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

Study Title: Epigenetic priming for Immune therapy in ER-positive breast cancer in biomarker select population

Principal Investigator:	Pamela N. Munster, MD Professor, Department of Medicine University of California San Francisco [redacted] San Francisco, CA [redacted] Telephone: [redacted]

This is a clinical research study. Your study doctor(s) Pamela Munster, MD from the UCSF Department of Medicine (Hematology/Oncology), will explain the study to you.

STUDY SUMMARY

Introduction: We are asking you to consider taking part in a research study being done by Dr. Munster at UCSF. You are being asked to take part in this study because you have stage IV estrogen-receptor positive (ER+) breast cancer.

The first part of this consent form gives you a summary of this study. We will give you more details about the study later in this form. The study team will also explain the study to you and answer any questions you have.

Research studies include only people who choose to take part. It is your choice whether or not you want to take part in this study. Please take your time to make a decision about participating. You can discuss your decision with your family, friends and health care team.

Purpose of the study: The researchers want to find whether a certain drug combination is better than another to control stage IV estrogen-receptor positive (ER+) breast cancer. This study will find out what effects, good and/or bad, pembrolizumab and tamoxifen and, for some individuals, vorinostat, have on patients and their breast cancer.

Study Procedures: If you choose to be in this study, you will be randomly assigned to one of two groups. One group will be asked to take one study drug daily for as long as their cancer does not get worse or progress. The other group will be asked to take two study drugs daily for as long as their cancer does not get worse or progress. In addition, everyone in this study, - regardless of their group - will need to come into UCSF Cancer Center for infusions of an additional study drug every 3 weeks for 30 minutes. Also, the

main study procedures include a physical exam, blood tests, CT scan, and tumor biopsy.

You will visit the research site approximately 7 times for each 9 week period (or for each 3 cycles). You will be in this study for about as long as your cancer does not get worse or progress.

Possible Risks: There are risks to taking part in a research study. Some of the most likely risks of participation in this study include:

- Cough
- Diarrhea
- Fatigue
- Hot flushes
- Itching of the skin
- Nausea

There are also rare but serious risks of participation, like:

- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss.
- Blood clots, including deep vein thrombosis (DVT) and pulmonary embolus.
- Cancer of the uterus

We'll tell you about the other risks later in this consent form.

Possible Benefits: You may benefit from participating in the study, but this cannot be guaranteed.

Your Other Options: You do not have to participate in this study. Your other choices may include:

- Getting treatment or care for your condition without being in a study.
- Taking part in another study.
- Getting no treatment or receiving comfort care to relieve your symptoms and discomfort.

Please talk to your doctor about your choices before agreeing to participate in this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the study. If you join this study, we will give you a signed copy of this form to keep for future reference.

DETAILED STUDY INFORMATION

This part of the consent form gives you more detailed information about what the study involves.

You are being asked to take part in this study because you have stage IV estrogen-receptor positive (ER+) breast cancer.

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. There are 3 study drugs: pembrolizumab, vorinostat, and tamoxifen. Depending on which arm you are randomly selected to be in, you will receive a different combination of the study drugs.

Pembrolizumab is an investigational drug. This means pembrolizumab, while approved for other types of cancer, 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 and 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.

Vorinostat is an investigational drug. This means vorinostat has not been approved by the U.S. FDA for use in 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.

Pembrolizumab and vorinostat are therefore both investigational drugs in this study.

Tamoxifen is an anti-hormonal drug that is U.S. FDA-approved to treat advanced breast cancer.

The purpose of this study is to:

- Find a drug combination to better control stage IV ER+ breast cancer and reduce the number of pills you take. This study will find out what effects, good and/or bad, pembrolizumab, vorinostat, and tamoxifen have on you and your stage IV ER+ breast cancer.

Merck, the manufacturer of pembrolizumab and vorinostat, is supplying pembrolizumab and vorinostat at no cost to study participants, and is providing funding to UCSF for this study.

How many people will take part in this study?

About 65 people will take part in this study.

About 35 people will be enrolled in Arm A, which will receive a combination of pembrolizumab, vorinostat, and tamoxifen.

About 30 people will be enrolled in Arm B, which will receive a combination of pembrolizumab and tamoxifen.

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

Before you begin the main part of the study:

You will need to have the following tests and procedures to find out if you can be in the main part of the study. Some of these tests and procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Clinical Assessments
  - You will have a physical examination that will include an assessment of vital signs, general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.
  - You will be asked how well you perform activities of daily living, like dressing yourself and getting out of bed.
  - You will be asked about your medical history, including history of prior treatments and any side effects related to prior treatment.
  - You will be asked what medications you are taking, including over-the-counter medicines, vitamins, or herbal treatments.
  - You will be asked about any side effects from your cancer or any prior treatments

- Laboratory Assessments
  - About 2 tablespoons of blood will be drawn by inserting a needle into a vein.
    - About 1 tablespoon of blood will be used for safety testing.
    - About 1 tablespoon of blood will be used for research biomarker testing. Biomarkers are substances in your tissues that may provide information on any changes to your genes or DNA, how your cancer cells are responding to study treatment and whether your cells are becoming resistant (no longer responding) to the study treatment.
  - If you are a woman of childbearing age, a blood test (less than ½ tsp) will be done to see if you are pregnant. (or at Cycle 1 Day 1)

- Imaging Procedures
  - You will have either a CT scan or an MRI scan of the breast. Whichever scan you have performed at screening, you will have performed throughout the remainder of the study.
  - **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.
  - **MRI SCAN (if CT scan is not advised):** 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.

- Tissue Collection
  - **FINE NEEDLE ASPIRATION (FNA)** (or at Cycle 1 Day 1)**:** This is a special type of biopsy. The doctor will insert a fine (very thin) needle through your skin and into your tumor and will remove a very small sample (less than ½ a teaspoon) of your tumor. Either an ultrasound or CT scan will be used to guide the placement of the needle. You will sign a separate consent form for this procedure. This procedure will take about 15-30 minutes.

During the main part of the study:

If the tests and procedures show that you can be in the main part of the study, and you choose to take part, then you will be "randomized" into one of the study arms described below. Randomization means that you are put into an arm by chance. A computer program will place you in one of the arms. Neither you nor your doctor can choose the arm you will be in. You will have an equal chance of being placed in any arm.

- **If you are in Arm A, you will receive a combination of pembrolizumab, vorinostat, and tamoxifen**
- **If you are in Arm B, you will receive a combination of pembrolizumab and tamoxifen**

Pembrolizumab

- Pembrolizumab is given through the vein every 3 weeks of the 21-day cycle.
- Please see last page of consent for complete List of Prohibited Medications.

Vorinostat (if you are randomly selected to be in Arm A)

- Vorinostat is taken by mouth once a day for 4 days and then not taken for 3 days, weekly, every 21-day cycle.
    - We will ask you to keep a pill diary. In this diary, you will write the date, the time and the number of pills you take, and any new side effects you have. A side effect is an unwanted response to a medicine. If you miss any pills, you should also write that in the diary. Your study nurse will give you complete directions for how to keep the diary. This should take about 1-2 minutes each week and will be collected by the study nurse at your clinic visits.
- Please see last page of consent for complete List of Prohibited Medications.

Tamoxifen

- Tamoxifen is taken by mouth once a day every day of the 21-day cycle.
    - We will ask you to keep a pill diary. In this diary, you will write the date, the time and the number of pills you take, and any new side effects you have. A side effect is an unwanted response to a medicine. If you miss any pills, you should also write that in the diary. Your study nurse will give you complete directions for how to keep the diary. This should take about 1-2 minutes each week and will be collected by the study nurse at your clinic visits.
- Please see last page of consent for complete List of Prohibited Medications.

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

Cycle 1, Day 1

- Study Treatment/Drug Administration
  - You will receive pembrolizumab through a vein at UCSF.
  - You will be given enough vorinostat capsules to last you until your C2D1 (if you are randomly selected to be in Arm A). Each week you will take vorinostat for 4 days and then not take it for 3 days.
    - You will be given a pill diary for vorinostat.
  - You will begin taking tamoxifen. Tamoxifen will be prescribed by your study doctor and can be picked up at your normal pharmacy.
    - You will be given a pill diary for tamoxifen.
- Clinical Assessments
  - You will have a physical examination that will include an assessment of vital signs, general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.
  - You will be asked how well you perform activities of daily living, like dressing yourself and getting out of bed.
  - You will be asked what medications you are taking, including over-the-counter medicines, vitamins, or herbal treatments.
  - You will be asked about any side effects you're having.
- Laboratory Assessments
  - About 2 tablespoons of blood will be drawn by inserting a needle into a vein.
    - About 1 tablespoon of blood will be used for safety testing.
    - About 1 tablespoon of blood will be drawn by inserting a needle into a vein to be used for research biomarker testing.
- Tumor Tissue Collection
  - You will have a biopsy of your tumor tissue (fine needle aspiration) if you did not have one at screening.

Cycle 1, Day 10-12

- Laboratory Assessments
  - About 1 tablespoon of blood will be drawn by inserting a needle into a vein to be used for research biomarker testing.

Cycle 1, Day 15

- Clinical Assessments
  - You will have a physical examination that will include an assessment of vital signs, general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.
  - You will be asked how well you perform activities of daily living, like dressing yourself and getting out of bed.
  - You will be asked what medications you are taking, including over-the-counter medicines, vitamins, or herbal treatments.
  - You will be asked about any side effects you're having.
- Laboratory Assessments
  - About 1 tablespoon of blood will be drawn by inserting a needle into a vein to be used for safety testing.

Cycle 2, Day 1

- Study Treatment/Drug Administration
  - You will receive pembrolizumab through a vein at UCSF.
  - You will be given enough vorinostat capsules to last you until your C3D1 (if you are randomly selected to be in Arm A). Each week you will take vorinostat for 4 days and then not take it for 3 days.
  - You will be given a pill diary for vorinostat.
  - You will continue taking tamoxifen. Tamoxifen will be prescribed by your study doctor and can be picked up at your normal pharmacy.
    - You will be given a pill diary for tamoxifen.
- Clinical Assessments
  - You will have a physical examination that will include an assessment of vital signs, general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.
  - You will be asked how well you perform activities of daily living, like dressing yourself and getting out of bed.
  - You will be asked what medications you are taking, including over-the-counter medicines, vitamins, or herbal treatments.
  - You will be asked about any side effects you're having.

- Laboratory Assessments
  - About 1 tablespoon of blood will be drawn by inserting a needle into a vein to be used for safety testing.

Future Cycles (Day 1)

- Study Treatment/Drug Administration
  - You will receive pembrolizumab through a vein at UCSF.
  - You will be given enough vorinostat capsules to last you until the first day of your next cycle (if you are randomly selected to be in Arm A). Each week you will take vorinostat for 4 days and then not take it for 3 days.
  - You will be given a pill diary for vorinostat.
  - You will continue taking tamoxifen. Tamoxifen will be prescribed by your study doctor and can be picked up at your normal pharmacy.
    - You will be given a pill diary for tamoxifen.

- Clinical Assessments
  - You will have a physical examination that will include an assessment of vital signs, general appearance, skin, head and neck (including ears, eyes, nose and throat), respiratory, cardiovascular, abdomen, lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.
  - You will be asked how well you perform activities of daily living, like dressing yourself and getting out of bed.
  - You will be asked what medications you are taking, including over-the-counter medicines, vitamins, or herbal treatments.
  - You will be asked about any side effects you're having.

- Laboratory Assessments
  - About 2 tablespoons of blood will be drawn by inserting a needle into a vein.
    - About 1 tablespoon of blood will be used for safety testing.
    - About 1 tablespoon of blood will be used for research biomarker testing.
  - If you are a woman of childbearing age, a blood test (less than ½ tsp) will be done to see if you are pregnant.

- Imaging Procedures
  - You will have a CT scan or an MRI of the breast.

- Tumor Tissue Collection
  - You will have a biopsy of your tumor tissue (fine needle aspiration) at the end of Cycle 3.

When you are finished receiving pembrolizumab, vorinostat, and tamoxifen:

- Clinical Assessments
  - You will be asked about any side effects you're having.

- Imaging Procedures
  - You will have a CT scan or an MRI of the breast.

Study location:

All study procedures will be done at Helen Diller Family Comprehensive Cancer Center.

How long will I be in the study?

You will be asked to take pembrolizumab, vorinostat, and tamoxifen for as long as your cancer does not get worse or progress. After you are finished taking pembrolizumab, vorinostat, and tamoxifen, the study doctor will ask you to visit the office for follow-up exams for at least 9 weeks post-start of treatment. We would like to keep track of your medical condition for the rest of your life. We would like to do this by calling you on the telephone once every 3 months to see how you are doing. Keeping in touch with you and checking on your condition every 3 months helps us look at the long-term effects of the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. She will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the pembrolizumab, vorinostat, and tamoxifen 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 she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the pembrolizumab, vorinostat, and tamoxifen. 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 you experience while taking part in the study.

Pembrolizumab, which is approved in the USA and some other countries, is available by

prescription to treat several different cancers but may not be approved to treat your type of cancer.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.

Risks related to pembrolizumab

Very Common (out of 100 people, 20 or more people may have the following)

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

Common (out of 100 people, at least 5 but less than 20 people may have 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 (out of 100 people, 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 (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 (out of 100 people, 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 (Guillain-Barre 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, have 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 causes 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).

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.

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

Risks related to vorinostat

Likely (out of 100 people, 10 or more people may have the following)

- Feeling tired, tiredness, weakness.
- Diarrhea, which is frequent, loose watery stools, which can cause dehydration and may require hospitalization and treatment with intravenous fluids. Severe and prolonged diarrhea can be life-threatening.
- Feeling sick to the stomach
- Strange taste in the mouth.
- Excess sugar in the blood, if severe may require hospitalization and urgent treatment. (diabetes)
- Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine. This may mean that your kidneys are not functioning properly.
- Excess protein in the urine. This may cause fluid retention.
- Low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion.

Less Likely (out of 100 people, 1-9 people may have the following)

- Loss of appetite (anorexia)
- Weight loss
- Muscle spasms
- Hair loss (alopecia)
- Dry mouth
- Chills
- Fever
- Vomiting
- Dizziness
- Constipation

- Low number of red blood cells that can causes tiredness and shortness of breath. May require a blood transfusion.
- Headache
- Itching
- Swelling in hands or feet
- Cough
- Upper respiratory infection
- Dehydration
- Shortness of breath

Rare but serious

- 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 related to tamoxifen

Likely (out of 100 people, 20 or more people may have the following)

- Hot flushes
- Nausea and vomiting
- Fatigue
- Vaginal discharge

Less Likely (out of 100 people, 10-19 people may have the following)

- Blood clots
- Changes in vision
- Changes in liver functions

Rare but serious

- Cancer of the uterus

Risks related to Study Procedures

BLOOD DRAWS
The risks of drawing blood include temporary discomfort from the needle stick, bruising, and rarely, infection.

CT SCAN
CT scans involve the risks of radiation. In addition, if contrast material (iodine dye) is

used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. 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 with contrast. If you are taking metformin (or similar drugs by mouth to treat high blood sugar), such treatment will be stopped for 2-3 days around the time a scan is planned in order to avoid kidney side effects.

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

MRI SCAN

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 earplugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

Contrast agent (gadolinium) risks:

A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than 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 (FINE NEEDLE ASPIRATION – FNA)

The biopsy has small but serious risks. The general risks associated with this procedure are pain, discomfort, infection, and bleeding. 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.

DRUG INTERACTIONS

You must also review with your study doctor all of your medications (including supplements and herbal or natural substances) at every visit, as well as notify your study doctor before starting any new medications, supplements, or herbal treatments while participating in the study because there is a risk of serious interaction with some kinds medications. Please go over the “Medications and Foods to Avoid” list at the end of this form with your study doctor and keep it for your reference.

LOSS OF PRIVACY

There is a risk of loss of privacy. We will do our best to make sure that your personal information will be kept private. Your samples will be labeled with a code that cannot be used to identify you directly. The list that links your identity to the code on the sample will be kept separate from the samples. The researchers using your samples will never be given your identity. However, we cannot guarantee complete privacy.

RADIATION RISKS

This research study involves exposure to radiation. Not all this radiation exposure is necessary for your medical care and is for research purposes only. This amount of radiation may result in a very small increased risk of future cancer. However, the UCSF Radiation Safety Committee believes that this risk, given your overall medical condition, is acceptable. If you have any questions regarding the use of radiation or the risks involved, please consult your study doctor.

RANDOMIZATION
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.

REPRODUCTIVE
You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

RISK OF INADEQUATE TISSUE
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
The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

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

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope pembrolizumab, vorinostat, and tamoxifen 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 pembrolizumab, vorinostat, and tamoxifen 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.

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

How will my specimens and information be used?

Researchers will use your blood and tissue 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 cancer studies in the future. We will not share your name or any other personal information that would let the researchers know who you are. We will not ask you for additional permission to share the de-identified information and specimens.

Your blood and tissue 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 studies will not be returned to you and will not be put in your medical record. The research will not change the care you receive.

Researchers may use your blood and tissue specimens 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 specimens and data to be kept and used for future research. However, we hope we will learn something that will

contribute to the advancement of science and understanding of health and disease. If your specimens, the data or any new products, tests or discoveries that result from this research have potential commercial value, you will not share in any financial benefits.

If you decide later that you do not want your information to be used for future research, you can notify the investigator in writing at,

Pamela N. Munster, MD
Professor, Department of Medicine
University of California San Francisco
[redacted]

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

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records and may be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Authorized representatives from the following organizations may review your research data for the purpose of monitoring or managing the conduct of this study:

- Representatives of Merck & Co., Inc.
- Representatives of the University of California
- Representatives of the Food and Drug Administration (FDA)

Are there any costs to me for taking part in this study?

Merck will provide pembrolizumab and vorinostat at no cost to you.

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may

not cover all standard medical care costs if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer.

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, Dr. 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, 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 Institutional Review Board at 415-476-1814.

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

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

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

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

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s) Dr. Munster at 415-885-7810.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns

you may have about the study, please call the office of the Institutional Review Board at 415-476-1814.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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OPTIONAL RESEARCH PARTICIPATION

This section of the informed consent is about optional future contact of participants in the main study. You can still be in the main study even if you say "no" to allowing optional future contact.

Future Contact

We want to know if we may contact you in the future to see if you are interested in participating in other research studies.

If you agree and we contact you to tell you about a study, you have no obligation to actually participate in any study. You can decide when you are told about the study if you want to receive more information about the study. There would be a new consent process for that study.

If at any time you decide you no longer want to be contacted about future studies, please let us know by calling [redacted]

Making Your Choice

Please read the sentence below and mark your choice by putting your initials in the "Yes" or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at 415-476-1814.

No matter what you decide to do, it will not affect your care or your participation in the main study.

1. **Someone may contact me in the future about taking part in more research.**

YES	***NO***

CONSENT

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

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

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

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

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

LIST OF PROHIBITED MEDICATIONS

CC# 197520: Epigenetic priming for Immune therapy in ER-positive breast cancer in biomarker select population

The following is a list of medications to avoid while you are on this study. If you go to any clinic or medical visit, please take this list with you for the doctor's reference.

Before you begin treatment, Dr. Munster or one of her associates will review all medications you are taking. Make sure you talk with Dr. Munster before you start or stop taking any medications. This list contains only the most common drugs that are known to interact with the drugs used in this study. It is very important to discuss all medications that you are taking with your study doctor. This information will be reviewed at each study visit.

In addition to the listed medications, you should also avoid live vaccines including Zostavax, MMR (measles, mumps, rubella), but ultimately check with your provider.

The following is a list of prohibited drugs. You should not take these drugs while in this study.

Generic Name	Brand Names ®
BCG (Intravesical or vaccine) - ok if on ARM B	Theracys. TICE-BCG
BuPROPion	Wellbutrin
Cladribine - ok if on ARM B	Mavenclad
Conivaptan	Vaprisol
Dacomitinib	Vizimpro
Deferiprone - ok if on ARM B	Ferriprox
Dexamethasone	Prozac
Fludrocortisone	
FLUoxetine	Prozac
Hydrocortisone (topical is okay)	Cortef
Idelalisib	Zydelig
PARoxetine	Paxil
Methylprednisolone	Medrol
Ospemifene	Osphena
Prednisone	Deltisone
Tipranavir	Aptivus
Triamcinolone (topical, inhaled is ok)	Kenalog