INSTITUTE: National Cancer Institute

STUDY NUMBER: 16-C-0135 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)

Continuing Review Approved by the IRB on 05/08/17

Amendment Approved by the IRB on 06/26/17 (C) Date posted to web: 07/18/17

Drug and Ablative Therapy

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, 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). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

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.

As you are among the second group of ~ 50 subjects enrolling on the study, you will be assigned to take durvalumab and tremelimumab with TACE, RFA or cryoablation. The first group of 20 subjects will be will be assigned to take durvalumab and tremelimumab without 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. The research team will explain these exams and tests to you. You will have:

- Confirmation of diagnosis (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).
- History and physical exam
- Review of current medications and past treatments
- Blood work
- Urine laboratory tests
- Tumor measurements using special x-rays called computerized tomography (CT or CAT scans) or magnetic resonance imaging (MRI) of your chest, stomach, and pelvis areas
- A heart test called an electrocardiogram or ECG to check your heart
- Urine or blood pregnancy test

During the study

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, 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. 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). Once you have complete 4 cycles of study therapy you will continue to receive durvalumab only, until your disease worsens, you experience intolerable side effects or you have completed 12 months of study therapy, whichever comes first.

When you are finished taking the drugs (treatment)

You will be seen within 60 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.

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
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 or MRI
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 or MRI (every 8 weeks from third cycle)

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

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a

woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice at least two effective forms of birth control before starting study treatment, during study treatment, and for 6 months after you finish study treatment. If you are a man, you should not donate sperm before, during and for 6 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

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

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

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
- 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 and abdominal pain. 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 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

Likely

- Diarrhea
- Rash/dry itchy skin
- Liver problems: Increases in the blood level of substances called enzymes found within your liver cells may occur. 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. A patient 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.
- Fatigue
- Difficulty breathing
- Nausea
- Constipation
- Decreased appetite
- Vomiting
- Fever
- Pain in muscles and joints

Less Likely

- 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 (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.
- 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: 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, 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.

Rare

- 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. This event can occur commonly in patients who receive a combination of durvalumab and tremelimumab but has been reported uncommonly in patients who received durvalumab on its own. These complications may be permanent and may require hormone replacement.
- 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.
- Type 1 Diabetes mellitus which may cause increased blood glucose levels (called 'hyperglycaemia'): 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.
- 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 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 heart beat, shortness of breath and swelling of your legs. Tell your study doctor right away if you experience any of these symptoms.

A new drug may show an increase in side effects or unexpected effects as more studies are conducted. For your safety, you will be followed closely by your Study Doctor and the study staff for any undesirable or unexpected side effects during your participation in this study and each time you receive durvalumab.

There may be other side effects of durvalumab that are unknown. Other immune-mediated side effects are possible that have not been observed, and can result in inflammatory side effects in

any organ or tissue. You will be told about any new findings that develop during the course of this study that may affect your decision to stay in the study.

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

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

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

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 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.

Radiation

TACE/RFA/Cryoablation and Tumor biopsies will be done by a specialist using the CT scanner or ultrasound machine to guide any of these procedures to ensure accuracy. Thus, you might be exposed to three CT scans. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in these procedures is 3.0 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

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.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. 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 Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

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 Cancer Institute Institutional Review Board
- Qualified representatives from MedImmune, Inc, the pharmaceutical company who produces tremelimumab and durvalumab.

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.

Genomic data of your microbes and your health information will be put in a controlled-access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your microbial genomic data and health information will not be labeled with your name or other information that could be used to identify you. Researchers approved to access information in the database have agreed not to attempt to identify you.

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

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.

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.

OTHER PERTINENT INFORMATION

1. Confidentiality. 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.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The 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 National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. 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., Building 10, Room 12N226, Telephone: 240-760-6114. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative | Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian | Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian | Date | Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM MAY 8, 2017 THROUGH MAY 7, 2018.

Signature of Investigator | Date | Signature of Witness | Date

Print Name | Print Name