

NCT# 03232892

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Phase II trial to evaluate trametinib in patients with advanced *NF1* mutant non-small cell lung cancer.

This is a clinical trial, a type of research study. Your study doctor, Collin Blakely, MD, PhD, or one of his associates from the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, will explain this study to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have been diagnosed with either late locally advanced or metastatic (cancer that has spread beyond its original site) non-small cell lung cancer (NSCLC) with a mutation in the neurofibromatosis type 1 (*NF1*) gene, which has been confirmed in prior testing.

Why is this study being done?

The purpose of this study is to test the safety of the study drug trametinib (Mekinist) in patients like you, with advanced *NF1* mutant NSCLC, and to find out what effects, good and/or bad, trametinib has on you and your cancer. The study drug, trametinib, is an investigational drug. Investigational means that trametinib has not been approved by the U.S. Food and Drug Administration (FDA) for use in lung cancer, including NSCLC. Trametinib is approved by the FDA for the treatment of certain patients with advanced melanoma.

Trametinib acts by targeting the MEK protein and disrupting the tumor growth signaling pathway called the RAS-MAPK pathway. Previous studies with *NF1*-mutant NSCLC laboratory models suggested that MEK inhibition with Trametinib may cause tumors to shrink.

The American Cancer Society is providing funding to UCSF for this study. Novartis, the makers of trametinib, is also providing funding to UCSF for this study, and is supplying the study drug free of charge.

How many people will take part in this study?

Up to 27 patients will take part in this study across multiple sites, including 15 at UCSF.

What will happen if I take part in this research study?

Everyone who participates in this study will receive the study drug trametinib.

Before you begin the main part of the study...

If you sign the consent form and agree to participate in the study, you will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. Some of these exams, tests or procedures are part of routine cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

All procedures must be done within 28 days prior to starting the study drug.

Screening

This visit will take approximately 5-6 hours to complete.

- Medical history review – You will be asked about your health, any current and past illnesses.
- Performance status (you will be asked about your general health, how you have been feeling, and about how well you can do your regular daily activities).
- A full review of all of the medications you are taking, including any prescription or non-prescription medications such as vitamins, herbals, and recreational drugs. This will also include a review of all of your prior treatments for cancer.
- Full physical examination including vital signs (blood pressure, heart rate, respiratory rate, and body temperature) height, and weight.
- Blood (about 1-3 tablespoons) will be drawn for routine tests including:
 - Routine safety tests
 - Clotting tests
 - Tumor markers
 - Biomarkers - Biomarkers are substances in your tissues that may provide information on any changes to your genes or DNA, how your cancer cells are responding to study treatment and whether your cells are becoming resistant (no longer responding) to the study treatment.
- Pregnancy testing – if you are a woman of child bearing potential (either a blood test or a urine test, and must be done within 3 days before starting the study drug)
- Urinalysis (routine urine test)
- ECG (electrocardiogram) in triplicate – an ECG records the electrical activity of your heart. 12 wires or “leads” will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical “record” of your heart activity. The ECG will be performed three times in series. This takes about 45 minutes.
- Echocardiogram (ECHO) or MUGA scan to assess your heart function
 - An ECHO examination uses sound waves to make pictures of your heart, which helps determine how well your heart squeezes blood. You will be asked to lie on your left side while a technician places a probe with gel on your chest to create images of your heart to determine the function and size. The procedure is done in the cardiology department and will take approximately 45-60 minutes.
 - A MUGA scan is a test that makes a motion picture that shows how well your heart pumps blood. The scan is performed by taking a small sample of your own

blood that is then “labeled” with a radioactive substance. The labeled blood sample is then re-injected into a vein in your arm and allowed to circulate in your body. Once the labeled blood has circulated around your body, a series of images (similar to a movie) are taken of your heart. You will be asked to lie flat on a table and remain still for about 10-20 minutes while the pictures of your heart are being taken. This test is done in the Nuclear Medicine department and takes about 90 minutes.

- Tumor assessment by CT scan of the thorax, abdomen, pelvis and brain; or MRI (Magnetic Resonance Imaging)
 - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally, intravenously, or rectally (less likely). Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. A rectal contrast fills up the loops of your lower bowel so the doctors can see your tumor better. After you have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the radiology department and takes about half an hour.
 - An MRI scan takes an image of your head or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). Gadolinium is contrast material that causes some tumors to appear much brighter than normal tissue on MRI scans (these tumors may not be visible without gadolinium). The contrast material may be given to you in your arm through an intravenous catheter (a tiny tube inserted into a vein). You will then lie down on a narrow bed which will be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will lie there quietly for about one hour, during which time you will hear a loud machine-like noise. The MRI scan is done in the radiology department and takes approximately an hour and a half to complete.
- Eye exam - a complete eye exam performed by an ophthalmologist or an experienced optometrist (eye doctor). The eye exam will include checking your eyesight, eyelids, eyelashes and surfaces of your eyes. To make this exam easier, your eye doctor will also put drops in your eyes. Your eye doctor may also measure the amount of tears your eyes produce by placing little strips of paper in the corners of your eyes for 3 minutes. The eye exam will take about 45 minutes.
- Tissue collection for research will be required at screening, with another two optional tissue collections in Cycle 2 and at the end of treatment. Tissue will be sequenced (testing the genes) in order to look for changes and differences. Tissue will also be used for biomarker research. The researchers will grow cancer cells outside of the body for further research on response and resistance to treatment. Please see the section About Using Blood and Tissue for Research at the end of this consent form for more information.

- Archival tissue – if there is leftover tissue from a prior biopsy or surgery you have had and if you agree, the study team will request this sample for this study.
- Fresh biopsy – if leftover tissue from a prior biopsy or surgery is not available, the study doctor will obtain a small piece of tumor tissue using a special needle. The biopsy will only be performed if the study doctor determines it is medically safe.
 - This procedure will be done at the site where we can most easily get a piece of the tumor and the biopsy can involve the lungs, liver, bone, lymph node, skin or other. The biopsy needle will be inserted into tumor tissue, using a CT to guide the procedure, and a small piece of the tumor will be removed. 1-3 passes with this needle will be made. This procedure takes about 30 minutes.
 - If the above procedure cannot be done, another way the biopsy may be obtained is via a bronchoscopy. This involves passing a flexible tube (bronchoscope) through your mouth or nose and into your airway to remove a lung tissue sample. You may be sedated for this procedure. This procedure takes about 1 hour.

During the main part of the study...

If the exams, tests and procedures show that you can be in the main part of the study, and you choose to take part, then you will have the procedures listed below.

Study Treatment:

Each cycle of treatment is 28 days.

You will receive a month's supply of the study drug at the beginning of each cycle at your clinic visit. Trametinib is given by mouth and will be taken once a day. Trametinib should be taken one hour before or two hours after a meal. If you miss a dose of trametinib, you can make it up as long as your next dose is at least 12 hours later. If your next dose is sooner than that, skip the missed dose. For your clinic visits on Day 1 of each cycle, you will be asked to take your dose of trametinib at clinic.

You will receive a diary with detailed information on how and when you should take trametinib. You will record the date, time and the number of pills of each study drug you take each day. You must bring your diary to the clinic at each visit for review by the study team.

If the exams, tests, and procedures show that you can be in the main part of the study, and you choose to take part, then you will need the following tests and procedures.

Clinic visits will take about 2 hours but may take up to 5-6 hours if tumor imaging or biopsy is done.

Cycle 1, Day 1

This visit will take approximately 5 hours to complete.

- Review of side effects you may be experiencing

- Review of medications that you are taking
- Physical exam including vital signs
- Ask how well you can perform the regular activities of daily life
- Blood samples (approximately 4 tablespoons) for the following tests:
 - Routine safety testing
 - Clotting tests
 - Biomarkers
- Blood or urine pregnancy test (if not done in last 3 days)
- Urine sample
 - Urinalysis
- Your daily dose of trametinib (your study doctor will advise when to take this)
- Triplicate ECG

Cycle 1, Days 8

This visit will take approximately 1 hour to complete.

- Review of side effects you may be experiencing
- Review of medications that you are taking
- Ask how well you can perform the regular activities of daily life
- Blood sample (approximately 4 tablespoons) for biomarkers

Cycle 1, Days 15

This visit will take approximately 1-3 hours to complete.

- Review of side effects you may be experiencing
- Review of medications that you are taking
- Ask how well you can perform the regular activities of daily life
- Blood sample (approximately 4 tablespoons) for biomarkers
- Eye exam (does not need to be on this day, but must be done before Cycle 2 Day 1).

Cycle 2 and beyond, Day 1

For cycle 2 and beyond, you will only need to attend clinic on the first day of each 28 day cycle. These visits will take approximately 5-6 hours to complete.

- Review of side effects you may be experiencing
- Review of medications that you are taking
- Physical exam including vital signs
- Ask how well you can perform the regular activities of daily life
- Blood samples (approximately 4 tablespoons) for the following tests:
 - Routine safety testing
 - Clotting tests
 - Biomarkers
- Pregnancy testing – if you are a woman of child bearing potential
- Urine sample for:
 - Urinalysis

- Your daily dose of trametinib (your study doctor will advise when to take this)
- Triplicate ECG
- Cardiac assessment (ECHO or MUGA) – Cycles 2, 5, 8, and then every 3 cycles thereafter
- CT or MRI scan of your chest, abdomen and pelvis – Cycles 3, 5, 7, and every other cycle thereafter
- CT or MRI scan of your brain (if there were brain metastases found in screening) – Cycles 3, 5, 7, and every other cycle thereafter
- Eye exam – to be done prior to Cycle 2, again at 6 months, and then every year thereafter
- OPTIONAL tumor biopsy (Cycle 2 only) – to assess response to study drug.

When you are finished receiving study treatment....

End of Treatment Visit

This visit will take approximately 1-3 hours to complete.

Approximately 30 days after the last dose of the study drug, you will return to the study clinic for the following assessments:

- Review of side effects you may be experiencing
- Review of medications that you are taking
- Physical exam including vital signs
- Ask how well you can perform the regular activities of daily life
- Blood samples (approximately 4 tablespoons) for the following tests:
 - Routine safety testing
 - Clotting tests
 - Biomarkers
- Triplicate ECG
- Urine sample for:
 - Urinalysis
- CT or MRI scan of your chest, abdomen and pelvis
- CT or MRI scan of your brain (if there were brain metastases found in screening)
- OPTIONAL tumor biopsy

Follow Up Visits

These visits will take approximately 2-4 hours to complete.

After your End of Treatment Visit, you will be asked to come into the clinic every 3 months for up to 1 year to evaluate your health, any remaining illnesses, and any side effects you may have experienced since the administration of the last dose. The following assessments will be performed:

- Review of side effects you may be experiencing
- Review of medications that you are taking
- Physical exam including vital signs
- Ask how well you can perform the regular activities of daily life
- Blood sample (approximately 4 tablespoons) for the following tests:

- Routine safety testing
- Clotting tests
- Urinalysis
- CT or MRI scan of your chest, abdomen and pelvis (if your disease has not worsened since entering the study)
- CT or MRI scan of your brain (if there were brain metastases found in screening)

Study location: All study procedures will be done at UCSF Helen Diller Family Comprehensive Cancer Center.

How long will I be in the study?

The length of time you are on the study will depend upon how you are feeling, how well you tolerate trametinib and whether your disease responds to the study drugs. You can continue receiving the study drug for up to 24 months from study entry, as long as you have no severe side effects and your cancer has not gotten worse. Once you have stopped taking the study drug, you will be followed for every 3 months for up to 1 year. It is estimated that this study will reach completion 4 years from the time it opens.

Can I stop being in the study?

Yes. You can decide to stop at any time. If you decide not to participate in the study or to withdraw from the study, the quality of your medical care or any benefits to which you are otherwise entitled will not be affected. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules.

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious.

Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, or may never go away.

There also is a risk of death.

You should talk to your study doctor about any side effects that you experience while taking part in the study.

Possible Risks of Trametinib

Common (seen in 10% or more of people)

- Diarrhea, nausea
- Constipation, heartburn, vomiting
- Swelling of the arms and legs
- Tiredness
- High blood pressure
- Bleeding
- Cough
- Shortness of breath
- Dry mouth
- Rash
- Dry and/or itchy skin
- Hair loss
- Chills, fever

Occasional (seen in between 1% and 10% of people)

- Skin infection, skin reddening, skin breaks
- Anemia (a lack of red blood cells) which may require blood transfusion
- Abnormal heartbeat
- Blurred vision or other visual disturbances
- Dry eyes, swelling and redness of the eyelids
- Swelling of one or more limbs (lymphedema)
- Pain
- Sores in the mouth which may cause difficulty swallowing
- Facial swelling
- Infection
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Change in heart function
- Loss of appetite, dehydration
- Dizziness, headache
- Nose bleed
- Redness, pain or peeling of palms and soles
- Pneumonitis (inflammation of the lung)
- Increased levels of the enzyme creatinine phosphokinase in your blood, potentially indicating damage to muscle or the heart
- Increased levels of certain enzymes in the blood that may indicate liver damage

Rare but Serious (seen in less than 1% of people)

- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Changes in the eyes (blood clot or retinal detachment) which can cause blindness
- Scarring of the lungs (interstitial lung disease)
- Sudden loss or decrease of kidney function (“acute renal failure”)
- Swelling with fluid in abdomen (ascites)
- Loss of consciousness (syncope)
- Blood clot in lungs (pulmonary embolism)
- Intestinal obstruction or perforation, inflammation of the colon

Risks and side effects related to the study procedures

Safe handling risks: Handling the study drug and having contact with urine, feces or vomit from patients receiving the study drug may pose some risk to you and your caregivers. To avoid exposure to the study drug and any associated risks, you and your family members/caregivers will be educated by a member of the study team on how to safely handle the study drug, properly dispose of the study drug, and how to clean products that may be contaminated with the study drug.

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, infection, and fainting.

Electrocardiogram (ECG) risks: The ECG involves placing electrodes on the skin. You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own. Please let your doctor know if you are aware of any allergies.

Eye Exam: During the eye examination, your pupils will be dilated with eye drops to allow a good view of the back of the eye. This will result in some blurred vision lasting for a few hours. You will not be able to drive during this time. Before the test, tell your eye or study doctor if you are allergic to dilating or anaesthetic (numbing) eye drops. In some people, the dilating or anaesthetic eye drops can cause brief episodes of nausea, vomiting, dryness of the mouth, flushing, and dizziness. In rare cases, severe reactions can occur. If you experience any side effects after the examination, tell your study doctor or your eye doctor immediately.

Echocardiogram (ECHO) risks: The cardiac echogram might cause you to be uncomfortable from the pressure of the probe on your chest or lying still for the examination.

MUGA scan risks: The MUGA scan involves exposure to radiation (see above). Like all injections it may feel like a small sting and there may be possible bruising at the injection site. You may be uncomfortable lying flat.

Radiation risks: This research study involves exposure to radiation. Not all this radiation exposure is necessary for your medical care and is for research purposes only. This amount of radiation may involve a low risk of cancer. However, we believe that this risk, given your

overall medical condition is not clinically relevant. If you have any questions regarding the use of radiation or the risks involved, please consult your study doctor.

CT scan risks: CT scans involve the risks of radiation. In addition, if contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan with contrast. If you are taking metformin (or similar drugs by mouth to treat high blood sugar), such treatment will be stopped for 2-3 days around the time a scan is planned in order to avoid kidney side effects.

Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. If contrast material is used, you may feel discomfort when it is injected by vein. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.

MRI risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys.

Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

Tumor biopsy risks: The biopsy has small but serious risks. While we make every effort to minimize the pain related to the procedure, the procedure is usually uncomfortable and sometimes painful. Wherever the biopsy is done in your body, it can lead to bleeding in that area, damage of organs near where the biopsy is done, or infection. While it is uncommon, sometimes bleeding or pain from the biopsy will require you to stay overnight in the hospital or require you to go to the operating room to control any bleeding. We check your laboratory values before the biopsy to make sure that the procedure is as safe as possible and to minimize your chance of having a complication. We try to take as little tissue as possible when we do the biopsy, and this means that sometimes the biopsy procedure can be unsuccessful and require a repeat biopsy to get enough tissue. If sedation is required for the biopsy, this may cause hypoventilation (slow or shallow breathing) or hypoxia (decrease of oxygen reaching body tissues). Other potential risks will be described to you and discussed with you by doctors who conduct these biopsies.

Additional tumor biopsy risks: You may agree to have two additional optional tumor biopsies. Having additional tumor biopsies done for research purposes might cause pain, discomfort, infection, bleeding and injury to nearby organs.

Lung biopsy risks: A pneumothorax (when air leaks into the space between the lung and chest wall, potentially making the lung collapse) may occur. Symptoms include sudden chest pain and shortness of breath. Treatment may involve inserting a flexible tube or needle between the ribs to remove the excess air. If you have a bronchoscopy, you may also experience a pneumothorax, bleeding at the biopsy site, allergic reaction to medicine and hoarseness.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. If you are a woman and become pregnant after receiving the study drug, or are male and your partner becomes pregnant during the study, you must notify the study doctor right away. Women should not breastfeed a baby while on this study. It is important to understand that both men and women need to use birth control while on this study and for at least 4 months after your last dose of the study drugs. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Unknown Risks: The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the study drug will be more useful against cancer compared to the usual treatment, there is no proof of this.

We do know that the information from this study will help doctors learn more about trametinib as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- 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, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about your choices before deciding if you will take part in this study.

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you.

Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation.

Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis or analyze your blood or tumor samples include:

- Novartis and its authorized agents
- The University of California
- The National Cancer Institute (NCI) and other government agencies, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.

What are the costs of taking part in this study?

Novartis is supplying trametinib at no cost to you.

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Collin Blakely, MD, PhD, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him [REDACTED].

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the UCSF Institutional Review Board (IRB) at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor Collin Blakely, MD, PhD, [REDACTED].

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the UCSF Institutional Review Board (IRB) at 415-476-1814.

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.

OPTIONAL RESEARCH

Please note: This section of the informed consent form is about additional research studies that are being done using left-over or “extra” blood and tumor samples after the main research has been completed. You can still be a part of the main study even if you say "no" to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

About Using Tissue, Blood and Urine for Future Research

To better understand what effect trametinib is having on your cancer, biomarker studies will also be conducted as companion research to the main study. Biomarkers are important biological ‘indicators’ which can be measured from the samples that are collected from you such as blood, urine, and tumor tissue. Biomarker studies are done to look at changes in genes and proteins and are important because they help us learn about your cancer in addition to the effect of the drug on your body and your cancer. Biomarker studies will be performed on blood and urine samples collected. If you agree, any leftover blood, urine and tumor specimens collected during this study would also be saved (“banked”) for future research to learn more about cancer and other diseases.

You will also be undergoing a tumor biopsy (at screening). The study doctor would like you to consider participating in another two optional tumor biopsies at the following time points for the biomarker studies:

- Cycle 2, Day 1
- 30 days after your last dose of study drug (at the end of treatment visit).

The research that may be done with tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care. Results from the future research may be published but your data will not be reported individually.

Things to Think About

The choice to let us keep specimens for future research is optional and is up to you. No matter what you decide to do, it will not affect your care.

Your specimens will be stored in a repository at UCSF. If you decide now that your specimens can be kept for future research, you can change your mind at any time. Just contact the study doctor, Collin Blakely, MD, PhD, in writing at the address below, and let us know that you do not want us to keep your specimens.

Collin Blakely, MD, PhD

[REDACTED]
San Francisco, CA 94143-1705

Any identifiable specimen that remains will no longer be used for research and destroyed. However, if any research has already been done using portions of your specimens, the data will be kept and analyzed as part of those research studies.

In the future, people who do research may need to know more about your health. While the study doctor may give them reports about your health, he will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your specimen will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future. You will not be paid for allowing your tumor samples to be used in research even though the research done with your samples may help to develop new products in the future. You will not receive any payment or financial benefit from any products, tests, or discoveries derived from these samples.

Benefits

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Confidentiality: Donating specimens may involve a loss of privacy, but information about you will be handled as confidentially as possible. The manager of the tissue bank and select tissue bank staff members will have access to information about you but they will not release any identifying information about you to researchers using your specimen. The UCSF IRB and other University of California personnel also may see information about you to check on the tissue bank such as for auditing purposes.

All records will be coded and permanently kept in password protected electronic files or locked files with access limited to the study investigators. All collected specimens will be assigned a corresponding code number by the study investigators and will then be processed without

knowledge of your identity. Only the UCSF investigator has access to the records that link this coded ID number to you. In addition, specimens shared with other researchers, and the coded ID number will be used to identify your specimens.

Genetic information about your blood, urine or tumor samples that results from this study does not have medical or treatment importance at this time, so you will not receive the results of this testing. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to employers, health providers, insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives. Therefore, your genetic information potentially could be used in ways that could cause you or your family distress, such as by revealing that you (or a relative) carry a genetic disease or by leading to the denial of employment or insurance for you (or a relative). To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record.

It is also possible that your or your family's privacy could be invaded in ways that are currently not possible but made possible in the future by advances in technology. For instance, some scientists performing research with tissue bank materials may try to determine the code of part or all of your chromosomes. This coding could be a way to accurately identify the sample as coming from you. If a scientist publishes your coding, the source of that coding could be identified as you if someone else has your code through other means to compare to the published coding. The likelihood of this happening is very small, but future technology developments may increase the possibility of this occurring.

Additionally, due to the rarity of the cancer and the likelihood that the research done with the tissue samples will be published in the future, it may be possible to identify you from publications even though your name will not be used in any published reports.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence put your initials in the "Yes", or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at 415-476-1814.

No matter what you decide to do, it will not affect your care.

1. I agree to the optional tumor biopsy at Cycle 2, Day 1.

YES	NO
------------	-----------

2. I agree to the optional tumor biopsy at the end of treatment visit (30 days after the last dose of the study drug).

YES	NO
------------	-----------

3. Any leftover blood, urine and tissue samples collected for this clinical trial may be kept for future research.

YES	NO
------------	-----------

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date

Participant's Signature for Consent

Date

Person Obtaining Consent

Date

Witness – Only required if the participant is a non-English speaker