PRINCIPAL INVESTIGATOR: Tim Greten, M.D.

STUDY TITLE: A Phase I/II Study of Pexa-Vec Oncolytic Virus in Combination with Immune Checkpoint Inhibition in Refractory Colorectal Cancer

STUDY SITE: NIH Clinical Center

Cohort: Affected patient

Consent Version: 07/07/2020.

WHO DO YOU CONTACT ABOUT THIS STUDY?

Tim Greten, MD, by phone at 240-760-6114 or email Tim.greten@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 Pexa-Vec and Durvalumab, given with or without Tremelimumab cause your tumor to shrink. We will also look at the safety of both combinations.

Pexa-Vec, Durvalumab and Tremelimumab are investigational drugs designed to boost the body's immune system. Investigational means that these drugs alone or in combination have not been approved by the US Food and Drug Administration either as a prescription or over the counter drug.

Pexa-Vec is a genetically inactivated vaccinia virus modified in the lab to kill cancer cells and produce human proteins, which helps to activate your immune system. To date, over 360 patients in clinical trials, including at least 60 with colon cancer, have been treated with Pexa-Vec with few side effects. Clinical studies have also shown reduction in tumor size with no effect on normal tissue.

Durvalumab targets a protein on tumor cells called PDL-1. PDL-1 normally maintains the balance of the immune system. In cancer, PDL-1 helps tumors evade detection and elimination by the immune system. Durvalumab may increase the immune system's ability to identify and destroy cancer cells. To date Durvalumab has been given to more than 1800 patients as part of ongoing studies either alone or in combination with other anti-cancer agents. It is possible that Pexa-Vec and Durvalumab will work together to keep the cancer from blocking the immune response against the tumor.

Although Tremelimumab is not approved by the FDA, it has been evaluated in a number of clinical studies, and in over 1000 patients. Tremelimumab is similar in how it works to another drug (called ipilimumab) which was recently approved by the FDA. Tremelimumab has been tested in a small group of patients with pancreatic cancer and in general was well tolerated. It has not been tested however in combination with Pexa-Vec, which is one of the main goals of this study.

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 been treated for colorectal cancer that has spread to other parts of the body. During the screening process, you will be tested to determine whether your cancer cells have a certain deficiency in DNA repair. You will be enrolled if you do not have the deficiency (status =microsatellite stable (MSS) OR if you have the deficiency (status = microsatellite instability high (MSI-H) and your disease has gotten worse on anti-PDL-1 therapy (e.g., nivolumab, pembrolizumab).

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 35 participants 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 (including 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:

- A review of any past or current medical conditions, medicines you are taking and cancer history.
- Physical examination, including vital signs, height and weight
- Electrocardiogram (ECG) and Echocardiogram to evaluate your heart.
- Review of your symptoms and your ability to perform your normal activities.

- Imaging Assessments –a computed tomographic scan (CT) that produces a picture of your body using a small amount of radiation. (Magnetic resonance imaging (MRI) that uses a magnetic field to produce an image of your tumor and of your brain may be done if your study doctor thinks MRI is needed).
- You will have blood drawn for routine blood tests to find out if you are anemic, have low blood counts and if your liver, kidneys, and other organs are working well.
- Blood tests to evaluate if you were exposed to HIV, Hepatitis B or C
- Test for tuberculosis if your doctor thinks that it is needed
- Pregnancy test if you are a woman who can have children.
- You will be asked to provide a sample of your tumor from a previous surgery so that we may confirm your diagnosis and microsatellite status. If a sample is not available, you will need to have a biopsy of your tumor.
- 24-hour urine sample if the study doctor thinks it is needed
- Examination by a cardiologist (heart doctor) if you have a history of heart disease

During the study

There will be two parts to this study: A and B. The first 3 - 16 participants will be enrolled in part A; after part A is complete, we will decide whether to enroll an additional 3 – 16 participants in part B. The participants enrolled in part A will receive treatment with Pexa-Vec in combination with Durvalumab. The participants enrolled in part B will receive treatment with Pexa-Vec in combination with Durvalumab and Tremelimumab. For all participants, study treatment will be divided into cycles each lasting approximately 28 days.

Part A

The first 3 - 6 participants enrolled in part A will receive the lowest dose of Pexa-Vec to be tested in combination with Durvalumab. If more than one person experiences 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 unacceptable side effects, the next 3- 10 participants enrolled in part A will receive a higher dose of Pexa-Vec in combination with Durvalumab.

During first two cycles, you will get Pexa-Vec in combination with Durvalumab. Starting from cycle 3 you will have Durvalumab treatment only. You will be treated until your disease worsens or you have intolerable side effects.

Once enrollment and a full assessment of the safety in part A has been completed, we will, if considered safe and effective, begin enrolling participants to part B.

Part B

The first 3 - 6 participants enrolled in part B will receive the lower dose of Pexa-Vec in combination with Durvalumab and Tremelimumab. If more than one person experiences 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 unacceptable side effects, the next 3 - 10 participants enrolled in part B will receive the higher dose of Pexa-Vec in combination with Durvalumab and Tremelimumab.

During first two cycles, you will get Pexa-Vec in combination with Durvalumab and one dose of Tremelimumab. Starting from cycle 3 you will have Durvalumab treatment only. You will be treated until your disease worsens or you have intolerable side effects.

Drug administration and schedule

Pexa-Vec will be administered to you through an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) every 2 weeks for 8 weeks.

Durvalumab will be administered through an IV on the Day 1 of each Cycle. (Day 1 of cycle 1 = 12 days after the first dose of Pexa-Vec)

If you are enrolled in part B in addition to Pexa-Vec and Durvalumab you will receive Tremelimumab. Tremelimumab will be administered through an IV on the Day 1 of cycle 1.

The infusions of Pexa-Vec, Durvalumab and Tremelimumab will last approximately 1 hour. Your vital signs will be monitored for at least 20 hours after the first dose of Pexa-Vec and for at least 1 hour after the first dose of Durvalumab +/- Tremelimumab. For subsequent doses, if there are no side effects related to the infusion the monitoring period may be reduced.

During the visits

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 ECG will be performed every 4 weeks (every cycle). You will also have scans every 8 weeks (every 2 cycles) to monitor your disease.

Pre-medication

About 30 -60 minutes before each dose of Pexa-Vec you will be given Acetaminophen (Tylenol) to help prevent any side effects or allergic reactions. In addition, because there is a risk of low blood pressure, you will be given IV fluids before each Pexa-Vec infusion and asked to stop taking any medications for high blood pressure for 48 hours before and after Pexa-Vec

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 every cycle.
- Tumor biopsies: procedures 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. You will be required to have two biopsies: once before treatment and once after treatment, either on day 1 of cycle 1 or on day 1 of cycle 2 depending on a random selection (like a flip of a coin). We may ask you to allow us to perform third biopsy around day 1 of

cycle 4, but this biopsy is optional and you will be asked to sign a separate consent if you agree to have this optional biopsy. Please see page 15 for the risks of biopsy.

- Genetic testing – Your tissue will help us study how genes might play a role in colorectal cancer. The testing will be limited so to genes that are not known to cause diseases; therefore, we will not share the results of these research tests with you.

WHEN YOU ARE FINISHED TAKING THE DRUGS

After you have finished taking the study drugs, you will be asked to return to clinic once a month for a safety follow up visits. At these visits, you 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 these visits, we will obtain the information from you by telephone.

BLOOD DONATION

You should not donate blood while in the study and for 3 months after the last Durvalumab infusion or 6 months after the last dose of Durvalumab + Tremelimumab combination therapy, whichever comes later.

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.

Women

If you are a woman who can become pregnant, you will need to practice abstinence if that is your usual lifestyle or two effective forms of birth control before starting study treatment, during study treatment, and for 3 months after the last Durvalumab infusion or 6 months after the last dose of Durvalumab + Tremelimumab combination therapy, whichever comes later. You should also refrain from breast feeding during this time.

Men

If you are the partner of a woman who can become pregnant and you have not had a vasectomy, you will need to practice abstinence if that is your usual lifestyle or two effective forms of birth control before starting study treatment, during study treatment, and for 3 months after the last Durvalumab infusion or 6 months after the last dose of Durvalumab + Tremelimumab combination therapy, whichever comes later. You should also refrain from donating sperm during this time.

All

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:

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

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

Pexa-Vec

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Pexa-Vec, more than 20 and up to 100 may have:
• Short-lived (2-3 days) flu-like feelings including fever, chills, headache, nausea, vomiting. • Chills - that may be strong enough to cause shaking with a feeling of coldness. This reaction commonly occurs with or before fever and is called rigors. If needed, anti-rigor medication may be prescribed before and after treatment.

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Pexa-Vec, more than 20 and up to 100 may have:

- Low blood pressure – which may cause feeling faint. In this case stop temporarily any medication for high blood pressure or medications which can affect your blood pressure. Your study doctor will know all the medications you are taking (including herbal or over-the-counter remedies) and will instruct you on when to stop any medications and when it is safe to start them.
- Rashes. Small (less than 1 cm) superficial skin or oral small blister or pimple containing Pexa-Vec may develop after Pexa-Vec treatment. If they develop, it is typically within 1 week after the first IV infusion only. These blisters or pimples generally resolve within approximately the following 2–3 weeks. All blisters or pimples to date have been self-limited and resolved without complications or the need for specific anti-viral treatment.

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Pexa-Vec, from 4 to 20 people may have:

- Muscle aches, tiredness, weakness
- High blood pressure. An increase in blood pressure can lead to headache, vision problems, and rarely, to heart problems or stroke. In previous trials with Pexa-Vec, some patients experienced temporary low or high blood pressure. All patients recovered, but some required medications for blood pressure support and overnight hospital stays for observation.
- Abdominal Pain. A few patients experienced pain due to temporary swelling of the tumor(s) following Pexa-Vec injection
- Faster than usual heart rate
- Injection site pain. If needed, pain medication may be prescribed before and during treatment.

VERY UNCOMMON, SOME MAY BE SERIOUS

In 100 people receiving Pexa-Vec, between 1 and 4 people may have:

- High liver enzyme levels. Liver enzymes are proteins found in the blood released by your liver. Elevated liver enzymes could be a sign that certain liver functions are abnormal.
- High blood bilirubin levels. Bilirubin is a substance made during the normal breakdown of red blood cells. Higher than normal levels of bilirubin may indicate different types of liver problems.
- Low lymphocyte count. Lymphocytes are cells found in your blood responsible for your immune system.
- Decrease in appetite, sometimes significant, loose stools
- High blood sugar (hyperglycemia) requiring more frequent monitoring
- High blood platelet count
- Low platelet count. Platelets are cells found in your blood to help form a blood clot. A very low platelet count could lead to difficulty stopping bleeding, if you experience an injury.
- Low hemoglobin (a protein in your red blood cells that carries oxygen to your body's organs and tissues and transports carbon dioxide from your organs and tissues back to your lungs) that may cause hypoxia (low oxygen in your tissues) and dizziness.
- Low red blood cell count. Red blood cells are found in your blood and carry oxygen throughout your body. A low red blood cell count can lead to tiredness and low energy.
- Low white blood cell count and low neutrophil count (cells of the immune system that fight infection). This decrease is typically brief and often white blood cell counts return to pre-treatment levels within 4 days following treatment
- High white blood cell count. Your study doctor may choose to assess you for other sources of infection
- Low sodium in the blood (Hyponatremia), which can cause fatigue, muscle weakness, or cramping
- Rash including herpes zoster (shingles)
- Sweating, feeling hot or cold

VERY UNCOMMON, SOME MAY BE SERIOUS

In 100 people receiving Pexa-Vec, between 1 and 4 people may have:

- Insomnia or confusion
- Swelling of your lower limbs
- Swelling of lymph nodes
- Pain in muscles, bones, joints, back pain, flank pain, and pain in extremities
- Pain in your mouth and throat, inflamed and sore mouth
- Abdominal discomfort or distention, ascites (accumulation of fluid in the abdomen), flatulence, and indigestion.

RARE, SOME MAY BE SERIOUS

In 100 people receiving Pexa-Vec, less than 1 person may have:

- Heart attack, also known as myocardial infarction (or damage of heart muscle due to lack of blood supply), which may be diagnosed by an increase of cardiac enzymes (chemicals released by the heart in the blood) associated with symptoms of chest pain or changes to the electrical activity of your heart traced during an electrocardiogram (EKG or ECG) test. It is not known if heart attack was definitely caused by Pexa-Vec as there were other risk factors (e.g., high blood pressure, diabetes, and others). The damage to your heart could be permanent and, in some cases, life-threatening or even lead to death. Your physician will review your medical history and current medications to determine if you are fit enough to participate in the study. However, the chance you could develop cardiac injury (or a heart attack), while rare, cannot be ruled out.
- Portal vein thrombosis, which is a blockage or narrowing of the portal vein (the blood vessel that brings blood to the liver from the intestines) by a blood clot or liver tumor growing into your blood vessel. Blockage of liver blood vessels by liver tumor is a common finding in liver cancer patients that is seen in more than 40 out of 100 liver cancer patients at the time of diagnosis which may worsen spontaneously or lead to other complications. Your physician will review your medical history and current medications to determine if you are fit enough to participate in the study. It is not known if the worsening of portal vein thrombosis was definitely caused by Pexa-Vec as there were other factors that could have contributed to the events, however the chance you could develop worsening of portal vein thrombosis, while rare, cannot be ruled out.
- Prothrombin time shortened. Prothrombin is a protein produced by your liver. It is one of many factors in your blood that help it to clot appropriately.
- Cough, shortness of breath, flu and other upper respiratory infections
- Weight loss

RARE, SOME MAY BE SERIOUS In 100 people receiving Pexa-Vec, less than 1 person may have:
• Low protein levels, electrolyte imbalance, and increased bilirubin in your blood • Dehydration • Constipation • Night sweats • Immune reaction symptoms of which include fever, nausea, chills, low blood pressure, tachycardia, weakness, headache, and potentially others. • Lethargy, confusional state • Mouth ulceration, herpes • Wound complication, pain in your side and procedural pain • Enlarged lymph nodes

There may be other side effects of Pexa-Vec that are unknown. You will be told about any new findings that develop during this study that may affect your decision to stay in the study

Durvalumab

Most of the possible side effects listed below are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. Some side effects do not need treatment while others generally get better with treatment. Some patients may need to delay doses of durvalumab to allow the side effects to get better. The most important possible side effects, which are listed below, may occur because of the way durvalumab works on the immune system and they have been seen in patients treated with durvalumab in clinical studies. Side effects like these have also been seen in clinical studies with other drugs that are very similar to durvalumab. Management of these side effects may require the administration of drugs such as steroids or other agents that can affect your immune system and reduce inflammation.

Very common **In 100 people receiving durvalumab, more than 10 may have:**
• Diarrhea, • Rash/dry itchy skin, • Liver problems: Increases in the blood level of substances called enzymes found within your liver cells. The enzyme changes are unlikely to make you feel unwell, however, if these blood enzyme levels become very high, your study doctor may need to stop the study medication. You may develop inflammation of the liver called hepatitis; however, this is uncommon. Signs and symptoms of this include yellowing of the skin or whites of the eyes, dark urine, severe nausea and vomiting, pain in the

Very common **In 100 people receiving durvalumab, more than 10 may have:**
upper right side of your abdomen, skin itchiness, not feeling hungry and bleeding or bruising more easily than normal. • Feeling tired • Nausea • Vomiting • Abdominal pain • Accumulation of fluid causing swelling • Upper respiratory tract infections • Decreased appetite • Shortness of breath • Cough • Fever

Common **In 100 people receiving durvalumab, from 1 to 10 may have:**
• Inflammation in the lungs (pneumonitis): symptoms may include but are not limited to a new or worsening cough, shortness of breath possibly with fever. Preliminary data suggested that there may be the tendency of higher frequency and severity in Japanese patients compared with non-Japanese patients: tell your study doctor right away if you have any of these symptoms as it may need to be treated urgently. • Low thyroid (Hypothyroidism): this is when the thyroid gland produces less thyroid hormone than it should which causes the metabolism to run too slow. Symptoms may include but are not limited to fatigue, increased sensitivity to cold, constipation, dry skin, unexplained weight gain, puffy face, muscle weakness, slow heart rate, thinning hair, impaired memory. The condition can be treated with replacement thyroid hormone. • High thyroid (Hyperthyroidism): this is when the thyroid gland produces too much thyroid hormone. Symptoms include anxiety or nervousness, weight loss, frequent and loose bowel movements, breathlessness, feeling hot and possibly having heart palpitations. Depending on the severity of the symptoms, treatment may include just monitoring the symptoms, treating the symptoms themselves and/or giving medicine to block the thyroid hormone. • Kidney problems: you may have an increase of creatinine levels in a blood test

Common **In 100 people receiving durvalumab, from 1 to 10 may have:**
(creatinine is a protein marker that measures kidney function) but not have any symptoms or feel unwell. Uncommonly a patient may experience nephritis which is an inflammation of the kidneys that stops the kidneys from working properly. • Nervous system problems: symptoms can include unusual weakness of legs, arms, or face, numbness or tingling in hands or feet. In rare situations there is the potential for the inflammation of the nervous system to be severe and cause damage to the nerve cells or breakdown in the communication between nerves and muscles: tell your study doctor right away if you have problems swallowing, if you start to feel weak very quickly and you are having trouble breathing. • Infusion Related Reactions: reactions may occur during or after the infusion of study medication. The reaction may cause fever or chills and a change in blood pressure or difficulty in breathing which might be serious. Tell your study doctor right away if you experience any of these symptoms even if it has been several days after the infusion has been completed. • Inflammation of the intestine (colitis). It may cause abdominal pain and diarrhea with or without blood. Fever may be present. It may require you to receive additional fluids. If left untreated, in rare occasions this may lead to a tear in the wall of the intestine which can be serious and life threatening. Tell your study doctor right away if you have any of these symptoms. • A hoarse voice • Painful urination • Night sweats • Pneumonia • Oral thrush • Dental and oral soft tissue infection • Pain in muscles and joints • Influenza.

Uncommon **In 100 people receiving durvalumab, 1 or fewer may have:**
• Inflammation of the pancreas (pancreatitis). Pancreatitis usually causes symptoms of persistent upper abdominal pain (sometimes made worse by eating and drinking), nausea, vomiting and general weakness. Pancreatitis usually settles with simple measures but it can be a serious condition and can be fatal. You should immediately tell your study doctor if you develop any of these symptoms. You may get an increase

Uncommon In 100 people receiving durvalumab, 1 or fewer may have:
of lipase and amylase levels in a blood test (related to the pancreas) but not have any symptoms or feel unwell. Lipase and amylase are enzymes or protein markers that measure the function of your pancreas. Uncommonly these increases may be associated with pancreatitis. • Allergic reactions: These can cause swelling of the face, lips and throat, breathing difficulties along with hives or nettle like rash. You should immediately tell your study doctor if you develop any of these symptoms. • Problems with your adrenal glands (Adrenal Insufficiency): may cause stomach pains, vomiting, muscle weakness and fatigue, depression, low blood pressure, weight loss, kidney problems, and changes in mood and personality. These complications may be permanent and may require hormone replacement • Problems with the pituitary gland (hypopituitarism): Hypopituitarism refers to decreased output of hormones from the pituitary gland in the brain and may be caused by inflammation of the pituitary gland (hypophysitis). Symptoms may include headaches, thirstiness, and trouble seeing or double vision, leakage of breast milk or irregular periods in women. These complications may be permanent and may require hormone replacement. • Inflammation of the muscles or associated tissues, such as blood vessels that supply the muscles (Myositis/polymyositis). Symptoms can include muscle weakness and aches, tired feeling when standing or walking, muscle pain and soreness that does not resolve after a few weeks.

Rare side effects In 1,000 people receiving durvalumab, 1 or fewer may have:
• Type 1 Diabetes mellitus which may cause increased blood glucose levels (called 'hyperglycemia'): symptoms may include weight loss, increased urination, increased thirst, and increased hunger. Type 1 diabetes will require replacement of insulin through injection. Tell your study doctor right away if you have any of these symptoms. • Problems with the pituitary gland (hypopituitarism): hypopituitarism refers to decreased output of hormones from the pituitary gland in the brain and may be caused by inflammation of the pituitary gland (hypophysitis). Symptoms may include headaches, thirstiness, and trouble seeing or double vision, leakage of breast milk or irregular periods in women. These complications may be permanent and may require hormone replacement. • Inflammation of the heart muscle (myocarditis). Symptoms can include chest pain,

Rare side effects In 1,000 people receiving durvalumab, 1 or fewer may have:
rapid or abnormal heartbeat, shortness of breath and swelling of your legs. Tell your study doctor right away if you experience any of these symptoms. • Inflammation of the membrane surrounding the heart • Growths of tiny collections of inflammatory cells in different parts of the body • Inflammation of the middle layer of the eye and other events involving the eye (e.g. inflammation of the cornea and optic nerves) • Inflammation of the brain or the membranes that cover the brain and spinal cord • Hardening and tightening of the skin and connective tissues and loss of skin color • Pemphigoid and hematological events (e.g., abnormal breakdown of the red blood cells and low levels of platelets) • Inflammation of the blood vessels and rheumatological events (inflammatory disorder causing muscle pain and stiffness and autoimmune arthritis) • New allergies to previously exposed substances, other than durvalumab. For example, it is possible that you could develop an allergy to shellfish or IV contrast while taking durvalumab. These allergies may be severe and life threatening.

In addition to the possible risks identified in patients treated with durvalumab, other immune-mediated side effects are possible that have not been observed and can result in inflammatory side effects in any organ or tissue.

Tremelimumab (Part B only)

Because Tremelimumab activates the immune system, the main side effects we are concerned about are auto-immune side-effects. Your study team will give you medicines to help lessen side effects if they occur. Many side effects go away with those medicines and others may go away soon after you stop the study drug. In some cases, side effects can be serious, long lasting, or may never go away. There are no known long-lasting side effects from Tremelimumab at this time.

The following are side effects that have been associated with Tremelimumab and are common with combination therapy of Tremelimumab and Durvalumab:

- Diarrhea
- Rash that can result in severe and life-threatening symptoms
- Pruritus (itching)
- Fatigue
- Nausea

- Vomiting
- Anorexia (loss of appetite)
- Headache
- Abdominal Pain
- Auto-immune changes to the pituitary gland leading to hormonal changes.
- Inflammation of the colon which can lead to abdominal pain and diarrhea with or without blood. If left untreated, this may lead to a tear in the wall of the intestine which can be serious and life threatening.
- Inflammation of the liver called hepatitis, that can be fatal.
- During or after drug infusion having fever, chills, change in blood pressure or difficulty in breathing which might be serious
- Allergic reactions, causing:
  - swelling of the face, lips and throat
  - difficulty in breathing which might be serious
  - hives or nettle like rash
  - change in blood pressure
- New allergies to previously exposed substances, other than Tremelimumab. For example, it is possible that you could develop an allergy to shellfish or IV contrast while taking Tremelimumab. These allergies may be severe and life threatening.

You should also not receive a live vaccination 30 days before receiving Tremelimumab and for 6 months after receiving your last doses of Tremelimumab. Discuss any vaccinations you may need with your Study Doctor.

Tell your study doctor right away if you have any of these symptoms as it may need to be treated urgently.

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 CT scans

If contrast dye is used, there is a risk for allergic reaction to the dye. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling. If you are allergic to or sensitive to medications, contrast dye, iodine, or shellfish, please notify your study doctor. If you have had kidney failure or other kidney problems in the past, please notify your study doctor.

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.

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

During your participation in this research study, you will be exposed to radiation from CT scans and up to three CT guided biopsies (two mandatory and one optional). The amount of radiation exposure you will receive from these procedures is equal to approximately 10.1 rem. A rem is a unit of absorbed radiation.

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

The CT scans that you get in this study will expose you to the roughly the same amount of radiation as 33.7 years of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1 out of 100 (1%) and of getting a fatal cancer is 0.5 out of 100 (0.5%).

You may not participate in this study if you are pregnant. If you are able to become 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.

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 causes your tumor to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. There is no evidence that the experimental treatment benefits participants with your type of tumor. 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 become pregnant
- if you start another cancer therapy
- if you receive a certain type drug (tumor necrosis factor inhibitor)
- 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

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 Medimmune/Astrazeneca and /or Sillajen Inc 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 Medimmune/Astrazeneca and /or Sillajen Inc 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.

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

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

If you 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 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 National Cancer Institute (NCI) 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 Medimmune/Astrazeneca, the pharmaceutical company who produces Durvalumab and Tremelimumab.
- Qualified representatives from Sillajen Inc, the pharmaceutical company who produces the Pexa-Vec vaccine.

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, Tim Greten, M.D., gretentf@mail.nih.gov, 240-760-6114. 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: _____.