Principal Investigator: Hannah Robinson, MD
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Study Title: A phase II trial of tiragolumab in combination with atezolizumab and bevacizumab in patients with previously treated, microsatellite stable, metastatic colorectal adenocarcinoma.

Key Information

Please read all the information below and ask questions about anything you don't understand before deciding if you want to take part.

You are being asked to be in a research study. Participation in Research is voluntary.

Purpose of the Study: We are doing this study to learn more about how a combination of drugs including tiragolumab, atezolizumab, and bevacizumab work together to treat colorectal adenocarcinoma. The combination of tiragolumab, atezolizumab, and bevacizumab has not been approved by the FDA and is therefore investigational.

Procedures: If you agree to participate, the following will happen: There will be three phases of the study- screening, treatment, and follow-up. For screening, you will be asked to complete a medical record review, performance assessment, blood tests, urinalysis, physical examination, either an MRI or CT scan, and tumor biopsy. For the treatment phase, you will receive the treatment drugs in 21-day cycles and be seen for a treatment visit prior to each cycle, which will include additional screenings and assessments. You will receive atezolizumab intravenously at a dose of 1200mg, bevacizumab intravenously at a dose of 15mg/kg, and tiragolumab at a dose of 600mg on day 1 of each 21-day cycle. You will have an end-of-treatment visit within 35 days of deciding to come off the study. You will also be contacted via telephone calls or clinic visits every 3 months after discontinuing study treatment.

Risks: Participation in research involves risks, including the following:

Most common risks of tiragolumab:
Reactions associated with infusion (infusion-related reaction, events occurring during or within 1 day of infusion); symptoms may include fever, chills, shortness of breath, rash, nausea, and changes in blood pressure.

Most common risks of atezolizumab:
Back pain, cough, decreased appetite, diarrhea, fatigue, fever, headache, itching of the skin (pruritus), joint pain (arthralgia), lack of energy (asthenia), muscle and bone pain (myalgia, musculoskeletal pain and bone pain), nausea, rash, shortness of breath (dyspnea), urinary tract infection, vomiting.

Most Common Risks Associated with Bevacizumab:
Back pain, headache, taste change, dry skin, inflammation of the skin (redness and scaling of the skin), rhinitis (inflammation of the lining inside the nose) and watery eyes, cough, low blood sodium, low blood magnesium, impaired wound healing (following surgery, wound may be slow to heal or may not heal fully), high blood pressure, infections, sepsis, ovarian failure, kidney problems (too much protein in urine), low platelets in blood, low white blood cell count.

Allergic reaction
It is possible to experience serious allergic or infusion-related adverse effects (i.e., possible chills and/or hives) to the study medications, which could become life-threatening or fatal. Symptoms of an allergic reaction may include swelling of the face, tongue, or throat, redness, and warming of the skin, itching, sneezing or runny nose, stomach pain, loose stools, lightheadedness, or fainting, trouble breathing, irregular or racing heart rate.

Immune Reaction
In rare situations, an immune reaction can occur. This reaction can cause side effects related to severe inflammation and/or severe infection. Several organs in your body (for example, liver, kidney, lungs, and bone marrow) may become involved, causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Symptoms may include very low blood pressure that does not respond to standard treatment, very high fever, cough, severe shortness of breath requiring oxygen therapy and/or intubation, severe dizziness, confusion, weakness, decreased urination with failure of the kidneys, abnormal liver function, very low blood cell counts, and/or bleeding within the organs.

Risks of Tumor Biopsies:
Discomfort or pain, bleeding, bruising, infection, damage to surrounding area depending on where the tumor is located. If you have a biopsy from the lung, you could also have something called pneumothorax. This is where air escapes between the lung and the chest wall.

Benefits: There is no guarantee that your health will improve if you join this study. This study may lead to information that could help patients and health care providers in the future.

Alternatives: You may be able to receive any of the treatments in this study without participating in this study. Please discuss standard treatment and care options with your doctor.

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about how a combination of drugs including tiragolumab, atezolizumab, and bevacizumab work together to treat colorectal adenocarcinoma. Atezolizumab is currently FDA-approved for the treatment of several cancers, but is not approved for treatment of colorectal cancer. Bevacizumab is FDA-approved in combination treatments for multiple cancers, including colorectal cancer. Tiragolumab is not FDA-approved for the treatment of colorectal cancer or any other types of cancer. This is considered an 'experimental' study, which means that the combination of tiragolumab, atezolizumab, and bevacizumab has not been approved by the FDA.

Tiragolumab and atezolizumab are antibody medications that activate the immune system by interacting with targets on immune cells and cancer cells (TIGIT, PDL1). Bevacizumab is an antibody medication that targets processes related to cancer blood vessel formation. Clinical trials are evaluating tiragolumab in combination with other medications including atezolizumab and bevacizumab in other types of cancer. The purpose of this study is to learn about the effects of tiragolumab, atezolizumab, and bevacizumab in treating microsatellite stable, advanced or metastatic colorectal cancer.

You are being asked to be in this research study because you have previously been diagnosed with and treated for microsatellite stable, advanced or metastatic colorectal adenocarcinoma.

Other people in this study

Up to 54 people from your area will participate in the study. This study will only be open at the University of Colorado Cancer Center.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care that you receive.

There are three stages of being in the study with different procedures:

- Before starting the study (Screening)
- During the study (Treatment)
- End of study (After treatment follow-up)

There are also optional parts to this study that will be explained later on in this form. You can choose to take part in the main study without participating in these optional procedures.

The next section explains what will be expected of you, and what you can expect if you take part in this study.

Study Procedures and Visits:

Below are the study procedures and schedule of events (when each procedure will take place) for this study. Some procedures are the same as you would receive as standard of care treatment of your disease even if you did not take part in this trial. If you have had some of these procedures recently, they may not need to be repeated. Some procedures are required only for this research study and will be called “research” procedures.

1. Screening (Before Study Treatment)

After you sign this consent form you will have the following done to see if you can be in this study:

- Review your medical and cancer history, including any treatments that you have had. We will record your date of birth, gender, race, and ethnicity.
- Review of any symptoms or side effects that you still have from other cancer treatments.
- Physical examination
- Vital signs including temperature, height and weight, blood pressure, heart rate, respiratory rate, and oxygen status.
- Performance status assessment: We will ask questions about how much activity you can do at home and about any fatigue you may have with those activities.
- Review of medications that you take. Your study doctor will let you know which other medications you can and cannot take while taking part in this study from the time you first receive the study drugs through the time you complete the study and/or start a new cancer treatment. You should tell your study doctor about the medications, supplements, and vitamins that you take.
- EKG (**Research**). This is a simple, non-invasive procedure that records the electrical activity of the heart. Electrodes are placed on the skin of the chest and connected in a specific order to a machine. Output usually appears on a long scroll of paper that shows a printed graph.
- Tumor imaging by CT scan and/or MRI scan with contrast. You may also need additional types of scans to assess your cancer if your doctor recommends them (for example, a whole-body bone scan). If you have already had scans within 4 weeks of signing the consent form, you may not have to repeat these. ○ A CT scan uses x-rays to take pictures of parts of the body and structures inside the body. You will likely need to receive IV contrast with this scan to see the tumors better. ○ An MRI scan uses a magnetic field and pulses of radio waves to make pictures of organs and structures inside the body. You will likely need to receive IV contrast with this scan to see the tumors better. ○ A nuclear bone scan uses an injection of tiny amounts of radioactive material to look at areas in the body that are repairing themselves. The radioactive materials will light up at these sites and can show the presence of cancer deposits in the bones. A bone scan includes the injection and the actual scan.
- Blood tests:
    - Complete blood count (CBC/differential) including types – white blood cells (that fight infection), red blood cells (that carry oxygen) and platelets (that help blood clot) **(Standard of Care)**

  - Comprehensive serum chemistry panel, magnesium, and phosphorus **(Standard of Care)**
  - Thyroid tests (free T3, free T4 and TSH) **(Standard of Care)** ○ Tests for viral infections: HBsAb, HBsAg, Total HBcAb, HBV DNA, Hep C antibody, HCV RNA, HIV, EBV VCA, Nuclear antigen IgG, and EBV PCR) **(Research)** ○ Blood clotting tests (aPTT, PT/INR)(Standard of Care)
  - Pregnancy test (if you are a person who is able to bear children)(Standard of Care)Peripheral blood samples (Research)
  -
- Urinalysis (Standard of Care)
- Tumor biopsy (**Research**). There are two treatment groups (cohorts) in this study. If you are assigned to Cohort A, you will receive a research tumor biopsy prior to starting study treatment. You will also receive a tumor biopsy after you start study treatment, as discussed below. If you are assigned to Cohort B, you will not receive any tumor biopsies. If you are assigned to Cohort A and receive a tumor biopsy, your doctors will work with you to determine the best tumor spot to biopsy. If your doctor does not feel it is possible to safely obtain a biopsy and/or if you are unwilling to have a biopsy performed, you will not be permitted to enroll in Cohort A of this study.
  - The biopsy will most likely be a core biopsy. In a core biopsy, a hollow needle is inserted through the skin into the tumor. A small core of tissue is removed using the needle. Depending on the location of the tumor, we may take up to 5 cores of tissue for research. Your doctor may use ultrasound or x-ray equipment to guide the needle to the correct position.
  - The purpose of the tumor biopsy is to learn more about the response of the immune system to the study treatment. This will help researchers understand why the treatment is or is not effective.

2. Treatment (During the Study)

During the Treatment portion of the study, you will receive the study drugs. You will receive the same study drugs regardless of the cohort you are in. You will receive the study drugs in 21-day cycles. You will receive atezolizumab intravenously at a dose of 1200mg on day 1 of each 21day cycle. You will receive bevacizumab intravenously at a dose of 15mg/kg on day 1 of each 21-day cycle. You will receive tiragolumab at a dose of 600mg on day 1 of each 21-day cycle. You will be seen for a Treatment Visit prior to every cycle of treatment.

The following procedures will be done at every Treatment Visit:

- Review of medications
- Review of side effects from the study drugs
- Physical examination
- Vital signs including temperature, weight, blood pressure, heart rate, respiratory rate, and oxygen status.
- Performance status assessment
- Urine pregnancy test (if you are a person who is able to bear children)

- Urinalysis
- Blood tests, including:
    - Complete blood count (CBC/differential) including types—white blood cells, red blood cells, and platelets
    - Comprehensive serum chemistry panel and magnesium
    - Blood clotting tests (PT/INR and aPTT) ○ CEA (tumor marker)
- Treatment with study drugs ○ You will receive the study drugs in 21-day cycles. You will receive atezolizumab intravenously at a dose of 1200mg on day 1 of each 21-day cycle. You will receive bevacizumab intravenously at a dose of 15mg/kg on day 1 of each 21day cycle. You will receive tiragolumab at a dose of 600mg on day 1 of each 21day cycle.

Some procedures will only be done on specific days during the treatment or as needed as determined by your medical team:

- EKGs will be done as needed.
- Certain blood test (amylase, lipase) will be drawn on Cycle 1 Day 1, and thereafter as clinically necessary.
- Thyroid testing (TSH, Free T3, Free T4) will be done on Cycle 1 Day 1, and Day 1 of every 4 cycles thereafter.
- Tumor assessments (CT/MRI scans) will be done every 9 weeks during Treatment.
- Research blood samples (**Research**) will be drawn only on Cycle 1 Day 1 and Cycle 3 Day 1 (or sooner if you stop the study treatment sooner).
- If you are assigned to Cohort A, an additional research tumor biopsy (**Research)** will be performed around the time of Cycle 3 Day 1 of treatment (within 3 days before or after your third round of treatment). This tumor biopsy may be performed sooner if you stop the study treatment sooner.

3. End of Study (After Treatment Ends)

   You may remain on the study for as long as the study treatment is helping you, and you and your study doctor agree that it is safe for you to continue on the study treatment.

   There are several reasons that the study could be stopped early:

   - If there is evidence that the treatment is dangerous to other patients.
   - If there is evidence that the treatment is not effective at treating colorectal cancer.
   - If the drug company decides not to continue providing the study drugs.

   You will be removed from the study if any of the following happen:

   - The treatment is not helping your cancer.
   - You are having side effects that are keeping you from being able to receive the
   - study treatments.
   - You decide not to participate in the study anymore.
   - You are unable to keep appointments and stay on the study schedule.

- You become pregnant.
- You are found to have a new serious medical condition that makes it too dangerous for you to remain on study (for example, a new viral infection).

When you do discontinue the study treatment, we will continue to watch you for safety and side effects. You will have an end-of-treatment visit within 35 days of deciding to come off the study. You will also be contacted via telephone calls or clinic visits every 3 months after discontinuing study treatment.

The following procedures will be performed at the end-of-treatment visit:

- Review of medications
- Review of side effects from the study drugs
- Physical examination
- Vital signs including temperature, weight, blood pressure, heart rate, respiratory rate, and oxygen status
- Performance status assessment
- Physical examination
- Urine pregnancy test (if you are a person who is able to bear children)
- Urinalysis
- Tumor assessment (CT/MRI scan). This may not need to be repeated if it was already done in the prior 6 weeks.
- Documentation of any new anti-cancer therapies
- Blood tests, including:
    - Complete blood count (CBC/differential) including types—white blood cells, red blood cells, and platelets
    - Comprehensive serum chemistry panel and magnesium ○ Thyroid tests (TSH, free T3, free T4; **Research**)
    - Blood clotting tests (PT/INR and aPTT)

At any time during the Screening, Treatment, or Follow-Up sections of the study, your study doctor may decide to order additional tests or procedures if needed for your safety or to treat medical conditions.

	Screening	**Treatment Period (21-day cycles)**		**Final Study/ Treatment Discontinuation Visit**	**Survival Follow-Up**
		Cycle 1	**Cycle ≥ 2**		
Day (Window)	**-28 to -1**	**D1**	**D1 (± 2 days)**		**(± 14 days)**
Informed consent	X				
Oncologic history	X				

Demographic data	X				
Medical history	X				
Concomitant treatments	X	X	X	X	
ECOG performance status	X	X	X	X	
Baseline signs and symptoms	X				
Adverse events	X	X	X	X	
Vital signs[i]	X	X	X	X	
Weight	X	X	X	X	
Height	X				
Complete physical examination	X				
Limited physical examination		X	X	X	
12-lead ECG	X	Perform as clinically indicated			
Hematology	X	X	X	X	
Chemistry	X	X	X	X	
Amylase, Lipase		X	Perform as clinically indicated		
Thyroid Testing (TSH, free T3, free T4)	X	X[r]	X (every 4 cycles)		
Coagulation (INR and aPTT)	X	X	X	X	
CEA		X	X		
HIV, HBV, and HCV serologies	X				
EBV serology	X				
Pregnancy Test	X	X	X	X	
Urinalysis	X	X	X	X	
Atezolizumab dosing (every 3 weeks)		X	X		
Bevacizumab dosing (every 3 weeks)		X	X		
Tiragolumab dosing (every 3 weeks)		X	X		

Tumor assessments/RECIST 1.1[z]	X	Every 9 weeks (± 1 week)		X	
Research blood samples		X	X (C3D1)		
Research tumor biopsy	X		X (C3D1)		
Survival follow-up				X	X

What are the possible discomforts or risks?

As with any canc er medication, side effects may occur when taking these study drugs.
While taking part in this study, and being treated with the study drugs, you will be watched carefully for any side effects. Some side effects may go away after you stop taking the study drugs. Some side effects can be long lasting and may never go away or could even lead to **death**.

You should talk to your study doctor about any side effects or discomfort you may have. The study doctor may give you some medicine that will help with some side effects. The study doctor may also interrupt or discontinue the study drugs. You will be notified by your study doctor of any new side effects seen in other patients that occur during the time you are on the study. This may affect you wanting to continue in this research study.

Discomforts or side effects you may experience while in this study include the following:

Risks of tiragolumab:
Several clinical trials evaluating tiragolumab alone and in combination with other cancer medications have been conducted, and several are in process. The most common side effects attributed to tiragolumab in these studies are listed below.

Very common (occurs in more than 10% of patients)

- Reactions associated with infusion (infusion-related reaction, events occurring during or within 1 day of infusion); symptoms may include fever, chills, shortness of breath, rash, nausea, and changes in blood pressure.

Common (occurs in 1%-10% of patients)

- Inflammation of the liver (hepatitis); symptoms may include yellowing of the skin, pain in the stomach area, nausea, vomiting, itching, fatigue, bleeding or bruising under the skin, and dark urine. A fatal case has been reported.

Side Effects Known to Be Associated with Tiragolumab When Used in Combination with Atezolizumab

Very common (occurs in more than 10% of patients)

- Decreased level of red blood cells in the blood (anemia)
- Joint pain (arthralgia)
- Decreased appetite
- Itching of the skin (pruritus)
- Rash

Common (occurs in 1%-10% of patients)

- Abnormal pancreatic enzyme test (amylase increased and lipase increased)
- Increase in certain liver enzymes, which may indicate inflammation of the liver (blood alkaline phosphatase increased)
- Decreased level of potassium in blood (hypokalemia)
- Infection of the lung (pneumonia)
- Stomach area pain (abdominal pain)

Side Effects Potentially Associated with Tiragolumab

It is possible that your immune system may cause inflammation in your tumor but also in the healthy parts (normal tissue) of the body. Doctors call these immune-mediated side effects, as your immune system is working against your own body. Immune-mediated side effects, as seen with other drugs stimulating the immune system (for example, atezolizumab) may affect all parts of the body, including (but not limited to) the nervous system, skin or mucous membranes, eyes, gut, hormone system, heart, pancreas, kidneys, lungs, muscles, blood vessels, and blood cells.

This can cause damage to the normal tissue. For signs and symptoms associated with possible tissue damage, please refer to the sections describing immune-mediated side effects with atezolizumab.

Risks of atezolizumab:

Atezolizumab is FDA approved to treat certain types of cancer. Known risks/ possible side effects are outlined below.

Very common (occurs in more than 10% of patients)

- Back pain
- Cough
- Decreased appetite
- Diarrhea
- Fatigue
- Fever
- Headache

- Itching of the skin (pruritus)
- Joint pain (arthralgia)
- Lack of energy (asthenia)
- Muscle and bone pain (myalgia, musculoskeletal pain and bone pain)
- Nausea
- Rash
- Shortness of breath (dyspnea)
- Urinary tract infection
- Vomiting

Common (occurs in 1%-10% of patients)

- Allergic reaction or intolerance to medication (hypersensitivity)
- Chills
- Decreased level of potassium in blood (hypokalemia)
- Decreased level of sodium in blood (hyponatremia)
- Decreased oxygen supply in body resulting in shortness of breath (hypoxia)
- Difficulty swallowing (dysphagia)
- Dry mouth
- Dry skin
- Flu-like illness
- Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine
- Increased blood sugar level (hyperglycemia)
- Increase in certain liver enzymes, which may indicate inflammation of the liver (ALT/AST increased)
- Inflammation of the heart sac, fluid buildup in the heart sac (pericardial disorders)
- Inflammation of the intestines (colitis)
- Inflammation of the liver (hepatitis)
- Inflammation of the lungs (pneumonitis)
- Infusion-related reaction
- Low blood pressure (hypotension)
- Low platelet count in the blood, which may make you more likely to bruise or bleed (thrombocytopenia)
- Mouth and throat pain (oropharyngeal pain)
- Inflammation of the nose and throat (nasopharyngitis)
- Stomach area pain (abdominal pain)
- Underactive thyroid gland (hypothyroidism)

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

- Decreased production of hormones by the adrenal glands (adrenal insufficiency)
- Diabetes mellitus
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis)
- Inflammation of the heart muscle (myocarditis)
- Inflammation of the kidneys (nephritis)

- Inflammation of the pancreas (pancreatitis), including increase in pancreatic enzymes (such as amylase and lipase)
- Inflammation of the pituitary gland (hypophysitis)
- Inflammation of the spinal cord (myelitis)
- Inflammation or damage of the muscles (myositis)
- Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis)
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome)
- Overactive thyroid gland (hyperthyroidism)
- Red, dry, scaly patches of thickened skin (psoriasis)
- Reduced ability to move face muscles (facial paresis)
- Severe high levels of sugar and acids in the blood or urine (diabetic ketoacidosis)
- Severe skin or mucosal reactions (severe cutaneous adverse reactions)
- Build-up of certain white blood cells that may cause organ damage and destruction of other blood cells (hemophagocytic lymphohistiocytosis)

Immune-Mediated Side Effects Include:

- Inflammation of the intestines (colitis); symptoms may include diarrhea, blood in stool, and pain in stomach area
- Inflammation of the thyroid glands (hypothyroidism, hyperthyroidism); symptoms may include headaches, fatigue, weight loss, weight gain, change in mood, hair loss, and constipation
- Inflammation of the adrenal glands (adrenal insufficiency); symptoms may include dizziness, irritability, fainting, low blood pressure, skin darkening, and craving of salty foods
- Inflammation of the pituitary gland (hypophysitis); symptoms may include fatigue and headaches that will not go away, increased thirst, increased urination, and changes in vision ○ Side effects that may occur at the same time include hypothyroidism and adrenal insufficiency (see above for details).
- Inflammation of the liver (hepatitis); symptoms may include yellowing of skin, pain in stomach area, nausea, vomiting, itching, fatigue, bleeding or bruising under the skin, and dark urine
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis); symptoms may include neck stiffness, headache, fever, chills, vomiting, seizure, irritability, and eye sensitivity to light
- Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis/facial paresis); symptoms may include weakness in the arm and leg muscles or face muscles, double vision, and difficulties with speech and chewing
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome); symptoms may include tingling in fingers and toes, fatigue, and difficulty walking
- Inflammation of the spinal cord (myelitis); symptoms may include pain, abnormal sensations such as numbness, tingling, coldness or burning, weakness in the arms or legs, and bladder and bowel problems. These symptoms may develop over a few hours to a few days and may sometimes progress gradually over several weeks.

- Inflammation of the lungs (pneumonitis); symptoms may include new or worsening cough, shortness of breath, and chest pain
- Inflammation of the heart muscle (myocarditis); symptoms may include shortness of breath, decreased exercise tolerance, fatigue, chest pain, swelling of the ankles or legs, irregular heartbeat, and fainting
- Inflammation of the heart sac with buildup of fluid in the sac (in some cases) (pericardial disorders); symptoms are similar to those of myocarditis and may include chest pain (usually over the front of the chest, sharp, and worsened by deep breathing and better when you sit up and lean forward in case of inflammation of the heart sac), cough, irregular heartbeat, swelling of the ankles, legs or abdomen, shortness of breath, fatigue, and fainting
- Reactions associated with infusion (events occurring during or within 1 day of infusion); symptoms may include fever, chills, shortness of breath, and sudden reddening of the face, neck, or chest
- Inflammation of the pancreas (pancreatitis); symptoms may include abdominal pain, nausea, vomiting, and fever
- Condition of high levels of sugar in the blood (diabetes mellitus); symptoms may include increased thirst, increased hunger, frequent urination, irritability, and fatigue
- Inflammation of the kidneys (nephritis); symptoms may include changes in urine output and color, pain in pelvis, and swelling of the body and may lead to failure of the kidneys
- Inflammation or damage of the muscles (myositis, myopathies including rhabdomyolysis); symptoms may include muscle pain and weakness, urine with a dark brown or reddish color, nausea, and vomiting
- Severe skin or mucosal reactions (severe cutaneous adverse reactions); symptoms may include itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area
- Build-up of certain white blood cells (histiocytes and lymphocytes) in various organs (hemophagocytic lymphohistiocytosis), including the bone marrow, liver, and spleen, leading to their damage and destruction of other blood cells; symptoms vary depending on affected organs (see ‘Immune Reaction’ section below)

Allergic Reactions

Allergic reactions may occur with atezolizumab and typically occur while it is being given into your vein or shortly after it has been given. Symptoms could include nausea, vomiting, skin reactions (hives or rash), difficulty breathing, or low blood pressure. These reactions could be mild or severe and might lead to death or permanent disability. If you experience any of these symptoms, your study doctor will interrupt, or even stop, the delivery of atezolizumab into your vein. Your study doctor may also give you some drugs to treat these symptoms.

Side Effects Potentially Associated with Atezolizumab

The following are side effects that may be associated with atezolizumab:

- Development of special antibodies to atezolizumab (proteins made in the body that respond to a substance that is foreign to the body) by your immune system ○ If you develop these special antibodies, it may affect your body's ability to respond to atezolizumab in the future.
- Potential to cause harm to a developing fetus
- Inflammation of the eye (uveitis); symptoms may include eye pain and redness, vision problems, and blurry vision
- Inflammation of the blood vessels that can lead to damage of different organs (vasculitis); symptoms may include fever, fatigue, weight loss, weakness, general aches and pains, rash, headache, lightheadedness, shortness of breath, and numbness
- Breakdown of red blood cells (autoimmune hemolytic anemia); symptoms may include fatigue, fever, lightheadedness, paleness of the skin, yellowing of the skin and/or eyes, weakness, and inability to do physical activity

Immune Reaction

In rare situations, an immune reaction can occur with administration of atezolizumab. This reaction can cause side effects related to severe inflammation and/or severe infection. Several organs in your body (for example, liver, kidney, lungs, and bone marrow) may become involved, causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Symptoms may include very low blood pressure that does not respond to standard treatment, very high fever, cough, severe shortness of breath requiring oxygen therapy and/or intubation, severe dizziness, confusion, weakness, decreased urination with failure of the kidneys, abnormal liver function, very low blood cell counts, and/or bleeding within the organs.

If you experience any of these symptoms, you should notify your doctor immediately, as you may need immediate treatment and hospitalization. Your study doctor may give you drugs to treat these symptoms.

Risks Associated with Bevacizumab

The following side effects have been described with bevacizumab use when given alone or in combination with other chemotherapy. The following are commonly observed (> 10% of patients) side effects that are usually not considered serious with bevacizumab use:

- Back pain
- Headache
- Taste change
- Dry skin
- Inflammation of the skin (redness and scaling of the skin)
- Rhinitis (inflammation of the lining inside the nose) and watery eyes
- Cough
- Low blood sodium
- Low blood magnesium

The section below describes serious side effects reported with bevacizumab. For complete information regarding bevacizumab, please refer to Avastin® (bevacizumab) patient information or ask your doctor.

Serious Side Effects with Bevacizumab

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

- Impaired wound healing (following surgery, wound may be slow to heal or may not heal fully)
- High blood pressure
- Infections
- Sepsis
- Ovarian failure
- Kidney problems (too much protein in urine)
- Low platelets in blood
- Low white blood cell count

Common (occurs in 1-10% of patients)

- Gastrointestinal perforation (a hole that develops in the stomach or intestine). Symptoms include pain in the abdomen, nausea, vomiting, constipation, or fever
- Bleeding (includes coughing up blood and bleeding from the lungs), nose bleeds, bleeding in the stomach, brain, spinal cord, or vaginal bleeding
- Stroke and heart problems (blood clots in the legs, lungs, arteries or veins, mini stroke, heart attack, and chest pain)
- Fistula (formation of an abnormal passage between two organs)—gastrointestinal and non-gastrointestinal
- Infusion-related reaction with the first dose (symptoms include increased blood pressure, shortness of breath, chest pain, chills, and excessive sweating)
- Heart failure (especially in patients who have taken certain chemotherapy known to cause cardiac toxicity)

Less Common but Important (occurs in fewer than 1% of patients)

- Neurologic disorder (symptoms include headache, seizure, lethargy, confusion, blindness, and other visual disturbances and may be associated with increased blood pressure)
- Gall bladder perforation— a hole that develops in the gall bladder wall
- Osteonecrosis of the jaw—a condition where tissue cells are destroyed, resulting in the jawbone becoming exposed
- Necrotizing fasciitis—a bacterial infection that can destroy soft tissue

Allergic reaction

It is possible to experience serious allergic or infusion-related adverse effects (i.e., possible chills and/or hives) to the study medications, which could become life-threatening or fatal. Symptoms of an allergic reaction may include swelling of the face, tongue, or throat, redness, and warming of the skin, itching, sneezing or runny nose, stomach pain, loose stools, lightheadedness, or fainting, trouble breathing, irregular or racing heart rate. Your doctor will be monitoring you for these reactions and may decide that you need other medication to help stop them from happening, he/she will discuss this with you during your time on the trial.

For the prevention of infusion-related adverse effects and possible allergic reactions you might receive a premedication of an antihistamine drug and an anti-inflammatory drug 30 to 60 minutes before every infusion. The regimen may be modified based on local treatment standards and guidelines.

Other possible risks of this study include:

Tumor biopsies:
If you are enrolled in Cohort A, 2 tumor biopsies will be performed as a part of this study. We will try to biopsy the same tumor each time. We will also try to pick the easiest tumor to biopsy. This is so that we keep the discomfort and risk as low as possible. However, anytime you have a biopsy there are risks of:

- Discomfort or pain
- Bleeding
- Bruising
- Infection
- Damage to surrounding area depending on where the tumor is located
- If you have a biopsy from the lung, you could also have something called pneumothorax. This is where air escapes between the lung and the chest wall.

Complications from biopsies including bleeding or infection could lead to:
- the need for further treatment,
- blood transfusions, or
- hospitalization with extra procedures

Blood draws:
Blood draws for study purposes will be done at the same time as your usual blood tests for labs. These labs help us check the effect of the study drugs and monitor for safety while on the study drugs. There should not be any additional risk from the risk of usual blood draws.

These risks include:
- Bleeding
- Bruising
- Pain or discomfort
- Rarely infection
- Fainting

- Formation of a small clot
- Swelling or irritation to the vein and surrounding area

Risk of CT (Computed Tomography) Scan:
As part of this study we will perform CT scans to monitor your cancer. A CT scan is a way of taking detailed pictures inside your body by using X-rays. X-rays are a type of radiation. The amount of radiation that one CT scan will deliver to your body (give you) is about the same as you would get from living in your environment for 1 year.

Risks of MRI (Magnetic Resonance Images):
In this study we may perform MRIs of different parts of your body. The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working. You should NOT have an MRI if you have certain metal or electronic devices inside your body. Heart pacemakers and insulin pumps are examples of electronic devices.

The MRI machine is a small round tube. It might make you uncomfortable if you do not like tight spaces. The most common side effect of having an MRI is flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. Some people also experience warmth and reddening of the skin. This usually goes away after a few minutes.

Risks of Bone Scan:
As part of this study, we may perform a bone scan if your doctor feels it is important to help monitor your cancer. A bone scan is a way of seeing if there are any problems with the way your bones are growing and can help show if cancer is growing in the bone.

To do the bone scan we will need to inject a radioactive tracer into your blood stream. You will get some radiation from this tracer. The amount of radiation that this procedure will give you is about the same as you would get from your environment in 1 year. This is an estimate. The amount of radiation you receive could be higher or lower, depending on how much tracer is injected into your body, and on your body size. There is a small chance that you can develop cancer.

Risks of IV Contrast:
During the CT scan or MRI, intravenous (IV) contrast (liquid used to improve pictures of the inside of the body) may be used. The IV contrast will enter your body through a needle that is inserted into a vein of your arm. Although rare, the IV contrast may cause medical problems including allergic reactions. These allergic reactions may be mild (for example, rash or itchiness) or may be serious and life-threatening. Please notify the study doctor if you have ever had a reaction to contrast material. The IV contrast may also cause kidney problems, especially if you are dehydrated or have poor kidney function.

During the insertion of the needle (used to insert the IV contrast), you may feel discomfort. Occasionally, it can cause light-headedness or fainting. You may also experience bruising or swelling at the injection site. There are also very small risks of infection, excess bleeding, or clotting at the injection site.

You will be asked to sign an additional consent form before any contrast is given to you. Tell your doctors if you have any history of:

- allergy to shellfish or iodine,
- previous problems with contrast injections, or
- problems with your kidneys

Pregnancy:
If you are able to have children, this clinical research may involve unknown risks to unborn children. You must practice medically accepted methods of birth control that are approved by the doctor(s). This is required while you are on this study and sexually active. Birth control should also last for at least 6 months after the last dose of bevacizumab, 5 months after the last dose of tiragolumab, or 90 days after the last dose of atezolizumab, whichever is longest.

Examples of acceptable methods of birth control include:
- birth control pills,
- depo-progesterone injections,
- intrauterine devices (IUD)

Pregnancy tests will be done on all individuals who might be able to get pregnant. This will be done at the start of the study and with every cycle of study treatment, as well as at the endof-treatment visit.

Men should not father children while in the study. They should use a suitable contraceptive (condoms) with intercourse. The use of contraceptives should last for at least 6 months after the last dose of bevacizumab and 90 days from the last dose of tiragolumab, whichever is longer. Men should also refrain from donating sperm during this time period.

If you or your partner becomes pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus, which are currently unclear.

If you or your partner becomes pregnant during the study, you should notify the study doctor right away.

Treatment Beyond Disease Progression:

During your participation, it is possible for your cancer to appear to be progressing based on imaging scans. Tumors may increase in size, or you may develop new tumor(s) (though you may not feel it) while on the study drugs.

Since the increased size of your tumors/appearance of new tumors suggests that your cancer may have worsened while taking the study drugs, continuing treatment with the same drugs is not considered standard medical practice for your cancer. Standard of care would include stopping current therapy and evaluating alternative treatment options.

However, the study drugs may activate the immune system, and since it takes time for immune effects to occur, you will be given the option of continuing to receive the study drugs to see if they work in the longer term.

Before you decide if you want to continue with the same study drugs, it is important for you to understand what continuation involves, and the possible benefits, risks and discomforts. If you choose to continue receiving treatment with the study doctors, your tumors may still get worse. If this happens, your treatment with the study drugs will need to be stopped, and you and your study doctor will need to discuss alternative treatments for your disease.

Confidentiality:
There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

The study may include additional risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researchers to learn more about the effects of the study drugs tiragolumab, atezolizumab, and bevacizumab on your disease. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study as described previously.

Are there alternative treatments?

There may be other ways of treating your cancer. These may include:

- Receiving treatment for your cancer without participating in this study.
- Receiving another experimental therapy.
- Receiving comfort/palliative care.
- Choosing to get no treatment at all.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

This research is being sponsored by Dr. Hannah Robinson at the University of Colorado. Genentech, Inc., is providing the drugs tiragolumab, atezolizumab, and bevacizumab. Genentech, Inc., will also pay for procedures not considered to be standard of care (research procedures) as outlined below.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

You and your insurance will have to pay for visits, procedures, and other care that are part of routine care for your medical condition. You will be responsible for co-payments and deductibles that are standard for your insurance coverage. The study will pay for visits, procedures and care done only for the research; these include, though may not be limited to, research blood samples, research tumor biopsies (if assigned to Cohort A), and the study drugs tiragolumab, atezolizumab, and bevacizumab.

The study drugs tiragolumab, atezolizumab, and bevacizumab will be provided at no cost to you. However, you and your insurance will be billed for preparing and administering these study drugs.

If you need more information about these costs, please discuss this with your study team or contact the Patient Financial Services Office at 866-429-6045 or UCHselfpayestimate@uchealth.org].

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Hannah Robinson immediately. Her phone number is (303) 724-8681 (clinic), or after hours call 720-848-0000 to speak with the on-call team.

In the event of an illness or injury resulting from your participation in this study, you should seek appropriate medical care. However, you and/or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Hannah Robinson. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Robinson at 720-808-0071. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Robinson with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.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.

Optional Consent for Data & Specimen Banking for Future Research

Dr. Robinson would like to keep some data and leftover blood and tissue from previous biopsy procedures and blood draws but not used for other tests. If you agree, the data and leftover samples will be kept and may be used in future research to learn more about colorectal cancer. The research that is done with your samples is not designed to specifically help you. It might help people who have cancer and other diseases in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your samples will not affect your care.

The choice to let Dr. Robinson keep the data and leftover blood and tissue samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your data and samples can be kept for research, you can change your mind at any time and contact your study doctor to let him or her know that you do not want Dr. Robinson to use your data or samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Robinson decides to destroy them.

When your data and leftover samples are given to other researchers in the future, Dr. Robinson will
not give them your name, address, phone number or any other information that will let the researchers know who you are.

The possible benefits of research from your data and leftover samples include learning more about what causes cancer and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. Dr. Robinson will protect your records
so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage by Dr. Robinson.

Please read each sentence below and think about your choice. After reading each sentence, circle “yes” or “no.” If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your samples, you may still take part in the study.

1. I give my permissions for my data, leftover blood and tissue samples taken during the study to be kept by Dr. Robinson for use in future research to learn more about how to prevent, detect, or treat colorectal cancer.

☐ Yes
☐ No
Initials_____

2. I give my permissions for my archival tissue samples to be kept by Dr. Robinson for use in future research to learn more about how to prevent, detect, or treat colorectal cancer.

☐ Yes
☐ No
Initials_____

3. I give my permissions for my data, blood and tissue samples to be used for research about other health problems (for example causes of heart disease, osteoporosis, and diabetes).

☐ Yes
☐ No
Initials_____

4. I give my permission for my study doctor (or someone he or she chooses) to contact me in the future to ask me to take part in more research.

☐ Yes
☐ No
Initials_____

Who will see my research information?

The University of Colorado Denver | Anschutz Medical Campus (the University) and its affiliated health systems have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver | Anschutz Medical Campus
- University of Colorado Health

- Colorado Department of Public Health and Environment

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the University and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information, but confidentiality cannot be guaranteed.

If you test positive for HIV, Hepatitis B, or Hepatitis C in this study, we must report your name to the Colorado Department of Public Health and Environment. Finding out that you have HIV or Hepatitis may make it hard for you to get insurance.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Hannah Robinson, MD
University of Colorado, Anschutz Medical Campus
Mail Stop 8117, 12801 E 17th Avenue, Room 8126
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- The Institutional Review Board that is responsible for overseeing this research (COMIRB).
- The study doctor and the rest of the study team.
- *Genentech,* who is the company paying for this research study.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.)
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Testing for or infection with diseases reportable to the Public Health department, including but not limited to: Human Immunodeficiency Virus (HIV), hepatitis (all forms) tuberculosis, or other sexually transmitted diseases.
- Tissue samples and the data with the samples.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University and the health systems involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, the University or the health systems involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature: _____ Date: _____

Print Name: _____

Consent form explained by: _____ Date: _____

Print Name: _____

----------Use the following only if applicable----------

A signature of a witness is required for consent of non-reading subjects and consent using a short form.

Witness Signature: _____ Date: _____

Print Name: _____

Witness of Signature

Witness of consent process