Protocol Update #10
01/15/2015

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO CALGB 40601

RANDOMIZED PHASE III TRIAL OF PACLITAXEL +TRASTUZUMAB + LAPATINIB VERSUS PACLITAXEL + TRASTUZUMAB AS NEOADJUVANT TREATMENT OF HER2-POSITIVE PRIMARY BREAST CANCER

Investigational agent supplied and distributed for this trial by the NCI:
Lapatinib (GW572016 NSC #727989, IND [redacted])

Companion study CALGB 70501

X	**Update:**		**Status Change:**
	Eligibility changes		Activation
	Therapy / Dose Modifications / Study Calendar changes		Closure
	Informed Consent changes		Suspension / temporary closure
	Scientific / Statistical Considerations changes		Reactivation
	Data Submission / Forms changes		
X	Editorial / Administrative changes		
	Other :		

No IRB approval of this amendment is required.
Please follow you local IRB guidelines.

UPDATES TO PROTOCOL:

- In keeping with new CTEP PIO requirements, the name of the lead group on the title page of the protocol has been updated from "Cancer and Leukemia Group B" to "Alliance for Clinical Trials in Oncology."
- The NCTN participating groups have been added to the lower left of the protocol cover page.

UPDATES TO THE MODEL CONSENT:

No changes have been made to the model consent form.

A replacement protocol document and model consent form have been issued.
This study remains closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

MODEL CONSENT FORM

RANDOMIZED PHASE III TRIAL OF PACLITAXEL + TRASTUZUMAB + LAPATINIB VERSUS PACLITAXEL + TRASTUZUMAB AS NEOADJUVANT TREATMENT OF HER2-POSITIVE PRIMARY BREAST CANCER

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 in the trial. 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 study because you have breast cancer that is HER2-positive that your doctor thinks may benefit from chemotherapy plus drugs that target the HER2 protein. You and your doctor decided that it was best for you to have medical therapy followed by surgery. This clinical trial is testing neoadjuvant (neoadjuvant means "given before surgery") chemotherapy combining two different HER2-targeting drugs, lapatinib and trastuzumab, given with chemotherapy before surgery for cancers like yours. Medical therapy such as chemotherapy is often given before surgery because it allows your doctor to measure tumor shrinkage due to the drugs you are given and may allow less surgery. Surgery to remove any remaining cancer after neoadjuvant chemotherapy is considered to be the standard of care. Surgery is considered to be part of this study because information will also be collected about the type of surgery that you have after the medical study therapy.

Why is this study being done?

The purpose of this study is to see if combining two anti-HER2 drugs, lapatinib and trastuzumab, with the chemotherapy drug paclitaxel before surgery increases tumor shrinkage in the breast. Researchers will study whether there is any cancer left in the breast tissue when the surgeon removes the lump or the breast, and evaluate if there is any difference in the likelihood of there being no cancer left when comparing the breast tissue of the participants who have received trastuzumab plus lapatinib plus chemotherapy or trastuzumab plus chemotherapy. In addition, tests on breast tissue samples from research biopsies done before you start the neoadjuvant chemotherapy and from tissue removed at surgery may help us understand why some cancers shrink with this kind of treatment while others do not. If you participate, you will have biopsies of your tumor, then will receive either trastuzumab plus paclitaxel or trastuzumab and lapatinib plus paclitaxel. After this treatment, you will have breast cancer surgery to remove any remaining breast cancer tissue.

Paclitaxel has been approved by the Food and Drug Administration (FDA) of the United States for the treatment of breast cancer after surgery or for the treatment of breast cancer that has spread to other parts of the body. Lapatinib has been approved by the FDA for the treatment of HER2 positive breast cancer that has spread to other parts of the body. Trastuzumab has been approved by the FDA for the treatment of HER2 positive breast cancer after surgery or for the treatment of breast cancer that has spread to other parts of the body. The use of these drugs before surgery is considered by the FDA to be investigational or research.

How many people will take part in the study?

About 300 participants will take part in this study.

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

Routine Medical Tests

You will need to have the following exams, tests or procedures to find out if you can be in the study. None of these tests or procedures are experimental, they are a routine part of regular cancer care and may 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.

- A medical history and physical examination (questions about your health, your other medical problems, your medications, and any allergies you might have as well as a general medical examination)
- A heart test called a MUGA scan or echocardiogram (measures your heart's ability to pump)
- Blood tests
- Measurement of your breast cancer by MRI, ultrasound or mammogram.

Many of these tests and procedures will be repeated during the study. Some of them may be done more often because you are taking part in this study.

Research Procedure

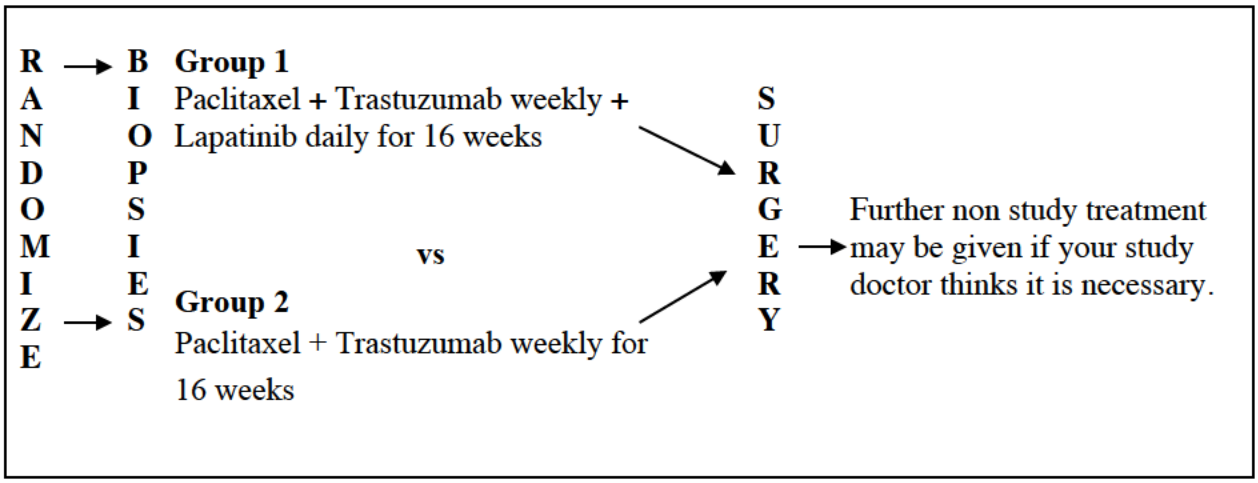
- Biopsies of your cancer tissue will be taken before you begin treatment to collect tissue for research purposes. This will be done before study treatment begins, however if there is enough of your cancer tissue left over from your biopsy taken at the time of your diagnosis you may not need to have these additional biopsies. If you need to have the additional biopsies, the biopsies may be performed at the time when a clip is placed in the tumor bed so that your surgeon can locate the site of the tumor at the time of surgery. The clip is placed via a catheter, which is inserted into the breast tissue. This procedure is done in an outpatient setting using a local anesthetic. During clip placement, tissue samples from your tumor (biopsies) for research purposes will be taken through the same catheter used to place the clip.

You will be "randomized" into one of the two study groups described below. Randomization means that you are put into a group by chance. 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 an equal chance of being placed into either of the two groups.

If you are in **Group 1** you will be treated with the chemotherapy drug paclitaxel, and the anti-HER2 drug trastuzumab, both given by vein once a week for 16 weeks plus the anti-HER2 tablet lapatinib that you take by mouth daily at home for 16 weeks, followed by surgery. The tablets must be taken on an empty stomach (either 1 hour before or 1 hour after a meal). The tablets should not be crushed. You should not take antacids for 1 hour before and 1 hour after taking the lapatinib tablets. If you miss a dose and remember later that day, you can take it then, otherwise skip the dose and take the next days dose as scheduled. Do not take two doses in one day. If you become ill and vomit or throw up within 1 hour after taking after taking your lapatinib dose, check whether you can see the tablets. Unless you can see ALL of the tablets that you took, do not repeat the dose. Just skip that days dose. If you do see ALL of the tablets, then repeat the dose.

If you are in **Group 2** you will be treated with the chemotherapy drug paclitaxel and the antiHER2 drug trastuzumab. Both are given by vein weekly for 16 weeks, followed by surgery.

If you receive lapatinib you will be asked to record the day, number of tablets taken and the time of each dose of lapatinib on the "CALGB: 40601 Lapatinib Medication Calendar". You will be asked to bring the calendar with you to each clinic visit.



During the study treatment you will have physical examination, routine blood tests every 4 weeks. A MUGA scan or echocardiogram will be performed after you have completed 8 weeks of study treatment and prior to surgery, or more often if your study doctor feels it is necessary.

After you have completed the study treatment you will have routine blood tests, a MUGA scan and echocardiogram will be performed and your breast cancer will be measured by your study doctor or his/her staff during a physical examination, as well as by MRI, ultrasound or mammogram at the end of this time in order to see if it has shrunk, and if so how much. You will then have surgery to remove any remaining breast cancer.

After surgery, physical examinations will be done every 6 months for first 2 years, then annually for 10 years from the time of study entry.

After surgery, your study doctor may recommend that you receive radiation therapy and/or additional chemotherapy. Your study doctor will discuss those additional treatment options with you.

How long will I be in the study?

You will be in the study for 16 weeks of study treatment followed by surgery about one month after your last dose of study treatment. Your study doctor will continue to follow your condition for 10 years from study entry.

Can I stop being in the 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 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 is also a risk of death from both standard drugs and the study drugs.

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

PACLITAXEL + TRASTUZUMAB + LAPATINIB

Likely (have been seen in 20% of patients):

- Nausea
- Vomiting
- Diarrhea
- Rash
- Decreased appetite
- Temporary lowering of the number of white blood cells (neutrophils are cells that help your body fight infection; see also neutropenic fever and infection below)
- Temporary lowering of the number of red blood cells (may cause a feeling of tiredness, and shortness of breath)
- Temporary lowering of the number of blood platelet cells (cells that help your blood clot)
- Loss of scalp and body hair
- Numbness or tingling in the fingers or the toes, which may continue after you have stopped the treatment
- Temporary pain in the muscles, back, joints or bone

Less Likely (have been seen in 20% or less patients):

- Neutropenic fever: fever associated with dangerously low levels of a type of white blood called neutrophils (see above risk of lowered white blood cells)
- Infection (See above risk of lowered white blood cells)
- Fatigue
- A rash that looks like acne
- Flushing (temporary redness in the face and neck)
- Itching
- Dehydration
- Abdominal bloating and/or pain
- Gas
- Heartburn
- Change in taste

- Abnormal liver function as seen on a blood test: ALT, AST, bilirubin, alkaline phosphatase and GGT). Rarely this leads to liver failure (see below).
- Abnormal blood test of bone health: alkaline phosphatase
- Headache
- Flu-like symptoms such as body aches, fever, chills, tiredness, loss of appetite, cough
- Sores in the mouth or throat (like canker sores)
- Reaction during the infusion of trastuzumab, which may include changes in blood pressure fever, chills, difficulty breathing and kidney damage. This can be life threatening.
- A condition in which the heart muscle is abnormally enlarged or thickened, which could result in heart failure and could be serious
- Decreased heart function as seen on a heart test like echocardiogram, which can be serious
- Irregular heartbeat - this sometimes leads to fainting or the heart stopping, which could be serious
- Fluid around the heart or inflammation of the heart
- Shortness of breath, cough or wheezing
- Hives
- Allergic reaction of stuffy or runny nose, sneezing
- Voice changes
- Loss of some or all of the fingernails or toenails
- Pain in the area of your cancer
- Pain, including chest pain not related to the heart

Rare, but Serious (have been seen in only 2 – 3% or less of patients, but might be serious):

- Severe allergic reactions with difficulty breathing and difficulty getting enough oxygen
- Severe lung disease causing great difficulty breathing
- Inflammation of lung tissue, or fluid in the lungs
- Liver failure which may cause itching, yellow eyes or skin, dark urine, pain or discomfort in the right upper area of the belly (stomach). Tell your study doctor if you get any of these symptoms. Your doctor will order simple blood tests to check how your liver is working.

PACLITAXEL + TRASTUZUMAB

Likely (have been seen in 20% of patients):

- Nausea
- Vomiting
- Decreased appetite
- Temporary lowering of the number of white blood cells (neutrophils are cells that help your body fight infection; see also neutropenic fever and infection below)
- Temporary lowering of the number of red blood cells (may cause a feeling of tiredness, and shortness of breath)
- Temporary lowering of the number of blood platelet cells (cells that help your blood clot)
- Loss of scalp and body hair
- Numbness or tingling in the fingers or the toes, which may continue after you have stopped the treatment
- Temporary pain in the muscles, back, joints or bone

Less Likely (have been seen in 20% or less patients):

- Neutropenic fever: fever associated with dangerously low levels of a type of white blood called neutrophils (see above risk of lowered white blood cells)
- Infection (See above risk of lowered white blood cells)
- A condition in which the heart muscle is abnormally enlarged or thickened, which could result in heart failure and could be serious
- Decreased heart function as seen on a heart test like echocardiogram
- Heart damage as seen on a blood test
- Irregular heart beat- this sometimes leads to fainting or the heart stopping, which could be serious
- Fluid around the heart or inflammation of the heart
- Shortness of breath, cough or wheezing
- Rash
- A rash that looks like acne
- Hives
- Allergic reaction of stuffy or runny nose, sneezing
- Headache
- Diarrhea
- Fatigue
- Reaction during the infusion of trastuzumab, which may include changes in blood pressure fever, chills, difficulty breathing and kidney damage. This can be life threatening.
- Sores in the mouth or throat (like canker sores)
- Abnormal liver function as seen on a blood test: ALT, AST, bilirubin, alkaline phosphatase and GGT). Rarely this leads to liver failure (see below).
- Abnormal blood test of bone health: alkaline phosphatase
- Flu-like symptoms such as body aches, fever, chills, tiredness, loss of appetite, cough
- Voice changes
- Abdominal pain
- Pain in the area of your cancer
- Pain, including chest pain not related to the heart

Rare, but Serious (have been seen in only 2 – 3% or less of patients, but might be serious):

- Severe allergic reactions with difficulty breathing and difficulty getting enough oxygen
- Severe lung disease causing great difficulty breathing
- Liver failure
- Inflammation of lung tissue or fluid in the lungs

Drugs that work similarly to lapatinib have rarely been known to cause heart muscle weakness, which could lead to heart failure. They have also rarely been associated with lung or breathing problems. Your doctor will be performing tests to measure the pumping function of your heart (MUGA scans or echocardiograms) before beginning, after completing 8 weeks of study treatment and before surgery. Let your doctor know if you develop any shortness of breath or breathing difficulties during the study and your doctor will evaluate your lung function as appropriate.

Some patients may have a severe or life-threatening reaction during or after treatment with trastuzumab. These reactions can involve a drop in blood pressure and shortness of breath, and have resulted in death in several patients. These severe reactions may be more common in patients who already have breathing difficulties or lung disease. If you develop any clear discomfort during or after a treatment with trastuzumab, you should contact your physician immediately or go to the nearest Emergency Care facility.

There are many drugs (prescription and over the counter medications) and dietary supplements (including what are sometimes called "complementary" or "alternative" medicines), which may interact with the drugs used in this study. Grapefruit, or some grapefruit juice preparations may also interact. Drug interactions could lead to increased side effects. Your study doctor will review all of the medications and supplements you are currently taking before starting this study. You should also tell your study doctor if you eat grapefruit or drink grapefruit juice. You should not take any new medications or dietary supplements, including those prescribed by other doctors, without first discussing it with your study doctor or pharmacist.

Reproductive risks: Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study. If you are a woman of childbearing potential you must practice an effective, non-hormonal method of birth control while receiving study treatment and for at least 2 months after completing or discontinuing study treatment. Ask about birth control counseling and more information about preventing pregnancy. You should not nurse your baby while on this study.

RESEARCH BIOPSIES

The research biopsy is done in a similar way to biopsies done for diagnosis. Common side effects of biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, a skin infection can occur. You will sign a separate consent form before the biopsies are taken. This will be a standard surgical consent form from the institution where the biopsy procedure takes place.

SURGERY

You will sign a separate consent form before surgery. This will be a standard surgical consent form from the institution where the surgery takes place. The possible risks and side effects of the surgery that you will have will be explained to you at that time.

For more information about risks and side effects, ask the researcher or your regular doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that combining anti-HER2 drugs with chemotherapy will be more useful against cancer compared to just one anti-HER2 drug alone, there is no proof of this yet. It is possible that receiving the study

treatment before surgery may have a possible benefit of allowing you to have breast conserving surgery, where any remaining cancer is removed, but not the breast itself. We do know that the information from this study will help doctors learn more about drugs as a treatment for cancer. This information could help future cancer patients.

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

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study

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:

- The Cancer and Leukemia Group B (CALGB)
- GlaxoSmithKline (the makers of lapatinib) and their collaborators
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

If your doctor is participating in this study through the Cancer Trials Support Unit (the CTSU is a clinical trials service sponsored by the NCI to provide greater access to cancer trials), a record of your progress will also be kept by the CTSU. If your record is used or disseminated for such purposes, it will be done under conditions that will protect your privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

The CALGB has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services or for purpose of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

What are the costs of taking part in this 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 lapatinib used in this study will be provided to your doctor for you, free of charge by the Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI). You or your health plan/insurance company will be responsible for the cost of the trastuzumab and the paclitaxel.

The cost of the MUGA scan or echocardiogram assessments done before you start study treatment, before surgery, and to evaluate side effects of study treatment (if necessary) are standard of care and will be billed to your health plan/insurance carrier. There will be no cost to you or your health plan/insurance carrier for the Week 8 assessment which will be done for research purposes and you will not be billed for it.

Research Tumor Tissue Biopsies

Neither you nor your health care plan/insurance carrier will be billed for the following the tissue collection procedures for the tissue samples used for research:

1) The pre-treatment tissue samples for research purposes;

2) If you have consented to have research tissue samples collected at the time of surgery;

3) Or if you do not have surgery and consent to have a separate biopsy procedure for research tissue collection after you have completed study treatment.

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 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.

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 study?

It is important that you tell your study doctor, _____ [investigator's name(s)], 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 _____ [telephone number].

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.

What are my rights if I take part in this 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.

A Data and Safety Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. 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 study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]

RELATED STUDIES

Please note: the following 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.

One of the main reasons for doing this study is to test blood and tissue samples to find out if doctors in the future will be able to predict which patients will benefit from specific drugs or combinations of drugs. Not all patients will respond the same way to the drugs used in this study. We hope the samples collected in this study will help doctors be able to select the best drugs for patients in the future.

The results of these research studies will not be provided to you or your doctor, nor will the results have any effect on your treatment. It is unlikely that what the researchers learn from these studies will have a direct benefit to you. However, the information learned from these studies may benefit other patient in the future.

The results from these studies may be published, but individual patients will not be identified in these publications.

There will be no charge to you for participating in these research studies. Your sample will only be used for research and will not be sold. The research done with your sample may help to develop new products in the future.

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 is very small.

If you decide to participate and then change your mind at any time about participating in these studies for any reason, you should contact your institution and let them know that you do not want the researchers to use your sample. The sample will then no longer be used for research. It will either be destroyed or returned to your institution for storage. The sample will also be returned to your institution upon request if needed for any other medical or legal reasons.

Required collection of tissue before treatment starts:

By signing this consent form, you are agreeing to have additional biopsies before you begin treatment. Four small samples of your tumor will be removed and sent to the CALGB Pathology Coordinating Office. This is required in order for you to participate in this study because the research done on the tissue is a very important part of this study. The researchers want to learn why some cancers shrink with this study treatment while others do not. You or your insurance company will not be charged for the costs of obtaining the tissue. You are also agreeing to allow these biopsy samples to be used for research.

Optional studies on blood:

The researchers would like to investigate whether substances in your blood are related to the way that your body responds (or doesn't respond) to the study treatment that you receive in this trial.

You will have about 4 tablespoons of blood drawn before the first dose of study treatment, about about 3½ tablespoons before the third dose of chemotherapy (day 15) and about 3½ tablespoons before the last dose of paclitaxel (week 16). The blood may be drawn at the same time that blood will be drawn for routine testing.

1) My blood specimens may be used for the research described above.

_____Yes _____No Initials_____

Optional studies on tissue taken at the time of surgery:

The researchers would also like to collect additional samples of tissue, that will be taken at the time of surgery, that will allow them to evaluate the effects of the study treatment.

2) Samples of my tissue may be collected at the time of surgery to evaluate the effects of the study treatment.

_____Yes _____No Initials_____

Optional studies on tissue after completing study treatment, if you do not have surgery:

If you or your study doctor decide not to pursue surgery after completing study treatment, the researchers would like to perform another biopsy of your tumor to evaluate the effects of study treatment.

3) I agree that an additional biopsy of my tumor tissue may be collected for research purposes if I do not have surgery after completing study treatment.

_____Yes _____No Initials_____

Storage of tissue and blood

The researchers would also like to store any portion of the blood and tissue that is obtained prior to and at the time of surgery that is not used up by the related studies described above. These samples may be stored indefinitely. You can still take part in the treatment study, and the research study described above without giving your consent for your specimens to be stored.

It is not possible for you or the CALGB to know what studies of cancer may be appropriate in the future. We ask that you give permission in advance for other studies to be performed using these specimens.

Please read each sentence below and think about your choice. After reading each sentence, check "Yes" or "No". If you have any question, please talk to your study doctor or nurse.

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

4) My specimens may be kept for future use in research to learn about, prevent, or treat cancer.

_____Yes _____No Initials_____

5) My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____Yes _____No Initials_____

6) Someone may contact me in the future to ask me to take part in more research.

_____Yes _____No Initials_____

Optional genetic studies on blood:

Researchers are also interested to learn how certain genes influence the effectiveness and side effects of the drugs used in this study. In order to study the genes, one additional tablespoon of blood will be taken before the first dose of treatment. DNA will be removed from your blood sample. DNA is the substance that makes up your genes. Genes are the units of inheritance that are passed down from generation to generation. They are responsible for eye color, hair color, blood type, and hundreds of other traits. These are also called genetic studies.

There are specific risks associated with genetic studies. To help you make your decision, additional information about participation in genetic studies is included at the end of this consent form. This information identifies how your personal information will be protected by the CALGB and its researchers.

7) My blood specimen may be used for the genetic research described above.

_____Yes _____No Initials_____

Safeguards of Confidentiality in Studies Involving Genes (genetic studies):

It is possible to use blood samples to study many different kinds of genes. The CALGB recognizes this possibility and will take the following steps to protect your privacy and to protect you from having your sample tested for any genetic changes not directly related to cancer:

- Blood samples will be stored at a CALGB laboratory. The CALGB Statistical Center will perform all analyses of data and store all study results. Your blood sample will not be stored with your name on it. Instead, it will be labeled with a special CALGB identification number. The only location where your name and special identification number will be stored together is at the CALGB Statistical Center. The greatest effort will be made to see that all personal information that can identify you is kept under conditions that protect your privacy.
- Information about your participation in this study and results of any tests performed on your sample will be kept only at the CALGB Statistical Center at Duke University. This information will not be made available to your doctors or to individual researchers at CALGB. Test results from this study will not be put in your medical records. All study information, including test results, is stored under conditions that limit access in order to protect the privacy of the people participating in this study.
- Your blood will be used only for the study of genes involved in cancer.
- There are no absolute legal protections against discrimination on the basis of genetic information. Instances are known in which a patient has been required to provide genetic

information before applying for health insurance and/or a job. Since neither you nor your physician will be notified of the results of this test, it is unlikely that any discrimination could take place.

The same precautions to protect your privacy will be in place for such future studies. Future investigators will receive blood samples with the special CALGB identification number only, and your blood sample will not be identified with your name. These future investigators must apply to the CALGB and have their research project reviewed and approved by the CALGB.

If you decide now to give a sample of blood and then change your mind at any time about participating in the study, just contact your institution and let them know that you do not want the researchers to use your sample. The results from these studies may be published, but individual patients will not be identified in the publications.

Additional Optional Genomic Research Studies

In this study we will have an additional project that involves studying the genetic material from your cancer tissue taken before study treatment. We will compare the genetic material from your cancer tissue to the genetic material from your normal tissue to find the differences that exist. By combining this information with information from your study records, it may be possible to identify the genetic changes that are associated with your particular type of cancer. With this knowledge, future treatments for breast cancer could become customized to a patient's unique genetic make-up. For this particular project we need to ask specific permission from you because certain information from your DNA samples will be released anonymously into public databases. You can still be a part of the treatment study even if you say "no" to taking part in these additional studies.

- Your coded tissue samples will be sent to an NCI-sponsored storage facility, known as the CALGB Pathology Coordinating Office. The samples will be processed there and portions of your samples then will be sent to different types of laboratories as part of this project. One type of laboratory will analyze your DNA by a method called sequencing. Other types of laboratories will study your samples by different methods
- Information from analyses of your coded samples and your coded medical information will be put into databases along with information from the other research participants. These databases will be accessible by the Internet.
    - Anonymous information from the analyses will be put in a completely <u>public</u> database, available to anyone on the Internet.
    - Your coded medical information and information from more detailed analyses of your coded samples will be put in a <u>controlled-access</u> database. The information in this database will be available only to approved researchers.

Please note that traditionally-used identifying information about you, such as your name, address, telephone number, or social security number, will NOT be put into either the public or controlled-access databases for this project.

Potential Risks of Participating in the Project

- Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we have put in place, it is impossible to guarantee that links between you and the genetic information we have obtained will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that genetic information from them could be used to try and

identify your sample from the publicly available information. Similarly, it may be possible that genetic information from you could be used to help identify them.

- While neither the public nor the controlled-access databases developed for this project will contain information that is traditionally used to identify you, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a relative) in another database and be able to identify you (or your relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.
- Since some genetic variations can help to predict the future health problems of you and your relatives, it is possible this information might be of interest to employers, health providers, insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives. Therefore, your genetic information could be used in ways that could cause you or your family distress, such as revealing that you (or a relative) carry a genetic disease or by leading to the denial of employment or insurance for you (or a relative). We emphasize that we will do everything we can to protect your private information.
- There also may be other privacy risks that we have not foreseen.

  While we believe that the risks to you and your family are very low, we are unable to tell you exactly what all of the risks are. There are some state laws that protect against genetic discrimination by employers or insurance companies, but there is no federal law yet that prohibits such discrimination.

8) I agree to provide my tissue for the DNA sequencing project. I understand that my coded genetic information and coded medical information will be placed in databases accessible by the Internet.

_____Yes _____No Initials_____

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 Web site 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

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant_____ Date_____