VUMC Institutional Review Board
Informed Consent Document for Research

Study Title: BRE23172 - Neoadjuvant Neratinib in Stage I-III HER2- Mutated Lobular Breast Cancers NCT05919108
Version Date: 16OCT2023
PI: Laura Kennedy, MD

Part 1 of 2: MASTER CONSENT
Treatment Consent Form

Name of participant: _____ Age: _____

You are being invited to take part in a research study. This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study this consent form includes two parts. Part 1 of this consent form is the Master Consent and includes information that applies to all study sites. Part 2 of the consent form is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts together are the legal consent form and must be provided to you.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:
You are being asked to take part in this research treatment study because your breast tumor has an eligible *EGFR* or *HER2* mutation and you have been diagnosed with a special type of breast cancer called lobular carcinoma.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

This study is looking to see if adding a new drug, neratinib, to your normal therapy is better at treating your cancer than the endocrine therapy you would normally have. Neratinib is approved by the FDA to treat a type of breast cancer that is HER2-positive or HER2-overexpressing following surgery. This study will see if adding neratinib before surgery can be helpful at treating tumors that have a mutation in *HER2* or *EGFR*.

You may experience side effects during your participation in the treatment study. Common side effects from the normal endocrine-based therapy include hot flashes, flushing, headache, dizziness, mood

disturbances, increased sweating, whole body pain, nausea, constipation, swelling and water retention, tiredness, abnormal increase in liver enzyme tests, vaginal discharge and bleeding, and abnormal increase in cholesterol. Common side effects from neratinib include diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, inflammation of the mouth, decreased appetite, muscle spasms, indigestion, liver damage, nail disorder, dry skin, abdominal distention, weight decreased and urinary tract infection. You will be asked to take a drug to prevent the diarrhea and we will closely monitor your other symptoms to make sure they do not get too severe.

This study will also collect a fresh tumor biopsy after the first four weeks of treatment and tissue from your surgery for additional research studies to look at how the biology of the tumor changes with treatment. Additionally, some of the tumor tissue collected will be used to develop breast cancer models that can be used for future studies.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research treatment study because you have just been diagnosed with early-stage (stage I-III) lobular breast cancer and your tumor has an eligible mutation in *EGFR* or *HER2*. As part of this study, you will receive the new drug, neratinib, along with your normal endocrine therapy you would receive if you were not participating in this study. This treatment will be followed by surgery.

You will either receive endocrine only therapy OR neratinib plus endocrine therapy for 4 weeks. You will then undergo a research biopsy, which will be followed by 20 more weeks of neratinib plus endocrine therapy. After 24 weeks of therapy, you will undergo your normal breast surgical procedure. The study team will review your medical record and collect additional information on how you are doing for a period of time up to 10 years.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain

a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:

Side effects from neratinib include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving neratinib, more than 10 and up to 100 may have:
• Diarrhea • Nausea • Abdominal pain • Vomiting • Stomatitis – inflammation and redness of the mouth that can lead to pain and difficulty talking, eating, and sleeping • Dyspepsia – abdominal discomfort, described as burning sensation, bloating or gassiness, nausea, or feeling full too quickly after starting to eat • Fatigue • Decreased appetite • Muscle spasms • Rash
UNCOMMON, SOME MAY BE SERIOUS In 100 people receiving neratinib, from 1 to 10 may have:
• Abnormal swelling of the abdomen • Dry mouth • Increased SGOT (AST/SLT) – enzymes that are normally present in liver and heart cells; indication of liver failure • Urinary tract infection • Weight decreased • Dehydration • Nose bleed • Dry skin • Nail disorder • Skin ulcer

If you are post-menopausal, your endocrine-based therapy will include letrozole.

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Side effects of letrozole (Standard of Care) include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving letrozole, more than 10 and up to 100 may have:
• Increase in total cholesterol • Hot Flashes/Flushes • Arthralgia/Arthritis • Night Sweats • Bone Fractures • Weight increase • Nausea
UNCOMMON, SOME MAY BE SERIOUS In 100 people receiving letrozole, from 1 to 10 may have:
• Fatigue • Muscle aches and pains • Swelling • Weight decrease • Vaginal bleeding • Back pain • Depression • Vaginal Irritation • Headache • Pain the arms and legs • Loss of bone mineral density • Dizziness/Light-Headedness • Hair loss • Vomiting • Cataract • Constipation • Breast pain

For patients who are not postmenopausal (women) or surgically sterile (absence of ovaries and/or uterus or vasectomy), agreement to remain abstinent or to use two adequate methods of contraception (e.g., condoms, diaphragm, vasectomy/vasectomized partner, tubal ligation), during the treatment period and for at least 30 days after the last dose of study treatment. Hormone based oral contraceptives are not allowed on study.

If you are pre-menopausal, your endocrine-based therapy will include letrozole with ovarian suppression with leuprolide or goserelin. Leuprolide or goserelin are standard therapies used for ovarian suppression during breast cancer treatment.

Common side effects (>10%) of leuprolide include: hot flush; injection site pain; upper respiratory infection; and fatigue.

Common side effects (>10%) of goserelin include: hot flushes; headache; sweating; acne; rapid and often exaggerated changes in mood; depression; decreased sexual desire; vaginal inflammation; nausea; breast atrophy; red, itchy rash and white scales on the scalp; and swelling in the arms, legs, and feet.

Other Risks:
Tumor biopsy: The risks of a biopsy can include bleeding, pain, and infection. To reduce these risks, the site of the biopsy will be numbed, and sterile techniques will be used. Your doctor will discuss with you the safest method and location to perform these biopsies. You will sign another consent form that will describe the biopsy procedure, associated risks, and options to minimize side effects.

Breach of confidentiality: As this study involves the use of your identifiable information, there is a potential for a breach of confidentiality. To prevent this, the data and tissue samples collected on this study will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password.

Good effects that might result from this study:
The benefits to science and humankind that might result from this study: This study will teach us if adding a tumor-targeted therapy to treat early-stage breast cancer is better at treating your cancer than endocrine-based therapy alone. This study will also help us better understand how the biology of the tumor will change with targeted treatment.

Procedures to be followed:
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 treatment study. Some of these tests or procedures are part of your regular cancer care and will be done even if it turns out that you do not take part in this study. If you have had some of these test or procedures recently, they may or may not have to be repeated.

- **Physical/ Breast Exam with Tumor Measurement (palpation):** During the screening visit you will have a physical exam, which will include measuring your weight and vital signs (blood pressure, heart rate, and breathing rate) and breast exam. 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.
- **A medical history**, which includes questions about your health, current medications, any allergies, and hormone status of your breast cancer.

- **Performance status,** which evaluates how you are able to carry on with your usual activities.
- **Blood tests.** Blood will be drawn to measure blood counts, organ function and for other safety reasons.
- **Serum (blood) pregnancy test** for women of child-bearing potential. About 1 to 2 teaspoons of blood is required for this test.
- **An assessment of your tumor** by one or more of the following standard assessment tools: Mammogram, Ultrasound, or breast MRI
- **Research blood tests:** A blood sample will be collected to study DNA related to your cancer. DNA (deoxyribonucleic acid) is found in each cell of your body and circulating tumor DNA is DNA from the tumor that is released into the bloodstream. The blood sample will be approximately 1.5 tablespoons.

After the procedures listed above confirm you are still eligible to participate in the research treatment study, you will begin study treatment.

You will be randomly assigned ("randomized") into one of the study groups:

- Treatment A: normal endocrine therapy for 4 weeks
- Treatment B: normal endocrine therapy plus neratinib for 4 weeks

The choice of endocrine therapy will be dictated by your doctor and menopausal status.

Randomization means that you are put into a group by chance. You and your doctor will know what group you will be in. You will have a 50% chance of being placed in Arm A and a 50% chance of being placed in Arm B.

All participants will then undergo a research breast tissue biopsy.

After the first 4 weeks, all participants (Treatment A and Treatment B) will receive the endocrine therapy plus neratinib for 20 weeks. After therapy is over, all participants will undergo breast surgery. Type of breast surgery will be based on your preference and provider recommendations. This study is not dictating type of breast surgery.

Every 4 weeks while on treatment, the following will occur:

- **Performance status,** which evaluates how you are able to carry on with your usual activities.
- **Blood tests.** Blood will be drawn to measure blood counts, organ function and for other safety reasons.

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The following will occur at Week 16 and Week 24:

- **Physical/ Breast Exam with Tumor Measurement (palpation):** During the screening visit you will have a physical exam, which will include measuring your weight and vital signs (blood pressure, heart rate, and breathing rate) and breast exam. 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.

The following will occur at Week 4 and Week 6:

- **Research blood tests:** A blood sample will be collected to study DNA related to your cancer. DNA (deoxyribonucleic acid) is found in each cell of your body and circulating tumor DNA is DNA from the tumor that is released into the bloodstream. The blood sample will be approximately 1.5 tablespoons.

Prior to surgery, the following will occur:

- **An assessment of your tumor** by one or more of the following standard assessment tools: Mammogram, Ultrasound, or breast MRI

At the time of surgery, tissue samples from your tumor will be collected for planned research studies.

Leftover tissue from samples collected as part of this study will be kept for an unknown length of time (maybe years) for future research. The samples will be destroyed when they are no longer needed. Your samples may be used to make new products, tests or findings. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

Your samples and information about you may be shared with others to use for research. To protect your privacy, we will not release your name.

Reasons why the study doctor may take you out of this study:
Your doctor will talk with you about going off the study if:

- Your health changes and the study is no longer in your best interest
- New information becomes available that may affect your health or your willingness to continue in the study.
- The study is stopped by the sponsor, Institutional Review Board (IRB) or the Food and Drug Administration (FDA).

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What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:
A description of this clinical trial will be available on 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 Web site at any time.

Clinical Trials Reporting Program.
Vanderbilt's NCI-Designated Cancer Center or the Sponsor registers National Cancer Institute (NCI)-supported clinical trials with NCI though their Clinical Trials Reporting Program (CTRP) to provide study related information. The data provided will include the following identifiable information that may identify you: birth month/year and five-digit zip code. NCI uses the data to manage and enhance the nation's investment in cancer research.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you. Future research may include whole genome sequencing (human germline or somatic specimen with intent to generate genome or exome sequencing).

Study Results:
You will be told whether or not your breast tumor has a mutation in *EGFR* or *HER2*. You will not be directly informed of the study results. At study completion, all results will be available on www.clinicaltrials.gov, as required by U.S. Law. Study results may also be presented in meetings or in publication.