CONSENT FOR CANCER RESEARCH

Project Title: **CASE 10107 Safety and Efficacy of Single Agent Adjuvant Trastuzumab (Herceptin®) in Older Women with Early-Stage and Locally Advanced Breast Cancer: A Phase II Trial**

University Hospitals Principal Investigator: **Cynthia Owusu, M.D.**

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at University Hospitals (UH).

You are being asked to take part in a clinical trial, which is a research study conducted in order to answer specific medical questions. Research studies are voluntary and include only people who choose to participate. Please take your time to decide if you want to participate in this study. Some people find it helpful to talk about the study with their family and friends before they make a decision. It may also be useful to talk with your doctor and other people on your health care team about the study. If you have questions or want to know more about the study, you can ask them for more information.

In order to decide whether or not you should agree to be part of this research study, you should know enough about the study's risks and benefits to make a decision about participating. This process is known as informed consent. A member of the study staff will explain the research study to you. This consent form gives you detailed information about the research study. Once you understand the study, its risks, and its benefits, you will be asked to sign the form if you choose to participate. You will be given a copy of this consent form to keep.

INFORMATION ABOUT THE RESEARCH

Why Are You Being Asked To Take Part In This Research?

You are being asked to participate in a research study of early-stage Her2 positive invasive breast cancer. Her2 positive means that the cancer makes too much of a protein called Her2. Too much of this protein can cause normal cells to receive too many growth signals which can turn a normal cell into a cancer cell and can change the way it responds to treatment. TRASTUZUMAB (Herceptin®) targets Her2-positive breast cancer cells and blocks the Her2 protein on the surface of the cancer cell to slow down or stop cancer growth. TRASTUZUMAB (made by Genentech, Inc.) in combination with chemotherapy is a standard treatment for early-stage Her2-positive breast cancer that is larger than 1cm. Trastuzumab is currently not recommended for patients with breast cancer that is lcm or less in size. However some patients are unable or unwilling to undergo treatment with chemotherapy. The purpose of this study is to determine if for those patients who are unable or unwilling to undergo treatment with the combination of TRASTUZUMAB (Herceptin®) and chemotherapy, trastuzumab alone is safe and can control cancer effectively, irrespective of the size of breast cancer.

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You are being asked to participate in this study because you have an early-stage Her2 positive invasive breast cancer, you have undergone primary tumor therapy (mastectomy or lumpectomy), and you are either unable or unwilling to have chemotherapy. The purpose of this trial is to learn if TRASTUZUMAB (Herceptin®) will help control your symptoms and disease. You may also receive either adjuvant radiation therapy or endocrine therapy in addition to the 52 weeks of treatment with TRASTUZUMAB if your primary oncologist recommends such treatment. The word "adjuvant" means something that is added in order to increase the treatment's medical effectiveness.

Why is this study being done?
TRASTUZUMAB alone or in combination with chemotherapy has proven to be very effective in the adjuvant setting for younger patients with Her2-positive breast cancer. Although older patients have a greater incidence and death rate from cancer, they have been under-represented in clinical trials, particularly, breast cancer clinical trials. The main purpose of this study is to determine the benefit of adjuvant treatment with TRASTUZUMAB without chemotherapy in older women (60 years of age, or older).

How many people will take part in the study?
Approximately 124 patients will take part in this study at four locations in the United States of America including approximately 35 at University Hospitals Cleveland Medical Center.

What Is Involved In This Study
During this study you will have the following exams and procedures. The exams and procedures are described below and summarized in the Study Calendar on page 5.

Before you begin the study…
If you agree to take part in this study, you will be asked to sign this consent form. You will then have certain examinations and tests (called "screening tests") to help your study doctor determine if you are eligible to receive treatment as part of this study. Many of the following evaluations are part of regular cancer care and may be done even if you do not join the study. If you have had some or all of these evaluations recently, they may not need to be repeated. Your doctor will decide if tests need to be repeated.

<u>You will have the following assessment tests within 21 days of starting treatment:</u>

- Physical exam; including height, body weight and vital signs (blood pressure, pulse rate, body temperature).

- Medical history; including any medicines you are taking or have taken in the past. This includes over-the-counter medications, vitamins, natural/herbal supplements, etc.
- Baseline laboratory tests (approximately 2 tablespoons will be drawn) including complete blood count (CBC), electrolytes, liver function tests
- Special laboratory tests to monitor cardiac (heart) function (approximately 2 tablespoons will be drawn).
- Baseline Quality of Health and Comprehensive Geriatric (Older Women) Assessment.
- Echocardiogram (ECHO) or Multi Gated Acquisition (MUGA) Scan – tests of heart function and structure. (If you have previously had this test done, within 3 months of your current breast cancer diagnosis, then you will not have to have it repeated).

During this study…

If you are eligible for this study, you will receive the following treatments:

1. On Day 1, week 1, you will receive an initial dose (also called a loading dose) of TRASTUZUMAB, by vein, over 90 minutes (receiving drug by vein over a certain period of time is called infusion). If this first dose is well tolerated, (or once a subsequent dose becomes tolerated) the infusion time may be reduced to 30 minutes.
2. During the maintenance phase, you will receive TRASTUZUMAB, by vein, every 3 weeks to complete 52 weeks of treatment. If during the maintenance phase a dose of TRASTUZUMAB is delayed the dose of TRASTUZUMAB will not be made up.

<u>You will have the following tests and procedures while you are on study:</u>

Every 3 weeks while you are undergoing treatment with TRASTUZUMAB

- Blood draw (approximately 2 tablespoons) to check your overall health as well as your kidney and liver functions
- Vital signs (blood pressure, pulse rate, body temperature, and body weight)
- Assessment of any adverse side effects from treatment

Every 6 weeks while you are undergoing treatment with TRASTUZUMAB

- Physical exam, including vital signs (blood pressure, pulse rate, body temperature and body weight)
- Blood draw (approximately 2 tablespoons) to look at serum cardiac (heart) physiologic markers
- Assessment of any adverse side effects from treatment

Assessment every 4 weeks until return of normal cardiac function

- Echocardiogram (ECHO) or MUGA scan for patients with significant left ventricular cardiac dysfunction requiring trastuzumab to be with held

Every 3 months during treatment until the end of year one

- Echocardiogram (ECHO) or MUGA Scan – tests to check heart function

Every 6 months during treatment until the end of year one

- Quality of Health and Comprehensive Geriatric (older women) Assessment
- Cardiac history

Every 6 months after you have stopped treatment – until the end of year five or until disease-free endpoint reached

- Blood draw (approximately 2 tablespoons) to check your overall health, kidney and liver functions
- Physical exam, including vital signs (blood pressure, pulse rate, body temperature and body weight)
- Assessment of any adverse side effects from treatment
- Cardiac history

At 60 months from start of treatment with Trastuzumab

- Echocardiogram (ECHO) or MUGA Scan – tests to check heart function
- Blood draw (approximately 2 tablespoons) to look at serum cardiac (heart) physiologic markers

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Table 4: Study Calendar for Screening, Treatment and Surveillance Period						
	Screening	**Treatment**			**Surveillance**	
	Pre study period	**Week 1**	**Weeks 2-51**	**Week 52 End of Treatment**	**Year 2 to end of year 3**	**Year 4 to end of Year 5**
Eligibility	✓					
Review study procedures	✓					
Sign informed consent	✓					
Demographics	✓					
Baseline history and Physical Examination	✓					
Cardiac History	✓		Every 6 months	✓	Every 6 months	Every 6 months
Administer QOL and CGA tools	✓		Every 6 months	✓		
CBC, Complete Metabolic profile	✓		Every 3 weeks	✓	Every 6 months	Every 6 months
Cardiac markers	✓		Every 6 weeks	✓	†	Cardiac Markers only @60mths
MUGA/Echo*	✓		Every 3 months	✓		@60mths
Loading dose of trastuzumab		✓				
Maintenance dose of trastuzumab			Every 3 weeks	✓		
Limited physical examination and history			Every 6 weeks	✓	Every 6 months	Every 6 months
Assessment of adverse events			Every 3 weeks	✓		
†Cardiac markers will not be tested during the surveillance period *MUGA/ECHO measurements will be done every 4 weeks for patients who develop significant left ventricular cardiac dysfunction requiring trastuzumab to be held.						

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How long will I be in this study?
You will be in this study as long as your tumor has not grown larger; you have not suffered unacceptable side effects; or until you or your doctor have decided that continuing in this study is no longer in your best interest, or the study comes to an end at the end of five years. If your disease worsens, side effects become severe, new scientific developments occur that indicate that the treatment is not in your best interest, or your physician feels that this treatment is no longer in your best interest, you will be informed and the treatment will be stopped. Further treatment options would be discussed.

You will receive an initial dose of TRASTUZUMAB on Day 1 and during the maintenance phase of the study you will receive treatment with TRASTUZUMAB every three weeks to complete 52 weeks of treatment.

Can I Stop Being In The Study?
Yes. You can decide to stop participating in this study at any time. Tell the study doctor if you are thinking about stopping and he or she will tell you how to stop safely, and discuss what follow-up care and testing will be right for you. It is important to tell your doctor if you are considering stopping so that any risks from the medications can be evaluated.

Refusing to participate will involve no penalty, loss of benefits, or prejudice to your later care. If you do not take part in the study, or if you withdraw from the study, you will continue to receive care. In the event that you withdraw from the study, you will continue to be followed and clinical data will continue to be collected from your medical records.

RISKS AND DISCOMFORTS
What Are The Risks Of The Study?
Most drugs have side effects associated with them and the drug, TRASTUZUMAB, used in this study may involve other risks, including possible life-threatening reactions that are not known at this time. There is always a risk involved in taking an investigational drug, but you will be monitored closely for these side effects, and if your doctor thinks it is necessary, your study drug will be stopped. If you are experiencing any side effects, you should notify your doctor immediately. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long lasting, permanent and possibly fatal. You may experience some, none, or all of the following side effects.

Risks and side effects related to TRASTUZUMAB:

Likely

These side effects occur in **25% or more** of patients receiving trastuzumab:

- Weakness
- Fever
- Headache
- Diarrhea
- Pain
- Chills
- Nausea
- Cough

Likely

These side effects occur in **10-24%** of patients receiving trastuzumab:

- Abdominal pain
- Back pain
- Loss of appetite
- Dizziness
- Shortness of breath
- Infection
- Vomiting
- Difficulty sleeping
- Skin rash or ulceration
- Allergy-type symptoms like sneezing, nasal stuffiness, and postnasal drip

Less Likely

These side effects occur in **3-9%** of patients receiving trastuzumab:

- Flu-like symptoms
- Decreased red blood cell count (may lead to tiredness, shortness of breath)
- Blood tests that show changes in liver function
- Decreased white blood cell count (may lead to infection)
- Reaction to the infusion including: fever, chills, hives, rash, joint pain, pain at the tumor site, shortness of breath, low or high blood pressure, and sweating may occur during the infusion and last about 24 hours
- Cardiotoxicity: Decreased ability of the heart to pump blood. If severe, you could have shortness of breath and other symptoms of heart failure. (If mild, you may not have any symptoms.)
- Swelling
- Rapid or irregular heartbeat
- Depression
- Nerve problems that are usually temporary including pain, tingling, burning, or numb feeling (pins and needles) in the hands, feet, or area around mouth or throat, which may cause problems walking or performing activities of daily living
- Sore throat
- Voice changes
- Allergic reaction (including chills, rash, hives, itching, flushing, swelling, low blood pressure, wheezing, and shortness of breath)
- Pain in the chest area
- Pain in the muscles, bones, and joints

Rare but Serious

*These side effects occur in **less than 3%** of patients receiving trastuzumab:*

- Severe reaction to the infusion
- Severe allergic reaction
- Blood clot in a blood vessel
- Thrombocytopenia (a reduction in the number of platelets that may increase the risk of bleeding)
- Severe lung problems (including shortness of breath, fluid in the lungs, low levels of oxygen in the blood, and damage that could be permanent)

You will be given any new information about the study medication that becomes known during the course of this study that the study physician or the study sponsor believes might reasonably affect your willingness to continue to take part in the study.

There is always the possibility that you may have a reaction or side effects that are currently unforeseen or unknown and unanticipated. It is important that you report any reactions or side effects to your study doctor. You will be monitored for side effects by study personnel and, if the side effects are severe enough you will be withdrawn from the study.

Blood drawing risks:
There may be bruising, bleeding or inflammation (swelling) at the sites where blood samples are taken. Care will be provided to avoid these complications.

Are There Benefits To Taking Part In The Study?
There is no guarantee that you will benefit from taking part in this study. You may receive little or no benefit from TRASTUZUMAB treatment. TRASTUSUMAB as a single agent and also in combination with chemotherapy has been proven to be very effective in the adjuvant setting for younger patients with Her2 positive breast cancer. This study proposes to explore the benefits of adjuvant TRASTUZUMAB in older women (60 years or older).

Alternatives to Participation
You may choose not to take part in this study. If you decide not to participate, you can discuss your alternative therapy options to treat your breast cancer with your doctor. There are other approved treatments available for your cancer. For example, you may choose to receive chemotherapy in combination with TRASTUZUMAB which is the standard treatment, chemotherapy alone, or radiation therapy. You may choose to receive no therapy or just receive medications to improve your comfort and reduce the pain associated with your cancer. You could also consider participation in another clinical study. Your doctor or the study doctor can explain the other treatments that are available to you.

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What are the costs of taking part in this study?
You will not be paid for taking part in this study.

You will not be responsible for the cost of research related visits including the study procedures and laboratory tests that are directly due to your taking part in this study.

TRASTUZUMAB will be provided for free with this study.

You and/or your health plan/insurance company will be responsible for the cost of the personnel required to give this drug. All of the medical tests, evaluations, procedures and recommendations that are considered standard cancer care will be the responsibility of you and your insurance company.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Expenses such as parking, travel, and lodging associated with the study will not be reimbursed to you.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

RESEARCH RELATED INJURIES
What Happens If An Injury Occurs?

If an injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals or another medical facility; but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research-related injury. To help avoid injury, it is very important to follow all study directions.

Genentech, Inc., who provides funding for this study, will not provide financial assistance for injury, medical or other costs. Additionally, Genentech, Inc. will not pay for lost wages or other damages or losses or for medical expenses that have been covered by medical or hospital insurance or by third party or governmental programs providing such coverage.

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Further information about research-related injuries is available by contacting the University Hospitals Cleveland Medical Center's Research Subjects Rights at (216) 983-4979.

Confidentiality

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

If you decide to participate in the study, the study doctor and staff will collect medical and personal information in a centralized computer or data registry at the Seidman Cancer Center, Cleveland, Ohio. Members of independent ethics committee or the institutional review board (IEC/IRB) for the study will have access to this information at the site in order to check that the study is done properly. Your permission to the study doctor and staff to use this information or share it with others as described below for the study doesn't automatically end at a particular time.

You should know that once identifiable medical information about you is given to someone that is not a health care provider, it is not protected by the US federal privacy rules called the HIPAA Privacy Regulations

HIPAA AUTHORIZATION SECTION

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Cynthia Owusu, M.D. and her research staff at Case Western Reserve University, University Hospitals Cleveland Medical Center; as well as Genentech, Inc. for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research includes:

- your name, initials, address, telephone number, date of birth and other demographic information;
- your medical history (including the history and diagnosis of your disease and your family medical history) and the name of your physician(s) and locations where you received any treatment;

- specific information about the treatment/therapy you receive during the Research Study and treatment you received prior to the Research Study (including treatments and therapies, surgeries, hospitalizations and medications);
- information about other medical conditions that may affect your treatment, including information relating to mental health, behavioral health and psychiatric disorders; Human Immunodeficiency Virus (HIV) test results, Acquired Immunodeficiency Syndrome (AIDS), and AIDS-related conditions; and alcohol and drug dependence or abuse;
- medical data, including physical exam findings, laboratory test results, tumor measurements, CT scans, MRIs, X-rays, ultrasounds and other radiologic scans, photographs of areas of disease and pathology results;
- information on side effects (adverse events) you may experience and how these side effects were treated;
- long-term information about your general health status and the status of your disease or medical condition;
- data that may be related to tissue and/or blood samples that may be collected from you;
- numbers or codes that identify you, such as your social security number, medical record number, and Research Study case number;
- identifiers and serial numbers from medical devices; and
- your entire medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the University Hospitals Institutional Review Board, and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Genentech, Inc., who provides funding for this study; including companies/representatives that work for Genentech, Inc.;
- Contract Research Organization(s) or study monitor(s) involved in the Research Study;
- Representatives of the University Hospitals Institutional Review Board (IRB) and any Institutional Review Board Accrediting body:
- The Department of Health and Human Services, The Food and Drug Administration; Office of Human Research protections, and other national and international government agencies and regulatory agencies;
- Your insurance company;
- The National Committee for Quality Assurance; and the Joint Commission for Accreditation of healthcare Organizations;
- Other institutions (including their investigators) jointly conducting the research

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Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to
Cynthia Owusu, M.D.
Case Comprehensive Cancer Center
University Hospitals Cleveland Medical Center
11100 Euclid Avenue
Cleveland OH 44106

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the University Hospitals cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

University Hospitals will not use your information collected in this study for another research purpose without your written permission; unless the University Hospitals Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation

Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Cleveland Medical Center or elsewhere; however, University Hospitals Cleveland Medical Center have no plan to provide free care or compensation for lost wages.

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Disclosure of Your Study Records

Efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Institutional Review Board may review your study records. If this is a treatment study, the records must be available to the Food and Drug Administration, the study sponsor, and possibly foreign regulatory agencies. If your records are reviewed, your identity could become known.

Contact Information

_____ has described to you what is going to be done; the risks, hazards, and benefits involved. You can reach the person who described this study to you at _____. Further information with respect to illness or injury resulting from a research procedure as well as a research subjects' rights is available from the Institutional Review Board (IRB) at University Hospitals IRB at 216-844-1529.

Emergency or after-hours contact information

You can contact Dr. Cynthia Owusu at 216-844-7670 or 216-844-3951 and you will be transferred to the answering service, which can put you in contact with Dr. Owusu or the oncologist (cancer doctor) on call.

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Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____ _____ _____
Signature of Participant Date Printed Name of Participant

_____ _____ _____
Signature of Witness Date Printed Name of Witness

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent