COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL
200 FR. 4 (2011-1)

Study Title: A Pilot Pre-operative Window Trial of Black Cohosh in Women with Ductal Carcinoma in Situ

Principal Investigator: Erin Hofstatter, MD
Yale Cancer Center
Yale School of Medicine
333 Cedar Street
New Haven, CT 06519
Phone: 203-785-7309, Fax: 203-785-5792
Email: erin.hofstatter@yale.edu

Funding Source: Yale Cancer Center

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to look at whether or not Black Cohosh, an herbal, over the counter medication, is an effective treatment for early breast cancer. There are many different preparations of Black Cohosh available over the counter. For this study, we will use the Remifemin® formulation of Black Cohosh. You have been asked to take part because you have been diagnosed with Ductal Carcinoma in Situ of the breast (DCIS). This means that your cancer has remained inside the ducts in the breast. We are looking to enroll 40 participants here at The Smilow Breast Center at YNHH.

If you decide to participate in this study, it will mean that your surgery will be scheduled to take place 2-5 weeks after beginning the black cohosh. If you were not in the study, it is possible your surgery might be scheduled sooner than 2 weeks. If you would prefer not to have any effect on your surgery date, you should not agree to this study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, and any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participate in this study you will have the following assessments and procedures completed at the screening visit. This visit will take place the same day you see your surgeon for surgical planning and consenting. Your surgical plan will be decided by you and your surgeon.

- Study consent review and signing
- Study Eligibility & review of inclusion/exclusion criteria
- Medical History
- Medication Review
- Study blood work including Comprehensive metabolic panel, (Sodium, potassium, kidney & liver function), hormone panel (Follicle Stimulating Hormone, Luteinizing Hormone and Estradiol), complete blood count (White & Red blood cells and platelet count). ***Labs not required as part of your preoperative workup will be done at the same time, so you only have to have labs drawn once before surgery.***
- Urine pregnancy test will be performed unless you are postmenopausal or surgically sterile

You will have your preoperative and study blood work drawn prior to leaving the clinic. Because the results will not be immediately available, your physician will need to review the study labs before you can begin study medication. Study medication (Remifemin®) will be sent home with you along with very specific instructions **NOT** to start it until you have received a phone call and have spoken with the Principal Investigator, research nurse or your treating physician. You can expect to receive a phone call the day after your blood is drawn. A separate instruction sheet outlining these directions will be reviewed and signed by you and a copy provided. We considered that it might it be difficult and in some cases impossible for you to come back to the clinic for the sole purpose of picking up study drug, so we opted to send it home with you pending your lab results. If you are considered ineligible because of abnormal lab results, you **MUST** return the study medication unopened at your next earliest visit to the hospital (e.g. day of surgery). This should happen rarely, but it is for your safety.

You will receive 70 pills of Remifemin®, to take 20 mg orally twice per day. After approximately 2-5 weeks, you will have your surgery as planned with your surgeon. You will likely have a small number of leftover pills remaining at the time of surgery. Any unused study medication must be returned to the research nurse at the time of surgery.

You will take the final dose of study medication the evening prior to surgery. On the day of surgery you will be met by study personnel in the operating room holding area. You will return all unused study medication at this time so that we can assess how much medication was taken. You will also be assessed for medication tolerability and adverse events that may have occurred over the previous 2-5 weeks. Study blood work including Comprehensive metabolic panel, (Sodium, potassium, kidney & liver function), hormone panel (Follicle Stimulating Hormone, Luteinizing Hormonal and Estradiol), and complete blood count (White & Red blood cells and platelet count) will be drawn prior to your surgery. Ideally this will be done when your

intravenous (IV) is started so that you don't need to have an additional needle stick. If there is any problem starting your IV you may need to have your blood drawn separately.

A safety phone call will be made approximately 30 days after surgery to see how you are doing and to assess adverse events.

Schedule of Events:

Evaluations	**Screening/Enrollment**	**Day of Surgery**	**30 day telephone F/U**
Study Eligibility – Inclusion/Exclusion	X		
Informed Consent	X		
Medical History	X		
Concomitant Medications	X		
CBC, w/auto diff	X	X*	
Complete Metabolic panel	X	X*	
Urine Pregnancy Test	X*		
Hormone Panel (LH, FSH, estradiol)	X*	X*	
Study Medication Dispensing	X*		
Tissue Sample	X (core biopsy)	X (surgical specimen)	
Medication compliance		X	
Adverse Events		X	X
Radiographic Assessments	X	X	

* Indicates billable to study

After your surgery, per the standard of care, your breast tissue will be reviewed by a pathologist and the results will be discussed with you by your surgeon at your first visit after surgery. Only after the tissue review is complete, a sample of the breast tissue for research analysis will be obtained, along with a sample of your pre-drug/pre-surgical core biopsy. This will allow us to measure Ki67 in the specimens before and after study medications. Ki67 is a biomarker commonly used to measure cell changes. There are no additional study related biopsies needed if you choose to participate.

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

Risks and Inconveniences

Medical risk from participation in this study is small. Several previous clinical trials using Remifemin® have demonstrated safety and tolerability of this supplement. Reported side effects from Remifemin® are uncommon, occurring in 0%-12% of patients. Side effects, when experienced, have been reported as mild and reversible. Reported side effects include:

- headache
- stomach upset
- nausea/vomiting
- weight gain
- vaginal spotting/bleeding
- dizziness
- joint pain
- breast tenderness

Rare cases of liver toxicity have also been reported. However, the safety and tolerability of Remifemin® is very well documented in the literature and a recent review of multiple clinical trials showed no evidence of adverse effect on liver function. As a precaution, we will check your liver function before and after taking Remifemin® for 2-5 weeks. However, no change in liver function is expected from involvement in this trial.

You should contact the Principal Investigator if you have any side effects. If side effects do not resolve, you will be instructed to stop study drug. Some discomfort and potential for infection associated with the blood draw is possible. All precautions will be taken in an effort to minimize these risks.

By agreeing to participate in this study, you understand that your breast surgery will not take place until approximately 2-5 weeks after you start taking Remifemin. This represents a delay of one to two weeks as compared to the usual timing of surgery. This delay is felt to be safe and unlikely to pose significant medical risk. However, if you believe that this delay would pose any psychological stress or worry for you, then you may not want to participate in the study.

There is no anticipated injury related to the study itself. However, surgery has risks and these are not lessened by participating in this study. Risks associated with your breast surgery will be covered in detail in a separate surgical consent.

Data security risks from participation in this study are deemed to be minimal. Clinical information will not be released without your written permission, except as necessary by local and federal regulatory agencies. All data will be stored electronically on the OnCore research database which is password-protected on encrypted computers and accessible only by research personnel. Paper source documents and consent forms containing identifying, confidential and/or sensitive information will be stored in a locked cabinet in the Investigator's or Research Nurse's office and will be accessible only to research personnel.

Benefits

There may be no benefit, but potential benefits may include a decrease in size and aggressiveness of the cells in your type of cancer. This in turn could help us to develop improved short- and long-term outcomes, such as improved surgical margins, and/or decreased local recurrence. Potential identification of a new agent for the treatment and/or prevention of early stage breast cancer would be of benefit to society.

Economic Considerations

This study is paid for by the Yale Cancer Center. Most study related assessments are standard of care. Therefore, you will still be responsible for any co-pays required by your insurance company for standard treatment. Assessments not considered standard of care will be covered by departmental funds. There is otherwise no cost or payment to patients who participate.

The study-related tests that are not considered standard of care will be paid for by the study and include the following: urine pregnancy test at screening, hormone panel at screening and day of surgery, complete blood count and metabolic panel on day of surgery. Also covered is measurement of Ki67 on your core biopsy and surgical specimen and study medication. Remifemin® will be supplied and paid for by the study (see also schedule of events page 3.) There is no reimbursement for your time, travel or parking. There are no extra visits associated with participation. All study visits will be done in conjunction with your surgical visit and day of surgery.

Treatment Alternatives/Alternatives

The alternative to participating in this study is to simply have surgery. There may be different surgical options related to your diagnosis of non-invasive ductal carcinoma. These options will be discussed with you by your surgeon.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name, diagnosis, treatment and historical health information. Clinical information will not be released without your written permission, except as necessary by local and federal regulatory agencies. The tissue samples that will be collected as part of this study will be coded using your initials, study number and date and time of tissue collection. All data will be stored electronically on the OnCore database which is password-protected on encrypted computers and accessible only by research personnel. Paper source documents that include consent forms and data containing identifying, confidential and/or sensitive information will be stored in a locked cabinet in the Investigator's or Research Nurse's office and will be accessible only to research personnel.

If you agree to participate you will be assigned a study number. Meaning we will replace your identifying information with a code that doesn't directly identify you. The research team will

only give information to others identified by this number to carry out this research study. The link to your personal information will be kept for up to 5 years after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:

- Historical medical and laboratory records required to determine eligibility as well as those services provided in connection with this Study.

- The entire research record and any medical records held by YNHH and Yale Medical group created from: Historically as required to determine eligibility to Study completion.

- The following information:
    - Records about phone calls made as part of this research
    - Records about your study visits including surgery
    - Information obtained during this research regarding
        - Physical exams
        - Laboratory, x-ray, pathology and other test results
        - Records about any study drug you received

Information about you and your health which might identify you may be used by or given to:

-
- Representatives from Yale University and the Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator: Dr. Erin Hofstatter
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study: Yale University Human Investigation Committee, Yale Cancer Center

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale New Haven Hospital is required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However to better protect your health information; agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

In Case of Injury

Medical risks to patients from participation in this study are small. There are rare but potential drug side effects. While there have been rare case reports of suspected liver toxicity from black cohosh, the abundance of the published literature demonstrates the safety of black cohosh.

You will have a standard surgical procedure but there is no anticipated injury related to the study itself. However, surgery has risks and these are not lessened by participating in this study. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participation in this study is voluntary. You are free to choose not to take part in this study. Your health care outside the study, the payment for your health care, and your health care benefits will not be affected if you do not agree to participate. However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. If you cannot tolerate the study medication or no longer wish to take it you may withdraw from the study. If you sign this authorization, allowing the researchers to use your study information, and you change your mind, please understand that the researchers may continue to use information from your participation that has already been collected. To withdraw from the study, you can tell a member of the research team at any time that you no longer want to take part. If you do not want the researchers to continue to use the information they have already collected, you can also send a written notice to revoke this authorization to the principal investigator, Erin Hofstatter, MD, Yale Cancer Center, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06519, Phone: 203-785-7309.

This authorization to use and disclose your health information will never expire unless and until you change your mind and revoke it.

The researchers may withdraw you from participating in the research if necessary. As previously discussed, if your lab results are abnormal you will receive a telephone call indicating that you are no longer eligible and that you may NOT start study medication. You will need to consult with your surgeon to discuss whether or not this impacts your scheduled surgery. Medication will have to be returned at your next visit to the clinic/hospital. The PI may withdraw you from the study if you are not tolerating the medication. While this should rarely happen, it would be for your safety.

If you choose not to participate or if you withdraw consent at any time, it will not harm your relationship with your own doctors or with Yale-New Haven hospital. You will still receive the care necessary to treat your non-invasive breast cancer.

Questions

We have used some technical terms in this form. Please feel free to ask questions about anything you don't understand and to consider this research and the consent form carefully. Take as much time as you need before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject:_____

Signature:_____

Date:_____

_____ _____
Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator *Dr. Erin Hofstatter at 203-737-1600.* If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688. If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED IN THE HIC OFFICE

THIS FORM IS VALID ONLY THROUGH:
May 15 2015

HIC PROTOCOL #:
1205010204

INITIALED:
dlp