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June 15, 2021

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Please find attached Amendment #5 to **APEC1621C**, *NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 subprotocol of tazemetostat for patients with tumors harboring alterations in EZH2 or members of the SWI/SNF complex*

Amendment #5 provides a response to a Request for Amendment (RA) from CTEP, dated May 11, 2021. The CAEPR within the protocol and associated risk information contained within the consent document for Tazemetostat, NSC 791066 have been modified to satisfy the RA received. Additionally, minor administrative changes have been included in to the protocol. CRFs have been updated to include changes to the language of the inclusion criteria. No changes have been made to the training module Please contact us if you have any further questions.

Sincerely,

Samuel Baird, MPH, Protocol Coordinator for
Susan Chi, M.D., **APEC1621C** Study Chair, and
Donald Parsons, M.D., PhD, PI, Chair, Molecular Analysis for Therapy Choice

I. ICD Changes:

Section	Comment
Throughout	Updated version dates.
Risks of Study	• Updated risk list to version 2.4, March 30, 2021, per RA request. • Moved herbal supplements paragraph below reproductive risk paragraph, as the risk of special interests are of greater importance.

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

APEC1621C

NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) – Phase 2 Subprotocol of Tazemetostat in Patients with Tumors Harboring Alterations in EZH2 or Members of the SWI/SNF Complex.

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.

Overview

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

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

The overall goal of this study is to test any good and bad effects of the study drug tazemetostat on your tumor.

The treatment involves a cancer fighting medicine called tazemetostat. The treatment on this study takes about 26 months and is divided into 26 cycles of therapy. A cycle is 28 days (4 weeks).

The dose for the children enrolled on the study will be based on the side effects seen in adults. Between 20 and 49 children will receive tazemetostat. Your dose will not be increased. If you have bad side effects, your dose may be decreased. Dosing is done this way because we do not yet know the best dose to use in children.

All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

This study uses the study drug tazemetostat, the common side effect of this drug is tiredness. Some less common but notable side effects are: A new cancer resulting from treatment of earlier cancer.
The full list of risks for drug tazemetostat are available in the section What side effects or risks can I expect from being in the study?

You can ask your study doctor questions about side effects at any time.

We hope that this study will help you personally, but we do not know if it will. The potential benefits to you associated with participation in this study are described in the section Are there benefits to taking part in the study?

You have a choice between another treatment and this clinical trial.

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

Why am I being invited to take part 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.

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

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. You have a choice between another treatment for your cancer and this clinical trial.

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 (recurs) 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, the best treatment is not known.

You are being asked to participate in this study because you have a recurrent 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 tazemetostat. 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. Tazemetostat is experimental because it has not been proven to work in a situation like yours.

We are using tazemetostat in this study because it has been shown to block the growth of cancer cells with specific genetic changes in an important cell-signaling pathway (called the EZH2 and SWI/SNF pathway) in test tubes and in animals and has reduced tumor size in some patients in clinical studies. Genes in this pathway are frequently changed in many types of cancers. You are eligible for this study because your tumor was found to have a specific genetic change in one of these genes. Tazemetostat is an experimental drug in the treatment of your tumor or type of cancer, we do not know if it will work against the type of tumor you have.

Phase 1 studies of tazemetostat have been completed in adults and children with cancer. The goal of Phase 1 studies is to find the highest dose of a study drug that can be given without too many side effects. In the Phase 1 studies, researchers determined the dose of tazemetostat that can be given without too many side effects. If your tumor is located in the central nervous system (CNS, brain or spine), you will receive the same dose that is used in the pediatric Phase I study. If your tumor is located outside of the CNS, you will receive a lower dose which is similar to the dose given to adults with cancer. If you have bad side effects, your dose may be decreased.

The overall goals of this study are to:

- **The main goal is to test any good and bad effects of the study drug tazemetostat on your tumor.**
- **A second goal of the study is to evaluate side effects that might be caused by tazemetostat.**

What will happen on this study that is research?

The treatment involves cancer fighting medicine called tazemetostat. The treatment on this study can last up to 26 months.

In this study you will receive tazemetostat by mouth twice daily, continuously for 28 days. A cycle is 28 days (4 weeks). Between 20 and 49 children will receive tazemetostat. Your dose will not be increased. If you have bad side effects, your dose may be decreased.

Tazemetostat is given by mouth can be taken without regard to meals. If you vomit after taking the medication, the dose will not be repeated.

You will be given specific instructions regarding how to take the study drug. You will also be given a medication diary to fill out at home each time the oral medicine, tazemetostat is taken. Use the diary to record the date and time you take tazemetostat, and any side effects 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 drug you take and how it made you feel.

Diagram of Treatment
This chart shows the treatment on this study and describes once cycle of study therapy:

Drug	How the drug will be given	Days
Tazemetostat	by mouth, twice a day	1-28

Research Study Tests and Procedures
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 and neurological exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests-to monitor your blood counts and blood chemistries
- 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, to monitor your response to treatment
- Heart Function Test–,EKG
- Bone X-ray tests to check your bone development

Optional Research Study Tests

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 5 or more cycles of therapy), to see if a blood test can show whether or not the tumor DNA has changed from when the tumor was biopsied. These studies may help children and young adults who receive this drug in the future. The information learned would not change the way you are treated, and the results of these tests will not be given to you.

You do not have to do these tests if you do not want to. You can still be in the study if you do not want to do these tests. At the end of this consent form, there is a place to record your decision about taking part in each test.

What side effects or risks can I expect from being in the study?

Treatment Risks
All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in the COG Family Handbook for Children with Cancer. Parents will be taught more about caring for their child when his or her blood counts are low.

Risks of Study

The table below show the most common and the most serious side effects that researchers know about tazemetostat. 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 tazemetostat include those which are:

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving tazemetostat, from 4 to 20 may have:
• Anemia which may require blood transfusion • Constipation, diarrhea, nausea, vomiting • Tiredness • Bruising, bleeding • Loss of appetite, weight loss • Hair loss • Dry skin

RARE, AND SERIOUS In 100 people receiving tazemetostat, 3 or fewer may have:
• Cancer of bone marrow caused by chemotherapy • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • A new cancer resulting from treatment of earlier cancer • Cough; shortness of breath • Increased risk of sunburn

Side Effects or Risks of Special Interest:

The following side effects or risks have been identified, requiring additional monitoring, or tests, to potentially minimize the occurrence of these events.

T-cell lymphoblastic lymphoma or T-cell acute lymphoblastic leukemia (T-LBL/T-ALL)

- A 9-year-old subject treated with tazemetostat in a study being conducted in children developed a type of non-Hodgkin lymphoma, which is also called T-cell lymphoblastic lymphoma (T-LBL), after receiving tazemetostat for 14 months.

During pre-clinical animal testing, T-LBL, including lymphoid hyperplasia in the thymus, was observed in one model, rats, but not in other animal models. It was noted by the company that in rats, these events were observed at the highest doses, doses higher than have been used in humans.

B-cell acute lymphoblastic leukemia

- A patient with diffuse large B-cell lymphoma developed B-cell ALL after approximately 46 months of treatment with tazemetostat. The observed development of with B-cell ALL may be due to the underlying diffuse large B-cell lymphoma or prior therapy for the lymphoma.

As per the tazemetostat Investigator Brochure, V10.0, this is the only case of T-cell lymphoma that has occurred out of a total of 90 children enrolled in tazemetostat clinical

trials. In addition, there have been no cases of T-LBL/T-ALL or B-cell ALL in the 725 adult patients treated across multiple studies conducted in different types of cancer. The company will continue to monitor all patients treated with tazemetostat very carefully for the development of secondary malignancies.

Reproductive risks:

Women should not become pregnant during the study and for at least 30 days after the last dose of tazemetostat. Men should avoid fathering a child while on this study and for 90 days after the last dose of tazemetostat because tazemetostat 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. If a female caregiver is pregnant or suspects she is pregnant, she should not handle tazemetostat. Women should not breastfeed a baby while on this study.

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.

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

If you have a drop in your 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.

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

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.
- You should avoid too much sun exposure. If you plan to be in the sun please use adequate sun protection.

You can ask your study doctor questions about side effects at any time.

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 drugs.

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.

The use of the experimental drug tazemetostat instead of another treatment may cause more side effects.

The tazemetostat treatment that is being studied could be less effective than another treatment.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

You may lose time at school, work 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 normally do not discuss.

Are there benefits to taking part in the study?

We hope that this study will help you personally, but we do not know if it will.

Potential benefits to you could include:

- may cause your cancer to stop growing or to shrink for a period of time.
- fewer side effects than other kinds of chemotherapy

With any cancer treatment, sometimes treatment does not make the cancer go away. Or, sometimes treatment makes the cancer go away for a while but the cancer comes back later.

We expect that the information learned from this study will benefit other patients in the future.

What other options are there?

Instead of being in this study, you have these options:

- **Getting treatment for your cancer without being in a study**
- **Taking part in another study.**
- **Getting comfort care, also called palliative care.** This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

How many people will take part in the study?

The total number of people enrolled on this study is expected to be 49.

How long is the study?

People in this clinical trial are expected to receive treatment on this study for up to 26 months. After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health for about 30 days after your last dose of tazemetostat. By keeping in touch with you for a while after you complete treatment, we can better understand the long-term effects of the study treatments.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:

- If he/she believes that it is in your best interest
- If your disease does not respond to the treatment or gets worse
- If you experience side effects from the treatment that are considered 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
- If new information becomes available that shows another treatment would be better for you
- The study is stopped
- If you are female and get pregnant

What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. 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 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 Children's Oncology Group will do their best to make sure that any information that goes out to others will not identify who you are. Information about this Certificate of Confidentiality is included in Attachment 1.

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

- **Children's Oncology Group and research partners**
- **The NCI's National Clinical Trials Network and the groups it works with to conduct research (including the Imaging and Radiation Oncology Core (IROC))**
- **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 of this hospital**

- **Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The study sponsor and any drug company supporting the study or their designated reviewers**

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

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

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

What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

The NCI will provide tazemetostat at no charge while you take part in the study. The NCI does not cover the cost of getting tazemetostat ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the tazemetostat to the NCI for some reason. If this does happen, other possible options are:

- You might be able to get the tazemetostat from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no tazemetostat available at all, no one will be able to get more and the study would close.

If a problem with getting tazemetostat occurs, your study doctor will talk to you about these options.

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.

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 studies.

Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

This study includes providing specimens to the researcher, there are no plans for you to profit from any new product developed from research done on your specimens

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or your willingness to continue in the study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. XXXX or your doctor at XXXX.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX Institutional Review Board (IRB) Administrator at XXXX.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at XXXX.

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.

Visit the NCI's website at http://cancer.gov/

If you are in the United States, you may call the National Cancer Institute's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237)

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

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

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Specimens for optional research tests

The choice to let us use blood samples for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies.

If you decide that your blood can be used for research, some of your health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

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

If you decide now that your blood sample can be used for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any specimens that we have will be destroyed.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

1.) My blood may be sent to a COG laboratory and studied to see if a blood test can show whether or not the tumor DNA has changed from when the tumor was biopsied.

Yes_____ No_____ _____ / _____
Initials Date

Signature

I have been given a copy of all 13 pages of this form. The consent form includes one (1) attachment.

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

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

Attachment 1

Certificate of Confidentiality

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.