PRINCIPAL INVESTIGATOR: Tim Greten, M.D.

STUDY TITLE: A Pilot Study of Combined Immune Checkpoint Inhibition in Combination with Ablative Therapies in Subjects with Hepatocellular Carcinoma (HCC) or Biliary Tract Carcinomas (BTC)

STUDY SITE: NIH Clinical Center

Cohort: Affected patient

Consent Version: 04/13/2021

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?

This research is being done to study the safety and effectiveness of the combination of durvalumab (formerly known as MEDI4736) and tremelimumab with and without trans-arterial catheter chemoembolization (TACE), radiofrequency ablation (RFA), or cryoablation.

Depending on time when you are entering the study, you will be treated with durvalumab and tremelimumab only or with combination of durvalumab and tremelimumab with TACE, RFA or cryoablation.

Tremelimumab is an experimental drug that has not been approved by the U.S. Food and Drug Administration (FDA). Although tremelimumab is not approved by the FDA, it has been evaluated in a number of clinical studies, and over 1000 patients, most of whom had melanoma. 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 liver cancer or hepatocellular cancer (HCC) and in general was well tolerated.

Durvalumab is an investigational drug designed to boost the body's immune system by targeting 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. "Investigational" means that durvalumab has not been approved by the Food and Drug Administration (FDA) as either a prescription or over-the-counter drug.

If you receive TACE, a small catheter will be placed into the artery at the groin and chemotherapy will be injected directly into the liver. A material which closes off the vessels supplying blood to the tumor is also injected. If you receive RFA, you will be put to sleep and a needle will directly be placed into the tumor and your tumor will be burnt (or part of it). If you receive cryoablation, you will be put to sleep and a needle will be put directly into the tumor and the tumor will be frozen (or part of it). TACE, RFA, and cryoablation are standard procedures that are used to treat tumors. However, in this study RFA and cryoablation will be used in order to stimulate an immune response, rather than complete eradication of the lesion as per standard of care indication. Once it is determined which procedure you will receive your doctor will explain the procedure in full detail.

This is the first study in which both drugs taken together will be tested in combination with TACE, RFA, or cryoablation, which is the main goal 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 advanced hepatocellular cancer (HCC) or biliary tract cancer that has not responded to other types of therapy, and your doctor has determined that you are not a candidate for liver transplantation.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 90 people will take part in this study.

DESCRIPTION OF RESEARCH STUDY

Before you begin the study

Before you begin this study, you will have several exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care and may be done even if you do not join the study. If you recently had some of the tests, they may not need to be repeated. You must provide a sample tumor tissue for an NCI lab to evaluate. The tissue may be from a previous surgery or biopsy. If none is available, we will ask you to undergo a biopsy to provide a fresh sample.

During the study

All participants:
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will begin treatment.

Before you begin treatment, you will have a biopsy of your tumor using a needle.

In this study, therapy will be divided into cycles, each lasting 28 days. Treatment involves receiving tremelimumab and durvalumab through an IV on day 1 of each cycle. You will receive tremelimumab for up to 4 cycles.

Once you have complete 4 cycles of study therapy you will continue to receive durvalumab only, until your disease worsens, or you experience intolerable side effects.

If you assigned to drug treatment only:
You will be asked to undergo optional tumor biopsies during cycle 2 on day 8 (day 36) and after you have completed the third cycle (day 85) of tremelimumab and durvalumab.

If you assigned to drug treatment and ablative procedure:
On day 36 you will receive the TACE, RFA or cryoablation procedure. You will have two additional biopsies of your tumor; one during TACE, RFA or cryoablation procedure and an optional one after you have completed the third cycle (day 85).

WHEN YOU ARE FINISHED TAKING THE DRUGS (TREATMENT)

You will be seen for safety follow up visits approximately 60 and 90 days after completion of the study treatment to assess for possible delayed or ongoing side effects and overall clinical status. At this visit, you will have basic blood tests as well as blood collected for research purposes. If you are unable to return for this visit, we will obtain the information from you by telephone or e-mail.

After this safety visit, we will call you or e-mail approximately once every 6 months to ask about your health and about any other medications you may have taken for your cancer. If you still have unresolved health issues, caused by study drug, you will be invited to NIH for additional tests and treatment.

STUDY CALENDAR

Cycle 1

Day 1	• History and physical exam • Review of current medications and treatments • Routine and research blood tests • Research rectal swab* • Tumor biopsy • Tremelimumab infusion • Durvalumab infusion
Day 8	• Routine and research blood tests
Day 15	• Routine and research blood tests
Day 22	• Routine blood tests
Cycle 2	
Day 1	• History and physical exam • Review of current medications and treatments • Routine and research blood tests • Research rectal swab* • Tremelimumab infusion • Durvalumab infusion
Day 8 **(Day 36)**	• Routine and research blood tests • RFA/TACE/Cryoablation (will be determined by your study doctor) and tumor biopsy during this procedure (if you are assigned to this treatment) **or** • Tumor biopsy (optional) (if you are assigned to drug treatment only)
Day 15	• Routine blood tests
Day 22	• Routine blood tests
Cycle 3	
Day 1	• History and physical exam • Review of current medications and treatments • Routine and research blood tests

	• Tremelimumab infusion • Durvalumab infusion • CT Scan
Day 8	• Routine and research blood tests
Day 15	• Routine blood tests
Day 22	• Routine blood tests
Cycle 4	
Day 1 **(Day 85)**	• History and physical exam • Review of current medications and treatments • Routine and research blood tests • Research rectal swab* • Tumor biopsy (optional) • Tremelimumab infusion • Durvalumab infusion
Day 8	• Routine and research blood tests
Day 15	• Routine blood tests
Day 22	• Routine blood tests
Subsequent Cycles	
Day 1	• History and physical exam • Review of current medications and treatments • Routine and research blood tests • Durvalumab infusion • CT scan (every 8 weeks from third cycle)

* Rectal swabs will be used to study microbes living in your gut, including sequence of microbial genes.

Blood draws

You will have blood drawn during the study. These samples will be drawn to monitor your health during the study at every visit to the Clinical Center (about 5 teaspoons at each visit) and for research purposes (about 13 tablespoons)

BIRTH CONTROL

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 6 months after you finish study treatment (the restricted period). If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant during the restricted period, please contact study team as soon as possible.

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

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

Tremelimumab

The following are side effects that have been associated with Tremelimumab:

- Diarrhea
- Rash
- Pruritus (itching)
- Fatigue
- Nausea
- Vomiting
- Anorexia (loss of appetite)
- Headache
- Abdominal Pain
- Muscle pain

- Auto-immune changes to the pituitary gland leading to hormonal changes.
- Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools, abdominal pain and this may lead to a tear in the wall of the intestine which can be serious and life threatening. This is also known as 'colitis'. Colitis has the potential to be life threatening and require prolonged hospitalizations. As part of its management it may require treatment with steroids which may place you at increased risk for severe infections.
- 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.
- Kidney problems: You may have an increase of creatinine levels in a blood test (creatinine is a protein marker that measures kidney function) but not have any symptoms or feel unwell. Less commonly a patient may experience nephritis which is an inflammation of the kidneys that stops the kidneys from working properly.
- 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 unusual symptoms. You may get an increase 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.
- Inflammation of the liver which is also known as hepatitis. In extreme cases this may result in liver failure and death.
- Occasionally you can also get a skin rash related to the treatment and this can also result in severe and life-threatening symptoms.
- Problems related to Tremelimumab infusion
- There is a remote chance that you may have a serious allergic reaction (anaphylaxis) to Tremelimumab. Anaphylaxis may cause a serious drop in blood pressure, difficulty in breathing, severe hives, and sometimes death. Your doctor will monitor you very closely after you receive the Tremelimumab and will have medications available to treat any allergic reactions that might occur. Less serious allergic reactions, such as skin rash with or without itching and swelling, may also occur within hours to days after receiving the Tremelimumab. These effects usually get better without treatment.

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 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

Common In 100 people receiving durvalumab, from 1 to 10 may have:
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 (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

Common **In 100 people receiving durvalumab, from 1 to 10 may have:**
• 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 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, 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).

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.

There is a remote chance that you may develop new allergies to previously exposed substances, other than Durvalumab or Tremelimumab. For example, it is possible that you could develop an allergy to shellfish or IV contrast while taking Durvalumab or Tremelimumab. These allergies may be severe and life threatening.

TACE Procedure (only if you are assigned to this procedure)

Likely	Less Likely	Rare but Serious
• Abdominal pain • Fever • Nausea and/or vomiting	• Abdominal fluid buildup (Ascites) • Bleeding (at catheter insertion site) • Allergy to iodine contrast agent	• Liver failure • Kidney failure • Liver abscess formation • Stomach or duodenal ulcer • Pancreatitis • Cholecystitis (irritation of the gall bladder) • Arterial injury at catheter insertion site

RFA Procedure (only if you are assigned to this procedure)

The risks from the radiofrequency or microwave ablation procedure itself include a small chance of bleeding, injury to the normal liver tissue, and re-growth of the tumor. An infection, called an abscess, can develop in the treated tumor, and may require antibiotics and/or putting a temporary tube in the abscess to drain it. There should be minimal discomfort from the ablation procedure itself during the ablation procedure, because you will be "asleep" under general anesthesia. The length of time you will need to be in the hospital will vary but will be estimated by your doctors. This will be discussed with you in greater detail prior to the procedure. It is the intent of this trial to use RFA to stimulate the immune system. RFA will intentionally treat only part of the tumor(s), even if that particular tumor can technically be eradicated.

Cryoablation (only if you are assigned to this procedure)

The risks from cryoablation procedure itself include a small chance of bleeding, injury to the normal liver tissue, and re-growth of the tumor. Nerve damage may result. Completely frozen nerves can cause motor weakness or numbness in the area supplied by the nerves. There should be minimal discomfort from the cryoablation procedure itself during the procedure, because you will be "asleep" under general anesthesia. Following percutaneous cryotherapy, you should be able to resume your usual activities within one to three days. If you have had open cryoablation, you should be able to resume your usual activities within seven to 10 days. You should avoid lifting heavy objects for at least 72 hours. This will be discussed with you in greater detail prior to the procedure. It is the intent of this trial to use Cryoablation to stimulate the immune system. Cryoablation will intentionally treat only part of the tumor(s), even if that particular tumor can technically be eradicated.

Blood Sampling

Bruising or bleeding at the needle site; rarely infection. This is treated with bandages, pressure and, if infection, antibiotic medicines. For more information about risks and side effects, ask your study team.

Tumor Biopsy

If your doctor determines it is safe, we will obtain a piece of your tumor (biopsy) before you begin any study therapy, on day 36 and day 85 using a needle with minimal risk to you. You will be given local anesthesia (numbing medicine) and a sedative prior to the biopsy. The biopsy will be taken through a needle put through the skin into your tumor. After the procedure, the nurses will watch your blood pressure and other vital signs. The baseline biopsy is mandatory, and you cannot participate in this study if you do not agree to this biopsy. The day 36 biopsy is optional if you are assigned for drugs only treatment. If you are assigned to additional procedure, the day 36 biopsy will be performed during TACE/RFA/Cryoablation procedure. The day 85 biopsy is optional. If the first biopsy is too difficult or if you experience too much discomfort as a result of it, you will be able to continue on the protocol without undergoing the additional biopsy. However, an attempt at the first biopsy is needed to enter this study. There are other studies at NIH which may also be options for you, and which do not involve biopsies.

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.

Sedation

Biopsy will be performed under sedation. Sedation may cause headache, nausea and drowsiness. These side effects usually go away quickly.

Electrocardiogram

You may experience some minor skin irritation from the electrodes.

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

General anesthesia

Temporary confusion and memory loss, dizziness, difficulty passing urine, bruising or soreness from the IV drip, nausea, and vomiting, shivering and feeling cold, sore throat due to the breathing tube

Urine collection

There is no risk related to urine collection

Radiation

During your participation in this research study, you will be exposed to radiation from CT scans and CT guided biopsies.

If you are assigned to RFA or Cryoablation, these procedures also may be done by a specialist using the CT scanner to guide RFA or Cryoablation to ensure accuracy.

The amount of radiation exposure you may receive from CT scans used to evaluate your disease, or guide biopsies, RFA or Cryoablation is equal to approximately 9 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 30 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 0.9 out of 100 (0.9%) and of getting a fatal cancer is 0.5 out of 100 (0.5%).

If you are assigned to TACE procedure, you will be exposed to more radiation from one TACE procedure and your total exposure may be 16.2 rem (roughly the same amount of radiation as 54 years of background radiation). The risk of getting cancer from the radiation exposure in this case will increase to 1.6 out of 100 (1.6%) and of getting a fatal cancer to 0.8 out of 100 (0.8%).

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 see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These 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 he/she decides to close the protocol

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, 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 tremelimumab and durvalumab developed by MedImmune, Inc. through a joint study with your researchers and the company. The company also provides 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.

We may put your research data in a large database for broad sharing with the research community. These databases are commonly called data repositories. These data repositories might or might not be located at the NIH. The information in this database could include but is not limited to genetic information, ethnicity and sex. If your individual research data is placed in one of these repositories, it will not be labeled with your name or other information that could be used to easily identify you, and only qualified researchers will be able to look at your data. These researchers must receive prior approval from individuals or committees to access the data.

Your summary genomic data is being placed *in an* unrestricted database, so researchers will be able to access summary information about all the participants included in the study (including you), or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

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.

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.

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: _____.