PRINCIPAL INVESTIGATOR: Tim Greten, MD

STUDY TITLE: Phase II Study of Nivolumab (anti-PD1), Tadalafil and Oral Vancomycin in Patients with Refractory Primary Hepatocellular Carcinoma or Liver Dominant Metastatic Cancer from Colorectal or Pancreatic Cancers

STUDY SITE: NCI

Cohort: affected patient

Consent Version: 12/22/2021

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?

In this study we are planning to investigate if nivolumab given in combination with tadalafil and vancomycin will cause your tumors to shrink.

Nivolumab has been approved by the U.S. Food and Drug Administration (FDA) for patients with hepatocellular carcinoma, but not for patients with metastases in the liver from colorectal or pancreatic cancer. Nivolumab is an agent that targets and blocks a pathway that prevents your immune system from effectively fighting your cancer.

Tadalafil has been approved by the U.S. Food and Drug Administration (FDA) to treat high blood pressure, enlarged prostate and erectile disfunction. Tadalafil is a small molecular inhibitor, which has been recently shown to have exciting potential in shrinking of different tumors.

Vancomycin is an antibiotic, approved by the U.S. Food and Drug Administration (FDA) to treat a number of bacterial infections. We believe that bacteria living in your gut can be partially responsible for the development of your cancer. Vancomycin will kill most of bacteria in your gut and this might help to treat your cancer.

As tadalafil and vancomycin are not approved to treat cancer and nivolumab is not approved to treat patients with metastases in the liver from colorectal or pancreatic cancer, combined treatment on this study is considered to be experimental.

There are approved, standard of care drugs and/or procedures that may be used to treat your disease without being in this study. For example: there is chemotherapy and radiation therapy.

If you have hepatocellular carcinoma, there is also possibility to be treated with other FDA approved treatments such as lenvatinib or sorafenib or the combination of atezolizumab and bevacizumab. If you take part in this study first, your physician may decide giving you these treatments is not the best option after this study or they may not be available to you as they are presently only approved by FDA to be given prior to other treatment.

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

You are being asked to be part of this study because you have been diagnosed with hepatocellular carcinoma or have metastases to the liver from colorectal or pancreatic cancer for which standard treatment has not worked.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 27 people will be enrolled on the study.

DESCRIPTION OF RESEARCH STUDY

Before you begin the study

Before you begin this study, you will need to have the following exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care. These tests will be done under a separate protocol. You will be asked to provide a pathology report to confirm your diagnosis. If this documentation is not available, we will perform a biopsy (collect a sample of your tumor) to confirm your diagnosis.

During the study

Nivolumab will be administered to you by IV (through an intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) on Day 1 of each cycle (1 Cycle = 4 weeks).

You will take one tablet of tadalafil by mouth on Day 1 of Cycle 1 and continue every day of every cycle. Tadalafil may be taken with or without food any time during the day. If you miss the dose or vomit after taking tadalafil, please, do not increase next day dose and do not repeat taking tadalafil on this day.

You also will take vancomycin by mouth on Day 1 of Cycle 1 and continue for three weeks followed by one week without vancomycin treatment. You will continue this schedule of vancomycin dosing with three weeks on and one week off. Vancomycin should be taken 4 times a day. Try to space your doses out evenly throughout the day, so ideally, take a dose every six hour. You may take the capsules with or without food. If you need to take your vancomycin earlier than scheduled or you missed the dose, you can take it in the time period of +/- 2 hours of scheduled time. If you vomit after taking vancomycin, please, do not take immediately another capsule and proceed with next dose as scheduled.

We will use generic tadalafil and vancomycin on this study, meaning drugs you receive every cycle could look slightly different.

You will be given a Medication Diary to complete for each cycle. In the diary, you will be asked to record date and time of taking and missing doses of tadalafil and vancomycin. Please bring the diary with you at every study visit.

For every visit, please, also bring empty bottles and unused any medication you may have.

You will continue combined treatment with nivolumab, tadalafil and vancomycin unless your disease gets worse or you have unacceptable side effects.

If your doctor is convinced that unacceptable side effects are caused by one or two treatment drugs, this drug(s) will be discontinued, and you will continue treatment with another drug(s).

Treatment and all study involved procedures will be done during daily visits without planned hospitalization.

If treatment does not start during 28 days after enrollment, eligibility screening procedures and tests will be repeated.

Ongoing Procedures before treatment on the day 1 of every cycle

- Physical examination, including weight and vital signs.
- Review of your symptoms, medications and your ability to perform your normal activities.
- Routine blood tests to find out if you are anemic, have low blood counts, and if your liver, kidneys, thyroid, clotting system and other organs are working well.
- Blood tests for Hepatitis B and Hepatitis C (only if you were positive at screening).
- Blood tests to check tumor markers.
- Electrocardiogram (EKG – a record of your heartbeat) to evaluate your heart.
- Pregnancy test if you are a woman who can have children.

Procedures before treatment on first day of every other cycle:

- Imaging Assessments –a CT (a series of x ray images taken of parts of your body) of your chest, abdomen and pelvis every 8 weeks.

Procedures before treatment performed only once:

- Blood test to evaluate your human leukocyte antigen (HLA)

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 tablespoons at each visit to occur about once a month) and for research purposes as described in the next sections (about 12 tablespoons at visits to occur twice a month).

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 will be collected during every cycle to study how well your immune system fights the tumor, and to check level of tadalafil and vancomycin in your blood. One sample collected before treatment will be used to evaluate all your genes.
- We are planning to do your bile acid analysis, before you start treatment, at day 10 of cycle 1 and after approximately 6 months of being on treatment. Bile acid is produced by your liver and by bacteria in your gut. We will give you liquid meal to drink within 10 minutes. We will collect blood at the 0, 0.5, 1, 1.5, 2, 2.5 and 3-hour time points after the liquid meal.
- Two mandatory tumor biopsies will be collected before therapy and during the second cycle of vancomycin therapy. The second biopsy might be done sooner if your disease worsens before the scheduled sample. Please see section Risks from Biopsy for possible risks of biopsy. If you have a biopsy during confirmation of your eligibility, the baseline biopsy will not be repeated. You can participate in the study only if you agree to undergo the biopsy procedures. Although it is not clinically needed, samples will be used for disease evaluation; leftover samples will be used to study the response of your immune system and do genetic testing to study all genes in your tumor, how efficiently they are working, genetic changes that can be connected to tumor development and response to treatment.
- Stool samples or rectal swab will be collected during every cycle to determine how the bacteria in your gut are changing, whether bacteria resistant to vancomycin are developing and to check your bile (on days of bile acid analysis).
- Before you start treatment, at day 10 of cycle 1 and after approximately 6 months of being on treatment you will complete a food diary and see a nutritionist to discuss your diet. Completion of diary and the discussion will take you about 30 minutes.

Genetic testing and return of results

Your samples contain genes, which are made up of DNA (**d**eoxyribo**n**ucleic **a**cid) which serves as the "instruction book" for the cells that make up our bodies. We will use the tissue samples, saliva and blood you provided to learn about how the genes in your tumor compare to genes in normal

tissue. Your tissue will help us study how genes might play a role in rare cancer and other diseases. We will not share the results of these research tests with you.

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

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

However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding that is believed to be clinically important based on medical standards at the time that we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a genetic counseling here at Clinical Center (no charge) or referral to an outside genetic healthcare provider (at your expense) to discuss the results.

You should not assume that if you are not contacted, you do not have any gene variants that might be related to a disease.

When you are finished taking the drugs

Approximately 28, 60 and 90 days after you have finished taking the study drug, you will be asked to return to Clinical Center for a safety follow up visits. At these visits, you will be asked questions about your health, get a physical exam and undergo blood tests.

If you still have unresolved health issues, caused by study drug, you will be invited to NIH for additional tests and treatment.

If you are unable to return for these visits, we will obtain the information from you by telephone or e-mail.

After these safety visits we will call or e-mail you every 6 months to ask you about your general well-being.

BIRTH CONTROL

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

If you are a woman who can become pregnant or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 5 months (women) or 7 months (men) after the last drug

infusion. Men are also asked to refrain from donating sperm during study therapy and for 7 months after the last dose. 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 for women include:

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

Men must use a male condom plus spermicide (this is not needed if you had a vasectomy).

RISKS OR DISCOMFORTS OF PARTICIPATION

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

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

Nivolumab used in this study may affect how different parts of your body work such as your liver, kidneys, heart, blood and brain. The study doctor will be testing your blood and perform neurological exam and will let you know if changes occur that may affect your health.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, 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 Nivolumab

Side effects of nivolumab may happen anytime during treatment or even after your treatment has ended. Some of the common and less common side effects can be serious. **Call or see your healthcare provider right away if you develop any problems listed below or if the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS **In 100 people receiving nivolumab, more than 20 and up to 100 may have**
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving nivolumab, from 4 to 20 may have:**
• Low counts of blood cells, which may require blood transfusion • Swelling and redness of the eye • Pain • Diarrhea, nausea • Dry mouth • Fever • Swelling and redness at the site of the medication injection • Bruising, bleeding • Pain or swelling of the joints • Loss of appetite • Loss of sleep • Reaction during or following a drug infusion which may cause fever, chills, rash • Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: o Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath. o Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving nivolumab, from 4 to 20 may have:

- Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

RARE, AND SERIOUS
In 100 people receiving nivolumab, 3 or fewer may have:

- Dry eyes
- Sores in the mouth which may cause difficulty swallowing
- Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:
  - Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
  - A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
  - Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
  - Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
  - Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
  - Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
  - Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement
  - Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of

RARE, AND SERIOUS In 100 people receiving nivolumab, 3 or fewer may have:
breath, swelling of the face or throat o Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received nivolumab therapy, since the risk and severity of transplant-associated complications may be increased

Getting medical treatment right away may keep these problems from becoming more serious. Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Risks from Tadalafil

VERY COMMON In 100 people receiving tadalafil, up to 11 may have:
• headaches

COMMON In 100 people receiving tadalafil, from 2 to 10 may have:
• stomach upset, • pain in belly, • diarrhea, • nausea, • reflux disease, • muscle or back pain, pain in arms and legs, • flushing (redness or warmth of the face, neck, or chest), • flu-like symptoms (such as stuffy nose, sneezing, or sore throat), • infection, • cough

RARE
In 100 people receiving tadalafil, 1 or fewer may have:

- fatigue,
- face swelling,
- chest pain,
- heart problems,
- low blood pressure,
- elevated liver enzyme in the blood
- dry mouth,
- hemorrhoids,
- dizziness,
- lack of sleep,
- rash,
- blurred vision, changes in color vision, eye pain, swelling around eyes
- abnormal ejaculation

Tell your doctor if you have rare but serious side effects including:

- a painful or prolonged erection lasting 4 or more hours;
- sudden decreased vision (including permanent blindness, in one or both eyes);
- a sudden decrease or loss of hearing, sometimes with ringing in the ears and dizziness

Risks from Vancomycin

- serious allergic reactions (anaphylactoid reactions), including low blood pressure, wheezing, indigestion, hives, or itching
- problems with your kidneys
- hearing loss
- low white blood counts
- nausea
- fever
- chills

- rash
- dizziness,
- low blood pressure, or pain and muscle spasm of the chest and back.

Vancomycin is usually prescribed to treat a bacterial infection for 10-14 days. In this study you will receive vancomycin for a much longer period of time. Because of this, there is a potential risk that in future if you need to be treated with this antibiotic for other reasons (such as an infection), it might not work for you.

Risks from Blood Collection

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

Risks from Biopsy

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

Risks of sedation.

Biopsies will be done under sedation. Potential side effects of sedation include headache, nausea and drowsiness. These side effects usually go away quickly.

Risks of EKG

You may experience some minor skin irritation from the electrodes.

Questionnaires risk

Questionnaires may contain questions that are sensitive in nature. Please, only answer questions that you are comfortable with.

Stool Collection or Rectal swabs

There is no physical risk involved with stool or rectal swab collection

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.

What are the risks of radiation from research?

During your participation in this research study, you will be exposed to radiation from CT scans and two CT guided biopsies. The amount of radiation exposure you will receive from these procedures is equal to approximately 8.2 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 27.3 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 0.8 out of 100 (0.8%) and of getting a fatal cancer is 0.4 out of 100 (0.4).

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.

Privacy Risks Associated with Genetic Testing

It may be possible that genetic information from you could be used by law enforcement agencies or other entities to identify you or your blood relatives.

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

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

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

Protections against misuse of genetic information

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

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 can increase the time it takes for your disease to get worse. We do not know if you will receive personal, medical benefit from taking part in this study. Potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

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

- Getting standard FDA approved treatment or care for your cancer without being in a study. This may include other chemotherapy or radiation therapy. For patients with hepatocellular cancer, there are other FDA approved treatments and combinations to consider before taking part in this study as you may not be able to receive them if you take part in this study first. You should discuss these other options with your doctor.
- 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 need to take medication that is not allowed on the study
- if you become pregnant
- 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 Bristol-Myers Squibb 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 cannot 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 Bristol-Myers Squibb through a joint study with your researchers and the companies. The company also provide financial support for this study.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

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

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

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

Genomic Data Sharing

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

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

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

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

You will not receive compensation for participation in this study.

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

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

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

Will taking part in this research study cost you anything?

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

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor (Center for Cancer Research)
- Qualified representatives from Bristol-Myers Squibb, the pharmaceutical company who produces nivolumab

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 should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

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: _____.