

Kansas City Clinical Oncology Program

A Randomized Phase III Trial of Adjuvant Therapy Comparing Chemotherapy Alone (Six Cycles of Docetaxel Plus Cyclophosphamide or Four Cycles of Doxorubicin Plus Cyclophosphamide Followed by Weekly Paclitaxel) to Chemotherapy Plus Trastuzumab in Women with Node-Positive or High-Risk Node-Negative HER2-Low Invasive Breast Cancer

This is a clinical trial, which is a type of research study. You are being asked to take part in this study because you have early stage breast cancer that has been removed by surgery. Your doctor has told you that chemotherapy and other therapy after surgery will lower the chance of your cancer returning.

Your breast tumor has already been tested to find out if there are too many copies of the HER2 gene in the tumor cells or too much HER2 protein on the surface of the tumor cells. When there are too many copies of the HER2 gene or too much HER2 protein, the breast cancer is called "HER2-positive." Test results have shown that your breast cancer tumor is **not** HER2-positive, which means that your tumor cells have a low HER2 level. In this consent form, a low level of HER2 will be called "HER2-low." This study is only for women with HER2-low breast cancer.

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 the study doctor for more information.

Who is conducting the study?

This study is being conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP).

Why is this study being done?

- The main purpose of this study is to learn if adding a targeted therapy, trastuzumab (Herceptin®), to standard treatment with chemotherapy for early stage, HER2-low breast cancer, will prevent breast cancer from returning.

Trastuzumab is called a targeted therapy because it targets the tumor cells by blocking the HER2 protein on the surface of the cancer cell to slow down or stop cancer growth. Trastuzumab is a standard treatment for HER2-positive breast cancer. In this study, trastuzumab is considered to be investigational because it has not been studied for use in treating HER2-low breast cancer. Studies that already have been done with trastuzumab focused on breast cancers that were strongly HER2-positive. However, in some of these studies, tumor samples were checked in a central laboratory to confirm the HER2 testing results. Some breast cancers that were thought to be HER2-positive were actually HER2-low. The researchers then looked at the results of treatment in patients with HER2-low tumors. They found that trastuzumab seemed to have benefit in keeping the cancer from returning even when the HER2 levels were in the normal range. The B-47 study is being done to learn more about using trastuzumab to treat HER2-low breast cancer.

- A second purpose of this study is to learn if adding trastuzumab to treatment with chemotherapy will help women with HER2-low breast cancer live longer.
- In order to learn more about certain characteristics of cancer tumors, this study includes special research tests that will be done on samples of the tumor that were removed during

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582

your surgery for breast cancer and on your blood samples that will be collected during the study. Information about these study requirements will be explained to you in more detail later in this consent form.

- Another goal of this study is to find out how the drugs used in this study affect menstrual cycles (monthly periods) and if these changes in menstrual cycles have any effect on breast cancer. As part of this study goal, you will be asked to allow blood samples to be collected.
- The B-47 study will also explore the possibility that other medical conditions, medications you may be taking, or other factors such as alcohol intake, smoking, and weight may affect breast cancer. You will be asked to complete questionnaires and allow blood samples to be taken to help answer these questions.

How many people will take part in the study?

About 3,260 women from different cancer treatment centers will take part in this study.

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

Before you begin the study: You will need to have the following tests and exams to find out if you can be in the study. These tests and exams are 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. This will be up to your study doctor.

- History and physical exam
- Blood tests to check your blood counts and organs that can be affected by study therapy
- Chest x-ray or scan of the chest
- Mammogram or MRI of your breasts
- Bone scan, bone x-rays, or other bone tests only if you have bone pain or your blood tests show an increase in a bone-related protein
- Scan of the liver only if your blood tests show abnormal liver function
- Pregnancy test if you are a woman of childbearing potential

You will also need to have the following tests that are not part of regular cancer care and are **being done for the purpose of the study.**

- Echocardiogram or MUGA scan
- ECG (electrocardiogram)

You already had a test done on a sample of your tumor to find out if your breast cancer is HER2-positive. This is part of regular cancer care. More than one type of test can be used to find this out. For this study, a specific test called immunohistochemistry (IHC) needs to be done with a sample of your tumor to know if your breast cancer is HER2-low. If another type of HER2 test was done but not an IHC test, an IHC test must be done to confirm your breast cancer is in the HER2-low range. When IHC is done as the second test, it may not be considered to be part of regular cancer care but will need to be **done for the purpose of this study.**

During the study: Before you join the study, you and your doctor will choose one of two combinations and schedules of chemotherapy drugs (either chemotherapy A or B). If all the required tests and exams show that you can be in the study and if you choose to take part, you will be "randomized" to one of the study arms described below. Randomization means that you are put into a study arm by chance.

A computer program will place you in one of two study arms. Neither you nor your doctor can choose the study arm you will be in. You will have an equal chance of being placed in either study arm.

- If you are in Arm 1, you will receive the chemotherapy that you and your doctor chose. You will not receive trastuzumab.
- If you are in Arm 2, you will receive the chemotherapy you and your doctor chose and you will also receive trastuzumab.

You will begin your study therapy within 2 weeks after you join the study. All of the study drugs will be given through a vein. You will receive your study drugs according to one of the schedules described in the next section. The period of time between treatments is called a **cycle**.

Study therapy - Group A chemotherapy (Arm 1):

You will receive docetaxel and cyclophosphamide once every 3 weeks for 6 cycles. Each treatment will take about 1½ hours.

Study therapy - Group A chemotherapy (Arm 2):

You will receive docetaxel, cyclophosphamide, and trastuzumab once every 3 weeks for 6 cycles. The first treatment will take about 3 hours for you to receive all of the drugs. If you have no problems receiving the drugs during the first cycle, it will take about 2-2½ hours to receive cycles 2 through 6.

After you complete the treatment cycles that include chemotherapy and trastuzumab, you will continue to receive trastuzumab once every 3 weeks until about 1 year after your first dose of trastuzumab. It will take about 30 minutes for you to receive each trastuzumab treatment.

Study therapy - Group B chemotherapy (Arm 1):

You will receive doxorubicin and cyclophosphamide (AC) for 4 cycles. You will receive AC either every 2 weeks or every 3 weeks. Your doctor will decide which schedule is better for you. Each treatment will take about 1 hour. Three weeks after your last dose of AC, you will receive paclitaxel once a week for about 12 weeks. Each paclitaxel treatment will take about 1 hour.

Study therapy - Group B chemotherapy (Arm 2):

You will receive doxorubicin and cyclophosphamide (AC) for 4 cycles. You will receive AC either every 2 weeks or every 3 weeks. Your doctor will decide which schedule is better for you. Each treatment will take about 1 hour. Three weeks after your last dose of AC, you will receive paclitaxel and trastuzumab once a week for about 12 weeks. The first treatment will take about 2½ hours for you to receive both drugs. If you have no problems receiving the drugs during the first treatment, it will take about 1½ hours for the remaining treatments.

After you complete the treatment cycles that include chemotherapy, you will continue to receive trastuzumab every 3 weeks until about 1 year after your first dose of trastuzumab. It will take about 30 minutes for you to receive each trastuzumab treatment.

A summary of the study therapy is outlined on the tables below. You and your doctor will choose either Group A or Group B chemotherapy. You will be randomized to receive only chemotherapy (Arm 1) or chemotherapy plus trastuzumab (Arm 2). All of the drugs included in your study therapy will be given through a vein.

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582

Group 1A	Group 2A	Group 1B	Group 2B
Docetaxel + Cyclophosphamide every 3 weeks for 6 cycles	Docetaxel + Cyclophosphamide + Trastuzumab every 3 weeks for 6 cycles	Doxorubicin + Cyclophosphamide every 2 weeks <i>or</i> every 3 weeks for 4 cycles	Doxorubicin + Cyclophosphamide every 2 weeks <i>or</i> every 3 weeks for 4 cycles
	<i>Followed by</i>	<i>Followed by</i>	<i>Followed by</i>
	Trastuzumab every 3 weeks until 1 year after the first dose	Paclitaxel every week for 12 doses	Paclitaxel + Trastuzumab every week for 12 doses

Other therapy

Hormonal therapy: If your breast cancer is affected by hormones (estrogen or progesterone), your doctor will also prescribe at least 5 years of hormonal therapy. You will begin the hormonal therapy after you complete your chemotherapy. Your doctor will discuss this further with you.

Radiation therapy: Your doctor may advise you to have radiation therapy. Your doctor will discuss this with you.

Tests and exams during study therapy:

You will need to have the following tests and exams. They are part of regular cancer care.

- Physical exams on a regular basis during chemotherapy and after your last dose of chemotherapy
- Blood tests on a regular basis during chemotherapy to check for treatment side effects

The following tests and exams are not part of regular cancer care and are **being done for the purpose of the study.**

- Physical exam every 9 weeks during trastuzumab therapy alone (only for patients who receive trastuzumab)
- Echocardiogram to check for changes in heart function that could be caused by doxorubicin or trastuzumab (a MUGA scan may be done instead of an echocardiogram)
 - Patients receiving chemotherapy and trastuzumab will have an echocardiogram at about 3, 6, 9, and 12 months after joining the study
 - Some patients receiving only chemotherapy will have an echocardiogram at about 1 year after joining the study. Your doctor will talk to you about whether or not you will have an echocardiogram at this time point.

Approval Date: 2/21/12 to 6/22/12
Assurance #: FWA00003582

Follow-up tests and exams:

You will need to have the following tests and exams. They are part of regular cancer care.

- Physical exam about every 6 months until 5 years after you joined the study, and then about every year until 10 years after you joined the study
- Mammogram about every year until 10 years after you joined the study.

B-47 questionnaires:

The researchers who are conducting the B-47 study want to learn about the effect that certain personal health behaviors might have on breast cancer.

You will be asked to complete questionnaires about your health and certain health behaviors, such as use of tobacco and alcohol, when you join the study and every year until 5 years after you join the study.

Each of the questionnaires will take about 5 minutes of your time to complete. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

How long will I be in the study?

You will be in the study for 10 years. During that time, your chemotherapy will take about 4½ to 6 months, depending on the chemotherapy you are receiving and the treatment schedule. If you are in Group 2A or 2B, trastuzumab therapy will take about 1 year. After you complete your study therapy, your study doctor will ask you to visit the office for follow-up exams (as described above) for 10 years from the time you joined the study. We would like to keep track of your health during that time. Keeping in touch with you and checking on your condition helps us to look at the long-term effects of the study therapy.

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. It is important to tell the study doctor if you are thinking about stopping so any risks from the therapy can be evaluated by your doctor. Another reason to tell your study doctor that you are thinking about stopping is to discuss the follow-up care and testing that would be best for you.

You can choose to stop in one of two ways:

- You can stop your study treatment, but still allow your study doctor to report your health status to the NSABP; or
- You can stop your study treatment and request that no new information be reported to the NSABP.

Also, your study doctor may stop you from taking part in this study if he or she believes it is in the best interest of your health, if you do not follow the study rules, or if the study is stopped by the NSABP.

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582

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

You may have side effects while on the study. Most of these are listed here, but there may be other side effects that we cannot predict. Side effects will vary from person to person.

Everyone taking part in the study will be watched carefully for any side effects. During the study, we will do tests and exams to see if the dose of the drugs you are receiving during your therapy should be changed or delayed. The tests will also help monitor any side effects you may have. 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 study therapy. In some cases, side effects can be serious, long lasting, or may never go away. There also is 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 docetaxel and cyclophosphamide (Groups 1A and 2A):

Likely

These side effects occur in **more than 20%** of patients receiving docetaxel and cyclophosphamide:

- Fever
- Infection
- Decrease in the total number of white blood cells or in the number of neutrophils, also called granulocytes, which are a type of white blood cells
- Lack of enough red blood cells (anemia)
- Weakness or loss of strength
- Fatigue or tiredness
- Shortness of breath
- Fluid retention (swelling or bloating)
- Taste changes
- Irritation or sores in the lining of the mouth and throat
- Loss of appetite
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Inflammation or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Pain in muscles
- Hot flashes
- Hair loss
- Nail changes, including discoloration or peeling; nail loss can happen
- Rash, inflammation, peeling, or darkening of the skin. This usually occurs on the palms of the hands and soles of the feet but may also appear on the arms, face, or body

Less likely

These side effects occur in **3 to 20%** of patients receiving docetaxel and cyclophosphamide:

- Decrease in the number of a type of blood cell that helps to clot blood (platelet)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Irregular heart beats
- High or low blood pressure
- Dizziness
- Dehydration (when your body does not have as much water and fluid as it should)
- Increase in the blood levels of liver enzymes
- Sore (ulcer) somewhere in the digestive tract
- Eye problems, including redness, irritation, tearing, blockage of the tear ducts, and blurred vision
- Allergic reaction
- Redness, tenderness, discoloration, or swelling of the skin where the drug is administered
- Hardening of the walls of the veins used for chemotherapy
- Pain in joints

Rare but serious

These side effects occur in **less than 3%** of patients receiving docetaxel and cyclophosphamide:

- Serious, potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness
- Liver failure
- Heart problems, such as chest pain (unstable angina), irregular heart beats, fainting, heart attack, heart failure, and inflammation of the sac around the heart
- Lung damage, such as shortness of breath, inflammation or scarring of the lungs that can be permanent, and Acute Respiratory Distress Syndrome, a condition where there is severe damage to the lungs
- Gastrointestinal problems, such as irritation, inflammation, bleeding, blockage, or perforation (opening of a hole) in the stomach or bowel
- Kidney damage, including kidney failure
- Lack of enough red blood cells (anemia) that may be severe enough to require a red blood cell transfusion
- Severe infection
- Acute leukemia (cancer of the blood cells)
- Skin and tissue damage in the area surrounding the vein where the chemotherapy drugs are administered
- Irritation and redness of the skin in areas where radiation was given
- Stevens-Johnson Syndrome, which is a group of symptoms that may include a blister-like rash, which may be severe enough to require hospitalization and may cause tissue death; fever, inflamed eyes; redness, swelling and painful sores on lips and in the mouth
- Blood clots that may be life-threatening
- Bladder irritation that causes bleeding
- Inflammation of the pancreas causing abdominal pain

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582

Risks and side effects related to doxorubicin and cyclophosphamide (Groups 1B and 2B):

Likely

These side effects occur in **more than 20%** of patients receiving doxorubicin and cyclophosphamide:

- Hair loss
- Nausea
- Vomiting
- Decrease in the total number of white blood cells or in the number of neutrophils, also called granulocytes, which are a type of white blood cells
- Lack of enough red blood cells (anemia)
- Fatigue or tiredness
- Hot flashes
- Temporary red discoloration of urine (not blood)

Less likely

These side effects occur in **3 to 20%** of patients receiving doxorubicin and cyclophosphamide:

- Diarrhea
- Constipation
- Loss of appetite
- Taste changes
- Irritation or sores in the lining of the mouth and throat
- Infection
- Decrease in the number of a type of blood cell that helps to clot blood (platelet)
- Irregular heartbeat
- Eye irritation
- Nail changes, including discoloration or peeling; nail loss can happen
- Rash, inflammation, peeling, or darkening of the skin. This usually occurs on the palms of the hands and soles of the feet but may also appear on the arms, face, or body
- Hardening of the walls of the veins used for chemotherapy
- Increase in the blood levels of liver enzymes
- Headache
- Pain in joints, bones, or muscles

Rare but serious

These side effects occur in **less than 3%** of patients receiving doxorubicin and cyclophosphamide:

- Acute leukemia (cancer of the blood cells)
- Skin and tissue damage in the area surrounding the vein where the chemotherapy drugs are administered
- Blood clot in a blood vessel
- Decrease in the ability of the heart to pump blood
- Lung problems such as scarring of the lungs that can cause shortness of breath, low levels of oxygen in the blood, and damage that can be permanent
- Severe infection
- Bladder irritation that causes bleeding

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582

- Lack of enough red blood cells (anemia) that may be severe enough to require a red blood cell transfusion
- Serious, potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness

Risks and side effects related to paclitaxel (Groups 1B and 2B):

Likely

These side effects occur in **more than 20%** of patients receiving paclitaxel:

- Inflammation or degeneration of the peripheral nerves (those nerves outside of the brain and spinal cord) causing numbness, tingling, or burning
- Decrease in the total number of white blood cells or in the number of neutrophils, also called granulocytes, which are a type of white blood cells
- Lack of enough red blood cells (anemia)
- Irritation or sores in the lining of the mouth and throat
- Infection
- Nausea
- Vomiting
- Diarrhea
- Hair loss
- Pain in joints, bones, or muscles
- Allergic reaction

Less likely

These side effects occur in **3 to 20%** of patients receiving paclitaxel:

- Decrease in the number of a type of blood cell that helps to clot blood (platelet)
- Redness, tenderness, discoloration, or swelling of the skin where the drug is administered
- Slow or irregular heartbeat
- Low blood pressure
- Fever
- Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Increased blood levels of liver enzymes

Rare but serious

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

- Inflammation or degeneration of the peripheral nerves (those nerves outside of the brain and spinal cord) causing numbness, tingling, or burning that may cause problems walking or performing activities of daily living and may be long lasting
- Serious, potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness
- Lung problems such as inflammation of the lungs that can cause shortness of breath, low levels of oxygen in the blood, and damage that could be permanent
- Heart problems

Risks and side effects related to trastuzumab (Groups 2A and 2B):

Less likely

These side effects occur in **3% to 20%** of patients receiving trastuzumab:

- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- A condition in which the heart muscle is abnormally enlarged or thickened
- Decrease in the heart's ability to pump blood
- Fluid in the sac around the heart
- Inflammation of the sac around the heart
- Fast heartbeat with regular or irregular rhythm
- Belly pain
- Diarrhea
- Irritation or sores in the lining of the mouth
- Sore throat
- Voice changes
- Nausea
- Vomiting
- Chills
- Fatigue or tiredness
- Difficulty sleeping
- Fever
- Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Chest pain not heart-related
- Pain
- Reaction that can occur during or following the infusion of drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Swelling
- Infection
- Increase in the blood level of a liver or bone enzyme (alkaline phosphatase)
- Increase in the blood levels of liver enzymes (AST and GGT)
- Decrease in a type of white blood cells neutrophil or granulocyte
- Loss of appetite
- Depression
- Pain in back, joints, bones, or muscles
- Pain in the area of the tumor
- Headache
- Inflammation or breakdown of the peripheral nerves (those nerves outside of the brain and spinal cord) causing numbness, tingling, burning
- Stuffy or runny nose, sneezing
- Cough
- Shortness of breath
- Decrease in the oxygen supply to a tissue
- Acne
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582

- High or low blood pressure

Rare but serious

These side effects are **rare but serious**, occurring in **less than 3%** of patients receiving trastuzumab:

- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness
- Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs
- Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath
- Inflammation of the lungs that may cause difficulty breathing and can be life-threatening
- Abnormal build up of fluid in the lungs
- Scarring of the lungs that can cause shortness of breath and interfere with breathing
- Blood clot in a blood vessel
- Kidney damage
- Severe damage to the lungs which can lead to fluid in the lungs and can be life-threatening
 - Sudden constriction of the muscles in the walls of the bronchioles (small airways of the lung)
 - Build up of a large amount of fluid between the layers of tissue that line the lungs and chest cavity
 - Inflammation of the lungs

It is important that you contact your study doctor as soon as you experience any side effects whether you think the treatment has caused them or not. You must also tell your study doctor if you have any illnesses or if you have started any new medication. This includes medications available without a prescription (over the counter) and alternative medicines. If you have any questions or concerns about any of the information provided above, about the possible side effects of treatment, or the possible consequences of treatment for those side effects, please ask your study doctor or study staff for more information.

Reproductive risks: The drugs in this study can affect an unborn baby. Therefore, you should not become pregnant while on this study and for at least 6 months after your last dose of study therapy. You should ask about counseling and more information about non-hormonal methods of preventing pregnancy. If you feel you might be pregnant, even though you practiced birth control, you must notify your study doctor immediately. A pregnancy test may be performed.

You should also not breastfeed while on this study and for at least 6 months after the last dose of study therapy.

Approval Date: 2/21/12 to 6/22/12
Assurance #: FWA00003582

If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments. This may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent.

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

What are my responsibilities?

- Keep your study appointments. If you cannot keep an appointment, contact your study doctor or study staff to reschedule as soon as you know that you will miss the appointment.
- Tell your study doctor or study staff about any medications you are taking.
- Tell your study doctor or study staff about any side effects, doctors' visits, or hospitalization that you may have whether or not you think they are related to the study therapy.
- Tell your study doctor if you have been in a research study in the last 30 days or are in another research study now. While participating in this research study, you should not take part in any other research project without approval from your study doctor. This is to protect you from possible injury arising from such things as extra drawing of blood samples, possible reaction between research drugs, or other hazards.

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 adding trastuzumab to chemotherapy will be more useful in treating HER2-low breast cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about trastuzumab given with chemotherapy as a treatment for HER2-low breast cancer. This information could help future breast 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 this study
- Taking part in another study
- Getting no treatment

Talk to your study 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.

Some of the coded research information may be sent to a central database. The information will continue to be made available for approved research. Your name or contact information will not be put in the database.

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

- the National Surgical Adjuvant Breast and Bowel Project (NSABP);
- F. Hoffman-La Roche, Ltd. And Genentech, a Member of the Roche Group (the company supplying trastuzumab);
- a local Institutional Review Board (IRB), a group of people who review the research study to protect your rights;

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582

- the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to clinical trials; and
- government agencies, including the NCI or its authorized representatives, the FDA, the Office for Human Research Protections (OHRP), and Health Canada. These agencies may review the research to see that it is being done safely and correctly.

A description of this clinical trial will be available on <http://www.clinicaltrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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.

Tests and drugs for which there is no charge in this study:

- Trastuzumab will be provided by Genentech, a Member of the Roche Group, at no cost for the B-47 study. However, you or your insurance company will need to pay for the costs of the supplies and for the personnel who give you the drug.
- There will be no charge to you or your insurance company for tests and exams that are not part of regular cancer care and **are being done for the purpose of this study**. These tests include the ECG required before you joined the study, the IHC test on your tumor sample to confirm your breast cancer is HER2-low (if needed), and the echocardiograms (or MUGA scans) required before you joined the study and during the first 12 months of the study.

Docetaxel, cyclophosphamide, doxorubicin, and paclitaxel are commercially available. You and/or your health plan/insurance company will be responsible for the costs of these drugs and for the supplies and the personnel required to give these drugs.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the trastuzumab for some reason. If this would occur, other possible options are:

- You might get the trastuzumab from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no trastuzumab available at all, no one will be able to get more and the study would close.

If a problem with getting trastuzumab occurs, your study doctor will talk to you about these options.

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://www.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.

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582

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 study 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.

The Data Monitoring Committee (DMC), 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. You may be asked to sign another consent form in response to new information.

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 Kansas City Clinical Oncology Program Institutional Review Board at 913-948-5588.

Tumor and Blood Sample Collection for the NSABP B-47 Study

What about the use of my blood and tumor for research?

Required submission of tumor: By signing this consent form, you are agreeing to allow a small sample of tumor, which was removed during your breast cancer surgery, to be sent to the NSABP for use by the NSABP. This sample will be used for the research purposes of the NSABP B-47 study and is required in order to take part in this study.

Optional collection of blood: The NSABP would like to have samples of your blood before you start the study therapy and again at about 1 year after you join the study. The blood samples will be collected and sent to the NSABP for research related to the B-47 study. You can still take part in the B-47 study even if you do not agree to the optional collection of these blood samples.

Optional collection of blood for women in the menstrual history study: If you have not gone through menopause and you have not had your uterus removed, the NSABP would like to have samples of your blood. A blood sample will be collected before you begin your therapy, at 3 and

Approval Date: 2/2/12 to 6/22/12

6 months, then every 6 months until 2 years after you join the study. These samples will be sent to the NSABP to do research related to the B-47 study. You can still take part in the B-47 study even if you do not agree to the optional collection of these blood samples.

About using blood and tumor for research: The research that will be done with your blood and tumor samples is not designed to specifically help you. It might help people who have cancer in the future. Your sample will be used for genetic research (about traits that are passed on in families), but you will not be able to be identified. 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 records. The research using your blood and tumor samples will not affect your care.

The blood and tumor samples will be used for the purpose of the NSABP B-47 study. Some of the research tests will be done soon, but others will be done in the future when the best methods are ready to test the samples. The tumor samples and genetic material from some of the blood samples will be stored at the NSABP.

The NSABP will study the blood and tumor samples and may give them to other researchers approved by the NSABP for the purposes of the B-47 study. Any research using your samples must also be approved by an Institutional Review Board (IRB). An IRB is a group of people who review the research to determine if it is being done correctly and safely.

People who do research with your blood and tumor samples may need to know more about your health. While the NSABP may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your blood and tumor 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, but you will not be paid.

You can change your mind at any time after your blood and tumor samples are sent. Just *contact your study doctor* and let him or her know that you no longer want the NSABP to use your blood and tumor samples. Any remaining samples will no longer be used for research. (You will still be able to take part in the B-47 study.) Otherwise, your samples will be kept until used up, or until the NSABP decides to destroy them.

Information gained from studies done on your samples can be very useful to researchers. Several groups, including the National Institutes of Health (NIH), have asked that some of this information be placed in a central database. Therefore, some coded research information may be sent to a central database for continued use in approved research. The goal is to speed up the process for discovery of new treatments, prevention, and diagnosis of disease. Your name or contact information will not be put in the central database. Once your coded information is transferred to a central database, it will not be possible for you to withdraw the information.

Benefits and risks: The possible benefits of research using your blood and tumor samples include learning more about what causes cancer and how to treat it. There is a risk of the release of information from your health records. The NSABP will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small.

Costs of the sample submission: There will be no cost to you or your insurance company for the collection, shipping, testing, and storage of the blood and tumor samples for this study.

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582

Use of Required Tumor Sample for the NSABP B-47 Study

By signing this consent form, you are agreeing that a tumor sample may be kept by the NSABP and used for the purposes of the B-47 study. Because the research using this sample is an important part of the B-47 study, it is required for participation in the B-47 study. If you do not agree to the use of a sample of your tumor, you cannot take part in the B-47 study.

Making Your Choices

Please read the sentences below and think about your choice. After reading each sentence, circle "yes" or "no." If you have questions, please talk to your doctor or health care team member. Remember that no matter what you decide about the optional collection and use of your blood samples, it will not affect your care and you may still take part in the B-47 study.

Optional Blood Samples for B-47 Study (All Patients):

1. Samples of my blood may be collected before I begin study therapy and 1 year after I join the study and sent to the NSABP for research related to the B-47 study.

YES

NO

Optional Blood Samples for the B-47 Study (For women who are premenopausal and whose uterus has not been removed):

2. Samples of my blood may be collected before I begin study therapy, at 3 and 6 months, and then every 6 months until 2 years after I join the study and may be sent to the NSABP for research related to the Menstrual History study and to the B-47 study.

YES

NO

Contact in the Future for Other Research:

Remember, no matter what you decide, you may still take part in the NSABP B-47 study.

3. My study doctor (or someone he or she chooses) may contact me in the future to ask me to take part in more research.

YES

NO

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)

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

Release

Approval Date: 2/21/12 to 6/22/12
Assurance #: FWA00003582

By signing this form you authorize KCCOP to access and obtain information that is required for the study. This may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

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 17 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 _____

Signature of Person Obtaining Consent _____

Date _____

Print patient's name

Signature of person conducting the
informed consent discussion

Date

Print name of person conducting the
informed consent discussion

Approval Date: 2/2/12 to 6/22/12
Assurance #: FWA00003582