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CONSENT FORM

CTSU N063D/BIG 2-06 ALTTO: Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Study – A Randomized, Multi-center, Open-Label, Phase III Study of Adjuvant Lapatinib, Trastuzumab, their Sequence and their Combination in Patients with HER2ErbB2 Positive Primary Breast Cancer.

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CTSU N063D/BIG 2-06 ALTTO: Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Study – A Randomized, Multi-center, Open-Label, Phase III Study of Adjuvant Lapatinib, Trastuzumab, their Sequence and their Combination in Patients with HER2ErbB2 Positive Primary Breast Cancer.

A randomized, multi-centre, open-label, phase III study of adjuvant lapatinib, trastuzumab, their sequence and their combination in patients with HER2/ErbB2 positive primary breast cancer

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have early stage HER2 positive (HER2+) breast cancer that has been surgically removed.

Why is this research study being done?

This purpose of this research study is to:

- **Find out what effects (good and bad) the study treatment has on you and your cancer.**
- **Compare four different study treatment combinations to see if one is better**
- **Find out what effects this study has on your quality of life.**

Because of recent research by NCCTG, the standard treatment for HER2+ breast cancer now includes trastuzumab (Herceptin®). However, not all patients with HER2+ breast cancer do better with trastuzumab, so investigators are trying to find out why.

GW572016 (lapatinib, brand name: Tykerb®) is a new drug that is taken every day by mouth. Lapatinib is considered “investigational” in this study. “Investigational” means that the FDA has not approved lapatinib as a treatment for early breast cancer.

This study is comparing trastuzumab to lapatinib and each drug alone to two combinations of trastuzumab and lapatinib. The four treatments being studied here are:

- **Group 1 - The standard treatment - trastuzumab alone for one year**
- **Group 2 - Lapatinib alone for one year**
- **Group 3 - Trastuzumab for 18 weeks followed by a 6 week break, and then lapatinib for up to 28 weeks**
- **Group 4 - Trastuzumab and lapatinib together for one year**

The true benefit of taking lapatinib either instead of trastuzumab or with trastuzumab is not known.

How many people will take part in the research study?

About 4000 people are expected to take part in this study across the United States and North America. About 8400 people are expected to take part in this study throughout the world.

What will happen if I take part in this research study?

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 may be done even if you do not join the study.

- **Blood and/or urine tests**
This study also has required laboratory tests on blood samples for research purposes. More information is in the “About Using Biological Samples for Research” section of this form.
- **Physical exam**
- **Chest x-ray or CT, and mammogram or breast MRI**
- **Lab tests of your breast cancer tissue to see if it is HER2 positive (HER2+)**

This testing will be done by sending a sample of your breast cancer tissue from your original breast cancer surgery to an NCCTG laboratory at Mayo Clinic in Rochester, MN. This testing will be done to confirm your tumor is HER2+. Your tumor must be HER2+ to be able to take part in this study. You will be told to the results. Once the central review is completed the breast cancer issue will be kept for research on breast cancer. This research is a study requirement. More information is available in the “About Using Biological Samples for Research”.

- **Echocardiogram or MUGA scan to see how your heart is working**

An echocardiogram is an ultrasound of your heart that looks at how your heart is working by measuring how much blood is moved out of the left side of the heart with each heartbeat (called “ejection fraction”). A MUGA scan is done by injecting a radioactive dye into your bloodstream and watching your heart on an x-ray screen to see how well it is working.

During the study ...

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures on a regular basis during this study. They are part of regular cancer care.

- blood and/or urine tests
- physical exams
- echocardiogram or MUGA scan
- mammogram or breast MRI

You will be "randomized" into one of the study groups in the table below. Randomization means that you are put into a group by chance (as in a roll of the dice). A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have a one in four chance (25%) of being placed in any group. You will have a three in four chance (75%) of receiving lapatinib.

Patients in all groups will receive docetaxel (Taxotere®) plus carboplatin (Paraplatin®) once every 3 weeks for 18 weeks.

If your doctor decides that you need hormone therapy, it will be started after you finish chemotherapy (including docetaxel and carboplatin) and will continue for at least five years. Also, if your doctor prescribes radiotherapy, it will be started after you are finished chemotherapy (including docetaxel and carboplatin).

Docetaxel (Taxotere®) Carboplatin (Paraplatin®) and trastuzumab (Herceptin®) are given IV, that is, through a needle into a vein in your arm or hand, or into a port if you have one.

If you are in Groups 1, 3 or 4, you will receive docetaxel plus carboplatin once every three weeks with trastuzumab once a week for 18 weeks. Groups 1 and 4 will then receive trastuzumab once every 3 weeks until you reach one year of treatment. Group 4 will also take lapatinib every day until one year.

Group 2 will receive docetaxel plus carboplatin once every three weeks for 18 weeks and take Lapatinib every day until one year.

If you are in Group 3, after you complete the first 18 weeks with docetaxel plus carboplatin and trastuzumab, you will have a break from study treatment for 6 weeks. After the break you will start taking lapatinib every day until you have received a total of one year of treatment.

Lapatinib (Tykerb®) comes in tablets that you take by mouth. You will take lapatinib one time every day. You will get a new supply of lapatinib from your clinic about every 8 weeks. You should take all your lapatinib tablets with water at the same time every day. You must not take lapatinib with grapefruit juice and you should avoid grapefruit and grapefruit juice while you are taking lapatinib. You must take lapatinib on an empty stomach – one hour before or one hour after eating. You should not use any antacids (like

Tums or RolAids) for one hour before and one hour after you take lapatinib. If you miss a dose, you should skip that dose and start with the next dose. If you become ill and vomit or throw up after taking your lapatinib dose, do not retake the dose. Wait until your next scheduled dose to begin taking Lapatinib again. You must tell the study staff every time you miss a dose or vomit after taking a dose.

Many patients have diarrhea (loose stools) when taking lapatinib. Your doctor or nurse will give you a prescription for loperamide or a similar medicine to take if you get diarrhea. Start taking this medicine right away at the first signs of diarrhea. Be sure to tell your study team right away if you have diarrhea that does not go away within 24 hours after you take this medicine.

You will need to bring your lapatinib bottles with you to every clinic visit.

Lapatinib does not work with some other medications, drugs, supplements, herbal products and other medicines (called “CYP3A4 inhibitors” or “CYP3A4 inducers”). Be sure to inform your doctor of all medications, including over-the-counter medications, vitamins, supplements, herbal products, herbal teas, traditional Chinese medicines or other medicines which you are taking. Your doctor will tell you if it is okay to continue taking them or whether you must stop taking them while you are taking lapatinib.

1 Year (12 months) with Docetaxel plus Carboplatin

	Months 1-5 (18 weeks)	Months 5-6	Months 6-12
All Groups	Docetaxel plus carboplatin once every 3 weeks		
Group 1	Trastuzumab weekly	Trastuzumab once every 3 weeks	Trastuzumab once every 3 weeks
Group 2	Lapatinib every day	Lapatinib every day	Lapatinib every day
Group 3	Trastuzumab weekly	6 week break then lapatinib every day	Lapatinib every day
Group 4	Trastuzumab weekly and lapatinib every day	Trastuzumab once every 3 weeks and lapatinib every day	Trastuzumab once every 3 weeks and lapatinib every day

When you are finished taking the study drugs ...

We will follow your progress for 5 years after you start the study. After you have completed treatment, you will come to the clinic every 3 months through Year 2, then every 6 months until you’ve been in the study for 5 years. Then you will come to the clinic once a year until you have been in the study for up to 15 years.

Study Chart

While you are in this study, you will receive paclitaxel (Taxol®) or docetaxel (Taxotere®) for the first 3 months (Design 2); or docetaxel (Taxotere®) plus carboplatin (Paraplatin®) for 18 months (Design 2B). You will receive trastuzumab, lapatinib or both trastuzumab and lapatinib every three weeks in this study. This three-week period of time is called a cycle. The cycle will be repeated 17 times. Each cycle is numbered in order. The charts below show what will happen to you during Cycle 1 and future treatment cycles as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Cycles 1-6 for All Groups (Design 2B only)

Day	What you do
Before starting your first study treatment you may have:	<ul style="list-style-type: none"> • Routine blood tests • Physical exam • Echocardiogram/MUGA scan • Complete Questionnaire Booklet (Cycle 1 and Cycle 5) • Other treatments or tests if your doctor thinks you need them
Day 1	<ul style="list-style-type: none"> • Get docetaxel into a vein for 60 minutes (you will get docetaxel once per cycle) • Get carboplatin into a vein for 30 minutes (you will get carboplatin once per cycle) • Groups 1, 3 and 4: Get trastuzumab into a vein for up to 90 minutes (first time only) - usually 30 minutes after first time • Groups 2 and 4: Begin taking lapatinib. You will continue to take lapatinib every day until the end of study treatment, unless told to stop by your healthcare team. <p style="text-align: center;">*Remember to bring your lapatinib bottles to every clinic appointment*</p>
Day 8	<ul style="list-style-type: none"> • Get routine blood tests (if applicable) • Groups 1, 3 and 4: Get trastuzumab into a vein for 30 minutes • Groups 2 and 4: Continue taking lapatinib every day
Day 15	<ul style="list-style-type: none"> • Get routine blood tests (if applicable) • Groups 1, 3 and 4: Get trastuzumab into a vein for 30 minutes • Groups 2 and 4: Continue taking lapatinib every day

Cycles 7-8 (Design 2B - Group 3)

Break from treatment for 6 weeks – you may have routine blood tests, physical exams, scans or other treatments or tests if your doctor thinks you need them.

Cycles 7-8 (Design 2B - Groups 1, 2, 4)

Day	What you do
Before each cycle as part of your regular cancer care you may have:	<ul style="list-style-type: none"> • Routine blood tests • Physical exams • Echocardiogram (Echo) or MUGA scan • Other treatments or tests if your doctor thinks you need them
Day 1	<ul style="list-style-type: none"> • Groups 1 and 4: Get trastuzumab into a vein for 30 minutes • Groups 2 and 4: Continue taking lapatinib. You will continue to take lapatinib every day until the end of study treatment, unless told to stop by your healthcare team. <p>*Remember to bring your lapatinib bottles to every clinic appointment*</p>
Days 2-21	<ul style="list-style-type: none"> • Groups 2 and 4: Continue taking lapatinib every day

Cycles 9-17 (Design 2 and Design 2B - All Groups)

Day	What you do
Before each cycle as part of your regular cancer care you may have:	<ul style="list-style-type: none"> • Routine blood tests • Physical exams • Echo or MUGA scan • Other treatments or tests if your doctor thinks you need them
Day 1	<ul style="list-style-type: none"> • Groups 1 and 4: Get trastuzumab into a vein for 30 minutes • Groups 2, 3 and 4: Continue to take lapatinib every day until the end of study treatment, unless told to stop by your health care team <p>*Remember to bring your lapatinib bottles to every clinic appointment*</p>
Day 2-21	<ul style="list-style-type: none"> • Groups 2, 3 and 4: Continue to take lapatinib every day until the end of study treatment, unless told to stop by your health care team • Other treatments or tests if your doctor thinks you need them.

At 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 months after starting the study (All Groups)

What you do

- | |
|---|
| <ul style="list-style-type: none"> • Get routine blood tests • Have physical exam • Have echocardiogram or MUGA scan (at 12, 18, 24, 36, 48 and 60 months) • Have mammogram or breast MRI yearly • Complete Questionnaire Booklet (at 12, 36 and 60 months) • Other treatments or tests if your doctor thinks you need them |
|---|

At 6, 7, 8, 9 and 10 years after starting the study (All Patients)

What you do

- Get routine blood tests
- Have physical exam
- Have echocardiogram or MUGA scan yearly
- Have mammogram or breast MRI yearly
- Other treatments or tests if your doctor thinks you need them

How long will I be in the research study?

You will be in this study for up to 15 years. You will receive the study treatment for 1 year. After you are finished taking the study drugs, the study doctor will ask you to visit the office for follow-up study exams every 3 months until 2 years after you started the study, then every 6 months until 5 years from when you started the study. After that your study doctor will ask you to visit the office for follow-up study exams yearly until 10 years from when you started the study. Then, we would like to keep track of your health every year for up to 15 years after you started the study.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the 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 the drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you. 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; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

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 may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. There may also be a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the docetaxel (Taxotere®) include those which are:

Likely risks of docetaxel (happen more than 20% of the time)

- Low white blood cell count, which may increase the risk of infection, slower healing
- Low red blood cell count, which may result in anemia, tiredness, and/or shortness of breath
- Tiredness and/or general weakness
- Unusual sleepiness

- **Sick to stomach or throwing up (nausea and/or vomiting)**
- **Mouth sores**
- **Loose stools (diarrhea)**
- **Loss of appetite (anorexia), change in taste (dysgeusia), and/or weight loss**
- **Loss of hair (alopecia)**
- **Headache**
- **Shortness of breath**
- **Muscle or joint pain**
- **Changes in the fingernails and toenails (may change color, break or fall off)**
- **Inflammation of the eyes – may cause itchiness, redness, swelling**
- **Loss of feeling or numbness and tingling in fingers and toes**
- **Irritation (redness, soreness) or loss of skin on palms of the hands or soles of the feet**

Less likely risks of docetaxel (happen less than or equal to 20% of the time)

- **Rash, redness and/or swelling of the skin**
- **Allergic reactions, which may involve rash, fever, swelling, chills, or low back pain**
- **Watery eyes**
- **Inflammation of veins (vasculitis) – may cause rash, itching, pain**
- **Irregular heartbeat**
- **Low platelet count, which may increase risk of bleeding**
- **Seizures**
- **Liver problems, which may result in yellowing of skin and eyes**
- **Pain in the upper right area of the belly (abdomen)**
- **Swelling of feet**
- **Increased fluid around the lung and heart, which may cause shortness of breath**

Rare but serious risks of docetaxel (happen less than 2-3% of time)

- **Lung inflammation, which may involve shortness of breath, cough, and/or fever**
- **Permanent bone marrow damage that could result in leukemia**
- **Liver failure**
- **Hole in the intestine, which may require surgery**
- **Death**

The following side effects have been reported for patients taking part in other docetaxel research studies. It is not known if these side effects were related to the docetaxel.

- **Heart failure**
- **Low or high blood pressure**
- **Hearing problems**
- **Kidney failure**

Carboplatin possible side effects:

Likely risks of carboplatin (happen more than 20% of the time)

- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Loss of appetite (not feeling hungry, not wanting to eat)
- Weight loss
- Low white blood cell counts leading to an increased risk of infections with or without fever
- Low platelet count leading to an increased risk of bleeding
- Low red blood cell count causing anemia
- Change in blood tests, especially loss of magnesium

Less Likely risks of carboplatin (happen 20% of the time or less)

- Numbness and/or tingling of the hands and feet, usually this goes away after the drug is stopped, however for some patients this effect may not ever go away
- Hearing problems
- Kidney problems as seen on a blood test
- Liver problems as seen on a blood test
- Low or high blood pressure
- Mouth sores
- Taste changes
- Fever
- Vision problems
- Allergic reactions (rash, hives, redness, itching, swelling, and difficulty in breathing with wheezing)
- Other skin rashes
- Difficult bowel movements (constipation)
- Diarrhea (loose stools)
- Hair loss or thinning

Rare but serious risks of carboplatin (happen less than 2-3% of the time)

- Secondary leukemia and/or myelodysplastic syndrome (damage to the bone marrow that affects normal blood cell production)

Trastuzumab possible side effects:

Less likely (20% or less of people taking trastuzumab have these effects)

- Fever associated with dangerously low levels of a type of white blood cells (neutrophils)
- Heart stops pumping blood (cardiac arrest)
- Heart muscle becomes abnormally enlarged or thickened (cardiomyopathy)
- Disease in heart's ability to pump blood during the "active" phase of the heartbeat (systole) – decreased left ventricle ejection fraction (LVEF)
- Fluid in the sac around the heart (pericardial effusion)
- Inflammation (swelling) of the sac around the heart (pericarditis)
- Fast heartbeat with regular rhythm (sinus tachycardia)
- Fast heartbeat usually in an area above the heart's chambers (supraventricular tachycardia)

- Belly pain
- Diarrhea (loose stools)
- Sores in the mouth and throat
- Nausea (feeling sick to your stomach) Vomiting (throwing up)
- Chills
- Weakness, fatigue (feeling very tired, run down)
- Fever
- Flu-like symptoms
- Chest pain not heart-related
- Body pain
- Reaction during the infusion of trastuzumab that may be life-threatening – may have low blood pressure, fever, chills, difficulty breathing or kidney damage
- **Infection (pneumonia, urinary tract, etc.)**
- **Decrease in red blood cells (anemia)**
- **Decreased number of a type of white blood cells (neutrophils/granulocytes)**
- **Decrease in the total number of white blood cells (leukocytes)**
- **Increase blood level of a liver or bone enzyme (alkaline phosphatase)**
- **Increased blood level of a liver enzyme (AST/SGOT)**
- **Increased blood level of a liver enzyme (GGT)**
- **Increased blood level of a heart muscle protein (troponin I) that may mean damage to the heart muscle**
- **Loss of appetite (not feeling hungry, not wanting to eat)**
- **Joint pain**
- **Back pain**
- **Bone pain**
- **Muscle pain**
- **Tumor pain**
- **Headache**
- **Neuropathy (numbness, tingling, or other nerve problems, usually in hands and feet)**
- **Adult Respiratory distress syndrome (ARDS)**
- **Runny or stuffy nose, sneezing**
- **Sudden chest tightness and difficulty breathing (bronchospasm)**
- **Cough**
- **Shortness of breath**
- **Low level of oxygen in the blood (hypoxia)**
- **Build up of fluid between layers of tissue in lungs and chest cavity (pneumonitis)**
- **Acne**
- **Skin rash with macules (flat discolored areas) and papules (raised bumps)**
- **Hives, itching**
- **High blood pressure**
- **Low blood pressure**

Rare but serious risks of trastuzumab which may or may not be related to the drug, but which have been seen in fewer than 2-3% of patients receiving trastuzumab

- Allergic reaction – abnormal reaction of the body to substances called allergens – (including life-threatening low blood pressure, shortness of breath and death)
- Severe allergic reaction (anaphylaxis)
- Abnormal buildup of fluid in the lungs – may have trouble breathing (pulmonary edema)
- Scarring of the lungs that can cause shortness of breath and interfere with breathing (pulmonary fibrosis)

Trastuzumab contains benzyl alcohol, a preservative that is known to cause side effects in newborns. This drug should not be given to anyone with a known allergy or sensitivity to benzyl alcohol.

The long term effects of trastuzumab are unknown.

Lapatinib possible side effects:

Likely risks of lapatinib (happen >20% of the time)

- Nausea (feeling sick to stomach)
- Loose stools (diarrhea)
- Rash, flaking or shedding of outer layer of skin

Less likely risks of lapatinib (happen ≤20% of the time)

- Fatigue (feeling very tired, run down, or weak)
- Acne; pimples
- Itching
- Nail changes, including nail loss
- Headache or head pain
- Flatulence (passing gas)
- Heartburn or sour stomach
- Belly cramping/pain
- Feeling of fullness or tightness in the belly
- Vomiting (throwing up)
- Dehydration (loss of fluid in the body),
- Loss of appetite (not feeling hungry, not wanting to eat)
- Flu-like symptoms (achy, fever, chills, tiredness, loss of appetite, cough)
- Flushing (sudden reddening of the face and/or neck)
- Irritation or sores in the mouth and throat or somewhere in the gastrointestinal tract
- Taste changes (powdery taste in the mouth)
- Increased blood level of a liver enzyme as seen on a blood test (ALT/SGPT)
- Increased blood level of a liver enzyme (AST/SGOT) as seen on a blood test

- **Increase in a liver pigment (bilirubin) in the blood that may be a sign of liver problems**

Rare but serious risks of lapatinib (seen in less than 2-3% of patients receiving lapatinib)

- **Abnormal electrical conduction within the heart (prolonged QTc interval)**
- **Decrease in the ability of the heart to pump blood during the “active” phase of the heartbeat (systole) – may make breathing difficult or heavy**
- **Liver damage leading to liver failure. Liver damage may cause itching, yellow eyes or skin, dark urine, pain or discomfort in the right upper area of the belly. Tell your doctor immediately if you get any of these symptoms.**
- **Interstitial pneumonitis – infection and inflammation (swelling) in the lungs (may have trouble breathing)**
- **Severe allergic reaction that develops rapidly – symptoms may include fever, chills and skin rash, (less commonly the symptoms may include wheezing or trouble breathing, drop in blood pressure, or swelling of the throat; swollen eyelids, lips or tongue, pain in muscles or joints, collapse or blackout.)**

GSK has found a chemical which is present in lapatinib in very small quantities that can cause changes to genes (DNA). However, many cancer drugs can damage genes, including drugs which are being given with lapatinib in this trial and/or those you may have previously received in your cancer treatments or might receive as alternate treatment. The benefits of these drugs are believed to be greater than their risks in patients with cancer. While the risk of harm to you from this chemical in lapatinib is thought to be low, the risk to an unborn baby, while unknown may be higher. The requirements for not being pregnant or becoming pregnant while on this study are described below (under “Reproductive risks”) and must be followed

The long term effects of lapatinib are unknown.

It is possible that trastuzumab taken together with lapatinib may increase the risk of heart problems.

As with any medication, allergic reactions are a possibility with lapatinib or trastuzumab.

The risks of drawing blood include pain, bruising or rarely infection at the needle site. Some of the tests that will be done as part of your regular cancer care (MUGA scans, X-rays, CT scans, mammograms) will expose you to controlled amounts of radiation. While each exposure is within acceptable limits, these exposures add up over a lifetime and increase the risk of developing cancer.

The MUGA exam requires that a small amount of radioactive dye be injected into your vein and this allows the doctors to see the action of your heart and how well it is working. The injection has similar risks to having blood drawn as stated above and also exposes you

to a certain amount of radiation. There is a risk of allergic reaction to the dye. The collection of your blood or the injection of substances such as dyes into your blood may cause pain, swelling, bruising, irritation or redness at the site, infection at the site of the needle puncture, or feeling faint. Your study team will take steps to prevent these reactions from happening.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study. It is important you understand that you need to use birth regulation (regulation highly effective: abstinence, IUD, birth control pills, tubal ligation or partner's vasectomy and less effective: condom, diaphragm or cervical cap) while on this study. Check with your health care provider about what kind of birth regulation (regulation highly effective: abstinence, IUD, birth control pills, tubal ligation or partner's vasectomy and less effective: condom, diaphragm or cervical cap) methods to use and how long to use them. Some methods might not be advised for use in this study.

If you become pregnant during this study, tell your study doctor right away. She or he will discuss stopping study treatment with you and any other steps that need to be taken.

If you are a woman who is able to become pregnant, you will have a pregnancy test before you can start this study. If the pregnancy test is positive, you will not be able to take part in this study.

While you are taking part in this study, you are at risk for these side effects. For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope adding lapatinib to standard breast cancer care or using lapatinib instead of trastuzumab in standard breast cancer care will be as good against cancer as the usual treatment, there is no proof of this yet. It is possible that lapatinib may not work as well as trastuzumab, and your cancer may come back sooner. We do know that the information from this study will help doctors learn more about lapatinib as a treatment for cancer and how it works in combination with trastuzumab and/or other cancer treatments. This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer. Your other choices may include:

- **Getting treatment or care 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.

Will my medical information be kept private?

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.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **North Central Cancer Treatment Group (NCCTG)**
- **Breast International Group (BIG)**
- **Breast European Adjuvant Studies Team (BrEAST)**
- **Frontier Science Foundation (FSTRF)**
- **GlaxoSmithKline Group of Companies (GSK)**
- **Institutional Review Boards (IRBs)**
- **Government agencies, like National Cancer Institute (NCI), the Food and Drug Administration (FDA), involved in keeping research safe for people**
- **The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials**

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. 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.

The study agent, lapatinib will be provided free of charge while you are taking part in this study. However, if you should need to take the study agent much longer than usual, the stock of free study agent that has been supplied to the NCI could run out. If the free supply runs out, your study doctor will discuss with you how to get more drug from the manufacturer. You may be asked to pay for it.

In addition, if your insurance company will not cover trastuzumab, GSK has offered to cover the cost of the drug.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's website at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

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.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at the phone number on the cover sheet.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

If you are injured by the investigational medicine being studied or by any procedure that is done to you as specified by the study, the company providing the lapatinib for this study, GlaxoSmithKline (GSK), will pay for reasonable and necessary medical expenses to treat the injury that are not covered by your health plan. GSK is not offering to compensate you for any other expenses, but you keep all of your legal rights if you sign this consent form.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

For questions about the study or a research-related injury, contact *the Northwest Community Clinical Oncology Program, 253-403-1461*. For questions about your rights as a research participant, call *MultiCare Health System Institutional Review Board at 253-403-3877*. The Institutional Review Board (IRB) is a group of people who review research studies to protect your rights.

The physician(s) involved with the medical care of the patient is available to answer ANY question(s) concerning the research/drug program. In case of a problem or an emergency, the physician should be contacted by telephone (see cover sheet).

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.

Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This “Quality of life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete five questionnaires: one on your first visit (called “baseline”), then about 13 weeks (3 months), and 52 weeks (12 months) later, three years later, and the last one 5 years after your first visit. It takes about 15 minutes to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the five questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please mark your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the five (5) Quality of Life Questionnaires.

Yes No Please initial here: _____ Date: _____

Patient Reported Outcomes Study

We want to know your view of how your day-to-day living has been affected by the treatments used on this study. This “Patient Reported Outcomes” study looks at how you are coping and at your symptoms for diarrhea, fatigue, and rash. Specifically, we want to know how severe your symptoms are, how much distress these symptoms cause you and how much they interfere with your life on a daily basis. This study also looks at whether patients are able to keep up with their assigned treatments.

This information will help doctors better understand what happens to patients during treatment and the specific effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer and how they use them.

You will be asked to complete a questionnaire at twelve different times: one on your first visit (called “baseline”), then at Week 1, Week 7, Week 13, Week 19, Week 25, Week 37, Week 52 and then Month 13, Month 15, Month 18 and Month 24. All of the time points match with office visits and AE evaluations, except Month 13. For this time point, you will be given a booklet at the Week 52 visit and asked to fill it out during Month 13 and mail it back to the doctor’s office. You will also receive a phone call from the nurse/CRA at this time point (as there is no office visit) to ask you about the three symptoms related to this substudy (diarrhea, rash, and fatigue) as well as to remind you to return the questionnaire. It takes about 10 minutes to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the twelve questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please mark your answer.

I choose to take part in the Patient Reported Outcomes Study. I agree to fill out the twelve (12) Patient Reported Outcomes Questionnaires.

Yes No Please initial here: _____ Date: _____

About Using Biological Samples for Research

This study also has required laboratory tests that will be performed to study small samples of blood and tumor tissue. A blood sample (about 5 tablespoons) will be done by drawing some blood from a vein. The blood will be taken just before treatment starts about 3 months after starting treatment, then again at 1 year (after you complete study treatment) at about 18 months and at 2 years after you start the study. If you need to stop study treatment before 1 year, we would still like to get All the blood samples. The tissue sample will be from your original surgery for breast cancer. No additional surgeries or biopsies will be done to get this tissue. The samples will be sent to laboratories associated with NCCTG, where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

Pharmacogenetic Research

As part of this study, GlaxoSmithKline (GSK) would like to use a very small portion of your blood samples (described above) for pharmacogenetic research. Pharmacogenetics looks at how a drug or medicine works for different people based on inherited traits. For example, these studies look to see if the drug is absorbed at a different rate, if there are more or different side effects, or if the drug works better or worse based on those traits. You will not need to have any more blood drawn for this research, but you can choose whether NCCTG gives a portion of your blood sample to GSK.

NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to GSK. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to GSK. Your samples will be given to them with a code number. If researchers at GSK decide you need to be contacted about the results of the research, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, and your clinic will contact you.

Please read the following statements and mark your choice:

1. My blood sample may be used by GSK for pharmacogenetic research related to this study (ALTTO).

Yes

No

Please initial here: _____ Date: _____

Recurrence of Breast Cancer

If your cancer comes back after you start this study, we at NCCTG would like to have the same kind blood and tissue samples listed above. The blood sample will be about 5 tablespoons taken with a needle from a vein in your arm or hand. The tissue samples would be from any additional biopsy or surgery you may have done to diagnose the return of your cancer. No additional biopsies or surgeries would be done to get this tissue.

Please read the following statements and mark your choice:

1. If my cancer comes back (recurs) I agree to provide blood samples to laboratories associated with NCCTG for research testing planned as part of this study.

Yes No Please initial here: _____ Date: _____

2. If my cancer comes back (recurs), I agree to provide tumor tissue samples (if available) to laboratories associated with NCCTG for research testing planned as part of this study.

Yes No Please initial here: _____ Date: _____

Future Research

We will keep some of the blood and tissue that are left over for future research on breast cancer to look at genes and proteins that may be involved in predicting benefit and safety of the study drugs. Also, if you agree, the samples may be used in research to learn more about other aspects of breast cancer and other diseases.

Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. You may obtain this information sheet at the following web address:

<http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>, or by requesting a copy from your study team.

The research that may be done with your samples is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the samples for future research about other aspects of breast cancer and other diseases is up to you. No matter what you decide to do, it will not affect your care. If you decide now that your samples can be kept for research about other aspects of breast cancer and diseases, you can change your mind at any time. Just contact the clinic where you joined this study and let them know that you do not want us to use your tissue. Then any samples that remain will no longer be used for research about other aspects of breast cancer and diseases. Your samples will continue to be used for research on breast cancer, as required for this study.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, we will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). If this research involves germline genetic research that could identify you or your family specifically, you will be asked at that time whether your samples can be used or not. Even if you give your permission and your samples are used for this kind of research, the results will not be given to you nor will they be put in your health records. Your samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future. If that were to happen you would not be paid.

Benefits

The benefits of research using samples include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the 253403-3877.

No matter what you decide to do, it will not affect your care.

Please read the following statement and mark your choice:

I understand that my samples will be kept for future research about breast cancer to look at genes and proteins which may help predict who can safely take the study drugs and who can benefit most from the study drugs..

I agree that my samples may **also** be kept for use in research to learn about, prevent or treat other aspects of breast cancer and other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Please initial here: _____ Date: _____

Sample Storage

If you want your sample(s) destroyed at any time, write to the Secretary of the MultiCare Institutional Review Board at 315 Martin Luther King Jr., Way, Tacoma, WA 98405, the phone number is 253-403-3844.

NCCTG has the right to end storage of the samples without telling you.

The samples will be stored at NCCTG, Mayo Clinic, Rochester, Minnesota, USA, and may be used by researchers from or associated with the Breast International Group (BIG) or Breast European Adjuvant Studies Team (BrEAST). Other outside researchers (not currently part of this study) may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. Your samples will be given to them with a code number. If researchers outside NCCTG decide you need to be contacted about the results of the research, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, and your clinic will contact you.

Please read the following statement and mark your choice:

I understand that my samples may be sent to the Breast International Group (BIG) and/or Breast European Adjuvant Study Team (BrEAST) or laboratories linked to these groups for future research about breast cancer.

I agree that my samples may **also** be sent to other outside researchers for use in research.

Yes No Please initial here: _____ Date: _____

Where can I get more information?

**You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615**

You may also visit the NCI website at <http://cancer.gov/>

- **For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>**
- **For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study, and that you have read and understood all the information on this form.

Patient's name (printed or typed)

Patient's Signature Date

Physician name (printed or typed)

Physician Signature Date

Signature of person conducting the
Informed consent discussion

Date

Authorization (Permission) to Use or Disclose (Release) Identifiable Health Information for Research

Participant's Name: _____

Birth Date: _____

1. What is the purpose of this form?

The Northwest Community Clinical Oncology Program (NWCCOP) on that does research to learn about the causes of cancer, and how to prevent and treat cancer. Researchers would like to use your health information for research. This information may include data that identifies you. Please carefully review the information below. If you agree that researchers can use your personal health information, you must sign and date this form to give them your permission.

2. What personal health information do the researchers want to use?

The researchers want to copy and use the portions of your medical record that they will need for their research. If you enter a Northwest CCOP research study, information that will be used and/or released may include the following:

- the history and diagnosis of your disease;
- specific information about the treatments you received, including previous treatment(s) you may have had;
- information about other medical conditions that may affect your treatment;
- medical data, including laboratory test results, tumor measurements, CT scans, MRIs, x-rays, and pathology results;
- information on side effects (adverse events) you may experience, and how these were treated;
- long-term information about your general health status and the status of your disease;
- data that may be related to tissue and/or blood samples that may be collected from you; and
- numbers or codes that will identify you, such as your social security number and medical record number.

You may request a blank copy of the CTSU data forms from the study doctor or his/her research staff to learn what information will be shared.

3. Why do the researchers want my personal health information?

The Northwest CCOP will collect your health information and share it with the North Central Cancer Treatment Group (NCCTG) and the CTSU Operations Center if you enter a cooperative group research study. The (NCCTG) centers will use your information in their cancer research study. **CTSU N063D/BIG 2-06 ALTTO: Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Study – A Randomized, Multi-center, Open-Label, Phase III Study of Adjuvant Lapatinib, Trastuzumab, their Sequence and their Combination in Patients with HER2/ErbB2 Positive Primary Breast Cancer.**

4. *Who will be able to use my personal health information?*

The Northwest CCOP will use your health information for research. As part of this research, they may give your information to the following groups taking part in the research. The Northwest CCOOP may also permit these groups to come in to review your original records that are kept by the Northwest CCOP so that they can monitor their research study.

- the Biostatistical Center and Operations Center North Central Cancer Treatment Group (NCCTG)
- the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute that supports the research of the CTSU;
- Public Health agencies and other government agencies (including non-U.S.) as authorized or required by law;
- other people or organizations assisting with the Northwest CCOP research efforts (this may include **Pharmaceutical Company(ies) (or designee[s]) and any subcontractors**), the company(ies) sponsoring the research); and
- central laboratories, central review centers, and central reviewers. The central laboratories and review agencies may also give your health information to those groups listed in the five bullets above.
- Breast International Group (BIG)
- Breast European Adjuvant Studies Team (BREAST)
- Glaxo SmithKline Group of Companies (GSK)

5. *How will information about me be kept private?*

The Northwest CCOP will keep all patient information private to the extent possible, even though the Northwest CCOP is not required to follow the federal privacy laws. Only researchers working with the Northwest CCOP will have access to your information. The Northwest CCOP will not release personal health information about you to others except as authorized or required by law. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

6. *What happens if I do not sign this permission form?*

If you do not sign this permission form, you will not be able to take part in the research study for which you are being considered.

7. *If I sign this form, will I automatically be entered into the research study?*

No, you cannot be entered into any research study without further discussion and separate consent. After discussion, you may decide to take part in the research study. At that time, you will be asked to sign a specific research consent form.

8. What happens if I want to withdraw my permission?

You can change your mind at any time and withdraw your permission to allow your personal health information to be used in the research. If this happens, you must withdraw your permission in writing. Beginning on the date you withdraw your permission, no new personal health information will be used for research. However, researchers may continue to use the health information that was provided before you withdrew your permission.

If you sign this form and enter the research study, but later change your mind and withdraw your permission, you will be removed from the research study at that time.

To withdraw your permission, please contact the person below. He/she will make sure your written request to withdraw your permission is processed correctly.

Karyn Hart, RHIT, CCRP
Program Coordinator
Northwest CCOP
315 Martin Luther King, Jr., Way
Tacoma, WA 98405
(253) 403-1461

9. How long will this permission last?

If you agree by signing this form that researchers can use your personal health information, this permission has no expiration date. However, as stated above, you can change your mind and withdraw your permission at any time.

10. What are my rights regarding access to my personal health information?

You have the right to refuse to sign this permission form. You have the right to review and/or copy records of your personal health information kept by the Northwest CCOP. You do not have the right to review and/or copy records kept by the Northwest CCOP or other researchers associated with the research study.

Signatures

I agree that my identifiable health information may be used and disclosed for research purposes described in this form.

Signature of Patient or Patient's Legal Representative: _____ Date: _____

Printed Name of Legal Representative (if any): _____

Representative's Authority to Act for Patient: _____

Signature of Person Obtaining Authorization: _____

Printed Name of Person Obtaining Authorization: _____