INSTITUTE/CENTER: NIH Clinical Center

PRINCIPAL INVESTIGATOR: Jibran Ahmed, M.D.

STUDY NUMBER: 18-C-0033

STUDY TITLE: Phase I Study of Recombinant Interleukin-15 in Combination with Checkpoint Inhibitors Nivolumab and Ipilimumab in Subjects with Refractory Cancers

Cohort: Triplet

Consent Version: 2/9/2024

WHO DO YOU CONTACT ABOUT THIS STUDY?

Dr. Jibran Ahmed, Principal Investigator: 240-605-1927

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

Why is this study being done?

The purpose of this study is to test any good and bad effects of 3 study drugs: IL-15, nivolumab, and ipilimumab. IL-15 works by activating your immune system, and nivolumab and ipilimumab are drugs that unblock your immune cells. Researchers hope that administering these drugs together will allow your immune cells to recognize and then attack your cancer cells, causing your tumor to shrink. All 3 of these drugs are experimental; IL-15 is not yet approved for use by the Food and Drug Administration (FDA), and nivolumab and ipilimumab are FDA-approved for only specific types of cancer. Up to 50 people will take part in this study.

What is the usual approach to my cancer?

You are being asked to take part in this study because you have cancer that does not respond to treatment. People with your type of advanced cancer usually receive radiation and chemotherapy.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual approach described above
- You may choose to take part in a different study, if one is available
- You may choose not to be treated for cancer, but you may want to receive comfort care to relieve symptoms

What are the study groups?

Participants in the study will receive all 3 study drugs: IL-15, nivolumab, and ipilimumab. The first study participants will receive the lowest doses. If the drugs do not cause serious side effects, they will be given to other study participants at higher doses. The doses will continue to increase until side effects occur that require the doses to be lowered.

Treatment will be given in the outpatient setting, so you won't have to stay overnight in the hospital or clinic. IL-15 will be given as an injection under the skin. Nivolumab and ipilimumab will be given by vein into your arm (nivolumab over a time period of 30 minutes and ipilimumab over a time period of 1.5 hours). You may need to stay at the hospital for 2-3 hours after the first time you receive any of these drugs so that your doctor can monitor you.

The study drugs are given in 42-day (6-week) periods called cycles. During the first four cycles, you will receive IL-15 during the first and third weeks, and you will receive the other study drugs together with IL-15 at various points. After you have completed 4 treatment cycles, you will stop receiving IL-15, but will be able to continue the other study drugs.

How long will I be in this study?

You will be treated with the combination of IL-15, nivolumab, and ipilimumab for the first four 6-week cycles (a total of 24 weeks). The treatment cycles will then include treatment with only nivolumab and ipilimumab. You may continue to receive nivolumab and ipilimumab for as long as your cancer does not get worse, the side effects are tolerable, and you agree to stay on study.

After you stop treatment, you will remain in the study for monitoring while your doctor continues to watch you for side effects and follow your condition for 4 months from your last treatment date or until you start a new treatment. If you were removed from the study due to intolerable side effects, you will be followed until these resolve.

What extra tests and procedures will I have if I take part in this study?

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

Before you begin the study:

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

- An EKG (electrocardiogram) and ECHO (echocardiogram) to check your heart
- Pregnancy test in women who are able to become pregnant
- Additional tests, such as a CT scan, may be required to evaluate the extent of your disease

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra tests. They are not part of the usual approach for your type of cancer.

During the study:

- CT scans or other imaging tests such as MRI (an examination using magnetic field and radio waves) or PET (an examination using a special injected dye) that detect your tumor will be done while you are receiving the study drugs so that any benefit of the drugs can be determined
- For some patients, blood tests to measure tumor markers will be performed at the same time as the CT scans or other imaging tests
- Blood tests to measure the effect of the study drugs on circulating tumor cells and immune cells in your blood. These samples are required in order for you to take part in this study because the research on the sample is an important part of the study. Approximately 6 tablespoons of blood will be drawn. If you respond to treatment and provide a biopsy at the time of response, we will need to collect an additional blood sample from you to find out whether the genetic features found in your tumor are also present in your blood. This blood collection will be about 1 teaspoon.
- Tumor biopsies may be required before you receive study drug and again at the end of cycle 1. If you respond to treatment, you may be asked to provide an additional biopsy. Biopsies are a very important part of this trial and are done for research purposes. They are the only way for study scientists to see if your immune cells are in the tumor and if they are attacking your cancer cells.
    - In the early part of the study (called the dose escalation phase), tumor biopsies will be optional. During this time, if a patient decides not to have biopsies collected, he or she will still receive the study drugs and other tests that are part of the study.
    - At a certain point in the study (called the expansion phase), willingness to undergo tumor biopsies will be required for taking part. We will tell you if biopsies are required before you decide to take part in the study. After the initial biopsy, if you decide not to have further biopsies, you will still receive the study drugs and have other tests that are part of the study.
    - If you respond to treatment, the study doctor may ask to collect an additional biopsy.

  Here are some other important points about tumor biopsies:
    - Tumor biopsies are only collected by trained personnel. Biopsies are collected using a small needle under imaging guidance (CT, MRI, or ultrasound as deemed appropriate by the interventional radiologist performing the biopsy). Imaging helps

the specialized radiologist know that the needle has been placed into the tumor mass.

- Typical risks of biopsy collection include, but are not limited to, bleeding, infection, pain, and scarring. If you experience any complications from the biopsy, medical care will be offered to you. You will be counseled in more detail about biopsies, and you will be asked to sign a separate consent form that will describe the procedures and risks at that time. Your safety is the most important thing at all times. If upon attempting the first biopsy, no tissue can be obtained or it has caused you harm, further biopsies will not be done. After you are enrolled in this study, if for any reason the biopsies cannot be done safely, you may still receive the study drugs but the biopsies will not be done.
- If you respond to treatment, one of the tests performed on your biopsy samples may be genomic sequencing. Your tumor tissue contains genes, which are made up of DNA (deoxyribonucleic acid) and serve as the "instruction book" for the cells that make up our bodies. Genomic sequencing will determine the exact order of the DNA building blocks in your tumor. We know that variations in some tumor genes play an important role in how cancers respond to drugs. Identifying tumor gene variations in patients on this trial will help scientists understand which patients might respond best to this drug combination.

  To identify the genetic differences in your tumor compared to the genes you were born with, we will compare the genes in your tumor to the genes in your blood (germ line sequencing). While looking for these changes, we may also find gene variants that increase a person's chances to develop a health problem. The types of gene changes we may find include:

  - Changes in genes that are related to cancer.
  - Changes in genes that are related to diseases other than cancer.
  - Changes in genes that are not known to cause any disease. These are known as normal variations.
  - Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

  These types of gene changes may or may not have a direct effect on you or your family members. It is important for you to know that everyone carries these types of gene changes and that we expect to find these types of changes in many of our participants. You will only be informed of genetic changes that researchers involved in this study feel are urgently important for your health or your family's health and that knowledge of these changes has the potential to provide a significant benefit for you or your family.

A study calendar that shows how often these tests will be done is attached. You will also receive a Drug Interaction Patient Handout and a wallet card that describes potential drug-interactions while participating in this trial.

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

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

There is also a risk that you could have side effects from the study drugs. The study doctor will be testing your blood and will let you know if changes occur that affect your health.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon,some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

It is very important that you report any and all side effects that you have as soon as you experience them.

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

Possible Side Effects of IL-15:

In studies with humans, risks and side effects related to the IL-15 included the following:

POSSIBLE, SOME MAY BE SERIOUS
• Anemia which may require blood transfusion • Abnormal heartbeat • Pain in belly • Diarrhea, nausea, vomiting • Chills, tiredness, fever • Swelling of arms, legs • Swelling and redness at the site of the medication injection

- Severe blood infection
- Bruising, bleeding
- Infection, especially when white blood cell count is low
- Muscle weakness
- Dizziness, headache
- Shortness of breath
- Dry skin
- Rash
- Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles
- High blood pressure which may cause blurred vision
- Low blood pressure which may cause feeling faint

In addition to the side effects listed above, IL-15 may cause increased sensitivity to sunlight or lamps.

PLEASE NOTE THE FOLLOWING IN REVIEWING THE RISKS BELOW

Nivolumab and ipilimumab may result in severe and possibly fatal side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving these drugs. In clinical trials, most immune-mediated side effects were reversible, and doctors managed them by stopping nivolumab or ipilimumab temporarily, giving corticosteroids, and providing supportive care.

Possible Side Effects of Nivolumab:

Special precautions

Side effects of Nivolumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when Nivolumab is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Nivolumab, more than 20 and up to 100 may have:

- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Nivolumab, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Swelling and redness of the eye
- Pain

- Diarrhea, nausea
- Dry mouth
- Fever
- Swelling and redness at the site of the medication injection
- Bruising, bleeding
- Pain or swelling of the joints
- Loss of appetite
- Reaction during or following a drug infusion which may cause fever, chills, rash

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

- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving nivolumab, 3 or fewer may have:

- Swelling of arms and legs which may cause a feeling of heaviness and tightness
- Dry eyes
- Sores in the mouth which may cause difficulty swallowing
- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss
- Swelling of the bowels

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

- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.

Possible Side Effects of Ipilimumab:

Special precautions

Side effects of ipilimumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab is used in combination with nivolumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab, more than 20 and up to 100 may have:

- Diarrhea, nausea
- Tiredness

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Skin: itching; rash, blisters including inside the mouth (can be severe); hives

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab, from 4 to 20 may have:

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain
- Difficulty swallowing, eating
- Constipation, vomiting
- Weight loss, loss of appetite
- Fever
- Dehydration
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Low blood pressure which may cause feeling faint

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

- Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness

- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving ipilimumab, 3 or fewer may have:

- Bleeding
- Blockage of the bowels which may cause constipation
- Fluid around heart
- Severe illness with multiorgan failure
- Confusion

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

- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck

If you experience diarrhea, or any symptom listed in the "Rare, and Serious" categories above, it is important that you contact the study doctor immediately.

- Dr. Jibran Ahmed (principal investigator): (240) 605-1927
- Ashley Bruns (research nurse): (240) 858-3162
- NIH Clinical Center page operator (for the physician on call): (301) 496-1211

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

It is also very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial, or if you stop taking any regular medicines or start taking a new medicine while you take part in this study. Ipilimumab, nivolumab, and rhIL-15 all have the potential to interact with other drugs which can cause side effects. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal, nutritional products, and dietary supplements such as St. John's Wort.

Reproductive risks

You should not get pregnant, breastfeed, or father a baby while in this study. The effects of ipilimumab, nivolumab, and rhIL-15 could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. Birth control should be used prior to beginning study treatment, during the study, and for 5 months (women) and 7 months (men) after the last treatment. If you become pregnant or suspect you are pregnant while participating in this study, inform the study doctor immediately.

Potential Risks Related to Research-Related Imaging Studies

During your participation in this research study, you will be exposed to radiation from up to 2 CT-guided research tumor biopsies and up to 7 CT scans or FDG-PET/CT scan each year. The amount of radiation exposure you will receive from these procedures is equal to approximately 10 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT or FDG-PET/CT scans that you get in this study will expose you to the roughly the same amount of radiation as 33 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 4 out of 10 people (40%) will get cancer during their lifetime, and 2 out of 10 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 0.1 out of 10 (1%) and of getting a fatal cancer is 0.05 out of 10 (0.5%).

Risks Associated with Genetic Testing

Privacy risks

Your privacy is very important to us and we will use many safety measures to protect your privacy. Your research samples will be stored with a coded identifier, not your name. Any personal data about you will also be stored in a sequence computer database with that code identifier. All information that can directly link you to the tissue or personal information will not be shared with investigators using your specimens for research. This includes information that contains your name, medical record number, date of birth, or address.

There are protections in place that restrict who can see the results of your genetic tests. However, there remains a risk someone could get unauthorized access or break into the system that stores information about you. Every precaution will be taken to minimize this risk. There also may be other privacy risks that we have not foreseen.

Genetic variant results that we return to you will become part of your medical record at the NIH. In spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. For instance, if you or a family member releases information about you or your involvement in this study, or an insurer, employer, or other person obtains your written consent to receive information from your NIH medical record, your identity, information about your enrollment in this study and genetic variant results may be included in a release of your medical records.

Protections against misuse of genetic information

Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

There are state and federal laws that protect against genetic discrimination. There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA also does not apply to members of the United States military, to veterans obtaining health care through the Veteran's Administration or the Indian Health Service. GINA does not forbid insurance medical underwriting based on your current health status, including your cancer. GINA also does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. However, your cancer diagnosis will often be considered more important that genetic information about risk for developing another condition when evaluating you during medical underwriting.

Emotional and psychological risks

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond. Although your genomic information is unique to you, you share some genomic similarities with your children, parents,

brothers, sisters, and other blood relatives. Therefore, learning your testing results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

What possible benefits can I expect from taking part in this study?

This study is unlikely to help you. The knowledge gained from this study may help others in the future who have cancer.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI) or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the Clinical Center Patient Representative at (301) 496-2626.

Study Chart

Day	Patient Activity
Before starting study drug	• Check in at the Outpatient Clinic • Medical history and physical exam • Echocardiogram and EKG to test your heart • Tumor measurements by CT/MRI or PET • Routine blood and urine tests • Pregnancy test for women who are able to become pregnant • Blood samples for research will be taken • Tumor biopsy for research will be taken
Cycles 1-4, Days 1-3	• Go to the NIH Clinical Center for treatment • Physical exam • Routine blood and urine tests • IL-15 will be given through injection under the skin • Blood samples for research will be taken
Cycles 1-4, Days 4-7	• Go to the NIH Clinical Center for treatment • IL-15 will be given through injection under the skin
Cycles 1-4, Day 8	• Go to the NIH Clinical Center for treatment • Physical exam (Cycles 1 and 2 only) • Routine blood and urine tests (Cycles 1 and 2 only) • IL-15 will be given through injection under the skin • Blood samples for research will be taken (before nivolumab and ipilimumab) • Nivolumab and ipilimumab will be given by vein in your arm (about 30 minutes for nivolumab and 1.5 hours for ipilimumab)
Cycles 1-4, Day 15	Cycles 1 and 2 only: • Check in at the Outpatient Clinic • Physical exam • Routine blood and urine tests • Blood samples for research will be taken
Cycles 1-4, Day 22	• Go to the NIH Clinical Center for treatment • Physical exam (Cycles 1 and 2 only) • Routine blood and urine tests (Cycles 1 and 2 only) • Blood samples for research will be taken • IL-15 will be given through injection under the skin • Nivolumab will be given by vein in your arm (about 30 minutes)
Cycles 1-4, Days 23-28	• Go to the NIH Clinical Center for treatment • IL-15 will be given through injection under the skin

Day	Patient Activity
Cycles 1-4, Day 29	• Go to the NIH Clinical Center for treatment • Physical exam (Cycles 1 and 2 only) • Routine blood and urine tests (Cycles 1 and 2 only) • IL-15 will be given through injection under the skin
Cycles 1-4, Day 36	• Check in at the Outpatient Clinic • Physical exam (Cycles 1 and 2 only) • Routine blood and urine tests (Cycles 1 and 2 only) • Blood samples for research will be taken • Nivolumab will be given by vein in your arm (about 30 minutes)
Cycles 1-4, Day 42	• Check in at the Outpatient Clinic • Tumor measurements by CT/MRI or PET • Blood tests for tumor markers may be done • Tumor biopsy for research will be taken • ***There will be a 1-week break between cycle 4 and cycle 5***
Cycle 5 and onwards, Day 1	• Go to Clinical Center for treatment • Physical exam • Routine blood and urine tests • Blood samples for research will be taken • Nivolumab and ipilimumab will be given by vein in your arm (about 30 minutes for nivolumab and 1.5 hours for ipilimumab)
Cycle 5 and onwards, Day 15	• Check in at the Outpatient Clinic • Blood samples for research will be taken • Nivolumab will be given by vein in your arm (about 30 minutes)
Cycle 5 and onwards, Day 29	• Check in at the Outpatient Clinic • Blood samples for research will be taken • Nivolumab will be given by vein in your arm (about 30 minutes)
Cycle 5 and onwards, Day 42 (every other cycle)	• Tumor measurements by CT/MRI or PET • Blood tests for tumor markers may be done

WILL YOUR SPECIMENS OR DATA BE SAVED FOR USE IN OTHER RESEARCH STUDIES?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding cancer, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

WILL YOUR SPECIMENS OR DATA BE SHARED FOR USE IN OTHER RESEARCH STUDIES?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to

ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. Someone will work with you to provide more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

IL-15, nivolumab, and ipilimumab will be supplied at no charge while you take part in this study. The cost of getting the study drugs ready and giving them to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that one or more of the study drugs may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

The NIH and the research team for this study are using drugs developed by Bristol-Myers Squibb through a joint study with your study team and the company. The company also provides financial support for this study.

CLINICAL TRIAL REGISTRATION and RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

Your privacy is very important to us and the researchers will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept in a central database for research. Your name or contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

In addition to the above which is handled by the study sponsor (the Cancer Therapy Evaluation Program or CTEP), we may put your research data in a large database for broad sharing with the research community. These databases are commonly called data repositories. These data repositories might or might not be located at the NIH. The information in this database could include but is not limited to genetic information, ethnicity and sex. If your individual research data is placed in one of these repositories, it will not be labeled with your name or other information that could be used to easily identify you, and only qualified researchers will be able to look at your data. These researchers must receive prior approval from individuals or committees to access the data.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and drug companies (makers of the study drugs) supporting the study
- The Institutional Review Board, IRB, a group of people who review the research with the goal of protecting the people who take part in the study
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.

- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

Policy Regarding Research-Related Injuries

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal

Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

Problems or Questions

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

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor Jibran Ahmed at: 240-605-1927. For questions about your rights while in this study, call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713 if you have a research-related complaint or concern.

Consent Document

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____