Certification of Completion of the Informed Consent

IRB #

Title:

I have discussed the "Informed Consent for Participation in Research Activities" in its entirety for the above referenced research study, with the research participant listed below (or the research participant's legally authorized representative). During the review of the consent form, the possible benefits, risks and discomforts involved in his/her participation on the study, as well as potential alternatives were reviewed.

The research participant has been encouraged to ask questions, and all questions asked by the participant have been answered. The research participant affirmed that he/she has received all information that he/she desires at this time, and a copy of the signed consent form has been provided to the participant.

PRINTED NAME of Person Obtaining Informed (Consenter)	SIGNATURE	TITLE	DATE	TIME

ADULT INFORMED CONSENT

IRB #16058:
TITLE: Phase II Study of the Combination of Pembrolizumab, Endocrine Therapy and Palbociclib in Postmenopausal Patients with Newly Diagnosed Metastatic Estrogen Receptor Positive Breast Cancer

Protocol Version date: 02/01/2023

PRINCIPAL INVESTIGATOR: Joanne Mortimer, M.D.

24-HOUR TELEPHONE NUMBER: 626-256-HOPE (4673), Extension 85200
DAY TIME TELEPHONE NUMBER FROM THE HOURS OF 8:00 AM TO 5:00 PM: 626-256-HOPE (4673), Extension 89200

EXPERIMENTAL PARTICIPANT'S BILL OF RIGHTS

The rights below are the rights of every person who is asked to be in a research study, also known as an experiment or research study. As a research participant, you have the following rights:

1. To be told what the research study is trying to find out.
2. To be told what will happen to you and whether any of the procedures to be used are different from what would be used in standard practice.
3. To be told about the discomforts, side effects and risks of the things that will happen to you as part of the research study.
4. To be told if you can expect any benefit from participating in the research study.
5. To be told of the other choices you have and how they may be better or worse than being in the research study.
6. To be told what medical treatment is available if any complications arise.
7. To be allowed to ask any questions concerning the research study, both before agreeing to be in the study and during the course of the study.
8. To refuse to participate in the research study or to change your mind about participation after the study is started. To be informed that this decision will not affect your right to receive the care you would receive if you were not in the study.
9. To receive a copy of the signed and dated research study consent form.
10. To be free of pressure when considering whether you wish to agree to be in the research study.

ADULT INFORMED CONSENT

IRB # 16058: TITLE: Phase II Study of the Combination of Pembrolizumab, Endocrine Therapy and Palbociclib in Postmenopausal Patients with Newly Diagnosed Metastatic Estrogen Receptor Positive Breast Cancer
PRINCIPAL INVESTIGATOR: Joanne Mortimer, M.D.

You are invited to take part in a clinical trial, a type of research study, because you have been newly diagnosed with metastatic estrogen receptor positive breast cancer, and have not previously had combination therapy with endocrine therapy (letrozole or fulvestrant) and Palbociclib. We hope to learn if adding the drug pembrolizumab with the endocrine drugs (Letrozole or fulvestrant) and Palbociclib will improve response to treatment.

This research study is sponsored by the City of Hope. Merck & Company is the company that makes pembrolizumab. Both City of Hope and Merck & Company provide funding to cover the costs of conducting this study.

This trial will study an additional 25 people. Previously, it has enrolled 22 people on other treatment groups (cohorts 1 and 2). The new group (cohort 3) will be started on palbociclib (3 weeks on 1 week off, starting day -28) and letrozole (daily) or fulvestrant (days -28, -14) for the first 28 days prior to adding pembrolizumab on day 1 of cycle 1.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future. Please take as much time as you need to read the consent form. If you find any of the language difficult to understand, please ask questions. If you decide to participate, you will be asked to sign this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

A. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a trial, which tests the safety of an investigational (experimental) intervention and also tries to define the appropriate dose of the investigational intervention to use for further studies. "Investigational" means that the intervention is being studied.

The current study is designed to test the safety and side effects of adding pembrolizumab to endocrine therapy (letrozole or fulvestrant) and palbociclib in patients who have metastatic estrogen receptor positive breast cancer. The goal of the study is to learn if using these 3 drugs together gets better results than we typically see from using the 2 drugs without pembrolizumab.

All four drugs have been approved by FDA for treating cancer, but this is the first study that combines pembrolizumab with endocrine therapy (Letrozole or fulvestrant) and Palbociclib.

What is known about this study drug?

Pembrolizumab (approved in USA and several other countries) is available by prescription to treat certain cancers, including malignant melanoma (a type of skin cancer), head and neck squamous cell carcinoma, and non-small cell lung cancer that has spread to other parts of a patient's body. Other trials are studying pembrolizumab for the treatment of more than 30 types of cancer, as a single therapy or in combination with other therapies, to see if it is effective and what side effects are associated with its use. As of 03-Sep-2016, pembrolizumab had been given to about 21,036 men and women with various cancers in clinical trials, for as long as 2 years. Safety was studied across several cancers treated with different doses of pembrolizumab: 2 mg/kg every 3 weeks, 10 mg/kg every 2 or 3 weeks, and 200 mg fixed dose every 3 weeks. The side effects seen were similar.

Letrozole (or Fulvestrant) and Palbociclib are a type of treatment called endocrine therapy. Endocrine therapy is the most effective treatment for estrogen receptor positive breast cancer. The combination of letrozole (or Fulvestrant) and palbociclib is the current standard of care for treatment of newly diagnosed metastatic breast cancer patients.

B. WHAT IS INVOLVED IN THE STUDY?

If you decide to take part, this is what will happen:

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Demographics,** which include personal information such as name, date of birth, gender, and race.
- **Physical Exam,** a complete physical exam will include an evaluation of your head, neck, abdominal area, hair, nails, and limbs. The study doctor will also listen to your heart and lungs. Your vital signs (heart rate, blood pressure and body temperature), height and weight will also be measured and recorded.
- **Menopausal status**, which evaluates whether you are able to have children.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.

- **Pregnancy test** if you are a woman of childbearing potential by drawing about ½ teaspoon of blood usually from a vein in your arm.
- **Blood tests** to check your blood counts and organ function (about 2 teaspoons) of blood will be drawn from a vein in your arm
- **Stool sample collection,** a stool sample collection kit will be provided with detailed instruction. The test will identify the make-up of bacteria in one's gut. Stool sample must be collected within Day-28 to C1D1 (baseline) before starting treatment on study.
- **12-Lead Electrocardiogram (ECG),** An ECG measures the natural electrical activity of the heart. Having an ECG requires placement of electrical sensors on your chest near your heart, on your wrists and on your ankles.
- **Tumor Biopsy,** to confirm your diagnosis and to assess PD-L1 expression (biomarker)
- **An assessment of your tumor** by one or more of the following standard assessment tools: X-ray, CT (Computerized Tomography) scan or MRI (Magnetic Resonance Imaging) or
- **Brain scan,** only for those patients with known brain metastasis
- **Blood tests (correlative studies)** for research purposes to assess biomarkers (about 6 teaspoons of blood will be drawn from a vein in your arm)

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Study Procedures:

If you are eligible to participate in this research study, the following test and procedures will occur. A chart summarizing the timing of these tests and procedures is also provided below. Some tests and procedures may be part of your standard of care.

- **Infused Study Drug:** You will be given the study drug pembrolizumab 200mg once every 3 weeks (21 days) into your vein (by intravenous infusion) over about 30 minutes. This treatment will continue as long as you are responding or as long as your condition is stable.
- **Endocrine Therapy Drugs:** You and your treating physician will have the choice of using letrozole (an oral drug) or fulvestrant (an injectable drug given intra-muscularly, administered by entering a muscle) as endocrine therapy to combine with palbociclib. Each treatment cycle lasts 3 weeks (21 days) which is defined by pembrolizumab cycles. Letrozole (2.5mg) will be given daily by mouth every 4 weeks. Palbociclib will be given daily for 3 weeks by mouth with no doses on the 4th week. Fulvestrant will be given at 500mg as intramuscular injections on day -28, day -14 and day 1 (every 2 weeks for 3 doses) followed by every 4 weeks dosing. This treatment will continue until your condition worsens or your cancer continues to grow or spread.

- **Clinical Exams:** During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Vital signs and weight**
- **Performance status**, which evaluates how you are able to perform your daily usual activities.
- **Blood tests**
    - **Blood tests** to check your blood counts and organ function (about 2 teaspoons of blood per blood draw will be drawn from a vein in your arm)
    - **Blood tests** for research purposes to assess biomarkers (about 6 teaspoons of blood per blood draw will be drawn from a vein in your arm)
- **Stool test to** identify the make-up of bacteria in one's gut. Stool sample collection kit will be provided. Sample will be collected at 12 weeks and end of the study.
- **Scans (or Imaging tests):** We will assess your tumor by CT Scan, bone scan. MRI may also be used.
- **Tumor biopsies:** A tumor biopsy will be performed on cycle 2 day 1 (+/- 7 days) and another tumor biopsy will be performed at the end of the study to assess disease status and how your cancer is responding to treatment. Additional optional tumor biopsies during the study treatment are allowed.
- **Other Medications**: You may be pre-medicated with drugs, as necessary, to reduce the chance of having a sensitivity reaction to the study treatment. If you tolerate the study treatment without a reaction, then pre-medications may be changed by your doctor.

  Prohibited Medications/Herbs/Food: While you are receiving study treatment, you should not take other medications without first discussing them with the study doctor. These include:

  - Anti-cancer chemotherapy
  - Vaccines
  - Herbal supplements
  - Glucocorticoids such as (but not limited to): Dexamethasone, Prednisolone, Prednisone, Methylprednisolone, Hydrocortisone
  - Others – Please discuss any medications you are taking with your study doctor

  While you are receiving treatment, you should not eat grapefruit or drink grapefruit juice. The reason you should not take other medications is that they may interfere with the study medication.

End of Treatment: Treatment will continue if you are responding to the treatment or as long as your condition is stable. Treatment will be discontinued for any of the following reasons:

- You choose to withdraw from the study
- Your condition worsens
- You experience unacceptable side effects
- You acquire another illness that prevents further administration of the treatment
- Your doctor feels it is in your best interest
- You have a confirmed positive pregnancy test or become pregnant
- You do not comply with the treatment regimen or study procedures

Research Study Calendar:

	Screening	Treatment Cycles								End of Treatment	Post-Treatment		
		1	2	3	4	5	6	7	8	Discontinuation	Safety Follow-up	Follow Up Visits	Survival Follow-up
Medical History & Demographics	X												
Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Physical Exam		X	X	X	X	X	X	X	X				
Vital signs / Weight	X	X	X	X	X	X	X	X	X				
Review for any side effects	X	X	X	X	X	X	X	X	X	X	X		
Menopausal Status	X												
Performance Status	X	X	X	X	X	X	X	X	X	X			
Pregnancy Test	X												
Blood Test	X	X	X	X	X	X	X	X	X	X	X		
Stool test	X					X				X			
ECG	X												
Tumor Imaging Scans	X				X				X	X			
Brain Imaging Scans	X				X				X	X			
Tumor Biopsy * (standard of care)	X		X							X			
Blood collection for research studies**	X		X	X	X		X	X		X	X		
Receive study drug pembrolizumab		X	X	X	X	X	X	X	X				
Receive Palbociclib***		X	X	X	X	X	X	X	X				
Receive Letrozole/ or Fulvestrant***		X	X	X	X	X	X	X	X				
Post-study anti-cancer therapy status												X	X
Survival status													X

* For cohort 1&2, we will obtain biopsies of tumor tissue(s) prior to study initiation and at the end of study. Optional on-treatment biopsies are allowed for assessment of immune response.

For Cohort 3, baseline (screening), Cycle 2 Day 1(+/- 7 days) on treatment and optional end of treatment biopsy will be acquired.

** Optional peripheral blood or biopsy sample can be taken if research participant was off trial due to reasons other than disease progression

***For Cohort 3, research participants will receive palbociclib and endocrine therapy (letrozole or fulvestrant) starting day-28. Palbociclib will be given 3 weeks on 1 week off. Fulvestrant dose 500mg on day -28 and day -14. On cycle 1 day 1, pembrolizumab will be added to the combination of palbociclib and endocrine therapy.

Planned Follow-up:

After you have completed study treatment, you will be asked to return to in 30 days so that we may assess for any side effects. Additionally, we will want you to return to the clinic every 6 months for the next 3 years, followed by a final visit 1 year later.

Keeping in touch with you and checking your condition every year helps us look at the long-term effects of the research study.

C. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this research study for approximately 3 years.

D. WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

There are risks to taking part in any research study. One risk is that you will not benefit from this combination of study drugs or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. You will be monitored closely for any severe, life-threatening side effects listed below. Some of these side effects may be permanent. Appropriate medical care will be provided, if necessary, including additional treatment, hospitalization, and/or surgery.

Possible risks and discomforts you could experience during this study include: **Risks associated with the Palbociclib**

You may experience risks or discomforts when taking part in this study, which include some that are common such as low blood cell counts, infections, gastrointestinal (stomach and intestines) symptoms, fever, and fatigue; some that are rare, such as life-threatening infections and sepsis; and some that are unknown at this time. This is not a complete list of risks or discomforts. A comprehensive list of risks and discomforts is provided below.

Commonly Occurring Side Effects (greater than 30 in 100 research participants) with Palbociclib

- Decreases in neutrophil blood cells (may increase the risk for infection)
- Decreases in white blood cells (infection fighting cells)
- Infections
- Fatigue

Commonly Occurring Side Effects (10 to 30 in 100 research participants) with Palbociclib

- Decreases in hemoglobin (may cause weakness)
- Decreases in platelets (may cause bleeding and/or bruising)
- Inflammation of the mouth
- Diarrhea, constipation, nausea, vomiting
- Joint pain, back pain, pain in hands and feet
- Hair loss
- Rash
- Cough, shortness of breath
- Headache, dizziness
- Decreased appetite
- Hot flash, insomnia (inability to sleep)
- Fever
- Common cold

Occasional Side Effects (5 to 10 in 100 research participants) with Palbociclib

- Fever with low levels of white blood cells that help fight infection (neutrophils) with a fever
- Heart palpitations
- Blurred vision
- Inflammation of the eye (conjunctivitis)
- Constipation
- Vomiting
- Abdominal pain
- Gas (flatulence)
- Enlarging or ballooning of the abdomen (abdominal distention)

- Abdominal discomfort
- Dry mouth
- Upset stomach and indigestion (dyspepsia)
- Inflammation of the mouth
- Swelling in the arms, legs, hands, and feet
- Pain
- Fever
- Chills
- Infection-related swelling or irritation of the mucous membranes. These are linings of the nose, mouth, eyes, lungs, intestine, or vagina that which produce mucus in an effort to filter out bacteria, viruses, and other invaders. Chest pain
- Loss or lack of body strength
- Infection of the nose, sinuses, and throat area (Upper respiratory tract infection). The common cold is an example of an upper respiratory infection.
- Pneumonia
- Inflammation of the airways that carry air into the lungs (bronchitis)
- Infections such as colds, flu, pneumonia, and other types (viral infection)
- Decreased appetite
- Low blood potassium, which may cause symptoms including nausea, fatigue, muscle weakness, or tingling sensations
- High blood sugar, which may cause increased urination and thirst
- Joint pain
- Back pain
- Muscle spasms
- Pain on the side of your body
- Muscle pain
- Pain in the arms and legs
- Nerve damage – may experience temporary numbness, tingling and pricking sensations, sensitivity to touch, or muscle weakness. You may suffer more extreme symptoms, including burning pain (especially at night), muscle wasting, paralysis, or organ or gland dysfunction. People may become unable to digest food easily, maintain safe levels of blood pressure, sweat normally, or experience normal sexual function. In the most extreme cases, breathing may become difficult or organ failure may occur leading to death.
- Headache
- Dizziness
- Lack of taste
- Reduced sense of touch or sensation
- Anxiety
- Depression

- Difficulty sleeping
- Shortness of breath, with or without exertion
- Cough
- Nose bleed
- Throat pain or difficulty swallowing
- Rash
- Hair loss
- Itchy skin
- Night sweats
- High blood pressure
- Low blood pressure
- Increased blood creatinine, which may mean there is a problem with the kidneys
- Increased body weight
- Decreased body weight
- Runny nose
- Mouth/throat pain
- Pain in the muscles and bone including around the chest and neck
- Muscle weakness, asthenia (general weakness)
- Pain in hands and feet
- Dry skin
- Tooth ache
- Pain during urination
- Nail disorder
- Falling down
- Gum pain
- Altered mood
- Increases in tear production

Rarely Seen Side Effects (less than 5 in 100 research participants) with Palbociclib

- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Blurred vision, increased tearing, dry eye
- Interstitial lung disease (an inflammation of the lungs which can cause cough and shortness of breath)
- Severely low levels of white blood cells in the blood. White blood cells are a type of cell that helps fight infection and are also called neutrophils. Low white blood cells may impact your body's ability to fight infection and may occur with or without a fever.
- Chest pain due to a lack of oxygen getting to the heart. This condition is referred to as a "heart attack." In the most severe cases this condition can lead to death.

- A medical condition in which inflammation and injury of the large intestine result from a lack of blood supply (ischemic colitis). This condition may lead to a need for surgery and in the most severe cases can lead to death.
- Severe diarrhea
- Severe fever
- Severe pneumonia
- Dehydration
- Condition in which the body produces too much acid, or when the kidneys are not removing enough acid from the body (metabolic acidosis). Most symptoms are caused by the underlying disease or condition that is causing the metabolic acidosis. Metabolic acidosis itself usually causes rapid breathing, confusion or lethargy (extreme fatigue). Severe metabolic acidosis can lead to shock or death. In some situations, metabolic acidosis can be a mild, chronic (ongoing) condition.
- Thoughts of suicide
- Lung disease that can develop after exposure to certain substances (allergic alveolitis).
- Not enough oxygen passes from the lungs into the blood (respiratory failure)
- Urinary tract infection
- The bone marrow does not produce enough red blood cells, white blood cells, or platelets (bone marrow failure)
- Sudden death
- Shingles, a virus that involves a painful skin rash with blisters
- Bleeding in the eye
- Cataracts in both eyes
- Elevated liver enzyme levels in the blood, which may indicate a problem with liver function
- Low number of red blood cells that can cause tiredness and shortness of breath. May require a blood transfusion.
- Blood clot formed in the veins of the leg which may manifest as a dull ache or heaviness in the limb. If the clot moves to other organs (such as the lung or heart) it can be serious or life threatening.
- Liver failure
- Inflammation of the ear canal. Fluid that accumulates in the middle ear can cause pain, general hearing loss, fever, irritability, headache, anorexia and vomiting.
- A potentially life threatening infection that characteristically causes scarring of the kidney
- A serious condition that occurs in response to an infection that causes widespread inflammation, resulting in a condition called sepsis where not enough blood is supplied to vital organs. Symptoms may include a fast heart rate, fever, confusion and rapid breathing. Sepsis can rapidly lead to a life threatening condition and in the most severe cases lead to death.

Risks associated with the Letrozole

Commonly Occurring Side Effects (10 in 100 research participants) with Letrozole

- Hot flashes and sweats
- Pain in joints and bones
- Tiredness and weakness (fatigue)
- Increased levels of cholesterol in the blood
- Nausea
- Trouble sleeping
- Drowsiness

Occasional Side Effects (less than 10 in 100 research participants) with Letrozole

- Skin rashes
- Headaches
- Dizziness
- Generally feeling unwell or sick (malaise)
- Fluid retention causing ankle and or finger swelling
- Loss of appetite or indigestion
- Hair thinning
- Diarrhea
- Constipation
- Vaginal dryness
- Lower interest in sex (reduced libido)
- Sadness or depression
- A cough and breathlessness
- Weakening of the bones (osteoporosis) caused by lack of estrogen over a long period of time – your bones may be more likely to break.
- Vaginal bleeding
- Muscle pain
- Weight gain
- Higher blood pressure than normal (hypertension)
- Pain in the abdomen or belly

Rarely Seen Side Effects (less than 1 in 100 research participants) with Letrozole

- Nervous disorders such as anxiety, nervousness, feeling irritable, drowsiness, memory problems, difficulty sleeping
- Changes in sensation, especially touch
- Eyesight changes such as blurred vision
- Red, sore eyes
- A faster heart rate or feeling of the heart beating (palpitations)

- Joint stiffness (arthritis)
- Pain, stiffness, and clicking in a finger or thumb and a small lump in the palm at the base of the affected finger or thumb. This condition is called trigger finger and the affected finger may get stuck when bent towards the palm. Tell your doctor or nurse if you have this
- Pain, a weaker grip, and numbness and tingling in one or both hands, particularly in the fingers and thumb. This condition is called carpal tunnel syndrome and is caused by pressure on the nerve that passes through the wrist into the hand. Tell your doctor or nurse if you have this
- Breast pain
- A high temperature (fever)
- Taste changes
- A dry mouth and feeling thirsty
- Weight loss
- Urine infections

Risks associated with fulvestrant

Commonly Occurring Side Effects (10 in 100 research participants) with fulvestrant

- Injection site reactions, such as pain and/or inflammation
- Abnormal levels of liver enzymes (in blood tests)
- Nausea (feeling sick)
- Weakness, tiredness

Occasional Side Effects (less than 10 in 100 research participants) with fulvestrant

- Headache
- Hot flashes
- Vomiting, diarrhea, or loss of appetite
- Rash
- Urinary tract infections
- Back pain
- Increase of bilirubin (bile pigment produced by the liver)
- Thromboembolism (increased risk of blood clots)
- Allergic (hypersensitivity) reactions, including swelling of the face, lips, tongue and/or throat

Rarely Seen Side Effects (less than 1 in 100 research participants) with fulvestrant

- Vaginal bleeding, thick, whitish discharge and candidiasis (infection)
- Bruising and bleeding at the site of injection
- Increase of **Gamma-glutamyl transferase** (**GGT**) (an enzyme (protein) found in the liver and bile ducts), a liver enzyme seen in a blood test
- Inflammation of the liver (hepatitis)
- Liver failure
- Reduced number of platelets (which help blood clotting)

Risks associated with Pembrolizumab

What is known about this study drug?
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 the body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e., causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Very Common side effects seen in at least 20 or more out of 100 patients with pembrolizumab:

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

Common side effects seen in at least 5 but less than 20 out of 100 patients with pembrolizumab:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)

- Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps and/or feel sick to your stomach (hyponatremia)

Uncommon side effects seen in at least 1 but less than 5 out of 100 patients with pembrolizumab

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

Rare and serious side effects seen in less than 1 out of 1,00 patients with pembrolizumab:

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome)
- Inflammation of the muscles so you may feel weak or have pain in your muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches (uveitis)
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint,

muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)

- Type 1 diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting (myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy (thyroiditis)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis). Symptoms 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.

Tell your study doctor right away if you have problems swallowing, if you start to feel weak very quickly and you are having trouble breathing, if you have chest pain, rapid or abnormal heart beat, shortness of breath and swelling of your legs.

In addition to the above side effects, pembrolizumab can 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.

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab.

These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis)
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)

Risks from Foods and Drugs

Because the effect of the study drugs taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

Risks Associated with Blood Draw

Risks of blood draws include mild pain or discomfort, bruising and swelling around the puncture site, dizziness or fainting, or infection (rare).

Cancer research often includes biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures done only for the purposes of research.

Risks Associated with Biopsies:

Biopsies are normally performed under the guidance of an imaging technique. Each procedure requires a separate consent prior to the biopsy. The risks may include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.
- Rarely, an infection at the biopsy site.

Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

- Rarely, an infection at the biopsy site
- Rarely, nerve injury at the biopsy site

Risk of Incidental Findings:
It is possible the research procedures could find a medical problem unrelated to the purpose of this study that you did not know about before. If during the research procedures we learn information that may be important for you to know about, such as the possibility of a previously unknown medical condition, we will tell you. You may authorize the release and communication of the findings to your personal doctor. These findings may require additional testing or treatment. You will be responsible for the cost of any additional tests or related treatment.

Risks associated with Breach of Confidentiality*:*
There is a small risk that people who are not connected with this study will learn your identity or your personal information.

E. HOW WILL YOUR INFORMATION BE KEPT CONFIDENTIAL?

Any information learned from this study in which you might be identified will be confidential and disclosed only with your permission. Every effort will be made to keep any information collected about you confidential. However, it is impossible to guarantee that information about you will not be mistakenly released. If, despite our best efforts, identifying information about you is released, it could negatively impact you or your family members. This risk is small.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and any drug company supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.

- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
- Pfizer and Merck, the drug manufacturers.

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.

F. WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS RESEARCH STUDY?

There is no guarantee that you will receive any benefits from this study. The possible benefit of the study drug combination in the treatment of breast cancer is not known. If you decide to participate in this study, your health will be monitored very closely. By being in this study, you will give doctors more information about how well the study drug works. It may help doctors understand your condition better and may help future patients with this medical condition.

G. WHAT OTHER OPTIONS ARE THERE?

If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual approach for your cancer,
- You may choose to take part in a different study, if one is available, or
- You may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

H. ARE THERE ANY PAYMENTS TO YOU FOR TAKING PART IN THE STUDY?

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

I. WHAT ARE THE COSTS?

The investigational drug, Pembrolizumab will be provided free of charge up to 24 months (35 cycles) of treatment by sponsor. Pembrolizumab use beyond 24 months is not mandatory. Pembrolizumab can be continued through commercial supply, which will be the responsibility of you and/or your insurance carrier.

Palbociclib will be provided free of charge by sponsor for cohort 2 participants who are currently on study. For cohort 3, either study supply or commercial supply of palbociclib will be used.

The commercially available endocrine therapy drug, Letrozole or fulvestrant will be the responsibility of you and/or your insurance carrier.

The standard of care procedures provided to you will be the responsibility of you and/or your insurance carrier. You will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by your insurance carrier. You and/or your insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if you were not in a research study.

However, neither you nor your insurance carrier will be responsible for the research procedures related to this study.

Financial counselors are available Monday through Friday, 8:00 a.m. to 5:00 p.m. For additional questions, please call City of Hope Financial Support Services: 626-256-HOPE (4673), extension: 80258.

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:
www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

J. WHAT HAPPENS IF YOU GET INJURED AS A RESULT OF THIS STUDY?

If you think you have been hurt by taking part in this study, tell the study doctor as soon as possible. It is a City of Hope policy that in the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured research participant. However, financial compensation will not be available.

However, by signing this form you have not given up any of your legal rights.
There are no plans for any of the sponsors of this study to pay you or give you other compensation for the injury.

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

Your participation in this research study is voluntary. You are free to withdraw your consent for participation in this study without any loss of benefits, penalty, or interference with any future treatment at City of Hope.

L. WHOM DO YOU CALL IF YOU HAVE QUESTIONS OR CONCERNS?

The principal investigator, Dr. Joanne Mortimer, M.D. or a colleague, Dr. _____, responsible for your care or treatment, has offered to and has answered any and all questions regarding your participation in this research study. If you have any further questions or in the event of a research related injury, you can contact Dr. Joanne Mortimer, M.D. at (626) 256-HOPE (4673) ext. 89200 or Dr. _____ at (626) 256-HOPE (4673) ext. _____.

This study has been reviewed and approved by the Institutional Review Board (IRB). If you have any questions regarding your rights as a research participant, you may contact a representative of that Board, from the Office of Human Research Subjects Protection, at (626) 256-HOPE (4673) ext. 62700.

M. WILL I BE INFORMED OF NEW INFORMATION?

You will be informed of any significant new findings related to this study which might affect your willingness to continue to participate.

N. ADDITIONAL STUDY SECTION:

This section is about an optional study you can choose to take part in. You will make your selection at the end of this section.

The results may not be added to your medical records and you or your study doctor may not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say "no" to this study. If you sign up for but cannot complete this study for any reason, you can still take part in the main study.

At the end of the document, circle your choice of "yes" or "no" for the following study.

Additional Optional tumor biopsies

If you choose to take part in this study, the study doctor may ask you to have additional tumor biopsies for real-time assessment of immune response. It is expected that these biopsies will show better evidence of any dynamic changes in your tumor while receiving study treatment. Tumor biopsy samples taken before start of study treatment may not predict response to therapy. It is believed that on-treatment biopsies may better capture immune responses. Your study doctor will advise you if additional tumor biopsies are recommended.

You may be asked to sign a separate consent form for the biopsy procedure.

Risks Associated with Biopsies:

The possible risks include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- At the biopsy site you may experience:
    - Minor bleeding, tenderness, scarring, infection (rare)

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part.

Please circle your answer: I choose to take part in the additional optional tumor biopsies.

YES NO

This is the end of the section about optional study.

O. SIGNATURE SECTION

SIGNATURE FOR CONSENT: By signing this consent form, you are making a decision to participate in this research study. Your signature on this informed consent form indicates that you:

1. Have read and understood the information in this form.
2. Have had the information in this form explained to you.
3. Have had a chance to ask questions and these questions were answered to your satisfaction.
4. Have been informed that you will receive a copy of this signed consent form, which includes the "Experimental Subject's Bill of Rights."

I hereby agree to be a research participant in this research study:

_____ _____

Research Participant's Signature Date Time
(Date and time must be in research participant's handwriting)

_____

Print Research Participant's Name

INDIVIDUAL OBTAINING CONSENT SIGNATURE

_____ _____

Signature of Individual Obtaining Consent Date Time

_____

Print Name of Individual Obtaining Consent

FOR USE WITH IRB APPROVED TRANSLATED SHORT/LONG CONSENT FORMS FOR NON ENGLISH SPEAKING PARTICIPANTS ONLY

NOTE: To determine who should sign below, review the guidance document, *Consenting Non English Speaking Research Participants (Pediatric or Adult) – Who Signs What?*

Interpreter: By signing here, I attest that I have acted as interpreter and facilitated this consent process.

_____ _____ _____

Interpreter's Signature Date Time

_____

Print Interpreter's Name

FOR USE WHEN A WITNESS IS REQUIRED:

Witness: By signing here, I attest that I witnessed the consent process and that the entire consent form was discussed.

_____ _____ _____

Witness' Signature Date Time

_____

Print Witness' Name

IRB #16058: TITLE: Phase II Study of the Combination of Pembrolizumab, Endocrine Therapy and Palbociclib in Patients with Metastatic Estrogen Receptor Positive Breast Cancer

AUTHORIZATION TO USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION (PHI) FOR PURPOSES OF THIS STUDY:

I. **Purpose of this Authorization**: The information about your health is something that is protected by law and cannot, except for certain purposes, be disclosed (shared) without your permission. As part of this research, you are agreeing to allow City of Hope to use and share with others your protected health information ("PHI"), as needed for the research. If you agree to participate in the study named above (called the "Study"), you must sign this authorization in addition to the *Study Consent Form*.

II. **The Information About You that is Covered By this Authorization**: PHI refers to information that we maintain about you that identifies you and includes the information contained in your medical record. Your medical record consists of information related to your health and the treatment we provide to you, such as your medical history, the results of physical exams, blood tests, x-rays and other diagnostic and medical procedures. If you sign this authorization, you are allowing City of Hope and the individuals indicated below to use and share any PHI we maintain about you that is required for your participation in the Study.

III. **Purposes for Uses and Sharing of your PHI; Who Will Use, Share and Receive your PHI**: Your PHI will be used and shared with others for the purpose of doing this research as described in the *Study Consent Form*. Your PHI will also be used to keep the research sponsor informed about this Study, for reporting to those individuals and authorities responsible for overseeing our research activities to make sure that the activities are properly conducted, and to report to regulatory agencies as required by the Study.

The people authorized to use and share your PHI for purposes of the Study include the Principal Investigator and the research staff supporting the

Study; your City of Hope physicians and the health care team; and the Health Information Management Services Department (i.e., Medical Records Department). This also includes any agents or contractors used by these individuals or groups for purposes of conducting or managing this Study. At the City of Hope, the Institutional Review Board ("IRB"), and other City of Hope research regulatory committees will have access to your PHI as necessary to monitor research.

You are also allowing your PHI to be shared with the Office for Human Research Protections ("OHRP") and with any person or agency as required by law. In addition, certain other regulatory agencies, including, the Food and Drug Administration ("FDA"); the National Cancer Institute ("NCI"), will have access to your PHI.

Your information will also be shared with Pfizer and Merck, the drug manufacturers, as necessary for research purposes and to conduct the Study.

Use and disclosure of your PHI may also continue for as long as the sponsor needs to maintain the PHI for purposes of obtaining approval of the drug from the FDA or for other FDA reporting.

This authorization will allow us to use and share your PHI for the Study. No other additional uses and disclosures other than for the purposes of the Study is included in this authorization. City of Hope's Notice of Privacy Practices will continue to protect your non-Study information. If necessary, another separate permission will be obtained from you for any non-Study uses or sharing of your PHI.

IV. **Expiration of this Authorization**: This authorization to use and share your PHI will expire twenty-five (25) years from the date that you sign this authorization

V. **Further Sharing of Your PHI**: Your privacy is important and this is the reason for having rules which control who can use or see your PHI. City of Hope maintains control over your PHI at present, but once we share this

information with a third party (for example, an individual or agency outside of the City of Hope), then it is no longer possible to maintain the same level of protection. The persons outside our control may not be governed by federal or state privacy laws and it is possible that they could share your PHI with others for whom you have not given permission.

The information from this Study may be published in scientific journals or presented at scientific meetings but your identity will be kept confidential.

VI. **<u>Your Rights Under this Authorization</u>**: You may cancel this permission to use and share your PHI at any time by contacting City of Hope's Privacy Officer at (626) 256-HOPE (4673) ext. 64025. You should ask for the form, *Revocation (Cancellation) of Authorization for Use of Protected Health Information for Research*. Fill this form out and return it as the form instructs. Your cancellation begins when the Health Information Management Department of City of Hope receives this form. If you cancel this authorization to use and share your PHI, you will no longer be able to participate in the Study. This is because the research under this Study cannot be conducted without your PHI.

Once you cancel your permission to use and share your PHI, the researchers and others involved in conducting the Study will no longer be able to use or share your PHI for this research. PHI already used and shared up to this point as part of this Study will continue to be used for purposes of this research. This means that any uses of your PHI and any PHI shared about you by City of Hope prior to receiving your cancellation (revocation) form cannot be taken back. While no further PHI about you will be shared for the Study, your PHI already shared will continue to be used in the overall Study.

VII. **<u>Signing this Authorization is Your Choice</u>:** Your ability to obtain care at the City of Hope will not be affected by your decision to sign this authorization form. You will be able to continue to receive health care at City of Hope if you choose not to sign this authorization form or if you sign this form and later cancel your permission to use and share your PHI.

If you agree to the use and sharing of your PHI, please sign below. You will be given a copy of this authorization form.

_____ _____ _____

Research Participant's Signature Date Time

(date and time must be in research participant's handwriting)

_____

Print Research Participant's Name

INDIVIDUAL OBTAINING CONSENT SIGNATURE

_____ _____ _____

Signature of Individual Obtaining Consent Date Time

_____

Print Name of Individual Obtaining Consent

FOR USE WITH IRB APPROVED TRANSLATED SHORT/LONG CONSENT FORMS FOR NON ENGLISH SPEAKING PARTICIPANTS ONLY

NOTE: To determine who should sign below, review the guidance document, *Consenting Non English Speaking Research Participants (Pediatric or Adult) – Who Signs What?*

Interpreter: By signing here, I attest that I have acted as interpreter and facilitated this consent process.

_____ _____ _____

Interpreter's Signature Date Time

_____

Print Interpreter's Name

FOR USE WHEN A WITNESS IS REQUIRED:

Witness: By signing here, I attest that I witnessed the consent process and that the entire consent form was discussed.

_____ _____ _____

Witness' Signature Date Time

_____

Print Witness' Name