NCT03433469

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

CC# 17658: A phase II study to evaluate neoadjuvant osimertinib therapy in patients with surgically resectable, EGFR-mutant non-small cell lung cancer

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This is a clinical trial, a type of research study. This study is taking place at UCSF, UC Davis, UC San Diego, and University of Colorado. Your research study doctor Collin Blakely, M.D. or one of his 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 research study doctor.

You are being asked to take part in this study because you have non-small cell lung cancer (NSCLC) and are planning to undergo surgery.

Why is this study being done?

The purpose of this research study is to see how safe and effective osimertinib is when given before the surgical removal of lung cancer. When treatment is given before surgery, it is called "neoadjuvant treatment". The aim of neoadjuvant treatment is to shrink the cancer prior to surgery and decrease the likelihood of the cancer returning following surgery.

Osimertinib is given via an oral tablet, which can reduce tumor growth by blocking the action of a certain mutant protein (EGFR). It has been approved by the Food and Drug Administration (FDA) for use in patients with advanced NSCLC who have specific EGFR mutations (L858R, Exon 19 deletion, or T790M), however, it has not been approved for use in early-stage lung cancers before surgery. This means that the use of osimertinib in this study is experimental.

If your tumor has not been tested for the EGFR mutation, EGFR-mutation testing will be performed for this study. This testing will be done using the single-gene EGFR mutation test or UCSF 500 test, which are not approved by the FDA, or using tests that are FDA-approved for patients with advanced-stage lung cancer. The use of EGFR-mutation tests for patients with early-stage lung cancer, and the assignment of patients to treatment with an EGFR inhibitor (osimertinib), based on the results of the test, is investigational.

If you choose to participate in this study, osimertinib will be given to you before surgery. As a result, your surgery will be delayed between one to two months, depending on how you respond to osimertinib.

AstraZeneca Pharmaceuticals LP will provide funding to UCSF to conduct this study and will provide osimertinib at no cost to you. The Damon Runyon Cancer Research Foundation, Doris Duke Charitable Foundation, and V Foundation are also providing funding to conduct the study.

How many people will take part in this study?

About 27 people with NSCLC will be participating in this study at UCSF, the University of California San Diego, the University of California Davis, and the University of Colorado. About 21 people will participate at UCSF.

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

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

You will need to have the following exams, tests, or procedures (screening procedures) to find out if you can be in the main part of the study. If the screening procedures show that you are eligible, then you can continue to the main part of the study. If during screening you are found to be not eligible, then your study participation will end at this point.

Most of these screening procedures are part of regular 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.

You must complete your screening procedures within 30 days prior to receiving the study drug unless otherwise stated. Your screening visit may take between 8 - 10 hours depending on which procedures you have.

- Physical exam, including measurements of height and weight
- Vital signs (blood pressure, heart rate, breathing rate, and body temperature)
- Medical history will be obtained, including the signs and symptoms of your cancer, details of other treatments you have received for your cancer as well as how you responded to them.
- Performance status, to assess your ability to perform daily activities
- Review any current and new medications that you are taking in addition to any herbal supplements or remedies
- Blood (about 4 Tablespoons) will be drawn by inserting a needle in a vein.
    - About 1.5 Tablespoons will be used for safety laboratory testing, including blood cell counts, blood chemistry levels, and coagulation assessment.

  - About 2.5 Tablespoons will be sent to Guardant Health (Redwood City, CA) to be used for research biomarker testing. Biomarkers are substances in your blood and tissue that may provide information on any changes to your genes or DNA, how your cancer cells are responding to study drug, and whether your cells are becoming resistant (no longer responding) to the study drug.

- Urine sample for standard urine tests, mainly to check for any protein in your urine, which can be a sign of kidney damage.
- If you are a female of child-bearing potential, you will be asked to complete a urine or blood pregnancy test within 3 days before starting the study drug.
- You will discuss contraception options with your study doctor
- Electrocardiogram (ECG)
  - An 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. This takes about 15-30 minutes.
- Echocardiogram (ECHO) or MUGA
  - An echocardiogram 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.
- CT scan of your chest, abdomen, and pelvis
  - 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.

- If you are unable to undergo a CT scan, you may have an MRI scan instead. An MRI scan takes an image of your 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.
- Please note that a PET-CT and brain imaging (MRI or CT) must be performed within 60 days prior to starting study drug.

- Tissue biopsy:
  - You will not need to have a tissue biopsy performed if your study doctor thinks that it is unsafe for you to have it performed.
  - If you need to have a tissue biopsy performed, we will obtain a small piece of fresh tumor tissue using a special needle. This tissue will be used to study biomarkers and EGFR mutation (only if your tumor has not previously been tested for EGFR mutation). Biomarkers are substances in your blood and tissue that may provide information on any changes to your genes or DNA, how your cancer cells are responding to the study drug, and whether your cells are becoming resistant (no longer responding) to the study drug. 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 and a small piece of the tumor will be removed. 1 - 4 passes with this needle will be made. A CT, MRI, or ultrasound may be used to help guide placement of the needle. This procedure takes about 30 minutes. When enough tissue is available, UCSF will give Guardant Health (Redwood City, CA) a small portion of this tissue for DNA analysis.
  - Needle Size:
    - As part of this study, we may use a larger needle size than normal for some biopsies scheduled as part of your routine medical care. We may also use this larger needle for an optional biopsy done only for this research study. This larger needle can collect more tumor tissue than the normal needle.
    - The normal size for a lung biopsy locator needle is about 0.04 inches ($4/100^{th}$ of an inch). The larger research needle size for a lung biopsy

locator needle is about 0.06 inches (6/100th of an inch). The research needle size is about 0.02 inches (2/100th of an inch) wider than the normal needle size.

During the main part of the study...

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

You will need to come to the clinic to undergo these tests and procedures and to see the study doctor.

Study drug:

You will receive osimertinib tablets on day 1 of each cycle (one cycle = 28 days) and will be advised to take one tablet orally every day for 28 days. You will take osimertinib for 1-2 cycles, and then keep taking it until 3-7 days before your surgery. You may receive a second cycle of osimertinib if you have responded well to the study drug, you haven't had any bad side effects, and/or the thoracic surgeon believes you would benefit from another cycle. The maximum amount of time you may take the study drug is 10 weeks, and you will not be receiving the study drug after the surgery. Your study doctor will discuss this with you.

Cycle 1, Day 1

This visit will take about 2 hours.

- Physical exam, including measurement of weight
- Vital signs
- Performance status
- Review of side effects you may be experiencing
- Review any current and new medications that you are taking in addition to any herbal supplements or remedies
- You will be provided with a medication diary
- Blood (about 4 Tablespoons) will be drawn by inserting a needle into a vein.
    - About 1.5 Tablespoons will be used for safety laboratory testing, including blood cell counts, blood chemistry levels, and coagulation assessment.
    - About 2.5 Tablespoons will be used for research biomarker testing.
- Urinalysis
- Blood or urine pregnancy test (if you are a female of childbearing potential)
- ECG

- You will be provided with a 28 day supply of osimertinib tablets

Cycle 1, Day 15

This visit will take about 1 to 2 hours.

- Physical exam, including measurement of weight
- Vital signs
- Performance status
- Review of side effects you may be experiencing
- Review any current and new medications that you are taking in addition to any herbal supplements or remedies
- Blood (about 1.5 Tablespoons) will be drawn by inserting a needle into a vein.
    - This will be used for safety laboratory testing, including blood cell counts, blood chemistry levels, and coagulation assessment.
- ECG

Cycle 1, Day 28

This visit is only for those who are not undergoing a second cycle of osimertinib. This visit will take about 3-8 hours, depending on what tests and procedures you have.

- Physical exam, including measurement of weight
- Vital signs
- Performance status
- Review of side effects you may be experiencing
- Review any current and new medications that you are taking in addition to any herbal supplements or remedies
- Review your medication diary
- Blood (about 4 Tablespoons) will be drawn by inserting a needle into a vein.
    - About 1.5 Tablespoons will be used for safety laboratory testing, including blood cell counts, blood chemistry levels, and coagulation assessment.
    - About 2.5 Tablespoons will be used for research biomarker testing.
- ECG
- ECHO or MUGA
- CT/MRI scan of your chest, abdomen, and pelvis
- OPTIONAL, or at the discretion of the study doctor:
    - Urinalysis

    - Blood or urine pregnancy test (if you are a female of childbearing potential)
- OPTIONAL: Tumor tissue biopsy
    - If you are unable to undergo surgery, and will not be having a second cycle of osimertinib, we will ask if you are willing to undergo a second biopsy within 30 days of Cycle 1, Day 28.
    - If you agree to a second biopsy, more information about this optional second biopsy is included at the bottom of this consent.
- You will be provided with osimertinib tablets to take until 3-7 days before your surgery (up to a 14 day supply)

Cycle 2, Day 1

The Cycle 2 visits are only for those receiving a second cycle of osimertinib. This visit will take about 2 hours.

- Physical exam, including measurement of weight
- Vital signs
- Performance status
- Review of side effects you may be experiencing
- Review any current and new medications that you are taking in addition to any herbal supplements or remedies
- Review your medication diary
- Blood (about 4 Tablespoons) will be drawn by inserting a needle into a vein.
    - About 1.5 Tablespoons will be used for safety laboratory testing, including blood cell counts, blood chemistry levels, and coagulation assessment.
    - About 2.5 Tablespoons will be used for research biomarker testing.
- Urinalysis
- Blood or urine pregnancy test (if you are a female of childbearing potential)
- ECG
- If you are having a second cycle of osimertinib, you will be provided with a 28 day supply of osimertinib tablets
- ECHO or MUGA
- CT/MRI scan of your chest, abdomen, and pelvis

Cycle 2, Day 15

This visit is only for those receiving a second cycle of osimertinib. This visit will take about 1 to 2 hours.

- Physical exam, including measurement of weight
- Vital signs
- Performance status
- Review of side effects you may be experiencing
- Review any current and new medications that you are taking in addition to any herbal supplements or remedies
- Blood (about 1.5 Tablespoons) will be drawn by inserting a needle into a vein.
    - This will be used for safety laboratory testing, including blood cell counts, blood chemistry levels, and coagulation assessment

Cycle 2, Day 28

This visit is only for those receiving a second cycle of osimertinib. This visit will take about 6 to 8 hours.

- Physical exam, including measurement of weight
- Vital signs
- Performance status
- Review of side effects you may be experiencing
- Review any current and new medications that you are taking in addition to any herbal supplements or remedies
- Review your medication diary
- Blood (about 4 Tablespoons) will be drawn by inserting a needle into a vein.
    - About 1.5 Tablespoons will be used for safety laboratory testing, including blood cell counts, blood chemistry levels, and coagulation assessment.
    - About 2.5 Tablespoons will be used for research biomarker testing.
- ECG
- ECHO or MUGA
- CT/MRI scan of your chest, abdomen, and pelvis
- OPTIONAL: Tumor tissue biopsy
    - If you are unable to undergo surgery, we will ask if you are willing to undergo a

second biopsy within 30 days of Cycle 2, Day 28.

- If you agree to a second biopsy, more information about this optional second biopsy is included at the bottom of this consent.

- You will be provided with osimertinib tablets to take until 3-7 days before your surgery (up to a 14 day supply)

When you are finished receiving study drug….

Day of Surgery

You will undergo surgical resection of your tumor within 14 days of your last scans. Following your surgery, you will stay as an inpatient for approximately 3-7 days; however, your stay may be longer depending on the type of surgery you have and whether there are any complications. On the day of the procedure, you will also have the following tests:

- Blood (about 4 Tablespoons) will be drawn by inserting a needle into a vein.
  - About 1.5 Tablespoons will be used for safety laboratory testing, including blood cell counts, blood chemistry levels, and coagulation assessment.
  - About 2.5 Tablespoons will be used for research biomarker testing.
- ECG
- Tumor tissue collection
  - During your surgery, the study team will take some of the tumor tissue that is removed to study biomarkers.

Day 15 following surgery

On day 15 following your surgery, you will have the following tests. This visit will take less than one hour.

- Blood (about 2.5 Tablespoons) will be drawn by inserting a needle into a vein.
  - This will be sent used for research biomarker testing.

End of Treatment Visit

You will be asked to come into the clinic 30 days following your Day 15 post-operative visit, for the following tests and procedures. This visit will take about 2 to 3 hours.

- Physical exam, including measurement of weight
- Vital signs
- Performance status

- Review of side effects you may be experiencing
- Review any current and new medications that you are taking in addition to any herbal supplements or remedies
- Blood (about 4 Tablespoons) will be drawn by inserting a needle into a vein.
    - About 1.5 Tablespoons will be used for safety laboratory testing, including blood cell counts, blood chemistry levels, and coagulation assessment.
    - About 2.5 Tablespoons will be used for research biomarker testing.
- Urinalysis
- Blood or urine pregnancy test (if you are a female of childbearing potential)
- ECG

Long Term Follow-Up

You will be asked to complete follow-up visits for up to 5 years after surgery to monitor for additional therapies and survival status.

- During the first year after your End of Treatment visit, you will have a follow-up visit every 3 months in clinic.
- After this first year, you will have follow-up visits every 6 months either in clinic or by telephone.

During this time, you will have tumor scans (CT/MRI of the chest/abdomen/pelvis) every 6 months as part of your routine care, unless your study doctor thinks it is in your best interest to have tumor scans more often.

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

How long will I be in the study?

You may receive study drug on this study for up to 10 weeks. The period of time you receive study drug will depend on how you tolerate and respond to the study drug. You will also be asked to complete follow-up visits for up to 5 years after your surgery to monitor for additional therapies and survival status.

You may continue to participate in the study until one of the following occurs:

- You complete the study drug, have your surgery, and complete follow-up (for a period of up to 1 year)
- The study doctor decides your cancer condition is worse or thinks it is in your best interest to stop being in the study

- You decide to no longer participate
- You experience side effects from the study drug that you find unacceptable or have unexpected events that affect your health and safety
- You need an alternative health treatment not allowed in this study
- You become pregnant or inform your study doctor that you intend to become pregnant
- The study has ended

If you do not take the study drug as directed or follow the study procedures as directed by your study doctor, he/she may discontinue your participation in the study.

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. The study doctor 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 osimertinib or the surgery 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.

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. Although many side effects may go away soon after you stop taking an experimental drug, in some cases, side effects can be serious, long-lasting, or may never go away. There is also a risk of death.

You must talk immediately with your study doctor about any side effects you experience while taking part in the study.

Possible side effects associated with Osimertinib

The side effects listed below have been reported by patients who have received osimertinib in clinical trials.

The majority of side effects with osimertinib are mild. Some do not require treatment and others frequently respond or resolve with appropriate treatment. Some patients may require interruption of osimertinib to treat these side effects.

Very Common (events occurring in at least 10% of subjects)

- Diarrhea: This may come and go and can usually be treated with an anti-diarrhea drug like loperamide.
- Rash: This type of skin effect can usually be treated with creams and lotions, or antibiotic therapy.
- Itching: This is usually mild and may be associated with a rash.
- Dry Skin
- An infection of the tissue folds around the nails (paronychia). These types of effects can usually be treated with creams and lotions and may require antibiotic therapy.
- Back pain
- Cough
- Difficulty passing stool (constipation)
- Decreased appetite
- Decrease in the number of red blood cells (anemia)
- Fatigue
- Headache
- Joint pain
- Nausea
- Shortness of breath (dyspnea)
- Sores in the mouth and esophagus, which may be painful and cause difficulty swallowing (stomatitis)
- Upper respiratory tract infection: A common viral infection that affects the nose, throat, and airways. Symptoms usually resolve within two weeks and include a scratchy or sore throat, sneezing, stuffy nose, and cough. Treatment includes rest and medications to relieve symptoms.
- Vomiting

Common (events occurring in at least 1% but less than 10% of subjects)

- Acne: This type of skin effects can usually be treated with creams and lotions or antibiotic therapy.
- Changes in electrical activity in the heart (ECGs) have been seen in some patients treated with osimertinib. These changes may be drug related. Similar changes in the ECGs of patients receiving other medications have led to heart rhythm changes, some of which have been life-threatening. These changes in the ECG usually occur without symptoms.

In some patients, may cause rapid or irregular heart beating, dizziness, light-headedness, chest discomfort, shortness of breath, and losing consciousness. These or other new symptoms should be reported immediately to your doctor.

- Condition in which the number of white blood cells called neutrophils (neutropenia) are abnormally low. This increases the risk of infection, which may be serious or life threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.
- Changes to eyelashes (such as an increase in curly or coarse eyelashes or increase in hair on the face). These types of effects can usually be treated with creams and lotions and may require antibiotic therapy.
- Changes in the way your heart works. Osimertinib may cause changes in the muscle of the heart. Tell your doctor right away if you have symptoms of a heart problem which may include: new or worsening shortness of breath while at rest or with activity; cough; tiredness; swelling of your ankles, feet, or legs; sudden weight gain. You will be monitored throughout the study and your study doctor may tell you to stop taking osimertinib or may give you specific treatment.
- Skin reactions may occur at any time, but most likely start within 2 weeks of starting study drug. You may consider applying over-the-counter moisturizing cream to face, hands, and feet twice daily from the start of the study to help prevent dry skin.
- Common cold (nasopharyngitis): swelling of the nasal passages and the back of the throat
- Feeling weak and having no energy (asthenia)
- Increased levels of alanine aminotransferase, an enzyme that increases when the liver is damaged.
- Increased levels of aspartate aminotransferase, an enzyme that is found mostly in the liver, but also in muscles. When your liver is damaged, it releases aspartate aminotransferase into your bloodstream.
- Raised body temperature; fever (pyrexia)
- A vague feeling of bodily discomfort, feeling bad (malaise)
- A blockage in 1 or more of the blood vessels that supply blood to the lungs. Most often these blockages are caused by blood clots that form elsewhere and then travel to the lungs. In rare cases, blockages can also be caused by air bubbles, tiny globs of fat, or pieces of tumor that travel to the lungs. (pulmonary embolism)
- A condition in which there is a lower-than-normal number of lymphocytes (a type of white blood cell) in the blood. (Lymphopenia). A disorder that abnormally low levels of lymphocytes in the blood characterize. (Lymphocyte count decreased)
- Raised, itchy areas of skin that are usually a sign of an allergic reaction, known as hives. (Urticaria)

Rare but Serious (anticipated in less than 1% of subjects)

- Low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion. (thrombocytopenia)
- Inflammation of the lungs, in which the alveoli (tiny air sacs) are filled with fluid. This may cause a decreased in the amount of oxygen that blood can absorb from air breathed into the lung. This can cause shortness of breath and difficulty breathing. If severe, this can be life threatening. (pneumonitis, interstitial lung disease)
- Aplastic Anemia - Rare reports of aplastic anaemia have been reported in association with osimertinib treatment. Some cases had a fatal outcome. Before initiating treatment, patients should be advised of signs and symptoms of aplastic anaemia including but not limited to persistent fever, bruising, bleeding, and/or pallor. If signs and symptoms suggestive of aplastic anaemia develop, close patient monitoring and drug interruption or discontinuation of osimertinib should be considered. Osimertinib should be discontinued in patients with confirmed aplastic anaemia.

Additional risks:

- **Delay in surgery risks:** If you choose to participate in this study, your surgery will be delayed between one to two months, depending on how you respond to osimertinib. In addition, taking osimertinib prior to surgery may cause side effects that could further delay your surgery, or mean that you cannot have your surgery.
- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.
- **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.
- **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:** 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. 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. See Radiation Risks.
- **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. The additional amount of radiation that you will receive as a result of participating in this

study will be a maximum of approximately 14 mSv, which is equivalent to slightly less than 5 times the yearly natural background of radiation in the US, which is 3 mSv (a mSv, or milliSievert, is a measurement of radiation). This amount of radiation may involve a low, lifetime risk of cancer. If you are pregnant or breastfeeding, you SHOULD NOT participate 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 (see above). 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 research 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.

  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. 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.

- **PET/CT scan risks:** The PET/CT involves exposure to radiation. The radiation exposure comes from a tracer which is a radioactive chemical injected into a vein in your arm. The tracer lets the doctor see how your cells are functioning. As with all injections, it may feel like a small sting and there may be possible bruising at the injection site. For some patients, having to lie still on the scanning table for the length of the procedure may cause some discomfort or pain. The radioactive solution does not remain in your system for a long period of time. See Radiation Risk.

- **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 pocketknives 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 earplugs. 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 research 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 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 for you to undergo the MRI scans.

Gadolinium can build up in the brain, however, it is unknown how this will impact your health. Some types of gadolinium are more strongly linked to buildup in the brain. UCSF prefers to use gadobutrol, which is less likely to build up in the brain, compared to other types of gadolinium. However, for some types of liver imaging, a less stable agent called gadoxetate is sometimes required.

Gadolinium as an MRI imaging agent will only be used when medically necessary for your care. When it is medically necessary, the study doctors believe that the clear benefits of using gadolinium for imaging outweigh the unknown risks, which are minimized by using gadobutrol.

- **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. The biopsy can lead to bleeding in the local 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. Risks specific to lung biopsies are described below. Other potential risks will be described to you and discussed with you by doctors who conduct these biopsies.

  Needle Size: For all biopsies, the doctor performing the procedure will choose a needle size and biopsy location that decrease potential risks, while optimizing the chance to obtain adequate tissue for research.

  Biopsies using a larger size needle will make a bigger hole at the biopsy site. This bigger hole may increase your chance of experiencing the risks listed under "Tumor biopsy risks" and "complications of lung biopsies."

- **Complications of lung biopsies:**
  - **Pneumothorax/chest tube:** 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 hospitalization to insert a chest tube (flexible tube or needle between the ribs to remove the excess air). The chest tube is attached to a vacuum system which sucks your lung back to normal volume. The chest tube is removed usually in several days after the lung has healed. A chest tube can be associated with pain, bleeding, and infection.

Pneumothorax has been reported to occur in 1 - 30 out of 100 (15% to 30%) of lung biopsies. Treatment with a chest tube has been reported in 8 - 15 out of 100 (8% to 15%) of pneumothorax caused by lung biopsy.

Using a larger needle size instead of a regular needle size increases the chance of pneumothorax by up to 10%.

- **Bleeding in the lung:** Lung biopsies may cause bleeding in the lung. You may not feel anything if the bleeding occurs, or you may feel pain or have difficulty breathing. If you experience bleeding you will be monitored, and a flexible tube to remove the blood may be inserted in your chest. Significant bleeding has been reported to occur in less than 1 in 100 (1%) of lung biopsies.

  Using a larger needle size instead of a regular needle size has not been shown to increase the chance of bleeding in the lung.

- **Death from blood vessel air bubble:** Lung biopsies also include a very small risk of an air bubble forming in your blood vessels. This air bubble can lead to an irregular heartbeat, low oxygen supply, collapsed blood vessels, stroke, or death. Death has been reported to occur in less than 1 in 1000 (0.1%) of procedures.

  It is unknown if using a larger needle size instead of a regular needle size increases the chance of death.

- **Genetic testing confidentiality risks:** There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small but cannot promise that they will not occur.
- **Reproductive risks:** You should not become pregnant or father a baby while on this study because the drug in this study can affect an unborn baby. Women should not breastfeed a baby while in 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.
- **Safe Handling of Medications:** Handling osimertinib and having contact with any urine, feces, or vomit from patients receiving osimertinib may pose some risk to you and your caregivers. To avoid exposure to osimertinib 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 osimertinib, properly dispose of osimertinib, and how to clean products that may be contaminated with osimertinib.

- **Risk of inadequate specimens for diagnostic purposes:** Providing parts of your surgically-removed tissue for research could, in rare cases, result in too little tissue being available for your doctors to make a clinical diagnosis (or complete other clinically important tests). To minimize this risk, a Pathologist (or a pathology designee) carefully evaluates every tissue specimen at the time of surgery to decide if it can safely be provided for research. With this process in place, we believe the risk of negatively impacting your clinical care through providing tissue for research is extremely small (below 1%).
- **Unknown Risks:** The experimental study drug may have side effects that no one knows about. You will be told about any important new findings that may affect your decision to remain in the research study.

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

Are there benefits to taking part in the study?

It is unknown if there will be any benefit from being in the study. You may experience some improvement in your disease during the study, but this cannot be guaranteed. However, taking part may help patients with NSCLC get better care in the future.

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 research study.
- Taking part in another research 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 research study.

Will my medical information be kept private?

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 and may 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 receive, look at, and/or copy your medical records for research, quality assurance, and data analysis include:

- AstraZeneca Pharmaceuticals, LP
- Guardant Health
- 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 including health authorities in other countries.

What are the costs of taking part in this study?

AstraZeneca Pharmaceuticals LP will supply the study drug Osimertinib 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.

Before you agree to be in this study, you may want to contact your healthcare payer/insurer to see if your plan will cover the costs required as part of your participation. You may request more information about the costs of participating in this study and discuss this with the study team.

If you have any questions, your doctor and the study team will be able to provide you with answers.

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 research study.

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

It is important that you follow carefully all the instructions and the scheduled visits given by the study doctor and his staff regarding this study.

It is important that you tell your research study doctor, Collin Blakely, M.D., if you feel that you have been injured because of taking part in this research study. You can tell the doctor in person or call him at [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 or the study sponsor, 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 UCSF Institutional Review Board at 415-476-1814.

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

Taking part in this research study is your choice. You may choose either to take part or not to take part in the research study. If you decide to take part in this research study, you may leave the research 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 research study will not affect your medical care. You can still get your medical care from our institution.

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

In the case of injury resulting from this research 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 research study doctor about any questions, concerns, or complaints you have about this research study. Contact your research study doctor Collin Blakely, M.D. at [redacted]

If you wish to ask questions about the research 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 research study, please call the UCSF Institutional Review Board 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.

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OPTIONAL RESEARCH

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

Use of Tissue for Research

During this study, you are going to have blood draws, and a tumor biopsy, and surgery. Your doctor will remove some blood and tumor tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care and to study biomarkers (i.e. genetic testing). Biomarkers are substances in your blood and tissue that may provide information on any changes to your genes or DNA, how your cancer cells are responding to study drug, and whether your cells are becoming resistant (no longer responding) to the study drug.

We would like to keep some of the blood and tumor tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about other diseases. Please read the information sheet called "How Is Tissue Used for Research" to learn more about tissue research.

Your tissue may be helpful for research. The research that may be done with your tissue is not designed specifically to help you. It might help people who have 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.

How will my genetic information be shared?

Genetic information (also known as genotype data) and the medical record data (also known as phenotype data) may be shared broadly in a coded form for future genetic research or analysis. We may give certain medical information about you (for example, diagnosis, blood pressure, age if less than 85) to other scientists or companies, not at UCSF, but we will not give them your name, address, phone number, or any other identifiable information. Research results from these studies will not be returned to you unless in very rare circumstances the study team believes you would benefit from being informed.

Optional Tumor Biopsy

If you agree to be in the main part of this study, you will have a tumor biopsy and surgery. If you are unable to undergo surgery, the study doctor would like to instead perform an additional

tumor biopsy within 30 days after your last dose of the study drug. This biopsy is optional. The optional biopsy will be similar to the biopsy you had at the beginning of this study before you began taking the study drug. If you choose not to have this optional tumor biopsy, you can still participate in the main part of the study.

Things to Think About

The choice to let us keep the leftover tissue for future research, and/or undergo the optional tumor tissue biopsy, is up to you. No matter what you decide to do, it will not affect your care. There will be no direct benefit to you from allowing your tissue and data to be kept and used for future research. However, we hope we will learn something that will contribute to the advancement of science and understanding of health and disease. If the tissue, data, or any new products, tests, or discoveries that result from this research have potential commercial value, you will not share in any financial benefits. If you decide later that you do not want your tissue to be kept, or your information to be used for future research, you can notify the investigator in writing at

Dr. Collin Blakely
University of California, San Francisco
[redacted]

and any remaining identifiable tissue and data will be destroyed. However, we cannot retract any data that has been shared with other researchers. Also, if you decide now that you are willing to have the optional tumor biopsy (in the event you are unable to undergo surgery), you can also change your mind at any time.

People who do research may need to know more about your health. While your 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.

Information obtained from any research will remain strictly confidential and information that identifies you will not be made publicly available.

Benefits

There is no direct benefit to you.

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

Risks

Optional tumor biopsy: The risks of tumor biopsies and complications of lung biopsies are described earlier in this consent form in the section “Additional Risks.” The doctor performing

the procedure will choose a needle size and biopsy location that decreases potential risks while optimizing the chance to obtain adequate tissue for research.

Confidentiality: There is a risk that information from your health records could be released. 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.

Donating data may involve a loss of privacy, but information about you will be handled as confidentially as possible. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security. Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. Taking part in a genetic study may also have a negative impact or unintended consequences on family or other relationships. It is possible that future research could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.

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 Institutional Review board at 415-476-1814.

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

1. In the event that I cannot undergo surgery, I agree to undergo an optional tumor tissue biopsy and allow biomarker testing on my tumor sample.

YES	NO

2. My specimens (blood and tumor) and associated data may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

YES	NO

3. Someone may contact me in the future to ask me to take part in more research.

YES	NO

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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.

_____

Participant's Name (print)

_____ _____

Participant's Signature for Consent Date

_____

Name (print) of Person Obtaining Consent

_____ _____

Signature of Person Obtaining Consent Date

_____

Name (print) of Witness (only required if the participant is a non-English speaker)

_____ _____

Signature of Witness (only required if the participant is a non-English speaker) Date