PRINCIPAL INVESTIGATOR: Tim Greten, MD

STUDY TITLE: Phase II Study of Combination of Trametinib (MEK inhibitor) and Hydroxychloroquine (HCQ) (autophagy inhibitor) in Patients with KRAS Mutation Refractory Bile Tract Carcinoma (BTC).

STUDY SITE: NIH Clinical Center

Cohort: Affected Patient

Consent Version: 09/15/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

Tim Greten, MD, by phone at 240-760-6114 or email gretentf@mail.nih.gov

KEY INFORMATION ABOUT THIS RESEARCH

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). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to take part in this study because you have cancer of your bile duct. Your cancer is in the slender tubes of the biliary tract that carry the digestive fluid, bile, through the liver. Such cancer tumors are often characterized by having an abnormal or mutated gene. Doctors call this gene mutation a "KRAS" status. You are being asked to participate in a study to find out if a combination of drugs can slow the progression of your KRAS mutated cancer of the biliary tract.

The purpose of this study is to see if using a combination of trametinib and hydroxychloroquine (HCQ) increases the period of time it takes for your disease to get worse.

Trametinib and hydroxychloroquine are considered investigational which means they are not approved by the U.S. Food and Drug Administration (FDA) as drugs for the treatment of biliary tract cancer.

Trametinib has been found to be effective in the treatment of advanced malignant melanoma, usually in combination with other drugs.

Hydroxychloroquine is used to prevent or treat malaria caused by mosquito bites. It was shown that hydroxychloroquine may increase tumor sensitivity to existing cancer treatments.

There are other standard of care drugs and/or procedures that may be used to treat your disease. For example: there is chemotherapy and radiation therapy. These can be given to you by your regular cancer doctor if you are not in this study. You may also be able to participate in another clinical trial either at the NIH or another institution using other drugs.

The treatment given in this study and the known possible side effects may or may not be significantly different than if you were to receive standard of care or participate in another clinical trial. Trametinib is known to cause rash, bleeding, problems with the heart and vision. Hydroxychloroquine may cause abdominal pain, nausea and headache.

If you decide to join this study, here are some of the most important things that you should know that will happen:

- First, we will perform initial tests to find out if you fit the study requirements. We will do standard blood tests and scans to test your health and see the status of your disease. We also will evaluate KRAS status of your tumor, performing research test. If you have confirmation of KRAS mutation status of your tumor done by FDA approved test, this research test will not be done.
- It is very important to us to understand how your tumor is affected by study treatment. To answer this question, we will collect tumor biopsies (samples) from you before treatment and after starting treatment. You can only take part in this study if you agree to these biopsies. The most common risks of biopsy include pain and the chance of bleeding at the site of the biopsy. The site of biopsies will be determined by a group of doctors to obtain the safest possible location, most commonly the liver.
- If you fit the study requirements and decide to take part, you will start your treatment with trametinib and hydroxychloroquine tablets that are taken by mouth every day. We will then send you home with a supply of trametinib and hydroxychloroquine that you will need to take regularly.
- We will need to see you at the Clinical Center once every month while you are receiving treatment. We also need you to do standard blood tests every week for first 2 months and every 2 weeks after that. You can come to Clinical Center for these tests or you can have blood drown at your local lab and send us results. Study treatment will last for as long as you are tolerating and benefiting from the study drugs. Each monthly visit to the Clinical Center should last no more than 8 hours.
- As described above and later in more detail in this consent form, you may have side effects if you take part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, and may include death. You will be seen regularly during the study. You will have clinical, laboratory, and imaging tests to see how you are doing and see how your disease is responding. We will also collect required samples from you (such as: blood and tumor tissues) for both clinical and research purposes.
- After the study treatment has ended, we would like to see you in the Clinical Center approximately one month later to check on your health. After this visit we will call or e-mail you 2 and 3 months later and every 6 months after that to see how you are doing

for the rest of your life or until the study is stopped. If you stop treatment for reasons other than worsening of your disease before 5 months have passed since the start of study therapy, we will continue to invite you for imaging studies approximately every 8 weeks until your disease gets worse or 5 months have passed since the start of study therapy, whatever comes earlier. You can have these studies done locally and send us the results.

- You will need to practice an effective form of birth control during the study treatment and for 4 months after you finish study treatment (the restricted period). Breastfeeding should be stopped for the restricted period.
- You will need to avoid intensive physical activities such as running, hiking uphill, fast cycling, strength training and even heavy gardening during the study treatment. These strenuous exercises may interfere with blood tests needed to evaluate possible heart damage caused by study treatment. Please, discuss your physical activities with your study doctor.
- Some drugs and vaccines are not allowed during this study. Please, let your doctor know about all medicines you are taking or planning to take.
- It is important that you do not drive a car or work with machinery if you are experiencing any sudden visual changes during study therapy.

This study may benefit you by shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Even if you do not benefit from this study, the results from our research will help others in the future.

You are free to stop taking part in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information 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 you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term “you” refers to you as the decision-maker and/or the individual being asked to participate in this research.

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 is a research study. The purpose of this this study is to find out if a combination of drugs can slow the progression of your KRAS mutated cancer of the biliary tract.

You are being asked to take part in this study because you have cancer of your bile duct. Your cancer is in the slender tubes of the biliary tract that carry the digestive fluid, bile, through the liver. Such cancer tumors are often characterized by having an abnormal or mutated gene. Doctors call this gene mutation a "KRAS" status. You are being asked to participate in a study to find out if a combination of drugs can slow the progression of your KRAS mutated cancer of the biliary tract.

Trametinib and hydroxychloroquine are not approved by the FDA as drugs given alone or in combination to treat biliary tract cancer, therefore the use of these drugs in this study is investigational.

Trametinib is used in the treatment of advanced malignant melanoma, usually in combination with other drugs.

Hydroxychloroquine is used to prevent or treat malaria caused by mosquito bites. It was shown that HCQ may increase tumor sensitivity to existing cancer treatments.

WHAT WILL HAPPEN DURING THE STUDY?

You will take hydroxychloroquine and trametinib by mouth every day during treatment cycles (1 Cycle = 28 days).

Hydroxychloroquine should be taken 2 times a day. Try to space your doses out evenly throughout the day, so ideally, take a dose between 6-9 am and between 6-9 pm with a meal or a glass of milk. If you need to take your hydroxychloroquine earlier than scheduled or you missed a dose, you can take it up to 2 hours before or after the scheduled time. If you vomit after taking hydroxychloroquine, please, do not immediately take another tablet unless the tablet is visible. You should simply proceed with next dose as scheduled.

Trametinib should be taken once a day, preferably at the same time every day. You should take tablets two hours after a meal and one hour before the next meal with a cup of water. If you miss a dose, you may take it immediately on that day, **if** the next dose is at least 12 hours later. If the next dose is less than 12 hours later, just continue with the next dose as per schedule. Please remember to keep doses at least 12 hours apart. If you vomit after taking trametinib, please, do not immediately take tablets again, do not increase the dose at the next time dosage, just continue with next dose as per schedule.

You will be given a Medication Diary to complete for each cycle. In the diary, you will be asked to record the date and time of each dose of hydroxychloroquine and trametinib. You will also be asked to record missed doses. **Please bring the diary with you at every study visit.**

At each visit, please also bring any empty bottles and unused medication you may have.

Treatment will continue until you have unacceptable side effects, or you are no longer benefiting from the study therapy.

If your study doctor is convinced that you have unacceptable side effects caused by one of treatment drug, this drug will be stopped, and you may continue treatment with the other drug if your study doctor finds that it is in your interest.

Some drugs and vaccines are not allowed during this study.

Please, let your study doctor know about all medicines you are taking or planning to take. **Do not start any new drugs, herbal remedies, or dietary supplements before talking to your study doctor.**

Before you begin this study.

Before you begin this study, you will need to have standard clinical exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care. If you are not eligible, you will not participate in the study.

- A review of any past or current medical conditions and cancer history.
- Physical examination, including vital signs.
- Review of your symptoms and your ability to perform your normal activities.
- Electrocardiogram (EKG – a record of your heartbeat) and Echocardiogram (ultrasound used to see how blood moves through your heart) to evaluate your heart.
- Consultation with a cardiologist (heart specialist) if your study doctor thinks it is necessary.
- Checking your vision and the health of your eyes (ophthalmologic exam).
- Computer tomography (CT) scans, a series of x-ray images of your chest, abdomen and pelvis
- Routine blood and urine 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. If needed, we may also collect all of your urine for 24 hours to test your kidneys.
- Tuberculosis test if your doctor thinks it is necessary
- Pregnancy test if you are a woman who can have children
- As part of this study, we may test you for infection with Hepatitis B, C and HIV, the virus that causes AIDS. If you were infected with any of these viruses, you will be able to take part in this study only if any of these viruses is not detected in your blood. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infections, and the importance of informing your partners at possible risk because of your HIV infection.

You will also be asked to provide pathology report/documentation 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. Please see Risks from biopsy for the risks of biopsy. We also will evaluate KRAS status of your tumor. If you do not have confirmation of KRAS mutation status done by FDA approved test, we will perform research test which is not a standard cancer care test, a research test needed for this treatment.

If treatment does not start within 28 days after enrollment to this study, some tests may need to be repeated.

During the study

Ongoing procedures before treatment and every 4 weeks:

- Physical examination, including weight and vital signs.
- Electrocardiogram (EKG – a record of your heartbeat) to evaluate your heart.
- Review of your medications and your ability to perform your normal activities.
- Discussion of any symptoms you might be having.
- Blood test to check if you have muscle or heart damage.
- Blood test to check your heart if your doctor thinks it is necessary.
- Pregnancy test if you are a woman who can have children before taking the drug.

Ongoing procedures every week for 8 weeks and every 2 weeks after that:

- Routine blood tests to find out if you are anemic, have low blood counts, and if your liver, kidneys, clotting system and other organs are working well.

Ongoing imaging assessments/scans performed before treatment and every 8 weeks:

- A computer tomography (CT) scan (a series of x-ray images t) of your chest, abdomen and pelvis.

Additional procedures after 4 weeks and every 12 weeks after that:

- Echocardiogram (ultrasound used to see how blood moves through your heart) to evaluate your heart.
- Checking your vision and the health of your eyes. You may do these tests with your local ophthalmologist and bring us the results.

Blood draws

You will have blood drawn during the study. These samples will be drawn to monitor your health during the screening and study participation at every visit to the Clinical Center (about 4 tablespoons at each visit) and for research purposes as described in the next sections (about 7 tablespoons at visits to occur once a month).

Additional research testing

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 and perform tests for purposes of research only:

- Blood samples will be collected before treatment, once every month for 4 months and every 3 months after that to study how well your immune system fights the tumor and how drugs are working. One sample collected before treatment will be used to evaluate all of your genes.
- Two required tumor biopsies will be collected before therapy and after 6 weeks of therapy. The second biopsy might be done sooner if your disease worsens before the scheduled sample. Please see section the "Risks from biopsy" section of this consent form for possible risks of biopsy. If you have a biopsy during screening, the baseline biopsy will not be repeated. You can take part in the study only if you agree to have 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;
  - all genes in your tumor and how efficiently they are working;
  - majority of your proteins and how efficiently they are working;
  - metabolites, the small molecule intermediates and products of metabolism to understand if there is connection between these metabolites and development of cancer and response to treatment.

Tumor and blood samples may be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) in the cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow. RNA (also called ribonucleic acid) carries the instructions from the DNA to the parts of your cells that make proteins.

To look at your DNA and RNA, we may do what is called "DNA and RNA sequencing." This is where we will do special tests in the lab to look at the sequence, or order, of how your DNA and RNA are put together. This is what makes you unique.

To determine which parts of the DNA and RNA have mutated, we will compare the DNA and RNA in your tumor cells to the DNA and RNA from normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA and RNA that are common to a particular type of tumor.

However, you should know that 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 or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases.

There may be exceptions to what we share with you and this is described later in this consent form in the section Return of research results.

When you are finished taking the drugs (treatment)

Approximately one month after you have finished taking the study drugs, you will be asked to return to the Clinical Center for a follow up visit. At this visit, you will be asked questions about your health, get a physical exam and undergo blood tests.

After this visit, we will call or e-mail you once a month during next two month to ask you about your health.

If you have been taken off treatment for reasons other than worsening of your disease before 5 months have passed since the start of study therapy, you will continue to have imaging studies approximately every 8 weeks until worsening of your disease or 5 months after start of study drugs whatever comes earlier. You can have these studies at your home institution and send us results.

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

Once you stop coming to Clinical Center for visit and your scans, we will call or e-mail you every 6 months to ask you about your general well-being.

HOW LONG WILL THE STUDY TAKE?

You will come to the NIH Clinical Center to check status of your health at least once a month until your disease gets worse or you have unacceptable side effects at which time, we will stop treatment.

Visits to the clinic will range from 4-8 hours in length.

After stopping treatment, we would like to see you in the NIH Clinical Center one month later and follow you after that for the rest of your life by telephone or e-mail.

If you stop treatment for reasons other than worsening of your disease, we would like to invite you for imaging studies approximately every 8 weeks until worsening of your disease or 5 months have passed since the start of study therapy whatever comes earlier.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have up to 30 people take part in this study.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

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

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 longer.

- 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 a side effect, as it is important that this is treated to avoid more severe 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.

Risks of the drug trametinib

Very common (in 100 people receiving trametininb, more than 10 may have): be sure to tell your study doctor about any of these side effects.

- Skin rash or acne-like rash
- Diarrhea
- Bleeding (hemorrhage) from various sites, including nose bleeding (epistaxis), gastrointestinal hemorrhage, intracranial hemorrhage, hemoglobin decreased
- Nausea
- Feeling tired
- Swelling of the hands/feet (peripheral edema)
- Increase of blood pressure
- Vomiting
- Constipation
- Stomach pain
- Shortness of breath
- Cough
- Dry or itching skin
- Fever
- Dry mouth
- Unusual hair loss or hair thinning

Common (in 100 people receiving trametinib, from 1 to 10 may have): be sure to tell your study doctor about any of these side effects.

- Visual problems - such as blurry vision, and decreased vision. **It is important that you do not drive a car or work with machinery if you are experiencing any visual changes.** These symptoms go away in most cases.

- Facial swelling
- Swelling around the eyes
- Dehydration (low levels of water or fluid)
- Swelling of and/or redness and/or pain of the lining inside the mouth or nose
- Redness, swelling or pain in the mouth
- Changes in how the heart pumps blood – changes in your heart may cause an irregular heartbeat, shortness of breath, swelling in your legs and /or tiredness
- Swelling in an arm or leg as a result of fluid build-up
- Decreased red blood cells
- Increased blood level of protein from the muscle
- Redness, chapping or cracking of the skin
- Redness, tenderness and possibly painful hands and feet
- Rash with pus-filled lesions
- Weakness
- Inflammation of hair follicles in the skin
- Infection of the skin (cellulitis)
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles (paronychia)
- Inflammation of the lung– which you may notice as shortness of breath, or may be seen in chest CT scans
- Elevated liver enzymes which may suggest damage to the liver
- Hypersensitivity/ allergic reaction- may present with symptoms like fever, rash, abnormal liver enzymes and visual changes.
- Chest pain, difficulty breathing, coughing up blood

Uncommon (**In 100 people receiving trametinib, 1 or fewer may have**):

- Heart pumping less efficiently – you may symptoms like shortness of breath, extreme tiredness and swelling in ankles and legs
- Breakdown of muscle, which can lead to symptoms including muscle pain and kidney damage (rhabdomyolysis)
- Inflammation of the lung (interstitial lung disease) – may present with symptoms such as shortness of breath, changes in chest CT scam
- Visual problems (different from above) including:

- Retinal detachment
- Separation of the light-sensitive membrane in the back of the eye (the retina) from its supporting layers (retinal pigment epithelial detachment, chorioretinopathy) which can result in blurry vision
- Swelling of the optic nerve (papilledema) – may present with symptoms like headache, nausea and vomiting, vision problems
- Blockage or bleeding of the vein draining the eye which in severe cases can lead to vision loss (retinal vein occlusion):

While these types of visual problems often improve, there is a risk that they may not improve.

- Hole in intestine (GI perforation)
- Inflammation in the intestine (colitis)
- Heart rate decreased (bradycardia)
- Pain or swelling in your legs (deep vein thrombosis)

The side effects listed above are based on all side effects reported in patients. If you notice any of these side effects notify your study doctor or study nurse right away.

There may be other side effects that may happen that are not known now. For example, all drugs can cause an allergic reaction in some patients.

Certain problems can be dangerous if not treated quickly; call your study doctor right away if you:

- Feel very tired or faint
- Feel pain or sick in your stomach and not want to eat
- Bruise easily or develop itching
- Have yellow eyes or skin, or dark urine
- Become confused
- Difficulty breathing
- Pain or swelling in your legs

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 of the drug hydroxychloroquine

Very common (in 100 people receiving hydroxychloroquine, more than 10 may have): be sure to tell your study doctor about any of these side effects.

- Abdominal pain
- Nausea

- Headache

Common (in 100 people receiving hydroxychloroquine, from 1 to 10 may have): be sure to tell your study doctor about any of these side effects.

- Rash
- Diarrhea
- Vomiting
- Anorexia
- Dizziness
- Blurred vision
- Change in liability

Uncommon (**In 100 people receiving hydroxychloroquine, 1 or fewer may have**):

- Pigmentary changes in skin and mucous membranes
- Bleaching of hair
- Hair loss
- Liver injuryMuscle weakness
- Retinopathy (vision changes)
- Hearing ringing, clicking, buzzing, or hissing in one or both ears
- Nervousness

Rare with frequency not reported:

- Skin problems such as hives, pustules, swelling, photosensitivity, scaling of the skin
- Low blood counts
- Liver failure
- Allergic reaction
- Inflammation of the heart muscle
- Low blood sugar
- Nerve problems such as seizures, vertigo (sensation of spinning) and discoordination
- Vision loss
- Psychosis and suicidal behavior
- Difficulty breathing

Risks from biopsy

This procedure usually causes only brief discomfort at the site from which the biopsy is taken. Risks of biopsy may include bleeding, injury to internal organs, and infection. Rarely, these complications from biopsy could result in hospitalization and require additional medical care.

Risks from sedation

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

Risks from CT scans

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

Risks of ophthalmologic exam

Ophthalmologic exam may cause slight discomfort, blurry vision and light sensitivity that will go away in a few hours.

Risk from electrocardiogram

You may experience some minor skin irritation from the electrodes.

Risk from echocardiogram

You may experience some minor discomfort

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.

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 genes are unique to you, you share some genes with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your genetic 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 genetic information 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

What are the risks related to pregnancy?

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 4 months after you finish study treatment (the restricted period). You must tell the study doctor if your birth control method fails during the restricted period. If you become pregnant during the study, 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. If you think or know you have become pregnant during the restricted period, please contact the study team as soon as possible.

Breastfeeding should be stopped for the restricted period.

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 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 the 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.

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

During your participation in this research study, you will be exposed to radiation from CT scans and two CT guided biopsies. The amount of radiation exposure you will receive from these procedures is equal to approximately 9.3 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 31 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%).

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.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

However, the potential benefit to you might include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer.

Are there any potential benefits to others that might result from the study?

In the future, other people might benefit from this study because what we learn in this study may eventually be used to treat others with your disease.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether to be in this study, the study team will discuss the other options that are available to you. Instead of being in this study, you could:

- choose to be treated with radiation or with drugs already approved by the FDA for your disease
- choose to take part in a different study, if one is available
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

You should discuss with your doctor your other choices and their risks and benefits.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

When we are examining your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as “incidental medical findings”.

These include:

- 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.

Since the analyses that we perform in our laboratory are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing, the genetic changes that we find may or may not be valid. Therefore, we do not plan to inform you of all of the genetic 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 believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future.

EARLY WITHDRAWAL FROM THE STUDY

Your doctor may decide to stop your therapy for the following reasons:

- if your disease worsens or comes back during treatment
- if you become pregnant
- if you have side effects from the treatment that your doctor thinks are too severe
- if your study doctor thinks it is in your best interest
- if you need medication not allowed on this study
- if study drugs become unavailable
- if new information shows that another treatment would be better for you
- if the study is stopped for any reason

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

After the therapy is stopped, we would like to see you for a safety visit approximately one month after stopping therapy.

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.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved for use in other research studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these

specimens and data for other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding cancer, or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will your specimens or data be shared for use in other research studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas that are similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this. We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. These researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

Will your genomic data be shared outside of this study?

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.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others that should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

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. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides 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.

CONFLICT OF INTEREST(COI)

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

The NIH and the research team for this study are using trametinib developed by Novartis through a joint study with your study team and the company. The company also provides financial support for this study.

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

Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. Your information may be given out if required by law. For example, certain states require doctors to

report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you.

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 of National Cancer Institute.
- Qualified representatives from Novartis, the pharmaceutical company who provides trametinib.

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data , and as further outlined in the following sections.

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 information that 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 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 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**.

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: _____.