COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL: SMILOW CANCER CENTER

Study Title: A SINGLE ARM, NEOADJUVANT, PHASE II TRIAL OF PERTUZUMAB AND TRASTUZUMAB ADMINISTERED CONCOMITANTLY WITH WEEKLY PACLITAXEL AND FEC FOR CLINICAL STAGE I-III HER2-POSITIVE BREAST CANCER

Principal Investigator: Lajos Pusztai, MD, DPhil
333 Cedar Street, PO Box 2080032
New Haven, CT 06520

Funding Source: Genentech, Inc.

Invitation to Participate and Description of Project

You are invited to take part in a research study because you have clinical stage I-III, HER2-positve breast cancer that may benefit from preoperative chemotherapy. The main goal of this clinical trial is to test if adding a new drug, pertuzumab (Perjeta), improves the anticancer activity of the currently most effective treatment that includes trastuzumab (Herceptin) given together with chemotherapy (paclitaxel, 5-fluorouracil, epirubicin, and cyclophosphamide). The study will also test the safety of this therapy. If you agree to participate, you will receive 6 months of chemotherapy concomitant with trastuzumab and pertuzumab before surgery. Subsequently, you will undergo surgery to remove any cancer from your breast and axillary lymph nodes that may have survived the chemotherapy.

This clinical trial represents experimental therapy because pertuzumab is not approved by the US Food and Drug administration to be given concomitant with epirubicin. Several clinical studies demonstrated that when pertuzumab is given together with chemotherapy and/or trastuzumab the combination treatment has greater anti-cancer effect than any of the drugs alone which provides the rationale for our study. All treatments other than pertuzumab that you will receive during this clinical trial are standard of care.

Up to 64 subjects will take part in this study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments.

Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Tests and procedures that would be performed for your care whether you are on this study or not are referred to as "standard of care." All of the tests and procedures listed below that will be performed at your study visits should you choose to participate are considered to be standard of care.

If you agree to take part in this study, you will be asked to do the following:

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and would 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 depend of the date of the exam.

- Medical history and complete physical exam including your breasts and regional lymph nodes.
- Bilateral mammograms and ultrasonogram of the regional lymph nodes if clinically suspicious. During these exams a marker clip will need to be placed in the breast to identify the cancer for surgery.
- CT scans of the chest, abdomen, pelvis and bone scan or PET-CT may be needed to assess if the cancer has spread beyond the breast and lymph nodes. Your physician will decide if you need these tests or not.
- Routine laboratory blood tests to measure your blood counts and your kidney and liver function and electrolytes in your blood.
- Assessment of your heart function through a nuclear scan or echocardiography.
- Pregnancy test for women of childbearing potential.

Tests during the study …

If the above assessment shows that you can be in the study, and you choose to take part, then you will need the following tests and procedures. All of these are part of regular cancer care.

- Before each chemotherapy you will need to have a test called complete blood count to check the number of red blood cells, white blood cells, and platelets in your blood. This will be done once a week during weekly treatments and once every 3 weeks during every 3-week treatments (see section below on treatment). Results from this test will determine if you can receive chemotherapy on that day or a treatment needs to be delayed.
- Every 3 weeks during treatment you will have a clinic visit with your physician who will review your medical history and perform physical examination.

- Repeat assessment of your heart function after the first 12 weeks of therapy, after completion of all chemotherapy and every 3 months thereafter for a total of 12 months (5 heart studies total) using the same method as used before treatment started.
- Repeat laboratory blood tests to measure kidney and liver function every 3 weeks during your therapy.
- Mammography and ultrasonogram of the regional lymph nodes after the first 12 weeks of therapy is completed and at the completion of all chemotherapy before surgery.

Your treatment during this study…..

This is a single arm, Phase II clinical trial which means that all women will receive the same treatment and the goal of the study is to determine how well this treatment works to eradicate cancer from your breast (and lymph nodes). The total duration of treatment is 24 weeks. During the first 12 weeks (weeks 1-12) you will receive paclitaxel (also called Taxol) chemotherapy once weekly x 12 treatments concomitant with weekly trastuzumab (also called Herceptin) as well as pertuzumab (also called Perjeta) given once every 3 weeks. During the second 12 weeks (weeks 13-24), you will receive 5-fluorouracil (also called 5FU), epirubicin (also called Ellence) and cyclophosphamide (also called Cytoxan) concomitant with trastuzumab and pertuzumab each given once every 3 weeks (21 days) for 4 treatments.

The duration of each treatment session lasts between 1.5 – 3.0 hours. All drugs in this study are given through a needle in your vein (intravenously). You will need to have a central venous access, a catheter or port inserted in a large vein, in order to receive therapy. You and your physician will decide together what catheter is most convenient for you. The exact dose and schedule of your treatment is included in the table below.

AGENT	DOSE	ROUTE	RETREATMENT INTERVAL
Pertuzumab	First dose: 840 mg. Maintenance dose: 420 mg	IV	Once every 3 weeks x 24 weeks (8 treatments total)
Trastuzumab weekly	First dose: 4 mg/kg. Maintenance dose: 2 mg/kg	IV	Once every week x 12 weeks durings weeks 1-12 (12 treatments total)
Trastuzumab every 3 weeks	6 mg/kg	IV	Once every 3 weeks during weeks 13 - 24
Paclitaxel	80 mg/m^2	IV	Once every week from during 1 -12 (12 weekly cycles total)
5-fluorouracil	500 mg/m^2	IV	Once every 3 weeks during weeks 13 - 24 (4 cycles total)
Epirubicin	75 mg/m^2	IV	Once every 3 weeks during weeks 13 - 24 (4 cycles total)
Cyclophosphamide	500 mg/m^2	IV	Once every 3 weeks during weeks 13 - 24 (4 cycles total)

You will be given anti-nausea medications and additional medicines to reduce the risk of allergic reactions to drugs before each chemotherapy.

After completion of all chemotherapy treatments…

- You will have surgery to remove any cancer from the breast and regional lymph nodes. You and your surgeon will decide together what the most appropriate surgery is for you. You may have your whole breast removed (mastectomy) or only parts of the breast that contained cancer (lumpectomy). All patients will have sampling of the lymph nodes in the axilla (arm pit) during the breast surgery.

After Surgery …

- Your treatment after surgery will follow standard clinical practice. This includes completion of a total of 12 months of treatment with trastuzumab (including the 6 months before surgery) and patients with estrogen receptor positive cancer will also take anti-estrogen therapy (tamoxifen or an aromatase inhibitor drug) for 5-10 years. Depending on the type of surgery that you had, you may also require radiation therapy to the breast and lymph node regions. After completion of all treatment, your physician will continue to see you regularly every 3 months and your cardiac function will be monitored with repeat cardiac tests as part of routine care at month 9 and month 12.
- Your medical records may be checked periodically in the future to find out your health status. You may also be contacted by the phone to find out about your health status as part of good clinical, practice.
- After completion of your surgery you may opt to participate in other clinical studies.

How long will I be in the study?

Your experimental treatment will last for 6 months and then you will continue to be followed for an additional 6 months. Your participation in this study will last a total of 12 months.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the treating physician, your study doctor, if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from stopping early can be discussed with you by your study 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.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest or if you do not follow the study rules; or if the study is stopped.

Risks and Inconveniences

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team will give you medicines to help lessen side effects. Many side effects go away soon after the completion of this experimental chemotherapy combination. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study. This is very important to do, even if the side effects are occurring in between your visits with the study doctor, because if you are having side effects your chemotherapy dose may be held or adjusted.

The most important side effect of this experimental therapy is increased risk for heart damage due to the combined treatment with trastuzumab pertuzumab and epirubicin.

There is small risk (1-2%) that your cancer may continue to grow despite treatment. You doctor will closely follow your cancer by physical exam and repeat mammogram or ultrasonogram if necessary. If the cancer grows, you will discontinue therapy and may undergo surgery to remove the cancer or receive other treatment.

Risks and side effects related to the paclitaxel treatment include the following:

Likely (occurring in > 20% of patients)

- Fatigue
- Hair loss
- Pain, numbness, tingling, swelling, or muscle weakness in hands and/or feet (neuropathy). These symptoms usually get better or go away without medication within 3 weeks of stopping treatment.
- You may get joint and muscle pain a few days after your treatment. These symptoms usually disappear in a few days.

Less Likely (occurring in < 20% of patients)

- Nausea (feeling as if you're about to throw up) or vomiting (throwing-up)
- Low blood pressure
- Shortness of breath

- Cough
- Inflammation or irritation of the mucous membranes in the mouth or throat.
- Heart burn
- Diarrhea – increased frequency of bowel movements with loose, watery stool
- Low white blood cell counts which may make you more susceptible to infection
- Low platelet counts which may make you bruise more easily and bleed longer if injured
- Low red blood cell counts which may cause tiredness, shortness of breath or fatigue
- Abnormal blood tests reflecting problems with liver function

Rare but serious (occurring in < 3% of patients)

- Liver failure including brain and nervous system damage that occurs as a complication of liver disorders.
- Severe heart problems including chest pain, high blood pressure, and abnormal heart rhythms that prevent the heart from pumping blood normally and could be life threatening
- Blood clots in the lungs
- Damage to the eyes resulting in decreased vision.
- Serious, sometimes life threatening gastrointestinal (GI) perforations have occurred rarely. A GI perforation is the development of an opening or hole in the wall of the bowel or stomach that may require surgery to repair.

Risks and side effects related to the 5-fluorouracil, epirubicin, and cyclophosphamide treatment include:

Likely (occurring in > 20% of patients)

- Fatigue
- Hair loss
- Low white blood cell counts which may make you more susceptible to infection
- Low platelet counts which may make you bruise more easily and bleed longer if injured
- Low red blood cell counts which may cause tiredness, shortness of breath or fatigue

Less Likely: (occurring in < 20% of patients)

- Nausea and vomiting
- Sores in the mouth
- Heartburn
- Tingling pain and redness of the hands and feet (Hand-foot syndrome)
- Change in color of fingernails and toenails

- Loosening of fingernails and toenails
- Inflammation or damage to the skin and around the IV tubing.
- Bone or joint pain
- Cramps in the legs or back

Rare but Serious: (occurring in < 3% of patients)
- Heart damage
- Increased risk of blood cancer or other secondary cancers

Irritation at the Chemotherapy Infusion Site:

Chemotherapy may cause irritation and tissue damage at the site of injection. These reactions are caused by the intravenous fluid that contains chemotherapy leaking into the surrounding area. Reactions may include pain, redness, swelling of the surrounding skin or of the vein itself, and ulceration of the skin (open sores). If you notice anything unusual at the site of the injection (where the needle is inserted), either during or after treatment, tell your nurse right away who will notify your study doctor.

Risks and side effects related to the trastuzumab (Herceptin) treatment include the following:

Likely (occurring in > 20% of patients)

- Chills
- Fever
- Body pain

Less likely (occurring in < 20% of patients)

- Headache
- Diarrhea
- Abdominal pain
- Back pain
- Infection
- Flu-like symptoms
- Vomiting
- Cough
- Shortness of breath
- Rhinitis or pharyngitis – Runny nose and sore throat
- Insomnia
- Rash
- Dizziness
- Swelling (usually of the feet, ankles or hands)

- Weakness
- Nausea

Rare but serious (occurring in < 3% of patients)

- Allergic reactions that may include itching and rash, shortness of breath or even a drop in your blood pressure. Most of these events occur within 24 hours of infusion. However, delayed reactions have occurred. If a person experiences severe allergic reaction, trastuzumab will be discontinued.
- Interference with the pumping action of the heart leading to heart failure. The incidence of heart problems (heart failure) increase in people with heart disease or other risk factors such as radiation to the chest, advancing age, and use of other heart-toxic drugs (such as epirubicin and cyclophosphamide). Your doctor will check your heart function before you start taking Trastuzumab and will monitor your heart closely during your treatment. Trastuzumab will be discontinued if symptoms of heart failure appear.

Risks and side effects related to the pertuzumab (Perjeta) treatment include the following:

Note, pertuzumab is not used alone and the following side effects were observed when it was used in combination with trastuzumab and docetaxel chemotherapy.

Likely (occurring in > 20% of patients).

- Diarrhea
- Hair loss
- Low white blood cell count
- Nausea
- Fatigue
- Rash
- Peripheral neuropathy (numbness & tingling in hands and feet)

Less likely (occurring in <20% of patients).

- Decreased appetite
- Mouth irritation or mouth sores
- Weakness
- Anemia
- Swelling
- Muscle aches
- Nail changes
- Joint aches
- Shortness of breath
- Headache
- Fever
- Abnormal taste

- Upper respiratory tract infection
- Vomiting
- Itching
- Watery eyes
- Difficulty sleeping
- Dizziness
- Abdominal pain
- Dry skin
- Allergic reactions/hypersensitivity reactions

Rare but serious (occurring in < 3% of patients)

- Hypersensitivity reactions, anaphylaxis, and allergic reactions.
- Interference with the pumping action of the heart leading to heart failure.

Other instructions

Tell your study doctor about all of your medicines. Include prescription medicines, over the counter drugs, vitamins, and herbal products. Some medicines can react with the study drugs that you receive and may cause serious side effects.

Keep a list of your medicines, and show it to your study doctor or pharmacist. Talk to your study doctor before starting any new medicines.

Reproductive risks:

You should not become pregnant or father a baby while on this study or within six months from completion of treatment because the drugs in this study can affect an unborn baby and cause serious birth defects.

Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study.

Check with your study doctor about what kind of birth control methods to use and how long to use them. If you become pregnant while participating in this study, inform your study doctor immediately.

For more information about risks and side effects, ask your study doctor.

Risks associated with procedures during this study:

This study does not involve any special procedures. Placement of either an intravenous (IV) line or port-o-cath for chemotherapy administration is part of routine care and are very safe procedures. However, there is a slight chance that multiple needle-sticks may be necessary to make sure the IV is placed correctly. You might feel a small amount of pain when the IV is placed but it does not last very long. A bruise or an infection might develop where the IV is placed. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Infections can also be treated with outpatient antibiotics but rarely they may require hospital admission. Rarely a blood clot may develop in the vein where the intravenous line is placed.

Benefits

This treatment combination may make your cancer completely disappear from your breast (and lymph nodes) and could improve your chance for cure. During this clinical trial you will receive the currently most effective chemotherapy for HER2 positive breast cancer (trastuzumab concomitant with paclitaxel, 5 fluorouracil, cyclophosphamide and epirubicin) and in addition you will also receive a new HER2 targeted drug, pertuzumab.

While doctors hope this chemotherapy combination will be more useful against cancer compared to the best current treatment, there is no proof of this yet.

We hope the information learned from this study will benefit other patients with breast cancer in the future.

Economic Considerations

You and/or your health plan/ insurance company will need to pay for the routine standard of care portions of your treatment. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Pertuzumab (the only experimental part of your treatment) and trastuzumab will be provided by Genentech, Inc free of charge. The chemotherapy drugs paclitaxel, 5-fluorouracil, epirubicin, and cyclophosphamide are commercially available and considered standard of care and will be charged to you or your insurance company. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be charged in the usual way, to your insurance company.

You will not be paid for taking part in this study.

Treatment Alternatives/Alternatives

Your other choices, if you choose not to take part in this study, may include:

- Getting similar but not identical treatment for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable infectious diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and address. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept indefinitely. The data will be kept in this anonymous form indefinitely.

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g., health insurance company, disability provider.)

The information about your health that will be collected in this study includes:

- The entire research record and any study related medical records held by Yale New Haven Hospital

Information about you and your health which might identify you may be used by or given to:

- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Your providers who are participants in the Electronic Medical Record (EMR) system
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator: Lajos Pusztai, MD, DPhil
- The Co-Principal Investigator: Michael DiGiovanna, MD, Ph.D.
- Genentech, Inc. (the study sponsor)
- Health care providers who provide routine or research services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Study collaborators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine, Yale-New Haven Hospital, and the Smilow Cancer Center are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

The sponsor will see the research information we collect about you when they come to Yale to monitor the conduct of this research study. For this study the sponsor includes Genentech, Inc. Yale researchers will also send the sponsor your health information during the study or at the end of the study. When Yale researchers send information about you to the sponsor, they will not send information that directly identifies you such as your name, street address, or social security number.

The sponsor may also use the information about you for other purposes related to this research or to similar research studies.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

In Case of Injury

If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. You do not give up any of your legal rights by signing this form

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you do not agree to participate. However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

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 will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Withdrawing From the Study

If you do become a study participant, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future study related appointments.

The study doctor may decide to take you off this study if your disease gets worse despite the treatment; if the side effects of the treatment are too dangerous for you; or if new information about the treatment becomes available and this information suggests the treatment will be

ineffective or unsafe for you. It is unlikely, but the study may also be stopped early due to lack of funding.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. If you choose not to participate or if you withdraw, it will not harm your relationship with your doctors or with Yale School of Medicine, Yale New Haven Hospital, the Smilow Cancer Center, or St. Francis Hospital and Medical Center. We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor of your choice.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by sending written notice to the study doctor:

Lajos Pusztai M.D. (Medical Oncology)
Yale University Cancer Center
Smilow Cancer Hospital
Section of Medical Oncology
333 Cedar St., PO Box 208032
New Haven, CT 06520-8032
Tel: 203-737-8309
Fax: 203-785-5792

If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project as described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use and give out information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to participate in this research.

I also confirm that I have received a Trial Alert Card providing contact details of the study doctor and agree to carry this card with me at all times.

Study Participant (print name)	Signature	Date
Person obtaining consent (print name)	Signature	Date
Person obtaining consent (print name) – only if applicable, otherwise blank	Signature	Date
Interpreter/ Witness (print name) – only if applicable, otherwise blank	Signature	Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Lajos Pusztai, at 203-737-8309. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.