# INFORMED CONSENT DOCUMENT – TREATMENT CONSENT

**Project Title: A Phase II Study of Neratinib Alone and in Combination with Fulvestrant in Metastatic HER2 Non-amplified but HER2 Mutant Breast Cancer**

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This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights and responsibilities as a research participant. By signing this form you are agreeing to participate in this study.

- You should read and understand the information in this document including the procedures, risks, and potential benefits.
- If you have any questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

## WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you have been diagnosed with metastatic breast cancer that is negative for HER2 overexpression, but the cancer has been found to have a mutation in HER2.

HER2 is a protein involved in normal cell growth. Some types of breast cancer test positive for overexpression HER2 and some test negative, and there are different treatments depending on whether the breast cancer is positive or negative. However, doctors are discovering that there is a third group of people—people who have HER2-negative breast cancer with mutations in HER2. Doctors are looking at whether people with a HER2 mutation might respond to the same treatment as people with HER2-positive breast cancer.

Neratinib is a drug which has been shown to be effective for treating HER2-positive breast cancer in clinical trials. The purpose of this research study is to test the cancer of people who have HER2-negative to see if it has a HER2 mutation and, if so, see how the cancer responds to neratinib.

Neratinib is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA).

Fulvestrant is a routine treatment for ER-positive breast cancer. ER-positive breast cancer means that the cancer cells may receive signals from estrogen that could promote their growth. If you are in a group of people that have ER-positive breast cancer, you will also receive fulvestrant while you are enrolled in this study. People enrolling in this study without ER-positive breast cancer will receive neratinib alone.

Fulvestrant has been approved by the FDA for the treatment of ER-positive breast cancer, but is considered investigational in the context of this study because the combination of fulvestrant and neratinib is not approved by the FDA.

## WHAT WILL HAPPEN DURING THIS STUDY?

All treatment will be given in either the outpatient or inpatient setting at Siteman Cancer Center. We feel it is important to remind you that any procedures, whether you choose to take part in this study or not, will require you to remain at the Siteman Cancer Center up to several hours. There may also be a wide variability in the length of clinic visits due to the unique characteristics of your medical history and health condition, and clinic factors such as physician availability, staffing shortages, and weather delays. This will also vary depending upon your needs at the visit as determined by your physician. It is important that you are able to be available to complete the procedures at each visit to ensure that your safety and treatment needs are met.

**Before you begin study treatment:**

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

- Physical exam, including taking of vital signs, measuring your height and weight, reviewing your medical history, evaluation of your performance status, and talking about any symptoms or health problems you're having
- If your HER2 mutation testing was performed at a facility outside of Washington University and the results are unclear, approximately 2 teaspoons of blood will be drawn from you for this study to see whether the mutation is tumor-specific; if it is not, you will not be able to continue in the study
- Blood tests to check your blood counts and organ function (approximately 2 teaspoons of blood will be drawn from a vein in your arm)
- A pregnancy test (blood or urine) if you are a woman of childbearing potential (approximately 1 teaspoon of blood will be drawn from a vein in your arm, if necessary)
- EKG and either an echocardiogram or MUGA (a scan which involves the injection of a radioactive marker into a vein which allows your doctor to see how the tracer moves through your bloodstream) to see how well your heart functions
- CT scan (computerized tomography, which uses x-rays to create a picture of the bones and soft tissues in your body) or MRI (magnetic resonance imaging, which uses a magnetic field and radio waves to create a picture of the organs and tissues in your body) to evaluate your disease
- OPTIONAL tumor biopsy within 2 weeks prior to the start of neratinib. Research on the tumor biopsy will help to explain why patients may respond differently in this trial.

| |
|---|
| I agree to have a biopsy prior to the start of neratinib for research purposes:<br><br>___ yes ___ no _____ initials |

It is possible that after your medical history, tests, and procedures are reviewed, you will not be able to continue in this study. If this is the case, your study doctor will go over this with you.

**Procedures throughout the study:**
If you continue in the study, you will then begin taking neratinib. Neratinib is a medication taken by mouth which you should take once a day, every day of each 28-day cycle, at the same time (preferably in the morning). You should take neratinib with food. Do not take neratinib with grapefruit or grapefruit juice, as this could affect how your body processes the drug. You will be contacted by the study staff at 24, 48, and 72 hours after you take your first dose of neratinib. If you tolerate neratinib well, it is possible that the dose you are taking may increase at any point after you complete the first cycle of treatment.

One of the main side effects of neratinib is diarrhea. When you begin your treatment with neratinib, we will also prescribe loperamide (also known as Imodium) for you to begin takingat the same time as you take your first dose of neratinib. Diarrhea and vomiting can quickly lead to a loss of too much water from your body (dehydration). Make sure you drink enough liquids each day (8 to 10 large glasses or cups). If you have severe diarrhea and/or vomiting, even for a short period of time, call the study doctor immediately. Please review the supplemental document titled "Patient Instructions for the Management of Diarrhea" with your physician.

You will return to the clinic on Day 1 of each cycle to receive a refill. With each refill, you will receive a drug diary which you should use to record the number of pills taken each day and whether you experience any side effects. Please bring this drug diary and any unused pills with you to the clinic at the beginning of each cycle.

If you have ER-positive breast cancer, you will also begin receiving fulvestrant. Fulvestrant is given as two intramuscular injections on Day 1 of each cycle, and also on Day 15 of Cycle 1 only.

Each time you return to clinic at the beginning of a new cycle, you will have the following tests and procedures:

- Physical exam (exam will also take place on Days 8, 15 & 22 of Cycle 1)
- Blood tests to check your blood counts and organ function (approximately 2 teaspoons of blood will be drawn from a vein in your arm)
- CT scan or MRI (every other cycle)
- Talking about any additional medication you are taking or symptoms/health problems you are having

Additionally, 2 tablespoons of blood will be drawn for research purposes on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Day 1 of each odd numbered cycle, and at the end of treatment.

You may continue in the study as long as you wish or until you experience unacceptable side effects, your disease gets worse, or your doctor believes it is in your best interests to withdraw. It is possible that if your disease progresses while you are taking neratinib, you may be able to continue to receive neratinib in combination with a drug called trastuzumab if it is covered by your health insurance. The dosing and scheduling of trastuzumab will be done as dictated by your study doctor; trastuzumab is usually given as an IV infusion once every 2 weeks. Trastuzumab in combination with Neratinib is

considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA). If you are taking neratinib and fulvestrant and your disease progresses, you may be able to continue to receive both drugs in combination with trastuzumab if it would otherwise be part of your routine care. Trastuzumab is approved by the FDA for the treatment of HER2-positive breast cancer, but has not been approved by the FDA for the treatment of HER2-negative breast cancer and is considered investigational.

At the End of Treatment visit, you will have the following tests and procedures:

- Physical exam
- Blood testing
- CT or MRI

You may be asked to have an OPTIONAL tumor biopsy if your disease progressed on neratinib. The tumor tissue collected from this biopsy will be sent to a CLIA-certified laboratory at Washington University School of Medicine and a genetic mutation analysis will be performed on the tissue. CLIA-certified means that the Food and Drug Administration (FDA), Center for Medicaid Services (CMS), and the Center for Disease Control (CDC) work together to make sure the laboratory does quality laboratory testing. The analysis will check up to 122 genes to see if your tumor tissue has any mutations associated with those genes. The analysis will be reviewed by a doctor who is board-certified in Genetics. Only findings on the 122 genes will be returned to you and your doctor, these are called primary findings. The report that will be provided to you and your doctor will be a written report and it will highlight any mutations that may be associated with any FDA approved treatment options or any other courses of action that may be taken. The report will be provided to you and your doctor in 3-4 weeks after the biopsy is obtained if you agree to receive this report. There is not a test or another analysis to confirm these results as this analysis is a validated clinical test. The results will only be returned to you once as the research team will not be continuously checking samples as time passes to see if more relevant results are found. You may ask your doctor any questions about the results of the genetic mutation analysis. You may also ask your doctor for a listing of additional resources, such as a genetic counselor, if you feel that you would like to learn more about the report; however, you will be responsible for any costs associated with these additional services. Incidental findings are not being analyzed or reported. Incidental findings are findings from a genetic analysis that are outside from what is being studied.

The leftover tumor tissue will be used for research purposes to understand why the tumor progressed on neratinib.

| I agree to have a biopsy for research purposes if my tumor progresses on neratinib: |
| --- |
| ___ yes ___ no _____ initials |

I agree to receive the mutation analysis report from the tumor biopsy obtained when my tumor progressed on neratinib:

___ yes ___ no _____ initials

After you stop receiving treatment as part of this study, you will be contacted 30 days after your last treatment. This follow-up will involve either a telephone call from a research coordinator or having the research coordinator check through your medical records, or office visits (if needed).

Genomic Research

By participating in this trial, you agree that tumor samples from your previous breast cancer diagnostic or therapeutic procedures and the optional biopsies will be used for genetic and genomic research, including whole genome sequencing. In addition, all participants in this trial will have 2 teaspoons of blood drawn for genetic and genomic research, including whole genome sequencing.

Genes are a unique combination of molecules (called DNA) that we inherit from our parents. There are millions of tiny differences in our genes that determine things like our height or the color of our eyes. Some of these differences may make some people more or less likely to develop certain diseases or make people respond to medicine in different ways. Genomic research will look at the differences in specific genes or may involve sequencing a large amount of your DNA. This sequencing will provide a detailed description of your DNA and is also called whole genome sequencing. We may also perform a full genetic analysis of your tumor and blood samples to look for gene variations. This analysis may reveal information about your hereditary risk of developing other diseases or serious illness and, if this information were revealed, might affect your privacy. The samples will be stored for an indefinite period of time. The results of these research sequencing analyses of the blood will not be available to you or your treating physician.

This genetic information may be shared with other scientists over the internet. This is so scientists across the country can better work together to cure disease. Information will be shared two ways:

1. your genetic data will be shared through a publicly available database in a summary format grouped together with other individuals' data
2. individual-level data will be shared through a controlled-access database (which means that only people who have been authorized may view the information kept in the database)

Traditional information that can identify you, such as your name and address, will not be included in either database. However, it is possible that people could develop ways in the future to link the information in a genetic database back to you. For example, everybody's DNA (except identical twins) is unique, but some genetic information is shared with one's biological relatives, which might provide a method for comparison between databases if the information was available. Although the real risk is small, some people are concerned that this genetic information will be gathered by people other than scientists and used to identify or discriminate against you.

I agree to have whole genome sequencing performed on my samples for research purposes:

___ yes ___ no _____ initials

**Will you save my samples or research data to use in future research studies?**

As part of this study, we are obtaining blood, tissue, and data from you. We would like to use this blood, tissue, and data for studies going on right now as well as studies that are conducted in the future, including possible genetic research. These studies may provide additional information that will be helpful in understanding breast cancer, or other diseases or conditions, including research to develop investigational tests, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your blood, tissue, and data you give up any property rights you may have in it.

Your tumor tissue may also be used to develop cell or animal models for research. These models may be used for future research to test how the tumor responds to new treatments before they are tested in humans.

We will share your blood, tissue, and data with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at Washington University, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

Researchers may use your tissue specimens obtained from the OPTIONAL tumor biopsies to grow in mice and establish mice xenografts (which means that cells from your tumor will be transplanted into mice). These xenograft tumors along with de-identified genetic data will be shared with researchers so that they can use them in a variety of projects to develop laboratory tests to study the effects of various drugs on human tissues and cells, or may be grown as "preclinical models" in animals such as mice to learn how tumors respond to new drugs for cancer, including the development of tests, studies in genetics, and the evaluation of new treatments for cancer. The samples will be stored for an indefinite period of time.

If you change your mind and do not want us to store and use your blood, tissue, and data for future research, you should contact the research team member identified at the top of this document. The blood, tissue, and data will no longer be used for research purposes. However, if some research with your blood, tissue, or data has already been completed, the information from that research may still be used. Also, if it has been shared with other researchers it might not be possible to withdraw it to the extent it has been shared.

If you signed the screening consent form, you either agreed or did not agree to this. If you did not sign the screening consent form, please complete the boxes below indicating whether researchers can use your specimens and data for future research:

My tissue and blood may be stored and used for future research as described above.

___ yes ___ no _____ initials

My tissue and blood may be shared with other investigators and used by these investigators for the future research as described above.

___ yes ___ no _____ initials

My data may be stored and used for future research as described above.

___ yes ___ no _____ initials

My data may be shared with other investigators and used by these investigators for the future research as described above.

___ yes ___ no _____ initials

**HOW MANY PEOPLE WILL PARTICIPATE?**

Approximately 77 people will receive treatment with neratinib in the phase II portion of the study. A maximum of 67 people who enroll will receive fulvestrant in addition to neratinib. This study is taking part at Washington University and also at other research institutions in the country.

**HOW LONG WILL I BE IN THIS STUDY?**

If you agree to take part in this study, your involvement will last until one or more of the following occur:

- Your cancer gets worse
- You develop another condition that prevents you from receiving study treatment
- You develop unacceptable side effects
- You decide to withdraw from the study
- Your study doctor decides to withdraw you from the study

After you come off study, you will be followed for 30 days after your last treatment to check your health status (as described above).

## WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

**Some risks described in this consent document, if severe, may cause death.**

Risks of Neratinib

*Very Common (≥ 10%)*

- Diarrhea
- Nausea
- Abdominal pain
- Vomiting
- Pain, redness, swelling or sores in the mouth, and/or throat
- Fatigue
- Decreased appetite
- Muscle spasms
- Skin reaction (includes rash, dry skin, itching, skin eruption, skin redness, skin reaction on the palms of the hands or soles of the feet (such as tingling, numbness, pain, swelling, or reddening)

*Common (between 1 and 10%)*

- Increased liver enzymes, which could indicate liver damage
- Indigestion
- Urinary tract infection
- Weight loss
- Dehydration
- Nose bleed
- Abdominal distension
- Nail disorder (inflammation/infection, breaking or discoloration)
- Dry skin including deep skin cracking and/or dry mouth
- Blood creatinine increased (an increase in an enzyme that measures the function of the kidney)

*Uncommon (less than 1%)*

- Blood bilirubin increased (an increase in an enzyme that measures the function of the liver)
- Renal failure (damage to the kidney which may decrease its functioning)

Diarrhea and vomiting can quickly lead to dehydration. If you get very dehydrated, this could make your blood pressure low and could make it hard for your kidneys to clean your blood. If the dehydration is not treated, this could lead to a subtype of kidney failure called pre-renal failure. This kidney failure gets better when fluids are given. Patients who suffered from pre-renal failure while taking neratinib on other studies have all recovered their kidney function.

Symptoms of mild dehydration include thirst, decreased urine volume, abnormally dark urine, unexplained tiredness or fatigue, irritability and negative mood, headache, dry mouth and dry skin,

dizziness when standing, and in some cases insomnia. Other possible symptoms include cloudy urine and stinging during urination.

Make sure you drink enough liquids each day (8 to 10 large glasses or cups). If you have severe diarrhea and/or vomiting, even for a short period of time, and you are experiencing any of the above described signs of dehydration, call the study doctor immediately

*Other potential side effects of neratinib*
The side effects listed below have been reported with neratinib; however, the relationship of these events to treatment with neratinib is unknown at this time. They occurred in uncommon to rare (≥0.1% - < 1%) between 1 and 9 subjects in 1000, but can be ultimately life-threatening if not treated rapidly. Call your study doctor immediately if you experience any of the symptoms described in the section below.

- Severe liver damage. There have been reports of patients taking neratinib who have had severe changes in liver function tests which may indicate liver damage. Based on the reports observed so far, these changes appear to be reversible when neratinib is stopped. If you experience diarrhea or any worsening of fatigue, nausea, vomiting, abdominal pain or tenderness, fever, or rash, notify your doctor immediately as these may be associated with changes in liver function tests.
- Interstitial lung disease. One patient with non-small cell lung cancer who was treated with neratinib experienced interstitial lung disease, which is an inflammation of the lungs that is similar to pneumonia. This could have been caused by neratinib. The patient's health improved when she stopped taking neratinib and began to take steroids and anti-infection medication to treat this side effect. If you feel shortness of breath along with fever or cough, please let your study doctor know immediately.

**Risks of Taking Neratinib with Acid-Reducing Medication**
The absorption of neratinib in the stomach is dependent on stomach acidity. Medications that reduce the secretion of gastric acid in the stomach such as antacids, proton pump inhibitors (such as Lansoprazole), and H2-receptor antagonists (such as ranitidine) may affect how neratinib dissolves in the stomach. It has been observed that a single 240-mg dose of neratinib combined with a proton pump inhibitor lowered the absorption of neratinib up to seven-fold. It is not known whether separating the time of taking a proton pump inhibitor and neratinib reduces the interaction. If you are required to take a H2-receptor antagonist (such as ranitidine) to reduce stomach acid, take neratinib 10 hours after taking the medication and at least 2 hours before the next dose of that medication. If antacids are necessary, the antacid dose and the neratinib dose should be separated by 2 to 4 hours. If you have any questions, you should consult with your doctor about what type of acid-reducing medication you are taking.

Risks of Fulvestrant
Common, Some May Be Serious (in 100 people receiving Fulvestrant, more than 20 and up to 100 may have):

- Pain
- Tiredness
- Increased sweating
- Hot flashes, flushing

- Swelling and redness at the site of the medication injection

Occasional, Some May Be Serious (in 100 people receiving Fulvestrant, from 4 to 20 may have):

- Constipation
- Diarrhea
- Nausea
- Vomiting
- Loss of appetite
- Heartburn
- Swelling of the body
- Loss of bone tissue, broken bone, or decreased height
- Dizziness
- Headache
- Difficulty sleeping
- Fluid around lungs
- Swelling of the liver which may cause belly pain
- Worry, depression, mood swings
- Hair thinning
- Cough

Rare, and Serious (in 100 people receiving Fulvestrant, 3 or fewer may have):

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Liver damage which may cause yellow eyes and skin
- Vaginal bleeding
- Blood clot which may cause swelling, pain, shortness of breath
- Heart attack or heart failure which may result in chest pain, shortness of breath, swelling of ankles, and tiredness
- Stroke which may cause weakness, paralysis

<u>Risks of Trastuzumab</u>

- Fever
- Nausea
- Vomiting
- Infusion reactions, which could include flushing, shortness of breath, swelling, headache, or low blood pressure
- Diarrhea
- Infection
- Increased cough
- Headache
- Fatigue
- Shortness of breath
- Rash

- Low white blood cell count, which could increase your risk of infection
- Low red blood cell count, which could cause fatigue
- Muscle aches
- Congestive heart failure or other heart problems
- Weight loss
- Upper respiratory tract infections

- Low platelet count, which could increase your risk of bleeding
- Heartburn

Risks of Blood Draws

Possible side effects from a blood draw include fainting, dizziness, pain, swelling, bruising, or bleeding where the needle is inserted. There is also a slight possibility of infection where the needle is inserted.

Risks of Tumor Biopsies

Your doctor will inform you in detail about the risks associated with the biopsy. The level of risk will depend on where the tumor is located. In general, having a biopsy can cause pain, swelling, bleeding and/or infection at the site where the biopsy penetrates through your skin. There is also the possibility that having this procedure may shift some cells from the tumor into the surrounding tissues that come in contact with the biopsy needle. This means that the tumor may spread to that particular area. Depending on the area of the biopsy, a local anesthetic (to numb the area) may be injected into the skin, or a sedative medication may be given orally or intravenously. You will remain conscious during this procedure. The risks of this anesthetic are minimal and include bleeding, bruising, infection, and allergic reaction. The risks associated with use of a sedative are similar, but also included drowsiness, slurred speech, staggering gait, poor judgment, and slowed reflexes.

Risks of MUGAs

The MUGA (Multiple Gated Acquisition) scan is used to assess the function of the heart. The MUGA scan produces a moving image of the beating heart, and from this image several important features can be learned about the health of your heart. A small amount of low-level radioactive substance (tracer) is injected into your vein and temporarily "labels" your red blood cells. Then the heart is scanned by a camera which can "see" the marked blood and produce the moving image. The final product is a movie of the heart beating. Allergic reactions to the tracer are rare. Most of the tracer will be eliminated from your body within a day. You may have some pain or swelling where the tracer is injected into your vein.

Risks of Echocardiograms

An echocardiogram is a test that uses sound waves to create a moving picture of the heart. An instrument that transmits high-frequency sound waves called a transducer is placed on your ribs near the breast bone and directed toward the heart. You should feel no pain with this test. You may experience discomfort from lying quietly for a long period of time.

Risks of CT Scans

CT scans involve exposure to radiation. Although the amount of radiation exposure is higher than a typical x-ray, the risk of harmful effects from a single exam is very small. If you are scheduled for a CT

with contrast, the dye that is injected into a vein for the scan is usually well tolerated. Some people feel dizzy, queasy, or get a headache when given the dye or notice a cold feeling near the injection site. There is a rare chance of having an allergic reaction to the dye that very rarely can be serious or life threatening. You must tell your doctor if you have had bad reactions to dyes before. There is also a rare chance that a CT scan may cause a malfunction of worn or implanted electronic medical devices.*

* If you wear or have electronic medical devices implanted such as a pacemaker or a drug pump, please make sure you tell your study doctors and research staff. It was recently reported by the FDA that the CT scan may cause a malfunction of electronic medical devices.

Risks of MRIs

You may be uncomfortable inside the MRI scanner if you do not like to be in closed spaces ("claustrophobia"). During the procedure, you will be able to talk with the MRI staff through a speaker system. You can tell them to stop the scan at any time.

The MRI scanner produces a loud hammering noise, which has caused hearing loss in a very small number of patients. You will be given earplugs to reduce this risk.

If you have a device such as a pacemaker, bone hardware, or device placed in your uterus there may be additional risks. We will review what device you have and inform you of these risks. In general, these risks could be:

- heating or movement of the device
- device malfunction
- damage to the tissue that surrounds the device.

If you have a skin tattoo, including cosmetic tattoos (eye-liner, lip-liner) you could experience the following:

- irritation, swelling or heating in the area of the tattoos
- in rare instances a primary or secondary burn.

If you have a tattoo we will offer you a cold, wet washcloth to put over the tattoo to reduce this risk.

A contrast agent, such as gadolinium, may be used during the MRI scan to make the pictures clearer. Recent information shows that when you receive gadolinium repeatedly it may collect in the brain. This would apply whether you receive the gadolinium as part of a research study or as part of your healthcare. The importance of this information and how it impacts your health are not known.

Gadolinium given during pregnancy could cause a still birth or the baby could have skin diseases later in their childhood. If you are a woman of child-bearing age, you must have a negative urine pregnancy test within 24 hours prior to getting the gadolinium.

Risks of Pregnancy and Nursing

Some parts of this study might cause physical or mental problems in an unborn baby. You must tell the doctor immediately if there is any chance you are pregnant. You must also tell the doctor if your birth control method fails while you are on the study. If you are a woman of childbearing potential, you should avoid becoming pregnant for at least 3 months after finishing treatment. Additionally, you

should use a highly effective method of birth control during the time you are receiving treatment and for at least 3 months after finishing treatment. Highly effective methods of birth control include use of established oral, injected, or implanted hormonal methods of birth control, IUD, or IUS.

It is not known whether neratinib is excreted in human milk; mothers should discontinue nursing prior to taking neratinib.

Risks Associated with Genomic Research

It may be possible that genetic information from family members could be used to try to identify your sample. Similarly, it may be possible that genetic information from the sample could be used to help identify family members. Even though the online databases developed for this project will NOT contain information that is traditionally used to identify you, people may develop ways in the future that would allow someone to link the genetic or medical information in these databases back to you.

There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans and employers with greater than 15 employees to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance or long term-care insurance.

Risks of Breach of Confidentiality

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure, and we think the risk of accidental disclosure is very small. Please see the section in this consent form titled "*How will you keep my information confidential?"* for more information.

Even though the online databases developed for storing some information about your data, tissue, and blood will NOT contain information that is traditionally used to identify you, such as date of birth, social security number, medical record number, etc., people may develop ways in the future that would allow someone to link the genetic or medical information in these databases back to you. For example, someone could compare information in one of these databases with information from you (or a relative) in another database and be able to identify you (or your relative). It is also possible that there could be violations in the security of the computer system used to store the codes linking your genetic and medical information to you.

## WHAT ARE THE BENEFITS OF THIS STUDY?

You may or may not benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because it might help in the development of more effective treatments for HER2-negative breast cancer.

## WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could:

- get treatment or care for your cancer without being in a study

- take part in another study
- get no treatment
- get comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

**WILL IT COST ME ANYTHING TO BE IN THIS STUDY?**

As part of this study you will receive tests and procedures that are similar to what you would receive during routine clinical care of your condition. Your health plan/insurance company will be billed for some or all of these costs, and you will be responsible for any co-pays and deductibles that are normally required by your health plan/insurance. Not all insurance plans cover the costs associated with being in a study. Even if they do, you may be responsible for more out-of-pocket expenses, such as co-pays and deductibles, when there are more tests and procedures or more expensive tests and procedures involved in the study than if you were to receive routine clinical care outside the study.

If you wish to know whether there are more tests and procedures or more expensive tests and procedures in the study, you should ask your study doctor.

If you wish to know whether your insurance will pay, you should contact them directly, or speak with the study team about obtaining a financial pre-certification prior to enrolling in this study.

**WILL I BE PAID FOR PARTICIPATING?**

You will not be paid for being in this research study.

**WHO IS FUNDING THIS STUDY?**

Puma Biotechnology, Fashion Footwear Association of New York, Barnard Trust, and the Department of Defense are funding this research study. This means that Washington University is receiving payments from these sources to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from these sources for conducting this study.

**DOES THE INVESTIGATOR OR OTHER RESEARCH TEAM MEMBER HAVE A PERSONAL FINANCIAL INTEREST IN THIS STUDY?**

Dr. Michael Naughton, a member of the study team, is a paid speaker for AstraZeneca, the manufacturer of fulvestrant. Dr. Naughton is also a paid speaker and consultant for Genentech, the manufacturer of trastuzumab.

**WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?**

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator, Dr. Cynthia Ma, at (314) 362-8903 and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

**HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?**

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- Puma Biotechnology, manufacturer of neratinib
- Your primary care physician if a medical condition that needs urgent attention is discovered
- Public health agencies to complete public health reporting requirements
- Hospital or University representatives, to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and be available to your health care providers who are not part of the research team.
- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.
- The Siteman Cancer Center Clinical Trials Office
- The Quality Assurance and Safety Monitoring Committee at the Siteman Cancer Center for auditing purposes
- The independent research monitor, who is responsible for monitoring the conduct of this study

The research team will send study results to Puma Biotechnology. Information sent to Puma Biotechnology will be de-identified and will be used for the evaluation of this research study, the drug, and/or cancer. In the future, Puma Biotechnology may continue to use your health information that is collected as part of this study. For example, Puma Biotechnology may combine information from this study with the results of other studies to re-analyze the safety and effectiveness of the study drug, to evaluate other products or therapies, to develop a better understanding of a disease, or to improve the design of future research studies. Puma Biotechnology may also share information from the study with regulatory agencies in foreign countries.

The Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital is supported by funding from the National Cancer Institute (NCI). To meet NCI requirements, your PHI relating to your participation in this study (including your social security number) will be stored in a secure database at the Siteman Cancer Center. This database and also your treatment records may be reviewed by Siteman Cancer Center personnel. All information will be securely and confidentially maintained.

If you receive Medicare benefits, are injured as part of your participation in this research study and medical treatment relating to this injury is paid by anyone other than you or your insurance company, that payer will need to collect personal information about you. This information includes your name, date of birth, gender, social security number, Medicare identification number and information related to this research study. The payer will report this information to the Centers for Medicare & Medicaid Services (CMS), the federal agency that oversees the Medicare program, during your participation in the study and for as long as the payer is required by CMS to report this information. If you do not want to release your personal or treatment related information you have the right to refuse reimbursement by the payer for any research injury. The payer will not use this information for any other purpose.

To help protect your confidentiality, we will ensure that all patients identified and recruited for this study are within the HIPAA protected population of the research team at Washington University. You will have an opportunity to ask questions about this study privately. The research location will be in the clinic and treatment areas of the Center for Advanced Medicine where precautions are made to protect the privacy of all patients, not only research or non-research patients. Medical records are considered confidential and records are kept in a secured area accessible to those involved in the conduct of the study. You will not be identified by name in any publication or presentation of the results of this study unless prior written consent is obtained. Your information that is collected for the purpose of this study will be stored as coded information on paper forms in locked cabinets and locked offices or in a password-protected database that only the study personnel will have access to which is also maintained in a locked office. A master list will be stored off-line (in a locked cabinet in a locked office) and available only to the Principal Investigator and his designee(s). If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

This consent form or similar documentation that you are participating in a research study will be included in your clinical medical record. Anyone with access to your medical record, including your health insurance company will be able to see that you are participating in a research study.

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

**Are there additional protections for my health information?**

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?".

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

**If you decide not to sign this form, it will not affect**

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

**If you sign this form:**

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).

  To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at http://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the Investigator send you a copy of the letter.

  - **If you revoke your authorization:**
    - The research team may only use and share information already collected for the study.
    - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
    - You will not be allowed to continue to participate in the study.

## IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

## What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at http://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

If you decide to leave the study early, we will ask you to tell the study doctor if you are thinking about stopping so any risks can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

**Will I receive new information about the study while participating?**

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

**Can someone else end my participation in this study?**

Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because staying in the study would be harmful, you need treatment that is not allowed while on the study, you fail to follow instructions, you become pregnant, you develop a major side effect, or the study is canceled.

**WHAT IF I HAVE QUESTIONS?**

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Dr. Cynthia Ma, (314) 362-8903**.** If you experience a research-related injury, please contact Dr.

Ma as well; if this is after hours, you will be directed to the exchange number which will be covered by a resident or fellow on call. Please tell this person that you are a research participant.

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office, 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office website, http://hrpo.wustl.edu. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

**Do not sign this form if today's date is after EXPIRATION DATE: 01/13/22.**

_____ _____

(Signature of Participant) (Date)

_____

(Participant's name – printed)

**Statement of Person Who Obtained Consent**

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that they understand the risks, benefits, and procedures involved with participation in this research study.

_____ _____

(Signature of Person who Obtained Consent) (Date)

_____

(Name of Person who Obtained Consent - printed)