

Optional sample collections for unknown future 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.

Unknown future studies

If you choose to take part in this optional study, tumor tissue from your previous biopsy and a blood sample (5 mL, approximately 1 teaspoon) will be collected and stored. Storing samples for future studies is called "biobanking". The biobank is being run by the Pediatric Brain Tumor Consortium (PBTC) 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 samples. 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 (5 mL) of blood will be collected from a vein in your arm. 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, *insert name of study doctor for main trial*, at *insert telephone number of study doctor for main trial*, 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, *insert name of study doctor for main trial*, at *insert telephone number of study doctor for main trial*.

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

Samples for unknown future studies:
I agree that my samples and related health information may be kept in the biobank for use in future health research.

YES NO NOT APPLICABLE

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	**Date of Signature**

Permission by both parents is required 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.

Signature of person(s) conducting the informed consent discussion	**Date of signature**

Appendix A: Study Calendar

	Eligibility	Course 1	Courses 2–39	Courses 40+ (extended therapy patients)	Completion/ Discontinuation of Treatment
Physical Assessments					
Medical history	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Physical exam /height/weight/BSA [A]	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Vital signs	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Performance status	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Neurologic exam	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Smoking Status[A]		X			
Pulse Oximetry	X				
Laboratory Evaluations					
CBC WBC, HgB, Hct, Platelets, ANC, ALC [B]	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Serum Chemistry Sodium, Potassium, Bicarbonate, Chloride, Calcium, BUN, Creatinine, Glucose, Phosphorous, Magnesium, Albumin, Total Protein [B]	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Coagulation (PT, INR, aPTT) [B, I]	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
SGPT(ALT), SGOT(AST), Total Bilirubin [B, C]	X	Weekly	C2–C3: Weekly	Every 3 courses Prior to course	X
			C4–C39: Prior to each course	Every 3 courses Prior to course	
Serum or Urine pregnancy test (for females of childbearing potential) [D]	X	Prior to each course	Prior to each course	Every 3 courses Prior to course	X
CSF cytology (if clinically indicated)	X				

	Eligibility	Course 1	Courses 2–39	Courses 40+ (extended therapy patients)	Completion/ Discontinuation of Treatment
Other Assessments					
EKG (All EKGs taken should be in triplicate.)	**X**	**1–3 hours after the first dose of each week (e.g., Days 1, 8, 15, 22)**	**Prior to each course**	**Every 3 courses Prior to course**	**X[G]**
Right knee X-ray[E]	**X**		**Every 3 courses After course**	**Every 3 courses Prior to course**	**X**
Imaging Assessments					
Brain MRI (standard)[F]	**X**		**X**	**X**	**X**
Spinal MRI (if clinically indicated)[G]	**X**		**X**	**X**	**X**

A. Height/weight/BSA and smoking status required only once, prior to treatment, for Course 1.
B. To be done more frequently throughout the duration of treatment if required to monitor toxicities.
C. To be done every week during each course for the first 3 courses. Collect prior to each course for Courses 4–39 and then collect every 3 courses thereafter (prior to Courses 42, 45, 48, etc.). Collect for all patients at the completion/discontinuation of treatment.
D. To be done within 24 hours prior to each course. Pregnancy test should be repeated prior to Course 1 if the test used for eligibility is > 24 hours old prior to the start of treatment.
E. Obtain pre-treatment tibial x-ray (AP and lateral views) of the right knee, to be repeated every 3 courses (after Courses 3, 6, 9, etc.). If abnormalities are detected on routine X-rays, MRI scan of both knees should be performed.
F. Standard imaging is to be done every 8 weeks until Course 6 (after Courses 2, 4, 6), then every 12 weeks until Course 24 (after Courses 9, 12, 15, 18, 21, 24), then every 16 weeks until Course 39 (after Courses 28, 32, 36, 39), then perform every 36 weeks thereafter (after Courses 48, 57, 66, etc.). Collect for all patients at the completion/discontinuation of treatment.
G. MRI Spine should be done at the same time points as the standard MRI brain, if clinically indicated.
H. A follow-up EKG is required 28 days after the off-treatment date if an EKG assessment abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.
I. Increase the frequency of INR tests if savolitinib and warfarin are used concomitantly.