NCT# 02395627

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

CC# 147523: Reversing Therapy Resistance with Epigenetic-Immune Modification (Pembrolizumab, Vorinostat, Tamoxifen)

This is a clinical trial, a type of research study. Your study doctor, Pamela Munster, M.D., and her associates from UCSF Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco (UCSF) Medical Center will explain the clinical trial to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have locally advanced or metastatic breast cancer. Metastatic means the cancer has spread to areas of your body outside of your breast.

WHY IS THIS STUDY BEING DONE?

This is a research study to test a combination therapy in the treatment of patients with hormone receptor positive breast cancer. The study drug, pembrolizumab is an investigational drug. This means pembrolizumab has not been approved by the U.S. Food and Drug Administration (FDA) for use in breast cancer. In animal studies, lab experiments, and in some early human studies, pembrolizumab has been shown to prevent or slow the growth of cancer cells when used with other anti-hormonal therapy. It is now being tested in research studies in people with advanced cancer.

The study drug pembrolizumab will be given in combination with two other drugs, tamoxifen and vorinostat. Tamoxifen is an anti-hormonal drug that is United States FDA-approved to treat advanced breast cancer. Vorinostat is a drug that prevents or slows the growth of cancer cells, it is FDA approved for treatment in patients with T-cell lymphoma but it is not FDA approved for use in breast cancer. Vorinostat and pembrolizumab are therefore both investigational drugs in this study.

The purpose of this study is to:

- Test how well the study drug pembrolizumab works to keep your cancer from growing, when it is taken with tamoxifen and vorinostat.
- See which dose frequency of pembrolizumab is more effective in patients with breast cancer, when given in combination with tamoxifen and vorinostat.

Merck & Co, and AVON Foundation for Women are providing funding to UCSF to conduct the study. Merck & Co, the manufacturers of the study drugs, will also provide the study drugs at no cost to study participants.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 87 patients will be participating in this study, with 29 in each arm. If any or both of the arms show no benefit in the first 10 patients, this arm will be closed before 29 patients are enrolled in that arm.

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

This study has three arms, **Arm A, Arm B,** and **Arm C**. Your study doctor will tell you which arm and dose frequency group you will be participating in prior to your enrollment.

Arm A involves treatment with tamoxifen and vorinostat, and treatment with pembrolizumab every cycle.

Arm B involves treatment with tamoxifen and vorinostat, and treatment with pembrolizumab starting in the second cycle.

Arm C involves treatment with vorinostat, and treatment with pembrolizumab every cycle.

WHAT WILL HAPPEN AND HOW LONG WILL YOU BE IN THE STUDY?

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

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

Screening (before you begin the main part of the study)

After you have signed this consent, the screening tests listed below will be done within 28 days of your first dose of study drugs. Some of the tests listed below must be done within 4 days of your first dose of the study drugs. You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. Most of these exams, tests or procedures are a part of your regular cancer care (unless notes otherwise as **Research Purposes**). If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. There may be reasons you are not allowed to take part in this study. The study doctor or staff will discuss these with you.

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

- Physical exam , including review of vital signs, height, and weight
- Medical history including any past treatments or surgeries for your disease.
- Blood draw (approximately 1-2 tablespoons)
  - Complete blood count (CBC) with differential and platelet count
  - Comprehensive metabolic panel
  - Blood chemistry assessment
- Pregnancy test
- Tumor assessment by MRI (Magnetic Resonance Imaging) or CT scan of chest, abdomen, pelvis
  - A **CT scan** uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally, intravenously, or rectally (less likely). Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. A rectal contrast fills up the loops of your lower bowel so the doctors can see your tumor better. After you have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the Radiology Department and takes about half an hour.

  - An **MRI scan** takes an image of your head or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). Gadolinium is contrast material that causes some tumors to appear much brighter than normal tissue on MRI scans (these tumors may not be visible without gadolinium). The contrast material may be given to you in your arm through an intravenous catheter (a tiny tube inserted into a vein). You will then lie down on a narrow bed which will be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will lie there quietly for about one hour, during which time you will hear a loud machine-like noise. The MRI scan is done in the Radiology Department and takes approximately an hour and a half to complete.

The following procedures will be done for research purposes:

- Tumor biopsy
    - As part of this study, we will obtain a small piece of tumor tissue using a special needle. This procedure will be done at the site where we can most easily get a piece of the tumor and the biopsy can involve the lungs, liver, bone, lymph node, 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. The tissue biopsy is used to confirm your diagnosis and make sure you are eligible to be in this research study. The tissue is also being used to help us determine if certain types of tumors might respond better to certain treatments. This procedure takes about 30 minutes. You will sign a separate consent form for this procedure.

- Review of your medications (both prescription and over-the-counter) and side effects.

- Blood draw (approximately 2-3 tablespoons)
    - Pharmacokinetics (PK) - These are blood tests that will help determine the levels of study drug in your blood at different time points.
    - Test your thyroid hormone levels
    - Assays to monitor immune suppression

- ECOG performance status (Questions about how your disease is affecting your daily life).

During the main part of the study

This study will have three different treatment options which are referred to as **Arm A, Arm B**, and Arm C. You will be randomized to one of these treatment arms. Randomization means that you are put into a group by chance. A computer program will place you in one of the groups. Neither you nor your study doctor can choose the group you will be in. You will have an equal chance of being placed in any of the groups.

Arm A involves treatment with a daily oral dose of 20mg tamoxifen and oral dose of 400mg of vorinostat which you take for 5 days of a seven day week. The study drug pembrolizumab will administered to you intravenously in clinic starting cycle 1 and subsequent cycles.

Arm B involves treatment with a daily oral dose of 20mg tamoxifen and oral dose of 400mg of vorinostat which you take for 5 days of a seven day week. The study drug pembrolizumab will administered to you intravenously in clinic starting cycle 2 and subsequent cycles.

Arm C involves treatment with a daily oral dose of 400mg of vorinostat which you take for 5 days of a seven day week. The study drug pembrolizumab will administered to you intravenously in clinic starting cycle 2 and subsequent cycles.

The study drugs will be given to you in 'cycles.' Each cycle is 21 days or 3 weeks.

Treatment Period

You will need the following tests and procedures. Each of the following study visits will take about 2 hours.

Cycle 1, Day 1
This visit will take about 2 hours

- Physical examination
- Medical history
- Blood draw (approximately 2-3 tablespoons)
    - Complete blood count (CBC) with differential and platelet count
      Comprehensive metabolic panel
    - Blood chemistry assessment

The following procedures will be done for research purposes:

- Review of the medications you are currently taking
- Review of side effects
- Tumor biopsy – if not done at the time of screening
- Blood draw (approximately 2-3 tablespoons) – if not done at the time of screening
    - PK Sampling
    - Assays to monitor immune suppression – if not done at the time of screening
- ECOG

Cycle 1 Day 10 to 12
This visit will take about 1 hour

- Blood draw PK Samples (approximately 1 tablespoon)

Cycle 1 Day 8 and Day 15
This visit will take about 2 hours

- History and physical examination
- Vital signs
- Blood draw (approximately 1-2 tablespoons)
    - Routine safety tests including:
        - Complete blood count (CBC) with differential and platelet count
        - Blood chemistry assessment

The following procedures will be done for research purposes:

- Review of the medications you are currently taking
- Review of side effects
- Blood draw (approximately 1 tablespoon) – *Day 15 only*
    - Assays to monitor immune suppression

- ECOG

Cycle 2 Day 1
This visit will take about 2 hours

- History and physical examination
- Vital signs
- Blood draw (approximately 1-2 tablespoons)
  - Complete blood count (CBC) with differential and platelet count
  - Blood chemistry assessment

The following procedures will be done for research purposes:

- Review of the medications you are currently taking
- Review of side effects
- Administration of pembrolizumab for study participants in Arm B (see pg 4 'During the main part of the study' for schedule')
- Blood draw (approximately 1 tablespoon)
  - Test your thyroid hormone levels
- ECOG

Cycle 3 Day 1 and every subsequent cycles +/- 5 days
This visit will take about 2 hours

- History and physical examination
- Vital signs
- Blood draw (approximately 1-2 tablespoons)
  - Complete blood count (CBC) with differential and platelet count
  - Blood chemistry assessment
- You will have a CT scan or MRI (also cycles 6, 9 and 12 and then (and then every 6 cycles if clinically indicated)

The following procedures will be done for research purposes:

- Review of the medications you are currently taking
- Review of side effects
- Administration of pembrolizumab for study participants in Arm A and B (see page 4, During the main part of the study for schedule)
- Blood draw (approximately 2-3 tablespoons)
  - PK sampling
  - Test your thyroid hormone levels (every odd cycle)
- ECOG
- Pregnancy test, if clinically indicated

Cycle 3 Day 17 to 19
This visit will take about 2 hours

- Blood draw samples (approximately 3 tablespoon)
- Repeat tissue biopsy

Post treatment follow-up

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

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

HOW LONG WILL I BE IN THE STUDY?

You will receive treatment as long as your disease is not getting worse and you do not have any bad side effects. If treatment is stopped or you withdraw from treatment, you will be followed until any side effects from treatment have resolved.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely. The study doctor may ask to do some end-of-study tests.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug combination 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, if the study is stopped, or for any other reason.

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 combination. 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.

Risks associated with pembrolizumab

As of 03-September-2016, pembrolizumab had been given to about 21,036 subjects with various cancers in clinical trials. Men and women with cancer were treated, some for up to approximately 2 years. Safety was studied across several cancers treated with different doses: 2 mg/kg every 3 weeks, and 10 mg/kg every 2 or 3 weeks. The side effects seen were similar.

Very common side effects seen in more than 20% or more of patients, some may be serious (i.e. causing hospitalization, life-threatening or where noted, may cause death):

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

Common side effects seen in 5% to less than 20% of patients, some may be serious (i.e. causing hospitalization, life-threatening or where noted, may cause death):

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

Less common side effects seen in 1% to less than 5% of patients, some may be serious (i.e. causing hospitalization, life-threatening or where noted, may cause death):

- 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 or tired, tremble, sweat, have loose or 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 stomach with loose or watery stools and black, tarry, sticky stools or stools with blood or mucus

- Inflammation of the skin which may cause 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 side effects seen in less than 1% of patients, some may be serious (i.e. causing hospitalization, life-threatening or where noted, may cause death):

- Inflammation of the bowels/gut so you may feel stomach pain with loose or watery stools
- Inflammation of the nerves that may cause pain, weakness or tingling in the hands and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or pain in the 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 the back, 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, headaches, or see floaters
- 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 stomach, 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 behavior, double vision, few to no menstrual cycles, weakness, vomiting, 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 and muscle and stomach 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 (myocarditis) 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 (myasthenic syndrome).
- 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 (encephalitis). This may also include: disorientation, memory problems, seizures, changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness

In addition to the above, **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.

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.

Risks associated with vorinostat:

Very common (experienced by 10% of patients or more):

- Fatigue
- Diarrhea
- Nausea
- Taste changes
- Increased blood glucose level (hyperglycemia)
- Increased creatinine level (transient)
- Increased level of protein in the urine
- Low platelet count (thrombocytopenia)

Common (experienced by between 1% and less than 10% of patients)

- Loss of appetite (anorexia)
- Weight loss
- Muscle spasms
- Hair loss (alopecia)
- Dry mouth
- Chills
- Fever
- Vomiting
- Dizziness
- Constipation
- Low red blood cell count (anemia)
- Headache
- Itching

- Swelling in hands or feet
- Cough
- Upper respiratory infection
- Dehydration
- Shortness of breath

Uncommon (experienced by less than 1% of patients):

A rare, but serious side effect of vorinostat is blood clots, including deep vein thrombosis (DVT) and pulmonary embolus. You should seek emergency help and notify your health care provider immediately if you develop sudden chest pain and shortness of breath. Notify your health care provider within 24 hours if you notice that one leg is swollen, red, painful and/or warm to touch and the other is not.

Risks associated with tamoxifen

Risks for tamoxifen can also be obtained from the package insert available for the drug.

Side effects you may experience from tamoxifen listed are:

Likely (side effects occurring in at least 20% of subjects):
- Hot flushes
- Nausea and vomiting
- Fatigue
- Vaginal discharge

Less likely (side effects occurring in 10-20% of subjects):
- Blood clots
- Changes in vision
- Changes in liver functions

Uncommon (side effects occurring in less than or equal to 2% of subjects):
- Cancer of the uterus

Other study related risks include:

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

- **IV line risks:** may cause discomfort, irritation, mild bruising, bleeding, leakage of drug solution, and rarely, infection, nausea, and lightheadedness. Because pembrolizumab is an antibody, there is the possibility that you may experience an acute infusion reaction. These are side effects that develop during or immediately after the administration of pembrolizumab. Signs and symptoms may include:
    - Blood pressure changes (increase or decrease)
    - Headache

- Cough
- Dizziness
- Fast heart beat
- Feeling cold
- Feeling that the tongue is swelling or your airway is closing and you have trouble breathing
- Fever
- Joint pains
- Muscle pains
- Nausea
- Rash, hives, or itching
- Shortness of breath
- Sweating
- Tiredness
- Vomiting

- **Electrocardiogram (EKG/ECG) risks:** The ECG involves placing electrodes on the skin. You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own. Please let your doctor know if you are aware of any allergies.

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

- **Bone scan risks:** Bone scan side effects are not common, and when encountered are usually mild, such as nausea and vomiting, or you may become uncomfortable lying still for the duration of the examination. The bone scan involves an injection, in the vein of your arm, of a radiotracer (radioactive compound that localizes in the bone). The injection of the radiotracer may feel like a small sting and there may be possible bruising at the injection site. You will be exposed to a limited and medically acceptable dose of radiation during the procedure. There is always a slight risk of damage from being exposed to any radiation.

- **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 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.

- **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 pocket knives or key chains, are not allowed in the MRI room. If you have a piece

of metal in your body, such as a fragment in 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 ear plugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a 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: 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 reIquire 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.

- **Study Drug Combination**: The side effects of the combination of pembrolizumab with vorinostat and tamoxifen are not yet known. It is possible that this combination of drugs will cause new or more serious side effects than taking these drugs separately. You will be monitored closely for side effects and your doctor may change your medications if it appears that this combination is causing serious side effects. You should tell your doctor about any side

effects you experience while on this study. When additional information about side effects is known, you will be notified of any further study drug related effects.

- **Reproductive Risks:** You should not become pregnant 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.
- **Female:**
- It is not known if the study drug(s) may affect an unborn or nursing baby. If you are pregnant, trying to become pregnant or breast-feeding, you may not be in the study. The study doctor will perform a blood or urine pregnancy test before the start of and during the study, if you are able to have a baby.

If you are able to have a baby, you must avoid having sex (abstinence) or use reliable birth control methods during the study and for a period of 120 days after your last dose of pembrolizumab. The following birth control methods are allowed during the study as per local regulations or guidelines:

Two (2) of the following barrier methods in combination:

- Diaphragm
- Condom
- Copper intrauterine device (IUD)
- Contraceptive sponge
- Spermicide

OR

One (1) of the above barrier methods in combination with:

- Hormonal contraceptives (including oral, subcutaneous, intrauterine, or intramuscular) that are registered and marketed containing estrogen and/or a progestational agent

If you become pregnant during the study you must notify the study doctor right away. The study drug will be stopped and you will be taken out of the study.

Male:
There may be risks if you are male and your partner is pregnant or trying to become pregnant. If you are male and 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 for a

period of 120 days after your last dose of study drug pembrolizumab. The following birth control methods are allowed during the study:

Two (2) of the following barrier methods in combination:

- Diaphragm
- Condom
- Copper intrauterine device (IUD)
- Contraceptive sponge
-

OR

One (1) of the above barrier methods in combination with:

- Hormonal contraceptives (including oral, subcutaneous, intrauterine, or intramuscular) that are registered and marketed containing estrogen and/or a progestational agent

If your partner becomes pregnant during the study you must notify the study doctor right away. If your partner is already pregnant when you begin the study you must use a condom (male) during the study and for a period of 120 days after your last dose of pembrolizumab. You must also agree to not donate sperm during the study and for a period of 120 days after your last dose of study drug.

- **Randomization Risks:** You will 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. 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?

Taking part in this study may or may not make your health better. While doctors hope the study drug combinations will be more useful against cancer compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about the study drug combinations as a treatment for cancer. This information could help future cancer patients.

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.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

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

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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

- The study sponsor (Merck & co) or its representatives, including companies it hires to provide study-related services
- Researchers who are conducting this study at other research sites
- Food and Drug Administration (FDA), National Cancer Institute (NCI), or other government agencies involved in keeping research safe for people
- The University of California

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

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

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

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

Pembrolizumab and vorinostat, will be provided free of charge while you are participating in this study. However, the pembrolizumab infusion , and certain other procedures associated with the administration of other drugs are considered routine care and will be billed to your insurance.

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

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

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

WILL I BE PAID FOR TAKING PART IN THIS STUDY?

You will not be paid for taking part in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, Pamela Munster, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call her [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 & Co depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415- 476-1814.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

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

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

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

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s) Pamela Munster [redacted].

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814

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

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

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

What will happen if I agree to donate my specimens?

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

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

What risks are involved with donating specimens for research?

- Any extra blood we take will come through already scheduled blood draws done during this study, and should not cause you any added risk, discomfort, or pain beyond what we normally expect from blood draws.
- Confidentiality: Donating 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. Your name will not be used in any published reports from research performed using your specimen. The study doctor, Pamela Munster, MD and select tissue bank staff members will have access to information about you but they will not release any identifying information about you to researchers using your specimen. The UCSF Committee on Human Research and other University of California personnel also may see information about you to check on the tissue bank.

Things to Think About

The choice to let us keep the left over 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 tissue can be kept for research, you can change your mind at any time. Just contact the study doctor Pamela Munster, M.D at the address below, and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research.

Pamela Munster, M.D.
University of California, San Francisco
[redacted]
San Francisco, CA 94143[redacted]

Participation in this optional research is voluntary, and if you choose not to allow the tumor tissue samples to be collected for research or to use your blood for future tests, it will in no way affect your care or participation in the main study.

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

The results from these tests will not have any effect on your treatment.

_____ *I **do** allow for previously collected tissue to be collected and used for*
Initials *the research purposes as described above.*

_____ *I **do not** allow for previously collected tissue to be collected and used*
Initials *research purposes as described above.*

Additional blood - If you provide your consent, additional blood taken during your study blood draws will be collected. The blood will be sent to a laboratory where it will be stored and tests will be performed. Researchers will be performing tests that may provide additional information that may be helpful in understanding your response to pembrolizumab and vorinostat, and for future research about breast cancer**.**

The results from these tests will not have any effect on your treatment.

_____ *I **do** allow additional blood to be collected and used for the research purposes*
Initials *described above.*

_____ *I **do not** allow additional blood to be collected and used for the research*
Initials *purposes as described above.*

CONSENT

You will be 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.

By signing below, you agree that you have read or have been read this consent form and that you have had the chance to ask questions and they have been answered.

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

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