NCT# 02587650

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

Study Title: CC# 14859: A Phase II Trial of Targeted Kinase Fusion Inhibition in BRAF/NRAS Wild-Type Melanoma

This is a clinical trial, a type of research study. Your study doctors Adil Daud, MD and Iwei Yeh, MD, PhD or one of their associates from the UCSF Helen Diller Family Comprehensive Cancer Center will explain the clinical trial 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 locally advanced or metastatic melanoma that has spread or that cannot be cured by surgery.

Why is this study being done?

The purpose of this study is to test the effectiveness (how well the drug works), of an investigational drug based on your biomarker status. You are being asked to participate in this clinical trial because you have undergone screening for specific biomarkers prior to being enrolled in the main part of this study. The screening involves genomic testing. If you have already tested positive for the biomarkers relevant in this study in an approved lab, you may be eligible to participate in this clinical trial. If you have not been tested, you will be invited to participate in an affiliated UCSF study (Study #14-14351), where you are screened for the relevant biomarkers. **You will not be charged for biomarker testing if you participate in the screening study**. If you have already been screened at a separate approved lab, covered by your insurance, you may also be potentially eligible for enrollment in this clinical trial. The biomarker test is investigational, this means it has not been approved by U.S. Food and Drug Administration (FDA) for use in melanoma patients.

The biomarkers being tested for are ALK, BRAF, MET, NTRK1, NTRK2, NTRK3, RET and ROS1. 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. You will be assigned one of four study drugs depending on which biomarker is identified in your tumor. Two of these study drugs, ceritinib and regorafenib, have been FDA approved for use in patients with lung cancer and colorectal cancer, respectively however, their use in advanced melanoma patients is not FDA approved and is therefore an investigational use of the drugs in this study. Additionally, the other two study drugs, capmatinib (otherwise known as INC280) and entrectinib (otherwise known as RXDX-101) have not been approved by the FDA for use in cancer patients, including melanoma patients and is therefore an investigational use of the drugs

in this study. In animal studies, lab experiments, and in some early human studies, the study drugs, have been shown to prevent or slow the growth of cancer cells.

If you decide to participate, you will be enrolled into one of these 4 groups:

- Arm A: Treatment with ceritinib if you have been identified with the ALK biomarker
- Arm B: Treatment with capmatinib (INC280) if you have been identified with the MET biomarker
- Arm C: Treatment with regorafenib if you have been identified with the BRAF or RET biomarker
- Arm D: Treatment with entrectinib (RXDX-101) if you have been identified with the NTRK1, NTRK2, NTRK3 or ROS1 biomarker

Funding for this study is being provided by Bayer, Ignyta and Novartis.

How many people will take part in this study?

Approximately 35 patients will be participating in this study in sites across the US. About 15 people will take part in this study at UCSF.

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

If you give your consent to be in this study by signing this form, you will have tests and procedures (called "screening") done. These are done to reduce the risks of taking part in this study and to make sure it is okay for you to be in the study.

It is possible that after these tests are reviewed, you will not be able to be in the study. There may be other reasons why you cannot be in this study. Your study doctor or the clinic staff will discuss these reasons with you.

Your study doctor will also discuss with you the possibility of receiving or continuing treatment with ipilimumab or the anti-PD-1 antibodies, nivolumab or pembrolizumab. Ipilimumab is FDA approved for treatment of melanoma and your doctor will discuss with you if this is the best treatment option for you. FDA approval of ipilimumab was based on a clinical trial that showed that patients treated with ipilimumab had an overall survival of 10 months, whereas patients treated with an investigational tumor vaccine had an overall survival of 6 months. The response rate for patients treated with ipilimumab was 10.9% in one study. Both pembrolizumab and nivolumab are also approved for the treatment of melanoma, both are associated with prolonged responses in patients with melanoma such as yours and may improve survival. You may participate in this trial if either of these treatments fail or if you wish prior to using these treatments.

Screening period

After you have signed this consent, the screening tests listed below will be done within 30 days of your first dose of study drugs. 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. Most of these exams, tests or procedures are part of your regular cancer care (unless notes otherwise as Research Purposes). If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

The total time to complete the screening tests and procedures is about 8-12 hours. The screening procedures do not have to be completed in one day and you are allowed to take breaks if you have multiple tests in one day.

- You will have a complete physical exam and your current symptoms will be reviewed.
- You will be asked about your medical history including any past treatments or surgeries for your disease. Your performance status (your ability to carry out your daily activities) will be assessed.
- Your vital signs (height, weight, temperature, breathing rate, blood pressure, pulse, and oxygen saturation) will also be recorded.
- You will have an ECG (electrocardiogram).
    - **Electrocardiogram (ECG):** records the electrical activity of your heart. 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 procedure is done in the Cardiology Department takes about 15-30 minutes.
- Blood will be drawn to check your health, conduct routine safety tests and blood sugar levels. When your blood sugar is checked you will be asked to fast (no food or drink other than water) at least 12-14 hours before having blood drawn for this test. About 6 teaspoons of blood will be drawn for these tests.
- Urine tests
- You will have a CT scan. Your doctor may decide to do a MRI scan instead of a CT scan.
    - 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.

The following procedures will be done for research purposes:

- Questions about how your disease is affecting your daily life
- You will be asked to provide a piece of stored tumor sample from previous biopsies or surgeries you may have had in the past before you joined this study. This sample can be used to study your cancer. This will help researchers better understand the reasons for cancer development, growth, spread, and its response to treatment. Your consent to provide a sample of your stored tumor tissue if available is required to take part in this study.
- Blood will be drawn (approximately 2 tablespoons) for:
  - Blood safety and chemistry tests
- Pregnancy test (only required in women of child-bearing potential)

Treatment period

Based on the results of the screening visit tests and procedures, if you are eligible to participate in the study, you will return to the study doctor's office/clinic and will be assigned to either Arm A, Arm B, Arm C, or Arm D depending on which biomarker is identified in your tumor. The study doctor will let you know which treatment you have been assigned to.

Description of Study Treatment:

Upon entry into the study, you will be assigned by your biomarker status, to receive the following study drug:

- Arm A - ALK biomarker: You will be given study drug ceritinib, or;
- Arm B - MET biomarker: You will be given study drug capmatinib or;
- Arm C – BRAF or RET biomarker: You will be given study drug regorafenib, or;

- Arm D – NTRK1, NTRK2, NTRK3 or ROS1 biomarker: You will be given study drug entrectinib.

Each period of treatment is called a "cycle" and one cycle is 28 days long or 4 weeks. If you are assigned to Arm A, Arm B or Arm D you will take the study drug orally daily for all 28 days. If you are assigned to Arm C you will take the study drug orally for the first 21 days (3 weeks) of the 28 day cycle.

Day 1 of every cycle, ALL patients will come in for the following tests (each of these visits will take about 2 hours):

- Physical examination
- Vital signs
- Urine tests
- Blood will be drawn (approximately 3 tablespoons) for safety tests
- CT/MRI - odd cycles only (Cycle 3, 5, 7, etc.)

The following procedures will be done for research purposes:

- You will be given your study drug
- Evaluation of any side effects
- Questions about how your disease is affecting your daily life
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- Pregnancy test (women of child-bearing potential)
  You must have a negative pregnancy test to receive or continue receiving study drug. Following your first dose, you will have a pregnancy test (urine or blood) every 4 weeks.
- Tumor biopsy (skin or tissue) will be done at Cycle 2, Day 1 (± 7 days), at time of progression and/or at the discretion of your doctor. Punch or core biopsy is mandatory, and the procedure will be slightly different depending on whether the tumor is located on the skin or elsewhere.
  - **Tumor biopsy (skin):** In this procedure, your doctor will remove a small piece of skin (the size of a pencil eraser). The area of the biopsy will be numbed with local anesthesia before this biopsy is taken. You may get stitches in the area where the biopsy is taken from. The biopsy will take about 20 minutes to complete.
  - **Tumor biopsy (non-skin):** As part of this study, we will obtain a small piece of tumor tissue using a special needle. 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, or other. The biopsy needle will be inserted into tumor tissue and a small piece of the tumor will be removed. 1-3 passes with this needle will be made. The tissue is being used to help us determine if certain types of tumors might respond better to certain treatments. This procedure takes about 30 minutes. You will sign a separate consent form for this procedure.

Schedule for Each Arm

Outlined below is the schedule you will follow depending on your treatment arm. Your study doctor will help you understand this process. Additional ECGs and/or blood tests may be collected at the discretion of your doctor if deemed medically necessary.

Arm A patients – study drug Ceritinib

- ECG before and after drug dose on Cycle 1, Day 1; before drug dose on Cycle 2, Day 1; and before drug dose on Day 1 of all subsequent even-numbered cycles.every 4 weeks starting Cycle 1, Day 1

The following procedures will be done for research purposes:

- Coagulation tests – weekly the first 4 weeks starting Cycle 1, Day 1, every two weeks starting Cycle 2, Day 1; then every 4 weeks starting Cycle 3, Day 1

Arm B patients – study drug Capmatinib (INC280)

- Coagulation Blood tests – every two weeks starting Cycle 1, Day 1; then every 24 weeks starting Cycle 23, Day 1; then every 4 weeks starting Cycle 5, Day 1.
- Thyroid tests every 4 weeks starting Cycle 2, Day 1
- Urine tests – every two weeks starting Cycle 1, Day 1; then every 4 weeks starting Cycle 2, Day 1.
- ECG – every 8 weeks starting Cycle 3 Day 1.

Arm C patients – study drug Regorafenib

- Blood tests – weekly the first 4 weeks starting Cycle 1, Day 1, every two weeks starting Cycle 2, Day 1; then every 4 weeks starting Cycle 3, Day 1
- ECG on Cycle 3, Day 1, and on Day 1 of all subsequent odd cycles (every 8 weeks).

Arm D patients – study drug Entrectinib (RXDX-101)

- Blood tests – every two weeks starting Cycle 1, Day 1; then every 4 weeks starting Cycle 4, Day 1.
- Urine tests – every two weeks starting Cycle 1, Day 1; then every 4 weeks starting Cycle 4, Day 1.
- ECG on Cycle 1, Day 1, and on Day 1 of all subsequent cycles (every 4 weeks).

End of Treatment Visit End of Treatment Visit (this visit will take between 3-6 hours depending on your procedures)

- Physical examination
- Vital signs
- Blood will be drawn (approximately 3 tablespoons) for safety tests
- Urine tests
- ECG
- CT scan or MRI

The following procedures will be done for research purposes:

- Evaluation of any side effects
- Questions about how your disease is affecting your daily life
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- Tumor biopsy
- Skin biopsy
- Blood will be drawn (approximately 1 tablespoon) for:
  Blood chemistry tests
- Pregnancy test

Post treatment follow-up
Once you have discontinued all study treatments, your provider or study coordinator will give you a call within 30 days following the last dose of study treatment to see how you are doing (you will be asked about your health, any side effects, and any medications or treatments you might be taking); this is for research purposes). You will be followed for survival information and to see how you are doing via a telephone call every few months. You don't have to come back to the clinic.

Study location: All study procedures (clinic visits, biopsies, imaging studies, blood draws, urine studies) will be done at UCSF Helen Diller Family Comprehensive Cancer Center.

How long will I be in the study?

After you complete all of the planned study visits, you will be contacted approximately every 3 months (by office visit or telephone) to determine your health status. This will occur indefinitely.

Your total participation in this study from the time you have signed the informed consent form through to your last visit may be over one year (depending on how your cancer responds to treatment and how well you tolerate the treatment). If treatment is stopped or you withdraw from treatment, you will be followed until any side effects from treatment have resolved.

Can I stop being in the study?

Yes. You can decide to stop at any time. 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 drugs 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, or if the study is stopped.

What are my Responsibilities?

If you participate in this study, you will be expected to:

- Keep all study appointments and follow all instructions given to you by your study doctor and study staff.
- Describe how you feel and discuss possible side effects.
- Tell the study doctor about all medications you are taking including prescription, herbal supplements and over-the-counter medications.
- Discuss any medication (prescription or over the counter) that you wish to start taking with your study doctor before you start taking it.
- Tell the study doctor about any changes in your health.
- Tell the study doctor about all of the medications (prescription, over-the-counter, herbal) that you are currently taking. Even if it is not on the list of prohibited drugs, you may need to be monitored more frequently.
- Certain medications are prohibited while you are participating in this trial. Your study doctor will explain what these medications are. If you need treatment with any medications that are not allowed during your participation in this trial, you must inform the study doctor or the study staff. You will not be denied medications required to treat an illness you may have, but you may be required to stop taking the study medication. This is for your safety, since some medications may not work well with the study treatment, and you might have physical problems. Please keep in mind that you cannot take other investigational drugs on other clinical trials while you are being treated on this study. Please see the end of the consent form for a detailed list of prohibited medications while on any of the study drugs.

- Tell your study doctor about any medical treatments that you plan to receive during the study (such as elective surgery or radiation).
- Tell your study doctor or study staff if you change your address, telephone number, or other contact information.
- Use birth control for the duration of the study. If you are taking capmatinib, ceritinib or entrectinib, you will need to continue birth control for at least 7 days after your last dose of study drug. If you are taking regorafenib, you will need to continue birth control for at least 3 months after your last dose.
    - If you are woman of child-bearing potential, you should maintain total abstinence, have had your ovaries removed or a tubal ligation done at least 6 weeks before

starting study treatment, or practice two of the three following methods of contraception: (1) intrauterine device (IUD) placement, (2) barrier contraception (condom or occlusive cap, such as diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository, (3) use of oral, injected or implanted hormonal contraception.

- If you are a man, you should use a condom with spermicidal foam/gel/film/cream. If you have had a vasectomy, condom use is still required to prevent delivery of the drug via semimal fluid. You should also make sure your female partner is using highly effective contraceptive methods as described above.

- Tell your study doctor or study staff as soon as possible if you discover you become pregnant, or have fathered a child during the study or within the 7 days after your last dose of capmatinib, ceritinib or entrectinib; or within the 3 months after your last dose of regorafenib.

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.

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

Ceritinib risks

- A first-in-human study of ceritinib is currently being conducted and has enrolled over 300 patients who have been followed for an average of approximately 6 months. For patients in this study, the most common side effects include nausea, vomiting, diarrhea, abdominal pain, and fatigue.

- Elevation of liver laboratory tests in the blood has occurred in patients receiving ceritinib. In most cases, the elevation of liver laboratory tests in the blood has been mild to moderate. The elevation of liver laboratory tests in the blood of greater severity has also been reported which may lead to hospitalization and can be life-threatening. The elevation of liver laboratory tests in the blood has typically reversed with the interruption of ceritinib and often does not recur when a lowered dose of ceritinib is given. You will be closely monitored for any signs and symptoms related to the elevation of liver laboratory tests in the blood for your safety during the study.

- Some patients experience an inflammation of the lungs (pneumonitis) with symptoms of shortness of breath, cough and fever. Death from inflammation of the lungs

(pneumonitis) has been reported. In most cases, this condition can improve or resolve with interruption of ceritinib and medical treatment. If you develop shortness of breath, cough or fever, contact your study doctor immediately to report any of these symptoms.

- Sudden loss or decrease of kidney function ("acute renal failure") has been reported. The relationship between ceritinib and this condition is unclear. For your safety, your kidney function will be closely monitored during the study.

- Results from the first-in human study suggest that ceritinib can have an effect on the QT interval. QT is one of the measurements taken during an ECG (heart tracings). An effect on QT could lead to an irregular heartbeat which in rare instances can develop into a sudden, life-threatening condition. Slow heart rate, which is usually not serious, has also been noted in patients treated with ceritinib. For your safety, repeated ECG tracings will be performed throughout the study to closely monitor your heart activity. If you experience chest discomfort or changes in your heartbeat (fast or slow), contact your study doctor immediately to report any of these symptoms.

- Elevation of glucose in the blood has been reported in patients receiving ceritinib. You will be closely monitored for any signs and symptoms related to the elevation of glucose in the blood for your safety during the study.

- The elevation of pancreas enzymes in the blood has occurred in patients receiving ceritinib. In most cases, the elevation of pancreas enzymes in the blood has been mild to moderate. The elevation of pancreas enzymes in the blood has typically reversed with interruption of ceritinib, and in some cases, may not recur when a lowered dose of ceritinib is given. You will be monitored closely for any signs and symptoms related to the elevation of pancreas enzymes in the blood for your safety during the study. Few patients experience an inflammation of the pancreas (pancreatitis) with severe upper abdominal pain which may lead to hospitalization and can be life-threatening.

- Other side effects observed with ceritinib include the following: constipation, decreased appetite, rash, problems with the liver, pancreatitis, and changes in laboratory values (i.e. blood cell counts, electrolytes, amylase and lipase). Dehydration may occur as a result of diarrhea and vomiting. Some people have also developed problems in their esophagus.

- This may not be a complete list of possible side effects. You may experience a side effect that has not been experienced before.

- We do not know the full range of side effects of ceritinib when given either alone or in combination with other drugs. Some over-the-counter and prescription medications can reduce the effectiveness or increase the side effects of ceritinib. Likewise, ceritinib can increase the side effects or lessen the effectiveness of some other medications. You should always discuss the use of any drugs (over-the-counter drugs, prescription, or illegal drugs or health food supplements) with your doctor before taking ceritinib and while you are participating in this study.

At each visit, your doctor will ask you about any unusual symptoms. You will be closely monitored for any side effects and should report any changes in the way you feel to your doctor.

Capmatinib (INC280) risks

Patients treated with capmatinib have experienced:

- Swelling of the legs and arms
- Nausea – the feeling that you will vomit
- Fatigue – feeling tired
- Tremor
- Stomach pain (abdominal pain and upper abdominal pain)
- Pain in the joints, (arthralgia)
- Loose stool (diarrhea)
- Dizziness
- Cough
- Headache
- Pain in the arms and legs
- Pain in the bones and muscles
- Infection in the urinary tract
- Decreased lymphocytes in blood (lymphopenia)
- Lung Infection
- Increased liver enzymes (increased ALT, AST, Bilirubin, GGT)
- Increased pancreatic enzymes (Amylase and Lipase)
- Decreased appetite or loss of appetite
- Unexplained weight loss
- Itching (pruritis), skin rash, and/or dry skin
- Shortness of breath
- Increased potassium in blood (hyperkalemia)
- Increased creatinine in blood
- Decreased levels of phosphate in blood (hypophosphatemia)
- In animal experiments, capmatinib absorbs light in the UVA-range (sunlight), and caused skin to be sensitive to sunlight. It may be advisable not to sunbathe or use a solarium for a long period of time while taking capmatinib.
- Decreased levels of sodium in the blood (hyponatremia)

Rare but serious risk: There is a rare but serious risk of severe or fatal Interstitial Lung Disease or ILD. ILD means that your lungs are being damaged. Some of the events reported in studies with capmatinib have resulted in death. If you experience increasing shortness of breath or a persistent dry cough you should inform your study doctor as soon as possible.

Entrectinib risks

Based on testing of entrectinib in animals and preliminary data from other studies in patients with advanced cancer who have been treated with entrectinib, certain side effects are possible, as described below:

Likely (Side Effects That Occurred in > 10% patients)

- Fatigue
- Tingling, tickling, prickling, or burning sensation of skin
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- Loss of taste or a bad taste in your mouth
- Pain in muscles and joints
- Vomiting
- Confusion
- Diarrhea (if severe, could also result in low sodium and low potassium levels)
- Dizziness

Less Likely (Side Effects That Occurred in 2 to 10% patients)

- Constipation
- Neuropathy (nerve injury which could result in feeling of numbness or pain, or cause weakness)
- Pain in mouth or throat
- Rash
- Dry mouth
- Edema (swelling)
- Decreased appetite
- Ear pain
- Eye swelling
- Headache
- Indigestion
- Low levels of red blood cells (which carry oxygen)
- Low levels of white blood cells (which fight infection)
- Pain in arms or legs
- Trouble with balance
- Dry skin
- Flatulence
- High blood pressure
- Increased salivation
- Low blood pressure
- Low levels of platelets (which help with blood clotting)
- Nail infection
- Shortness of breath

- Stomach pain
- Tremors
- Voice spasms

Rare but serious (occurred in < 1% of patients)

- Allergic reaction involving the heart muscle

Regorafenib risks

Risks for regorafenib can also be obtained from the package insert available for the drug. Side effects you may experience from regorafenib listed are:

Likely (Side Effects That Occurred in > 20% patients)

- Anemia
- Increased AST
- Asthenia
- Proteinuria
- Hypocalcemia
- Hypophosphatemia
- Lymphopenia
- Decreased appetite and food intake
- Increased lipase
- Hand-foot skin reaction (HFSR)
- Hyperbilirubinemia
- Increased ALT
- Diarrhea
- Thrombocytopenia
- Mucositis
- Weight loss
- Infection
- Hypertension
- Dysphonia
- Hyponatremia
- Pain
- Fever
- Rash
- Hypokalemia
- Increased amylase
- Increased INR
- Hemorrhage

Less Likely (Side Effects That Occurred in 1 to 10% patients)

- Headache
- Alopecia
- Taste disorder
- Musculoskeletal stiffness
- Xerostomia
- Hypothyroidism
- Neutropenia
- Tremor
- GERD
- Myocardial ischemia and infarction

Rare but serious (occurred in < 1% of patients)

- Gastrointestinal fistula
- Keratoacanthoma/squamous cell carcinoma of the skin
- Pancreatitis

Other Risks

Risks of screening for kinase fusions: You are eligible for this study based on genetic analysis that identifies a kinase fusion rearrangement in your melanoma. This genetic testing is new and is not currently part of the standard of care of melanoma. If there is an error in this test, it is possible that you could receive a study drug that is ineffective because it targets a genetic mutation that your melanoma may not have.

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

Electrocardiogram (EKG/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.

No radiation risk beyond routine clinical care: This study involves radiation exposure as part of routine clinical care. You will not receive additional radiation as a result of participating in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.

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 a patient is dehydrated or has poor kidney function. The study doctors will ask 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.

Having a CT scan may mean some added discomfort. In particular, patients 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, patients may feel discomfort when it is injected. Patients may feel warm and flushed and get a metallic taste in their mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.

MRI scan risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during the 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 their 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. In particular, patients 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.

Contrast agent (gadolinium) for MRI:
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 an 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 to undergo the MRI scans.

Tumor Biopsy (non-skin): 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 hto 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. Additionally, if the biopsy involves the lungs, it can cause the lungs to deflate and if this occurs, you might require treatment to correct this. 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. Other potential risks will be described to you and discussed with you by doctors who conduct these biopsies.

Tumor Biopsy (skin): There will be some discomfort with this procedure, and there may be bleeding as well. One or two stitches at the biopsy site may be required, which would need to be removed one week later. This procedure may result in temporary pain and bruising. In addition, scarring may occur at the biopsy site. Infection at the skin biopsy site occurs rarely.

Drug Interaction Risks: You must also review with your study doctor all of your medications (including supplements and herbal or natural substances) at every visit, as well as notify your study doctor before starting any new medications, supplements, or herbal treatments while participating in the study because there is a risk of serious interaction with the study drug.

Reproductive Risks: You should not become pregnant or while on this study because the drugs in this study can affect an unborn baby. You must notify the investigator immediately if you become pregnant while you are taking part in this study. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. 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.

Safe Handling of Medications: Handling the study drug assigned to you and having contact with any 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, properly dispose of, and clean products that may be contaminated with your study drug.

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

Are there benefits to taking part in the study?

The study drugs may or may not lead to improvement of your melanoma. The knowledge gained from this study may be of help to other subjects with cancer in the future. Benefit may be expected from these study drugs, though this cannot be guaranteed.

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. Current FDA-approved, standard of care therapies for advanced melanoma that you may be eligible for include:

- Immunotherapy:
  - Nivolumab (Opdivo) or pembrolizumab (Keytruda): These are antibodies against a cell receptor called PD-1. Nivolumab is given intravenously every 2 weeks, and pembrolizumab is given intravenously every 3 weeks in a clinic setting. Both PD-1 antibodies have been shown in phase III trials to result in objective response rates of 30-40%, and to significantly prolong progression-free and overall survival compared to chemotherapy.

    Ipilimumab (Yervoy): This is an antibody against a cell receptor called CTLA-4. It is given intravenously every 3 weeks for 4 doses in a clinic setting. It has been shown in phase III trials to result in objective response rate of about 11% and to prolong overall survival compared to chemotherapy, but its role as a single agent has decreased with development of the PD-1 agents. The combination of ipilimumab plus nivolumab has been approved for advanced melanoma treatment as well. Combining these drugs has been shown in a phase III trial to increase objective response rate to about 60%, but with increased toxicity.
  - High-dose interleukin 2 (IL-2): This is a growth factor of T cells that is given intravenously in a hospital setting. It is associated with severe multiorgan toxicity and an objective response rate of about 15%, though a minority of patients have achieved durable response.
- Chemotherapy: Cytotoxic chemotherapy does not play a role in the initial management of advanced melanoma, but it can be an option for patients whose

  disease can no longer be controlled with immunotherapy or targeted therapy approaches. Dacarbazine, temozolamide, cisplatin, carboplatin and paclitaxel are examples of agents that can be used alone or in combination. These approaches have not been shown to increase overall survival, but can be associated with objective disease response in a minotiry of patients.
- eived at least one FDA- approved therapy for melanoma before enrolling in this study. If you have not yet received any drug for treatment of your melanoma, you may still participate in this study as long as you understand that you are taking the risk that your disease may spread without having received a standard of care, approved drug. If this is the case, please discuss your decision with your doctor.

- 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 study doctor about your choices before deciding if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. 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 include:

- The study sponsors Bayer Inc, Ignyta and or their representatives, including companies it hires to provide study-related services
- Novartis (the drug supplier) and its authorized agents
- Researchers who are conducting this study at other research sites
- Food and Drug Administration (FDA), National Cancer Institute (NCI), or other government agencies involved in keeping research safe for people
- The University of California
- Governmental agencies in other countries where the study drug may be considered for approval

To ensure the scientific integrity of the study, you may not be able to review some of your records related to the study until after the study has been completed. When the study is over, you may write to the study doctor to ask to see health data about you that was collected during the study and to correct any errors.

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for taking part in studies. Check with your health plan/insurance company to find out what they will pay for. Taking part in this study may or may not cost you or your insurance company more than the cost of getting routine cancer treatment. Ceritinib, regorafenib or entrectinib will be provided free of charge while you are participating in this study.

You will not be billed for any of the tests (such as optional biopsy, blood samples for biomarker testing) required specifically by the study. These are procedures noted above as "research purposes" in this consent form. Other procedures, which are also done in this study but are part of your routine care will be paid for by you or your insurance.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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 doctors, Adil Daud, M.D. or Iwei Yeh, 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 her at [redacted]3-9900.

> **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 or the study sponsor (BMS), depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research 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 doctors Adil Daud, M.D or Iwei Yeh, MD, PhD. at [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 Office of the Committee on Human Research at 415-476-1814.

ClinicalTrials.gov is a website that provides information about clinical trials. 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.

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the study. You may take part in these additional studies only if you want to. Everyone who is taking part in the study is being asked to take part in this optional study.

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

About Using Tissue Samples and Blood for Research

Your study doctor wants to use your blood and tissue samples to help better understand how the study drug works in your body, in addition to helping develop new ways to monitor and treat diseases. We would like to use your previous biopsies of your tumor tissue (called archival tissue) and any remaining tissue from biopsies on this study, for biomarker testing and to use some of your blood collected during your biomarker to be stored for future tests. If you decide to participate, your archived tissue will be collected at any time while you are on study and your additional blood samples will be collected during your already scheduled study blood draws.

What will happen if I agree to donate my specimens?

If you agree to let researchers collect and store your blood and tissue samples for future research, the following will happen:

- After all routine tests required for your care are finished, instead of discarding your leftover specimens we will save them in what is called a "tissue bank" for possible future research. We also will collect and save information from your medical record, including things like results of physical examinations, diagnostic tests, medical questionnaires and histories, and cancer diagnoses and treatments. We do not know for sure if your specimens or medical record will be used, but they might be used in research about breast cancer.
- We may give your specimens and certain medical information about you (for example, diagnosis, blood pressure, age) to other scientists or companies not at UCSF, including to a government health research database, but we will not give them your name, address, phone number, or any other information that would identify you. Reports about any research will not be given to you or your doctor.
- Your specimens will be kept for indefinitely. If you decide later that you do not want your specimens and information to be used for future research, you can notify the investigator in writing and we will destroy any remaining identifiable specimens and information if they are no longer needed for your care. 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.

What are the benefits?

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

What risks are involved with donating specimens for research?

Any extra blood we take will come through already scheduled blood draws done during this study, and should not cause you any added risk, discomfort, or pain beyond what we normally expect from blood draws.

Things to Think About

The choice to let us keep the left over tissue samples and blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact the study doctors Adil Daud, M.D and Iwei Yeh, MD, PhD in writing at the address below, and let us know that you do not want us to keep your specimens.

Adil Daud, M.D. and Iwei Yeh, MD, PhD
University of California, San Francisco
[redacted]

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, it 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.

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.

Previous tumor tissue - If you provide your consent, your tumor tissue previously removed during surgery or from old biopsies will be requested. The tumor tissue will be sent to a laboratory where tests will be performed. Researchers will be performing tests that may provide additional information that may be helpful in understanding your response to the study drug.

1. I agree to donate previously collected tissue to be used for research purposes as described above.

YES	NO

Additional blood - If you provide your consent, additional blood taken during your study blood draws will be collected. The blood will be sent to a laboratory where it will be stored and tests will be performed. Researchers will be performing tests that may provide additional information that may be helpful in understanding your response to the study drug, and for future research about melanoma. The results from these tests will not have any effect on your treatment.

2. I agree to the collection of additional blood samples to be used for research purposes as described above.

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.

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

Date	Participant's Signature for Consent
	Printed Name of Participant
Date	Signature of Person Obtaining Consent
	Printed Name of Person Obtaining Consent
Date	Witness Signature (Only required if the participant is a non-English speaker)

Medications to Avoid
CC# 14859: A Phase II Trial of Targeted Kinase Fusion Inhibition in BRAF/NRAS Wild-Type Melanoma

The following is a list of medications to avoid while you are participating in this study. If you go to any medical visit, please take this list with you for the doctor's reference.

Before you begin treatment, Dr. Daud or one of his associates will review all medications you are taking. Make sure you talk with Dr. Daud before you start or stop taking any medications. This list contains only the most common drugs that are known to interact with the drugs used in this study. It is very important to discuss all medications that you are taking with your study doctor. This information will be reviewed at each study visit.

If you are taking **capmatinib,** the followi rohibited:

alfentanil	azithromycin	Cipro-floxacin	Dexlan-soprazole	Elvite-gravir	grapefruit juice	Levo-methadyl	Ome-prazole	Pimo-zidefentanyl	saquinavir	terfenadine	tizanidine
amiodarone	bepridil	cisapride	Diergo-tamine	Ergo-tamine	Halo-fantrine	lopinavir	Panto-prazole	Posa-conazole	Seville (sour) oranges	tacrolimus	tofisopam
amprenavir	boceprevir	citalopram	diltiazem	Erythro-mycin	Halo-peridol	Meso-ridazine	pimozide	Proca-inamide	Star fruit	terfenadine	Troleando-mycin
aprepitant	Carba-mazepine	Clarithro-mycin	dofetilide	Eso-meprazole	ibutilide	methadone	Penta-midine	quinidine	St. John's wort	thioridazine	vavdetanib
arsenic trioxide	casopitant	cobicistat	Dom-peridone	Erythro-mycin	indinavir	mibefradil	probucol	Rabe-prazole	schisandra sphenanthera	tipranavir	verapamil
astemizole	chloroquine	conivaptan	Dron-edarone	flecainide	Itra-conazole	Moxi-floxacin	Pome-granate mitotane	rifabutin		telaprevir	voriconazole
atazanavir	Chlorpro-mazine	Cyclo-sporine	droperidol	Fluco-nazole	Keto-conazole	Nefa-zodone	Pheno-barbital	rifampin		telithromycin	
avasimibe	cimetidine	darunavir	Diso-pyramide	Fosam-prenavir	Lanso-prazole	Nelfinavir	phenytoin	ritonavir		theophylline	

If you are taking **ceritinib**, the following drugs are prohibited:

alfentanil	clarithromycin	disopyramide	erythromycin	ibutilide	moxifloxacin	procainamide	sparfloxacin	troleandomycin
amiodarone	chloroquine	diltiazem	ethotoin	indinavir	nelfinavir	quinidine	St. John's wort	vavdetanib
arsenic trioxide	chlorpromazine		felbamate	itraconazole	pentamidine	rifabutin	tacrolimus	voriconazole
astemizole			fentanyl	ketoconazole	phenobarbital	rifampin	telithromycin	warfarin sodium or any other Coumadin-derivative anticoagulatns
avasimibe	cisapride	droperidol	flecainide	levomethadyl	pimozide	ritonavir	terfenadine	
azithromycin	citalopram	elvitegravir	fosphenytoin	lopinavir	posaconazole	saquinavir	thioridazine	
bepridil	cyclosporine	enzyme inducing anti-epileptic drugs (EIAEDs)	Halofantrine	mesoridazine	primidone	sirolimus	tipranavir	
carbamazepine	diergotamine	ergotamine	haloperidol	mibefradil	probucol	sotalol	topiramate	

If you are taking **regorafenib**, the following drugs are prohibited:

- Other anticancer therapy (chemotherapy, targeted therapy, biologic therapy, or radiation therapy, hormonal therapy, bone marrow transplant or stem cell rescue)
- Erythropoietic stimulating agents (darbepoetin alfa, epoetin alfa)
- Any herbal remedies (e.g., St. John's wort).

Please tell your doctor if you are taking other drugs like warfarin, phenytoin, quinidine, carbamazepine, phenoparbital, cyclosporine or digoxin – if so, you may need to be monitored more frequently.

If you are taking **entrectinib**, the following drugs and procedures are prohibited:

- Other anticancer therapy (chemotherapy, targeted therapy, biologic therapy, or radiation therapy except palliative radiotherapy and anit-cancer surgery)