Alliance A011106 Model Informed Consent Document

ALTernate approaches for clinical stage II or III Estrogen Receptor positive breast cancer NeoAdjuvant TrEatment (ALTERNATE) in postmenopausal women: a phase III study

This is a clinical trial, a type of research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. 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 the study 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 are a postmenopausal woman with early stage breast cancer. This means that the cancer has not obviously spread to other parts of your body and is potentially curable. In addition, your breast cancer is highly positive for estrogen receptor, a protein that makes the cancer grow in the presence of the female hormone estrogen.

As well as removing the cancer from the breast by surgery, an important aspect of the treatment for early stage breast cancer is to use drugs that eliminate cancer cells spreading to other parts of the body that are too few to visualize by radiology exams (this treatment is termed "adjuvant therapy"). These approaches prevent the cancer growing in distant organs, which over time can cause very severe health problems. One type of drug, called anastrozole, inhibits the growth of cancer cells by decreasing the level of estrogen. Another type, called fulvestrant, prevents the function of the "estrogen receptor" - a protein that the cancer cells use to detect the presence of estrogen. These drugs are called "endocrine therapy". Five years of endocrine therapy after surgery has shown to reduce the risk of cancer from coming back by at least 50%. Sometimes longer periods of endocrine treatment are recommended. One of the aims of this study is to develop more effective endocrine therapy so fewer patients relapse and treatments with more side effects, such as chemotherapy, are unnecessary.

This study aims to definitively identify patients with estrogen receptor positive tumors that don't need chemotherapy despite being larger in size. Chemotherapy, which has many serious side effects, can then be reserved for the patients with endocrine therapy resistant disease. This study assesses an approach based on a simple biopsy test that monitors the response of the tumor when endocrine treatment is given for six months before surgery. By not operating immediately, but treating with an endocrine drug for a few months before surgery, patients with larger tumors can often avoid mastectomy. This is considered a standard of care. Using information on endocrine treatment response gained by treating before surgery in order to determine whether chemotherapy is necessary is one of the questions that will be investigated in this study.

Why is this study being done?

This study has several objectives. One purpose is to determine whether neoadjuvant endocrine therapy with fulvestrant or the combination of anastrozole and fulvestrant, is better than anastrozole when given before surgery to shrink the cancer and stop it from growing. Anastrozole inhibits tumor growth by reducing the levels of estrogen and has been approved by the Food and Drug Administration (FDA) of the United States for use after surgery for postmenopausal women with estrogen receptor positive breast cancer. It is also considered a standard of care to give anastrozole for a few months before surgery to shrink the tumor. Fulvestrant inhibits tumor cell growth by reducing the levels of estrogen receptor in the tumor cell. It is not approved by the FDA for use in women with early stage breast cancer before or after surgery, but is approved by the FDA for patients with advanced (Stage 4) estrogen receptor positive breast cancer that has spread to other parts of the body. Therefore, fulvestrant alone, and the combination of anastrozole and fulvestrant is the investigational treatment in this study.

The reason to study fulvestrant alone, or the combination of fulvestrant and anastrozole, before surgery are the results from studies in patients with advanced cancer, which have shown that these treatment approaches may be superior to anastrozole, the current standard of care. This study will therefore help to determine whether fulvestrant, either alone or in combination with anastrozole, should be used in patients with early stage estrogen receptor positive breast cancer.

One of the measures of effectiveness used by the researchers is to measure a growth monitoring protein in your breast cancer tissue called “Ki67” to determine if your breast cancer is responding to the study treatment. The study of the Ki67 protein requires a research biopsy from your breast cancer tissue that will be taken before you begin endocrine therapy and after four weeks of endocrine therapy. A researcher may also recommend another biopsy later in the neoadjuvant treatment if he or she wants to monitor the response further. Samples for Ki67 analysis will also be taken at the time of surgery.

The Ki67 measurement on the breast cancer tissue taken at the time of surgery will be combined with information on tumor size and under arm lymph-node involvement by cancer cells to calculate a Modified Preoperative Endocrine Prognostic Index (PEPI) score. The modified PEPI score helps your study doctor see if you responded to the endocrine treatment and decide whether you need chemotherapy after surgery.

In order to detect tumors that are very unlikely to be in the PEPI-0 category at an early time-point we will also conduct a biopsy after four weeks of treatment. If the Ki67 level remains high, the protocol recommends that you stop neoadjuvant endocrine therapy and you receive chemotherapy or immediate surgery. An additional aspect of the study is that researchers will use additional tumor and blood samples to investigate what factors in the tumor determine response to treatment, and to find new treatments for endocrine resistant tumors that could be more effective than chemotherapy.

How many people will take part in the study?

About 1475 women 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 examinations, tests or procedures to find out if you can be in the study. These examinations, tests or procedures 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.

Standard of Care Procedures:

- You will be asked to give your medical history and have a physical examination.
- Mammogram and an ultrasound of the breast with the cancer. If you have not had a mammogram of both breasts within the last 12 months a mammogram of both breasts will be done.
- Breast biopsy to confirm your diagnosis, if you have not already had one.
- Blood tests.

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.

During the Study

BEFORE SURGERY

Randomization:

You will be "randomized" into one of the three treatment groups (also called treatment "Arms"), 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 that you will be in. *If you are chosen to be in a treatment group that includes anastrozole you will complete a daily medication diary of when you took the tablet and return this to your study doctor at the time of your monthly visits.*

Treatment: Effective 11/01/2018, enrollment to the two arms containing fulvestrant (Arms II and III) are complete, and all new patients enrolled to the study will be assigned to Arm 1.

If you are randomized to treatment **Arm I**: You will take 1 anastrozole tablet once each day for 22 - 24 weeks (6 cycles). A treatment cycle is defined as 4 weeks. The last tablet will be taken the day before your surgery. Take the anastrozole by mouth, with a large glass of water (8 ounces) with or without food. If you miss a dose of anastrozole, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take your regularly scheduled dose. Do not take two doses in the same day.

If you are randomized to treatment **Arm II**: You will receive two injections of fulvestrant into the muscle of your buttocks (one injection in each buttock) on Days 1 and 15 of the first treatment cycle, and then on Day 1 of every cycle after that for a total 22 - 24 weeks (6 cycles). A treatment cycle is defined as 4 weeks.

If you are randomized to treatment **Arm III**: You will take 1 anastrozole tablet once each day for 22 - 24 weeks (6 cycles). The last tablet will be taken the day before your surgery. Take the anastrozole by mouth, with a large glass of water (8 ounces) with or without food. You will also receive two injections of fulvestrant into the muscle of your buttocks (one injection into each buttock) on Days 1 and 15 of the first treatment cycle, and on Day 1 of every cycle after that for a total 22-24 weeks (6 cycles). A treatment cycle is defined as 4 weeks. If you miss a dose of anastrozole, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take your regularly scheduled dose. Do not take two doses in the same day.

Research Procedures Before and During the Study

Required biopsies, four small samples of your breast cancer tissue for research purposes will be collected at the following 3 time points. This is required in order for you to participate in this study because the research that will be done on the tissue is a very important part of this study.

- Before you are randomized to a treatment arm or begin study treatment: These samples will be used to develop tests that may be able to predict response to treatment. These biopsies may be taken at the time when a clip is placed in the tumor bed (the area in your breast where the cancer is located) so that your surgeon can locate the site of the cancer at the time of surgery. The clip is placed through 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 cancer (biopsies) for research purposes will be taken through the same catheter used to place the clip. The biopsies may also be taken at the time you have an ultrasound if your doctor has recommended that you have one.

- After 4 weeks on study drug treatment: Part of these samples will be used for the Ki67 testing to see if you are responding to the study treatment and also to try and understand why the treatment is or is not working well.

- At the time of surgery: If you completed 6 cycles of study treatment on **Arm I**, **Arm II** or **Arm III,** these samples will be used to calculate the Modified PEPI score, to see if you responded to the study treatment and if you will need chemotherapy after surgery. In addition, research on these samples will help the researchers study what factors determine response to treatment. The surgery samples may be collected before surgery at the time when a seed is placed in the tumor bed (the area in your breast where the cancer is located) so that your surgeon can locate the site of the cancer at the time of surgery.

See the "Research on Tissue and/or Blood" section for more information about providing samples for research.

Testing and Visits:

While you are receiving study treatment with **Arm I, Arm II** or **Arm III**, you will have the following testing and visits:

- Office visit with your study team every four weeks (before each cycle) for tumor measurement.

  At each visit you will have a physical examination, a member of your study team will use a measuring tape, ruler or calipers (a mechanical measuring device with two curved hinged legs) to take a measurement of your breast cancer. A mammogram and an ultrasound of the breast will be performed if the tumor appears to have grown based on physical examination.

  If your breast cancer grew during therapy, you will be advised to discontinue study treatment and either proceed to chemotherapy or have surgery immediately after discussion between you and your study doctor. You will be asked to have an optional cancer tissue biopsy before switching your therapy or have the breast cancer tissue samples collected at the time of immediate surgery.

- A mammogram and an ultrasound of the breast with the cancer between days 15 and 28 of the last cycle of treatment (cycle 6).

- Required research biopsy at the end of week four to determine whether the breast cancer is responding to the study treatment based on the result of Ki67, an indicator of how fast the breast cancer cells are growing in the biopsy tissue.

  a. If the biopsy indicates that your breast cancer is responding to study treatment, you will continue that assigned study arm for a total of 22-24 weeks (6 cycles) unless cancer is not responding to therapy.

  b. If the biopsy shows that your breast cancer is not responding to the study treatment, your study doctor will recommend that you stop your current study treatment arm and switch to the chemotherapy drug paclitaxel or another combination of chemotherapy drugs chosen by you and your study doctor.

     If your study doctor feels that you would not tolerate paclitaxel or another combination of chemotherapy drugs, or if you decide not to receive chemotherapy, you can have surgery to remove any remaining breast cancer tissue.

Neoadjuvant Chemotherapy Group

You will only be asked to switch to the **Neoadjuvant Chemotherapy Group** to receive chemotherapy before surgery if the Ki67 test at the end of week 4 shows that the cancer is not responding to the originally assigned study treatment. The purpose is to reduce the tumor size and to determine whether the cancer responds to the chemotherapy drug that is being given.

The chemotherapy treatment in the **Neoadjuvant Chemotherapy Group** is decided by you and your physician. You have the option of receiving weekly paclitaxel for 12 weeks or other standard chemotherapy treatments.

Before chemotherapy treatment starts, you will have blood drawn for routine tests to check your blood cell count and the functions of liver and kidneys. If the tests indicate that you are able to receive chemotherapy and you agree to proceed, the following will happen:

If you are receiving 12 weeks of paclitaxel, it will be given once a week, through a vein (on days 1, 8, 15 and 22 of each 4-week cycle for a total of 3 cycles).

- Before each dose of paclitaxel on days 1, 8, 15 and 22, you will have a blood draw to check for routine blood counts.
- Before each cycle (on day 1 of cycles 1-3), you will have a blood draw for routine blood counts and liver and kidney function and an office visit. A member of your study team will use a measuring tape, ruler or calipers (a mechanical measuring device with two curved hinged legs) to take a measurement of your breast cancer.
- On day 2 of cycle 1 (the next day following the first dose of paclitaxel), you will be asked for a research breast cancer tissue biopsy. The biopsy samples will be analyzed so that a test can be developed to predict whether the breast cancer will respond to paclitaxel. Your participation in providing the breast cancer tissue sample is optional. If you do not want to have this biopsy it will not affect your care.

If you are receiving other chemotherapy drugs your study team will explain your treatment and test schedules during the treatments.

SURGERY

The surgery should be scheduled in the last 3 weeks of month 6 of the BEFORE-SURGERY therapy in **Arms I**, **II** or **III** (21-24 weeks of therapy) and between 3-6 weeks after BEFORE-SURGERY chemotherapy in **Neoadjuvant Chemotherapy Group**. You will have a mammogram and an ultrasound before surgery to measure your breast cancer. The surgery procedure is standard of care.

If you are assigned to **Arm I or Arm III**, you will take the last dose of anastrozole on the day before surgery. If you are assigned to **Arm II or Arm III**, your last dose of fulvestrant would be Day 1 of cycle 6. In case your surgery is delayed, you will receive another dose of fulvestrant 4 weeks from the last dose of fulvestrant.

If you received treatment on **Arm I, Arm II** or **Arm III**, a piece of breast cancer tissue is required to be taken for research purposes and for calculating a Modified PEPI score at the time of surgery.

If you received chemotherapy in the **Neoadjuvant Chemotherapy Group,** you will be asked to provide a piece of breast cancer tissue at the time of surgery for research purposes. Collection of this breast cancer tissue sample is optional. If you do not want to give a sample of your tissue at this time it will not affect your care.

AFTER SURGERY

You will have a study doctor's visit 2-4 weeks after surgery to decide whether you will need chemotherapy after surgery. Based on the Modified PEPI score your study doctor will decide if you need chemotherapy and endocrine therapy.

If your Modified PEPI score is "0," adjuvant (which means after surgery) chemotherapy is not recommended after surgery. If you received treatment on **Arm I**, you will receive 1 anastrozole tablet each day for 4 ½ years. If you received treatment on **Arm II**, you will receive fulvestrant injections on Day 1 and Day 15 during the first month, and then once a month for 1 ½ years, followed by anastrozole 1 tablet each day for 3 years. If you received treatment on **Arm III**, you will receive 1 anastrozole tablet each day and fulvestrant injections on Day 1 and Day 15 during the first month, and then once a month for 1 ½ years and then 1 anastrozole table for 3 years. After you complete the study defined treatment period of endocrine therapy, further therapy, if necessary, will be determined by your study doctor.

If your Modified PEPI score is "not 0," adjuvant chemotherapy is recommended. You will receive a standard treatment chosen by you and your study doctor. You will start the treatment approximately 2 to 8 weeks following your last surgery date. After you have completed the adjuvant chemotherapy your study doctor will decide what endocrine therapy you will take.

If you were treated on the **Neoadjuvant Chemotherapy Group**, after surgery your study doctor will decide with whether you will need adjuvant chemotherapy and what endocrine therapy you will take. You will have a mammogram of the both breasts if a lumpectomy was done, or the remaining breast if mastectomy was done, yearly for 10 years after surgery.

You will receive radiation therapy if your study doctor thinks it is necessary, which can be given at the same time that you are taking the endocrine therapy.

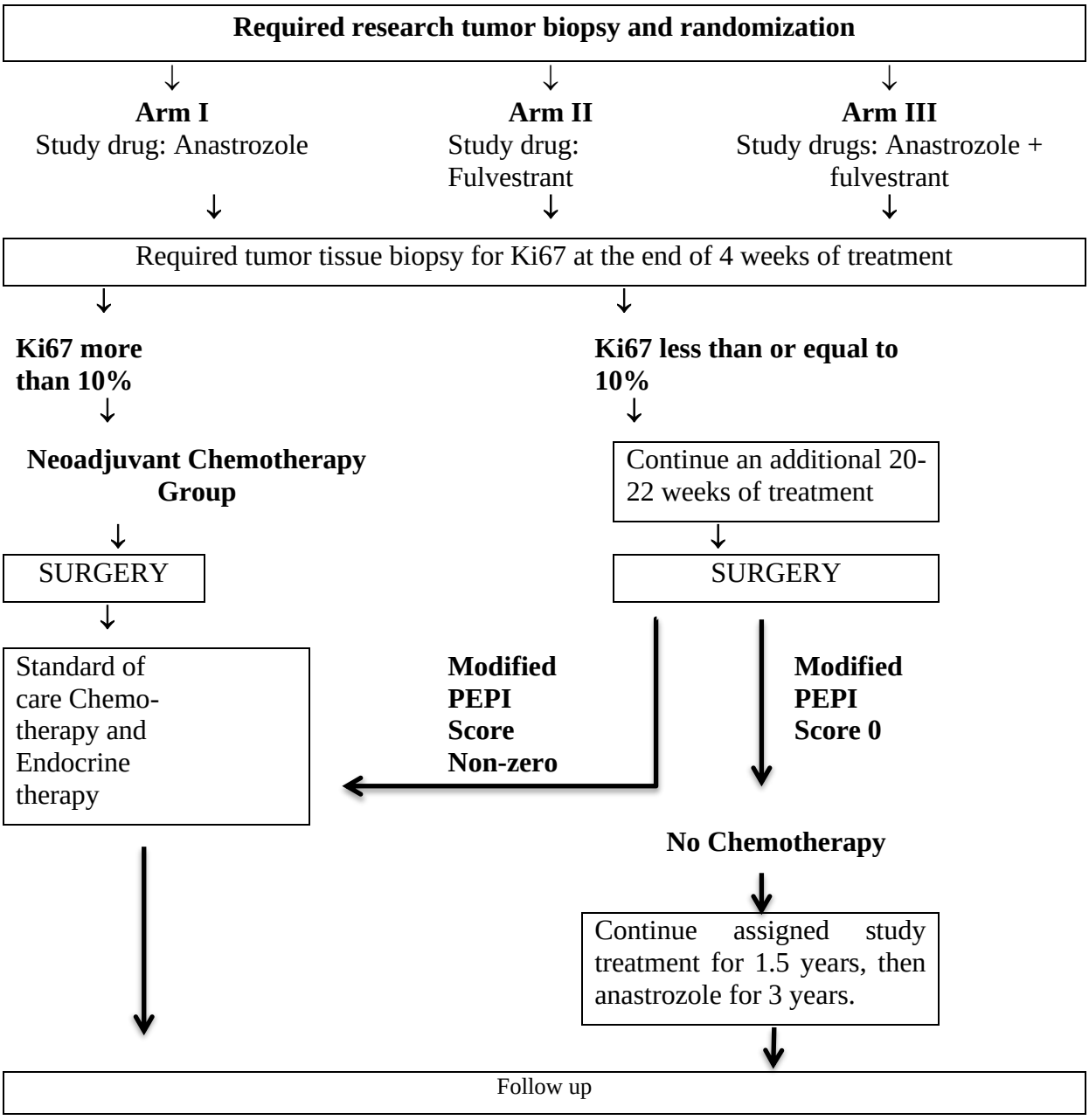
After surgery visits if you had a Modified PEPI score of "0":

You will see your study doctor every 6 months during years 1-5 after the start of adjuvant endocrine therapy, then once a year for years 6-10 after completion of endocrine therapy. You will have a yearly mammogram of both breasts if a lumpectomy was done or the remaining breast if a mastectomy was done, for 10 years after surgery.

After surgery visits if you had a Modified PEPI score of "not 0":

You will see your study doctor according to the standard of care. You will have a yearly mammogram of both breasts if a lumpectomy was done or the remaining breast if a mastectomy was done, for years 10 after surgery.

Another way to find out what will happen to you during the study is to read the chart below:



How long will I be in the study?

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 your study doctor if you are thinking about stopping so that any risks from the surgery can be evaluated by your doctor. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your 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?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

FULVESTRANT

COMMON, SOME MAY BE SERIOUS In 100 people receiving Fulvestrant, more than 20 and up to 100 may have:
• Pain • Tiredness • Increased sweating • Hot flashes, flushing • Swelling and redness at the site of the medication injection

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Fulvestrant, from 4 to 20 may have:
• Constipation, diarrhea, nausea, vomiting, loss of appetite, heartburn • Swelling of the body • Loss of bone tissue, broken bone, or decreased height • Dizziness, headache • Difficulty sleeping • Fluid around lungs • Swelling of the liver which may cause belly pain • Worry, depression, mood swings • Hair thinning • Cough

RARE, AND SERIOUS In 100 people receiving Fulvestrant, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Liver damage which may cause yellow eyes and skin • Vaginal bleeding • Blood clot which may cause swelling, pain, shortness of breath • Heart attack or heart failure which may result in chest pain, shortness of breath, swelling of ankles, and tiredness • Stroke which may cause weakness, paralysis

Because fulvestrant is administered as an intramuscular injection, it is likely you will experience bruising or soreness at the injection site. You may also experience fainting or bleeding.

ANASTROZOLE

COMMON, SOME MAY BE SERIOUS In 100 people receiving Anastrozole, more than 20 and up to 100 may have:
• Pain • Increased sweating • Hot flashes, flushing

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Anastrozole, from 4 to 20 may have:
• High blood pressure, which may cause headaches, dizziness, blurred vision • Rash, blister, sores on the skin • Severe skin rash with blisters and can involve inside of mouth and other parts of the body • Constipation, diarrhea, nausea, vomiting, loss of appetite, heartburn • Liver damage which may cause yellow eyes and skin • Swelling of the body • Loss of bone tissue, broken bone, or decreased height • Dizziness, headache • Tiredness • Difficulty sleeping • Swelling of the liver which may cause belly pain • Worry, depression, mood swings • Hair thinning

RARE, AND SERIOUS In 100 people receiving Anastrozole, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Vaginal bleeding • Blood clot which may cause swelling, pain, shortness of breath • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Fluid around the lungs • Stroke which may cause weakness, paralysis

PACLITAXEL

COMMON, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, more than 20 and up to 100 may have:
• Anemia which may cause tiredness, or may require blood transfusions • Infection, especially when white blood cell count is low • Diarrhea, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Bruising, bleeding • Pain • Muscle weakness • Numbness, tingling or pain of the arms and legs • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, from 4 to 20 may have:
• Abnormal heartbeat • Damage to the lungs which may cause shortness of breath • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving Paclitaxel, 3 or fewer may have:
• Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or a hole in the stomach which may cause belly pain or that may require surgery

Reproductive risks:
All women participating in this study will be postmenopausal. Postmenopausal women by definition should not be able to conceive or bear a child. However, in the unlikely event that you are able to become pregnant while taking part in this study you should be aware that the drugs used in this study can affect an unborn baby. Therefore, you should not become pregnant or breastfeed a baby while on this study. Also, because the drugs can remain in your body for weeks to months after you have stopped taking them, you should use an effective method to prevent pregnancy and you should avoid breastfeeding a baby for at least 3 months after your last dose of study treatment.

Risk of research biopsies:
The risks of providing four needle biopsies of your breast cancer include:

- Bleeding, infection and pain at the time the samples are removed.

Risk of blood draw:

- Bruising, infection or bleeding at the site of the needle insertion.
- Occasionally, some people may experience dizziness or feel faint when their blood is drawn.

Risks and side effects related to 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 your study 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 the study drug fulvestrant or the combination of fulvestrant and anastrozole will be more useful against cancer compared to the usual treatment, and using "Ki67" and "Modified PEPI score" to predict response to endocrine therapy, there is no proof of this yet. We do know that the information from

this study will help doctors learn more about endocrine 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:

- Having surgery for your cancer without being in a study
- Receiving anastrozole and surgery with chemotherapy/radiation if needed without being in a study
- Taking part in another study
- Having no treatment, hormonal therapy or surgery

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?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

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

- Montana Cancer Consortium
- The Alliance for Clinical Trials in Oncology (Alliance)
- The Alliance Data and Safety Monitoring Board, a group of experts who regularly review the progress of the study
- AstraZeneca, the manufacturer of fulvestrant
- The local IRB (a group of people who review the research to protect your rights) of this institution

- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research
- The National Cancer Institute (NCI) and the groups it works with to review research
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
- Other government agencies, like the Food and Drug Administration (FDA) and the Office for Human Research Protection (OHRP), involved in keeping research safe for people;
- Other oncology research groups who have endorsed this study

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

•You will not be asked if you agree to take part in the specific future research studies using your health information.
•You and your study doctor will not be told when or what type of research will be done.
•You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

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 fulvestrant used in this study will be provided to your study doctor free of charge by AstraZeneca, the company that manufactures it. If AstraZeneca stops supplying fulvestrant, your study doctor will discuss with you what to do. If you are assigned to receive anastrozole and

paclitaxel or another combination of chemotherapy drug chosen by you and your study doctor, you and/or your health plan/insurance company will be responsible for the cost of these drugs.

The research biopsies taken 1) before you are randomized and start study treatment (unless they are performed during a standard of care procedure), 2) at 4-week, and 3) at Cycle 1, day 2 for the Neoadjuvant Chemotherapy Group (if you received paclitaxel), will be paid for by the study.

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.

What happens if I am injured because I took part in this 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. Contact information for your study doctor is listed on the consent cover page.

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.

No funds have been set aside to compensate you in the event of injury.

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.

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 information for your study doctor is listed on the consent cover page.

For questions about your rights while in this study, call the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.
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.]*

Research on Tissue and/or Blood

This section of the informed consent is about additional research studies that are being done with people who are taking part in the main treatment study. There are both required studies and additional optional studies. You may take part in these additional optional 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 the additional optional studies. This is to inform you of the possible risks, benefits, and limits of giving your samples for research.

You are being asked to give some of your samples (called **specimens**) and related information to be used for research. This may help researchers learn more about how to prevent, find and treat cancer and other diseases.

The choice to have your samples used for the research described in this consent and stored for future research is up to you. No matter what you decide, it will not affect your medical care.

What are samples and where are they stored?
A sample is any material taken from your body such as tissue, blood, urine and other fluids. If you agree, your samples will be stored for research in a Cooperative Group bank supported by the National Cancer Institute. A Cooperative Group bank contains samples and information. Your samples are kept along with those from other people in this bank. Researchers then ask for samples from the bank to study them.

What information will be collected?
Your samples will be sent to the Alliance Central Specimen Bank (CSB) at Washington University in St. Louis and the Alliance Central Specimen Bank and Pathology Committee. Any personal information sent with the samples to the bank is <u>not</u> given to researchers. The personal information is used only by the bank. Your privacy will be protected to the fullest extent possible. This will be discussed later in the section "How will information related to my samples be protected?"

Other information that might be stored for future research includes:

- Dates of medical procedures
- Any diagnosis and stage of your disease (if you have cancer)
- Your age and race
- Medical and family history
- Treatments you had
- How you responded to treatments

What will happen to my samples if I agree to give them for research?
Your samples will be stored in a Cooperative Group bank. The samples will be kept until they are used up or destroyed. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

You or your doctor will not be given reports or other information about the research that uses your samples. This information will not be put into your health record. Results may be used for future research.

You will not be named or identified by other personal information if any results are published. Most publications contain results from many patients.

Your samples and related information will be used only for research and will not be sold. It is possible that research may help to create new products or treatments. If this should happen, you will not be paid.

Because the information gained from the research studies performed on your samples can be very useful to the research community, several groups including the National Institute of Health (NIH) have requested that some of these data be placed in a central database. Therefore, some of the coded research information may be sent to a central database. 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.

1) Anonymous information from the analyses will be put in a completely public database, available to anyone on the Internet.
2) Your coded medical information and information from more detailed analyses of your coded samples will be put in a controlled-access database. The information in this database will be available only to researchers who have received approval from an NIH Data Access Committee.

The goal is to speed up the process of discovery of new treatments, prevention and diagnosis of disease. The information will continue to be made available for approved research.

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.

What kind of research will be done with my samples?
Many types of research use normal or diseased (**cancerous**) samples. Researchers can study proteins, RNA and DNA (genes). The study of genes (DNA) is often called **genetic research**.

Your samples may be looked at:

- To see if a trait is passed down in families from one generation to the next (**inherited**). This type of research may help to explain why some cancers run in families or why some people have side effects of treatment while others do not. This is often studied through blood cells and DNA (**genes**).

- To learn about changes in the body that happened after you were born (**non-inherited**). For example, being in the sun too much can cause changes in cells that lead to skin cancer.

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

Required blood sample collection (for patients consented after Update #06 ONLY)

A blood sample, about 2 teaspoons, is required for all study participants. This sample will be used for studies on DNA (genes) as described above.

Note: This sample is not required at the time of consent for the optional blood samples described in questions #5 and #6 below, and this will not affect your continued participation in the trial.

Optional breast cancer tissue and blood sample collection:

These tissue and blood collections are optional. They are collected for research purposes to investigate whether substances in your breast cancer tissue or blood are related to the way that your body responds (or doesn't respond) to the study treatment that you receive in this study or banked for future research. You can still be a part of the main study even if you say "no" to taking part in any of following sample collections.

- If your study doctor thinks it is necessary to check your response at study week 12 while receiving treatment on **Arm I (anastrozole), Arm II (fulvestrant) or Arm III (anastrozole and fulvestrant),** you will be asked to give four small samples of your breast cancer tissue.

Week 12 sample collection → discontinued in Update #07

1) I agree to have the week 12 biopsy done for Ki67 analysis and research purposes.

My coded samples and related coded information **may be used** to learn about, prevent, find or treat my type of **cancer**. This may also include research on inherited traits (genes passed on in families).

Yes_____ No_____

- If you start treatment in the Neoadjuvant Chemotherapy Group and **if you receive paclitaxel**, you will be asked to give four small samples of your breast cancer tissue on Cycle 1, day 2.

2) I agree to have the breast biopsy done on Cycle 1 day 2 for research purposes.

My coded samples and related coded information **may be used** to learn about, prevent, find or treat my type of **cancer**. This may also include research on inherited traits (genes passed on in families).

Yes_____ No_____

- If the cancer grows during therapy, you will be asked to give a small piece of tumor tissue at the time of surgery, if surgery is the next treatment for participants on all treatment arms or Neoadjuvant Chemotherapy.

3) I agree to allow a small sample my tumor tissue to be taken for research purposes, at the time of surgery if surgery is the next treatment for my cancer.

My coded samples and related coded information **may be used** to learn about, prevent, find or treat my type of **cancer**. This may also include research on inherited traits (genes passed on in families).

Yes_____ No_____

- You will be asked to have about 4 teaspoons of blood drawn before you begin treatment, during study week 4 on endocrine treatment, and at the time of surgery. In addition, you will be asked to have about 4 teaspoons of blood drawn if you have agreed to give tumor tissue for research at the following time points: Cycle 1 Day 2 of neoadjuvant paclitaxel, or if cancer grows.

4) I agree to have my blood collected at these time points for research purposes.

My coded samples and related coded information **may be used** to learn about, prevent, find or treat my type of **cancer**. This may also include research on inherited traits (genes passed on in families).

Yes_____ No_____

- You will be asked to have about 8 teaspoons of blood drawn at 5 years after surgery and if the cancer comes back after surgery during the 10-year follow up period of the study.

5) I agree to have my blood collected at this time point for research purposes.

My coded samples and related coded information **may be used** to learn about, prevent, find or treat my type of **cancer**. This may also include research on inherited traits (genes passed on in families).

Yes_____ No_____

- If you switch to neo-adjuvant chemotherapy due to Ki67 over 10% at week 4 or 12, or have a PEPI score of 4 or higher, you will be asked to have about 8 teaspoons of blood drawn at the following additional time points: 2-8 weeks after surgery, and yearly for 10 years after surgery if the cancer has not come back.

6) I agree to have my blood collected at this time point for research purposes. My coded samples and related coded information **<u>may be used</u>** to learn about, prevent, find or treat my type of **cancer**. This may also include research on inherited traits (genes passed on in families). Yes_____ No_____

Will it help me if I give my samples for research?
Using your samples for research will probably not help you. We do hope the research results will help people in the future. The best way to prevent, find or treat cancer and other diseases is by studying human samples and data.

What are the risks of giving my samples for research?

- **<u>There can be mild pain, or some bleeding or bruising when blood is drawn.</u>** Rarely, an infection can happen where the needle was placed. Feeling dizzy or fainting can also happen, but may only last a few minutes after blood is drawn.

- The risk of research biopsies of breast cancer tissue include bleeding, infection and pain at the time the samples are removed.

- There is a risk that your information could be misused**.** The chance of this happening is very small. We have many protections in place to lower this risk. See the next section, "How will the information related to your samples be protected?" Your privacy will be protected to the fullest extent possible.

- There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. 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 will contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, 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.

- Very rarely health or genetic information could be misused by employers, insurance companies, and others. Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to employers, health providers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives. Therefore, your genetic information potentially could be used in ways that could cause you or your family distress, such as by 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).

  Some states have laws to protect against genetic discrimination [*list appropriate state information if your state has such laws]*. A new federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. To learn more about the GINA Law, please check the Internet or ask the study staff.

  Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because research results will not be returned to you or your doctor.

How will information related to my samples be protected?
We have many ways to protect the information related to your samples:

1. Your samples and information receive a unique code. Researchers only receive coded samples and information, and will not be able to link the code to you. Only approved people in the Alliance for Clinical Trial in Oncology can match you to the code on your samples and related information.
2. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include, but are not limited to, restricted access to buildings, rooms and freezers housing patient samples, numeric coding of both patient data and samples, and password protected access to databases housing patient data.
3. Before samples are given to researchers, studies are reviewed for the quality of the science and for patient protection. Records from research studies can be reviewed by the Cooperative Group, by the sponsor, and by government agencies. This is to make sure the research follows the rules of the Cooperative Group and state or federal laws.
4. In most cases, research results will not be returned to you or your doctor. If research results are required to make a decision regarding your treatment on this study then

research results may be shared with you or your doctor. If research results are published, your name and other personal information will not be given.

Making your choice

The choice to take part is up to you. You may choose not to let us use and store your samples. If you decide not to let us store and use your samples, you will still receive the same medical care. You may also take part in other research studies.

If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff at your hospital and let them know that you do not want your samples used for research [*Insert contact number]*. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers cannot be returned or destroyed.

Thank you for considering whether to allow your samples to be used for the research described above and/or banked for future research.

7. My coded samples and related coded information **may be kept for use** in future research to learn about, prevent, find or treat any type of **cancer**. This may also include research on inherited traits (genes passed on in families).

   Yes____ No_____

8. My coded samples and related coded information may be kept for use in future research to learn about, prevent, find or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease). This may also include research on inherited traits (genes passed on in families).

   Yes_____ No_____

9. Someone from my hospital or the Alliance may contact me in the future to ask me to take part in more research.
   Yes_____ No_____

Your signature below shows that you read, or had someone read the informed consent to you. It also shows that you had the opportunity to ask any questions and have had them answered to your satisfaction.

For questions about this study or if you have an injury while samples are collected, please talk to your study staff/doctor. Contact information for your study doctor is listed on the consent cover page.

For questions about your rights while in this study, call the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

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/

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

You will 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 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.

My signature agreeing to take part in the study:

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)