A Phase II Study of Tadalafil and Pembrolizumab in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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**Informed Consent Form: 7/13/2020**

University of California, San Diego
Consent to Act as a Research Subject

# A Phase II Study of Tadalafil and Pembrolizumab in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

Joseph Califano, MD and his colleagues are conducting a research study sponsored by the University of California, San Diego (UCSD) to find out more about the experimental drug combination of tadalafil and pembrolizumab. You are being asked to take part because you have head and neck cancer.

Your participation in this research study is voluntary. The purpose of this Informed Consent Form is to inform you about the nature of this research study so that you may make an informed decision as to whether you would like to participate. If you have any questions, please ask your study doctor or coordinator to explain any words or information that you do not understand.

## PURPOSE

The purpose of this study is to examine the effects of combining pembrolizumab and tadalafil.

Pembrolizumab is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC), melanoma (skin cancer), non-small cell lung cancer (NSCLC), and many other types of cancers.

Tadalafil is FDA approved for the treatment of erectile dysfunction, prostate gland enlargement, and high blood pressure that affects arteries in the lungs and heart. Tadalafil is considered experimental because it is not approved by the FDA for the treatment of cancer. In this study, pembrolizumab and tadalafil are also considered experimental because they have not been approved to be used in combination for head and neck cancer.

The combination of pembrolizumab and tadalafil may potentially increase the ability of your immune cells to help fight against the cancer cells.

Participation in this study is entirely voluntary. Approximately 30 participants will be enrolled at UC San Diego.

## DURATION OF THE STUDY / HOW LONG IS EACH VISIT?

The duration of your participation in this study will be determined by how your disease responds to the study drugs. The study treatment may continue until one of the following occurs:

- Cancer gets worse
- Side effects become too severe
- Your doctor feels it is no longer safe
- You decide to withdraw from the study

The duration of your participation is expected to be approximately 2 years.

Each of your study visits can last from approximately one to seven hours.

## PROCEDURES

Screening

You will complete a series of procedures or tests to determine if participating in this study is appropriate for you. Screening procedures may take more than one day to complete. Some of these may be part of your regular medical care and may be done even if you do not join the study. If you have had some tests recently, they may not need to be repeated. Your study doctor will talk to you about these tests. During the Screening Period you can expect the following:

- You will be asked about your medical history, treatment history and demographic information.
- You will be given a physical exam and your weight, height, and vital signs (heart rate and blood pressure) will be measured.
- You will be asked questions about your health and how your disease affects your daily life.
- You will be asked about any medications you are taking or have taken in the past.
- Samples of your blood (approximately 3-5 tablespoons) will be drawn for laboratory tests:
    - Hematology or CBC (Complete Blood Count), which includes: white blood cell count, red blood cell count, platelet count, hemoglobin (oxygen-carrying pigment in red blood cells), hematocrit (measures the amount of space red blood cells take up in the blood). This is to aid in diagnosing anemia (low red blood cell count which can result in fatigue), certain cancers of the blood, and to monitor blood loss and infection.
    - Blood chemistry, which measures the levels of a number of chemical substances that are released from various tissues in the body to evaluate the function of the liver and kidneys.

  - Thyroid gland function tests (T4 and TSH), which measures how well the thyroid gland is working.
  - Research blood sample

- A pregnancy test will be performed for all women of child bearing potential.
- You will have imaging scans to measure your disease. These may include CT scans, MRIs, or PET scans.
  - CT scan: The Computed Tomography (CT) scanner is a free-standing machine with a large hole in the center. You will be asked to lie on your back with your arms raised above your head on a narrow table that slides into the hole. Patients who have difficulty with enclosed spaces such as those found with some MRI scanners do not usually have a problem with this type of test. A dye may be injected into a peripheral vein to better evaluate certain diseases and organs. The radiologist will decide if this is necessary. Tell the technician or radiologist if you have any allergies to contrast dye or have had difficulty with prior CT scans. It is very important that you remain still throughout the exam and hold your breath when asked. This will allow for better images. The actual scan time is usually about two minutes, although the entire procedure may take up to 2 hours.
  - Positron Emission Tomography (PET scan). You will be taken into a special injection room, where the radioactive substance is administered as an intravenous injection (although in some cases, it will be given through an existing intravenous line or inhaled as a gas). It will then take approximately 30 to 90 minutes for the substance to travel through your body and accumulate in the tissue under study. During this time, you will be asked to rest quietly and avoid significant movement or talking. After that time, scanning begins. The scan is completely painless, but can be rather noisy and you have to lie very still inside the center of a large, doughnut-shaped machine for approximately 30 to 45 minutes.
  - MRI: Magnetic Resonance Imaging (MRI) may be done to measure your tumor. An MRI uses magnetism instead of x-rays to build up a picture of the inside of the body. The scan is completely painless, but can be rather noisy and you have to lie very still inside the center of a large, doughnut-shaped magnet for approximately 30-60 minutes to get a good picture. The imager makes a loud, banging noise while it is taking pictures. You will be given a set of ear plugs to help with the noise. If you have a pacemaker or other metal implants, the staff needs to know as the scan uses magnets.
- You may undergo biopsy of your tumor if your doctor feels it is appropriate.
  - Tumor biopsy: During your participation in this study you may be asked to undergo tumor biopsies. A biopsy is a procedure where a sample of your tumor is removed. Two types of samples may be collected. It will either be a fine needle aspirate (FNA) that collects cells and/or a core biopsy that collects

a small piece of tissue. You may need a general anesthetic (be asleep for the procedure) or a local anesthetic (have only the area of the biopsy numbed by injection) depend on the location of your cancer. There may be some temporary pain or discomfort associated with this routine procedure. The biopsy is helpful in describing your cancer before receiving the study drug, which allows us to determine whether a response during the study could have been predicted.

**If the screening procedures show that you can be in the study and you choose to take part, you will begin study treatment.**

During Study Treatment

**Study Drugs**
Each cycle of study drug will be 21 days.

- You will take a 10mg pill of Tadalafil daily by mouth for days 1-21 of each cycle. Tadalafil can be swallowed with water but cannot be crushed or dissolved in water. If you are unable to swallow the pill, it can be given to you in the form or an oral suspension (a special liquid preparation with study drug particles suspended in the liquid). You will also keep a pill diary. The study staff will provide you with the medication, will instruct you more on how to take it and store it, as well as explain the pill diary to you. If you miss a dose or if you vomit after taking a dose, please do not take another dose the same day. You will take your next dose the following day at your usual time.
- You will receive an intravenous (IV) infusion of 200mg Pembrolizumab on day 1 of each cycle. An IV infusion is a needle directly into a vein in your arm, which allows the medication to be given. You will receive this as an outpatient. You may receive other medications before the infusion to reduce side effects of Pembrolizumab. If your study doctor feels it is appropriate, he may change the dose of this study medication.

**Study Procedures**

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|---|---|
| **Cycle 1 - Day 8** | • Blood draw (chemistry and hematology) |
| **Cycle 1 - Day 15** | • Blood draw (chemistry and hematology) |
| **Every 3 weeks** | • Physical Exam<br>• Weight and vital signs<br>• Review of disease and side effects<br>• Review of current medications<br>• Review of pill diary and medication compliance<br>• Blood draw (chemistry and hematology)<br>• Pregnancy test for women of child-bearing potential<br>• CT or other imaging, as advised by study doctor |
| **30 days after study** | • Tumor biopsy |

| | |
|---|---|
| **treatment starts** | • Blood draw (research sample) |
| **Every 9 weeks** | • Blood draw (thyroid tests) |
| **Every 3 months** | • CT or other imaging studies as advised by study doctor |

After Study Treatment

| | |
|---|---|
| **Within 30 days after last dose of study medication** | • Physical Exam<br>• Weight and vital signs<br>• Review of disease and side effects<br>• Blood draw (chemistry, hematology, and thyroid tests)<br>• Review of current medications<br>• Pregnancy test, as advised by study doctor |
| **90 days after last dose of study medication** | • Review of side effects<br>• Review of current medications<br>• Additional tests may be performed, as advised by your study doctor |

The study team will follow up with you for up to 2 years after you complete the study treatment to see how you are doing. This will happen about every 3 months and may be completed with a phone call.

**Biological Samples**

As described in the study Procedures above, blood and tissue samples will be collected from you throughout the study.

Tumor biopsy will be performed if you have available tumor that can be biopsied under local anesthesia in the office. After local anesthetic is injected, doctor(s) participating in the study will remove a small portion of your tumor. There is a small risk of bleeding, infection, and discomfort associated with this procedure

Blood for research purposes will be harvested by removing about 4 tablespoons of blood before and during your study treatment. The blood and tissue tests for research will examine the effect the study drug has on your body.

These samples may be banked for future research in the laboratory of Dr. Joseph Califano and other researchers at UCSD. These specimens will be stored indefinitely. Researchers working for or with Dr. Califano will have access to the samples, and these samples will be associated with a study number. The study number is used to identify your participation in the trial and is associated with your identification and clinical information. These samples may be shared with researchers outside of UCSD Medical Center, but your personal health information will not be shared with researchers outside of UCSD Medical Center.

Biospecimens (such as blood, tissue, or saliva) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research, and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

If you decide later that you do not want the specimens collected from you to be used for future research, you may tell this to Dr. Califano, who will use his best efforts to stop any additional studies. However, in some cases, such as if your samples have already been tested, the data from these tests are no longer linked to your identity and cannot be removed from the research database

Dr. Califano, his associates, or his successors in these studies will keep your genetic information derived from the DNA specimen(s) for up to indefinitely. Genes are in every cell in your body, and give the cell instructions for how to grow and function. They are inherited from your parents. However, genes in cancer cells have changed from those in normal cells, giving rise to cancer

There will be no direct benefit to you from this study since you will not be provided with any results or information regarding your DNA test. The investigator, however, may learn more about head and neck cancer.

Federal and State laws generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

a) Health insurance companies and group health plans may not request your genetic information that we get from this research.

b) Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

c) Employers with 5 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that these laws **do not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

## RISKS OF PARTICIPATION

Participation in this study may involve some added risks or discomforts. While you are on this study, you are at risk for the side effects listed below. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the

study drug is stopped, but in some cases, side effects may be serious, long-lasting, and may even cause death.

Please tell your study doctor or a member of the study staff if you are experiencing any side effects regardless of whether or not you feel they are related to the study treatment.

***Risks of Pembrolizumab:***

The side effects listed below have been reported by patients who have received pembrolizumab. Some side effects may be serious or life-threatening and may lead to hospitalization or even death.

**Very Common Side Effects, Some May be Serious - Out of 100 people who receive pembrolizumab, 20 or more people may have the following:**

- Itching of the skin
- Fatigue or tiredness
- Muscle or stomach pain
- Decreased appetite
- Loose or watery stools
- Constipation
- Cough
- Difficulty breathing
- Nausea
- Rash
- Fever

**Common, Some May be Serious - Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:**

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

**Uncommon, Some May be Serious - Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:**

- Inflammation of the lungs so you may feel short of breath and cough. Sometimes this might lead to death
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools

- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or 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
- 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. These severe conditions can sometimes lead to death.

**Rare, Some May be Serious - Out of 100 people who receive pembrolizumab, less than 1 person may have 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
- Inflammation of the muscles so you may feel weak or have pain in your muscles 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
- 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, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- 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
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- 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
- 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. Sometimes this condition can lead to death

- 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.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- 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.

***Risks of Tadalafil***

In 100 patients, about 2 or more may experience these most common side effects, including headache, upset stomach or indigestion, back pain, limb pain, muscle pain, nasal congestion, and flushing or temporary redness of skin.

Other side effects listed below may also occur and in rare cases may be serious. In 100 patients, 2 or less people may experience the following.

Cardiac (heart) and nervous system problems, including:

- Chest pain
- Fast heart beat
- Heart attack
- Low blood pressure (may lead to dizziness or temporary loss of consciousness)
- Stroke or mini-stroke
- Migraine
- Seizure
- Dizziness or sensation of spinning
- Reduced sense of touch
- Tingling or numbness
- Difficulty sleeping or increased sleepiness

Stomach and digestive system problems, including:

- Vomiting
- Diarrhea
- Dry mouth
- Stomach pain
- Rectal (anal) bleeding

Muscular or skeletal problems, including:
- Joint pain
- Other pain

Eye and Ear problems, including:
- Sudden loss of vision in one or both eyes
- Blurred vision
- Changes in color vision
- Eye pain
- Swelling of eyelids
- Pinkeye
- Sudden decrease or loss of hearing (may experience ringing in ears or dizziness)

Nose and Lung problems, including:
- Difficulty breathing
- Nosebleed
- Sore throat
- Upper lung infection

Skin problems, including:
- Rash
- Itching
- Sweating
- Hives
- Stevens-Johnson syndrome - a rare, serious inflammatory disorder of your skin and mucous membranes (such as inside the mouth). Symptoms may include fever, widespread skin pain, red or purple rash, blisters on the skin and the surface areas of the mouth, nose, eyes, and genitals, and a shedding of skin following the blisters.
- Exfoliative dermatitis – symptoms may include redness and peeling of skin, hives, chills, fever, and fatigue

Urinary problems, including:
- Urinary tract infection
- Prolonged or painful erection lasting more than four hours

**Additional Risks and Discomforts Associated with Study Procedures**

There may be other risks associated with participation in this study that are currently unforeseeable.

***Allergic Reactions*:** As with any drug, there is the chance of an allergic reaction, which may include difficulty breathing, rash, flushing, weakness, dizziness, lightheadedness, and swelling.

***Intravenous (IV) Injection Side Effects:*** If the drug leaks from the vein, where the needle was inserted, it may cause skin irritation at the needle site and surrounding tissue. All injections into your vein can cause swelling, a burning sensation, tightness, bruising, bleeding, and/or nerve damage have a slight risk of pain, bleeding, infection, and rarely, fainting and/or nerve damage.

***Risks of blood draws:*** There is a risk of discomfort or pain, bleeding, swelling and a small arm bruise and swelling when blood is drawn. Rarely, a clot or infection may occur at the site of the blood draw. Some people also become faint, dizzy, or light-headed during or immediately after the blood draw.

***Risks of tumor biopsy:*** Pain, bleeding and infection at the biopsy site may occur. In rare cases, more severe bleeding may occur inside your body that may require hospitalization, surgery and blood transfusions or may result in death. It is very rare, but you may have an allergic reaction to the numbing medication, which may include difficulty breathing, rash, flushing, low blood pressure and swelling. Additionally, there is a moderate risk of nerve injury and local paralysis (complete loss of muscle function, which may or may not be permanent) or numbness if the biopsy is done on a lymph node close to nerves. Your study doctor will further explain the risks involved with a biopsy.

***Reproductive Risks:*** You should not become pregnant or father a baby while on this study because the drugs in this study can affect a fetus and cause serious birth defects. Women should not breastfeed a baby while on this study. Some of the drugs used in this study may make you unable to have children in the future. It is important you understand that you need to use birth control while on this study. If you are female and capable of child-bearing, a pregnancy test will be done before the study begins in order to be as sure as possible that you are not pregnant. Your participation requires that you use contraception methods (such as abstinence, diaphragm, condom, or intrauterine device) to prevent pregnancy for the duration of the study and for 4 months after the last dose of study medication.

Ask about counseling and more information about preventing pregnancy.

***Risks from Radiation:*** During your participation in this research study, you will be exposed to radiation from scheduled x-rays and/or imaging scans. The total exposure resulting from these imaging studies is calculated to be approximately 39.5 mSv for the first year and 31.6 mSv for additional years. If clinically indicated a CT of the head (2.5 mSv per scan), neck (2.5 mSv per scan), and chest (5.4 mSv per scan) will be performed. If clinically indicated a PET/CT will be performed with an exposure of 20.1 mSv per scan. This amount is more than you would receive from one year of natural exposure in the San Diego area, which is approximately 1.6mSv. Cumulative exposure from radiation may increase your risk of developing certain types of cancer in the future.

The principal investigator for this research study has determined and verified that all of the x-rays and/or imaging scans prescribed for this study would typically be performed as part of the standard medical care required to adequately monitor your current illness. Radiation exposure may be decreased if non-radiation imaging alternatives are utilized, such as an MRI instead of a CT. If you are especially concerned with radiation exposure, or you have had a lot of x-rays or imaging scans already, you should discuss this with the principal investigator for this study, Dr. Joseph Califano, or your regular doctor.

***Risks of CT and PET-CT Scans:*** The CT and PET-CT involves exposure to radiation. The radiation exposure comes from a tracer which is a radioactive chemical injected into a vein in your arm. The tracer lets the doctor see how your cells are functioning. As with all injections, it may feel like a small sting and there may be possible bruising at the injection site, and an allergic reaction is possible. The radioactive solution does not remain in your system for a long period of time. The imager makes a loud, banging noise while it is taking pictures. You will be given a set of ear plugs to help with the noise. You may experience feelings of claustrophobia or anxiety. You may also experience some discomfort and tiredness from lying still in a confined space during the imaging. For some people, having to lie still on the scanning table for the length of the procedure may cause some discomfort or pain.

***Risks of MRI Scans:*** As part of this study, Magnetic Resonance Imaging (MRI) may be done. The imager makes a loud, banging noise while it is taking pictures. You will be given a set of ear plugs to help with the noise. You may experience feelings of claustrophobia or anxiety. You may also experience some discomfort and tiredness from lying still in a confined space during the imaging. There are no known effects from exposure to magnetic fields (MRI). However, some people undergoing this procedure become anxious. If this happens to you, you can stop the procedure at any time. If you have metal clips or plates in your body or a pacemaker, you should tell your doctor about it. MRI may not be appropriate under some of the following conditions: a cardiac pacemaker; metal fragments in eyes, skin, or body; heart valve replacement; brain clips; venous umbrella; being a sheet-metal worker or welder; aneurysm surgery; intracranial bypass; renal or aortic clips; prosthetic devices such as middle ear, eye, joint, or penile implants; joint replacements; hearing aid; neurostimulator; insulin pump; I.U.D.; being pregnant or trying to become pregnant; shunts/stents; metal mesh/coil implants; metal plate/pin/screws/wires, or any other metal implants; and permanent eyeliner and/or eyebrows.

***Risks of IV Contrast:*** As part of this study a CT scan may be done. There may be some reactions related to the contrast dye used in CT scans. Contrast dye is usually administered when you get a CT scan. Contrast dye may also be used in MRI scans. Some people may develop hives and itching or other allergic symptoms from this dye, swelling of the heart, cramps of the voicebox, breathing distress caused by narrowing of the airways in lungs, low blood pressure, with loss of consciousness, and in rare cases, severe loss of blood and fluids leading to shock and death, fainting, seizures, and irregular heartbeats. In addition, if you have low kidney function, this dye can temporarily or permanently decrease your kidney function.

***Risks of Genetic Testing:*** Some people involved in genetic studies have felt anxious about the possibility of carrying an altered gene that they could possibly pass on to their children. Even though we will do our best to keep your information confidential, there is the possibility that your genetic risk for certain diseases is accidently divulged to the wrong source, if that happens you might be discriminated against obtaining life or health insurance, employment or ability to adopt children.

***Risks of Loss of Confidential Information:*** There is also a small risk that information from your health records will be released to an unauthorized party. 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. An identification code assigned by the study team to each participant will be used in place of your name to protect your identity when reporting trial-related data.

## BENEFITS OF PARTICIPATION

If you agree to take part in this study, there may not be direct medical benefit to you. Other patients in the future, however, may benefit from the information learned from this research study, and the investigators may learn more about tadalafil and pembrolizumab.

## ALTERNATIVES TO PARTICIPATION

If you choose not to take part in or stop participating in this research study, there may be other treatments. Refusal to take part in this study will not cause penalty or loss of benefits to which you are otherwise entitled.

You do not have to participate in this study to receive treatment for your cancer. Other possible treatments could include treatment with other drugs or drug combinations, participation in other research studies, or no cancer treatment. You can have supportive (comfort) care instead of or in addition to study treatment. Talk to your study doctor about this.

Pembrolizumab is commercially available meaning you do not need to participate in this research trial to receive it. Please talk to your doctor about these and other options.

## COSTS/COMPENSATION

### Tadalafil

The study drug, tadalafil, will be supplied at no cost while you take part in this study. The cost of getting the study drug, tadalafil, ready for you is also provided at no cost.

It is possible the study drug, tadalafil, may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

Research related procedures such as, research laboratory tests, are covered by the research study.

You and/or your health plan/insurance company will need to pay for all of the other costs of caring for your cancer while in this study, including the costs of tests, procedures, or other medicines, unless you are told that certain tests are supplied at no cost. Before you decide to be in the study, you should check with your health plan/insurance company to find out exactly what they will pay for.

Examples of procedures and drugs that may be billed include the following: the study drug pembrolizumab, routine clinic visits, routine laboratory tests, and routine imaging.

There will be no payment to you for participating in this study.

## COMPENSATION FOR RESEARCH-RELATED INJURY

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at (858) 246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

## VOLUNTARY PARTICIPATION

Participation in this study is entirely voluntary. If you choose not to participate or wish to withdraw your consent to participate in these study procedures at any time, it will in no way affect your regular treatments or medical care at this institution or loss of benefits to which you are entitled. Please contact Dr. Califano or a member of his study team, if you wish to withdraw from participation.

You will be informed of any new findings that might affect your willingness to continue participating in the study.

If health conditions occur which would make your participation in this study possibly dangerous, or if other conditions occur that would make participation in this study detrimental to you or your health, then your study doctor may discontinue your participation in this study.

Your study doctor or sponsor may stop your participation in this study at any time without your consent if:

- You become pregnant;
- You cannot follow the instructions given to you;
- You experience an unacceptable side effect;
- Dr. Joseph Califano or UCSD decides to end the study.

## DO YOU HAVE ANY QUESTIONS?

Dr. Joseph Califano and/or _____has explained this study to you, and answered your questions. You may contact Dr. Joseph Califano at (858) 822-6197. You may also call the hospital 24-hour paging system at (858) 657-7000 and ask for the oncologist on-call. If you have other questions or research-related problems, you may call the Moores UCSD Cancer Center Clinical Trials Office at (858) 822-5354.

If you have questions about your rights as a research participant, your participation in this study, and/or concerns about this study, you may call the UCSD Human Research Protections Program (a group of people who review the research study to protect your rights and welfare) at (858) 246-HRPP (858-246-4777).

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.

## CONFIDENTIALITY

The confidentiality of your research records will be maintained to the extent allowed by law. This includes using locked filing cabinets and the use of passwords will be required to access your personal data on computers. Access to your information will be limited to study personnel who need to use it for the purpose of the research in this study. Only the minimum necessary information required will be collected, stored, used and reported. Your medical information will not be made publicly available unless disclosure is required by law or regulation.

Data obtained from this study will be given to the sponsors of this study, UCSD, Eli Lilly, and Merck and/or its representatives, and may be published or given to regulatory authorities, including the Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, the UCSD Institutional Review Board, the Moores UCSD Cancer Center Data and Safety Monitoring Board (DSMB) and other governmental agencies in the United States or other countries in which regulatory approval of pembrolizumab and/or tadalafil, may be sought. Your identity will remain confidential. Study data is labeled with a code instead of your name or other information that can easily identify you.

You will be asked to sign a separate HIPAA authorization form to allow the study team to access and share information from your medical record. Your permission as described in this informed consent and HIPAA document does not have an automatic expiration date.

## SIGNATURE AND CONSENT

Your participation in this study is voluntary, and you may refuse to participate or withdraw from the study at any time without prejudice or loss of benefits to which you are otherwise entitled. You will receive a signed copy of this consent document and a copy of "The Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Impartial Witness

_____ _____
Signature of Impartial Witness Date

Human Research Protections Program
(858) 246-HRPP (858-246-4777)
(858) 246-3329 (FAX)

University of California, San Diego
9500 Gilman Drive, Mail Code 0052
La Jolla, CA 92093-0052

## EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The faculty and staff of the University of California, San Diego wish you to know:

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time, and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of a signed and dated written consent form when one is required.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

If you have questions regarding a research study, the researcher or his/her assistant will be glad to answer them. You may seek information from the Human Research Protections Program - established for the protection of volunteers in research projects - by calling (858) 246-HRPP (858-246-4777) from 7:30 AM to 4:00 PM, Monday through Friday, or by writing to the above address.