CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

PPD

October 28, 2022

PPD

RE: Request for Amendments with FDA requested language for Pediatric MATCH consents

Dear PPD

The study committee thanks CTEP for forwarding the Amendment Request dated October 17, 2022. In response to the request, please see attached Amendment #6 to APEC1621D. The complete list of changes can be found below.

Please contact us if you have any further questions.

Sincerely,

PPD

CHILDREN'S ONCOLOGY GROUP

SUMMARY OF CHANGES: INFORMED CONSENT

In accordance with the above discussion, the following specific revisions have been made to the consent. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

1. #	Section	Page(s)	Change
1.	General	All	Updated version date of consent to match the current version of the protocol.
2.	Why is this study being done?	2	**Please know that your eligibility for this trial may have been determined in part on the basis of a laboratory-developed test that has not been reviewed or approved by the FDA** was added

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This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they must be justified in writing by the investigator and approved by the IRB.

SAMPLE INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

APEC1621D
NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) – Phase 2 Subprotocol of LY3023414

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

Why am I being invited to take part in this study?

You are being asked to take part in this research study because your tumor testing results submitted for the NCI-COG Pediatric MATCH screening protocol make you a candidate to receive the investigational drug (or "study drug") that we are testing in this study.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children and adolescents with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG. Only hospitals in the United States will participate in this study.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of treatment for this disease?

When a cancer comes back (relapses) or does not respond to therapy (is refractory), your doctor may recommend other anti-cancer drugs (chemotherapy), surgery, or radiation therapy. For certain cancers, a combination of one or more of these approaches is considered standard treatment. However, for other cancers such as cancers that recur, or for cancer for which therapy is no longer working, the best treatment is not known.

You are being asked to participate in this study because you have a relapsed or refractory tumor without a proven treatment strategy for cure.

Why is this study being done?

This is a Phase 2 study of a drug called LY3023414. In a Phase 2 study, the goal is to find out what effects, good and/or bad, a drug has on your tumor or type of cancer.

We are using LY3023414 in this study because it was shown to block the growth of cancer cells with mutations in an important cell-signaling pathway (called the PI3K/MTOR pathway) in test tubes and in animals. Genes in this pathway are frequently mutated in many types of cancers. You are eligible for this study because your tumor was found to have a mutation in one of these genes. LY3023414 is considered a study drug in the treatment of your disease. Although LY3023414 has been given to a small number of adults, we do not know if it will work against the type of tumor you have. Please know that your eligibility for this trial may have been determined in part on the basis of a laboratory-developed test that has not been reviewed or approved by the FDA

A Phase 1 study of LY3023414 to find the highest dose of an experimental drug that can be given without too many side effects has been completed in adults with cancer. This study will be the first time that LY3023414 is given to children and adolescents.

The dose for the first group of children and adolescents enrolled on the study will be based on the side effects seen in adults. Between 2 and 6 children and adolescents will receive LY3023414 at this dose. If the side effects are not too severe, the next group of children and adolescents will receive a higher dose. If there are too many side effects, the next group of children and adolescents will receive a lower dose. Dosing is done this way because we do not yet know the best dose to use in children and adolescents. If you are enrolled early in this study you may receive a lower or higher dose than those who are enrolled later. A higher dose may be more likely to cause side effects. A lower dose may be less likely to have any effect on your tumor. Whatever dose you start at, your dose will not be increased. If you have bad side effects, your dose may be decreased.

The goals of this study are:

- **The main goal is to test any good and bad effects the study drug LY3023414 has on your tumor.**
- **A second goal of the study is to evaluate side effects that might be caused by LY3023414.**
- **To learn more about the pharmacology (how your body handles the drug) of LY3023414;**

How many people will take part in the study?

There will be between 4-24 patients participating in APEC1621D. About ___ will be treated at this hospital.

What will happen if I take part in this research study?

Before you begin the study…

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A medical history

- Physical exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- Urine tests
- Pregnancy test (if you are a woman who could have children)

We will also do whatever X-rays, CT scans, or other tests are needed to check your tumor. An EKG will also be obtained to check your heart rhythm at baseline.

In addition to the above exams, tests or procedures, your study doctor will confirm that you are able to swallow intact tablets whole.

During the study…

If the exams, tests and procedures show that you can be in the study, and you choose to take part, LY3023414 will be given by mouth twice a day for 28 days. This entire 4 week period is called a cycle. You may continue to receive LY3023414 for up to 6 cycles, which lasts about 6 months, unless you develop serious side effects or your tumor worsens.

You will be given specific instructions regarding how to take this study drug. You will also be given a medication diary to fill out at home. Use the diary to record the date and time you take the drug, and any side effects that you experience. Also record in the diary other medications and/or supplements you are taking and whether you vomited or missed a dose. This diary should be returned to the clinic, along with the medication bottle (even if it is empty) weekly during Cycle 1 and then at the end of every cycle. This will help us know how much of the study drug you take and how it made you feel.

During the study you will have tests and procedures to check for side effects and see how your tumor is doing. These tests are part of regular cancer care, but you may have them more often because you are on the study:

- Physical exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- MRI, X-rays, CT scans, or other tests that are needed to check your tumor
- Bone marrow examinations if needed for your type of tumor

Copies of the scans used to diagnose your cancer may be sent to a central review center. COG does this to double check the hospitals' results for research purposes only.

Circulating Tumor DNA Studies

We would like to collect blood samples (10-20 mL, or about 2-4 teaspoons) at Cycle 5 Day 1 and end of protocol therapy (only if you receive more than 5 cycles of therapy) to see if a blood test can show whether the tumor DNA has changed from when the tumor was biopsied.

_____/_____ Yes, I agree to participate in these additional circulating tumor DNA studies.

_____/_____ No, I do not agree to participate in these additional circulating tumor DNA studies.

Pharmacokinetic Studies
If you are enrolled early in this study, we would like to collect a total of 9 blood samples (about 2 mL or less than ½ teaspoon each sample) to see how much of LY3023414 is in your blood. These samples will be taken during Day 1 of Cycle 1 before the drug is given, and at 30 minutes, 1 hour, 2 hours, 4 hours and then at 6-8 hours after the drug is given. An additional sample will be obtained in Cycle 1 on Day 2 (about 24 hours after your dose on Day 1), before your dose on Day 15, and then 1-2 hours after your dose on Day 15.

If you are enrolled later in this study, we would like to collect two samples: before your dose on Day 15 of Cycle 1, and then 1-2 hours after your dose on Day 15.

_____/_____ Yes, I agree to participate in the pharmacokinetic studies.

_____/_____ No, I do not agree to participate in the pharmacokinetic studies.

A maximum volume of 18 mL (less than 4 teaspoons) will be drawn for pharmacokinetic tests in this study. *This amount of blood is safe to draw even from small children.*

How long will I be in the study?
You may be in the study for up to 6 cycles of therapy, which lasts about 6 months. Your doctor may decide to take you off study if any of the following occur:

- Your tumor gets worse
- The side effects of LY3023414 are too harmful for you
- You need a treatment that is not allowed on this study
- You are not able to follow study-related treatment instructions
- New information becomes available
- The study is not in your best interest
- The study is stopped
- You get pregnant

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from LY3023414 can be evaluated by your doctor. Also, your doctor can discuss what follow-up care and testing could be most helpful for you.

What side effects or risks can I expect from being in the study?
If you choose to take part in this study, there is a risk that LY3023414 may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

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

- **May not be able to take part in future studies.**

LY3023414 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug.
Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, 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 you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**
- **The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drug.**

The table(s) 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, the study doctor will discuss these with you.

Risks and side effects related to LY3023414 include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving LY3023414, more than 20 and up to 100 may have:
• **Diarrhea, nausea, vomiting** • **Tiredness** • **Loss of appetite**
OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving LY3023414, from 4 to 20 may have:
• **Anemia which may require blood transfusion** • **Belly pain** • **Constipation, heartburn** • **Sores in the mouth which may cause difficulty swallowing** • **Tingling in the mouth** • **Fever** • **Swelling of the body** • **Bruising, bleeding, weight loss** • **Dizziness, headache** • **Changes in taste** • **Feeling of "pins and needles" in arms and legs** • **Shortness of breath** • **Dry skin** • **Itching, rash**

RARE, AND SERIOUS In 100 people receiving LY3023414, 3 or fewer may have:
• **Change in the heart rhythm** • **Infection**

Some drugs or supplements may interact with your treatment plan. Talk to your doctor, pharmacist, or study team before starting any new prescription or over-the-counter drugs, herbals, or supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

If you have a drop in the red blood cell count, the cells that carry oxygen around the body you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.

If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the blood stream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell count is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Transfusions may be accompanied by or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S (acquired immune deficiency syndrome) and other infections.

Reproductive risks:
You should not become pregnant or father a baby while on this study and for 3 months after stopping LY3023414 because LY3023414 can affect an unborn baby. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. **Women should not breastfeed a baby while on this study.**

Risks of blood drawing or placing an intravenous catheter for blood drawing:
Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

The potential benefit of the treatment with LY3023414 is that it may cause your cancer to stop growing or to shrink for a period of time. It may lessen the symptoms, such as pain, that are caused by the cancer. It is extremely unlikely that this treatment will cure your cancer. Because there is not much information about the effect of LY3023414 on cancers in humans, we do not know if you will benefit from taking part in this study. Information learned from this study may help future patients with cancer.

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

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**

- **Taking part in another study**
- **Focusing on comfort care and quality of life instead of drugs to treat the tumor**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.
The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **The Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board (IRB) of this hospital**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The drug company partner (the company that makes LY3023414) or their designated reviewers**

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The NCI will provide LY3023414 at no charge while you take part in the study. The NCI does not cover the cost of getting LY3023414 ready and giving it to you, so you or your insurance company may have to pay for this. If, during the study, LY3023414 becomes approved for use in your cancer, you or your health plan may have to pay for study drug needed to complete this study.

Even though it probably won't happen, it is possible that the NCI may not be able to continue to provide LY3023414 for some reason. If this would happen, the study may have to close. Your study doctor will talk with you about this, if it happens.

You will not be charged for the costs of the special blood studies that are being done for research purposes only, such as the tumor DNA analysis or pharmacokinetic studies.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at **http://www.cancer.gov/clinicaltrials/learningabout.**

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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

It is important that you tell your study doctor, _____ *[investigator's name(s)],* 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 _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. There are no plans for the study to pay for medical treatment for injuries. In the case of injury resulting from this study, you do not lose any of your legal rights to seek compensation by signing this form.

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

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your regular medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. Whether you participate or not, you will continue to get the best medical care this hospital can provide.

Who can answer my questions about the study?

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

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Where can I get more information?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at https://www.childrensoncologygroup.org/index.php/cog-family-handbook.

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

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

You 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.

Signature

I have been given a copy of all _____ pages of this form.
I have read it or it has been read to me.

I have reviewed the information and have had my questions answered. I agree to take part in this study.

Participant:_____ Date:_____

Signature of Participant / Parent (or Guardian): Date:_____
_____

Physician or Responsible Investigator: Date:_____
_____

Signature of Physician or Responsible Investigator: Date:_____
_____