INSTITUTE:National Cancer Institute

STUDY NUMBER: 18-C-0033 PRINCIPAL INVESTIGATOR: Geraldine O'Sullivan Coyne, MD, PhD

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

Continuing Review Approved by the IRB on 11/20/18
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INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, 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). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

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
- or you may choose not to be treated for cancer, but you may want to receive comfort care to relieve symptoms

Why is this study being done?

The purpose of this study is to test any good and bad effects of three 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 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. At least six people will take part in this part of the study.

What are the study groups?

The participants in the study will be placed into one of two study groups. Each study group will be made up of at least 3 patients. One group will receive IL-15 in combination with nivolumab, and the other group will receive IL-15 in combination with ipilimumab.

The study drugs are given in 42-day (6-week) periods called cycles. You will be treated with the drug combination for four cycles (24 weeks). You will receive IL-15 during the first and third weeks of each cycle. Depending on which study group you are in, you will receive the other study drug at various points throughout the cycle. After you have completed 4 treatment cycles, you will stop receiving IL-15, but will be able to continue the other study drug.

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 or ipilimumab will be given by vein into your arm (nivolumab over a time period of 30 minutes or 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 for side effects.

How long will I be in this study?

You will be treated with the drug combination for the first four 6-week cycles (a total of 24 weeks). You may then continue to receive additional doses of either nivolumab or 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 drug on circulating tumor cells and immune cells in your blood will be optional. Approximately 2 tablespoons of blood will be drawn.
- Tumor biopsies before you receive study drug and again at the end of cycle 1 will be optional.

  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.

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 drug(s)/study approach. 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

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:

- Dry eyes
- Sores in the mouth which may cause difficulty swallowing

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 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. Geraldine O'Sullivan Coyne (principal investigator): (301) 402-9122
- 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:

This research study involves exposure to radiation from up to 2 CT scans (used in biopsy collections). This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 1.6 rem, which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would

like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

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

If you are pregnant, you may not participate in this protocol, as the fetus is more sensitive to radiation than children or adults.

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 stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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.

What are the costs of taking part in this study?

IL-15 and either nivolumab or ipilimumab (depending on which study group you are in) 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.

You will not be paid for taking part in this study.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information will be used for auditing or program evaluation internally by the NIH; or

- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this

research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your 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, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

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 company supporting the study
- The Institutional Review Board, IRB, is 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.

Conflict of Interest

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

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Where can I get more information?

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

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

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 Dr. Geraldine O'Sullivan Coyne at (301) 402-9122.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We *will not* contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used *for future* research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used.

Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Patient Study Calendar

Day	Patient Activity
Before starting study drugs	• 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 may be taken • Tumor biopsy for research may be taken
Cycles 1-4, Days 1-7	• Go to 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 may be taken (days 1-3 only)
Cycles 1-4, Day 8	• Go to 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 • *Depending on study group*: Nivolumab OR Ipilimumab will be given by vein in your arm (about 30 minutes for nivolumab or 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
Cycles 1-4, Day 22	• Go to 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 may be taken • IL-15 will be given through injection under the skin • *If applicable:* Nivolumab will be given by vein in your arm (about 30 minutes)
Cycles 1-4, Days 23-28	• Go to Clinical Center for treatment • IL-15 will be given through injection under the skin

Day	Patient Activity
Cycles 1-4, Day 29	• Go to 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 may be taken • *If applicable:* 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 may be taken • ***There will be a 1-week break between cycle 4 and cycle 5***
Cycle 5 and onwards, Day 1	• Physical exam • Routine blood and urine tests • Blood samples for research may be taken • *Depending on study group:* Nivolumab OR Ipilimumab will be given by vein in your arm (about 30 minutes for nivolumab or 1.5 hours for ipilimumab)
Cycle 5 and onwards, Day 15	• Blood samples for research may be taken • *If applicable:* Nivolumab will be given by vein in your arm (about 30 minutes)
Cycle 5 and onwards, Day 29	• Blood samples for research may be taken • *If applicable:* 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

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The 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 National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Geraldine O'Sullivan Coyne, Telephone: (301) 402-9122. If you have any questions about the use of your samples for future research studies, you may also contact the Office of the Clinical Director, Telephone: (240) 760-6070. You may also call the Clinical Center Patient Representative at (301) 496-2626.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____ _____
Signature of Adult Patient/ Legal Representative — Date

_____
Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.)

_____ _____
Signature of Parent(s)/Guardian — Date

_____
Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

_____ _____ _____
Signature of Parent(s)/Guardian — Date — Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM NOVEMBER 20, 2018 THROUGH DECEMBER 3, 2019.

_____ _____ _____ _____
Signature of Investigator — Date — Signature of Witness — Date

_____ _____
Print Name — Print Name