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STUDY TITLE: A Phase II Pilot Study of Avelumab in Combination with Hypofractionated Radiotherapy in Patients with Relapsed Refractory Multiple Myeloma

STUDY SITE: National Cancer Institute

Cohort: *Affected Patient*

Consent Version: *11/20/2020*

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 multiple myeloma that has relapsed (come back) after initial treatment and has spread to other parts of your body (such as your soft tissue or bones).

The purpose of this study is to find out if avelumab, when given together with radiation therapy, may help to treat your disease. We also hope to learn if giving these treatments together is safe.

Avelumab works to treat cancer by helping your immune system to fight the cancer. Avelumab is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat multiple myeloma. However, the FDA has given us permission to use avelumab in this study.

The radiation therapy used in this study is a standard type where a few doses of radiation are delivered to a few of the sites of your tumors. The tumor sites will be chosen by the study doctors based on their size and location in your body. We hope that the way we are giving the radiation in this study will kill cancer cells at the sites of the radiation. We also hope it causes your immune system to kill myeloma cells in other parts of your body with the help of the avelumab.

Although the radiation therapy used in this study is standard care, it is not usually given by itself. There are also no other drugs known to work together with radiation therapy for your type of disease. There are other drugs 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. For example, there are several FDA approved therapies that you may have or have not received that have been associated with clinical benefit in some patients, such as: daratumumab alone or in combination with lenalidomide, bortezomib, or pomalidomide; elotuzumab in combination with lenalidomide; or, panobinostat in combination with bortezomib. You must have been previously treated with and have failed treatment due to your myeloma progressing, not be a candidate for (ineligible), or not be able to tolerate these other therapies. Other drugs your regular cancer doctor may have already tried or could give without being in a study are chemotherapy drugs not FDA approved to treat multiple myeloma, such as melphalan and cyclophosphamide. All of these other drugs have significant side effects including lowering of blood counts, numbness and tingling, nausea and vomiting, diarrhea, skin rashes, hair loss, inflammation of the bladder and lungs, infections, and secondary cancers. 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:

- 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, bone marrow testing and imaging.

- If you are eligible to receive treatment, you will receive avelumab. Avelumab is given by infusion (IV) in the NIH Clinical Center every 2 weeks. You will receive avelumab for two (2) doses, then, after the third dose of avelumab, you will receive radiation treatment each day for 5 days only. You may continue to receive avelumab every 2 weeks for as long as you do not have serious side effects and your disease is responding to the treatment.

- 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 most common side effects that you may have from the avelumab include: tiredness, nausea, diarrhea, decreased appetite, and infusion reactions. Some of the other most common side effects that you may have from the radiation include: skin reddening and irritation, pain at the site(s) of radiation.

- You will be seen regularly during the study. You will have clinical, laboratory, and imaging tests to see how you are doing and to assess your disease. We will also collect required samples from you (such as: blood, urine, bone marrow, and tumor biopsies) for both clinical and research purposes.

- After the study treatment has ended, we will need to see you at the NIH Clinical Center about 30 days after the last dose. Then, again about every 3-6 months for up to about five (5) years to assess your health and to see how you are doing. If at any time your disease comes back or gets worse, we may continue to contact you by phone to see how you are doing for the rest of your life if you are no longer being seen at the NIH.

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.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

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?

This is a research study. The purpose of this research study is to see if the study drug avelumab given with radiation therapy may help to treat multiple myeloma.

We are asking you to join this research study because you have multiple myeloma that relapsed after initial treatment and has spread to your soft tissues and bones.

The FDA has asked us to make sure that you understand that there are a number of different ways to treat multiple myeloma. You should ask your regular cancer doctor to explain to you the different kinds of treatment options for your cancer. If you join this study, your cancer will be treated with a drug that will activate your immune system to fight your cancer and with radiation therapy. Radiation therapy can be prescribed by your regular cancer doctor, even if you are not in this study.

WHAT WILL HAPPEN DURING THE STUDY?

If you decide to take part in this study, you may receive up to five doses of radiation therapy to all or several of the sites in your body where the disease is located. At the same time, you will receive avelumab (an IV infusion).

You will receive treatment in cycles (each cycle is 4 week or 28 days long) on an outpatient basis in the NIH Clinical Center. You should not need to be admitted to the hospital unless needed for scheduling reasons, special testing, or your doctor feels that it is in your best interests.

For the first cycle, you will receive avelumab alone. During cycle 2 you will receive both avelumab (2 doses each cycle, 2 weeks apart) together with radiation therapy (for five days in a row after the first dose of avelumab). From cycle 3 on, you will receive avelumab alone (2 doses each cycle, 2 weeks apart).

During the study

Testing (screening) will have been performed under another consent or another protocol to determine whether you are eligible to take part in this study.

If the screening tests show that you are eligible to take part, you may then receive treatment for research purposes. All participants will receive the same treatment on study.

Avelumab will be administered to you through an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) once every 2 weeks (on days 1 and 15) of every cycle. Radiation treatment will be administered to you only for 5 days during Cycle 2. After you complete 5 days of radiation treatment, you may continue treatment with avelumab alone unless your disease gets worse or you have unacceptable side effects.

We will give you standard premedications before the 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. You will also be asked to stay at the clinic for about 30 minutes after receiving avelumab for monitoring.

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
- Bone marrow testing and imaging:
    - Bone marrow aspiration/biopsy will be done around day 15 of cycle 2 (after radiation treatment). This may also be repeated if needed to assess your response to treatment.
    - Imaging assessments:
        - You will have a [^{18}F]-FDG PET/CT scan done at baseline (unless the [^{18}F]-FDG PET/CT performed at screening was with 28 days prior to starting first dose of avelumab), around day 15 of cycle 2, and one just prior to the end of your treatment. These may be replaced with CT and/or MRI scans.

- The [^{18}F]-FDG PET/CT scans may be replaced with an MRI scan. An MRI creates pictures of the inside of your body using strong magnets instead of x-ray energy. At the time of each scan you will be asked to fill out a screening form to verify that it is safe for you to have the scan. You will also be asked to remove any metallic objects you may be wearing (for example, watches, earrings or piercings) and possibly to change into a hospital gown. Then you'll be asked to lie on a narrow bed that will move into the MRI scanner. Once you are comfortable, the table will be moved into the scanner (the scanner is a long, narrow tube that is open at each end). You will need to lie still on the table during the scan which will take about 30 minutes to complete. You will hear normal "hammering" or clicking and squealing noises during the scan. While in the scanner you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the technician running the scan the entire time and will be provided an emergency button to squeeze at any time if you decide you want the scan to stop.
- The [^{18}F]-FDG PET/CT scans may be replaced with CT scans. The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures showing the inside of your body. During the procedure, you will need to lie still on a table inside the CT machine. The table will move you in and out of the machine during the scan and you will be instructed to hold your breath. The scan itself will only take a few minutes to complete, the entire visit will take about 30 minutes.

  - X-rays will also be done of the sites of the cancer in the bones.

- Research questionnaires about quality of life (PROMIS)

Additional research testing

In addition to the tests that we will conduct to determine whether you are having side effects or if you are responding to the study therapy, we will also collect samples from you for purposes of research only. The samples are being done to look at the effects of therapy on your immune system and markers of tumor activity, including collecting and testing tumor cells. Unless noted otherwise below, the samples will be collected at least once each cycle and at the time your disease responds to treatment or gets worse (required), and at the end of treatment (optional).

The samples included for these studies include:

- Blood and urine samples
- Optional bone marrow aspiration/biopsy collected at the end of treatment and at your safety visit: a portion of these samples may also be used for the clinical tests above. You will be asked to sign a separate consent at the time of each biopsy, and will be given the opportunity to decide whether or not you want to participate in the optional study.
- Tumor biopsy: an optional biopsy of tumor lesions in soft tissues or bones may be collected at any time if it is felt to be safe. You will be asked to sign a separate consent each time

you agree to have an optional biopsy. 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 a CT scan or ultrasound to help clearly locate your tumor when doing a biopsy. You can participate in the study even if you decide not to undergo the biopsy procedures. Although it is not clinically needed, samples will be used for disease evaluation first, with leftover samples used for the research studies.

- Imaging assessments: DW-MRI (diffusion weighted whole body magnetic resonance imaging scans) is a scan that looks at the whole body. DW-MRI scans will be performed before you receive any study drug (baseline), on day 15 of cycle 2, and at the beginning of cycle 4. In addition, DW-MRI scans will also be performed up to 4 more times: to evaluate changes in size or extent of your tumors(may possibly be up to 3 times), and optionally at the end of treatment. Although it is a test that can be done routinely in the clinic, it is used right now as a research test for your disease. Standard clinical operating procedures will be used for the test and image collection, and you and your doctors will receive the result of these imaging tests.
- Research questionnaires about quality of life (PROMIS): If you are a patient who can read, speak, and understand English or Spanish, we will also ask you to complete questionnaires. These are required and may be completed either on paper or electronically on a tablet such as an iPad. These will be done prior to and during treatment, about every 3-6 months during follow-up, and at the time your disease progresses. You will be asked questions about how you perform daily activities, your pain, and how you feel. The questionnaires should take no longer than about 20 minutes to complete.

All of your samples collected for research purposes on this study (such as the tumor and normal tissue) may be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) in the cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow.

To look at your DNA, we may do what is called "whole genome sequencing." This where we will do special tests in the lab to look at the entire sequence, or order, of how your DNA is put together. This is what makes you unique.

To determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA that are common to a particular type of tumor. To examine the tumor and normal tissue we may use several different techniques depending on the type of tissue we collect. These could include growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells), xenograft studies (placing or growing cells in another animal, such as mice), and looking in detail at the parts of the genes that produce specific proteins.

However, you should know that the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we share with you and this is described later in this consent form in the section for "Return of search results."

When you are finished taking the treatment

When you have finished taking the study drugs, you will be asked to return for a safety follow-up visit within about 30 days. At this visit, your will be asked questions about your health, get a physical exam and undergo routine blood and urine tests and research samples. We may also perform evaluations of your cancer (such as blood, urine, or imaging tests). We will follow-up with you again at about 3 months after treatment. If you are unable to return for this visit, we will obtain the information from you by telephone and/or from your outside primary doctor.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for as long as the study treatment benefits you. We will continue to follow you in clinic or by phone, and may perform tests to see how you are doing, about every 3 months for the first year after treatment, and about every 6 months until year 5. We will continue to follow you at least yearly after that if your cancer has not come back, gotten worse, or you have not started any new treatment for your disease.

If your cancer has worsened or you start another treatment, you will be contacted about every 3 months (by phone or in clinic if you continue to be seen here) to get information on any new medications, treatments, or procedures you are currently taking or have recently received for your cancer. You will be followed on this study for the rest of your life or until the study is stopped.

This study is expected to involve at least 15 visits and may involve more depending upon how long you receive treatment. Visits usually take about 3 hours each, but should not take longer than 8 hours.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

About 30 people will take part in this study at the NIH.

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

You should talk to your study doctor about any symptoms that you experience while taking part in the study.

If you choose to take part in this study, there is a risk that the avelumab and radiation may not be as good as the usual approach for your treating your cancer or condition.

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.

Avelumab and radiation therapy 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 be testing your blood and will let you know if changes occur that may 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, 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.

Below we show the most common and the most serious side effects that researchers know about. 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.

Risks from study therapy

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 (In 100 people receiving avelumab, more than 20 and up to 100**)**
• Fatigue (tiredness)
Occasional (In 100 people receiving avelumab, 4 to 20**)**

Common (In 100 people receiving avelumab, more than 20 and up to 100**)**

- Anemia (which may require blood transfusion)
- Nausea, diarrhea, vomiting
- Loss of appetite
- Flu-like symptoms including body aches
- Reaction during or following a drug infusion (fever, low blood pressure, flushing, dizziness, chills)
- Chills (feeling cold), fever
- Infection
- Bruising, bleeding
- Cough
- Dry skin
- Rash, itching, acne

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
- 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
- Myasthenia gravis, a disease that causes weakness in the skeletal muscles that worsens after periods of activity and improves after periods of rest. These muscles are responsible for functions involving breathing and moving parts of the body, including the arms and legs. Please let the study doctor know if you experience one of the following symptoms: weakness of the 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.

Allergic reactions or reactions in the context 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 (so-called H1 blocker) and acetaminophen 30 to 60 minutes before every infusion.

There is a risk of tumor lysis syndrome due to tumor shrinkage. This complication is caused by the breakdown products of dying cells and includes elevated blood potassium, elevated blood phosphorus, elevated blood uric acid and elevated urine uric acid, low blood calcium, and consequent acute kidney failure.

Special risks have been identified in similar trials utilizing drugs that inhibit the PD-1/L1 pathway in multiple myeloma using immunomodulatory drugs (pembrolizumab with lenalidomide or pomalidomide).

Recently, an important risk has been identified with the combination of PD-1 inhibitors and immunomodulatory drugs in multiple myeloma. This current study is utilizing a PD-L1 inhibitor without an immunomodulatory drug. Therefore, the below, may not be applicable to the current study but serves only to inform.

- Two clinical trials evaluating KEYTRUDA® (pembrolizumab), a PD-1 inhibitor, in combination with an immunomodulatory agent (either pomalidomide or lenalidomide) in patients with multiple myeloma demonstrated an increased risk of death for patients receiving KEYTRUDA® (pembrolizumab). PD-1 inhibitors and immunomodulatory agents are classes of drugs which are used for the treatment of cancer.
- Keynote-183 was a randomized trial which evaluated pomalidomide and low-dose dexamethasone with or without pembrolizumab in patients with relapsed and refractory multiple myeloma. With the current information, on an average it is estimated that the risk of death in the pembrolizumab treated arm is 1.6 times that of the control arm.
- Keynote-185 was a randomized trial which evaluated lenalidomide and low-dose dexamethasone with or without pembrolizumab in patients with newly diagnosed multiple myeloma. With the current information, on an average it is estimated that Pembrolizumab doubles the risk of death compared to the control arm.
- Description of the causes of death: Some patients in these studies developed fatal, serious side effects, including inflammation of the heart(myocarditis), rash with peeling of skin and/or mucous membranes, heart attack, cardiac arrest, cardiac failure, bleeding of the heart lining, respiratory tract infection, respiratory failure, blood clots in the lungs, sepsis, multiple organ failure, suicide, and sudden death. Some of the causes of death are unknown at this time.
- At this time, it is unknown if the increased risk of death seen in the trials evaluating KEYTRUDA® (pembrolizumab), a PD-1 inhibitor, will be seen in trials of PD-L1 inhibitors (or “other PD1 inhibitors”), as they are different monoclonal antibodies that target the same pathway.

- Though the combination of treatments on this study is different from the studies in which the increased rate of deaths was observed, it is unclear if the agents on this study either alone or in combination may have similar risks.

What are the risks of radiation from being in the study?

Radiation therapy

In general, the radiation therapy you receive on this study can cause the following side effects regardless of the site that is being treated.

- Tiredness
- Lowered blood counts
- Skin reddening
- Mild ache at the site that received radiation
- Nausea, vomiting
- Diarrhea
- Abdominal pain
- Feelings of claustrophobia
- Skin irritation
- Sore throat and trouble swallowing
- Late or delayed side effects (the side effects noted above, but they occur after the radiation has completed)

These side effects tend to go away after the radiation therapy is completed. However, there are some long-term or chronic side effects that primarily affect the small bowel, liver, kidneys, and spinal cord. Many of these side effects take months to years to develop. Rarely, treatment with radiation may also lead to developing other types of cancer, usually years after receiving the treatment. It is possible that you may experience some, all, or none of the side effects described above. It is also possible that your specific treatment may cause some side effects that we cannot anticipate. For that reason, you will be watched closely while you are receiving treatment for any signs that might signal the earliest stage of toxicity so that we can treat them early.

If any of these side effects occur, you must inform your study doctor immediately.

Overall radiation risk

During a year in this research study, your tumor may be exposed to 5 Gy from radiation therapy, received over the course of 5 days for a total of 25 Gy. You will also receive a much smaller amount of radiation from scans used to plan your treatment and measure your progress. Additionally, tumor biopsies may be done by a specialist using a CT scanner to guide the biopsy needle into the tumor to ensure accuracy. The total scans include FDG-PET/CT scans (or CT scans), skeletal surveys, CT guided biopsies. The amount of radiation from these scans adds minimal additional risk to the higher radiation doses received in the course of treatment. This radiation has been reviewed by the NIH Radiation Safety Committee and deemed appropriate for this study.

You may not participate in this study if you are pregnant. If you are capable of becoming pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

Risks of other procedures

- Blood draws may cause pain, redness, bruising or infection at the site of the needle stick. Rarely some people faint. The study team member may apply numbing cream to the area so that the needle stick won't hurt as much.
- Questionnaires: The questions asked on the questionnaires may make you feel uncomfortable. You are not required to answer questions that you do not want to answer.
- Bone Marrow Aspiration and Biopsy: A numbing agent that can cause a stinging or burning sensation may be injected at the site of your bone marrow biopsy. The biopsy needle will go through the skin into the bone and may produce a brief, sharp pain. As the bone marrow liquid is taken from the bone, there may be a brief, sharp pain. Since the inside of the bone cannot be numbed, this procedure may cause some discomfort, however not all patients experience discomfort.
    - Likely: discomfort or pain, redness, swelling, and/or bruising at the site of the needle insertion.
    - Less likely: bleeding from site of the needle insertion.
    - Rare: significant infection or bleeding from this procedure, allergic reaction to the anesthetic, formation of a scar at the site of needle entry.
- 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.
- [^{18}F]-FDG PET/CT scans: There is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely, death. The contrast material may also cause kidney problems. The study doctors will do a blood test prior to the test to confirm that it is safe you to receive the contrast.
- MRI scans (non DW-MRI): 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. DW-MRI scans: The DW-MRI scan requires you to remain still on your back for approximately 1½ hours. Even though adverse side effects are not anticipated, you should tell the doctors or nurses supervising the scan of any discomfort you experience during the scans.

What are the risks related to pregnancy?

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 30 days after you finish study treatment (the restricted period). 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. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant during the restricted period, please contact the research team member identified at the top of this document as soon as possible.

If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant during the restricted period. There may be unknown risks to a fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you think your partner has become pregnant during the restricted period, please contact the research team member identified at the top of this document as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, please discuss this with the study team.

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Privacy Risks Associated with Return of Incidental or Secondary Findings

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

However, the potential benefits to you might be the shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer.

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 information that will be gained from the research samples and testing.

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 with surgery, radiation or with drugs without being in a study; these or may not include treatments already approved by the FDA for your disease
- 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

When we are examining your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

These include:

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

Since the analyses that we perform in our laboratory are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing, the genetic changes that we find may or may not be valid. Therefore, we do not plan to inform you of all of the genetic results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

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 you need to use medications that are not allowed on this study
- if 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 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 primary 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 EMD Serono, Inc. (the pharmaceutical company who produces avelumab), or designated representatives.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will Your Specimens or Data Be Saved for Use in Other Research Studies?

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

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

_____ Yes _____ No

Initials Initials

Will Your Specimens or Data Be Shared for Use in Other Research Studies?

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

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

_____ Yes _____ No

Initials Initials

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

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future

research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

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.

Will Your Genomic Data Be Shared Outside of This Study?

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, 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 for as long as the study is open. When this study is closed, we may keep the samples 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?

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

You will not receive compensation for participation in this study.

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

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

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

Will taking part in this research study cost you anything?

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

- 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.

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

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

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, Inc., the pharmaceutical company who produces avelumab.

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 or 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, Dr. Dickran Kazandjian at kazandjiandg@mail.nih.gov or 240-480-0532. 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

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

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

Witness:

Signature of Witness*	Print Name of Witness	Date

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

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

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