NCT03217071

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

CC# 166520: PembroX: Enhancing the Immunogenicity of Non-Small Cell Lung Cancer with Pembrolizumab +/- Stereotactic Radiotherapy Delivered in the Preoperative Window, A Randomized Phase II Study with Correlative Biomarkers

This is a clinical trial, a type of research study. Your study doctors, Drs. Sue Yom, David Jablons, Matthew Gubens, Collin Blakely, or other participating doctors from the University of California, San Francisco (UCSF) Thoracic Oncology Program, 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 stage I-III non-small cell lung cancer (NSCLC) and are eligible for surgery.

If you choose to participate in this study, all study procedures will take place at the UCSF Helen Diller Family Comprehensive Cancer Center Mt Zion campus, although surgery will be done at the UCSF Parnassus campus.

Why is this study being done?

The purpose of this study is to find out if giving pembrolizumab, with or without a low dose of radiation therapy, improves the immune response in patients with NSCLC who are having surgery. The immune response is when the immune system attacks causes of disease.

Pembrolizumab is an immunotherapy drug that works by helping your immune system attack cancer cells. Pembrolizumab is approved by the United States Food and Drug Administration (FDA) for use in certain patients with skin cancer and non-small cell lung cancer. Pembrolizumab is being used in this study as an investigational drug, meaning it is not approved for use in patients with NSCLC who are eligible for surgery.

In this study, low-dose radiation therapy is combined with pembrolizumab to find out if radiation can boost the immune response of pembrolizumab. Radiation therapy is not used in this study to directly treat the tumor.

Who pays for this study?

Merck, the manufacturer of pembrolizumab, is supplying the study drug at no cost to study participants and covering the costs of radiation therapy, for patients who receive

radiation therapy, and is providing funding to the UCSF Helen Diller Family Comprehensive Cancer Center for this study.

How many people will take part in this study?

Forty people will take part in this study at UCSF.

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

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

If you choose to participate in this study, you will need to have the following tests and procedures done to make sure it is okay for you to be in the study. Some of these tests and 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 will also have some tests and procedures done for research purposes because you are participating in the study.

<u>To be done within 4 weeks of starting pembrolizumab (unless otherwise indicated):</u>

- You will be asked about your medical history including any past treatments or surgeries for your disease.
- You will have a physical exam and will be asked how you are feeling.
- Your vital signs, including height, weight, temperature, breathing rate, blood pressure, pulse, and oxygen in your blood levels will be recorded.
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- You will be asked how easy or hard it is for you to carry out your daily activities.
- A total of 3 tablespoons of blood will be taken by inserting a needle into a vein in your arm. The blood sample will be used for routine safety tests.
- If you are a woman of childbearing potential, you will have a urine or blood pregnancy test within 3 days of starting pembrolizumab.
- You will provide a urine sample for routine safety tests.
- You will have a **PET-CT** (Positron Emission Tomography - computed tomography) scan of your whole body within 75 days of starting pembrolizumab.

  If you have stage 2 or 3 NSCLC you will also have a **CT (**computed tomography) or **MRI (**magnetic resonance imaging) of your brain.

  - A **PET-CT** scan shows how the organs and cells work in your body and is done to show activity of the cells in your tumor. You will be asked to not eat for six hours before the scan and to drink at least two large glasses of water within one hour of the study. Your PET scan will begin with an

injection of a radioactive substance into a vein in your arm. You will be asked to rest quietly for a period of time (usually about 20 to 40 minutes) as the radioactive substance circulates throughout your body. After this time, you will be positioned within a large ring (similar to a big donut hole) on a scanning bed. Once positioned properly, the bed will move you into the scanner. As pictures are being taken, you will be asked to remain very still so clear images will be taken. The imaging time takes about one hour.

- A **CT** scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For this exam, you will need to lie still on a table inside a large doughnut-shaped machine. The table will move, and the machine will make clicking and whirring noises as the pictures are taken. If necessary, an iodine dye (contrast material) will first be given. The iodine dye makes tissue and organs more visible in the pictures. The iodine dye may be given orally (by mouth), intravenously (into a vein), or rectally (fill up the loops of your bowels). The CT scan is done in the radiology department and takes about 30 minutes.
- An **MRI** uses special equipment to make detailed pictures of body tissues and organs. For this exam, you will lie down on a narrow bed which will then be placed in a tunnel that is 6 feet long by 2 feet wide and open at each end. You will need to lie there quietly for about one hour, during which there will be a loud banging noise. You may feel warm during this procedure. If necessary, gadolinium (contrast material) will first be injected into a vein. The gadolinium makes tissue and organs more visible in the MRI. The MRI scan is done in the radiology department and takes about 90 minutes.

- You will be asked to undergo a tumor biopsy procedure, so that markers in your tumor tissue before and after receiving pembrolizumab, or pembrolizumab and radiation, can be compared. A biopsy involves removing a piece of the tumor tissue, usually with a needle. A CT scan or ultrasound may be used to help guide the needle. This procedure will be done at the site where we can most easily get a piece of the tumor. The biopsy needle will be inserted into tumor tissue and a small piece of the tumor will be removed. This will be done 1-3 times. This procedure takes about 30 minutes. If the study doctor determines that you should not have a biopsy done, because it is not safe or your tumor is not accessible, you may not need to have a biopsy done if you already had a previous biopsy done and we can obtain your prior biopsy sample.

During the main part of the study...

If the tests and procedures show that you can be in the main part of the study, and you choose to take part, you will receive pembrolizumab alone, or pembrolizumab in combination with a small amount of radiation therapy, before having surgery.

<u>There are two parts to this study, Part 1 and Part 2. If you choose to participate in this study, you will either be in the first part or second part, but not both.</u>

During Part 1:

- Pembrolizumab will be given to 6 study participants before surgery.
- *If pembrolizumab does not cause bad side effects in these participants,* the next 6 study participants will be given pembrolizumab, in combination with radiation therapy, before surgery.

During Part 2:

- *If the combination of pembrolizumab and radiation therapy does not cause bad side effects in participants during Part 1*, then study participants in Part 2 will be randomized (randomly assigned) to either receive pembrolizumab alone, or in combination with radiation therapy. Randomization means that you are put into a group by chance, like the flip of a coin.
- *If the combination of pembrolizumab and radiation therapy in participants during part 1 does cause bad side effects*, then all additional study participants will receive pembrolizumab alone.

Pembrolizumab

Pembrolizumab will be given in 'cycles.' Each cycle is 3 weeks (21 days). You will receive pembrolizumab once every 3 weeks for 2 cycles. Pembrolizumab will be given by intravenous (IV) infusion, meaning it will be given directly into your vein using a pump. This will take about 30 minutes.

Radiation Therapy *(Only if you are receiving radiation therapy in addition to pembrolizumab)*

If you are receiving radiation therapy in addition to pembrolizumab, you will be given a single low dose of stereotactic radiation therapy within 1 week of your second dose of pembrolizumab. The radiation will be given to part of the tumor. The radiation is not intended to treat the tumor. Its purpose is to increase the response of your immune system against the tumor.

Your radiation doctor (radiation oncologist) will schedule a special CT scan (CT simulation scan) to design radiation treatment that is appropriate for you. During this scan, you will lie flat on a table and will not be able to move. This procedure simulates the position that you will be in during radiation treatments. The simulation scan will take approximately 1 hour.

During radiation therapy, you will lie flat on a table and will not be able to move. You will receive a low dose of radiation aimed at a part of the tumor. The radiation treatment will take about 15 minutes.

The following tests and procedures will also be done during the main part of the study:

Day 1 Cycle 1 Pembrolizumab

- You will have a physical exam and will be asked how you are feeling.
- Your vital signs, including height, weight, temperature, breathing rate, blood pressure, pulse, and oxygen in your blood levels will be recorded.
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- You will be asked how easy or hard it is for you to carry out your daily activities.
- About 3 tablespoons of blood will be taken by inserting a needle into a vein in your arm. The blood sample will be used for routine safety tests and to look for markers that might signal a response to the study drug.

Day 1 Cycle 2 Pembrolizumab

- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- You will be asked about any side effects that you may be experiencing. A side effect is an unwanted response to a medicine.
- About 3 tablespoons of blood will be taken by inserting a needle into a vein in your arm. The blood samples will be used for routine safety tests and to look for markers that might signal a response to the study drug.

End of treatment/safety visit

- You will have a physical exam and will be asked how you are feeling.
- Your vital signs, including height, weight, temperature, breathing rate, blood pressure, pulse, and oxygen in your blood levels will be recorded.
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- You will be asked how easy or hard it is for you to carry out your daily activities.
- You will be asked about any side effects that you may be experiencing.
- A total of 3 tablespoons of blood will be taken by inserting a needle into a vein in your arm. The blood sample will be used for routine safety tests and to look for markers that might signal a response to the study drug.

Before your surgery (6 weeks within your last dose of pembrolizumab), the following will be performed:

- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- You will be asked about any side effects that you may be experiencing.
- A total of 3 tablespoons of blood will be taken by inserting a needle into a vein in your arm. The blood sample will be used for routine safety tests and to look for markers that might signal a response to the study drug.

Surgery – A biopsy will be taken at the time of your surgery. This sample will be tested for markers that that might signal or predict a response to the study drug.

Follow-up Visits: 30 days, 90 days, 180 days, 360 days after surgery:

- You will have a physical exam and will be asked how you are feeling.
- Your vital signs, including height, weight, temperature, breathing rate, blood pressure, pulse, and oxygen in your blood levels will be recorded.
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments.
- You will be asked about any side effects that you may be experiencing.
- You will be asked how easy or hard it is for you to carry out your daily activities.
- You will be asked about your health status and any anti-cancer therapy you are receiving.
- A total of 3 tablespoons of blood will be taken by inserting a needle into a vein in your arm. The blood sample will be used for routine safety tests and to look for markers that might signal a response to the study drug.
- You will provide a urine sample for routine safety tests.
- You will have a CT of your chest 1 year after your surgery.

How long will I be in the study?

You will receive pembrolizumab, the study drug, for 2 cycles (6 weeks) as long as your disease is not getting worse and you do not have any bad side effects. If the study drug is stopped or you withdraw from the study, you will be followed until any side effects from the study drugs have resolved. You will be asked to come into the office for follow-up visits one month, 3 months, 6 months, and 1 year after your surgery.

We would like to keep track of your medical condition for the rest of your life. We would like to do this by calling you on the telephone once a year to see how you are doing. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of 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. 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 pembrolizumab and radiation 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 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 pembrolizumab. 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.

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissue in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Risks Related to Pembrolizumab

Very common (seen in 20% or more of patients who receive pembrolizumab)

- Itching of the skin
- Loose or watery stool
- Cough

Common (seen in at least 5% but less than 20% of patients who receive pembrolizumab)

- Joint pain

- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, have muscle cramps and/or feel sick to your stomach (hyponatremia)

Less common (seen in at least 1% but less than 5% of patients who receive pembrolizumab):

- Inflammation of the lungs so you may feel short of breath and cough (pneumonitis).
- Too much thyroid hormone so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus (colitis)
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body, which can cause severe infection (Severe skin reactions, including Stevens-Johnson syndrome/or toxic epidermal necrolysis).

Rare (seen in less than 1% of patients who receive pembrolizumab):

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome)
- Inflammation of the muscles so you may feel weak or have pain in your muscles (myositis)

- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels), so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting (myocarditis).
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy (thyroiditis).
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body, such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis).

- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis) - symptoms include fever, fatigue, weight loss, and muscle and joint pain

In addition to what is specifically listed above, drugs that help stimulate the body's immune response against tumor cells (immunotherapy drugs), such as pembrolizumab, can cause severe inflammation to every organ.

Furthermore, it is possible that taking pembrolizumab may result in delay of your surgery or inability to have your surgery promptly. The study investigators do not believe that this is likely, but it is possible. The study investigators will be checking for this throughout the study and the study will be stopped if the drug is having this effect on patients.

Additionally, since pembrolizumab was approved (for melanoma) in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- **Inflammation of the joints which may include joint pain, stiffness, and/or swelling (arthritis)**
- **Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis).**
- **Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome).**
- **Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).**

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant that you have had.

Risks Related to Radiation Therapy

Radiation therapy aimed at the chest may cause these side effects:

- Difficulty swallowing
- Shortness of breath
- Breast or nipple soreness
- Shoulder stiffness
- Cough, fever, and fullness of the chest. This is known as radiation pneumonitis and happens between 2 weeks and 6 months after radiation therapy
- Radiation fibrosis, which is permanent scarring of the lungs from untreated radiation pneumonitis. The radiation oncologist knows how to lower the risk of fibrosis in the planning process.

Risks Related to Study Procedures:

- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, infection, and fainting.
- **Infusion risks:** As with most intravenous products, you may experience pain, irritation, swelling or bruising, or a slight chance of infection at the site where the intravenous catheter (small tube) is inserted into your vein. These side effects may also be observed at the site where blood is drawn for laboratory tests.
- **Radiation risks:** This research study involves exposure to a significant amount of radiation. The radiation therapy will be delivered at a prescription dosage of 12 Gy targeted at only part of the tumor. While this amount of radiation is not intended to treat your condition, it does involve a risk of a secondary cancer. However, the UCSF Radiation Safety Committee has reviewed the use of radiation in this research study and has designated this use as acceptable to obtain the benefits provided by the results of the study. If you are pregnant or breast feeding, 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. 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. You will be asked about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan with contrast.

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

metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.

- **PET-CT scan risks:** PET-CT scans involve the risks of radiation (see above). In addition, if a contrast material is injected, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a PET-CT scan.

  Having a PET-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 in your veins. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.

- **MRI risks:** Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like 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 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 on 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.

- **Tumor Biopsy risks**: While we make every effort to minimize the pain related to the procedure, the procedure is usually uncomfortable and sometimes painful. Patients may develop bruising, soreness or scarring at the biopsy site. Wherever the biopsy is done in your body, it can lead to bleeding in that area, damage of organs near where the biopsy is done, or infection. While it is uncommon, sometimes bleeding or pain from the biopsy will require you to stay overnight in the hospital or require you to go to the operating room to control any bleeding. 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.

  For biopsy procedures, patients usually receive local anesthesia (for example lidocaine), meaning the biopsy site is numbed. Side effects from local anesthesia are rare but may include convulsions or seizures, breathing problems, chest pain, rapid heart rate, irregular heartbeat, dizziness, bluish lips and fingernails, drowsiness, headache, itching, nausea and/or vomiting, raised red swellings on the skin, lips, tongue, or in the throat, restlessness, unusual tiredness or weakness, back pain, difficulty opening the mouth, inability to hold bowel movement and/or urine, loss of sexual function, temporary paralysis (loss of function) of legs, persistent or prolonged numbness or tingling (“pins and needles” sensations) of lips and mouth, and shivering.

  Imaging equipment may be used to guide the needle to the desired site. This may involve ultrasound or x-ray, see Radiation risks above. In addition, a patient may be injected with a contrast dye (for example iodine). Side effects of iodine can include hives, itching, light headedness, nausea and a metallic taste in the mouth. Rarely, iodine can cause a severe allergic reaction, including shock, very low blood pressure and cardiac arrest.
- **Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. 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.
- **Study Drug and Radiation Interaction Risks**: Pembrolizumab, alongside radiation therapy, taken in combination with other medicines may be associated with other risks that are unknown at this time. Although there is limited information on how pembrolizumab, alongside radiation therapy, might interact with other medications, it is important to share with your study doctor any medications (prescription, over-the-counter, and herbal supplements) that you are taking.
- **Randomization risks:** You may be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.
- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

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

Are there benefits to taking part in the study?

If you receive pembrolizumab with or without radiation and it proves to treat your condition more effectively, you may benefit from participating in the study, but 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.
- Taking part in another study.
- Getting no treatment.

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

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records 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 look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The University of California
- Merck & Co., Inc., the supplier of pembrolizumab, including companies it hires to provide study-related services.
- The National Cancer Institute (NCI) and other government agencies, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.

What are the costs of taking part in this study?

Merck is supplying the study drug pembrolizumab at no cost to you. Merck is also covering the costs of radiation therapy for patients assigned to receive radiation therapy during this study.

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. Any procedures done only for research will not be charged to you or your insurer. There is a possibility that your insurer may not cover standard medical care costs because you are in a research study or because you are receiving medical services out of network.

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 study.

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

It is important that you tell your study doctor, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call Dr. Yom 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 Merck, 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 Institutional Review Board at 415- 476-1814.

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

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

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

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

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor Sue Yom, MD [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 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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ADDITIONAL OPTIONAL RESEARCH SECTION:

Please note: This section of the informed consent form is about additional, optional research studies that are being done with people who are taking part in the main study. You may take part in these optional 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 optional studies.

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

Blood and Tissue Samples for Future Research

Blood and tissue samples are collected and used in the main study. We would like to keep some of the blood and tissue that is left over for future research. If you agree, the blood and tissue samples will be kept at UCSF and may be used in future research to learn more about cancer and other diseases.

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

Reports about future research done with your samples will not be given to you or your doctor. These reports will not be put in your health record and will not have an effect on your care.

Things to Think About

The choice to let us keep the leftover blood and tissue 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 samples can be kept for research, you can change your mind at any time. Just contact your study doctor:

Sue Yom, MD
UCSF Helen Diller Family Comprehensive Cancer Center
[redacted]

and let us know that you do not want us to use your blood and tissue samples. Then any samples that remain will no longer be used for research, but any data already collected will continue to be used.

In the future, people who do research may need to know more about your health. While UCSF 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.

Sometimes blood and tissue samples are used for genetic research (about diseases that are passed on in families). Even if your samples are used for this kind of research, the results will not be put in your health records.

Your blood and tissue samples will be used only for research and will not be sold. The future research done with your samples may help to develop new products in the future.

You will not be paid for donating your blood and tissue samples for future research.

Benefits

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

Risks

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

Risks specifically related to Genetic Testing

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.

Making Your Choice

Please read the 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 the Institutional Review Board at 415-476-1814.

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

1. I allow my samples (blood and tissue) from the main study to be stored and used for future medical research.

YES	*NO*

CONSENT

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

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

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

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

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