PRINCIPAL INVESTIGATOR: Julius Strauss, MD

STUDY TITLE: A Randomized Phase II Trial of Standard of Care Alone or in Combination with Ad CEA Vaccine and Avelumab in Patients with Previously Untreated Metastatic or Unresectable Colorectal Cancer

STUDY SITE: NIH Clinical Center (CC)

Cohort: Affected patient

Consent Version: October 30, 2019

WHO DO YOU CONTACT ABOUT THIS STUDY?

Julius Strauss, MD
Phone: 301-480-0202
Email: julius.strauss@nih.gov

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

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

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?

The purpose of this study is to investigate whether the study drugs avelumab and the Ad-CEA vaccine, given in combination with the standard of care therapy increases the time it takes for your disease to get worse in comparison to standard of care alone.

Avelumab is an investigational agent that targets and inhibits a pathway that prevents your immune system from effectively fighting your cancer. Ad-CEA is an investigational vaccine that may promote your immune system's response against cancer. Investigational means that they have not been approved by the FDA for treatment of your cancer.

The standard of care therapy used on this study is FOLFOX (**fol**inic acid [leucovorin] +5-**f**luorouracil [5-FU] + **ox**aliplatin) plus bevacizumab for up to 24 weeks, followed by capecitabine plus bevacizumab. These agents are approved by the FDA for the treatment of colorectal cancer that has spread to other sites.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You are being asked to take part in this study because you have been diagnosed with and have not been treated for colorectal cancer that has spread to other parts of the body. During the screening process, you will be tested to determine if your cancer has a mismatch repair deficiency (MMR-D), a mechanism of DNA repair that is not working properly in some cases. It is very important to identify if your tumor has this deficiency as it would mean that other treatment would be more appropriate. We will enroll only patients who do not have this mismatch repair deficiency.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 97 subjects at the National Cancer Institute and at the Georgetown Lombardi Cancer Center will take part in this study.

DESCRIPTION OF RESEARCH STUDY

For your safety, some medications and therapies are not allowed during the study. You should tell the study doctor before you take any new medications (includes prescription, herbal, and over-the-counter remedies) or start a new therapy during the study.

Before you begin the study

Before you can enroll on the study, you will have standard blood tests (including a pregnancy test if you are a woman that can have children), imaging studies (CT, MRI), a physical exam and any other tests needed to be certain that it is safe for you to participate in this study. You will not able to participate in the study if you are pregnant.

To be enrolled in this trial you will also need to provide a documentation, confirming your tumor and if it has a mismatch repair deficiency (MMR-D). If this is not available, we will perform a biopsy, a procedure using a needle to remove a piece of tissue or a sample of cells from your body so that it can be analyzed in a laboratory and is used to diagnose or evaluate the cancer.

During the study

We will ask you to provide a sample of your tumor if available from a previous surgery or biopsy.

The first 6 subjects enrolled (lead-in group) on the study will receive Ad-CEA, avelumab plus standard of care. If more than one of these 6 patients experience a side effect that is considered too serious by the study doctor during the first 28 days of treatment, we will not enroll any further participants.

If fewer than two experience unexpected side effects, the rest of the subjects will be selected by a computer to participate in one of two treatment arms on a 1:1 basis. This means that there is a 50% chance of being assigned to one arm or the other.

If you are assigned to Arm A you will receive standard of care therapy for colorectal cancer. If you are assigned to Arm B, you will receive Ad-CEA + avelumab + standard of care. For all participants, study treatment will be divided into cycles each lasting 14 days (2 weeks). You will be treated until your disease worsens or you have intolerable side effects. If you were assigned to Arm A and your disease worsens, your doctor will offer you the option of crossing over to Arm B. In this case, you will be treated until your disease worsens further or you experience intolerable side effects.

All Participants

Induction Therapy

For the first 12 cycles, standard of care chemotherapy will consist of FOLFOX + bevacizumab.

On the first day (Arm A) or second day (Arm B) of each cycle, you will receive FOLFOX + bevacizumab through an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm). The infusion will last approximately 2 days.

Note: If you experience intolerable side effects during the induction therapy, your study doctor may begin maintenance therapy prior to the completion of 12 cycles of induction therapy.

Maintenance Therapy

After you have completed induction therapy, standard of care chemotherapy will consist of capecitabine + bevacizumab. Your study doctor may also choose to add oxaliplatin if you have crossed over from Arm A during the maintenance phase.

You will be given a supply of capecitabine to take home. You will take capecitabine by mouth twice a day every day with water within 30 minutes after a meal.

On the first day (Arm A) or second day (Arm B) of each cycle, you will also receive bevacizumab (and oxaliplatin if it has been added to your treatment) through an IV. The infusion will last approximately 1 - 2 hours.

You will have a physical exam, answer questions about your health and have blood and urine tests each cycle to help us monitor your health. An EKG will be performed every 4 weeks (every other cycle) during the first four cycles and then every 8 weeks (every 4 cycles) starting with cycle 5. You will also have scans every 8 weeks (every 4 cycles) to monitor your disease.

Lead-in or Arm B (including crossovers) only

Ad-CEA vaccine will be injected every 2 weeks for three doses, every 4 weeks for three doses, then every 12 weeks.

Avelumab will be given to you through an IV on the first day of each 14-day cycle. Each infusion lasts for about an hour.

About 30 - 60 minutes before each dose of avelumab you will be given 2 medicines to help prevent any side effects or allergic reactions:

1) Acetaminophen (Tylenol)
2) An antihistamine such as Benadryl

Research tests

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. These studies include:

- Blood samples to study the effects of therapy on your immune system will be collected during cycles 1, 3, 5, 9 and every 4 cycles thereafter.
- Tumor biopsies (optional) might be collected before you start treatment and any time while you are on treatment after you have completed 4 cycles of therapy. These biopsies are not necessary for your treatment or evaluation of your disease, samples will be used for research only. Please see page 13 for the risks of biopsy. You will be asked to sign a separate consent each time you agree to have an optional biopsy. You can participate in the study even if you decide not to undergo the biopsy procedures.
- Genetic testing – Your tissue samples contain genes, which are made up of DNA (**d**eoxyribo**n**ucleic **a**cid) which serves as the "instruction book" for the cells that make up our bodies. We will use the tissue samples you provided at screening and other time points to learn about how the genes in your tumor compare to genes in normal tissue. Your tissue will help us study how genes might play a role in colorectal cancer and other diseases. We will not share the results of these research tests with you.

When you are finished taking the drugs

About 4 – 5 weeks after you have finished taking the study drugs, you will be asked to return for a safety follow up visit. At this visit, your will be asked questions about your health, get a physical exam and undergo routine blood and urine tests. If you are unable to return for this visit, we will obtain the information from you by telephone.

After the safety visit, we will call you or your physician approximately once a year to ask about survival and about any other medications you may have taken for your cancer.

BIRTH CONTROL

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. 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 4 months after the last avelumab infusion or 6 months after the last bevacizumab infusion, whichever occurs later. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

RISKS OR DISCOMFORTS OF PARTICIPATION

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

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

The vaccine and chemotherapy 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.

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

Here are important points about side effects:

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

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

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

Late side effects of the investigational agents may affect your ability to tolerate subsequent regimens of standard of care chemotherapy.

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

All Participants

Possible Side Effects of FOLFOX (Leucovorin, 5-Fluorouracil, Oxaliplatin)

Common (occurring in more than 20% of patients)

• Hair loss • Redness, pain or peeling of palms and soles • Rash, increased risk of sunburn, itching • Heartburn • Headache • Sores in mouth which may cause difficulty swallowing • Anemia which may require blood transfusion • Diarrhea, nausea, vomiting, constipation, loss of appetite	• Tiredness • Bruising, bleeding • Infection, especially when white blood cell count is low • Numbness and tingling of the arms and legs • Feeling of "pins and needles" in arms and legs • Pain • Fever, cough

Occasional (occurring in 4-20% of patients)

• Chest pain • Hoarseness • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Abnormal eye movement, blurred vision, watering eyes • Discomfort from light • Swelling, redness, tingling and pain of hands and feet • Blood clot which may cause swelling, pain, or shortness of breath • Abnormal heartbeat which may cause fainting • Hearing loss • Dry eye, mouth, skin • Swelling and redness of the eye • Blurred vision with chance of blindness • Visual loss • Problem with eyelid • Fluid in the belly • Passing gas	• Internal bleeding which may cause black tarry stool, blood in vomit or urine, or coughing up blood • Damage to organs which may cause shortness of breath • Chills • Swelling and redness at the site of the medication injection • Liver damage which may cause yellowing of eyes and skin • Kidney damage which may require dialysis • Weight gain, weight loss, dehydration • Dizziness • Changes in taste, voice • Abnormal body movement • Stroke which may cause paralysis, weakness • Inability to move shoulder or turn head • Bleeding from multiple sites including vaginal bleeding, bleeding of the testis, or bleeding of the brain • Muscle weakness • Seizure • Worry, confusion, depression

• Difficulty walking, opening mouth, talking, with balance and hearing, smelling, eating, sleeping, emptying the bladder • Swelling of the body which may cause shortness of breath • Blockage of the airway which may cause shortness of breath, wheezing	• Increased urination • Stuffy nose, hiccups, sinus problems • Scarring of the lungs • Increased sweating, flushing, hot flashes • High blood pressure

Rare and serious (occurring in fewer than 4% of patients)

- A new cancer resulting from treatment of earlier cancer
- Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness

Possible Side Effects of Bevacizumab

Common (occurring in more than 20% of patients)

• high blood pressure • blood clots in a vein (possible pain, swelling, and/or redness) • pain • nerve damage (loss of sensory function) • headache • dizziness • fatigue • hair loss (partial or total) • abdominal pain	• loss of appetite • constipation • diarrhea • mouth blisters/sores (possible difficulty swallowing) • digestive system bleeding • upset stomach • vomiting • abnormal taste	• failure of the ovaries to produce hormones, which may be permanent (possible stopped menstrual cycle) • bleeding • nosebleed • low white blood cell counts • difficulty breathing • weakness • abnormal kidney test (possible kidney damage)

Occasional (occurring in 3-20% of patients)

• blood clots in an artery (possible organ damage such as stroke and/or heart attack) • low blood pressure (possible dizziness/fainting) • heart failure • fainting • bleeding in the brain and/or spinal cord • stroke	• shedding and scaling of the skin (possible fatal loss of bodily fluids) • change of skin color • low blood levels of sodium (possible headache, confusion, seizures, and/or coma) • dehydration • gas • dry mouth	• inflammation or paralysis of the intestines • weight loss • nausea • uterine and/or vaginal bleeding • low platelet cell counts • pain (back/muscle) • voice changes • runny nose

• difficulty walking • dry skin • skin sores • opening of a wound	• hole in the intestines (possibly leaking contents into the abdomen) • bleeding gums	• lung inflammation (possible difficulty breathing) • infusion reaction (possible chills and/or hives)

Rare but serious (occurring in fewer than 3% of patients)

• severe heart problems • heart attack • chest pain due to heart trouble • severe increase in blood pressure (possible stroke) • brain injury that may be reversible (possible headache, confusion, seizures, and/or vision loss) • decreased brain function due to high blood pressure • decreased blood flow to part of the bowel (possibly causing death of tissue) • bleeding around the brain • temporary stroke symptoms • intestinal blockage • stomach and/or small intestine ulcer	• vein blockage in the abdomen hole in the gall bladder (possible abdominal pain, gall stones, nausea, and/or infection) • hole in the bladder • destruction of red blood cells • low red blood cell counts • bone destruction (including destruction of the jaw bone) • inflammation inside the eye • blurry vision • increased pressure in the eye (possible pain and/or blurry vision) • detached retina (possible partial blindness) • deafness	• kidney failure • decreased kidney function (possible kidney failure) • coughing up blood • increased blood pressure in the lungs (possible difficulty breathing and/or heart failure) • blockage in the lung (possible pain, shortness of breath, and/or failure to breathe) • abnormal hole inside the nose • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • wound healing problems

Bevacizumab may rarely cause an abnormal opening that develops between one area of the body and another (for example, an abnormal connection and opening in one or more places between the trachea [breathing tube] and esophagus, which may interfere with swallowing, digestion, and/or choking). This may result in death.

If you are taking Coumadin (warfarin) or other blood-thinning drugs, you may be at higher risk of blood clots and/or bleeding.

Possible Side Effects of Capecitabine

Common (occurring in more than 20% of patients)

• Swelling of the body • Blisters on the skin • Redness, pain or peeling of palms and soles • Pain • Diarrhea, loss of appetite, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Fever	• Anemia which may require blood transfusions • Infection, especially when white blood cell count is low • Bruising, bleeding • Feeling of "pins and needles" in arms and legs • Tiredness

Occasional (occurring in 4-20% of patients)

• Blurred vision, dry or itchy eyes • Muscle spasms, body aches • Abnormal heartbeat • Restlessness, irritability	• Swelling of face, fingers and lower legs • Constipation • Difficulty with balancing

Rare and serious (occurring in fewer than 4% of patients)

• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Difficulty speaking, walking or seeing • Internal bleeding which may cause blood in vomit or black tarry stools • Damage to the heart

Lead in and Arm B (including crossovers)

Possible Side-Effects of Ad-CEA

Common (occurring in more than 5 % of patients)

• Redness, pain and swelling at the injection site • Flu-like symptoms • Fever • Fatigue (tiredness) • Shortness of breath	• Pain • Loss of appetite • Chills • Constipation • Swelling arms, legs • Nausea

Occasional (occurring in less than 5% but more than 2 % of patients)

• Fluid around lungs • Anemia which may require transfusion	• Bloating • Blockage of the stomach

• Abnormal laboratory result	• Damage to the kidneys

Possible Side Effects of Avelumab

Common (occurring in more than 5 % of patients)

- Fatigue (tiredness)
- Nausea
- Diarrhea
- Decreased appetite
- Infusion-related reaction
- Chills (feeling cold)

Occasional (occurring in less than 5% of patients)

- Shortness of breath
- Rash
- Abdominal pain
- Non-cardiac chest pain

Allergic reactions or reactions in the context with the infusions 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.

In addition, immune-mediated side effects might be possible. These are:

- joint pain
- arthritis (inflammatory disease of the joint)
- pneumonitis (inflammatory disease of the lung)
- hypothyroidism (decreased function of the thyroid gland)
- hyperthyroidism (increased function of thyroid gland)
- thyroiditis (inflammatory disease of the thyroid gland)
- autoimmune hepatitis (inflammatory disease of the liver caused by the body's immune system)
- thrombocytopenia (decrease of the blood platelets)
- dry eyes
- inflammatory eye disease
- diabetes mellitus (high blood sugar levels)
- decreased function of the adrenal glands
- inflammatory disease of muscles characterized by pain and tenderness
- colitis (inflammatory disease of the large intestine)
- impairment of the brain function
- psoriasis
- nerve irritation

- autoimmune disorder (body's immune system approaches own cells)
- myocarditis

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.

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

Subjects Treated with Oxaliplatin but not FOLFOX

Possible Side Effects of Oxaliplatin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Oxaliplatin, more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting, constipation, loss of appetite • Tiredness • Bruising, bleeding • Infection, especially when white blood cell count is low • Numbness and tingling of the arms and legs • Feeling of "pins and needles" in arms and legs • Pain • Fever, cough

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Oxaliplatin, from 4 to 20 may have:
• Blood clot which may cause swelling, pain, or shortness of breath • Abnormal heartbeat which may cause fainting • Hearing loss • Dry eye, mouth, skin • Swelling and redness of the eye • Blurred vision with chance of blindness • Visual loss • Problem with eyelid • Fluid in the belly • Heartburn, passing gas • Difficulty walking, opening mouth, talking, with balance and hearing, smelling, eating, sleeping, emptying the bladder • Swelling of the body which may cause shortness of breath • Blockage of the airway which may cause shortness of breath, cough, wheezing • Bleeding from multiple sites including vaginal bleeding, bleeding of the testis, or bleeding of the brain

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Oxaliplatin, from 4 to 20 may have:
• Internal bleeding which may cause black tarry stool, blood in vomit or urine, or coughing up blood • Damage to organs which may cause shortness of breath • Sores in throat or mouth which may cause difficulty swallowing • Chills • Swelling and redness at the site of the medication injection • Liver damage which may cause yellowing of eyes and skin • Kidney damage which may require dialysis • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Weight gain, weight loss, dehydration • Dizziness, headache • Changes in taste, voice • Abnormal body movement including the eye and eyelid • Stroke which may cause paralysis, weakness • Inability to move shoulder or turn head • Muscle weakness • Seizure • Worry, confusion, depression • Increased urination • Stuffy nose, shortness of breath, hiccups, sinus problems • Scarring of the lungs • Hair loss, itching, rash, hives • Increased sweating, flushing, hot flashes • High blood pressure • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving Oxaliplatin, 3 or fewer may have:
• Redness, pain or peeling of palms and soles • Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness

Risks from Blood Collection

Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

Risks from Biopsy

This procedure usually causes only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site.

Tumor biopsies may be done by a specialist using the CT scanner or ultrasound machine to guide the biopsy needle into the tumor to ensure accuracy. To collect the optional research biopsies, you may be exposed to 2 CT scans. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this procedure is 1.5 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

Risks Associated with Genetic Testing

Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. While neither the public nor the controlled-access databases developed for this project will have information such as your name, address, telephone number, or social security number, it may be possible to identify you based on the information in these databases and other public information (including information you tell people or post about yourself). The risk of this happening is currently very low.

Protections against misuse of genetic information

Since some genetic variations can help to predict future health problems for you and your relatives, this information might be of interest to health care providers, life insurance companies, and others. However, Federal and State laws provide some protections against discrimination based on genetic information. For example, the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, GINA does not prevent companies that sell life insurance, disability insurance, or long-term care insurance from using genetic information as a reason to deny coverage or set premiums. GINA also does not apply to members of the United States military, individuals covered by the Indian Health Service, or veterans obtaining health care through the Veteran's Administration. Lastly, GINA does not forbid insurance medical underwriting based on your current health status though the Affordable Care Act limits consideration of pre-existing conditions by insurers.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to find out whether the experimental treatment increases the time it takes colorectal cancer to worsen when compared to standard of care. We do not know if you will receive personal, medical benefit from taking part in this study. Potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

STOPPING THERAPY

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 comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if the investigator decides to end the study
- if you have a positive pregnancy test

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

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 EMD Serono or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

CONFLICT OF INTEREST

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

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

The National Institutes of Health and the research team for this study are using therapies developed by EMD Serono and Etubics and a test developed by NantOmics through a joint study with your researchers and the companies. The companies also provide financial support for this study.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

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

These specimens and data will be used for future research and shared with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

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

Genomic Data Sharing

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.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

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.

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.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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 Etubics, the pharmaceutical company who produces the Ad-CEA vaccine.
- Qualified representatives from NantOmics, the company that will perform the genetic testing on this study.

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 records 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 medical 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, Julius Strauss, MD, Phone: 301-480-0202, Email: julius.strauss@nih.gov. 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: This section is only required if you are doing the oral short-consent process and this English consent form has been approved by the IRB for use as the basis of translation.

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: _____.