PRINCIPAL INVESTIGATOR: Kevin Conlon, M.D.

STUDY TITLE: Phase II Trial of Avelumab (Bavencio) with IL-15 in Subjects with Clear-Cell Renal Carcinoma

STUDY SITE: National Cancer Institute

Cohort: Standard

Consent Version: 05/12/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

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KEY INFORMATION ABOUT THIS RESEARCH

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). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to take part in this study because you have relapsed metastatic clear cell renal carcinoma (ccRCC) that has not responded to standard treatments.

The purpose of this study is to test whether IL-15 and avelumab, drugs that have shown positive results in the treatment of other cancers, but have never been administered together to treat your disease, can be effective at treating your disease. We will also look at how well these drugs are tolerated when administered together, identify the side effects of the combination treatment and its effects on your immune system.

Recombinant human interleukin 15 (IL-15) is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat metastatic clear cell renal carcinoma. However, the use of avelumab is approved to treat urothelial, Merkel cell carcinoma and recently has been approved for the first line treatment of people with advanced renal cell carcinoma given in combination with Axitinib (Inlyta®). If you have received this treatment combination previously, you still may be eligible for this trial due the different mechanism of action of the rhIL-15 avelumab combination. We are testing it in this research study to see whether giving recombinant human interleukin 15 (IL-15) in combination with the immune checkpoint inhibitor avelumab (also known as Bavencio) will improve outcome of therapy for your disease. Since IL-15 and avelumab have never before been given together to treat your disease, this treatment is considered investigational, or

experimental. The FDA has given us permission to use IL-15 and avelumab together in this study.

There are other drugs and treatments that may be used for your disease, and these can be prescribed by your regular cancer doctor, even if you are not in this study. They all work in different ways in the body as compared to IL-15 and avelumab, and with different side effects. If you would prefer other drugs or treatments, you should consider not joining this study.

If you decide to join this study, here are some of the most important things that you should know that will happen:

- In the first groups of participants enrolled (safety run-in), we want to find out the highest dose of IL-15 that is safe to use with avelumab. We will test 2 increasing doses of IL-15 in small groups. We also want to find out what kind of side effects IL-15 and avelumab might cause. After we find the best dose, we will enroll additional participants in a second portion of the study (dose expansion) to learn more about out whether IL-15 and avelumab can shrink your tumor(s).
- Before you begin the study, we will perform tests to find out whether you are eligible to participate (screening) that will include tests such as: a complete physical examination, blood and urine tests, and imaging of your disease. We will also need a tumor sample - which can be from a previous surgery. If you do not have a previous sample to provide, you will need to have a fresh biopsy done.
- If you are eligible to receive treatment, during the study, both drugs will be administered as intravenous infusions for up to four cycles of 28 days each. You will receive IL-15 over the course of the first five days of each cycle, and avelumab on days 8 and 22 of each cycle.
- You will be required to be hospitalized at the NIH Clinical Center for one week to receive the first cycle of IL-15. As long as you are accompanied by a caregiver or unless decided otherwise by the doctor, you will have the option of receiving the remaining cycles as an outpatient, but will still need to report to the hospital each day for the first five days of each cycle.
- You may experience side effects from taking part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, any may include death. Examples of some of the side effects that you may have include: changes in blood counts (such as low red or white cells), gastrointestinal (such diarrhea, nausea, vomiting), fatigue, and infections. Since this is the first time that IL-15 and avelumab are administered together, there may be side effects that we cannot predict.
- After the study treatment has ended, we will need to see you at the NIH Clinical Center periodically to assess your health and to determine what impact, if any, the study drugs may have had on your disease.

Just as we do not know what side effects you might have, we cannot know if you may benefit from taking part in this study. If you do not benefit directly, this study and the results from our research may help others in the future.

You are free to stop participating in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe more about the research study. This information should be considered before you make your choice. 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.

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 research study is to develop treatments for clear cell renal carcinoma (ccRCC) that are more effective than existing therapies.

We are asking you to join this research study because you have relapsed and/or refractory metastatic clear cell renal carcinoma for which no standard therapy exists, or standard therapy has failed.

IL-15 is a man-made version of a small protein (cytokine) that is naturally produced in your body by certain white blood cells and increases the activity and strength of the immune system. People with cancer can have a weak immune system. This weakness can be caused by the cancer itself, or by treatments such as radiation, chemotherapy or other drugs that work against the immune system. It is hoped that IL-15 can "boost" or strengthen a person's immune systems as they fight against cancer. In fact, in other clinical trials, all of the people who received IL-15 showed an increase in the number of their immune system cells. In some of the people, the growth was dramatic. We hope the same is true in this study.

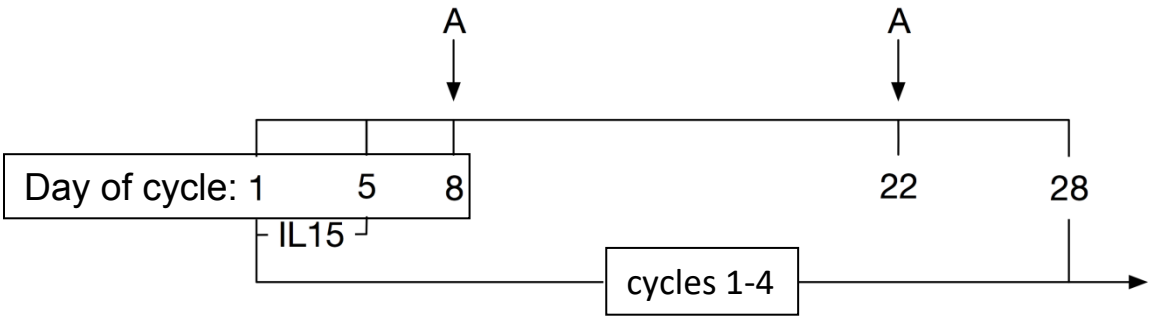
Avelumab is a monoclonal antibody which belongs to a family of molecules called anti-PD-L1 antibodies. PD-L1 is a cell surface protein, found in different human tumor types. It is believed to interrupt the immune system's ability to fight cancer. In order to be eligible for this clinical trial, your tumor must express PD-L1. Avelumab interferes with the activity of PD-L1 and is thought to potentially have an effect on the immune system (in particular white blood cells) in order to induce an anti-tumor attack. Avelumab works in two ways: it attaches to the surface of a tumor cell and marks the tumor cell for destruction by other cells of the immune system, and it prevents tumor cells from inactivating the immune system cells. Monoclonal antibodies are purified proteins that are specially made to attach to pieces of foreign substances (such as cancer cells). Recent evidence shows that IL-15 boosts the number of immune system cells which are responsible for destroying antibody-coated tumor cells.

Recombinant human interleukin 15 (IL-15) is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat ccRCC. However, the use of avelumab is approved to treat other cancers such as urothelial and Merkel cell carcinoma. We are testing it in this research study to see whether giving recombinant human interleukin 15 (IL-15) in combination with avelumab (also known as Bavencio) will improve outcome of therapy for your disease. Since IL-15 and avelumab have never before been given together, this treatment is considered investigational, or experimental. The FDA has given us permission to use IL-15 and avelumab together in this study.

WHAT WILL HAPPEN DURING THE STUDY?

- If you decide to take part in this study, you will be asked to:
- Receive IL-15 as a continuous intravenous infusion (civ) over 24 hours on days 1-5 of a 28-day cycle at one of the 2 dose levels. In addition, you will receive avelumab by intravenous infusion (IV). Avelumab will be given at a set dose on days 8 and 22 of each cycle. The avelumab will infuse over 1 hour.
- In order to confirm that the doses are safe, participants will be enrolled in groups:
    - Safety run-in groups: First, groups of 3-6 study participants will receive IL-15 and avelumab. The initial participants will receive the 2 mcg/kg dose of IL-15 and if there are no safety issues, the dose of IL-15 will be increased to 4 mcg/kg. After the safety is established for this dose level in the first 3-6 participants treated all subsequent participants will be treated at the recommended 4 mcg/kg dose of IL-15. During this dose escalation and safety evaluation and in all subsequent the dose of avelumab is the same and all participants receive both agents. Each group of participants will be checked closely for side effects for at least 4 weeks before enrolling at the next higher dose of IL-15 with avelumab.
    - Dose expansion group: Once the recommended dose of IL-15 with avelumab is established, up to 17 participants will be treated to learn more about the drugs and their potential effectiveness in the treatment of ccRCC. After the 4 mcg/kg dose level is confirmed to be safe, participants that are having significant expected rhIL-15 related side effects are allowed to be treated at lower doses of 3 or 2 mcg/kg to make the treatment more tolerable.
- All participants will be given treatment on an inpatient basis for the first week of the first cycle, and on an outpatient basis for subsequent weeks and cycles unless decided otherwise by the physician, based on clinical judgement. Treatment can continue for up to 4 (28-day) cycles. You will only be eligible for outpatient treatment if you have a caregiver to accompany you and help you manage the ambulatory infusion pump.

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows:



A= Avelumab infusion

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your doctor will discuss with you how long you will participate in the study which will depend on when you enroll in the study. Most participants will be followed for at least 3 years after finishing treatment and will be contacted periodically for as long as the study is open.

Screening

Before you begin the study, you will have several tests performed to check whether the study is suitable for you. This is called screening. Your doctor will review your medical history and the drugs that you are currently taking as well as the previous treatments of your disease to determine whether you can participate in this study.

A small part of your tumor tissue that was collected from any previous surgery or biopsy will be tested at NCI to confirm your diagnosis and to test whether your tumor expresses PD-L1, the target of avelumab. If no sample is available or if additional sample is needed to confirm your diagnosis, and to confirm that your tumor expresses PD-L1, then a fresh biopsy will be taken. You will be told if this mandatory biopsy is needed.

Some of these tests or procedures are part of regular care and may be done even if you are not being considered to join the study. If you have had some of these tests or procedures recently, they may or may not have to be repeated. The following tests and procedures will be performed prior to starting treatment:

- Your medical history, including previous cancer treatments, any current or previous medications (prescription, supplement, and over-the-counter medicines), will be reviewed. If you have medical records from another clinic or hospital, you will be asked to get copies of these records, or your study doctor may be able to request them on your behalf.
- A complete physical examination will be performed that will include your vital signs (blood pressure, pulse, body temperature, and respiratory rate) and recording your height and weight, and evaluation of your ability to carry out daily activities.
- Blood and urine tests will be collected to:

  - measure your liver, kidney, and thyroid function, red and white blood cells, platelets, electrolytes and others;
  - measure how well your blood clots;
  - test for Hepatitis B and C infection
  - test for human immunodeficiency virus (HIV) infection. This is the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.
  - run routine tests done in people with your type of cancer to confirm your diagnosis and the status of your disease.

- If you have received a live vaccine within 30 days of starting study treatment, you will not be able to immediately participate. Examples of live vaccines include but are not limited to: the intranasal influenza vaccine known as Flu-Mist, measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- For females of child-bearing potential, a pregnancy test will be done (urine or blood sample). You will not be able to participate if you are pregnant or you are breast feeding because we don't know how this medicine would affect your baby or your unborn child.
- You may have pulmonary function tests to test how well your lungs function and echocardiogram (ECHO) to check your heart function, if there is suspicion of diminished lung or heart capacity that may make the treatment too difficult or risky.
- An electrocardiogram (EKG) to make sure you do not have an irregular rhythm.
- Imaging will be done to check your disease, as needed.
  - Imaging will include a CT scan of neck, chest, abdomen and pelvis, and a PET/CT scan of the torso. Other body areas may be imaged if clinically indicated. For participants with suspected involvement of disease in the central nervous system, an MRI of the brain will be taken.

During the study

If the screening process shows that you are eligible for the study, and you choose to be in it, you may need to have a few additional standard tests completed if not done recently. You will also have additional samples collected for research tests.

You will come to the NIH Clinical Center for treatment and procedures. The treatment will be given in the inpatient setting for the first week of the first cycle and then in the outpatient setting at the Clinical Center for the remainder of the study. You will be given IL-15 as a continuous intravenous infusion as described in section "What will happen during the study?", over a 24-hour period for 5 days of each cycle. Your dose of IL-15 will be assigned depending on what dose level is open at the time of your enrollment (gradually increasing doses during the safety

run-in or the maximum tolerated dose during the dose expansion portion). Avelumab is also an IV infusion and will be given to you over about a 1-hour period.

A midline catheter may need to be inserted for each IL-15 infusion and maintained for the duration of the infusion. If you receive part of the treatment as an outpatient, you will get training on how to maintain the midline catheter and the ambulatory infusion pump before being discharged from the hospital. For the first five days of each cycle, you will need to report to the day hospital each day for an IL-15 bag change. Each IL-15 infusion is expected to start between 8am and 8pm, and bags will be replaced at the same time each day; however, if for any reason IL-15 infusion begins after hours (8pm-8am), you will need to come into the hospital during the night for nursing staff to manage the pump.

We will give you standard pre-medications before the IL-15 and avelumab infusions. These may include acetaminophen (Tylenol), nonsteroidal anti-inflammatory drugs (NSAIDs such as ibuprofen), an antihistamine (Benadryl), and in some cases histamine-2 blockers (Zantac). These are given to help prevent infusion related side effects. Your study doctor or a member of the study staff can explain these to you in more detail. Because of the unknown side effects, we will ask you to stay at the clinic for an additional 30 minutes after your infusion so we may monitor you.

Similar to the tests done at the beginning of the study, the following will be repeated during the study to see how you are doing and how the cancer may be responding to treatment:

- Review of medical history, and a physical exam (check weight and vitals), including obtaining information about how you function in your daily activities, side effects and symptoms, and review of medications
- Routine blood and urine tests
    - The most amount of blood to be drawn during any study visit/cycle is expected to be about 7 tablespoons. This includes testing for standard of care tests (i.e., complete blood counts) as well as blood for research.
- Tumor imaging (such as, CT scan, PET/CT) will be done to assess the sites of your disease every 8 weeks during treatment. An MRI of the brain and lumbar puncture is only required in participants with neurological symptoms. In participants with disease primarily on their skin, clinical photography and evaluation by a dermatologist will be used to assess the disease sites present on the skin. Other body areas may be imaged if clinically indicated. If your disease does not get worse, follow-up imaging may be done at 6 months after treatment, then annually, at the discretion of the clinical team.

Additional research testing

In addition, the following research samples will be collected, and some are optional:

- Blood Samples: Blood will be collected for required research studies to learn more about how IL-15 and avelumab affect your cancer A baseline sample will be collected at the beginning of the study prior to starting treatment, then during the first cycle of treatment, and at about the same time as each imaging assessment. If at any time your doctor thinks you have responded or your disease has worsened during or after treatment, we will again

collect samples. Optional blood samples may be obtained more frequently throughout the treatment cycles depending upon the days that you are seen in the clinic. You will be told which samples are required and which are optional.

- Tumor Biopsies: These are an optional part of the study and you will only be asked to do so if it is felt to be safe. We will ask you to undergo a tumor biopsy during the first Cycle of treatment and again if your disease should worsen during or after treatment on this study. The tissue is being collected for special research tests. Your doctor or the study team will discuss the biopsies with you. The biopsies to be performed are exclusively for research purposes and will not benefit you. They might help other people in the future. You may agree to biopsies now and change your mind later. If at any time you do not want to have a biopsy done, please tell us.

  Please place your initials in the blank next to Yes or No for the question below:
  I agree to having optional biopsies of my tumor taken for research.

  _____ Yes _____ No
  Initials Initials

  Usually tissue can be obtained safely and comfortably with local anesthesia. If you require sedation before undergoing a biopsy, you will be informed of the risks and you will be asked to sign an additional consent prior to undergoing the procedure. Biopsies will NOT be done on this study if they require general anesthesia. We may ask that you have ultrasound to help clearly locate your tumor when doing a biopsy.

When you are finished taking the drugs (treatment)

When you finish taking the experimental therapy, we will ask you to come to the clinic for follow-up visits and assessments 30 days after last treatment and at about the following times after treatment: every 60 days for the first 6 months, then every 90 days for 2 years and then every six months for as long as the study is open and your disease does not get worse or come back. These clinic visits will include having required blood samples collected for routine analysis and for research and may include CT or PET/CT scans. Visits usually take about 3 hours but should take no longer than 8 hours. If your disease worsens or comes back, we will contact you every 3 months to check on how you are doing and if you have started new treatment for your disease.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 25 people participate in this study at the NIH.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

If you choose to take part in this study, there is a risk that the recombinant human IL-15 and avelumab may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The recombinant human IL-15 and avelumab used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know 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, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

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

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

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

Risks of IL-15

You may have side effects from the IL-15 while on the study. We pay close attention to any side effects you have. However, we don't know all the side effects that may happen. Side effects may be mild or very serious. We may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the IL-15. In some cases, side effects can be serious, long lasting, or may never go away. It is possible that IL-15 could increase the growth of your cancer and could make your cancer worse. There also is a risk of death.

Please talk to us about any symptoms you have while you are in the study.

In studies with humans, <u>common and not very common risks and side effects related to the IL-15 included the following</u>:

POSSIBLE, SOME MAY BE SERIOUS
• Anemia (low red blood cells) which may require blood transfusion • Abnormal heartbeat • Pain in belly • Diarrhea, nausea, vomiting • Chills, tiredness, fever • Swelling of arms, legs • 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

Other risks seen with IL-15 that are possibly related to the drug include:

- Chest pain
- bronchopulmonary hemorrhage and diffuse alveolar hemorrhage (bleeding in the lungs)
- Confusion, psychosis (i.e., delusions, hallucinations)
- Kidney failure - signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling
- Papilledema (changes in vision due to increased pressure in the brain)
- Uveitis (inflammation of the eye – symptoms may include redness, pain, blurred vision)
- Pneumonitis (inflammation of the lungs) - symptoms may include new or worsening cough, chest pain, shortness of breath.
- Inflammation of the lining of the first part of the small intestine symptoms may include nausea, vomiting, stomach burning, pain, indigestion
- Liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure
- Decreases in blood levels of albumin, phosphorus (these are standard blood tests)
- Low number of white blood cells, cells that help fight infection (lymphopenia, leukopenia, neutropenia)
- Low platelets, cells that help blood to clot (thrombocytopenia)

- Low blood oxygen – symptoms may include changes in skin color, confusion, cough, fast heartbeat, shortness of breath
- Immune related adverse events: hives, hypothyroidism and production of autoantibodies – symptoms made include joint pain, tiredness fever, rashes, allergy-type symptoms, muscle weakness

Risks of Avelumab

Three types of risks are associated with avelumab: general signs and symptoms, reactions that occur during or following the infusion (infusion-related reactions), and immune side effects.

In studies with humans, common and not very common risks and side effects related to avelumab included the following:

COMMON, SOME MAY BE SERIOUS In 100 people receiving avelumab, more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving avelumab, from 4 to 20 may have:

- Anemia (low red blood cells) which may require blood transfusion
- Diarrhea, nausea, vomiting
- Chills, fever
- Flu-like symptoms including body aches
- Infection
- Reaction during or following a drug infusion which may cause fever, chills, rash, low blood pressure
- Bruising, bleeding
- Loss of appetite
- Cough
- Dry skin
- Itching, acne, rash

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

- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting [the term above is a clinical manifestation of lab values not previously listed on the risk list]
- Damage to the pancreas which may cause belly pain and hospitalization
- Pain or swelling of the joints
- Problem of the muscle (myositis), which can cause muscle pain and severe muscle weakness sometimes with dark urine

RARE, AND SERIOUS In 100 people receiving avelumab, 3 or fewer may have:
Avelumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body • Swelling and redness of the eye • Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness • Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly • A condition with high blood sugar (diabetes) which leads to tiredness, frequent urination or excessive thirst which may require treatment with insulin • 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 • Inflammation of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck • Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling • Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath

Other risks seen with Avelumab that are possibly related to the drug include:

- A condition that causes weakness (myasthenia gravis) in the skeletal muscles (muscles your body uses for movement) and eye muscles, drooping of one or both eyelids, blurred or double vision, a change in facial expression, difficulty swallowing, shortness of breath, impaired speech, or weakness in the arms, hands, fingers, legs, and neck.
    - A disease in which the immune system attacks the body's own tissues (Myasthenic syndrome). It can cause weakness in the upper legs, hips, and eye muscles.
- Inflammation in the pancreas (Pancreatitis), which may cause: upper abdominal pain, abdominal pain that radiates to your back, abdominal pain that feels worse after eating, fever, rapid pulse, nausea, vomiting, and tenderness when touching the abdomen.

Allergic reactions or reactions related with the infusions of avelumab might occur during treatment. Although avelumab is a fully human protein, the risk cannot be completely excluded. In general, these reactions are mild to moderate and can be handled with appropriate drugs, but in very rare cases severe to life-threatening and even fatal reactions might occur, which require advanced cardiac life support.

For the prevention of infusion-related adverse effects and possible allergic reactions you will receive a premedication of an antihistamine drug (H1 blocker) and acetaminophen 30 to 60

minutes before every infusion.

Other Study Risks

- Blood draws: The possible side effects of drawing blood include pain, bleeding, bruising, dizziness, light-headedness, fainting and, on rare occasions, local blood clot formation or infection with redness and irritation of the vein.
- EKG: Some skin irritation can occur where the EKG (also referred to as ECG) electrodes are placed. Once the electrodes are placed, the test will begin, is completely painless, and generally takes less than a minute to perform. After the test, the electrodes are removed.
- Imaging/scans: CT and/or MRI scans are used to monitor your disease while you are in this study. CT scans expose you to radiation and the amount depends on the number of body areas scanned. In addition, CT and MRI scans involve use of contrast (oral and/or IV) so that the cancer may be seen better on the images. Please ask the study doctor if you have questions about the risks of these scans. If done, MRI scans do not involve radiation risk. The scans that you will receive during this study are considered standard for your type of disease.
- Tumor biopsy: The likely side effects include discomfort or pain, redness, swelling, and/or bruising at the site of the needle insertion. Bleeding from the site of the needle insertion is a less likely risk. Rarely, significant infection or bleeding from this procedure, allergic reaction to the anesthetic, or formation of a scar at the site of needle entry occurs. If you will have sedation with the procedure, these risks will be discussed with you prior to the procedure. You will be asked to sign a separate consent form prior to any biopsy procedure.
- Midline Catheter Insertion: A non-tunneled central catheter is a soft tube a doctor puts into a vein leading to your heart. It is a way to take blood samples or give you fluids, medicines, or nutrients over a long period of time. Possible side effects include pain, bleeding, bruising, and, on rare occasions, swelling in your arm, chest, neck, or face on the same side as your catheter or infection.

Radiation Exposure from Imaging

During your participation in this research study, you will be exposed to radiation from CT of the neck, chest, abdomen, and pelvis. The amount of radiation exposure you will receive from these procedures is equal to approximately 9.1 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 that you get in this study will expose you to the roughly the same amount of radiation as 30 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 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 0.9 out of 100 (0.9 %) and of getting a fatal cancer is 0.5 out of 100 (0.5%).

MRI Risks

Your doctor may want you to get a magnetic resonance imaging (MRI) scan. We will obtain pictures of your brain for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your head. You will be in the scanner about 45 minutes. You may be asked to lie still for up to 15 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time.

It is very important for the experiment that you do not move your head or body inside the scanner. We will use padding around your head to help keep it in place.

We may place a bar in your mouth to help keep your head still.

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

Risks for gadolinium enhanced MRI scans:

Procedure

During part of the MRI you may receive gadolinium, a contrast agent, through an intravenous (IV) catheter. It will be done for medical purposes.

Risks

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis" which has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is not normal or if you received gadolinium within the previous month.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA recently issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well.

Some types of gadolinium contrast drugs are less likely to remain than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain.

We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

What are the risks related to pregnancy?

If you are capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. If you are a woman who is breast feeding or pregnant, you may not take part in this study because we don't know how this medicine would affect your baby or your unborn child. If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. If you are a woman who can become pregnant or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for six (6) months after you finish study treatment. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you or our partner have become pregnant during the restricted period, please contact the research team member identified at the top of this document as soon as possible.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

Because there is not much information about the drugs' effect on your cancer, we do not know if you will benefit from taking part in this study. Talk to your doctor about other approved agents and treatments that are available to you and that may provide clinical benefit without taking part in this study.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because of the knowledge gained from the study drug combination or the results of the research studies.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could

- choose to be treated or receive care for your cancer without being in a study. Treatments can be prescribed by your regular cancer doctor, even if you are not in this study. Your study doctor can talk to you more about these other treatment options, how they are given and their possible side effects.
- choose to take part in a different study, if one is available
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

You should discuss with your doctor your other choices and their risks and benefits.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

We will not return research results from this study.

EARLY WITHDRAWAL FROM THE STUDY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease worsens or comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if you become pregnant
- if the IL-15 and/ or the avelumab becomes unavailable
- if new information shows that another treatment would be better for you
- if you do not follow the study rules
- if the study is stopped for any reason

In this case, you will be informed of the reason therapy is being stopped.

After therapy is stopped, we would like to see you for a safety visit 30 and 90 days after your last dose.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

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 Division of Cancer Treatment and Diagnosis (DCTD) or designated representatives, and EMD Serono or designated representatives.

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 plan to use these specimens and data for studies going on right now, as well as studies in the future. These studies may provide additional information that will be helpful in understanding ccRCC, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the 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.

We may share your specimens and data with other researchers. 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 industry sponsors of research.

In addition to the use and sharing of your specimens and data described above, we might remove any information from your specimens and data that can identify you such as name, address, or medical record number, and then use the specimens and data for additional research studies at the NIH or other places. If we do this, we might not contact you to ask your permission or otherwise inform you.

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. 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 the specimens and data.

Please place your initials in the blank next to Yes or No for each of the questions below:

My specimens and data may be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

My specimens and data may be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. These researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data may be stored by the NIH as long as the study is open. When this study is closed, we may keep the data and any samples that are leftover for future research indefinitely.

Risks of Storage and Sharing of Specimens and Data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

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.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

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.

Cooperative Research and Development Agreement (CRADA)

The NIH and the research team for this study are using a study drug developed by EMD Serono through a joint study with your study team and the company. The company also provides financial support for this study.

Clinical Trial Agreements

The Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD) is providing IL-15 for this study to NIH without charge. No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

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

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. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. 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.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- Qualified representatives from EMD Serono, the pharmaceutical company who produces avelumab.
- Qualified representatives from DCTD, the manufacturer of IL-15.

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.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens and data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

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

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, Kevin Conlon, conlonkc@mail.nih.gov, 240-541-4559. You may also 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

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

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: _____.