To: CTEP Protocol and Information Office

From: Jibran Ahmed, MD, PhD

Branch: DCTD, NCI

Date: 05/02/2025

Re: Amendment #11 of Protocol #10561: "Rapid Analysis and Response Evaluation of Combination Anti-Neoplastic Agents in Rare Tumors (RARE CANCER) Trial: RARE 3 Tiragolumab + Atezolizumab"

We are responding to the CTEP comments following the disapproval of Amendment #10. TWe are also increasing the accrual ceiling and correcting duration of drug administration inconsistencies and answering comments following Amendment #07. Finally, the patient calendar in the consent form has also been updated. The new protocol version is 05-02-2025.

I. Changes Made by Study PI:

#	Section	Comments
1.	Footer	We updated the Version date to match the protocol.
2.	What is the purpose of this study	We updated the accrual ceiling as proposed in the protocol.
3.	What exams tests& procedures	We clarified which tests will be completed before the patient can receive the study drug.
4.	Patient Study Calendar	We clarified the timing of procedures required to determine patient eligibility for the study, and research procedures to be conducted at baseline. We also updated the maximum infusion duration for Tiragolumab to match the drug administration windows specified in the protocol.

Research Study Informed Consent Document

Study Title for Participants: Testing the combination of anti-cancer drugs atezolizumab and tiragolumab in people with advanced stage rare cancers

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10561, "Rapid Analysis and Response Evaluation of Combination Anti-neoplastic Agents in Rare Tumors (RARE CANCER) Trial: RARE 3 Atezolizumab and Tiragolumab" (NCT# 05715281)

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 an advanced cancer that is considered rare and for which there is no standard treatment.

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:

- Can the combination of the two study drugs, atezolizumab and tiragolumab, make your type of rare cancer stop growing or shrink?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your advanced rare cancer. The usual approach is defined as care most people get for the type of rare cancer you have.

What is the usual approach to my advanced rare cancer?

The usual approach for patients with your type of cancer who are not in a study is treatment with radiation, kinase inhibitor drugs, immunotherapy drugs, or chemotherapy drugs. There are no treatments that are FDA-approved for your health condition or proven to help patients with your health condition live longer, including radiation and chemotherapy.

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 be treated with the study drugs atezolizumab and tiragolumab. The Study Team will monitor your cancer and your safety. You will continue to get doses of atezolizumab and tiragolumab for as long as your cancer does not get worse, the side effects are tolerable, you agree to stay on study, and the study doctor agrees it is still in your best interest to take part in the study.

You may be able to continue treatment with the study drugs if you are experiencing benefits and feeling better, even if tests suggest that your cancer is getting worse. In this case, your doctor will discuss with you whether you meet the criteria for remaining on treatment. However, it is not known at this time if continuing treatment once disease has gotten worse is actually beneficial for you.

After you stop treatment, your doctor will continue to follow your condition for 30 days from your last treatment date or until you start a new treatment. During those 30 days, your doctor will watch you for side effects. This follow up will be a phone call from your study team. Follow up will consist of a telephone call from the Study Team between Day 27 and Day 30 after the last dose of the study drugs.

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 atezolizumab and tiragolumab may not be as good as the usual approach 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:

- Tiredness
- Infection
- Anemia (tiredness from low red blood cell counts)
- Diarrhea, nausea, vomiting
- Difficulty swallowing
- Fever
- Flu-like symptoms including body aches
- Allergic reaction
- Loss of appetite
- Pain in back
- Cough, shortness of breath, stuffy nose
- Itching, acne, rash

Atezolizumab and tiragolumab 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 (e.g., problems with control of metabolism, growth, stress response, blood pressure, sexual organs, pain, temperature, and blood sugar)
- 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
- Damage to organs in the body when the body produces too many white cells

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

Benefits

There is some evidence in people with another cancer that tiragolumab and atezolizumab can shrink or stabilize cancer, but we do not know if this will happen in people with your type of cancer. It is unlikely that this treatment will work in everyone with your cancer or help you live longer. This study may help the study doctors learn things that may help other people in the future.

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

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. our doctor can help you with this. 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:

1) Your health changes and the study is no longer in your best interest.
2) New information becomes available and the study is no longer in your best interest.
3) You do not follow the study rules.
4) For women: You become pregnant while on the study.
5) The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (the National Cancer Institute). 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 good and bad effects of the study drugs called atezolizumab and tiragolumab. Atezolizumab and tiragolumab could shrink your cancer, but it could also cause side effects, which are described in the risks section below. The study doctors hope to learn if the study drugs will improve your immune system's ability to fight the cancer cells in your tumor. We also plan to test the effect of the study drug in the tissue around your tumor, and in your blood.

The combination of atezolizumab and tiragolumab has already been approved by the FDA to treat certain types of lung cancer. The combination has not been approved by the FDA to treat your cancer.

There will be about 25 people taking part in this study.

What are the study groups?

Each person taking part in this study will receive the same dose of the study drugs atezolizumab and tiragolumab.

Treatment will be given in the outpatient setting, so you won't have to stay overnight in the hospital or clinic. You will get atezolizumab and tiragolumab through a vein in your arm over

1–3 hours (followed by observation at the Clinical Center for 1–2 hours) on the first day of each cycle. Each cycle lasts 21 days (3 weeks). See the study calendar for more information.

You will be able to get additional doses of the drugs as long as you stay in the study. These drugs are 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:

- An electrocardiogram (EKG) scan before you begin the study drug and during the study to check your heart
- A pregnancy test in women who are able to become pregnant before you begin the study drug

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

- You will need to have biopsies for the study:
    - The first biopsy will be at the start of the study, before you begin atezolizumab and tiragolumab treatment.
    - The second biopsy will be collected near the beginning of Cycle 3, although it may be earlier if it looks like your cancer is getting better.

  The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer. The purpose of these biopsies is to compare your body's immune response against your tumor before and after treatment with the study drugs. If the first biopsy is unsuccessful or the procedure has caused you harm, the second biopsy will not be done, but you may still remain in the study. You 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.

One optional tumor biopsy may be collected for research purposes if your tumor shrinks or goes away in response to treatment, or if the cancer gets worse or your tumor grows. There is more information about this optional biopsy in the "Optional biopsy collection for known laboratory studies" section near the end of this document.

- You will need to have blood samples collected for the study. The researchers will use the samples to learn more about how atezolizumab and tiragolumab work and which patients in the future might be most likely to respond to atezolizumab and tiragolumab. Each sample will be approximately 1 ½ tablespoons of blood. They will be collected at the following times:
  - At the start of the study, before you begin atezolizumab and tiragolumab treatment.
  - Before each subsequent dose of atezolizumab and tiragolumab (the first day of each cycle).
  - If your cancer gets worse or responds to the treatment.

The blood collected at the start of the study will also be tested to see if there are genetic changes in your cancer cells that are not in your normal cells. Changes found in your normal cells 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. Finding these changes would not affect your treatment in this study. We will not tell you anything we learn about your genes from research done on this study.

A patient study calendar is attached at the end of this document. It shows how often these exams, tests, and procedures 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 atezolizumab and tiragolumab 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.

Atezolizumab and tiragolumab 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 study treatment.

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 (in this case, your blood) for variations in tumor genes that may play an important role in how cancers respond to drugs. 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. The genetic tests used in this study will be done for research purposes only. The researchers will not give you any results from these tests and will not add any of the results to your medical record.

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 study drugs atezolizumab and tiragolumab 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:

- The study doctors do not know who will or will not have side effects. **If you experience diarrhea, it is important that you contact the study doctor immediately, even if the diarrhea is mild.**
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

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

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

This study is looking at a combination of drugs that are not usually used to treat this type of cancer. This different combination of drugs may increase your side effects or may cause new side effects.

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 Atezolizumab (MPDL3280A)
(Table Version Date: November 18, 2024)

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 inflammation and heart failure. Symptoms and signs of heart problem may include: shortness of breath, swelling of the ankle 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 (myositis, rhabdomyolysis), 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.
- Swelling or tenderness of blood vessels

Possible Side Effects of Tiragolumab

(Table Version Date: November 4, 2024)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving tiragolumab (RO7092284), more than 20 and up to 100 may have:

- Tiredness
- Rash

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving tiragolumab (RO7092284), from 4 to 20 may have:

- Anemia which may require blood transfusion
- Pain
- Constipation, diarrhea, nausea, vomiting
- Reaction during or following a drug infusion which may cause fever, chills, low blood pressure
- Bruising, bleeding
- Infection, especially when white blood cell count is low
- Weight loss, loss of appetite
- Numbness, tingling or pain of the arms and legs
- Hair loss, itching

Tiragolumab (RO7092284) 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
- 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

RARE, AND SERIOUS

In 100 people receiving tiragolumab (RO7092284), 3 or fewer may have:

- Prior viral infection that returns
- Damage to the organs (lungs, heart) which may cause shortness of breath
- Cough
- Blisters on the skin

Tiragolumab (RO7092284) 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 inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- A condition with high blood sugar which leads to tiredness, frequent urination or excessive thirst
- Swelling and redness of the eye
- Pain in belly
- Life threatening disorder where the immune system attacks the cells/organs of the body which may cause fever, rash, yellow eyes and skin, shortness of breath, headache, weakness, swollen lymph nodes

- Damage to muscle which may cause muscle pain, dark red urine
- Abnormal movement of the facial muscles
- Inflammation of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck
- 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.
- Swelling or tenderness of blood vessels

Additional Drug Risks

The study drug could interact with other drugs. Your study doctor will give you a wallet card that lists the study agents you are receiving. Share this information with your family members, caregivers, other health care providers, and pharmacists.

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

Imaging Risks

This research study involves exposure to radiation from up to 2 CT scans (used in research biopsy collections). This radiation exposure is not required for your medical care and is for research purposes only.

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

The CT scans that you get in this study will expose you to more radiation than you get from everyday background radiation. The amount of radiation from 2 CT scans is the same as 5 years of background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

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.

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 5 months after your last dose of study drug.

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 rare 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 and tiragolumab ready and giving it 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:

- Biopsies to measure your body's immune response against your tumor before and after treatment with the study drugs
- Blood tests to learn more about how atezolizumab and tiragolumab work and to learn which genes are only in your cancer cell DNA (cfDNA) and not in your normal cells DNA.

You or your insurance provider will not have to pay for the atezolizumab and tiragolumab 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 or the study agents 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.
- The NCI's Experimental Therapeutics Clinical Trials Network and the groups it works with to conduct 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.

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).

For questions about your rights while in this study, call the _____ (insert name of 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 your 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

Optional Study #1: Genomic Sequencing of Biopsies

If you choose to take part in this optional study, researchers will perform genomic sequencing on the mandatory biopsies collected 1) at the start of the study, before you begin atezolizumab and tiragolumab treatment, and 2) near the beginning of Cycle 3.

Your tumor contains genes, which are made up of DNA (deoxyribonucleic acid) and serve as the "instruction book" for the cells that make up our bodies. Genomic sequencing of your tumor tissue will determine the exact order of the DNA building blocks in your tumor DNA. We know that variations in some tumor genes play an important role in how cancers respond to drugs. Determining whether different tumor gene variations affect how atezolizumab and tiragolumab

work against tumors will help scientists understand which patients might respond best to this drug.

The information collected from genomic sequencing of your tumor DNA will be for research purposes only, and we will not give you any individual results from this sequencing or add this information to your medical records.

Optional Study #2: Additional Biopsy Collection for Laboratory Studies

If you choose to take part in this optional study, researchers will collect an extra tumor biopsy when your disease responds to treatment, gets worse or shows signs of getting worse.

- The researchers will use this tumor tissue to measure the effect of the study drugs on your tumor cells and on the immune cells inside of your tumor.
- The researchers will also use this tumor tissue to read the exact order of the DNA and RNA in your tumor cells so that they can learn more about changes in your cancer.

These tests are done for research only. We will not give you any individual results from these tests or add this information to your medical record.

What is involved in this optional sample collection?

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

- If you agree to participate in Optional Study #1 (Genomic Sequencing of Biopsies) a sample of tissue will be collected from the mandatory biopsies collected at the beginning of the study, and near the beginning of Cycle 3.
- If you agree to participate in Optional Study #2 (Additional Biopsy Collection for Laboratory Studies) a sample of tissue will be collected from an extra biopsy at the time that your tumor shrinks or your disease gets worse.
- Your research samples will be stored with a coded identifier, not your name. Any personal data about you will also be stored in a sequence computer database with that code identifier. Your sample will be stored by the researchers until they are used for research or destroyed. There is no limit on the length of time we will keep your samples and research information.
- 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 drawing blood from your arm are brief pain and maybe a bruise.
- Typical risks of biopsy collection include, but are not limited to, bleeding, infection, pain and scarring. There is also some risk associated with radiation exposure if a CT scan is involved in the biopsy procedure.

- 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:

- 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.
- 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.
- Your personal information will not be given to anyone unless it is required by law.
- 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 known future studies, Optional Study #1 (Genomic Sequencing of Biopsies):

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

YES NO

Samples for known future studies, Optional Study #2 (Additional Biopsy Collection for Laboratory Studies):

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

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 **Print name of participant**

_____ _____

Date of signature

_____

Signature of person(s) conducting the informed consent discussion

_____

Print name of person(s) conducting the informed consent discussion

_____

Date of signature

_____

Patient Study Calendar

Day	Patient Activity
Screening visit(s) to see if you are able to receive the study drug	• Check in at the Outpatient Clinic • Meet with your doctor and sign this document • Medical history and physical exam, including ECOG Performance Status (an assessment of how you are doing with your daily living activities) • Echocardiogram and EKG to test your heart • Tumor measurements by CT/MRI or PET • Routine blood tests • A urine test to make sure that your kidneys are working right. • Pregnancy test for women who are able to become pregnant • Meet with your doctor once test results are available to discuss if you are able to receive the study drug
In the 8 days before starting study drug	• Required blood tests for research • Tumor biopsy will be required
Cycle 1 Day 1	• Go to Clinical Center for treatment • Routine blood and urine tests • Atezolizumab will be given in a vein over 1 hour, followed by observation at the Clinical Center for 1-2 hours • Tiragolumab will be given after atezolizumab in a vein in your arm over 1 hour, followed by observation at the Clinical Center for 1-2 hours
Cycle 2 Day 1	• Go to Clinical Center for treatment • Medical history and physical exam • Routine blood and urine tests • Required blood tests to measure the effect of the study drug • Atezolizumab will be given in a vein (about 30 minutes to 1 hour) • Tiragolumab will be given after atezolizumab in a vein in your arm (about 30 minutes to 1.5 hour)
Cycle 3 and onwards, Day 1	• Go to Clinical Center for treatment • Medical history and physical exam • Routine blood and urine tests • Required blood tests to measure the effect of the study drug • Atezolizumab will be given in a vein (about 30 minutes to 1 hour) • Tiragolumab will be given after atezolizumab in a vein in your arm (about 30 minutes to 1.5 hour) • Tumor biopsy will be required at the start of Cycle 3
Cycle 4 and onwards	• Tumor measurement by CT/MRI or PET to measure any changes in the size of your tumors will be performed at the beginning of Cycle 4, and at the end of every 2 cycles after that (less often once you have been on study for >1 year) • *Extra tumor biopsy for Optional Study #1 if your cancer shrinks, gets worse or shows signs of getting worse* • *Total of 2 optional blood collections for Optional Study #2*