

## **Model Consent Form – Screening Consent**

### **Study Title for Study Participants:**

***Screening Test to find out the presence or absence of retinoblastoma protein (Rb1) in patients with brain tumors***

**Official Study title for Internet Search on <http://www.ClinicalTrials.gov>**

***PBTC-050: A Phase I and Surgical Study of Ribociclib and Everolimus (RAD001) in Children with Recurrent or Refractory Malignant Brain Tumors***

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*“You” refers to ‘you’ or ‘your child’ throughout this document. If you are the guardian of a minor or of a person under legal disability who is being asked to participate in this screening study, you may give consent on his/her behalf.*

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### **INTRODUCTION:**

This is a screening consent for a brain tumor clinical trial called PBTC-050. We are asking you to participate in a screening procedure for a research study and your consent to provide a tumor tissue sample for research. This is not the informed consent for this clinical trial.

In order to decide whether or not you agree to take part in the screening study, you should know enough about its risks and benefits to make your decision.

The study doctor or staff will explain the screening study to you and answer your questions about this testing. Screening study only include people who choose to take part. Before making your decision, please read the information below carefully. Please ask questions about anything you do not understand.

### **Clinical trial summary**

This screening process is for the research protocol entitled: “A Phase I and Surgical Study of Ribociclib and Everolimus (RAD001) in Children with Recurrent or Refractory Malignant Brain Tumors”. You are being asked to take part in the research study because you have a brain cancer of either High Grade Glioma or medulloblastoma or CNS embryonal tumor (NOS) or Ependymoma, or ATRT or DIPG. This study has two parts: Phase I and Surgical portion. Depending on which criteria you would meet, your study doctor will approach you to offer either Phase I or surgical portion of the study.

### **Why is this study being done?**

The purpose of this screening consent is to perform a test on a sample of your tumor tissue which was removed at the time of your initial diagnostic surgery/biopsy and has been stored in a hospital laboratory. This screening procedure is a test, called Rb1 screening test, to see if you qualify to take part in a main research study of either Phase I or surgical portion.

If you sign the screening consent, you are only agreeing to have this test done by allowing your study doctor to obtain your tissue sample from pathology. If the test result shows that you are

eligible to take part in the research study, a separate informed consent will be provided to you describing full in details about the study and the investigational drug(s). Agreeing to have your tumor tissue screened does not oblige you to agree to participate in the main research study. You can still decide not to participate in the main research study.

In order to participate in the main research study, your study doctor must assess whether your tumor tissue has a specific protein called Rb1 protein. This Rb1 protein is a protein that suppresses your tumor from growing. We want to find out whether your tumor has Rb1 protein or not so that we can consider you for participation in the main study. Up to 70 people, between the ages of 1 and 21 years old, will be screened throughout the United States.

Another purpose of this consent is we are asking you to let us store any leftover tumor samples after the screening test is completed at Cincinnati Children's Hospital Medical Center (CCHMC) for possible use in future research. This is optional and only if you agree, your tumor samples will be kept at a central place, called the Pediatric Brain Tumor Consortium Central Review and Biorepository (PBTC CRB).

### **What is involved in this screening procedure?**

This screening procedure will include sending a piece of tumor tissue collected from a previous surgery to a laboratory at Cincinnati Children's Hospital Medical Center. However, if this test was completed at your local institution in a CLIA certified laboratory, we will be able to review those results to determine if additional testing is needed to confirm Rb1 status. The Investigators will look for the presence of Rb1 protein in the tumor tissue. Results from this test will determine if you are eligible to take part in the main research study. If Rb1 protein is present, the study doctor or study nurse will discuss the main research study with you and you will be able to ask questions. If you are interested in taking part in the research study, you will be scheduled to have the rest of the eligibility procedures performed. You must meet all other eligibility criteria before you are able to participate in the main research study.

### **How long will I be in the study?**

Since this is just a screening procedure, your involvement in this study will be minimal. The screening test will be done as soon as possible after you sign this consent. The results will be given to your doctor who will discuss them with you and talk about the next steps.

After the screening procedure is completed:

If you are eligible and interested in taking part of the surgical study, this portion will take about 2 months. After you complete the surgical study portion, you will also be given an option of joining the Phase I portion.

The Phase I portion will take 1 to 2 years. You will receive ribociclib and everolimus for approximately 1 year (13 courses) and if there are no side effects, you may continue the study for another year (total 2 years).

### **Can I stop being in the study?**

Yes, you may withdraw this consent and discontinue your participation in the screening study at any time. To withdraw your consent, you must contact the study doctor and tell him/her that you are changing your mind.

If you change your mind and your samples have already been tested, those results will still remain part of the overall research data.

**What are the possible risks, side effects, and discomforts of this screening study?**

Since your tumor tissue has already been collected during the surgery, there are no additional risks to you involved with this screening test. However, there is a possibility that completing this test will result in exhaustion of tumor tissue.

**What are the benefits of participating in this study?**

There are no benefits from having this tissue testing done other than to show if you might be able to participate in the main research study.

**What other choices do I have if I do not take part in this study?**

If you decide not to take part in this study, you will not be able to take part in the main research study. You do have choices. For example:

- you may choose to take part in a different study, if one is available

**Is my participation in this screening procedure voluntary?**

Yes. Taking part in this screening procedure is voluntary. No matter what you decide to do, it will not affect the medical care you would normally receive from your doctor.

**Who will know about my participation in this screening study?**

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 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:

- Your referring physician.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study
- The Pediatric Brain Tumor Consortium, which coordinates this study
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping screening safe for people
- Novartis and its authorized agents

- Governmental agencies in other countries where the study drug may be considered for approval
- Cincinnati Children's Hospital Medical Center

A description of this clinical trial may be available on <http://www.ClinicalTrials.gov>. 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.

### **What are the costs of taking part in this study?**

The cost associated with this screening procedure will be covered by the study budget. Neither you nor your insurance provider will be charged.

### **Will I be paid if I take part in this screening procedure?**

Participation in this screening procedure is voluntary. No payment for participation will be given.

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

There is no risk of injury involved because this screening test will use previously collected tumor sample material.

### **What are my rights if I take part in this study?**

Taking part in the screening procedure is your choice. You may choose either to take part or not to take part in the screening procedure. No matter what decision you make, there will be no penalty to you and you will not lose any regular benefits. Your medical care will not be affected if you do not participate in this screening procedure. You can still get medical care from our institution.

### **Who can answer my questions about the study?**

You can talk to the study doctor about any questions or concerns you have about this study. Contact the study doctor (insert name of study doctor[s]) at (insert telephone number).

For questions about your rights while in this study, call the (insert name of center) Institutional Review Board (a group of people who review the research to protect your rights) at (insert telephone number).

### **Where can I get more information?**

You may call the National Cancer Institute's Cancer Information Service at:  
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at <http://cancer.gov/>

For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>. For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

### **Additional Study Section:**

This part of the consent form is about optional study that you can choose to take part in during the screening procedure. You will not get health benefits from this study. The researchers leading this optional study hope the results will help other people with cancer in the future. The results will not be added to your medical records and your study doctor will not know the results.

You will not be billed for this optional study. You can still take part in the screening test and also in the main study even if you say “no” to this optional studies. If you sign up for but cannot complete this study for any reason, you can still take part in the main study.

What is involved?

1. Your leftover tumor samples after the screening test is completed at CCHMC will be sent to the PBTC Central Review and Biorepository (PBTC CRB).
2. Your samples and some related health information may be stored in the PBTC Central Review and Biorepository (PBTC CRB), along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
3. Qualified researchers can submit a request to use the materials stored in the Repository. The science committee of the PBTC and/or the National Cancer Institute, will review each request. Researchers will not be given your name or any other information that could directly identify you.
4. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5. Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

1. There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored.
2. There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur. In general, we will not give you any individual results from the study of the samples you gave us. This is because it will probably be a long time before we will know how to interpret the information accurately. In the rare instance that one of the genes tested might turn out to be an important risk factor for a disease, and having that information could allow you to take steps to prevent, detect earlier, or better treat that disease, we will ask you whether you want to know those results. If so, we will contact you and your doctor to discuss more testing.
4. Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. The data resulting from

the genetic research may be deposited into a public or controlled access database made available to other researchers. Information that could directly identify you will not be included. However, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

How will information be kept private?

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

1. When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2. The list that links the unique code to your name will be kept separate from your sample and health information.
3. Researchers to whom the Pediatric Brain Tumor Consortium (PBTC) sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4. Information that identifies you will not be given to anyone, unless required by law.
5. If research results are published, your name and other personal information will not be used.

What are the possible benefits?

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?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want research samples to be used, you can contact your study doctor in writing, (insert name of study doctor) who will let the researchers know. Then, any sample that remains in the repository will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned. If data has been submitted to a data repository, please include in your letter a request to retrieve your data.

What if I have more questions?

If you have questions about the use of your samples for research, contact your study doctor, (insert name of study doctor), at (insert telephone number of study doctor).

Please circle your response and then initial and date on the line provided.

- **Leftover sample storage for future research**

If you choose to take part, tumor tissue collected for the screening test but not completely used for the analysis will be stored in the repository for future unspecified research. The researchers ask your permission to store and use your tumor sample and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time.

I agree to have my specimen collected and I agree that my specimen sample and related information may be used for the optional study described above.

YES \_\_\_\_\_

NO \_\_\_\_\_





## **Model Consent Form – Surgical Study**

### **Study Title for Study Participants:**

***Testing ribociclib in patients with brain tumors who require surgery***

**Official Study title for Internet Search on <http://www.ClinicalTrials.gov>**

***PBTC-050: A Phase I and Surgical Study of Ribociclib and Everolimus (RAD001) in Children with Recurrent or Refractory Malignant Brain Tumors***

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***“You” refers to ‘you’ or ‘your child’ throughout this document. If you are the guardian of a minor or of a person under legal disability who is being asked to participate in this study, you may give consent on his/her behalf.***

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This form describes your participation in a clinical trial. A clinical trial is a type of research study. Clinical trials include only people who choose to take part. This consent form gives you information about this study, to be discussed with members of your study team.

Please take time to make the decision about whether to take part. Please discuss this decision with your family and friends. If there are any questions, ask your study doctor or health care team for more explanation.

### **What is the usual approach to my brain cancer?**

You are being asked to take part in this research study because you have a brain tumor that has grown or recurred and that will be removed through a surgical resection as a standard treatment. Your tumor has one of the following types - either High Grade Glioma or medulloblastoma or CNS embryonal tumor (NOS) or Ependymoma, or Atypical teratoid rhabdoid tumor (ATRT). People who are not in a study are usually treated with chemotherapy, radiation or other investigational agents which may or may not be FDA approved. Sometimes, combinations of these are used and your study doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

### **What are my other choices if I do not take part in this study?**

If you decide not to take part in this study, you have other choices. Please talk to your doctor about these other options. For example:

- 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
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

### **Why is this study being done?**

This research study has two portions: Phase I and Surgical study. For now, we will talk to you about participation in the surgical portion of the study. Once you finish the surgical study, you will be asked again if you like to continue for participation in the Phase I study. The information about the participation in the Phase I study will describe more in details in the Phase I consent.

The purpose of this surgical study is to test the amount of a study drug called ribociclib in your tumor and blood prior and during surgery for removal of the recurrent tumor. We have also learned that this study drug works better if your tumor has an intact Rb1 protein. You have been approached for this study because we know that you will have your brain tumor tissue removed within a few weeks and that this Rb1 protein is present in your tumor tissue that is removed during this surgery.

Ribociclib has not been approved by the FDA (the U.S. Food and Drug Administration) for the treatment of brain cancer, therefore, is considered experimental for this trial. But it has been approved for other use. This drug has been tested for safety in adults and children. About 3 to 6 people, between the ages of 1 and 21 years old, are expected to taking part in this surgical study.

### **What are the study groups?**

There will be only one dose of the study drug, ribociclib for the surgical study. All study participants will get the same study drug, ribociclib in the form of either capsules or tablets or liquid solutions. You must take one formulation of ribociclib (i.e. liquid, capsules or tablets) prior to surgery. You will take ribociclib once daily at approximately the same time every morning for 7 to 10 days before surgery. The study doctor will tell you how many pills you should take. Ribociclib pills should be swallowed whole whenever possible. It is important to take the pills with a large glass of water at the same time every day preferably in the morning, at least an hour before or an hour after a meal.

If you forget to take your dose and if less than 6 hours of the scheduled dose, you may replace the dose of ribociclib on the same day. After more than 6 hours of missed dose, the dose should be withheld, and you should wait to take ribociclib until the next day (do not try to make-up the missed dose after 6 hours). Then continue treatment with the original dosing schedule. If vomiting occurs within 10 minutes, the dose should be repeated. We will give you a pill diary where you will document information about doses taken, missed doses and reason for missing dose(s). You should bring your diary to each clinic visit and your physician will review it with you.

We advise that you drink plenty of water or take hydration fluids to avoid dehydration if diarrhea occurs. You must also avoid eating grapefruit, Seville oranges or any products containing the grapefruit juice or Seville orange juice. You should not take any herbal or dietary supplements. Check with your study doctor if you are unsure what to avoid.

### **How long will I be in this study?**

You will receive the ribociclib for 7 to 10 days prior to the resection of your brain tumor tissue. During and after tumor resection, your study doctor will watch you for any significant side effects. The study doctor will continue to watch you and follow your condition until you are completely recovered from the surgery.

It is expected that this surgical study will take you about 2 months to finish. You will then return to your doctor for re-evaluation and your doctor will also discuss with you for an option of switching over to Phase I study. You will be given a copy of the Phase I consent which covers more details about that study. If you are interested in taking part, talk to your doctor.

### **What extra tests and procedures will I have if I take part in this study?**

Most of the exams, tests, and procedures you will have are part of routine medical care for this type of cancer and may be done even if you do not join the study. On some days when you have labs, your doctor may tell you that you can't have anything to eat or drink before your labs are drawn. However, there are some extra tests and/or procedures that will need to be completed if you take part in this study. They are considered research related procedures and not part of the usual approach for this type of cancer.

### **Before you begin the study:**

You will need to have the following extra tests and procedures to find out if you can be in the study:

- Screening for Rb1 protein

This study has a screening step. Because you have a type of brain tumor that is either High Grade Glioma or medulloblastoma or CNS embryonal tumor (NOS) or Ependymoma, or ATRT, this screening test was performed on your tumor tissue that was collected from a previous surgery and the test result showed that your tumor has an intact Rb1 protein. Based on this result, we know that you are eligible to see if you meet all other requirements to take part in the surgical study.

- Electrocardiogram (EKG)

An electrocardiogram is a simple, painless test that records the heart's electrical activity. To assess the activity of your heart, your study doctor will do an EKG before you start ribociclib.

- ECHO

An echocardiogram uses sound waves to make pictures of your heart, which helps to show how well your heart pumps blood. An ECHO will be done before you start ribociclib.

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the extra tests and procedures listed in the Study Calendar. They are not part of the usual approach for your type of cancer.

### **During the study:**

- Pharmacokinetics (PK) blood (required)

You 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 ribociclib stays in the blood for 5 specific time points after the drug is taken continuously for 7 to 10 days. This study will require about 1 teaspoon (5 milliliters) of blood to be collected from your arm or central line before you start ribociclib (day -7 or Day -10, Day -5, Day -2, on the day of surgery, during surgery when tumor tissue is collected).

- Pharmacokinetics (PK) tumor tissue (required)

A piece of your brain tumor tissue (about 50 to 100 mg) will be collected during the brain surgery. This is a required test because the researchers would want to see the amount of ribociclib that stays in the tumor after the drug is taken continuously for 7 to 10 days.

As a part of this study, you are providing tissue, blood and/or CSF samples and medical information which is labeled with a code. Traditional identifying information about you such as your name, address, telephone number, or social security number will not be included in your stored information. If there is any remaining tissue, blood, or CSF samples, we would like your permission to store those samples at the Pediatric Brain Tumor Consortium Central Review and Biorepository (PBTC CRB) for an unlimited period of time for future use in research related to cancer or, perhaps, in other research projects. Providing these samples is optional and you can choose to participate at the end of this document.

Test results will be identified by a unique code and the list that links the code will be kept separate from your sample and health information. In general, we will not give you any individual results from the study of the samples you gave us. This is because it will probably be a long time before we will know how to interpret the information accurately. We will tell you if we find you have a disease that could impact your health in the future.

Your health care plan/insurance carrier will not be billed for the collection of the tissues, blood and CSF samples that will be used for this study.

A study calendar which shows how often these tests and additional blood draws will be done is attached as an appendix to this consent form.

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

If you choose to take part in this study, there is a risk that:

- You may lose time at work, school, or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you do not normally discuss

The study drug, ribociclib used in this study may affect how different parts of your body work such as the liver, kidneys, heart, and blood. Your study doctor will be testing your blood and will address any changes that may affect your health.

There is also a risk that you could have side effects from the study drug, ribociclib.

Here are important points about side effects:

- Your 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, or some may never go away.
- Some side effects may interfere with your ability to have children
- Some side effects may be serious and may even result in death.

Here are important points about how to make side effects less of a problem:

- Tell your study doctor if you notice or feel anything different so they can see if you are having a side effect.
- Your study doctor may be able to treat some side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

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

### Side effects of ribociclib

VERY COMMON, SOME MAY BE SERIOUS In 10 people receiving ribociclib, more than 1 may have:	
<ul style="list-style-type: none"> <li>• Low number of red blood cells that can causes tiredness and shortness of breath. May require a blood transfusion</li> <li>• Fever</li> <li>• Low white blood cell counts which may lead to infection</li> <li>• Constipation</li> <li>• Diarrhea</li> <li>• Sores in mouth which may cause difficulty swallowing</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Tiredness</li> <li>• Decreased appetite</li> <li>• Swelling (arm/leg)</li> <li>• Change in the heart rhythm</li> <li>• Kidney infection</li> <li>• Back pain</li> <li>• Headache</li> <li>• Difficulty sleeping</li> <li>• Shortness of breath</li> <li>• Rash</li> <li>• Itching</li> <li>• Hair loss</li> <li>• Abdominal pain</li> </ul>	
COMMON, SOME MAY BE SERIOUS In 100 people receiving ribociclib, more than 1 may have:	
<ul style="list-style-type: none"> <li>• Low white blood cell count with fever</li> <li>• Low platelet count which may cause bleeding and bruising</li> <li>• Fainting episode</li> <li>• Dry eyes</li> <li>• Tears increased</li> <li>• Taste changes which may affect the way foods normally taste</li> <li>• Heartburn</li> <li>• Liver injury which may cause yellowing of eyes and skin or swelling</li> <li>• Low blood salts that may cause muscle cramping</li> <li>• Nose bleed</li> <li>• Reddening of the skin</li> <li>• Weight loss</li> <li>• Changes in heart rhythms that may cause dizziness or heart palpitations</li> </ul>	

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.

**Reproductive risks:** You should not get pregnant, breastfeed, or father a baby while in this study. The effects of ribociclib used in this study could be very damaging to an unborn baby. If you are of childbearing or child fathering potential, you must agree to use at least one of the following methods of birth control during the study and for 8 weeks following the last dose of ribociclib.

- Be sexually inactive (total abstinence)
- Combination of any of the two following methods
  1. Use of hormonal methods (contraceptive pills, injection, implant, vaginal ring, transdermal)
  2. Have an Intrauterine device in place
  3. Barrier methods: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

Check with your study doctor about what types of birth control, or pregnancy prevention, to use while in this study. If you or your partner becomes pregnant while participating in this study, please notify your study doctor immediately and if you are a female, you will not be able to continue in the study.

### **What possible benefits can I expect from taking part in this study?**

Taking part in this study may or may not make your health better. While researchers hope that once a day ribociclib for 7 to 10 days before removal of brain tumor tissue will be more useful against the usual treatment when compared (surgical removal of the brain tumor with or without ribociclib), there is no proof of this yet. We do know that the information from this study may help us learn more about the use of ribociclib and brain surgery as a treatment for brain tumor. This information may help people in the future.

### **Can I stop taking part in this study?**

Yes. You can decide to stop at any time. If you are thinking about stopping or decide to stop for any reason, tell your study doctor and he or she will tell you how to stop safely. It is important that any risks from the study drug can be evaluated by your study doctor. Your study doctor may discuss what follow-up care and testing could be helpful for you. If the study drug is stopped, you can decide whether or not to let your study doctor continue to provide medical information to the organization running the study.

Your study doctor will provide any new information or changes in the study that may affect your health or willingness to continue in the study.

The doctor may decide to take you out of the study at any time if your doctor believes:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB, Novartis (the drug supplier) or FDA.

**What are my rights in this study?**

Taking part in this study is your choice. No matter what your decision is, and even if your decision changes, there will be no penalty. You will not lose medical care or any legal rights.

For questions about your rights while taking part in this study, call the (institution name) Institutional Review Board (a group of people who review the research to protect your rights) at (institution telephone number).

**What are the costs of taking part in this study?**

Ribociclib will be supplied at no charge while taking part in this study. The cost of getting ribociclib ready and giving it to you may not be paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that ribociclib may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about other options.

You or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless your study doctor tells you certain tests are supplied at no charge. Before making a decision about participating in this study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You/your insurance company will not be charged for procedures that are being performed for research purposes only.

You will not be paid for taking part in this study.

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

It is important that you tell your study doctor, (Physician's Name) if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at (physician's telephone number).

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsor will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

Novartis will not provide payment for any medical expenses which you may incur as a result of your participation in this study. No other type of compensation will be provided by Novartis.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

**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 and/or receive copies of your records. These organizations are required to make sure your information is kept private, unless required by law to provide information to another group.

Some of these organizations are:

- The Pediatric Brain Tumor Consortium (PBTC), who coordinate this study
- Laboratories performing the required and optional research studies of tumor, blood and CSF samples
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- Federal agencies such as the Food and Drug Administration, the Office of Human Research Protections (OHRP) and the National Cancer Institute in the U.S.
- Governmental agencies in other countries where the study drug may be considered for approval.
- The pharmaceutical company, Novartis that supplies ribociclib and its authorized agents.
- Your insurance company or other health benefits plan (if charges are billed to these plans).

The PBTC will make every effort to keep your name and identifying information confidential. Coded patient data and images from brain scans will be transmitted over the internet to be analyzed by other PBTC researchers. The PBTC has procedures (data encryption) in place to make electronic transmission of research information as secure as possible. The data security involves coding the data in a way that only the authorized receiver can decode the data. The method used to transfer information is more secure than many methods used by financial institutions when conducting business over the internet.

### **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 Website will not include information that can identify you. At most the Website will include a summary of the results. You can search this Website at anytime

### **Who can answer my questions about this study?**

You can talk to your study doctor about any questions or concerns related to this study. Contact your study doctor (Physician's name) at (Physician's telephone number).



You will get a copy of this form. If you want more information about this study, ask your study doctor.

**Additional Studies Section:**

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say ‘no’ to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

*What are the possible risks?*

1. The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2. There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored.
3. There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur. In general, we will not give you any individual results from the study of the samples you gave us. This is because it will probably be a long time before we will know how to interpret the information accurately. In the rare instance that one of the genes tested might turn out to be an important risk factor for a disease, and having that information could allow you to take steps to prevent, detect earlier, or better treat that disease, we will ask you whether you want to know those results. If so, we will contact you and your doctor to discuss more testing.
5. Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. The data resulting from the genetic research may be deposited into a public or controlled access database made available to other researchers. Information that could directly identify you will not be included. However, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

*How will information be kept private?*

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

1. When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2. The list that links the unique code to your name will be kept separate from your sample and health information.
3. Researchers to whom the Pediatric Brain Tumor Consortium (PBTC) sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4. Information that identifies you will not be given to anyone, unless required by law.
5. If research results are published, your name and other personal information will not be used.

*What are the possible benefits?*

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?*

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

*What if I change my mind?*

If you decide you no longer want research samples to be used, you can contact your study doctor in writing, (insert name of study doctor) who will let the researchers know. Then, any sample that remains in the repository will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned. If data has been submitted to a data repository, please include in your letter a request to retrieve your data.

*What if I have more questions?*

If you have questions about the use of your samples for research, contact your study doctor, (insert name of study doctor), at (insert telephone number of study doctor).

For each of the optional studies below, please circle your response and then initial and date on the line provided.

**1. Optional Sample Collection for research studies and storage.**

Researchers are trying to learn more about cancer. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems. Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

**a. Optional Sample Collection for Repository:**

If you choose to take part in the sample collection for the repository, tumor tissue from a previous surgery is needed and a blood sample is strongly encouraged to provide stored genetic material from your tumor and your healthy tissue. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for future medical research. The future research that may be done is unknown at this time but may include genomic studies. These samples will be stored at the PBTC Central Review and Biorepository (PBTC CRB) where similar samples from other subjects are stored until requested for analysis.

I choose to have my tumor tissue specimen collected and I agree that this tumor tissue and related information may be used for the test described above.

YES \_\_\_\_\_ NO \_\_\_\_\_

I choose to have my blood specimen collected and I agree that this blood sample and related information may be used for the test described above.

YES \_\_\_\_\_ NO \_\_\_\_\_

**b. Leftover sample storage for future research:**

If you choose to take part, tissue, blood or CSF samples collected as a part of this study but not completely used for the analysis will be stored in the repository for future unspecified research. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time.

I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study (ies) described above.

YES \_\_\_\_\_ NO \_\_\_\_\_

**c. Contact regarding incidental genetic findings**

If you chose to participate in genetic testing of tumor and blood samples, you may choose to be contacted in the future if we find incidental genetic abnormalities in your blood sample. The results of these studies or your choice will not affect your participation in the current study.

I would like to be contacted in the future if significant incidental genetic abnormalities are found in my blood.

YES \_\_\_\_\_ NO \_\_\_\_\_

#### **4. Optional Laboratory Studies:**

##### **a. Pharmacokinetic CSF Study:**

If you choose to take part in this study, your study doctor would like to collect a cerebral spinal fluid (CSF) sample during the surgical tumor resection. In order to get to the fluid surrounding the brain, a surgeon may have to place a thin tube into the fluid filled spaces of the brain (the ventricles). This sample will help us learn how much of the drug gets into the CSF. This study will require 2 mL of CSF to be collected at the time of surgery. The risks related to the collection of CSF during surgery may include infection, bleeding, stroke, and the risk associated with the anesthesia. After surgery, the incision may become infected, which may require hospitalization and antibiotics.

I choose to have my specimen collected and I agree that my CSF sample and related information may be used for the laboratory study described above.

YES \_\_\_\_\_

NO \_\_\_\_\_

##### **b. Tumor material for Pharmacodynamics study**

If you choose to take part, researchers would like to study tumor material that is available from a previous surgery and a scheduled surgery. Researchers are looking for biological markers to help them understand the tumors better. This study will require a piece of your tumor to be collected from a previous surgery and a scheduled surgery.

I choose to have my specimen collected and I agree that my tumor tissue samples and related information may be used for the laboratory study described above.

YES \_\_\_\_\_

NO \_\_\_\_\_

This is the end of the section about optional studies.

## **SIGNATURE**

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 copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's Name: \_\_\_\_\_  
(Print Name)

\_\_\_\_\_  
Signature of Participant or Parent or Legal Guardian or Next of Kin      Date

\_\_\_\_\_  
Signature of 2<sup>nd</sup> Parent or Legal Guardian      Date

\_\_\_\_\_  
Signature of Investigator or Designee      Date

\_\_\_\_\_  
Signature of Witness      Date

### Attachment 1: Study Calendar (Surgical Study)

	Before the study	Before surgery	Surgery	After surgery	Switch to Phase I
Screening consent (if not previously tested for Rb1)	X				
Confirmation of intact Rb1	X				
Informed consent	for Surgical study				for Phase I
Ribociclib administration		1 x/day, for 7-10 days prior surgery			X
Medical history	X			X	
Physical exam /height/weight	X			X	
Vital signs	X			X	
Performance status	X			X	
Neurologic exam	X			X	
Review of eligibility assessments, AE, concomitant medications, prior therapy assessment	X			X	
<b>Laboratory Evaluations</b>					
Blood Counts (may also be done more often to watch abnormalities)	X			X	
Blood Chemistries including liver enzymes	X			X	
Lipids (fasting)	X				
Serum or Urine pregnancy test (for females of childbearing potential)	X	X		X	
<b>Other Assessments</b>					
EKG (may also be done when your doctor thinks you need it)	X				
Echocardiogram	X				
<b>Imaging Assessments</b>					
Brain MRI (standard) with diffusion	X		X	X	
Spinal MRI (if clinically indicated)	X		X	X	
<b>Correlative studies</b>					
PK blood		X	X		
PK tumor			X		

NCI Protocol #: PBTC-050  
Version Date: September 4, 2018  
Updated Date: September 26, 2018

	<b>Before the study</b>	<b>Before surgery</b>	<b>Surgery</b>	<b>After surgery</b>	<b>Switch to Phase I</b>
CSF PK (if consented)			X		
PD tumor (if consented)			X		

## Phase I - Model Consent Form

### Study Title for Study Participants:

*Testing ribociclib in combination with everolimus in patients with brain tumors*

Official Study title for Internet Search on <http://www.ClinicalTrials.gov>

*PBTC-050: A Phase I and Surgical Study of Ribociclib and Everolimus (RAD001) in Children with Recurrent or Refractory Malignant Brain Tumors*

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***“You” refers to ‘you’ or ‘your child’ throughout this document. If you are the guardian of a minor or of a person under legal disability who is being asked to participate in this study, you may give consent on his/her behalf.***

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This form describes your participation in a clinical trial. A clinical trial is a type of research study. Clinical trials include only people who choose to take part. This consent form gives you information about this study, to be discussed with members of your study team.

Please take time to make the decision about whether to take part. Please discuss this decision with your family and friends. If there are any questions, ask your study doctor or health care team for more explanation.

### **What is the usual approach to my brain cancer?**

You are being asked to take part in this research study because you have a brain tumor that has grown or recurred or has never gone away. Your tumor has one of the following types – either High Grade Glioma (HGG) or medulloblastoma or CNS embryonal tumor (NOS) or Ependymoma, or Atypical teratoid rhabdoid tumor (ATRT) or Diffuse Intrinsic Pontine Glioma (DIPG). People who are not in a study are usually treated with standard treatment which may have included surgery, chemotherapy, radiation or other investigational agents which may or may not be FDA approved. Sometimes, combinations of these are used and your study doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

### **What are my other choices if I do not take part in this study?**

If you decide not to take part in this study, you have other choices. Please talk to your doctor about these other options. For example:

- 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
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

### **Why is this study being done?**

This research study has two portions: Phase I and Surgical study. This consent is for Phase I study and we will talk to you about participation in the Phase I portion of the study.



The purpose of this study is to test the safety of study drugs called ribociclib and everolimus when given in combination. Each of these drugs has been tested in children as monotherapy but not as combination therapy. This study tests different doses of the drugs when given in combination to see which dose is safer in children.

We have also learned that ribociclib works better if your tumor has an intact Rb1 protein. You have been approached for this study because we know that this Rb1 protein is present in your tumor tissue.

Ribociclib and everolimus have not been approved by the FDA (the U.S. Food and Drug Administration) for the treatment of brain cancer; therefore, they both are considered experimental drugs for this trial. But they have been approved for other uses. These drugs have been tested for safety in adults and children. About 45 people, between the ages of 1 and 21 years old, are expected to take part in this Phase I study.

The goals of this study are:

- To see if patients with brain tumors can safely take these drugs combination, and to find the best dose that patients can take safely
- To learn what kinds of side effects happen in patients with brain tumors when they take ribociclib and everolimus in combination
- To learn how patients with brain tumors handle the combined study drugs, ribociclib and everolimus (for examples, how much drugs are absorbed, how the body breaks down the drugs). This is called a pharmacokinetic study, or PK study.

### **What are the study groups?**

Different doses of the study drugs, ribociclib and everolimus will be given to several study participants. The first several study participants will receive the dose level that we think it is suitable for pediatric population. If both drugs do not cause serious side effects, they will be given to other study participants at a higher dose. The doses will continue to increase for every group of study participants until side effects occur that require the dose to be lowered. Then the dose escalation part of the study is stopped. Additional study participants will receive ribociclib and everolimus at the same dose level that had the fewest side effects. The dose you receive will depend on when you enroll in the study.

All study participants will get the study drugs, ribociclib and everolimus. Ribociclib is available in the form of oral capsules, tablets and liquid solution. You may not take a combination of different formulations (i.e. liquid, capsules and tablets) within a course but may change to a different formulation before starting a next course. Everolimus is available in the form of a dispersible tablet that you can dissolve in water or other liquid before taking. A dissolvable tablet breaks up into small particles in water and allows for small doses when administering with a dose dispenser or a syringe, which makes it convenient for patients who may have problems swallowing.

You will take ribociclib once a day for 21 days followed by 7 days break and everolimus once a day for 28 days. This 28-day period (4 weeks) will constitute one course.

Everolimus and ribociclib can be taken with or without food. The ribociclib capsule or film coated tablet, should be swallowed whole, not chewed and taken with water. The everolimus tablet should be mixed with water. You will be provided with instruction on how to mix the drug at home and instructed by your physician. The amount of absorption of everolimus through exposure on the skin is not known. Caregivers are advised to avoid contact with suspensions of everolimus. Wash hands thoroughly before and after preparation of the suspension. These drugs should be taken at the same time every day preferably in the morning.

If you forget to take your pill(s) and if less than 6 hours of the scheduled dose, take ribociclib and/or everolimus on the same day. After more than 6 hours of missed dose(s), the dose(s) should be withheld, and you should wait to take the drug(s) until the next day (do not try to make-up the missed dose(s) after 6 hours). Then, continue treatment with the original dosing schedule. If vomiting occurs within 10 minutes, the dose(s) should be repeated. We will give you pill diary for each drug where you will document information about doses taken, missed doses and reason for missing dose(s). You should bring your diary(s) to each clinic visit and your physician will review it with you. Empty bottles and any remaining pills should also be returned to your study doctor at each visit.

We advise that you drink plenty of water or take hydration fluids to avoid dehydration if diarrhea occurs. You must also avoid eating grapefruit, Seville oranges or any products containing the grapefruit juice or Seville orange juice. You should not take any herbal or dietary supplements. Check with your study doctor if you are unsure what to avoid. We will provide you a drug information handout and wallet card as a resource for yourself, caregivers and other health care providers.

### **How long will I be in this study?**

You will receive the study drugs, ribociclib and everolimus for 13 courses (approximately 1 year). If you have benefited from receiving ribociclib and everolimus, and the study doctor agrees, you may be able to continue taking ribociclib and everolimus for another year (for a total 26 courses). Benefit means your disease is at least clinically and radiographically stable and you have not had any significant side effects. If you stop taking the study drugs due to side effects from ribociclib and/or everolimus, the study doctor will follow you weekly for the first 4 weeks and then every 4-weeks until these side effects are resolved.

When you finish therapy for 2 years, the study doctor will continue to watch you for side effects and follow your condition for 30 days after your last doses of ribociclib and everolimus. If the side effects that are continuing at the end of day 30, the study doctor may still follow you until they are resolved or until you start another cancer therapy or until your tumor grows. Follow up can be done by clinic visits and/or updates over the phone as determined by your study doctor.

### **What extra tests and procedures will I have if I take part in this study?**

Most of the exams, tests, and procedures you will have are part of routine medical care for this type of cancer and may be done even if you do not join the study. On some days when you have labs, your doctor may tell you that you can't have anything to eat or drink before your labs are drawn. However, there are some extra tests and/or procedures that will need to be completed if

you take part in this study. They are considered research related procedures and not part of the usual approach for this type of cancer.

Before you begin the study:

You will need to have the following extra tests and procedures to find out if you can be in the study:

- Screening for Rb1 protein

This study has a screening step. Because you have a type of brain tumor that is either High Grade Glioma or medulloblastoma or CNS embryonal tumor (NOS) or Ependymoma, or ATRT or atypical DIPG which has biopsied, this screening test was performed on your tumor tissue that was collected from a previous surgery and the test result showed that your tumor has an intact Rb1 protein. Based on this result, we know that you are eligible to see if you meet all of the other requirements for the Phase 1 part of this study.

- Electrocardiogram (EKG)

An electrocardiogram is a simple, painless test that records the heart's electrical activity.

- ECHO

An echocardiogram uses sound waves to make pictures of your heart, which helps to show how well your heart pumps blood.

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the extra tests and procedures listed in the Study Calendar. They are not part of the usual approach for your type of cancer.

#### **During the study:**

- EKG on day 15 of course 1, day 1 of course 2, 3 and then every 3 months before you take drugs and at the end of study treatment
- Echocardiogram before you take drugs on course 3, may be done more often if any abnormality is found during the study, and at the end of study treatment.
- Pharmacokinetics (PK) blood (required)

You 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 ribociclib and everolimus alone and the combination of these drugs stay in the blood for 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.

For the PK study with ribociclib alone, less than ¼ teaspoon (about 1 mL) of blood will be collected each time before you start ribociclib, then 1, 2, 4, 8 ( $\pm 1$ ), 24 ( $\pm 4$ ), 32 ( $\pm 4$ ), 48 ( $\pm 4$ ) hours after your first dose of ribociclib on day 1 of Course 1. The 48-hour blood draw will be collected before your next dose of either ribociclib or everolimus, on day 3. A total of 8 mL (milliliters) (about 15/8 teaspoon) of blood will be collected.

For the PK study with both ribociclib and everolimus combination, less than ½ teaspoon (about 2 mL) of blood will be collected each time before your first doses of ribociclib and everolimus, then at 1, 2, 4, 8 (±1), and 24 (±4) hours after you take both drugs on day 17 of Course 1 (± 2 days). The 24 hour-blood draw will be collected immediately before your next dose (day 18 of course 1). A total of 12 mL (about 2 ½ teaspoon) of blood for drugs combination will be collected.

For the PK study with everolimus alone, on Day 1 Course 2 less than ¼ of a teaspoon (about 1 mL) will be collected before you start everolimus and then 30 minutes, 1, 1.5, 2, 4, 6, 8 (±1), 24 (±4) hours after you take everolimus.

**It is important that you DO NOT TAKE either ribociclib or everolimus on the days of PK draws. Your study doctor will tell you when to take the study drug(s) on these days.**

As a part of this study, you are providing tissues, blood and/or CSF samples and medical information which is labeled with a code. Traditional identifying information about you such as your name, address, telephone number, or social security number will not be put included in your stored information. If there is any remaining tissues, blood, or CSF samples, we would like your permission to store those samples at the Pediatric Brain Tumor Consortium Central Review and Biorepository (PBTC CRB) for an unlimited period of time for future use in research related to cancer or, perhaps, in other research projects. Providing these samples is optional and you can choose to participate at the end of this document.

Test results will be identified by a unique code and the list that links the code will be kept separate from your sample and health information. In general, we will not give you any individual results from the study of the samples you gave us. This is because it will probably be a long time before we will know how to interpret the information accurately. We will tell you if we find you have a disease that could impact your health in the future. Your health care plan/insurance carrier will not be billed for the collection of the tissues, blood and CSF samples that will be used for this study.

A study calendar which shows how often these tests and additional blood draws will be done is attached as an appendix to this consent form. The correlative study calendar is also attached to this consent form.

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

If you choose to take part in this study, there is a risk that:

- You may lose time at work, school, or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you do not normally discuss

The study drugs, ribociclib and everolimus used in this study may affect how different parts of your body work such as the liver, kidneys, heart, and blood. Your study doctor will be testing your blood and will address any changes that may affect your health.

There is also a risk that you could have side effects from the study drugs, ribociclib and/or everolimus.

Here are important points about side effects:

- Your 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, or some may never go away.
- Some side effects may interfere with your ability to have children
- Some side effects may be serious and may even result in death.

Here are important points about how to make side effects less of a problem:

- Tell your study doctor if you notice or feel anything different so they can see if you are having a side effect.
- Your study doctor may be able to treat some side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

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

#### Side effects of ribociclib

<p>VERY COMMON, SOME MAY BE SERIOUS</p> <p>In 10 people receiving ribociclib, more than 1 may have:</p>
<ul style="list-style-type: none"> <li>• Low number of red blood cells that can causes tiredness and shortness of breath. May require a blood transfusion</li> <li>• Fever</li> <li>• Low white blood cell counts which may lead to infection</li> <li>• Constipation</li> <li>• Diarrhea</li> <li>• Sores in mouth which may cause difficulty swallowing</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Tiredness</li> <li>• Decreased appetite</li> <li>• Swelling (arm/leg)</li> <li>• Change in the heart rhythm</li> <li>• Kidney infection</li> <li>• Back pain</li> <li>• Headache</li> <li>• Difficulty sleeping</li> <li>• Shortness of breath</li> <li>• Rash</li> <li>• Itching</li> <li>• Hair loss</li> <li>• Abdominal pain</li> </ul>

<p>COMMON, SOME MAY BE SERIOUS</p> <p>In 100 people receiving ribociclib, more than 1 may have:</p>
---

- Low white blood cell count with fever
- Low platelet count which may cause bleeding and bruising
- Fainting episode
- Dry eyes
- Watering eyes
- Taste changes which may affect the way foods normally taste
- Heartburn
- Liver injury which may cause yellowing of eyes and skin or swelling
- Low blood salts that may cause muscle cramping
- Nose bleed
- Reddening of the skin
- Weight Loss
- Changes in the heart rhythm that may cause dizziness or heart palpitations

#### Side effects of everolimus

##### **COMMON, SOME MAY BE SERIOUS**

In 100 people receiving everolimus (RAD-001), more than 20 and up to 100 may have:

- Anemia which may require blood transfusion
- Diarrhea
- Sores in the mouth which may cause difficulty swallowing
- Tiredness
- Rash
- Swelling of arms or legs
- Nausea, vomiting
- Weight loss, loss of appetite
- Infections, especially when white blood cell count is low
- Headache
- Changes in taste
- Nose bleed
- Damage to the lungs which may cause shortness of breath
- Rash
- Itching
- Cough

##### **OCCASIONAL, SOME MAY BE SERIOUS**

In 100 people receiving everolimus (RAD-001), from 4 to 20 may have:

- Pain
- Constipation, Heartburn
- Dry mouth
- Fever
- Bruising, bleeding
- Shortness of breath
- Dry skin, nail disorder, acne, reddening of the skin
- Abnormal menstrual period
- High blood pressure which may cause headaches, dizziness, blurred vision
- Bleeding from different sites

**RARE, AND SERIOUS**

In 100 people receiving everolimus (RAD-001), 3 or fewer may have:

- Non-healing surgical site
- Kidney damage which may require dialysis
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

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.

**Reproductive risks:** You should not get pregnant, breastfeed, or father a baby while in this study. The effects of ribociclib and everolimus used in this study could be very damaging to an unborn baby. If you are of childbearing or child fathering potential, you must agree to use at least one of the following methods of birth control during the study and for 8 weeks following the last dose of ribociclib and everolimus.

- Be sexually inactive (total abstinence)
- Combination of any of the two following methods
  1. Use of hormonal methods (contraceptive pills, injection, implant, vaginal ring, transdermal)
  2. Have an Intrauterine device in place
  3. Barrier methods: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

Check with your study doctor about what types of birth control, or pregnancy prevention, to use while in this study. If you or your partner becomes pregnant while participating in this study, please notify your study doctor immediately and if you are a female, you will not be able to continue in the study.

**What possible benefits can I expect from taking part in this study?**

This study is unlikely to help you. We do know that the information from this study may help us learn more about the use of ribociclib and everolimus when given in combination for treatment in brain tumor. This information may help people in the future.

**Can I stop taking part in this study?**

Yes. You can decide to stop at any time. If you are thinking about stopping or decide to stop for any reason, tell your study doctor and he or she will tell you how to stop safely. It is important that any risks from the study drug can be evaluated by your study doctor. Your study doctor may discuss what follow-up care and testing could be helpful for you. If both drugs are stopped, you can decide whether or not to let your study doctor continue to provide medical information to the organization running the study.

Your study doctor will provide any new information or changes in the study that may affect your health or willingness to continue in the study.

The doctor may decide to take you out of the study at any time if your doctor believes:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB, Novartis (the drug supplier) or FDA.

**What are my rights in this study?**

Taking part in this study is your choice. No matter what your decision is, and even if your decision changes, there will be no penalty. You will not lose medical care or any legal rights.

For questions about your rights while taking part in this study, call the (institution name) Institutional Review Board (a group of people who review the research to protect your rights) at (institution telephone number).

**What are the costs of taking part in this study?**

The study drugs, ribociclib and everolimus will be supplied at no charge while taking part in this study. The cost of getting these study drugs, ribociclib and everolimus ready and giving them to you may not be paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that the study drugs, ribociclib and everolimus may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about other options.

You or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless your study doctor tells you certain tests are supplied at no charge. Before making a decision about participating in this study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You/your insurance company will not be charged for procedures that are being performed for research purposes only.

You will not be paid for taking part in this study.



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

It is important that you tell your study doctor, (Physician's Name) if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at (physician's telephone number).

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor.

The study sponsor will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

Novartis will not provide payment for any medical expenses which you may incur as a result of your participation in this study. No other type of compensation will be provided by Novartis.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

**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 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 Pediatric Brain Tumor Consortium, who coordinate this study
- Laboratories performing the required and optional research studies of tumor, blood and CSF samples
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- Federal agencies such as the Food and Drug Administration, the Office of Human Research Protections (OHRP) and the National Cancer Institute in the U.S.
- Governmental agencies in other countries where the study drug may be considered for approval

- The pharmaceutical company, Novartis that supplies ribociclib and everolimus and its authorized agents.
- Your insurance company or other health benefits plan (if charges are billed to these plans).

The PBTC will make every effort to keep your name and identifying information confidential. Coded patient data and images from brain scans will be transmitted over the internet to be analyzed by other PBTC researchers. The PBTC has procedures (data encryption) in place to make electronic transmission of research information as secure as possible. The data security involves coding the data in a way that only the authorized receiver can decode the data. The method used to transfer information is more secure than many methods used by financial institutions when conducting business over the internet.

### **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 Website will not include information that can identify you. At most the Website will include a summary of the results. You can search this Website at anytime

### **Who can answer my questions about this study?**

You can talk to your study doctor about any questions or concerns related to this study. Contact your study doctor (Physician's name) at (Physician's telephone number).

You will get a copy of this form. If you want more information about this study, ask your study doctor.

### **Additional Studies Section:**

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

### *What are the possible risks?*

1. The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2. There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored.
3. There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique. The

researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

4. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur. In general, we will not give you any individual results from the study of the samples you gave us. This is because it will probably be a long time before we will know how to interpret the information accurately. In the rare instance that one of the genes tested might turn out to be an important risk factor for a disease, and having that information could allow you to take steps to prevent, detect earlier, or better treat that disease, we will ask you whether you want to know those results. If so, we will contact you and your doctor to discuss more testing.
5. Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. The data resulting from the genetic research may be deposited into a public or controlled access database made available to other researchers. Information that could directly identify you will not be included. However, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

*How will information be kept private?*

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

1. When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2. The list that links the unique code to your name will be kept separate from your sample and health information.
3. Information that identifies you will not be given to anyone, unless required by law.
4. If research results are published, your name and other personal information will not be used.

*What are the possible benefits?*

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?*

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

*What if I change my mind?*

If you decide you no longer want research samples to be used, you can contact your study doctor in writing, (insert name of study doctor) who will let the researchers know. Then, any sample that remains in the repository will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned. If data has been submitted to a data repository, please include in your letter a request to retrieve your data.

*What if I have more questions?*

If you have questions about the use of your samples for research, contact your study doctor, (insert name of study doctor), at (insert telephone number of study doctor).

For each of the optional studies below, please circle your response and then initial and date on the line provided

**1. Optional Sample Collection for research studies and storage**

Researchers are trying to learn more about cancer. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems. Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

**a. Optional Sample Collection for Repository:**

If you choose to take part in the sample collection for the repository, tumor tissue from a previous surgery is needed and a blood sample is strongly encouraged to provide stored genetic material from your tumor and your healthy tissue. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for future medical research. The future research that may be done is unknown at this time but may include genomic studies. These samples will be stored at the PBTC Central Review and Biorepository (PBTC CRB) where similar samples from other subjects are stored until requested for analysis.

I choose to have my tumor tissue specimen collected and I agree that this tumor tissue and related information may be used for the test described above.

YES \_\_\_\_\_ NO \_\_\_\_\_

I choose to have my blood specimen collected and I agree that this blood sample and related information may be used for the test described above.

YES \_\_\_\_\_ NO \_\_\_\_\_

**b. Leftover sample storage for future research:**

If you choose to take part, tissue, blood or CSF samples collected as a part of this study but not completely used for the analysis will be stored in the repository for future unspecified research. The researchers ask your permission to store and use your samples and related health information

(for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time.

I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study (ies) described above.

YES \_\_\_\_\_ NO \_\_\_\_\_

**c. Contact regarding incidental genetic findings**

If you chose to participate in genetic testing of tumor and blood samples as described in section 4(c) below, you may choose to be contacted in the future if we find incidental genetic abnormalities in your blood sample. The results of these studies or your choice will not affect your participation in the current study.

I would like to be contacted in the future if significant incidental genetic abnormalities are found in my blood.

YES \_\_\_\_\_ NO \_\_\_\_\_

**4. Optional Laboratory Studies:**

**a. Pharmacokinetic CSF Study (with Ommaya):**

If you choose to take part in this study and if you have an Ommaya reservoir, a cerebral spinal fluid (CSF) sample will be collected from your Ommaya for research to determine how much of the drug gets into the CSF. This study will require about 2 mL (less than ½ teaspoon) to be collected before you take ribociclib and 1, 4 and 8 hours after the ribociclib dose on day 1 of course 1, day 17 of course 1 and day 1 of course 2.

I choose to have my specimen collected and I agree that my CSF sample(s) and related information may be used for the laboratory study described above.

YES \_\_\_\_\_ NO \_\_\_\_\_

**b. Pharmacokinetic CSF Study (without an Ommaya):**

If you choose to take part in this study but you do not have an Ommaya reservoir and have CSF collected at any time during study treatment for clinical purposes, your study doctor would like to collect an extra CSF sample from you for research to determine how much of the drug gets into the CSF. This study will require about 0.5 mL (about 1/8 teaspoon) to be collected at any time during treatment.

At approximately the same time the CSF sample is collected, the research doctor would also like to collect a sample of blood (about 0.5 mL) to be collected.

I choose to have my specimens collected and I agree that my CSF and blood sample and related information may be used for the laboratory study described above.

YES \_\_\_\_\_ NO \_\_\_\_\_

**c. Genomics**

Your blood and tissue samples contain genes, which are made up of DNA and which serve as the “instruction book” for the cells that make up our bodies. If you agree, a small piece of tumor material will be collected from a previous surgery for research. The researchers will look for biological markers to help them understand the tumors better.

I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study (ies) described above.

YES \_\_\_\_\_ NO \_\_\_\_\_

This is the end of the section about optional studies.

**SIGNATURE**

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 copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's Name: \_\_\_\_\_  
(Print Name)

\_\_\_\_\_  
Signature of Participant or Parent or Legal Guardian or Next of Kin      Date

\_\_\_\_\_  
Signature of 2nd Parent or Legal Guardian      Date

\_\_\_\_\_  
Signature of Investigator or Designee      Date

\_\_\_\_\_  
Signature of Witness      Date

### Attachment 1: Study Calendar (Phase I)

	Pre-therapy	Course 1	Courses 2- Course 13	Courses 14-26	When finish with the drugs
Screening consent (if not previously tested for Rb1)	X				
Confirmation of intact Rb1	X				
Study drugs administration (ribociclib – once/day x 21 days AND everolimus – once/day x 28 days)		X	X	X	
Medical history	X	Weekly	X	X	X
Physical exam /height/weight	X	Weekly	X	X	X
Vital signs	X	Weekly	X	X	X
Performance status	X	Weekly	X	X	X
Neurologic exam	X	Weekly	X	X	X
<b>Laboratory Evaluations</b>					
Blood Counts (may also be done more often to watch abnormalities)	X	Weekly	Weekly	X	X
Blood Chemistries including liver enzymes	X	X	X	X	X
Lipids (fasting)	X		Every other course	Every other course	X
Serum or Urine pregnancy test (for females of childbearing potential)	X	X	X	X	X
<b>Other Assessments</b>					
EKG	X	Day 15, before the drugs	Day 1 of Course 2,3; thereafter, every 3 <sup>rd</sup> course; before the drugs	every 3 <sup>rd</sup> course; before the drugs	X
Echocardiogram (may be done more often when your doctor thinks you need it)	X		prior to Course 3	May be done	X
<b>Imaging Assessments</b>					
Brain MRI (standard) with diffusion	X		After every 2 courses for the first 3 courses, then after every 3 courses until tumor worsens	every 3 courses until tumor worsens	When finished with drugs or when tumor worsens



	Pre-therapy	Course 1	Courses 2- Course 13	Courses 14-26	When finish with the drugs
Spinal MRI (if clinically indicated)	X		After every 2 courses for the first 3 courses, then after every 3 courses until tumor worsens	every 3 courses until tumor worsens	When finished with drugs or when tumor worsens

## Attachment 2: Correlative Studies Calendar (Phase I)

Correlative studies	Pre-therapy	Course 1	Course 2
PK blood			
Ribociclib PK samples		<b>D1 C1</b> <ul style="list-style-type: none"> <li>pre-dose, and 1, 2, 4, 8 (<math>\pm 1</math>), 24 (<math>\pm 4</math>), 32 (<math>\pm 4</math>), and 48 (<math>\pm 4</math>) hours after dose.<sup>A</sup></li> <li>1 mL each (8 mL total)</li> </ul>	
Everolimus PK samples			<b>D1 of C2</b> <ul style="list-style-type: none"> <li>pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8 (<math>\pm 1</math>), and 24 (<math>\pm 4</math>) hr after dose.<sup>B</sup></li> <li>1 mL each (9 mL total)</li> </ul>
Ribociclib + Everolimus PK samples		<b>D17 of C1 (+/- 2 days)</b> <ul style="list-style-type: none"> <li>pre-dose, 1, 2, 4, 8 (<math>\pm 1</math>), and 24 (<math>\pm 4</math>) hrs after dose</li> <li>2 mL each (12 mL total)</li> </ul>	
PK – serial CSF (if consented)		<b>D1 C1, D17 C1 and D1 C2</b> <ul style="list-style-type: none"> <li>pre-dose and at 1, 4, and 8 hours after dose</li> <li>0.5 mL each (2 mL total)</li> </ul>	
PK – single CSF (if consented)		Anytime during treatment	
Pre-trial tumor materials and PBMCs for Genomics (if consented)	X		
Tumor Tissue and blood for Biorepository (if consented)	X		

A. 48-hour time point will be collected prior to administration of either drug (ribociclib or everolimus) on Day 3.

B. The ribociclib dose on day 1 should be held and day 2 should be delayed until the last everolimus sample is collected on day 2