Research Study Informed Consent Document

Study Title for Participants: Testing the addition of an anti-cancer drug, entinostat, to the usual chemotherapy and immunotherapy treatment (atezolizumab, carboplatin and etoposide) for previously untreated aggressive lung cancer that has spread

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: P10399, A Phase 1 Study of Entinostat in Combination with Atezolizumab / Carboplatin / Etoposide in Previously Untreated Extensive-Stage Small Cell Lung Cancer (NCT# NCT04631029)

Overview and Key Information

What am I being asked to do?

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

We are asking you to take part in this research study because you have aggressive lung cancer that has spread.

Taking part in this study is your choice.

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

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

Why is this study being done?

This study is being done to answer the following question:

What is the highest dose of entinostat that is safe when taken in combination with carboplatin, etoposide, and atezolizumab in aggressive lung cancer that has spread?

We are doing this study because we want to find out if this approach is safe and tolerable for your aggressive lung cancer that has spread. The usual approach is defined as care most people get for aggressive lung cancer that has spread.

What is the usual approach to my aggressive lung cancer that has spread?

The usual approach for patients who are not in a study is treatment with chemotherapy drugs and drugs that target the immune system (immunotherapy). These drugs are approved by the Food and Drug Administration (FDA) for treatment of aggressive lung cancer that has spread.

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

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

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

If you decide to take part in this study, you will get atezolizumab, carboplatin, and etoposide, for up to 12 weeks. You may also be given entinostat. Then, after 12 weeks you will take entinostat and get atezolizumab for up to 1 year or until the side effects become too severe or your cancer progresses. Atezolizumab may continue beyond one year as part of your usual care if your physician believes this is safe and you are continuing to receive benefit, but this is not part of the study treatment.

After you finish your study treatment, your doctor and study team will watch you for side effects and monitor the status of your cancer. You will be seen 30 days after your last treatment for a clinic visit. After that, you will have the status of your disease checked about every 3 months for the first 2 years and then every 6 months for years 3-5. This means you will keep seeing your doctor for up to 5 years. If your cancer worsens or you start a new treatment, you will enter long-term follow-up. In person visits with the study team are not required, but the study team may reach out to you by telephone or email (if preferred) to see how you're doing if you are no longer seeing your doctor in the same office.

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 drugs may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

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

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

- Anemia which may require blood transfusion
- Nausea, vomiting
- Tiredness
- Bruising, bleeding
- Loss of appetite
- Headache
- Infection
- Pain
- Hair loss

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

Benefits

There is some laboratory and clinical evidence that entinostat may have benefit to patients with various types of cancer. There is some evidence in people with other types of lung cancer that adding entinostat to immunotherapy (therapy that uses substances to stimulate or suppress the immune system) can stabilize cancer for longer than immunotherapy alone. However, we do not know if this will happen in people with small cell lung cancer when entinostat is added to immunotherapy and chemotherapy. It is unlikely that this combination of drugs will help you live longer than the usual approach alone. This study may help the study doctors learn things that may help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.
If you decide to stop, let your study doctor know as soon as possible. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

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

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

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

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: 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 or nurse.

What is the purpose of this study?

The purpose of this study is to test the safety of a drug called entinostat in combination with atezolizumab, carboplatin and etoposide. Entinostat has been tested in animals and in people. Entinostat has also been tested in combination with immunotherapy in people, but the specific combination of drugs used in this study has not been tested in people. This study tests different doses of the drug to see which dose is safer for people. There will be about 36 people taking part in this study.

What are the study groups?

Different people taking part in this study will get different doses of the study drug entinostat in combination with atezolizumab, carboplatin and etoposide. Treatment schedule: You will take entinostat orally once every week for up to 4 cycles. You will take entinostat on an empty stomach, at least 1 hour before and 2 hours after a meal. You will get atezolizumab and carboplatin through a vein in your arm, on day 1 of each cycle, for up to 4 cycles. You will get etoposide through a vein in your arm, on days 1-3 of each cycle, for up to 4 cycles. Some people may not get entinostat during Cycles 1-4. From cycle 5 onwards, you will take entinostat orally once every week and get atezolizumab through a vein in your arm on day 1 of every cycle, for 1 year or until your side effects get severe or your cancer progresses. Each cycle lasts 21 days. See the study calendar for more information.

The first 3 people taking part in this study will get a low dose of entinostat. If the drug does not cause too many serious side effects, the next group of people in the study will get a higher dose. The study doctor will watch each group carefully as they increase the dose. If enough participants have serious side effects, then some participants may not receive entinostat during the first 4 cycles of the study. The dose you are assigned will be based on the side effects of the participants on the study before you.

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

What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- Blood tests to look at the health of your organs done weekly during the first cycle of treatment
- Physical exams and vital signs testing done weekly during the first cycle of treatment
- Electrocardiogram (EKG) before you begin study treatment

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

Your study doctor will need to use some of the tissue left over from your biopsy when you were diagnosed with cancer. This sample is a required part of the study. This sample will be used to look at the genetic information of the tumor and how the immune system may be fighting the tumor. This study will use genetic tests that may identify changes in the genes in your DNA. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer.

Finding these changes would not affect your treatment in this study. However, they could affect your health in other ways. Neither you nor your study doctor will be informed when the genetic sequencing or immune response research will be done. You and your study doctor will not receive reports of these studies, as they are intended for research purposes only and cannot be used to plan treatment.

If there is not enough tissue left over from your biopsy, your study doctor will need to do another biopsy to get this tissue before you begin study treatment. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer. You and your study doctor will not get the results of this testing. If you agree to take part in the study, you may need to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done.

Blood samples will also be taken for the study. The first blood sample will be collected before you begin the study drugs on day 1 of cycle 1. Blood will be collected multiple times on day 1 of cycle 1 and cycle 2. Additional blood samples will be collected on days 2, 8 and 15 of cycle 1, day 2 of cycle 2, and day 1 of cycles 2, 3, 4, 6, and 8, and when your disease gets worse (up to 7 tablespoons).

A patient study calendar is attached at the end of this document. It shows how often these procedures and other procedures that are part of standard clinical care will be done.

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

General Risks

If you choose to take part in this study, there is a risk that the study drugs 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 drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 5 months after you have completed the study.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Genetic Testing Risks

The genetic test used in this study will test your tumor and normal tissue (your blood) for genetic changes. Changes found in your normal tissue may be passed down in families. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down.

Genetic tests of normal tissue can reveal information about you and also about your relatives. You and your study doctor will not receive reports of these studies, as they are intended for research purposes only and cannot be used to plan treatment.

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection, significant bleeding, or collapsing of the lung can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

Blood Draw Risks

Some of the risks from drawing blood from your arm may include pain, bruising, light-headedness, and rarely, infection. For most people, needle punctures to get blood samples do not cause any serious harm. 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. If there is

any blood left over after all of the planned testing is complete, then this could be "banked" for future use in other research studies. This is optional and is described in the section "Optional studies".

Side Effect Risks

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

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

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. 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.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

You should notify your doctor immediately at the first sign of poorly formed or loose stools or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.

Drug Risks

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

Possible Side Effects of MS-275 (SNDX-275, entinostat)
(Table Version Date, September 10, 2018)

COMMON, SOME MAY BE SERIOUS In 100 people receiving MS-275 (SNDX-275, entinostat), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Nausea, vomiting • Tiredness • Bruising, bleeding • Loss of appetite • Headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MS-275 (SNDX-275, entinostat), from 4 to 20 may have:
• Pain • Constipation, diarrhea, heartburn • Swelling of arms, legs • Fever • Infection, especially when white blood cell count is low • Dehydration • Changes in taste • Cough, shortness of breath

RARE, AND SERIOUS In 100 people receiving MS-275 (SNDX-275, entinostat), 3 or fewer may have:
• Rash

Possible Side Effects of Atezolizumab (MPDL3280A)
(Table Version Date, March 11, 2021)

COMMON, SOME MAY BE SERIOUS In 100 people receiving atezolizumab (MPDL3280A), more than 20 and up to 100 may have:
• Tiredness • Infection

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving atezolizumab (MPDL3280A), from 4 to 20 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Difficulty swallowing • Fever • Flu-like symptoms including body aches • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Reaction during or following a drug infusion which may cause fever, chills, rash • Loss of appetite • Pain in back • Cough, shortness of breath, stuffy nose

- Itching, acne, rash

Atezolizumab (MPDL3280A) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.
- Pain in belly
- Pain or swelling of the joints
- Rash that develops on skin, nails, scalp and inside of mouth or vagina that may be painful

RARE, AND SERIOUS

In 100 people receiving atezolizumab (MPDL3280A), 3 or fewer may have:

- Bruising, bleeding

Atezolizumab (MPDL3280A) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: shortness of breath, swelling of the ankles and body.
- A condition with high blood sugar which leads to tiredness, frequent urination or excessive thirst.
- Swelling and redness of the eye
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine.
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin: blisters on the skin, including inside the mouth (can be severe), rash with blisters, skin rash developing 1-8 weeks after a drug is given, which may be accompanied by fever, lymph node swelling and organ failure.

Possible Side Effects of Carboplatin

(Table Version Date: October 23, 2018)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Carboplatin, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Vomiting, nausea • Pain • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Carboplatin, from 4 to 20 may have:
• Visual loss • Diarrhea, Constipation, belly pain • Changes in taste • Numbness and tingling in fingers and toes

RARE, AND SERIOUS In 100 people receiving Carboplatin, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Possible Side Effects of Etoposide
(Table Version Date: January 31, 2020)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Etoposide, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Nausea, vomiting • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Etoposide, from 4 to 20 may have:
• Seizure • Blurred vision with chance of blindness • Diarrhea, loss of appetite • Difficulty swallowing • Swelling and redness at the site of the medication injection

RARE, AND SERIOUS In 100 people receiving Etoposide, 3 or fewer may have:
• Liver damage which may cause yellowing of eyes and skin, swelling

RARE, AND SERIOUS In 100 people receiving Etoposide, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Stevens-Johnson syndrome which may cause severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Cancer of bone marrow caused by chemotherapy

Additional Drug Risks

The study drug could interact with other drugs. Ask your study doctor before starting any new medications. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. 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.

What are my responsibilities in this study?

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

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

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby or donate sperm while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 5 months after your last dose of study treatment.

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.
- the costs of getting the atezolizumab, carboplatin and etoposide
- the costs of getting the entinostat, atezolizumab, carboplatin and etoposide ready and giving them to you.

- the EKG in this study done before you begin study treatment
- your insurance co-pays and deductibles.

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

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

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- The biopsy for looking at genetic information in the tumor and your body's immune response to the tumor at the beginning of the study (required if there isn't enough tissue left over from your standard of care biopsy), and if and when your disease worsens (if you agree to the optional sample collection at this time).
- The research blood collections and analysis to look at your genetic information, your body's immune response to the tumor, and your body's use of the study drugs on day 1 of cycles 1, 2, 3, 4, 6 and 8; day 2 of cycles 1 and 2; days 8 and 15 of cycle 1; and if and when your disease worsens (if you agree to the optional sample collection at this time).

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

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

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

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

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

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

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

Some of these organizations are:

- The study sponsor and any company supporting the study agent now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.

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 some research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

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

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

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

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

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 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 you or your study doctor will not know the results.

Taking part in these optional studies 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 these 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 collections for known laboratory studies and/or storage for possible future studies

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

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

Known future studies

If you choose to take part in this optional study, researchers will collect your tumor tissue for research on evaluating the changes in your DNA and RNA that occur during treatment. Researchers will obtain genetic material (DNA and RNA) from your tumor cells. Your DNA and RNA will be used for genomic sequencing, which is sequencing of all or part of your DNA. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. This is usually done to look for changes in your genome that may cause health problems. The genomic sequencing will be done by an NCI-supported laboratory in Frederick, Maryland, known as the National Clinical Laboratory Network (NCLN) Genomics Laboratory at the Frederick National Laboratory for Cancer Research. The laboratory will compare the genomic sequences from your tumor and blood cells to identify how they differ. The differences between genomic sequences of your tumor and blood cells may be important to understand why you did or did not respond to the treatment you received.

Similarly, your tumor tissue and blood would be used to look at your body's immune response to the tumor before and during treatment. For both the genetic research and the immune response research, researchers hope to find changes present in tumor tissue that predict how patients with your type of cancer may respond to current or future treatments. These optional studies may improve the ability to select future treatments or treatment combinations for others in the future. This optional study will not affect the cancer treatment or approach that you receive.

Neither you nor your study doctor will be informed when the genetic sequencing or immune response research will be done. You and your study doctor will not receive reports of these studies, as they are intended for research purposes only and cannot be used to plan treatment.

Unknown future studies

If you choose to take part in this optional study, any of your tumor tissue or blood samples left over from the genomic sequencing and immune response analysis will be stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Nationwide Children's Hospital in Columbus, Ohio, and is supported by the NCI. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use. Your genomic sequence will also be stored in a secure NIH database for future use. 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.

Right now, we do not know what research may be done in the future using your tumor tissue and

blood 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.
- Future research studies may include genomic sequencing.
- 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 (such as blood) 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. Samples of tissue will be collected from an optional extra biopsy when your disease gets worse. For the biopsy procedure, the study doctor will use a needle to take pieces of your tumor. This process may be repeated several times in the same appointment in order to get enough tissue.
2. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts.
4. Researchers will not be given your name or contact information.
5. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection, significant bleeding, or collapsing of the lung can occur. The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.

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

How will information about me be kept private?

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

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

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

You will not benefit from taking part.

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

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

There are no costs to you or your insurance for exams, tests, and procedures done for research purposes only; these include the biopsy, blood draw, DNA/RNA sequencing, immune response testing and biobanking of your specimen(s). You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

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

If you decide you no longer want your samples to be used, you can call the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the biobank know. Then, any sample that remains in the biobank will be

destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I need my tissue or blood samples to be returned?

Tumor tissue or blood samples that remain in the biobank can be returned if needed for medically necessary events or procedures to assure appropriate medical care, such as for DNA or RNA analysis. Specimens may also be returned if tissue is needed to determine eligibility for enrollment in a research protocol or clinical trial. Every effort will be made to facilitate medically necessary events or procedures to assure appropriate medical care for a patient with a serious or life-threatening illness.

Tumor tissue or blood samples and genetic material (DNA and RNA) that is no longer in the biobank or that has already been given to or used by researchers cannot be returned. No samples will be returned for matters related to patients needing or wanting genetic testing to determine medically important risks.

What if I have questions about this optional sample collection?

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

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

Samples for known future studies:

I agree that my samples and related health information may be used for the laboratory studies described above.

YES NO

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 signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Patient Study Calendar

1 cycle = 21 days	Pre-Study (before you begin study treatment)	Cycle 1 D1	Cycle 1 D8	Cycle 1 D15	Cycle 2 D1	Cycle 3 D1	Cycyle 4 D1	Cycles 5-17 D1	End of study treatment (C18 or 30 days after you stop taking entinostat)	Follow-up evaluations
Entinostat		A*	A*	A*	A* (Days 1, 8, and 15)	A* (Days 1, 8, and 15)	A* (Days 1, 8, and 15)	A (Days 1, 8, and 15)		
Atezolizumab		B			B	B	B	B	B (if your doctor indicates it is necessary, this is not part of the study treatment)	B (if your doctor indicates it is necessary, this is not part of the study treatment)
Carboplatin, Etoposide		C			C	C	C			
Pre study procedures including Informed consent, demographics, medical history, height, and an assessment of how you perform everyday tasks and activities	X									
Concurrent meds, physical exam, vital signs	X	X	X	X	X	X	X	X	X	
Weight	X	X			X	X	X	X	X	
Blood draws for complete blood count and general health status	X	X	X	X	X	X	X	X	X	
Thyroid tests	X	X			X		X	X (Day 1 of every even cycle)	X (Day 1 of every even cycle)	
EKG (as your doctor indicates is necessary)	X									
Side effects evaluation		X	X	X	X	X	X	X	X	
Medical imaging scans for	X	Tumor measurements are repeated every 6 weeks for year 1.							Tumor measurements are repeated every 3 months for year 2, then	

1 cycle = 21 days	Pre-Study (before you begin study treatment)	Cycle 1 D1	Cycle 1 D8	Cycle 1 D15	Cycle 2 D1	Cycle 3 D1	Cycyle 4 D1	Cycles 5-17 D1	End of study treatment (C18 or 30 days after you stop taking entinostat)	Follow-up evaluations
tumor measurements									every 6 months thereafter, or as your doctor indicates it is necessary	
Follow up to check on the status of your disease									If you are no longer coming to the study site, study staff will call or email to check overall survival every 3 months for 2 years, then every 6 months for years 3-5.	
Pregnancy test (for women of child-bearing potential only)	X									
Tissue collection from a previous biopsy or surgery for research purposes	X									X
Tumor biopsy[D]	X									
Tumor biopsy (optional)										x
Blood collection for research purposes		X	x	x	X	X	X	x[E]		X

A: Entinostat: Dose as assigned; Days 1, 8, and 15 of each cycle. Take on an empty stomach, at least 1 hour before and 2 hours after a meal.

* If necessary, you may not start entinostat until cycle 5.

B: Atezolizumab: Dose as assigned; Day 1 of each cycle

C: Carboplatin, etoposide: Dose as assigned; Carboplatin Day 1, Etoposide Days 1-3, cycles 1-4

D: Tissue biopsy is not required if tumor tissue from your previous biopsy is available.

E: Day 1 of Cycles 6 and 8.