SUMMARY OF CHANGES

For Protocol Amendment #6 to: NRG-GY014

NCI Protocol #: NRG-GY014
Local Protocol #: NRG-GY014

NCI Version Date: January 11, 2023

This amendment is in response to an RRA from Dr. Richard Piekarz (rpiekarz@nih.gov)

Section	**Comments**
Footer	The NCI Version Date is now January 11, 2023.

What Risks Can I Expect. . . ?	Under Drug Risks, the condensed risk profile for tazemetostat has been modified:
	
	• Increase in Risk Attribution:
	  • Changed to Common from Occasional: Anemia which may require blood transfusion; Nausea; Vomiting; Tiredness
	  • Changed to Occasional from Also Reported on Tazemetostat Trials But With Insufficient Evidence for Attribution (i.e. added to the Risk Profile): Cold symptoms such as stuffy nose, sneezing, sore throat; Fever; Infection, especially when white blood cell count is low; Pain; Headache

Study Title for Participants: Testing Tazemetostat (EPZ-6438) in recurrent or persistent endometrioid or clear cell cancer of the ovary and recurrent or persistent endometrioid cancer of the uterus.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
NRG-GY014: A Phase II Study of Tazemetostat (EPZ-6438) in Recurrent or Persistent Endometrioid or Clear Cell Carcinoma of the Ovary, and Recurrent or Persistent Endometrioid Endometrial Adenocarcinoma

Overview and Key Information

What am I being asked to do? (20-OCT-2021)

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

We are asking you to take part in this research study because you have clear cell ovarian cancer that has been determined to have an ARID1A mutation and has grown or has recurred.

Taking part in this study is your choice.

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

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

Why is this study being done? (20-OCT-2021)

This study is being done to answer the following question: Can we lower the chance of your ovarian or endometrial cancer growing by using a new drug?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your ovarian or endometrial cancer. The usual approach is defined as care most people get for ovarian or endometrial cancer that has grown or recurred.

Note: After October 20, 2021, only patients with clear cell ovarian cancer with documented ARID1A mutations will be enrolled. Following completion of the first stage, no additional endometrial cancer patients will be enrolled on study.

What is the usual approach to my cancer of the ovary or endometrium?

The usual approach for patients who are not in a study is treatment with surgery, radiation, or drugs including: carboplatin, paclitaxel, gemcitabine, pegylated liposomal doxorubicin, topotecan, and bevacizumab (all FDA approved agents; bevacizumab is only FDA approved in ovarian cancer). Sometimes, combinations of these treatments are used. Your doctor can explain which treatment may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

If you were previously treated with chemotherapy, and have been off of chemotherapy for 6 months or more, you would be eligible for retreatment with a chemotherapy regimen containing a platinum drug (i.e. carboplatin). It is important to understand that other treatment options may exist aside from the medication being studied in this clinical trial.

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

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

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

If you decide to take part in this study, you will get the study drug tazemetostat until your disease gets worse or the side effects become too severe.

After your finish your treatment with tazemetostat, your doctor and study team will continue to follow your condition and watch you for side effects during clinic visits or by phone if you are unable to visit the clinic. They will check you every three months for two years after treatment. After that, they will check you every six months for three years. This means you will keep seeing your doctor for up to 5 years after treatment.

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

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

Risks

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

If you choose to take part in this study, there is a risk that the study drug, tazemetostat, may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer. This may be the case when you have had a long interval of time (6 months or more) since your last

chemotherapy treatment, as you may respond well to re-treatment with a platinum containing regimen (i.e. carboplatin).

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

The most common risks related to drawing blood from your arm are brief pain and maybe a bruise. **(08/13/2019)**

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

- Tiredness
- Anemia, which may require blood transfusion
- Neutropenia (low white cell count), which may increase risk of infection
- Thrombocytopenia (low platelet count), which may increase risk of bleeding
- Constipation, Diarrhea, Nausea, Vomiting

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

Benefits

Treatment with tazemetostat has shrunk or stabilized other cancers in adult patients, and may be effective in ovarian and endometrial cancer. It is unlikely that it will work in everyone with your cancer or help you live longer. This study may help the study doctors learn things that may help other people in the future.

If I decide to take part in this study, can I stop later? (20-OCT-2021)

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

If you decide to stop, let your study doctor know as soon as possible. It is important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

There are two options of stopping treatment:

1. The first option is that you stop treatment with tazemetostat, but you would continue follow up visits (no treatment) to see how you are doing. If you agree to let your study doctor continue to follow you, you will continue to be part of the study so that we can follow you to see how you are doing and if your cancer comes back. We would continue to collect information about how you and your cancer are doing and to see how the treatment affected you and your cancer. This is considered that you go “off treatment” but not “off study” and you would not withdraw consent.

2. The second option is to stop treatment and not allow your study doctor to collect any information on how you and your cancer are doing and how the treatment affected you

and your cancer. This is considered “withdrawal of consent” and you would go “off treatment” and “off study”.

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

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

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

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

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

What is the purpose of this study?

The purpose of this study is to test any good and bad effects of the drug called tazemetostat. Tazemetostat could shrink your cancer but it could also cause side effects, which are described in the risks section below. The study doctors hope to learn if the study drug will shrink the cancer by 30% or more compared to its present size. This drug is currently being tested in other cancers in adult and pediatric patients and has helped to shrink the tumors of some of the treated patients.

There will be 62 people taking part in this study. **(20-OCT-2021)**

What are the study groups?

In this study, everyone will get the study drug tazemetostat. Treatment schedule: You will take up to 4 tablets of tazemetostat by mouth two times every day of each cycle. Each 28-day period of time is called a cycle.

You also will keep a pill diary. This helps you keep track of when you take your pills. The study doctor will show you how to use this diary. Each time you visit the clinic, you must bring the pill diary, any remaining pills, and the pill bottle.

What exams, tests and procedures are involved in this study? **(08/13/2019)**

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety

and health. Most of these are included in the usual care you would get even if you were not in a study.

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

Your study doctor will need to use some of the tissue left over from your surgery or biopsy when you were diagnosed with cancer. Your study doctor will also collect a sample of your blood at one time during this study. These samples are a required part of the study. The tissue and blood samples will be used to determine if your tumor expresses a certain protein and has a certain gene change. You and your study doctor will not get the results of this testing.

With your permission, any of these samples that are remaining after completion of this research will be stored for future research. This will be discussed in the section on optional studies.

What risks can I expect from taking part in this study? (20-OCT-2021)

General Risks

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

You also may have the following discomforts:

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

The medication used in this study, tazemetostat, could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. If you are capable of becoming pregnant, it is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 6 months after your last dose of tazemetostat. Do not breastfeed during treatment and for 1 week after the last dose of tazemetostat..

Side Effect Risks (20-OCT-2021)

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

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

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.

- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

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

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

Drug Risks (20-OCT-2021) (06-APR-2022)

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

Possible Side Effects of Tazemetostat: (CAEPR Version 2.5, November 16, 2022) **(07-JUL-2020) (11-JAN-2023)**

COMMON, SOME MAY BE SERIOUS In 100 people receiving tazemetostat (EPZ-6438), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Nausea, vomiting • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving tazemetostat (EPZ-6438), from 4 to 20 may have:
• Pain • Constipation, diarrhea • Fever • Swelling of arms, legs • Infection, especially when white blood cell count is low • Cold symptoms such as stuffy nose, sneezing, sore throat • Bruising, bleeding • Weight loss, loss of appetite • Headache • Hair loss, dry skin

RARE, AND SERIOUS In 100 people receiving tazemetostat (EPZ-6438), 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 **(20-OCT-2021)**

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 (B-cell ALL)

- A patient with diffuse large B-cell lymphoma developed B-cell ALL after approximately 46 months of treatment with tazemetostat. The observed development of 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.

Additional Drug Risks (09-DEC-2021)

The study drug could interact with other drugs and food. Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with tazemetostat. No grapefruit juice, Seville oranges, or grapefruit can be consumed while on tazemetostat.

Your study doctor will give you a clinical trial wallet card that lists the study drugs you are taking. Share this information with your family members, caregivers, other health care providers, and pharmacists.

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

Imaging Risks

The CT scans that you get in this study will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

What are my responsibilities in this study? (20-OCT-2021)

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

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

Do not get pregnant or breastfeed while taking part in this study. Tell your study doctor right away if you think that you have become pregnant during the study or within 6 months after your last dose of study drug. Do not breastfeed during treatment and for 1 week after the last dose of tazemetostat.

What are the costs of taking part in this study?

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

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- Your insurance co-pays and deductibles.

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

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

You or your insurance provider will not have to pay for the tazemetostat while you take part in this study.

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

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay: If you do not have insurance, then you would need to pay for these medical costs.
If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

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

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

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

Some of these organizations are:

- The study sponsor, NCI-CTEP, and any company supporting the study now or in the future.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research, including NRG Oncology.
- The NRG Oncology Biospecimen Bank-Columbus (Biobank) and laboratories designated by NRG Oncology to perform testing as part of the study.

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.

Where can I get more information?

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

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

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

For questions about your rights while in this study, call the _____ Institutional Review Board at _____.

Optional studies that you can choose to take part in

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

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

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample storage for possible future studies (08/13/2019)

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

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

Unknown future studies

If you choose to take part in this optional study, any remaining samples will be stored. Storing samples for future studies is called "biobanking." The biobank is being run by NRG Oncology and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

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

Right now, we don't know what research maybe be done in the future using your samples. This means that:

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

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

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

1) Your sample will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
2) Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
3) Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. *(For non-US participants, adapt the following two sentences as needed.)* There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/.

How will information about me be kept private?

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

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

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

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

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

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

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

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the biobank know. Then, any sample that remains in the bank will be destroyed or returned to your study doctor. This will not apply to any samples or related information that have already been given to or used by researchers.

What if I have questions about this sample collection?

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

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

Samples for unknown future studies

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

Yes No

Contact for future research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

Yes No

This is the end of the section about optional studies.

My signature agreeing to take part in the Study

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

Participant’s Printed Name _____

Participant’s signature _____

Date of signature _____

Signature of person(s) conducting the informed consent discussion

Printed Name _____

Signature _____

Date of signature _____