

MC1776 / 17-009383

Neoadjuvant Therapy for Patients With High Risk Stage III
Melanoma: A Pilot Clinical Trial

NCT03554083

Document Date: 08/28/2024



Approval Date: August 28, 2024
Not to be used after: August 27, 2025

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Version #: Arm C
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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC1776 Neoadjuvant therapy for patients with high risk stage III melanoma: a pilot clinical trial (NeoActivate) – ARM C

IRB#: 17-009383

Principal Investigator: Matthew S. Block, M.D., Ph.D., Tina J. Hieken, M.D., and Colleagues

Key Study Information

This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision. You should not sign this form if you have any questions that have not been answered.	
It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits, or rights you would normally have if you choose not to take part.
Research Purpose	<p>The purpose of this research is to see if neoadjuvant therapy (treatment given before surgery) with the combination of atezolizumab and tiragolumab is safe and effective for treating newly diagnosed advanced stage melanoma. In addition, we are looking at how atezolizumab given as adjuvant therapy (treatment after the tumor is surgically removed) works to prevent recurrence of melanoma.</p> <p>You have been asked to take part in this research because you have been diagnosed with Stage III melanoma and are planning to have surgery for your cancer.</p>
What's Involved	Study participation involves having treatment before you have surgery (called "neoadjuvant" therapy). You may also have treatment after your surgery (called "adjuvant" therapy). If you choose to take part in this study, you will be given atezolizumab and tiragolumab every 21 days for up to 4 cycles prior to your surgery.



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	<p>If your cancer is completely removed during your surgery, you will have 8 more cycles of atezolizumab every 21 days.</p> <p>You will be asked to provide blood, stool, and tissue for research purposes as part of this study</p>
Key Information	<p>There are alternatives to taking part in this research. The research team will discuss the other treatment options with you.</p> <p>The main risks from this study are due to the drugs being used to treat your cancer. Tiragolumab and atezolizumab are investigational drugs which have not been approved by the FDA for the treatment of melanoma, although the FDA is allowing both drugs to be used in this study.</p> <p>Atezolizumab and tiragolumab are monoclonal antibodies that can affect your immune system. Side effects may occur in any body system or organ at any time. Be sure to tell your doctor if you experience any changes you were not expecting.</p> <p>The risks associated with study participation are completely described later in this form. Be sure to review them carefully.</p> <p>There are no additional costs to you for taking part in this study. The costs are described later in this consent form. Be sure to review them carefully.</p> <p>While our study is research and not guaranteed to offer help, you may benefit from the treatment if it works.</p>
Learn More	<p>If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.</p>



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Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you either a printed or electronic copy of this form to keep. A copy of this form will be put in your medical record.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.



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Contact Information

If you have questions about ...	You can contact ...
<ul style="list-style-type: none">▪ Study tests and procedures▪ Materials you receive▪ Research-related appointments▪ Research-related concern or complaint▪ Research-related injuries or emergencies▪ Withdrawing from the research study	<p>Principal Investigators: [REDACTED]</p> <p>Phone: MN: [REDACTED] [REDACTED]</p> <p>Phone: FL: [REDACTED]</p> <p>Institution Name and Address: Mayo Clinic 200 First St SW Rochester, MN 55905 Mayo Clinic 4500 San Pablo Road Jacksonville, FL 32224</p>
<ul style="list-style-type: none">▪ Rights of a research participant	<p>Mayo Clinic Institutional Review Board (IRB) Phone: [REDACTED] Toll-Free: [REDACTED]</p>
<ul style="list-style-type: none">▪ Rights of a research participant▪ Any research-related concern or complaint▪ Use of your Protected Health Information▪ Stopping your authorization to use your Protected Health Information▪ Withdrawing from the research study	<p>Research Participant Advocate (RPA) (The RPA is independent of the Study Team) Phone: [REDACTED] Toll-Free: [REDACTED] E-mail: [REDACTED]</p>
<ul style="list-style-type: none">▪ Billing or insurance related to this research study	<p>Patient Account Services Toll-Free: [REDACTED]</p>



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Other Information:

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.

A description of this research study will be available on <http://www.clinicaltrials.mayo.edu>. This website will not include information that can identify you. You can search this website at any time.

Why are you being asked to take part in this research study?

You are being asked to take part in this research study because you have been diagnosed with Stage III melanoma and you are planning to have surgery.

About 66 people will take part in this research study at Mayo Clinic. About 36 people will take part in this portion of the research study (Arm C).

Why is this research study being done?

This study is being done to see if neoadjuvant therapy (therapy given before surgery) with tiragolumab and atezolizumab is safe and effective for treating newly diagnosed advanced stage III melanoma. Additionally, we will be looking at how atezolizumab works as adjuvant therapy (therapy given after your tumor has been removed) in preventing recurrence of your melanoma.

Atezolizumab and tiragolumab are not approved by the FDA to treat melanoma. The combination of atezolizumab and tiragolumab is approved for treatment of other tumor types. The FDA has allowed the use of these drugs in this study.

Information you should know

Who is Funding the Study?

This study is being funded by Stand Up 2 Cancer (SU2C) Foundation through the American Association for Cancer Research (AACR); by Genentech, Inc.; and by the Mayo Clinic Comprehensive Cancer Center.



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Information Regarding Conflict of Interest:

Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her responsibilities for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study.

How long will you be in this research study?

You will receive treatment on this study for up to three months prior to your surgery to remove your melanoma tumor, and for up to six months after your surgery. Once you stop taking the study medications, you will need to return every three months for up to 3 years to see if your cancer comes back. After all other phases of the study are completed; we would like to keep track of your health for up to five years after you start this study.

What will happen to you while you are in this research study?

Before beginning research activities, you will be asked to sign this consent form.

Before starting the study drug, you will participate in a screening period. The screening period will help the study doctor find out if you are eligible to enter the study. You will need to have the following exams, tests, or procedures as part of your standard clinical care to find out if you can be in the study.

Prior to starting this study

- Physical exam including complete medical history, height, weight, and vital signs (blood pressure, temperature, pulse)
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood and urine tests
- Pregnancy test if you can become pregnant
- Imaging with PET/CT or CT and/or MRI of chest, abdomen, and pelvis
- Consultation with surgeon
- Biopsy of your melanoma to obtain tissue to determine whether your tumor is BRAF mutant (BRAFM) or BRAF wildtype (BRAFWT) and to place a marking clip in your tumor
- Electrocardiogram (ECG)



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These exams, tests or procedures are part of regular clinical care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This decision will be up to the Principal Investigator.

You will also have the following required tests, which are part of the research study:

- Research blood tests (70ml or about 5 tablespoons)
- Submission of stool samples and swabs for cheek cells and skin cells for microbiome studies
- Submission of research tissue samples (taken during your biopsy)

Neoadjuvant treatment

If you are eligible for this study, you will start treatment. Treatment is given in cycles. In this study the preoperative treatment cycles are 21 days long. You will receive up to four cycles of treatment prior to surgery. This treatment prior to surgery is called “neoadjuvant” therapy.

All patients will receive atezolizumab and tiragolumab. Atezolizumab and tiragolumab are both given through a vein in your arm or hand or central port if you have one. Prior to surgery, you will receive atezolizumab and tiragolumab about once every three weeks for up to four cycles.

Surgery

After you finish one-four 21-day cycles you will be scheduled for surgery as part of regular cancer care. We will ask you to provide a stool sample using a kit for microbiome testing and blood samples (about 3.5 tablespoons) prior to surgery. And we will collect tissue removed during your surgery to use for research. Once your surgery is completed, you will be told whether they were able to completely remove the cancer or you still have residual disease, and about the effect of the neoadjuvant treatment on the tumor.

Adjuvant treatment

After you have recovered from surgery, if you have residual disease, you will go to observation for clinical follow-up for up to 3 years. You will not receive any additional treatment as part of the clinical trial.

Postoperative treatment cycles are 21 days (3 weeks) long. If your disease was completely removed with surgery, you will restart treatment with atezolizumab for up to eight (21 day) cycles (six months). You will receive atezolizumab into a vein on Day 1 of each 21-day cycle.

You will have routine imaging at the end of your fourth and eighth cycles of treatment. We will ask you to collect a research stool sample using a kit and we will collect research blood samples (about 3.5 tablespoons) at the end of your last cycle of treatment.



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Observation

Once you finish treatment with atezolizumab, you will enter observation. During this phase you will return to be seen in the clinic every 3 months for up to 3 years after you started the study. You will have exams, blood testing, and imaging to see how your cancer is doing. We will also collect research blood samples (about 3.5 tablespoons) at each visit.

Table of Events for Neoadjuvant Treatment and Surgery

Timing	What will happen
Pre-Study	<ul style="list-style-type: none">• Routine tests and exams• Routine pregnancy test if you can become pregnant• Routine imaging of your cancer• Routine blood testing for coagulation• Biopsy of your melanoma including placement of a clip to mark the tumor
Prior to starting treatment	<ul style="list-style-type: none">• Routine blood tests and exams including thyroid testing and Epstein-Barr virus (EBV) testing and electrocardiogram (ECG)• Routine pregnancy test if you can become pregnant• Research blood samples (about 5 tablespoons)• Research tissue from previous biopsy or surgery• Research stool sample and cheek and skin swabs
Neoadjuvant Cycle 1, Day 1	<ul style="list-style-type: none">• Receive atezolizumab through a vein for about 1 hour, then wait for about an hour to see how you are doing• Receive tiragolumab through a vein for about 1 hour, then wait for about an hour to see how you are doing
Cycle 1, Days 23-28	<ul style="list-style-type: none">• Routine blood tests and exams• Research blood samples (about 5 tablespoons)
Cycles 2-4, Day 1	<ul style="list-style-type: none">• Receive atezolizumab through a vein for about half an hour if no issues in first cycle or about an hour if there were concerns in the first cycle then then wait for about an hour to see how you are doing• Receive tiragolumab through a vein for about half an hour if no issues in first cycle or about an hour if there were concerns in the first cycle, then wait for about an hour to see how you are doing
Cycles 2-4, Days 23-28	<ul style="list-style-type: none">• Routine blood tests and exams• Research blood samples (about 3.5 tablespoons)
Prior to surgery	<ul style="list-style-type: none">• Routine tests and exams• Routine blood testing including coagulation, thyroid and cortisol testing• Routine imaging• Research blood samples (about 5 tablespoons)• Research stool sample and cheek and skin swabs



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Timing	What will happen
At time of surgery	<ul style="list-style-type: none">• Research tissue samples (taken during surgery)• Research skin swab (taken by your surgeon)
Post-surgery	<ul style="list-style-type: none">• Recovery for up to 4 weeks• After surgery if your cancer is completely removed you will receive adjuvant treatment• If you have cancer remaining (residual disease) after surgery, you will go to Observation (other treatment off study may be recommended by your doctors)

Table of Events for Adjuvant Treatment (completely resected patients only)

Timing	What will happen
Prior to each treatment	<ul style="list-style-type: none">• Routine blood tests and exams including thyroid testing
Day 1 of each adjuvant cycle	<ul style="list-style-type: none">• Receive atezolizumab through a vein for about half an hour if no issues previously (or about an hour if there were concerns in previous cycles) then then wait for about an hour to see how you are doing
End of 4 th and 8 th adjuvant cycles only	<ul style="list-style-type: none">• Routine imaging• Routine blood tests and exams• Research blood samples (about 3.5 tablespoons)• End of last cycle only: Research stool sample (microbiome)

Table of Events for Observation

Timing	What will happen
Every 3 months for up to 3 years	<ul style="list-style-type: none">• Routine blood tests and exams including thyroid testing• Routine imaging• Research blood samples (about 3.5 tablespoons)
If your cancer comes back	<ul style="list-style-type: none">• Research stool sample (microbiome)• Research tissue samples (optional) – if you have a biopsy

Special Considerations

Because we need to understand how the treatment affects the cancer and your body, we would like to obtain a tissue sample if you do not have surgery or if your cancer comes back (recurrence).

If you do not have surgery, we would like to perform a research biopsy to obtain tissue. You would not have to pay for this biopsy.



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If your cancer comes back and you have another biopsy or surgery as part of your treatment, we would like to request a portion of that tissue. You would not need a new biopsy to obtain this tissue.

Please read the following statements and mark your choices:

1. If I do not have surgery after I have completed neoadjuvant treatment, I am willing to have a biopsy to obtain tissue for research. I understand I will not have to pay for this biopsy:

☐ Yes ☐ No Please initial here: _____ Date: _____

2. If my cancer comes back and I have a biopsy or surgery as part of diagnosis and treatment, I permit Mayo Clinic to obtain a tissue sample from that biopsy or surgery. I understand I will not need another biopsy or surgery to obtain this tissue.

☐ Yes ☐ No Please initial here: _____ Date: _____

What are the possible risks or discomforts from being in this research study?

Risks and side effects of atezolizumab

Very Common (occur in >10% of patients)

- Fatigue
- Cough
- Dyspnea (shortness of breath)
- Diarrhea
- Nausea
- Vomiting
- Decreased appetite
- Headache
- Constipation
- Pyrexia (fever)
- Peripheral edema (swelling in arms and legs)
- Arthralgia (joint pain)
- Back pain
- Rash
- Pruritus (generalized itching)
- Anemia
- Insomnia (difficulty sleeping)
- Urinary tract infection
- Weakness (asthenia)
- Musculoskeletal pain



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Common (occur in 1%–10% of patients)

- Abnormal thyroid function (hypothyroidism, thyroiditis)
- Increases in liver enzymes (ALT/AST) in the blood, which may indicate inflammation of the liver
- Inflammation of the liver (hepatitis) – may have yellowing of eyes or skin
- Decrease in potassium level in the blood (hypokalemia)
- Decrease in sodium level in the blood (hyponatremia)
- Low blood pressure (hypotension)
- Blood creatinine increased (may be a sign of kidney problems)
- Decreased level of platelets in the blood (thrombocytopenia) – may be more prone to bleeding
- Hyperglycemia (high blood sugar levels)
- Dry skin
- Colitis (inflammation of the large intestine)
- Night sweats or chills
- Trouble swallowing (dysphagia)
- Abdominal pain
- Dry mouth
- Stomatitis/nasopharyngitis (sores in or inflammation of the mouth, tongue, lips, or throat)
- Pain in mouth and throat (oropharyngeal pain)
- Hypoxia (shortness of breath)
- Pneumonitis (inflammation of the lungs)
- Chest discomfort or chest pain
- Influenza-like illness (congestion in the lungs and airways, fever, body aches)

Less common but important (occur in less than 1% of patients)

- Adrenal insufficiency – decrease in adrenal gland production
- Diabetes mellitus – may need to take insulin
- Diabetic ketoacidosis – blood sugar goes too low – can cause blackout
- Facial paresis – face may droop on one side
- Guillain-Barré syndrome – immune system attacks peripheral nerves (most people recover fully)
- Hemophagocytic lymphohistiocytosis – life-threatening hyper-inflammatory disorder that attacks multiple organs at once
- Hyperthyroidism – overactive thyroid – may feel anxious, lose weight, eye problems
- Hypophysitis – underactive pituitary gland – may cause problems in many organs
- Meningoencephalitis – swelling in brain and spinal cord
- Myasthenic syndrome/myasthenia gravis – may have muscle weakness
- Myelitis -inflammation of the spinal cord and sheath covering the muscles



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- Myocarditis – inflammation in the heart muscle
- Myositis – inflammation in the muscles
- Nephritis – inflammation in the kidneys
- Pancreatitis (including increase in amylase and lipase) - inflammation in the pancreas
- Psoriatic conditions – scaly rash
- Severe cutaneous adverse reactions – serious rash and destruction of the skin

Symptoms of Infection

Atezolizumab is designed to stimulate the body's cells that help fight tumors and also infections. It is possible that if you get a new infection (like the flu) while on **atezolizumab**, you may get too many inflammatory cells, making you sicker from that infection. It is important to tell your doctor immediately if you develop symptoms of an infection, such as a fever, chills, a stubborn cough, a cough that produces phlegm, persistent diarrhea, burning with urination, red or inflamed skin, or green or yellow discharge from a wound or sore.

Atezolizumab Antibodies

When you take **atezolizumab**, there is a small chance that your immune system might develop special antibodies (proteins made in the body that respond to a substance that is foreign to the body) to **atezolizumab** (hypersensitivity). If you develop these special antibodies, it may affect your body's ability to respond to **atezolizumab** in the future. Blood samples will be drawn to monitor for the development of these antibodies during the course of the study.

Allergic and Infusion-Related Reactions

Atezolizumab may cause side effects, similar to an allergic reaction, that occur while it is being given into your vein or shortly after it is given. These infusion reactions are rare (occurring in <1% of patients), and could include infusion-related reactions and cytokine release syndrome. You may have symptoms such as fever and chills, skin rash, swelling, nausea, vomiting, headache, cold-like symptoms, difficulty breathing, or low blood pressure. These reactions could be mild or severe and might lead to death or permanent disability.

If you experience these symptoms, your physician may slow down, interrupt, or even stop the delivery of atezolizumab into your vein. Your physician may also give you some drugs to treat these symptoms.

For your safety, the physician will monitor you for these events. For example, for the first four infusions (Cycles 1, 2, 3, and 4), you will have your blood pressure, pulse, body temperature, and respiratory rate measured about every 15 minutes during the infusion and 30 minutes after atezolizumab administration is completed. If you are receiving atezolizumab and experience a reaction that could be related to atezolizumab, your physician may stop the infusion, and you may be withdrawn from the study.



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Immune-Related Events

Atezolizumab is designed to increase the number of immune system cells that can fight cancer. These cells may cause inflammation within the tumor, as well as within normal tissue. Therefore, by taking atezolizumab, you may develop a condition in which there is inflammation against a part of your own body (an autoimmune disease). Your doctor will evaluate you for any symptoms of these types of conditions during your study visits.

If you feel sick before a scheduled study visit, you should tell your doctor immediately. Blood samples will be drawn to monitor for certain types of autoimmune diseases during the course of the study.

Common (occur in 1%–10% of patients)

- Immune-mediated pericardial disorders including pericarditis, pericardial effusion and cardiac tamponade (buildup of fluid in the sac surrounding the heart)
- Immune-mediated hypothyroidism (may feel tired, sluggish)
- Immune-mediated hyperthyroidism (overactive thyroid, may have weight loss, nervousness, eye changes)

Rare but Serious risks of atezolizumab (occur in less than 1% of patients)

- Autoimmune diabetes (body does not make enough insulin resulting in high blood sugar)
- Autoimmune pancreatitis (inflammation of the pancreas)
- Pneumonitis (a form of pneumonia in which airways in the lungs become inflamed with connective tissue)
- Colitis (inflammation of the colon or large intestine)
- Sarcoidosis (inflammation of the lymph nodes)
- Immune-mediated myasthenic syndrome, myasthenia gravis (muscle weakness)
- Myositis (inflammation of the muscles)
- Adrenal insufficiency (decreased ability of your glands to produce hormones)
- Changes in visual depth perception
- Gaze palsy (changes in ability to move both eyes in the same direction)
- Hypophysitis (inflammation of the pituitary gland)
- Myocarditis (inflammation of the heart muscle)
- Autoimmune hemolytic anemia (anemia caused by destruction of red blood cells)
- Vasculitis (inflammation of blood vessels)
- Severe cutaneous adverse reactions (SCARs) (inflammation of the skin including Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN))
- Immune-mediated nephritis (inflammation of the kidney)
- Immune-mediated myelitis (may have weakness, paralysis, numbness)



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- Immune-mediated facial paresis (may have numbness, drooping on one side of the face)
- Immune-mediated hepatitis (inflammation of the liver - may have yellowing of the eyes and skin, feeling tired)
- Immune-mediated meningoencephalitis (inflammation in the fluid around the brain and in the spinal cord - may have headache, nausea, vomiting)
- Hemophagocytic lymphohistiocytosis (HLH) including macrophage activation syndrome (MAS) - life-threatening hyper-inflammatory disorder that attacks multiple organs at the same time
- Immune-mediated neutropenia – low levels of white blood cells (neutrophils) which can lead to infection
- Immune-mediated cholangitis – a serious infection of the bile ducts, may have abdominal pain, vomiting, and diarrhea

You might experience some or all of these same side effects. It is also possible that you might experience side effects that are unknown at this time. As is true for any drug, there may be unknown and potentially serious or life-threatening side effects that could occur with atezolizumab.

Once atezolizumab is stopped, it is not known how long the side effects of atezolizumab will last.

Risks and side effects of tiragolumab

When tiragolumab is used alone, the following side effects have been seen:

Infusion-related reactions

The most common side effects of tiragolumab are infusion-related reactions, which occur in more than 10% of patients. These reactions can include fever (pyrexia), chills, anxiety, elevated blood pressure (hypertension), nausea, itching (pruritis), joint stiffness, rash, shortness of breath, temperature intolerance, and wheezing. These reactions can be serious.

Immune-mediated hepatitis

Tiragolumab can be linked with immune-mediated hepatitis, a serious liver condition – if you have pain in your upper right belly and/or unexplained nausea or vomiting, tell your doctor right away.

Embryo-fetal toxicity

Tiragolumab is expected to have adverse effects on pregnancy. Tiragolumab should not be administered to anyone who is pregnant.



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When tiragolumab is given with atezolizumab, the following side effects may occur:

Very Common (occur in more than 10% of patients)

- Belly (abdominal) pain
- Low count of red blood cells (anemia) – may feel tired, weak
- Joint pain (arthralgia)
- Loss of appetite – not feeling hungry, not wanting to eat
- Itching (pruritis)
- Rash
- Trouble sleeping (insomnia)
- Feeling tired (fatigue)
- Low level of sodium in the blood (hyponatremia)

Common (occur in 1-10% of patients)

- Increase in blood levels of enzymes made by the pancreas (amylase and/or lipase increased) – may feel nauseated
- Low levels of electrolytes in the blood (e.g., hypokalemia) – can lead to heart rhythm problems
- Low levels of a type of white blood cells (lymphopenia) – may increase the risk of infection
- Increase in blood levels of liver function tests (e.g., alkaline phosphatase increased)
- Inflammation of the lungs (pneumonia) – may have coughing, shortness of breath, trouble breathing

Rare effects (occur in less than 1% of patients)

- Infusion-related reaction
- Liver problems (hepatitis) – may have pain or bloating in belly, dark urine, pale or clay-colored stools, feel tired, have fever, yellow skin or eyes, loss of appetite, nausea, vomiting, diarrhea
- Rash including blistering rash (pemphigoid) or raised or discolored rash (maculo-papular)
- Increase in blood level of enzymes made by the pancreas (amylase increased) – may feel nauseated

Because tiragolumab affects the immune system, the following immune-mediated adverse effects are possible and have been seen in some patients:

- Immune-mediated hypothyroidism (about 12% of patients) – low levels of thyroid hormones, may feel tired, or sensitive to cold, have dry skin, constipation, or weight gain



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- Immune-mediated hyperthyroidism (less than 6% of patients) – overactive thyroid, may feel nervous, anxious, or irritable, have hyperactivity (inability to stay still), mood swings, difficulty sleeping, diarrhea, or feel tired, or sensitive to heat
- Immune mediated adrenal insufficiency (about 3% of patients) – low levels of cortisol, may feel tired or have muscle weakness, loss of appetite, weight loss, or belly pain
- Immune-mediated hypophysitis (less than 1% of patients) – low levels of pituitary hormones, may have unexplained fatigue, headaches, low levels of sodium (hyponatremia), or low blood pressure (hypotension)
- Immune-mediated diabetes mellitus (less than 2% of patients) – may result in a need for insulin or other medicines
- Immune-mediated pneumonitis (about 3% of patients) – may have coughing or shortness of breath
- Immune-mediated pancreatitis including increased levels of amylase and lipase in the blood (less than 5% of patients)– may have nausea, vomiting, fever, diarrhea
- Immune-mediated colitis (less than 2% of patients) – may have fever, diarrhea, blood or mucus in stool, or black, tarry stools, have severe belly pain, bloating
- Immune-mediated meningoencephalitis (less than 1% of patients) – may have headache or trouble thinking
- Immune-mediated severe cutaneous adverse reactions (SCARs) (less than 1% of patients) – severe skin rashes including Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), and drug-reaction with eosinophilia and systemic symptoms (DRESS) which may require hospitalization
- Immune-mediated myositis including rhabdomyolysis (less than 1% of patients) – may have abnormal blood levels of muscle enzymes including creatine kinase
- Immune-mediated ocular inflammatory toxicity (less than 1% of patients) – may have eye pain, temporary inability to see colors, temporary blindness
- Immune-mediated myocarditis (less than 1% of patients) – may have fatigue, chest pain or palpitations
- Immune-mediated nephritis (less than 2% of patients) – kidney problems – may have fatigue, nausea, reduced appetite
- Immune-mediated vasculitis (less than 1% of patients) – fever, weight loss, tiredness, pain, and rash
- Immune-mediated pericardial disorders (less than 1% of patients) – may have chest pain, shortness of breath, fatigue
- Immune-mediated facial paresis (less than 1% of patients) – may have drooping on one side of face
- Immune-mediated neutropenia – low levels of white blood cells (neutrophils) which can lead to infection
- Immune-mediated cholangitis – a serious infection of the bile ducts, may have abdominal pain, vomiting, and diarrhea



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Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), two overlapping syndromes caused by malfunction of the immune system. They may result in widespread inflammation and end-organ damage. There is one known case of reactivation of Epstein-Barr Virus (EBV) with serious consequences. If you have ever had EBV, please inform your doctor. To be safe, you should not take part in this trial if you have ever had EBV.

Other Risks Associated with Participation in this Research Study

Risks of delaying surgery for neoadjuvant (pre-surgical) therapy

Surgery is the standard treatment for stage III melanoma. By participating in this research study, you would delay surgery for your melanoma. While it is believed that the treatments given before surgery will improve the chance of long-term control of melanoma and may make your melanoma easier to resect surgically, it is possible that delaying surgery to allow for pre-surgical treatment may allow your melanoma to grow. If your melanoma grows significantly during the neoadjuvant (pre-surgical) period, there is risk that it may become unresectable.

Pregnancy

Because of the risks related to the study treatments, you will have to take precautions to prevent you or your partner from becoming pregnant while you are in the study. All the agents and procedures can cause harm to an unborn child if given to a pregnant person or to a person who fathers a child.

Because of the possible risks to an unborn child, if you can become pregnant, you will be asked to take a pregnancy test before starting this study. If you are pregnant, you will not be allowed to take part in this study.

You must use birth control during treatment and for 120 days after the last dose. Talk to your doctor about which birth control methods are acceptable.

If you miss a period, or think you might be pregnant during the study, or your partner becomes pregnant while you are on the study, you must tell the Principal Investigator immediately. The Principal Investigator may ask for your permission to collect information about the outcome of the pregnancy and newborn child.

Radiation Risk

You will be exposed to radiation if CT is used to perform the biopsy. You will be exposed to radiation from the PET/CT and CT scans required for your care. The amount of radiation has a low risk of harmful effects.



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If you can become pregnant, you must have a pregnancy test prior to the biopsy.

Blood draws

The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

Biopsies

Biopsies are normally performed under the guidance of an imaging technique, such as ultrasound or CT. Each procedure requires a separate consent prior to the biopsy. The risks may include:

- Pain and discomfort -The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- Minor bleeding at the biopsy site
- Tenderness at the biopsy site
- Scarring at the biopsy site
- Rarely, an infection at the biopsy site

Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

Standard of Care Risks

Your doctor will discuss the risks of these tests and procedures, which are part of regular care for your cancer:

- Imaging with PET/CT, CT, or MRI
- Surgery to remove cancer
- ECG

Risks Associated with Genomic Testing

This study involves testing your DNA, which is the genetic information you inherited from your parents (also known as genetic testing). This testing may include whole genome sequencing (mapping your entire genetic code). You will not be notified of the genetic test results, and they will not be put into your medical record.

Despite the GINA protections and the best efforts of the research team, there may still be a risk if information about you were to become known to people outside of this study.

Genetic information is unique to you, even without your name or other identifiers. For this reason, genetic information like DNA may be used to identify you and possibly your family members. We have procedures (such as, labeling your biospecimens with a password protected code known only to select research staff) to prevent people working with your DNA from discovering if it belongs to you.



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However, there is the risk this can happen as new ways of tracing genetic information are being developed that may make re-identification of genetic information possible.

Genetic Information Nondiscrimination Act (GINA)

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law.

Be aware that this new Federal law doesn't protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Confidentiality Risk

As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

Unforeseeable Risks

Many side effects go away shortly after the study drugs are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death. Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop, and you will be advised whether any additional tests may need to be done for your safety.



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In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time:

- If it is in your best interest,
- If you don't follow the study procedures,
- If the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

What if you are injured from your participation in this research study?

Where to get help:

If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries?

Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments, and coinsurance.

What are the possible benefits from being in this research study?

This study may not make your health better, although we are hopeful that the methods used in this study may be a more effective way to treat your cancer. It is hoped that the information learned from your participation in this study may help other patients with cancer in the future.



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What alternative do you have if you choose not to participate in this research study?

You don't have to be in this study to receive treatment for your condition. Your other choices may include:

- Treatment for your cancer without being on a study: Current options include nivolumab and ipilimumab which are FDA-approved and have shown clinical benefit in the adjuvant treatment of melanoma
- Treatment on a different research study
- No treatment

Talk to the Principal Investigator or your doctor if you have any questions about any of these treatments or procedures.

What tests or procedures will you need to pay for if you take part in this research study?

The study drugs: atezolizumab and tiragolumab will be provided by Genentech, Inc. You will not need to pay for them.

You will not need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Extra biopsy, if needed, to obtain tissue and place a marker clip at baseline
- Research blood tests and research testing on your blood
- Research testing on stool and cheek swabs
- Research testing on tumor tissue

However, you and/or your health plan will need to pay for all other tests and procedures that you would normally have as part of your regular medical care. These tests and procedures include:

- Routine exams, blood, and imaging scans as needed
- Surgery to remove your cancer
- Other drugs or treatments which are given to help you control side effects



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Lazarex Cancer Foundation

Participants in this clinical trial supported by Stand Up to Cancer (SU2C) have access to the IMPACT Patient Reimbursement Program through the Lazarex Cancer Foundation (LCF). This program offers reimbursement to qualifying patients for certain out-of-pocket expenses associated with participation in this clinical trial. If you are interested in applying for assistance, you or the site social worker can email Ryan Noonan, rnoonan@lazarex.org, and/or call LCF directly at (877) 866-9523 to request financial assistance.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the Contact Information section of this form.

Will you be paid for taking part in this research study?

You will not be paid for being in this study.

There is a very small chance that some commercial value may result from the use of your donated samples. If that happens, you won't be offered a share in any profits.

Will your information or samples be used for future research?

Your information and samples will be kept by the Sponsor, Mayo Clinic. The Sponsor can use your data and samples for research purposes as described in the research study. Your data and samples will be kept by the Sponsor in a coded format, which protects your identity. Mayo Clinic may destroy the samples at any time without telling you. We will test your tissue and blood as part of this study. In addition, we will keep your study information and samples for future research. If you agree to give your sample, it will be the property of Mayo Clinic.

In the future, information identifying you may be removed from the information and samples you have provided. After your identifiers are removed, the information and specimens may be used for future research or distributed to another investigator with obtaining additional authorization from you.

Identifying information: Your samples will be stored at Mayo and will be given a code (instead of your name) while they are stored and when they are used in research. This code allows your sample to be used without anyone knowing that it is your sample just by looking at the label.



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Anonymous information from analyses of your coded samples and your coded medical information will be put into databases along with information from the other research participants. These databases will be accessible by the Internet. The purpose of making sequence and medical information available is so that they can be used by scientific researchers to study cancer and other diseases.

Your coded medical information and information from more detailed analyses of your coded samples will be put in a controlled-access database. The information in this database will be available only to researchers who have received approval from Mayo Clinic.

This study may examine the genes you inherited from your parents (genetic testing), as well as the genetic changes within your tumor.

If at any time, genetic results are found to have clinical relevance, IRB review and approval will be sought to notify participants of the results. You will then be contacted and given the choice to learn the test results. At that time, you will be given general information on the potential risks, benefits, and costs of choosing to learn the test results. The risks of learning genetic test results may include emotional upset, insurance or job discrimination, and/or family conflicts from learning unknown information about your parents or blood relatives. Test results will only be put into your medical record if you chose to learn the results. Sometimes results should be released only through a genetic counselor, who can help explain the possible risks and benefits of learning the results.

Exceptions when your data and samples may be used without your permission:

- 1) When government rules allow your data and samples to be used without identifying you, even with a code.
- 2) When use of the sample is not considered human subject research.

To support future research, de-identified genetic information may be placed in databases accessible by the internet. Some of the information may be available to anyone using the internet, and some will be released only to approved researchers. Combined study information (including genomic summary results) may be published, but the information will not identify you.

Even though information traditionally used to identify you will not be shared, people may develop ways in the future to allow someone to link your genetic information back to you. For this reason, confidentiality cannot be guaranteed. It is also possible that re-identified information could be used in discriminating ways, and there could be additional unknown risks. We will make every effort to protect your confidentiality.



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Please read the following statements and mark your choices:

1. I permit my information and samples to be stored and used in future research to learn about, prevent, or treat cancer:

☐ Yes ☐ No Please initial here: _____ Date: _____

2. I permit my information and samples to be stored and used in future research to learn about, prevent, or treat any other health problems (for example causes of diabetes, heart disease, and Alzheimer's, or genetic links to alcoholism):

☐ Yes ☐ No Please initial here: _____ Date: _____

3. I agree to have my coded genetic information and coded medical information placed in password-protected secured databases for research analyses.

☐ Yes ☐ No Please initial here: _____ Date: _____

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

☐ Yes ☐ No Please initial here: _____ Date: _____

You may withdraw your consent for future use of your information and/or samples at any time, by writing to the Principal Investigator at the address provided in the "Contact Information" section of this consent form.

Your information and/or samples would be removed from any repository where they are stored, if possible. Information and/or samples already distributed for research use will not be retrieved. Because we cannot predict how your sample will be used in the future, we cannot promise that samples can be retrieved and destroyed.

It is possible that information identifying your samples or your data could be removed. These samples and data will no longer be linked to you. If that were to happen, the samples and data could be used for future research studies or given to another researcher without asking for your permission.



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How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study.

All of your research samples given to Mayo Clinic will be labeled with a code number and kept in locked storage. Only your study team will be able to link your samples with your identity. No one working with your samples will know your identity. If the results of the research are made public, information that identifies you will not be used.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so.

Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission (or “authorization”) to Mayo Clinic.

Your health information may be collected from:

- Past, present, and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Your health information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was conducted following the approved study plan, and applicable rules and regulations.

Your health information may be used and shared with:

- Mayo Clinic research staff involved in this study.
- Other Mayo Clinic staff involved in your clinical care.
- Researchers involved in this study at other institutions.
- Mayo Clinic, the sponsor of this study, and the people or groups hired by Mayo Clinic to help perform this research.
- The Mayo Clinic Institutional Review Board that oversees the research.



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- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- A group that oversees the data (study information) and safety of this research

How your information may be shared with others:

While taking part in this study, you will be assigned a code that is unique to you but does not include information that directly identifies you. This code will be used if your study information is sent outside of Mayo Clinic. The groups or individuals who receive your coded information will use it only for the purposes described in this consent form.

If the results of this study are made public (for example, through scientific meetings, reports or media), information that identifies you will not be used.

In addition, individuals involved in study oversight and not employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you. However, the individuals will not be allowed to record, print, or copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private, and it may no longer be protected by the Privacy Rule.

Your Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying 'no' will not harm your relationship with your own doctors or with Mayo Clinic.

If you cancel your permission for Mayo Clinic to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.



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You can cancel your permission for Mayo Clinic to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
Plummer Building PL 3-02
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Participant Advocate at: [REDACTED].

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission for Mayo Clinic to use and share your health information lasts forever, unless you cancel it.



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Enrollment and Permission Signatures

Your signature documents your permission to take part in this research.

Printed Name _____ Date / / : AM/PM

Signature _____

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name _____ Date / / : AM/PM

Signature _____