Research Study Informed Consent Document

Study Title for Participants: Testing a new combination of anti-cancer immune therapies, Atezolizumab and CDX-1127 (Varlilumab) with or without the addition of a third anti-cancer drug, Cobimetinib, for advanced-stage biliary tract cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10476, "A Randomized Phase 2 Study of combination Atezolizumab and CDX-1127 (Varlilumab) with or without addition of Cobimetinib in Previously Treated Unresectable Biliary Tract Cancers" (NCT# NCT0494128)

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 bile tract cancer which has grown after being treated with chemotherapy.

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:

How do any good and bad effects of using two types of anti-cancer therapies that target your immune system, atezolizumab and CDX-1127 (varlilumab), with or without the addition of a third anti-cancer drug called cobimetinib compare?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your biliary tract cancer. The usual approach is defined as care most people get for bile duct cancer.

What is the usual approach to my biliary tract cancer?

The usual approach for patients who are not in this study is treatment with more chemotherapy (FDA-approved), radiation, or have care focused exclusively on treating cancer symptoms (comfort care). If you have changes in your genes, including but not limited to changes in a gene called FGFR, your study doctor will inform you of any other available treatment options in addition to the usual treatment or this study. Your doctor can explain which may be best for you. These treatments can reduce symptoms and/or may stop the tumor from growing for several months or more.

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 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 either get three study drugs (atezolizumab, CDX-1127 [varlilumab], and cobimetinib), or you will get two-study drugs (atezolizumab and CDX-1127 [varlilumab]). You will continue to take your assigned study drugs until your disease gets worse, the side effects become too severe, your doctor believes it is no longer safe for you, or you want to discontinue the study drugs.

After you finish your study treatment, your doctor will continue to follow your condition every 3 months until the study closes, or you withdraw consent, and watch you for side effects.

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.

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:

- Diarrhea, nausea, vomiting
- Tiredness
- Swelling of the body
- Rash
- Infection
- Itching, rash

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

Benefits

It is not possible to know now if the study drugs will control your cancer more or extend your life further when compared to the usual approach. This study will help the study doctors learn things that will help 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. It's 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.

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 (the 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 a novel combination of anti-cancer medications that we hope will boost your immune system's ability to find and fight your cancer, called immunotherapy. Specifically, this study will evaluate any good and bad effects of using a combination of two types of antibody immunotherapies, atezolizumab and CDX-1127 (varlilumab), with or without another anti-cancer drug called cobimetinib.

Atezolizumab and CDX-1127 (varlilumab) together could help to shrink your cancer. Adding cobimetinib to atezolizumab and CDX-1127 (varlilumab) could help to shrink your cancer further, but it could also cause extra side effects, which are described in the risks section below. This study will allow the researchers to know whether atezolizumab and CDX-1127 (varlilumab) plus cobimetinib is better, the same, or worse than using the combination atezolizumab and CDX-1127 (varlilumab) alone.

The drugs, atezolizumab and cobimetinib, are already FDA-approved for treating other cancers, but they have not been studied in this kind of cancer. CDX-1127 (varlilumab) is another type of immunotherapy that is still in clinical trials and is not currently FDA-approved for biliary or other cancer types.

Another purpose of this study is for researchers to learn more about how the study drugs might affect the immune system to help fight your cancer.

Sixty-four people are expected to take part in this study.

What are the study groups?

This study has 2 study groups. You will be told which group you are in.

- **Group A**

  If you are in this group, you will get the study drugs atezolizumab, CDX-1127 (varlilumab), and cobimetinib. You will first get atezolizumab through a vein in the arm for 30 to 60 minutes and then you will get CDX-1127 (varlilumab) through a vein in the arm for 90 minutes every two weeks (on Days 1 and 15 of each cycle). You will take cobimetinib as a pill by mouth once a day at the same time each morning, with or without food on Days 1-21 of each cycle. On Days 1 and 15 of each cycle, you should take your cobimetinib before you receive your infusion of atezolizumab, CDX-1127 (varlilumab). If you are unable or forget to take your dose of cobimetinib in the morning/prior to your infusion, please still take that dose as long as it is within 4 hours of your regularly scheduled time of taking the cobimetinib. If you are unable to take your cobimetinib within 4 hours of your usually scheduled time, you should consider that day's dose missed. You should not take cobimetinib and you should resume your normal schedule and dose the next scheduled day. You should not make up the missed dose(s). Each cycle lasts 28 days. See the study calendar for more information.

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.

You will not be able to get additional doses of the study drugs, atezolizumab, CDX-1127 (varlilumab), and cobimetinib. These drugs are not approved by the FDA for treatment of your disease.

There will be about 32 people in this group.

- **Group B**

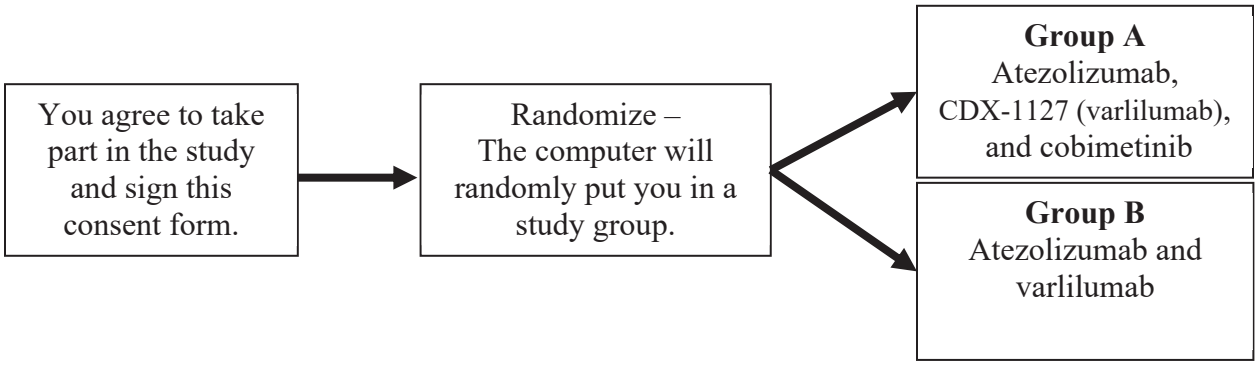
  If you are in this group, you will get the study drugs, atezolizumab and CDX-1127 (varlilumab). You will first get atezolizumab through a vein in the arm for 30 to 60 minutes and then you will get CDX-1127 (varlilumab) through a vein in the arm for 90 minutes every two weeks (on Days 1 and 15 of each cycle). Each cycle lasts 28 days. See the study calendar for more information.

  You will not be able to get additional doses of the study drugs, atezolizumab, and CDX-1127 (varlilumab). These drugs are not approved by the FDA for treatment of your disease.

  There will be about 32 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group A or Group B.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



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.

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests and procedures that you will need to have if you take part in this study.

Before you begin the study, you will need to have the following extra tests to find out if you can be in the study:

- Blood tests
- Ultrasound of the heart (echocardiogram)
- An eye exam
- A pregnancy test
- CT scan

During the study:

- Blood tests every month
- CT scan of abdomen every 8 weeks
- If you are in Group A:
  - A test of the electrical activity of your heart (EKG) before you start the study, 2 weeks after you start, once a month for 3 months, and then every 3 months, or more often if medically needed
    - Ultrasound of the heart (echocardiogram) at 1 month, then every 3 months, while on cobimetinib
- If you are in Group A: An eye exam every 2 months for 1 year, then every 6 months, while on cobimetinib

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. You and your study doctor will not get the results of this testing.

- You will also need to have two mandatory biopsies taken for the study. The first biopsy will be taken before you begin study treatment and the second one will be taken on Day 21 of Cycle 1 of the study. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer. Researchers want to see how the study treatments affect the tumor and the strength of your body's immune cells fighting the 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.

- You will also need to have mandatory blood samples taken for the study. The first blood sample will be taken before you begin study treatment. You will have additional blood samples taken on Day 1 of Cycles 1-6, 9 and 12 and Day 15 of Cycles 1 and 2 (before you start receiving atezolizumab and CDX-1127 (varlilumab) and 30 minutes after you finish receiving your infusion of the second study drug, CDX-1127 [varlilumab]), on Day 21 of Cycle 1 and in Week 12 of the study (at the end of Cycle 3), and when you finish study treatment. The blood samples will be used to monitor how your body's immune system is responding to the study treatment in terms of looking at changes in certain immune cell populations, levels of certain signaling molecules, antibodies, and other metabolites. We will also use these samples to see if your cancer has certain characteristics (e.g. mutations) that will help us understand how to better treat this disease in the future. Lastly, we will also be taking blood samples to monitor levels and clearance of the atezolizumab and CDX-1127 (varlilumab) treatments. You and your study doctor will not get the results of this testing.

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 or condition 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 study 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 150 days (about 5 months) after you have completed the study. This applies to both male and female participants.

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 can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

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 make it hard for you to have children.
4. 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.

Study Group A and Group B – Possible side effects of atezolizumab and CDX-1127 (varlilumab) are listed in the tables below.

Possible Side Effects of Atezolizumab (MPDL3280A)
(Version 2.4, September 14, 2023)

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.
- Damage to organs in the body when the body produces too many white cells
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck.
- Abnormal movement of the facial muscles
- Swelling of the spinal cord
- 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 CDX-1127 (Varlilumab)
(Table Version Date: September 14, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving CDX-1127 (varlilumab), more than 20 and up to 100 may have:
• Tiredness • Itching, rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving CDX-1127 (varlilumab), from 4 to 20 may have:
• Anemia which may require blood transfusion

• Diarrhea, nausea, vomiting • Chills, 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 • Headache

RARE, AND SERIOUS In 100 people receiving CDX-1127 (varlilumab), 3 or fewer may have:
• Fluid around heart • Blurred vision, watering eyes • Dry eye • Seeing spots before eyes • Damage to the liver • Kidney damage which may require dialysis • Numbness, tingling or pain of the arms and legs • Feeling of "pins and needles" in arms and legs • Damage to the lungs which may cause shortness of breath • Skin changes

Study Group A - In addition to side effects listed above, people who are in Group A may also have some side effects from cobimetinib. These side effects are listed below.

Possible Side Effects of Cobimetinib
(Table Version Date: March 25, 2020)

COMMON, SOME MAY BE SERIOUS In 100 people receiving cobimetinib (RO5514041, GDC0973), more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Swelling of the body • Rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cobimetinib (RO5514041, GDC0973), from 4 to 20 may have:
• Anemia which may require blood transfusion • Blurred vision or blindness, visual loss • Seeing flashing lights • Seeing spots before eyes

- Sores in the mouth which may cause difficulty swallowing
- Chills, fever
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Change in heart function
- Loss of appetite, dehydration
- Dizziness, headache
- Dry skin
- Increased risk of sunburn
- Itching, acne
- Bleeding

RARE, AND SERIOUS

In 100 people receiving cobimetinib (RO5514041, GDC0973), 3 or fewer may have:

- Damage to organs (heart, lungs) which may cause shortness of breath, swelling of ankles, and tiredness
- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Blood clot which may cause blurred vision or blindness
- Damage to muscle which may cause muscle pain, dark red urine
- A new cancer unrelated to an earlier cancer

Additional Drug Risks

The study drug could interact with other drugs and food. Your doctor will go over all your medications before you start the study. You will be asked to stop taking any herbal medicines, other chemotherapies, immunosuppressive drugs, some antibiotics, and other medications that may interact with the study drugs. In particular, certain medications can affect how one of the study drugs, cobimetinib (Group A), is used by your body. Examples of these interacting medications include (but are not limited to) clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, verapamil, carbamazepine, efavirenz, phenytoin, rifampin, and St. John's Wort. If you are taking one these interacting medications, you may be asked to switch to an alternative or stop if deemed safe by your doctor. In some cases where you would need to take a medication that could interact with cobimetinib for just a short amount of time, your study team may need to change the dose of your cobimetinib during that time. Your study doctor will give you a wallet card that lists the study drugs. 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 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 150 days (about 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 blood test before you begin study treatment to see if your cancer has certain characteristics (e.g. mutations)
- the cost of getting the study drugs, atezolizumab, CDX-1127 (varlilumab), and cobimetinib ready and giving them to you.
- 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 blood clot test before each study biopsy.
- The biopsy for research purposes before you begin study treatment and at Day 21 of Cycle 1.
- The blood collection for research purposes before you begin study treatment: Days 1 of Cycles 1-6, 9 and 12; Day 15 of Cycles 1 and 2; Day 21 of Cycle 1; Week 12 of the study (at the end of Cycle 3).

You or your insurance provider will not have to pay for the atezolizumab, CDX-1127 (varlilumab), or cobimetinib 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 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 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, 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 this 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 these studies is your choice. You can still take part in the main study even if you say "no" to these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these studies. If you sign up for, but cannot complete these studies for any reason, you can still take part in the main study.

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

Optional sample collections for 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.

Unknown future studies

If you choose to take part in this optional study, tissue and blood will be collected and stored. Storing samples for future studies is called "biobanking." These respective biobanks are run by Emory University and Johns Hopkins University. 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 may be done in the future using your blood and/or tumor 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?

- 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. 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 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 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

		Cycle 1 (28 days)				Cycle 2 (28 days)				Cycles 3+ (28 days)				
	Before you begin study treatment	Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	After you finish study treatment
Atezolizumab[A]		X	X			X	X							
CDX-1127 (varlilumab)[B]		X	X			X	X							
Cobimetinib[C]		X----------X				X----------X				X----------X				
Pre-study [Before you begin the study treatment] procedures including Informed consent, demographics, medical history, and height	X													
Review of all medications that you are taking	X	X				X								
Physical exam	X	X	X			X				X				X
Vital signs	X	X	X			X	X			X	X			X
EKG (Arm A only)[G]		X	X			X				X				
Weight and an assessment of how you perform everyday tasks and activities	X	X				X				X				X
Blood draws for complete blood count and general health status	X	X	X			X	X			X	X			X
Blood draw to test how your blood clots	X			X										
Blood or urine Pregnancy test for women of childbearing potential														
Thyroid tests	X					X				X				X
Blood test to assess muscle damage	X					Group A only				Group A only				
Blood test to check for cancer mutations	X													
Ultrasound to assess the size, shape, and position of your heart	X	1 month after first dose of cobimetinib , then every 3 months while taking cobimetinib												
Eye exam	X	Every 2 months for 1 year, then every 6 months while taking cobimetinib												

		Cycle 1 (28 days)				Cycle 2 (28 days)				Cycles 3+ (28 days)				
	Before you begin study treatment	Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	After you finish study treatment
Side effect assessment		X	X			X	X			X	X			X
Medical imaging scans for tumor measurements	X	Measurements are repeated every 8 weeks.												X
Blood test to detect toxins released from your tumor	X	X				X				X				X
Tumor biopsy for research purposes	X			X										
Blood collection for research purposes		X		X									X[D]	X
Blood collection for research purposes check the level of and behavior study drugs in your blood[E]		X	X			X	X			X[F]				

A: Atezolizumab: administered by a vein in your arm every two weeks.
B: CDX-1127 (varlilumab): administered by a vein in your arm every two weeks after you receive atezolizumab.
C: Cobimetinib: administered by mouth at the same time each morning, with or without food, for the first 21 days of each 28-day cycle. On Days 1 and 15 of each cycle, you should take your cobimetinib before you receive your infusion of atezolizumab and CDX-1127 (varlilumab). If you are unable or forget to take your dose of cobimetinib in the morning/prior to your infusion, please still take that dose as long as it is within 4 hours of your regularly scheduled cobimetinib dosing time. If you are unable to take your cobimetinib within 4 hours of your regularly scheduled time, you should consider that day's dose missed. In this case, you should not take cobimetinib and you should resume your normal schedule and dose the next scheduled day. Do not make up the missed dose.
D: At the end of cycle 3 (week 12 of treatment) only.
E: Blood collections will be done before you begin receiving atezolizumab and CDX-1127 (varlilumab) and 30 minutes after you finish receiving the second drug, CDX-1127 (varlilumab).
F: Cycles 3-6, 9 and 12 only.
G: Patients assigned to Arm A will have an EKG performed before the first treatment, after 2 weeks, monthly during the first 3 months and then every 3 months thereafter or more often as medically needed.