Informed Consent Form Title: An Exploratory Study of Neoadjuvant Endocrine Therapy in Hormone Receptor-Positive HER2-Negative Node-Negative Breast Cancer Patients to Assess Responses and Mechanisms of Endocrine Resistance

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Medical College of Wisconsin and Froedtert Hospital
INTRODUCTION TO THE INFORMED CONSENT

Name of Subject: _____

An Exploratory Study of Neoadjuvant Endocrine Therapy
in Hormone Receptor-Positive HER2-Negative Node-Negative Breast Cancer Patients to
Assess Responses and Mechanisms of Endocrine Resistance

Lubna Chaudhary, MD, MS
Department of Medicine
414-805-6700
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee WI 53226

You are invited to take part in this research. You can decide whether to take part in this project or not. You are free to say yes or no. If there is anything that you do not understand, please ask questions.

Definitions

Medical Oncologist – is a physician who specializes in drug-based treatments for cancer (for example chemotherapy and hormone therapy).
Performance status – an assessment of how much you can participate in your activities of daily living.
Principal Investigator - The Principal Investigator is responsible and accountable for the research project.

Purpose

This project is being done to assess if tumor-based biomarkers have a connection to disease response with anti-estrogen therapy.

Length

- You will be in this research project for about 4 weeks (+/- 1 week), depending on surgery date.
- We would also like to follow you annually for up to 5 years after your surgery.

Procedures

There is no placebo in this project. All patients will be treated with anti-estrogen therapy.

List of visits:

- Screening Visit
  - Total Number: 1
  - Total Time: 1 hour
- Week 1, Day 1 Visit
  - Total Number: 1
  - Total Time: 1 hour
- End of Treatment Visit
  - Total Number: 1
  - Total Time: 30 min
- Follow up Visits
  - Total Number: 5
  - Total Time: ~30 min

Procedures that will occur at various visits:

Invasive Procedures

- Additional biopsies for more tissue for Oncotype test, if applicable.
- Blood Sample Collection at screening or Week 1, Day 1 visit.

Non-invasive Procedures

- Physical Exam
- Vitals: blood pressure, pulse
- Medical History
- Performance status
- Recurrence Status
- Adverse Event assessment
- Current Medications assessment

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

Aromatase Inhibitors risks:

- Fatigue
- Joint musculoskeletal pain
- Loss of bone density over time

Tamoxifen risks:

- Fatigue
- Sweating / hot flashes
- Decreased libido

Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:

- Joining a different project
- Routine care for this condition
- Getting no treatment for this condition

If you have more questions about this project at any time, you can call Dr. Lubna Chaudhary at 414-805-6700.

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are being invited to participate in this research because you have been diagnosed with invasive breast cancer and are a candidate for anti-estrogen (hormonal) therapy.

A total of about 37 people are expected to participate in this research at the Medical College of Wisconsin/Froedtert Hospital, St. Joseph's Hospital, and Community Memorial Hospital.

The Director of the project is Dr. Lubna Chaudhary in the Department of Hematology and Oncology. A research team works with Dr. Lubna Chaudhary. You can ask who these people are.

Rock River Foundation and the Medical College of Wisconsin Cancer Center are funding the study.

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this project, you do not have to stay in it. You may stop at any time.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

In this study, we want to see if tumor-based biomarkers have a connection to disease response with anti-estrogen therapy. Biomarkers are part of the tumor cells and their levels in the tumor tissue may have a relationship with treatment response. We plan to look at your tissue samples before and after your anti-estrogen therapy for research purposes.

We would like to see if these biomarker levels might help predict treatment response in the future. The purpose is not to discover information that could be used to change your medical care or make a change to your diagnosis.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

<u>Screening procedures:</u>

If you decide to join, some screening tests will be done first to see if you are eligible.

- Breast mammogram and ultrasound on the side where your breast cancer is located. These exams may have already been done to diagnose your breast cancer.
- Medical Oncologist consultation
- OncotypeDx testing if recommended

- Physical exam including measurements of weight and vital signs (blood pressure, pulse) and performance status.
- Collect information on medications you are taking
- Collect information on your medical history and any current symptoms you have
- Specimen collection for study biomarkers from archived tumor tissue from your initial cancer diagnosis
- Blood tests will be obtained (approximately 3 tablespoons will be drawn from your vein) to assess your general health and organ function.
- Pregnancy test, if applicable

If you are interested in participating in the study, you will also need to meet with a medical oncologist prior to enrollment. A medical oncologist is a physician who specializes in drug-based treatments for cancer (for example chemotherapy and hormone therapy). Patients treated for early stage breast cancer usually see a medical oncologist after surgery, so this is a physician you would see regardless of whether you participate in the study.

The reason you need to meet with a medical oncologist is to determine whether you need to have a special genetic test on your tumor. Typically, this test is called Oncotype DX and is used to help determine whether or not you would benefit from chemotherapy. If the medical oncologist does not recommend an Oncotype DX be performed in your case, or you decide to not receive chemotherapy regardless of the results of the Oncotype DX testing, you may then be able to enroll on the study.

If an Oncotype DX test is recommended and you are willing to receive chemotherapy, then the doctors treating you will perform that test prior to surgery. The test will be performed on the tissue obtained at the time of the biopsy that diagnosed your cancer. The reason this needs to be done is that the anti-estrogen therapy you get on the study prior to surgery, is likely to induce changes within the tumor biology which could affect the results of the Oncotype DX test, and may cause a loss of information that would guide your treatment in the future. If there is insufficient tissue from the biopsy to perform the OncotypeDX test, you may be ineligible for the study. In that case, you may choose to undergo an additional biopsy to obtain additional tissue to perform the OncotypeDX test and thus become eligible for the study. However, if you choose that option, you or your insurance company will be charged for that additional biopsy. If you elect to undergo an additional biopsy, but no residual tumor is found, then, you would not be eligible for the study.

If the screening information shows that you meet the requirements, then you will be able to start the study. If the screening information shows that you cannot be in the research study, the study doctors will discuss other options with you and/or refer you back to your regular doctor.

Summary of Procedures:

If you are eligible to be in the study, you will begin your 4-week (+/- 1 week) treatment period of anti-estrogen therapy and have the following procedures done, most of which are part of your regular care.

Day 1 of the 4 week treatment period
(The screening visit and day 1 visit can be the same if performed within 28 days of enrollment)

- Physical exam including measurements of weight and vital signs (blood pressure, pulse) and performance status. Performance status is an assessment of how much you can participate in your activities of daily living.
- Collect information on medications you are taking
- Collect information on your medical history and any current symptoms you have
- You will take 1 of your prescribed anti-estrogen pills once a day by mouth with a glass of water. Tablets must be swallowed whole and not chewed or crushed.
- You must immediately inform your study doctor if you begin any new medications while on study.
- You should record the daily anti-estrogen pill you take each day and any side effects you experience on a calendar for the 4-week (+/- 1 week)period.
- You should bring your calendar with you to your doctor's visit prior to your surgery.
- If your anti-estrogen pill is Tamoxifen, avoid Grapefruit juice as this may decrease the metabolism of the drug.

Breast Cancer Surgery:
(Scheduled 4 weeks (+/- 1 week) after your first dose of anti-estrogen therapy)

- Breast mammogram and ultrasound will be done about 5 days before the surgery
- Sometime after your surgery, tests will be performed on your tumor tissue and on the tissue from your biopsy to see if the genes expressed in each sample have changed.

End of Treatment Visit
(Within 1 month after your surgery)

- Physical exam including measurements of weight and vital signs (blood pressure, pulse) and performance status. Performance status is an assessment of how much you can participate in your activities of daily living.
- Collect information on medications you are taking
- Collect information on your medical history and any current symptoms you have
- Specimen collection for study biomarkers from leftover tissue samples from your breast cancer surgery**.**

Follow- Up
(Annually (+/- 3 months) from surgery)

- Further follow-up visits would be per the discretion of the patient's treating physicians.

There will be a yearly medical record follow up review for 5 years from your surgery to check on how you have been doing. The study team will review your medical records (chart review), for appointments you may have had with your cancer care doctors, annually for 5 years to collect information on the status of your cancer.

Subjects will be presented with a separate consent form from the MCW Tissue Bank. The MCW Tissue Bank consent form will ask subjects if they would consent to bank any residual tissue from their initial biopsy as well as final breast cancer surgery after all the study biomarkers have been tested. The samples would be stored according to the MCW Tissue Bank quality control measures and would be deidentified. If subjects do not consent to have their tissue banked at the MCW Tissue Bank, they can participate in the study.

B2. HOW LONG WILL I BE IN THE PROJECT?

⇒ You will take the research required anti-estrogen therapy for 4 weeks (+/- 1 week) up to your surgery date.
⇒ You will be in this research project for about 5 years.

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.
⇒ The research doctor can tell you about the effects of stopping, and you and the research doctor can talk about what follow-up care would help you the most.
⇒ You might be asked to come back for one more visit to check your health.

The research doctor may take you out of this project at any time. This would happen if:
- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

B4. ARE THERE ANY SPECIAL INSTRUCTIONS WHILE I AM IN THE PROJECT?

Prohibited Medications
The following agents must be stopped at least one week prior to registration and must not be administered during the study intervention.

- Any agent with estrogenic properties, including herbal preparations. This also includes hormone replacement therapy of any type, or raloxifene.
- Strong CYP2D6 inhibitors will be prohibited with tamoxifen, as it can decrease the efficacy of tamoxifen. Avoid grapefruit juice, as it may decrease the absorption of this drug.
- Any other anti-neoplastic approach (cancer treatments), such as chemotherapy or radiation, must not be administered while the patient is receiving study treatment.

Concomitant Medications

All three aromatase inhibitors and tamoxifen are generally safe to administer with other medicines. Concomitant use of agents and herbal products that alter Estrogen Receptor function are specifically not allowed, as mentioned in the prohibited medications.

You should tell your study doctor about all medications (over the counter, herbal, and prescription) you are currently taking and check with your study doctor before beginning any new medications.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that this intervention may not help your condition or may make it worse. There also may be problems (side effects) we do

not know about yet, from the intervention itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems, side effects, or changes in your health.**

C2. RISKS OF AROMATASE INHIBITORS AND TAMOXIFEN

The anti-estrogen drugs (aromatase inhibitors, tamoxifen) may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away. The anti-estrogen drugs (aromatase inhibitors, tamoxifen) can affect individuals in different ways.

The side effects that other people have experienced so far with aromatase inhibitors are:

Likely:
- Fatigue
- Joint musculoskeletal pain
- Loss of bone density over time

Less likely:
- Hypertension
- Constipation
- Nausea/ vomiting
- Weight gain
- Sweating/ hot flashes
- Mood alteration (depression, anxiety)
- Hair thinning
- Headaches

Rare:
- Heart disease
- Chest pain

The side effects that other people have experienced so far with Tamoxifen are:

Likely:
- Fatigue
- Sweating/ hot flashes
- Decreased libido

Less likely:
- Difficulty with sleep
- Constipation
- Nausea/ vomiting
- Weight gain

- Mood alteration (depression, anxiety)
- Hair thinning
- Headaches
- Hypertension

Rare:

- Ischemic cardiovascular event-decreased blood flow & oxygen to the heart
- Thromboembolic event**- blood clot which may cause swelling, pain, shortness of breath**
- Uterine cancer

C3. OTHER RISKS OF THIS RESEARCH PROJECT

Other procedures that are part of the research also involve some risks:

- Blood Draw Risks:
    - The side effects that you might experience because of donating a blood sample for this study include possible discomfort and bruising at the needle entry site. Rare complications of any venipuncture (drawing blood from a vein) include fainting, arterial puncture, peripheral nerve injury, local infection, and local blood clot. There may be other unanticipated risks, but every precaution will be taken to assure your personal safety and to minimize discomfort. The person drawing your blood will observe you for side effects, but please inform him or her if you experience any discomfort or feel faint.

- Mammogram:
    - The benefits of mammography outweigh any possible harm from the radiation exposure. Modern machines use low radiation doses to get breast x-rays that are high in image quality. On average the total dose for a typical mammogram with 2 views of each breast is about 0.4 mSv. (A mSv is a measure of radiation dose.)
    - To put dose into perspective, people in the US are normally exposed to an average of about 3 mSv of radiation each year just from their natural surroundings. (This is called background radiation.) The dose of radiation used for a screening mammogram of both breasts is about the same amount of radiation a woman would get from her natural surroundings over about 7 weeks.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant

The anti-estrogen therapy in this project might affect a baby, before or after the baby is born. We do not know if the Anti-estrogen therapy can disturb the development of the embryo or fetus which causes harm to a baby, so we do not want anyone who might be pregnant to enter the project. You should not become pregnant or nurse a baby while in this project. You must tell the research doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the project.

Women who become pregnant or think they might be pregnant must inform their treating physician immediately. Pregnancy requires a woman to come off protocol treatment immediately.

Birth control methods for all subjects
Check with the research doctor about the birth control methods needed for this project and how long to use them. Some methods might not be good enough for this project. If you are having sex that could lead to pregnancy, you should use birth control while you are in this project.

This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy or tubal ligation)
- Use of an intrauterine device (IUD)
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam
- Use of diaphragm with condoms ("double barrier")
- Limiting sexual activity to a male partner who has had a vasectomy

You should continue using birth control for 3 months after stopping the anti-estrogen therapy.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

We don't know if this study will help you. Your condition may get better but it could stay the same or even get worse. We hope the information from this study will help us predict patients' responses to anti-estrogen therapy and potentially help doctors choose better treatments for their patients.

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

Most of the medical care that you will receive in this project is considered routine care for your condition and would be recommended whether or not you join the project. Costs for routine care will be billed to you or your insurance carrier. Activities / costs that are part of the project will not be billed to you or your insurance company. These are collection, analysis, processing of archived tumor samples, and research blood samples. Some insurers will not pay for drugs, tests or hospitalization that are part of research, so check with your insurer before you join this project. If you have questions regarding costs, please contact Dr. Lubna Chaudhary.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

There is no payment for being in this project,

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.
Your other choices may include:

- Joining a different research project
- The procedure or drug offered to you may also be available without being in any research project.

The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information about anti-estrogen therapy administered that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

Clinically relevant results, including individual results, will be disclosed to you. These results will be shared by one of your treating physicians when available.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries directly related to your participation in this research project will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctors right away. Contact information: Dr. Lubna Chaudhary at 414-805-6700.

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

- If you have more questions about this project at any time, you can call Dr. Lubna Chaudhary at 414-805-6700.
- If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this project?

To be in this research project, the research team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the project. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); BloodCenter of Wisconsin (BCW); Children's Hospital of Wisconsin (CHW); any Froedtert Health Affiliate-Froedtert Memorial Lutheran Hospital (FMLH), Inc.; Community Memorial Hospital (CMH) Menomonee Falls, Inc.; St. Joseph's Community Hospital (SJH) West Bend, Inc.; Froedtert & The Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:

- ⇨ Medical records of the care you receive for this project until approximately 5 years after your surgery.
- ⇨ Medical records dating from when you join this project until the end of your participation in the study.

E2. Who will see the health information collected for this project?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all project records.

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information and biospecimens, the information and biospecimens may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the research doctor about whether this could apply to you.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to Dr. Chaudhary at *9200 W. Wisconsin Avenue Milwaukee, WI 53226*. The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the project. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE PROJECT

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.

You can look up this project by referring to the ClinicalTrials.gov number (NCT03219476) or by asking the research team for a printed copy.

CONSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Legally Authorized Representative (if applicable**)** *please print*	**Signature of Legally Authorized Representative**	**Date**
Name of Witness (if applicable**)** *please print* (for short form consent process, or consent of blind or illiterate subject)	**Signature of Witness**	**Date**

*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the research team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. The Principal Investigator is responsible and accountable for the research project.*