NCI Community Oncology Research Program – Kansas City (NCORP-KC)

IBCSG 48-14/BIG 8-13/Alliance 221405

Study Title for Study Participants:

A study evaluating the pregnancy outcomes and safety of interrupting endocrine therapy for young women with endocrine responsive breast cancer who desire pregnancy

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

Alliance A221405: **P**regnancy **O**utcome and **S**afety of **I**nterrupting **T**herapy for women with endocrine respons**IVE** breast cancer

This study is being sponsored and conducted in North America by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients. The sponsor of this study outside of North America is the International Breast Cancer Study Group, or "IBCSG."

What is the usual approach for those who desire pregnancy during the time of planned endocrine therapy?

The usual approach for women who desire pregnancy while receiving endocrine therapy is to advise that they avoid pregnancy, as it is not known whether temporarily stopping endocrine treatment is safe in patients with a hormone receptor-positive early breast cancer. Endocrine therapy (also known as hormonal therapy) is designed to block or lower estrogens in the body.

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

You may decide not to get pregnant or to stop endocrine therapy without participating in this study.

Why is this study being done?

You are being asked to take part in this research study because you have been diagnosed with and treated for hormone receptor-positive early breast cancer, you are currently taking endocrine therapy, and you have expressed interest in getting pregnant. The best available evidence

suggests that pregnancy after breast cancer does not increase a woman's risk of developing a recurrence from her breast cancer. The most recent data also suggest that this is true in women with a hormone receptor-positive breast cancer. While delivery complications have been reported, available information does not suggest an increased risk for delivery complications or for newborns. This new study aims to clarify these results and to help determine how long a woman should wait before trying to become pregnant after breast cancer diagnosis and treatment. For women who want to become pregnant after a breast cancer diagnosis, taking five to ten years of adjuvant endocrine therapy may greatly reduce the chance of a successful conception. However, temporarily stopping endocrine therapy in these patients in order to try to achieve a pregnancy earlier has not been studied.

The purpose of this study is to determine whether having a child after temporarily stopping endocrine treatment is feasible and safe in patients with a hormone receptor-positive early breast cancer. Specifically, the study will investigate whether a temporary interruption of endocrine therapy, with the goal of permitting pregnancy and then resuming endocrine therapy to complete a standard course, is associated with a higher risk of breast cancer recurrence. In addition, the study aims to evaluate the success of pregnancy, the health of the newborn, and the patient's ability to breastfeed.

There will be about 500 women from about 12 countries taking part in this study.

What are the study groups?

All patients in this study will follow the same study plan. If you decide to participate in the study and meet the criteria to take part, you will temporarily stop your current endocrine therapy and attempt to become pregnant. You must have taken at least 18, and not more than 30, months of endocrine treatment before stopping; and you must wait three to five months after stopping endocrine treatment before attempting to become pregnant.

Whether you become pregnant or not, you should resume endocrine therapy within 2 years after the endocrine therapy interruption and complete five to ten years of treatment, according to your individual risk and preference, as planned with your treating oncologist.

During the time that you have temporarily stopped endocrine therapy, you will be asked to visit your doctor 3, 6, 12, 18 and 24 months after stopping.

In addition, you will receive a diary to record information on the pattern of your menses after stopping endocrine therapy.

As part of the study we will collect information on your pregnancy outcome (e.g., normal birth, caesarean section, miscarriage, etc.) and offspring outcome (e.g., no complications, preterm birth, low birth weight, birth defects, etc.). The breastfeeding pattern, if applicable (e.g., duration, which breast you use, etc.) will also be recorded.

Another way to find out what will happen to you during this study is to read the table below.

Day 0	Within 30 days after Day 0	3 to 5 months after Day 0	24 months after Day 0	After resuming endocrine therapy for up to 10 years after Day 0
Stop endocrine therapy	Register to the study	Start trying to become pregnant	Resume endocrine therapy	Follow up clinic visits

You will also be asked to provide blood and tissue samples for use in additional studies and for possible future studies. Please see the "Additional Studies Section" below for more information about these additional studies.

Quality of Life substudy (Psycho-Oncological Complementary Study): As part of a quality of life substudy, you will also be asked to complete questionnaires about your concerns related to fertility and your emotional well-being with respect to your decision to temporarily stop endocrine therapy at five time-points: Within one month after you have temporarily stopped endocrine therapy, and then yearly until four years after temporarily stopping the endocrine therapy. You will be asked to complete three questionnaires at each time point before or after a scheduled doctor's visit for this study. You will need about 15 minutes to complete these questionnaires.

Studies have shown that young survivors of breast cancer have concerns about their fertility, which may affect their psychological well-being. However, there is no information available on fertility concerns, decision-making and psychological well-being in women who interrupt their therapy to become pregnant. It is important to clarify how women feel during this important period so that in the future, women with breast cancer will have better information on which to base their treatment choices.

If you find completing the questionnaires stressful, then you do not have to continue. If you are concerned about your emotional well-being or your fertility, consult your doctor.

What extra tests and procedures will I have if I take part in this study?

At the time that you enroll to the study you will undergo an assessment to determine your fertility and you will be asked to complete a menstrual diary.

At the 3-month visit you will have:
- Blood tests to measure and to evaluate conditions that could affect ovulation like thyroid dysfunction and hyperprolactinemia (abnormally high levels of prolactin);

Optional procedures:*
- An optional transvaginal ultrasound to evaluate the effect of endocrine therapy on the lining of the uterus may be performed.
- If available at your hospital and indicated in your specific situation, your physician may propose an optional Antral Follicular Count (AFC), which is correlated with hormone status and fertility. It determines the number of eggs that may be maturing and could possibly become fertilized. In particular, AFC is a measure of the likelihood of response to in vitro fertilization (IVF) and is also a marker of fertility.

* You or your insurance provider may be asked to pay for these optional procedures.

At the 6-month visit you will have:
- Disease and pregnancy assessment

Optional procedures:*
- An optional transvaginal ultrasound to evaluate the effect of endocrine therapy on the lining of the uterus may be performed.
- Optional Antral Follicular Count (AFC), if available at your hospital.

* You or your insurance provider may be asked to pay for these optional procedures.

At the 12-month visit you will have:
- Disease and pregnancy assessment
- If you have not become pregnant by the time of the 12-month visit, you will have blood tests to assess your ovarian function.
    - If your ovaries do not work efficiently enough to get pregnant you should restart and complete endocrine therapy for breast cancer.
    - If your ovarian function is compatible with pregnancy or if cryopreserved oocytes/embryo/ovarian tissue is available, you will be referred to a fertility specialist for further evaluations and management.

At the 18- and 24-month visits you will have:
- Disease and pregnancy assessment

If you have not succeeded in getting pregnant after stopping endocrine therapy for twenty-four months, you should restart and complete endocrine therapy.

When you have resumed endocrine therapy, you will be asked to visit your doctor every 6 months until completion of at least 5 years of endocrine treatment and then at least yearly for a

total of 10 years from starting your participation in the study. Your doctor will document your general conditions and all hospital stays, if any, during the clinical study. S/he will ask you about all medications or treatments you received since your last visit.

The regular visits to your doctor are part of your standard medical care and are handled the same way as if you did not take part in the study.

How long will I be in this study?

You will be in the study for up to 10 years.

What possible risks can I expect from taking part in this study?

Information to date does not suggest that there is an increased risk of the cancer coming back due to pregnancy, but it is not known if temporarily interrupting endocrine treatment to allow for pregnancy could increase the risk of the cancer returning.

After stopping endocrine treatment, the side effects of the endocrine therapy should lessen. In particular, if you had ovarian function suppression, the production of ovarian hormones should return to normal levels, hot flushes may disappear, and menses restart. This can initially lead to general discomforts, ovulation pain, irregular and heavy menstruation.

The treatment for breast cancer that you received before enrolling on this study can make a woman post-menopausal, and possibly infertile and unable to become pregnant while on this study.

There is the risk that breast cancer will come back during the time of the study, whether you become pregnant or not. A new breast cancer may also develop during this time.

There is also the risk that participating in this study will cause you some distress, especially if you are unable to get pregnant. The decision to try to become pregnant as a breast cancer survivor and the limited timeframe for interruption of endocrine therapy in order to become pregnant may also be stressful. Please speak with your treating oncologist or care team if you are having a difficult time emotionally.

Procedure-Related Risks
A blood draw for laboratory tests can cause bruising at or near the site where the needle enters the vein and can increase the risk of infection.

Pregnancy/Birth Control:
All women who participate in the study are advised to use effective non hormone-containing contraception or be abstinent while waiting for three to five months after temporarily stopping endocrine treatment before attempting conception.

If you become pregnant less than 3 months after stopping endocrine treatment or after you have resumed endocrine therapy, you must tell your study doctor immediately so that s/he may discuss with you the potential danger to the fetus. Your doctor will need to report this information and the outcome of your pregnancy to the study sponsors. Exposure of a fetus to hormonal therapy may cause birth defects.

What possible benefits can I expect from taking part in this study?

We hope to learn more about temporarily stopping endocrine therapy when patients wish to become pregnant. We hope that the intervention within this clinical research study will be of benefit to you and/or help others, although we cannot guarantee this.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor or Institutional Review Board.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the Central Institutional Review Board at 888-657-3711.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for all of the costs of care while on this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

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

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Alliance for Clinical Trials in Oncology
- The International Breast Cancer Study Group (sponsors of the study outside of the U.S.)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION:
Sample Collections for Laboratory Studies and Optional Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue and blood. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

WHAT IS INVOLVED?

If you agree to take part in the main study, here is what will happen next:

1) Samples of blood and tissue will be collected at the time points listed below and will be sent to the Alliance Biobank and then stored in the IBCSG Tissue Bank in Milan (Italy), or as part of the IBCSG Tissue Bank in Brussels, Belgium, and kept and used under the responsibility of the Foundation Council of the IBCSG

Blood samples

Blood samples will be collected to evaluate different indicators related to fertility, pregnancy and breast cancer biology. These studies will involve extracting DNA (short for deoxyribonucleic acid, a molecule encoding the genetic instructions for life) or other material from the blood. They will be taken at the time points listed in the tables below.

Time point	**3 months after starting the study**	**6 months after starting the study, on day 2-5 of the menstrual cycle**	**After 12 months, on day 2-5 of the menstrual cycle ***
Amount of blood	2 teaspoons	1 teaspoon	2 teaspoons
***** If you do not have menses at month 12, the sample can be taken at any time. It will not be taken during pregnancy.			

These samples will be sent to the Alliance Biobank and then stored a Biobank in Brussels, Belgium.

In addition, the other blood samples (about 4 teaspoons) for the investigation of circulating tumor DNA (ctDNA) will be taken at the following time points:

Time point	Within 1 month after starting the study	After 6 months, (only if you are not pregnant)	2nd trimester of pregnancy	Between 3 and 6 months after restarting endocrine therapy	In case of tumor relapse
Amount of blood	4 teaspoons	2 teaspoons	2 teaspoons	2 teaspoons	2 teaspoons

These samples will be sent to the Alliance Biobank and then stored in a Biobank in Brussels, Belgium.

Tumor Tissue

In order for you to participate in this study, we need to be sure of the type of breast cancer that you have. Your doctor will be required to send a sample of tumor tissue that was collected when you were diagnosed with breast cancer to the Alliance Biobank, then the tissue will be studied at a central laboratory. This laboratory is called the IBCSG Central Pathology Office, and is located in Milan, Italy.

2) Your blood and some related health information will be sent to researchers for use in the studies described above. If you agree to future research studies (see below), remaining samples will be stored in the Biobanks, along with samples from other people who take part. The samples will be kept until they are used up. Your tissue samples and some related health information will be stored in the Biobank, along with samples and information from other people who take part. Information from your medical record will be updated from time to time.

3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.

4) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also 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 study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and Alliance or IBCSG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom the Alliance or IBCSG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for, but cannot complete any of the studies for any reason, you can still take part in the main study.

SAMPLES FOR FUTURE RESEARCH STUDIES:

1. My samples and related information may be kept in Biobanks for use in future health research.

   YES NO

2. I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

   YES NO

This is the end of the section about additional studies and optional biobanking.

Release

By signing this form you authorize NCORP-KC 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.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes'.*

Participant Name_____

Participant Signature _____ Date _____

Person Obtaining Consent_____

Signature of Person Obtaining Consent_____

Date _____