Protocol Title: PELOPS: Palbociclib and Endocrine therapy for LObular breast cancer Preoperative Study: A randomized phase II study of Palbociclib with endocrine therapy versus endocrine therapy alone for Invasive Lobular Carcinoma and Invasive Ductal Carcinoma

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A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have hormone receptor positive breast cancer and are a candidate for preoperative therapy. This research study is evaluating how well your breast cancer responds to preoperative treatment with Endocrine treatment in combination with a drug called Palbociclib or Endocrine treatment alone as possible treatments for this diagnosis. The study includes a 2-week window portion containing endocrine therapy followed by a 24-week treatment portion where patients are treated with either endocrine therapy alone or endocrine therapy in combination with palbociclib.

The names of the study interventions involved in this study are:

- Arm A: Tamoxifen (Window Portion)
- Arm B: Letrozole (Window Portion)
- Arm C:
    - Postmenopausal participants: Letrozole and Palbociclib (Treatment Portion)

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  - Premenopausal participants: Tamoxifen and LHRH agonist and Palbociclib (Treatment Portion)
- Arm D:
  - Postmenopausal participants: Letrozole (Treatment Portion)
  - Premenopausal participants: Tamoxifen and LHRH agonist (Treatment Portion)

For purposes of this research, you will be referred to as a "participant". It is expected that about 195 participants will take part in this research study.

Pfizer is supporting this research study by providing funding for the research study and the study drug.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of 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.

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.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the safety and effectiveness of an investigational intervention to learn whether the intervention works in treating a specific disease. "Investigational" means that the intervention is being studied. Is also means that the FDA (the U.S. Food and Drug Administration) has not yet approved Palbociclib in combination with endocrine therapy for use in participants with your type of cancer, but it has been approved for other uses (metastatic breast cancer).

Palbociclib is a drug that may stop cancer cells from growing. Palbociclib blocks activity of two closely related enzymes (proteins that help chemical reactions in the body occur), called Cyclin D Kinases 4 and 6 (CDK 4/6). These proteins are part of a pathway, or a sequence of steps, which is known to regulate cell growth.

Laboratory testing has suggested palbociclib may stop the growth of hormone receptor positive breast cancer.

Endocrine therapy prevents breast cancer cell growth by blocking estrogen stimulation. During the window portion of the study, endocrine therapy will consist of either tamoxifen or letrozole. During the treatment portion of the study postmenopausal participants will be treated with letrozole. Premenopausal participants will be treated with tamoxifen and and an injection medicine called LHRH agonist used to shut down ovary function. It is considered standard of care for breast cancer patients with hormone receptor positive breast cancer to take endocrine therapy.

A previous research study combining palbociclib with letrozole in women with advanced breast cancer has shown better disease control with the combination of the two drugs compared with letrozole by itself.

In this research study, we are evaluating two portions of treatment. In the window portion we are looking at tumor protein changes (known as Ki67) in participants treated with either Tamoxifen or Letrozole. In the treatment portion, we will evaluate palbociclib in combination with letrozole or letrozole alone as preoperative therapy. Premenopausal participants will be treated with tamoxifen plus LHRH in combination with palbociclib or tamoxifen and LHRH only in the treatment portion of the study.

We will also use tumor tissue from diagnostic, research biopsies and surgical specimen along blood specimens to be used for research. The research on your sample will include looking at genes (DNA), proteins, or the substances that make proteins (called RNA). Collectively, this research is called biomarker research and may help doctors to better understand your disease, how endocrine therapies work, and may help to identify which breast cancers may benefit most from palbociclib. As part of the research conducted using tumor samples or blood specimens, the researchers may identify gene(s) or mutations, which may increase risk of developing certain types of cancers. If this happens your doctor will be informed and you may be referred to a genetic counselor.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment including tamoxifen or letrozole.
- Take part in another research study.
- Receive the same endocrine therapy drugs, but not as part of a research study.
- Receive no therapy specific to your cancer.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

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.
- **A physical exam**, including vital signs and height and weight.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **An assessment of your tumor size** by mammogram, ultrasound or MRI.
- **CT scan and bone scan or PET/CT scan:** Participants with Stage III disease will be recommended to have these disease assessments.
- **Routine blood tests**, approximately 1-2 tablespoons of blood will be collected to check your blood and assess how well your organs are functioning.
- **Pregnancy test**, if you are a woman of child-bearing potential.
- **Lymph node evaluation**: If any of your underarm lymph nodes are found to be enlarged on physical examination or by radiology studies, a fine needle aspiration (FNA) or biopsy will be performed prior to receiving treatment.

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.

Additional research procedures to be performed at the time of screening but not required to determine eligibility:

- **Collection of tumor tissue** from your original breast cancer biopsy will be collected and used to confirm your response to the treatment that you receive.
- **Research tumor biopsy** will be taken from an area of your tumor before you begin study treatment to be used for research purposes. This biopsy is similar to the first biopsy done to establish the diagnosis of breast cancer. This biopsy is required to participate in this research study because the research done on the tumor tissue is a very important part of this research study. The researchers want to learn why some cancers shrink with this study treatment while others do not. The research biopsy is done in an outpatient setting using a local anesthetic.

After the screening procedures confirm that you are eligible to participate in the research study:

If you take part in this research study, postmenopausal women will be treated with a two-week course of endocrine therapy followed by the treatment portion. Premenopausal women will begin with the treatment portion of the study and will not receive the two-week course of endocrine therapy. Because no one knows which of the study options is best, the participants treated with the window portion first will be “randomized” into one of the study groups, Arm A or Arm B. Participants in the treatment portion will be also be randomized into one of the study groups, Arm C or Arm D. Randomization means that you are put into a group by chance. It is like flipping a coin.

Your study doctor will advise you about the order of treatments you will get after completion of screening tests. Your study doctor will also be able to tell you the treatment schedule you will receive if you agree to take part. However, neither you nor the research doctor will choose what group (A or B, C or D) you will be in. If you are in the window portion of the study, you will have an equal chance of being placed in Arm A or Arm B. You will have a two in one chance of being placed in Arm C or Arm D. Below are the study groups:

Window portion lasts two weeks (14 days):

- Arm A: Tamoxifen once per day
- Arm B: Letrozole once per day

Treatment portion lasts for 6 visits (known as cycles), with each cycle lasting 4 weeks (28 days), for a total of 24 weeks:

- Arm C:
  - Postmenopausal participants: Letrozole once per day, Palbociclib once per day on days 1-21 of each 28 day cycle
  - Premenopausal participants: Tamoxifen once per day, LHRH once per 28 days, Palbociclib once per day on days 1-21 of each 28 day cycle
- Arm D:
  - Postmenopausal participants: Letrozole treatment once per day of each 28 day cycle
  - Premenopausal participants: Tamoxifen once per day, LHRH once per 28 days of each 28 day cycle

Participants treated on Arm C will be offered treatment with palbociclib for 6 cycles after their surgery. Participants treated on Arm D will be offered treatment with palbociclib for 12 cycles after surgery.
If you take part in this research study you will be given a drug diary. You will be asked to document information in the drug diary about the study treatment you are being asked to take.

<u>Window Phase Day 1</u> (only for participants on Window portion)

- **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.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Research blood tests**, approximately 3 tablespoons of blood will be collected. Your blood is being collected so researchers can look at your DNA. It is important to have the DNA in order to compare it to the DNA in your tumor. This research blood collection is not optional. Your blood may also be used for future research studies.

<u>Window Phase Day 15</u> (only for participants on Window portion)

- **Research tumor biopsy** will be taken from an area of your tumor to be used for research purposes. This biopsy is similar to the first biopsy done

to establish the diagnosis of breast cancer. This biopsy is required because the research done on the tumor tissue is a very important part of this research study. The researchers want to learn why some cancers shrink with this study treatment while others do not. The research biopsy is done in an outpatient setting using a local anesthetic.

Treatment Phase Cycle 1 Day 1

- **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.
- **Routine blood tests**, approximately 1-2 tablespoons of blood will be collected to check your blood and assess how well your organs are functioning.
- **For participants who enroll into treatment portion directly: Research blood tests**, approximately 3 tablespoons of blood will be collected. Your blood is being collected so researchers can look at your DNA. It is important to have the DNA in order to compare it to the DNA in your tumor. This research blood collection is not optional. Your blood may also be used for future research studies.

Treatment Phase Cycle 1 Day 15

- **Routine blood tests**, approximately 1-2 tablespoons of blood will be collected to check your blood and assess how well your organs are functioning.

- **For participants who enroll into treatment portion directly: Research tumor biopsy** will be taken from an area of your tumor to be used for research purposes. This biopsy is similar to the first biopsy done to establish the diagnosis of breast cancer. This biopsy is required to because the research done on the tumor tissue is a very important part of this research study. The researchers want to learn why some cancers shrink with this study treatment while others do not. The research biopsy is done in an outpatient setting using a local anesthetic.

Treatment Phase Cycle 2 Day 1

- **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.
- **Routine blood tests**, approximately 1-2 tablespoons of blood will be collected to check your blood and assess how well your organs are functioning.

Treatment Phase Cycle 2 Day 15

- **Routine blood tests**, approximately 1-2 tablespoons of blood will be collected to check your blood and assess how well your organs are functioning.

Treatment Phase Cycle 3 to Cycle 6 Day 1

- **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.
- **Routine blood tests**, approximately 1-2 tablespoons of blood will be collected to check your blood and assess how well your organs are functioning.

Pre-surgery Visit:

- **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.
- **Routine blood tests**, approximately 1-2 tablespoons of blood will be collected to check your blood and assess how well your organs are functioning.
- **An assessment of your tumor size** by mammogram, ultrasound or MRI.
- **Research blood tests**, approximately 3 tablespoons of blood will be collected. Your blood is being collected so researchers can look at your DNA. It is important to have the DNA in order to compare it to the DNA in your tumor. This research blood collection is not optional. Your blood may also be used for future research studies.

Surgery to Remove Your Tumor: This will occur within six weeks after the last treatment. You and your surgeon will decide on the type of surgery (i.e.,

lumpectomy or mastectomy) as you would as part of standard care for your disease.

After the surgery to remove your tumor:

- **Collection of tumor tissue** from the surgery to remove your tumor

After Surgery (Post-Operative) Treatment:
Decisions about whether you will receive more therapy after your surgery is up to you and your treating physicians. If you receive further treatment, the choice of therapy is also up to you and your doctors. This is a decision you can make with your treating physicians. Decisions about post-operative therapy are not part of this research study. Participants treated with Arm D during the study will be offered treatment with palbociclib after their surgery.

Research Study Plan:

For participants on the window portion and treatment portion:

	Screening	Window Portion		Treatment Portion			Pre-Surgery	Post surgery
		Window Day 1	Window Day 15	Cycle 1 and 2, Day 1	Cycle 1 and 2, Day 15	Cycles 3 to 6 Day 1		
Medical history & Exam	X	X		X		X	X	
Blood tests	X			X	X	X	X	
Pregnancy test	X							
Mammogram, MRI, or Ultrasound	X						X	
Tissue collection	X							X
Tumor biopsies	X		X					
Research blood collection		X					X	

For participants on the treatment portion only:

	Screening	Cycle 1 and 2, Day 1	Cycle 1 and 2, Day 15	Cycles 3 to 6, Day 1	Pre-Surgery	Post surgery
Medical history & Exam	X	X		X	X	
Blood tests	X	X	X	X	X	
Pregnancy test	X					
Mammogram, MRI, or Ultrasound	X				X	
Tissue collection	X					X
Tumor biopsies	X		X (Cycle 1, Day 15 only)			
Research blood collection		X			X	

National Institutes of Health (NIH) Data Sharing Involving Germline Research:

In order to allow the greatest amount of research to be performed on the tissue that you donate, researchers for this study may share results of sequencing your genes (which shows how your DNA is organized) with other scientists. In particular, the National Institutes of Health (NIH) and other organizations have developed special data (information) repositories that analyze data and collect the results of certain types of genetic studies. These central banks will store your genetic information and samples, and provide them to qualified researchers to do more research. Some of this information may be made available over the internet and will be freely available to anyone who is interested (an open access database). Other, more detailed information may only be accessed by scientists at other research centers who have received special permission to review your de-identified data (a controlled access database). Neither type of database will contain information that is traditionally used to identify you, such as your name, address, medical record number, telephone number or social security number. However, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a relative) in another database and be able to identify you (or a relative). Because the DNA sequence of each individual is unique (with the exception of identical twins), there is a very remote possibility that if a complete sequence determination of your DNA were publicly disclosed, it could be used by a researcher to determine your identity. It is also possible that there could be violations to the security of the computer systems used to share the codes linking your genetic and medical information to you. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives.

Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters and other relatives. Consequently, it may be possible that researchers looking at your genetic information could guess your identity based on other genetic information that they might know about your relatives. Similarly, it may be possible that genetic information from you could be used to help identify your relatives.

There may be other privacy risks that we have not foreseen. While we believe the risks to you and your family are very low, we are unable to tell you exactly what all the risks are.

Biobanking:
Biological specimens (such as blood, tissue, and other specimens collected as a part of the study, and any materials that may be derived from these) will be collected and shared with an outside lab or collaborator for analysis. The specimens will not be identifiable. The specimens will be banked for future use.

Data Collection:
Data will be collected and shared with an outside collaborator for analysis. The data will not be identifiable. The data will be banked for future use.

Planned Follow-up:
We would like to keep track of your medical condition up to 10 years after you complete study treatment. We would like to do this by calling you on the telephone once a year to see how you are doing. Keeping in touch with you and checking your condition every year helps us look at the long-term effects of the research study.

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

You will be in this research study for about 6 months and will be followed for 10 years.

The research doctor may decide to take you off the research study for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens
- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed. The research doctor and research team will help arrange for your continued care.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this

research study, we encourage you to talk to the research doctor and your primary doctor first.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that the study drug(s) do not help treat your disease or make 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. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug(s) 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.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Palbociclib:

Likely (more than 30% chance that this will happen)

- Neutropenia. A condition in which the number of white bloods cells called neutrophils is abnormally low. This increases the risk of infection, which

may be serious or life threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing You will be monitored closely for this risk.

Frequent (between a 10 to 30% chance that this will happen)

- Fatigue. Participants experiencing fatigue while taking palbociclib should exercise caution when driving or operating machinery.
- Low number of red blood cells that can causes tiredness and shortness of breath. May require a blood transfusion. (Anemia)
- Diarrhea
- Nausea
- Low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life threatening and may required a blood transfusion.
- Decreased appetite
- Constipation
- Mouth blisters/sores
- Infection of the sinus or lung
- Vomiting
- Loss of touch or sensation of pins and needles or numbness on the skin
- Inflammation of the mouth
- Pain including: Abdominal pain, mouth/throat pain, back pain, joint pain, flank (side) pain, muscle pain, bone pain, pain in the hands and feet.
- Hair loss
- Rash
- Cough
- Shortness of breath
- Headache
- Dizziness
- Hot flush
- Inability to sleep (insomnia)

Occasional (Between a 5 to 10% chance that this will happen)

- Bloating
- Swelling in extremities (hands and feet)
- Nosebleed
- Muscle spasm or cramps
- Fever

- Dry mouth
- Fever with dangerously low white blood cell count
- Abnormal taste (this side effect is reversible)
- Abdominal pain
- Indigestion (heart burn)
- Feeling weak and having no energy
- Flu-like illness
- Increase in blood liver markers that may indicate liver damage
- Dry skin
- Itching in the mouth or throat
- High blood pressure
- Depression
- Increased risk of fall
- Irritation or sores in the lining of hollow organs (like the mouth, throat, stomach, and bowels)

Rare (Less than a 5% chance that this will happen)

- Abdominal swelling
- Chills
- Runny Nose
- Night Sweats
- Decreased sense of touch or sensation (this side effect is reversible)
- Weight loss
- Low blood pressure
- Hearts beats that are fast and hard
- Fever associated with dangerously low levels of white blood cells (neutrophils)
- Blurred vision
- Increased tearing
- Dry eye
- Abnormal electrical conduction within the heart which may lead to arrhythmias or irregular heartbeat.
- A blood clot that causes a sudden blockage in a lung blood vessel, usually due to a blood clot that traveled to the lung from the leg. A pulmonary embolism is a serious condition that can cause: permanent damage to part of your lung from lack of blood flow to lung tissue; low oxygen levels in your blood; damage to other organs in your body from not getting enough oxygen; if a clot is large, or if there are many clots, a pulmonary embolism can cause death.

Review of clinical trial data and post-marketing data for palbociclib revealed a possible relationship between palbociclib and the development of pneumonitis. Pneumonitis is inflammation in the lungs which may cause cough, shortness of breath, or difficulty breathing. If severe, this can be life-threatening. A definitive causal relationship was not established.

Risks Associated with Letrozole:

Frequent (between a 10 to 50% chance that this will happen)

- Hot flashes
- Increased sweating
- Fatigue
- Headache
- Insomnia
- High blood pressure
- Stomach pain
- Dizziness
- Joint, muscle, and bone pain
- Generalized pain, including backaches
- Weakness
- Decreased appetite
- Nausea
- Swelling in the legs
- Constipation
- Weight gain
- Shortness of breath
- Cough
- Loss of bone thickness (which can lead to broken bones)
- Increase in cholesterol level
- Depression
- Anxiety
- Diarrhea

Occasional (Between a 1 to 10% chance that this will happen)

- Skin rashes

Rare (Less than a 1 % chance that this will happen)

- Heart attack, in some people, this may be severe and can even lead to death.
- Death due to stroke or heart failure

Risks Associated with Tamoxifen

Frequent (between a 10 to 50% chance that this will happen

- Hot flushes
- Night sweating
- Vaginal discharge or dryness
- Irregular periods
- Vulvar itching
- Nausea

Occasional (Between a 1 to 10% chance that this will happen)

- Swelling
- Skin rash
- Hair thinning
- Elevated liver function tests, which may indicate that your liver is not functioning properly, and can cause malaise, fatigue, and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, this can be serious or life threatening

Rare (Less than a 1 % chance that this will happen)

- A side effect of Tamoxifen in pre-menopausal women may be loss of bone mineral density
- An infrequent side effect is blood clots. A blood clot in the leg can cause serious problems, including death, if it travels to the lungs.
- Participants taking tamoxifen may also be at a slightly higher risk for getting cataracts (a clouding of the lens inside the eye). Cataracts may lead to poor vision.
- Tamoxifen can raise sensitivity to blood thinners such as Coumadin
- Tamoxifen may cause changes in the lining of the uterus (endometrium). In addition, for every 1000 people who take tamoxifen each year, 1-2 people have developed cancer of the uterine lining (endometrial cancer), and even fewer have developed a cancer of the uterine muscle (uterine sarcoma). In women who are getting ovarian function suppression, any vaginal bleeding should be reported to your study doctor, as it may be a warning sign of uterine cancer.

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.

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, CT scans, x-rays, mammograms, and/or other scans utilizing radioactivity may be used to evaluate your disease. Please note that this radiation exposure is not necessary for your medical care but is required to obtain the desired research information. The frequency of these exams is slightly greater than what you would receive as standard care. In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

Risks Associated with MRI Scans:
As part of this study, you may have one or more “Magnetic Resonance Imaging (MRI) scans. When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the MRI. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
The drugs used in this research study may affect a fetus. While participating in this research study and for at least 6 months after taking Palbociclib, you should not become pregnant and should not nurse a baby. We can provide counseling about preventing pregnancy for study participants. Let your doctor know immediately if you become pregnant.

Effective forms of birth control which can be considered include:

- True abstinence
- Partner with a previous vasectomy
- Placement of an non-hormonal intrauterine device (IUD)
- Condom with spermicidal foam/gel/film/cream/suppository.
- Diaphragm or cervical vault cap

As reproductive studies have not been performed with Palbociclib there is a risk that you will be infertile and may not be able to have children in the future.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

This study may or may not help you because researchers do not know how the study drug will compare to the usual approach. This study may help researchers learn things that may help people in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.
You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the study drug(s). In some cases, the abrupt stopping of a drug can have risks in itself. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid to take part in this research study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You will not be charged for Palbociclib.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

Tamoxifen and letrozole are commercially available which means that the FDA has approved it for use in patients with another type of cancer. Because there is evidence that supports using this drug in patients with your type of cancer, you or your insurance company will be billed for the cost of tamoxifen and letrozole.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Beth Israel Deaconess Medical Center: (617) 667-5661
- Brigham and Women's Hospital: (617) 732-5524 or (617) 732-7485
- Brigham and Women's Hospital at Faulkner Hospital: (617) 632-3455
- Dana-Faber at Milford Regional Cancer Center: (508) 422-2970
- Dana-Farber at Steward St. Elizabeth's Medical Center: (877) 228-3873
- Dana-Farber/Brigham and Women's Hospital in Clinical Affiliation with South Shore Hospital: (781) 624-4329

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)

K. WHAT HAPPENS IF I AM INJURED OR SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. The treating hospital may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

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

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The study team plans to publish the results of this research study and when we do, we may be asked to make the data we collect available to other researchers. We will not include information that identifies you in any publications or to the researchers who request the data to do additional research.

The Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects Americans from being treated unfairly because of differences in their DNA that may affect their health and may prevent discrimination by health insurers and employers based on genetic information. GINA is intended to ease concerns about discrimination that might keep some people from getting genetic tests that could benefit their health and enable people to take part in research studies such as this without fear that their DNA information might be used against them by health insurers or their workplace. This protection does not extend to disability or life insurance. Additional information can be found at http://www.genome.gov/10002328

As a part of this study, your de-identified specimens or genetic data may be placed into one or more publicly accessible databases, such as the National Institute of Health's Database for Genotypes and Phenotypes (dbGaP). Through such databases, researchers from around the world will have access to de-identified samples or data for future research.

Participation in this study involves providing a specimen of your tissue. If the research doctor leaves the institution, the research and the tissue might remain at the DF/HCC or might be transferred to another institution.

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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.

M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Dana-Farber Cancer Institute (DFCI) and Brigham and Women's Hospital at Faulkner Hospital (BWH @ FH)

- Otto Metzger, MD: 617-632-3800
- Research Nurse Line: 617-632-3478

Beth Israel Deaconess Medical Center (BIDMC)

- Steven Come, MD: 617-667-4599

Dana-Farber at Milford Regional Cancer Center (DFCI @ MRCC)

- Michael Constantine, MD: 508-488-3700

Dana-Farber at Steward St. Elizabeth's Medical Center (DFCI @ SEMC):

- Caroline Block, MD: 617-632-4595

Dana-Farber/Brigham and Women's Cancer Center in Clinical Affiliation with South Shore Hospital (DFCI @ SSH)

- Meredith Faggen, MD: 781-624-4800

24-hour contacts:

DFCI and BWH @ FH: Otto Metzger, MD, or your research doctor by page at: 617-632-3352

BIDMC: Steven Come, MD, or your research doctor by page at: 617-667-4700

DFCI @ MRCC: Michael Constantine, MD, or your research doctor by page at: 508-488-3700

DFCI @ SEMC: Caroline Block, MD, or your research doctor by page at: 617-789-3000

DFCI @ SSH: Meredith Faggen, MD, or your research doctor by page at: 781-624-4800

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

N. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug for the

purpose of this or other research relating the study drug and its use in cancer; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, and its agent(s): Pfizer
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"

O. FUTURE USE OF DATA AND SPECIMENS

Your personal information and/or biospecimens collected during this study may be stored and used for future research. If so, any personal identifiers will be removed so that the information or samples cannot be linked back to you. As a result, we will no longer be able to identify and destroy them.

Investigators, including investigators from collaborating institutions, can request this data and samples for new research. Samples and data may also be shared with outside non-profit academic investigators as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate.

You will not be asked to provide additional informed consent for the use of your de-identified information or samples in future research.
Future research studies may include genetic research. Your genes are unique to you. At this time, you cannot be identified through this research. There is a risk that you might be reidentified in the future as genetic research progresses.

P. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

Adult Participants

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is illiterate

The consent form was read to the participant who was given the opportunity to ask questions.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate

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