NCT03248570

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

CC#16557: Phase 2 open label study of pembrolizumab in patients with metastatic castration resistant prostate cancer (mCRPC) with or without DNA damage repair defects

This is a clinical trial, a type of research study. Your research study doctor Lawrence Fong, 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 research study because you have prostate cancer that has progressed (worsened).

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to assess how prostate cancer patients with and without DNA damage repair defects respond to pembrolizumab. Tumors with DNA damage repair defects have more mistakes in their genes (mutations), whereas tumors with normal DNA damage repair have fewer mistakes. Tumors that have more mistakes in their genes may be more visible to the immune system. The aim of this study is to see whether tumors with DNA damage repair defects respond better to the immunotherapy, pembrolizumab.

Pembrolizumab has been approved for use in certain types of melanoma, lung cancer and head and neck cancer. However, it has not been approved for any other cancers. The use of pembrolizumab for prostate cancer is experimental, which means that it has not been approved by the United States Food and Drug Administration (FDA).

This research study is being sponsored by Merck, the company that makes pembrolizumab, is supplying pembrolizumab at no cost and is providing funding to UCSF for this study. The National Cancer Institute (which is part of the National Institute of Health) is also providing funding to UCSF to conduct this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 50 people will take part in this research study.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

DNA Damage Repair Testing

All patients enrolled in this study will receive pembrolizumab and participate in the same study assessments. However, participants will be placed into one of two groups, depending on DNA damage repair status. The study doctor will tell you if you will be in Group 1 or Group 2.

- Group 1: Normal DNA damage repair group
- Group 2: Defective DNA damage repair group

DNA damage repair status will be determined using two kinds of tests that look at different types of DNA damage repair in tumor tissue: the Promega Microsatellite Instability (MSI) test and a mutation sequencing test. If both of these tests show normal DNA damage repair, you will be in Group 1. If one or both of these tests show DNA damage repair defects, you will be in Group 2.

- Both kinds of tests look at errors that happen during DNA-replication. If the test results show that the DNA only has a few of these types of errors, this indicates normal DNA damage repair. If the test results show a lot of these errors, it can mean that repair of DNA-replication errors is defective. The Promega MSI test is not approved by the FDA for testing your type of prostate cancer, and the use of the test in this study is investigational.
- The mutation sequencing test (UCSF500, Foundation, or Strata) looks at your DNA to see what changes in your genes might cause defective DNA damage repair. UCSF500, Foundation, and Strata are not approved by the FDA for testing your type of prostate cancer, and the use of these tests in this study is investigational.

There are expected to be more patients who are eligible for Group 1 rather than Group 2. Because of this, when the study first opens, participants may receive treatment before test results from DNA repair status are known. Whether you are in Group 1 or in Group 2, you will receive the same treatment. Once Group 1 is full (and all participants DNA repair status results are available), the DNA repair status results must be known before participants can enroll to the remaining slots in Group 2. The study doctor will let you know your DNA damage repair status and what group you are in when the test results are available.

Study Drug

Pembrolizumab will be given during a time period called a cycle. Each cycle lasts 21 days. Pembrolizumab will be given to you by inserting a needle into the blood vessel in your arm (intravenous [IV] infusion). The infusion of pembrolizumab will be delivered over approximately 30 minutes. Pembrolizumab will be administered every 21 days and will continue until you are no longer benefiting from the drug.

If your disease worsens while receiving pembrolizumab, you will have the option of having a biopsy of your tumor tissue, and/or receiving taxane-based chemotherapy. The chemotherapy regimen will be decided by your treating physician, and may consist of a taxane chemotherapy (docetaxel or cabazitaxel) with or without a platinum chemotherapy (such as carboplatin). You may receive a minimum of 2 cycles and a maximum of 8 cycles of chemotherapy. Chemotherapy may be given with prednisone. If you have a clinical response to chemotherapy, you may then be retreated with pembrolizumab immunotherapy.

BEFORE YOU BEGIN THE MAIN PART OF THE STUDY...

Screening Period

You will need to have the following exams, tests and procedures to find out if you can be in the main part of the research study. Most of these exams, tests or procedures are part of routine cancer care and may be done even if you do not join the research study. You will complete the following tests or procedures within 28 days unless otherwise noted below before starting the study drug. If you have had some of these tests or procedures recently, they may not need to be repeated. This will be up to the study doctor. The total time to complete the screening tests and procedures is about 6-7 hours.

- Some general information about you such as race, ethnicity, age, gender will be collected
- Medical history (including history of prior cancer treatment)
- Physical exam, including height, weight
- Vital signs (temperature, breathing rate, blood pressure, and pulse)
- Review of medications that you are taking, including any over-the-counter medications, vitamins, herbal supplements and prior treatment for your cancer
- Assessment of how cancer is affecting your daily life
- Urine sample for routine safety testing
- Blood sample (about 4 tablespoons) for:
    - Safety tests
    - Thyroid function tests
    - PSA (Prostate-Specific Antigen test) - This is a test used to monitor your prostate cancer
    - LDH - This is a test to indicate whether you might have tissue damage, and if so, how much
    - Immune monitoring

- Tumor imaging by computed tomography (CT) scan and bone scan – within 14 days before starting the study drug
    - **CT scan:** A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally, intravenously, or rectally (less likely). Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. A rectal contrast fills up the loops of your lower bowel so the doctors can see your tumor better. After you have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the radiology department and takes about half an hour.
    - **Bone scan:** A bone scan is a test that makes detailed images of your bones and any tumors on them. Before the bone scan a radioactive substance is injected into your vein. About 3 hours later you will lie on a table under a machine which will make an image of your bones. The test itself will take about 1 hour, but the whole process takes up to 4 hours.
- Tumor tissue collection for DNA damage repair testing using Promega MSI and mutation sequence testing.
    - You will have a tumor biopsy.
        - Tumor biopsy: The study doctor will obtain a small piece of tumor tissue using a special needle. This procedure will be done at the site where we can most easily get a piece of the tumor and the biopsy can involve the lungs, liver, bone, lymph node, skin or other. The biopsy needle will be inserted into tumor tissue and a small piece of the tumor will be removed. 1 - 3 passes with this needle will be made. A CT scan may be used to help guide placement of the needle. This procedure takes about 30 minutes.
    - If DNA damage repair defects have been identified in a prior tumor biopsy, you may not need to have a biopsy at this time. We will only use the Promega MSI and a mutation sequencing test to look for defects that have not been found in prior testing. If your tumor has previously been tested for MSI status, the Promega MSI test will not need to be done for this study.
        - You will be asked to provide leftover tumor tissue from a prior biopsy or surgery for this testing. If no leftover tissue is available, you will have a tumor biopsy as described above, as long as it is safe to do so.

DURING THE MAIN PART OF THE STUDY...

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

Pembrolizumab Cycles – Every 21 Days

You will have the following exams, tests, and procedures at each clinic visit every 21 days. Each of the visits will take about 2 - 3 hours, but may take up to 6 hours, depending on the tests and procedures you have done.

- Physical exam, including weight
- Vital signs (temperature, breathing rate, blood pressure, and pulse)
- Assessment of how cancer is affecting your daily life
- Review of side effects you may be experiencing
- Blood sample (about 4 - 6 tablespoons) for:
    - Safety tests
    - Thyroid function tests
    - LDH – This is a test to indicate whether you might have tissue damage, and if so, how much
    - PSA – This is a test used to monitor your prostate cancer
    - Immune monitoring
- Tumor imaging (CT scan and bone scan) – every 12 weeks
- Pembrolizumab infusion

Optional Chemotherapy Cycles – Every 21 Days (for 2-8 cycles)

If your disease worsens while receiving pembrolizumab, you will have the option of having a biopsy of your tumor tissue and/or receiving standard of care taxane-based chemotherapy (docetaxel or cabazitaxel) with or without a platinum chemotherapy (such as carboplatin). You can receive a minimum of 2 cycles and a maximum of 8 cycles of chemotherapy, and it may be given with prednisone.

If you move onto this chemotherapy regimen, you will have the following tests exams, tests and procedures at each clinic visit every 21 days (for 2 to 8 cycles). Each of the visits will take about 2 - 3 hours, but may take up to 6 hours, depending on the tests and procedures you have done.

- Physical exam, including weight
- Vital signs (temperature, breathing rate, blood pressure, and pulse)
- Assessment of how cancer is affecting your daily life
- Review of side effects you may be experiencing
- Blood sample (about 4 - 6 tablespoons) for:
    - Safety tests
    - Thyroid function tests
    - LDH
    - PSA
    - Immune monitoring
- Tumor imaging – every 12 weeks
- Chemotherapy infusion

Optional Pembrolizumab Cycles – Every 21 Days

If you respond well to the chemotherapy, you will have the option of resuming pembrolizumab. If that is the case, you will have the following exams, tests, and procedures at each clinic visit every 21 days. Each of the visits will take about 2 - 3 hours, but may take up to 6 hours, depending on the tests and procedures you have done. You will also have the option of undergoing an additional biopsy of your tumor tissue.

- Physical exam, including weight
- Vital signs (temperature, breathing rate, blood pressure, and pulse)
- Assessment of how cancer is affecting your daily life
- Review of side effects you may be experiencing
- Blood sample (about 4 - 6 tablespoons) for:
    - Safety tests
    - Thyroid function tests
    - LDH
    - PSA
    - Immune monitoring
- Tumor imaging – every 12 weeks
- Pembrolizumab infusion

WHEN YOU ARE FINISHED RECEIVING THE STUDY DRUG…

End of Treatment Visit

At the time that you discontinue the study drug, you will have the following exams, tests, or procedures. They may not need to be repeated if you recently had them done. This visit may take about 2-3 hours.

- Physical exam, including weight
- Vital signs (temperature, breathing rate, blood pressure, and pulse)
- Assessment of how cancer is affecting your daily life
- Review of side effects you may be experiencing
- Blood sample (about 4 - 6 tablespoons) for:
    - Safety tests
    - Thyroid function tests
    - LDH
    - PSA
    - Immune monitoring
- Tumor imaging

Safety Follow-up Visit

You will be asked to return to the clinic within 30 days of the last dose of study drug. During this visit, you will have the following exams, tests or procedures. This visit will take about 2 hours.

- Physical exam, including weight
- Vital signs (temperature, breathing rate, blood pressure, and pulse)
- Review of side effects you may be experiencing
- Blood sample (about 2 tablespoons) for immune monitoring

Follow-Up

If you discontinue pembrolizumab for a reason other than disease progression, the following assessments will be performed every 12 weeks until either the study ends, your disease progresses, you start a new anti-cancer therapy, or death. These visits will take about 3-4 hours.

- Physical exam, including weight
- Vital signs (temperature, breathing rate, blood pressure, and pulse)
- Anti-cancer therapy status
- Blood sample (about 4 - 6 tablespoons) for:
    - PSA
    - Immune monitoring
- Tumor imaging

If your disease worsens or you start a new anti-cancer therapy, you will be contacted by telephone every 12 weeks to check your health status until death, withdrawal of consent, or the end of the study, whichever occurs first.

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 can continue receiving pembrolizumab as long as you respond to the study drug. However, if your disease worsens while receiving pembrolizumab, you will have the option of receiving taxane-based chemotherapy followed by pembrolizumab for those who have a clinical response to chemotherapy. The chemotherapy will be decided by your treating physician after discussion with you, and may consist of docetaxel or cabazitaxel with or without a platinum agent such as carboplatin. The length of time you are on the study will depend upon how you are feeling, how well you tolerate pembrolizumab and whether your disease responds to the study drug.

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 the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he 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 study drug. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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

Risks of Pembrolizumab (Keytruda)

Receiving pembrolizumab as a single drug may not be effective in treating your cancer. There is a risk that your cancer may get worse while receiving pembrolizumab.

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues 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.

Very common side effects (some may be serious) seen in 20% or more of patients treated with pembrolizumab include the following:

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

Common side effects (some may be serious) seen in 5% to less than 20% of patients treated with pembrolizumab include the following:

- 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, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatremia)

Uncommon side effects (some may be serious) seen in 1% to less than 5% of patients treated with pembrolizumab include the following:

- 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 syndromeor toxic epidermal necrolysis)

Rare side effects (some may be serious) seen in less than 1% of patients treated with pembrolizumab include the following:

- 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 have 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 (uveitis)

- 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 bellyaches, 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 will depend on the particular blood vessels that are involved in the inflammatory process, for example; if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue.
- Low levels of parathyroid hormone (a hormone made by 4 tiny glands in your neck) which may result in low blood calcium and cause muscle cramps or spasms; fatigue or

weakness; numbness, tingling or burning in your fingertips, toes or lips (hypoparathyroidism)

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 these side effects:

- 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 the right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).
- Inflammation or swelling of the nerve fibers of the eye which send visual information from your eye to your brain. This health condition often has a sudden onset of vision loss, loss of color vision, pain when moving your eyes, and/or loss of peripheral vision. It may affect one or both eyes at the same time (optic neuritis).

Also, the following side effects might be noticed during your treatment with pembrolizumab: 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.

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

Risks of Docetaxel

Like all medicines, docetaxel can cause side effects, although not everybody gets them.

The severity and frequency of side effects may vary depending on whether docetaxel is given alone or in combination with other anti-cancer medicines. Side effects that might be noticed during your treatment are listed below.

Very common side effects seen in more than 10% of patients:	**Common side effects seen in 1% to 10% of patients:**	**Uncommon and rare side effects seen in less than 1% of patients:**	**Side effects where the frequency is unknown:**
• Infection • Decrease in the number of red and/or white blood cells or platelets (your doctor will check this) • Fever • Allergic reactions as described above • Loss of appetite • Inability to sleep • Feeling of numbness, or pins and needles • Headache • Reduced sensation to touch • Increased tear formation • Swelling under the skin • Bleeding from the nose • Runny nose, inflammation of the nose and throat • Cough • Chest pain • Change in sense of taste • Shortness of breath/difficulty in breathing • Sores in your mouth (including tongue and/or lips and/or cheeks) • Diarrhea • Feeling and/or being sick • Constipation • Abdominal pain • Indigestion • Loss of hair • Redness and swelling of the palms of your hands or soles of your feet which may cause your skin to peel (this may also occur on your arms, face or body) • Change in the color of your nails, which may detach • Muscle aches or pain • Back pain or bone pain • Change or absence of menstrual period • Swelling of the hands, feet or legs • Feeling of weakness	• Fungal infection in the mouth • Inflammation of the skin • Dry mouth • Dizziness • Headache • Dehydration • Conjunctivitis • Impaired hearing • Difficulty or pain when swallowing • Irregular heart beat • High or low blood pressure (your doctor will check this) • Heart failure • Heartburn • Bleeding • Raised liver enzymes	• Fainting • Inflammation of the vein • Inflammation of the colon, small intestine or perforation of the large intestine • Fits or temporary loss of consciousness • Hearing loss • Heart attack • Blood clots • Pneumonia • Inflammation and /or fluid on the lungs which may cause you to cough, with or without frothy phlegm • Intestinal blockage causing abdominal pain • Skin redness at the site of previous radiation therapy • Acute myeloid leukemia. Your doctor will do blood tests to check for this. • Temporary visual disturbances e.g. flashes, flashing lights, reduced vision • Inflammation of the liver • Skin redness and/or blisters	• Blurred vision due to swelling of the retina within the eye (cystoid macular edema) • Decrease of sodium in your blood

Very common side effects seen in more than 10% of patients:	Common side effects seen in 1% to 10% of patients:	Uncommon and rare side effects seen in less than 1% of patients:	Side effects where the frequency is unknown:
• Tiredness or flu-like symptoms • Weight gain • Weight loss			

Risks of Cabazitaxel

Like all medicines, cabazitaxel can cause side effects, although not everybody gets them.

Very common side effects seen in more than 10% of patients:	Common side effects seen in 1% to 10% of patients:	Other reported risks
• Decrease in the number of red blood cells (anemia) or white blood cells • Decrease in the number of platelets (risk of bleeding) • Loss of appetite (anorexia) • Alteration in sense of taste • Shortness of breath • Cough • Stomach upsets including nausea • Vomiting • Diarrhea • Constipation • Abdominal pain • Short term hair loss (in most cases normal hair growth should return) • Back pain • Joint pain • Blood in the urine • Fatigue • Weakness • Fever	• Urinary tract infection • Lack of white blood cells associated with fever • Dehydration • Weakness of the arms and legs • Feeling of numbness, tingling, burning or decreased sensations in hands and feet • Dizziness • Headache • Decrease in blood pressure • Uncomfortable feeling in the stomach or belching after eating • Stomach pain • Cardiac rhythm alterations (mainly bradycardia and tachycardia) • Hemorrhoids • Gastro-esophageal reflux disease (heartburn) • Muscle pain • Pain when passing urine • Kidney disease • Sores in the mouth • Hypersensitivity	Loss of blood and perforation of your stomach and intestines (gastrointestinal hemorrhage and perforation, obstruction of the intestine due to paralysis of the intestinal muscles (ileus), and intestinal tissue death (entercolitis) leading to death, have been reported. Risk may be increased with neutropenia (decrease of white blood cells), age, steroid use, concomitant use of nonsteroidal anti-inflammatory drugs, anti-platelet therapy or anti-coagulants, and patients with prior history of pelvic radiotherapy, intestinal adhesions, ulceration and gastrointestinal bleeding.

Risks of Carboplatin

Like all medicines, carboplatin can cause side effects, although not everybody gets them.

Very common side effects (experienced in more than 20% of patients):	Common side effects (experienced in 6-20% of patients):	Less common side effects (experienced in less than 5% of patients):

• Lowered white blood cell count (leukopenia) • Lowered red blood cell count (anemia) • Lowered platelets (thrombocytopenia) • Low levels of a certain type of white blood cell known as a neutrophil (neutropenia) • Damage to nerves causing numbness in the hands and/or feet • Nausea and/or vomiting • Loss of appetite • Change in liver function without symptoms • Pain • Low levels of electrolytes (magnesium, calcium, potassium, sodium) • Hair Loss • Weakness, loss of strength • Kidney damage • Allergic reaction • Hearing loss • Infection • Cardiovascular disorders	• Bleeding • Diarrhea • Constipation • Altered taste • Mouth sores, sometimes making it difficult or painful to swallow • Respiratory disorders • Serious allergic reaction (anaphylaxis), which could be life-threatening with hives, wheezing, • Cough, dizziness, chills, rash, trouble breathing, chest or throat tightness, swelling in your • Face or hands, fever, itching, and low blood pressure.	• Heart failure, blood clot, stroke • Kidney failure

OTHER RISKS RELATED TO THIS STUDY INCLUDE:

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

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: This research study involves exposure to radiation. Some of this radiation exposure may be for research purposes only, and is not necessary for your medical care. This amount of radiation may involve a low, lifetime risk of cancer. However, we believe that this risk is not clinically relevant given your overall medical condition. If you have any questions regarding the use of radiation or the risks involved, please consult your study doctor.

CT scan risks: CT scans involve the risks of radiation (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.

Bone Scan: The bone scan involves exposure to radiation. The bone scan involves an injection, in a vein in your arm, of a radiotracer (radioactive compound that localizes in the bone). As with all injections, it may feel like a small sting and there may be possible bruising at the injection site. You may become uncomfortable lying still for the duration of the examination. See Radiation Risks.

Tissue biopsy: The biopsy has small but serious risks. While we make every effort to minimize the pain related to the procedure, the procedure is usually uncomfortable and sometimes painful. Wherever the biopsy is done in your body, it can lead to bleeding in that area, damage of organs near where the biopsy is done, or infection. While it is uncommon, sometimes bleeding or pain from the biopsy will require you to stay overnight in the hospital or require you to go to the operating room to control any bleeding. We check your laboratory values before the biopsy to make sure that the procedure is as safe as possible and to minimize your chance of having a complication. Additionally, if the biopsy involves the lungs, it can cause the lungs to deflate and if this occurs, you might require treatment to correct this. We try to take as little tissue as possible when we do the biopsy, and this means that sometimes the biopsy procedure can be unsuccessful and require a repeat biopsy to get enough tissue. Other potential risks will be described to you and discussed with you by doctors who conduct these biopsies.

Reproductive risks: There may be risks if your partner is pregnant or trying to become pregnant. If your partner is able to have a baby, you and your partner must avoid having sex (abstinence) or use reliable birth control methods during the study and from your first day of receiving study drug throughout the study period up to 120 days after your last dose of study drug.

The following birth control methods are allowed during the study:

Use of two (2) of the following in combination:

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Condom (male or female cannot be used together)
- Cervical cap with spermicide (only if your partner has not given birth)
- Contraceptive sponge (only if your partner has not given birth)
- Hormonal contraceptives (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

OR

One (1) of the following:

- Intrauterine Device (IUD)
- Vasectomy or surgical sterilization of your partner
- Contraceptive rod implanted into your partner's skin

If your partner becomes pregnant during the study you must notify the study doctor right away. You must also agree to not donate sperm from the day study treatment begins and for a period of 120 days after your last dose of study drug.

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 treatments 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?

There is no guarantee that you will receive any benefits from this study, and taking part in this study may or may not cause your health to improve. Receiving pembrolizumab alone may not be effective in treating your cancer. Information from this study may help doctors learn more about pembrolizumab and the treatment of prostate cancer. This information may benefit other patients with prostate cancer or a similar condition in the future.

HOW WILL MY SPECIMENS AND INFORMATION BE USED?

Researchers will use your specimens and information to conduct this study. Once the study is done using your specimens and information, we may share them with other researchers so they can use them for other studies in the future. We will not share your name or any other personal information that would let the researchers outside of UCSF know who you are. We will not ask you for additional permission to share the de-identified information and specimens.

Your specimens will be stored in a repository, also called a 'tissue bank', at UCSF. The manager of tissue bank and select tissue bank staff members will have access to your specimens and information about you, but they will not release any identifying information about you to researchers using your specimens. We may give your specimens and certain medical information

about you (for example, diagnosis, blood pressure, age if less than 85) to other scientists or companies not at UCSF, including to an unrestricted or controlled-access government health research database, but we will not give them your name, address, phone number, or any other identifiable information. Your specimens and information will be kept indefinitely until they are used up or destroyed. Research results from these future studies will not be returned to you and will not be put in your medical record. Future research performed on your de-identified samples will not change the care you receive.

Researchers may use your specimens (for example, blood, tissue, saliva, etc.) to look at all of your DNA (this is called "whole genome sequencing. DNA contains information that determines things like eye color, height, or disease risk that are passed on from parent to child. 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.

Donating data and specimens 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.

There will be no direct benefit to you from allowing your data and specimens 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 data or specimens, 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 information to be used for future research, you can notify the investigator in writing at:

Lawrence Fong, MD
[redacted]
San Francisco, CA 94143

and any remaining data will be destroyed. However, we cannot retract any data has been shared with other researchers.

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. You may be able to receive treatment with drugs approved to treat your type of cancer (such as abiraterone, enzalutamide, docetaxel, cabazitaxel or carboplatin).
- Taking part in another study.
- Receiving no treatment at this time.
- 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.

Talk to your doctor about your choices and their risks and benefits before you decide 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 the personal 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. Your signed consent form and some of your research tests will be 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
- The National Cancer Institute (NCI) and other government agencies, e.g., the FDA, involved in keeping research safe for people.
- Merck and its authorized agents

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Merck will provide pembrolizumab at no cost to you while you are participating in this study. You will not be billed for DNA damage repair testing using the Promega MSI test and a mutation sequencing test.

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 all standard medical care costs because you are in a research study or because you are receiving medical services out of network.

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 research study doctor, Lawrence Fong, 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 [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 Merck, depending on a number of factors. The University and Merck 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 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 research study doctor about any questions, concerns, or complaints you have about this research study. Contact your research study doctor Lawrence Fong, M.D. at 415-353-7171

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 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 study.

Optional Tumor Biopsies/Future Research

About Optional Tumor Biopsies and Future Research

Depending how your disease responds to pembrolizumab, the study doctor would like to perform up to 2 additional tumor biopsies:

1. If your disease worsens while receiving pembrolizumab, you may have an additional biopsy before beginning chemotherapy described under "Optional Chemotherapy Cycles."

2. If you have a clinical response to this chemotherapy and begin taking pembrolizumab again, you may have an additional biopsy within 28 days of restarting pembrolizumab.

These biopsies are optional. If you choose not to have one or both of these optional tumor biopsy, you can still participate in the main part of the study.

The optional biopsies will be similar to the biopsy described in the section "Before you begin the main part of the study."

If you agree to the optional tumor biopsies, we will share the specimens with other researchers so they can use them for other studies in the future. The specimens will be shared and certain medical information about you will be shared, as described in the section entitled **"**How will my specimens and information be used?" Please review this section to learn about what information about you will be shared, who it will be shared with, and the risks of sharing your medical information and tumor tissue for future research.

Things to Think About

The choice to undergo the optional tumor biopsies and give your specimens to researcher's 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 you want to have the optional research biopsies, you can change your mind at any time before the procedures. Just contact us and let us know that you do not want to have the optional research biopsy.

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

The risks of tumor biopsies are described in the section "Other Risks Related to This Study Include"

The risks of donating tumor tissue for future research are described in the section "How will my specimens and information be used?"

Making Your Choice

Please read the sentence below and think about your choice. After reading the 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 agree to undergo an optional tumor tissue biopsy if my disease worsens while receiving pembrolizumab. This tumor tissue will be kept for use in future research to learn about, prevent, or treat cancer (including DNA and genetic tests).

YES	NO

2. I agree to undergo an optional tumor tissue biopsy if I begin taking pembrolizumab again after chemotherapy. This tumor tissue will be kept for use in future research to learn about, prevent, or treat cancer (including DNA and genetic tests).

YES	NO

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

YES	NO

********** End of Optional Research Section **********

CONSENT

You have been given a signed and dated copy of this consent form and a copy of the Experimental Subject's Bill of Rights to keep.

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

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

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

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