INFORMED CONSENT DOCUMENT

Project Title: **A Randomized, Double-Blind, Placebo Controlled Trial Investigating the Effect of Vandetanib on Cellular Markers of Proliferation and Apoptosis in Invasive Breast Cancer**

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This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you have been diagnosed with breast cancer.

The purpose of this research study is to test whether a drug called vandetanib has an effect on tumor growth markers. Vandetanib is currently used to treat a specific, rare type of thyroid cancer. Vandetanib is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration for use in treating breast cancer. This study will compare vandetanib to a placebo. A placebo is an inactive substance made to look/taste like an active medicine. You will either get the study drug, vandetanib or a placebo. The placebo is being used to make sure other factors, such as your biopsy, do not affect the marker.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 100 people will take part in this study conducted by investigators at the University of Iowa.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for up to 4 months. This will include the consultation visit, preoperative assessment, breast cancer surgery, and the follow-up clinic visit after

surgery. The clinic visits will take about 2 hours and the surgery may involve hospitalization. These visits are part of your care for breast cancer and will be necessary regardless of your study participation. Due to study participation, at your preoperative assessment visit, follow up labs and EKG will be performed to document any effect of the study drug, which could increase the length of that visit by up to an hour. At that time you will also be asked questions about drug side effects and how often you took the study drug. Taking part in this study will not alter the standard treatment you will receive or the timing of your surgery.

WHAT WILL HAPPEN DURING THIS STUDY?

If you are a patient from Mercy Medical Center in Cedar Rapids, some of your tests and procedures will be done in Cedar Rapids, and some will be done at University of Iowa Hospitals and Clinics. The lists below tell which tests and procedures will happen in each place. There is additional information following the lists that contain more information about these tests and procedures.

If you are a patient at the University of Iowa Hospitals and Clinics, all of the tests and procedures below will be done at the University of Iowa Hospitals and Clinics.

If you are a patient from Mercy Medical Center in Cedar Rapids, the following tests and procedures will be done in Cedar Rapids:

- Physical exam including vital signs and measurement of your height and weight;
- Blood tests that are considered standard-of-care
- Surgery
- Followup physical exam after surgery including vital signs

You will also sign a release form so that your medical information can be sent to the University of Iowa Hospitals and Clinics.

If you are a patient from Mercy Medical Center in Cedar Rapids, the following tests and procedures will be done at University of Iowa Hospitals and Clinics:

During the Screening visit**:**
- Informed Consent discussion and signing
- EKG (electrocardiogram – an electrical tracing of your heartbeat)
- Pregnancy test if you are a woman of child-bearing potential
- Any blood tests required for the research study that weren't done in Cedar Rapids as standard-of-care
- Study drug will be prescribed and dispensed to you

During the visit which occurs the day before surgery:
- Vital signs will be taken
- EKG
- Return of study drug that wasn't taken
- Blood tests that are considered research

Additional information regarding the tests and procedures listed above:

Medical Tests

The following exam and tests must be done to make sure that you are eligible for this study. None of these tests are experimental. They are routine. Depending on when you last had the blood tests, they may need to be repeated: The lab tests are to check your general health prior to surgery. We will check your calcium, magnesium, potassium, creatinine, liver function tests, complete blood count and blood clotting studies. They would be done even if you were not in this study and you or your insurance company will be responsible for the payment for these tests. These blood tests will be repeated after completion of the study and the investigators will pay for study related tests. If you are of child-bearing age, we will do a pregnancy test.

Study procedures

We will do a physical exam, record your height and weight, check your blood pressure/pulse, and record how well you are doing generally. Blood will be drawn for lab tests and an EKG will be done to check your heart.

If you are able to continue in the study you will be randomized to either receive either study drug or a placebo. This means that whichever drug you receive will be determined purely by chance, like flipping a coin. You will have a 50/50 chance of receiving any one of the study drugs. Neither you nor the research team will know which study drug you are receiving, but we will be able to get this information quickly if needed to help make the best decisions about your medical care. Regardless of which group you are in you will take a pill once a day for 7 to 14 days as described below. You will be asked to record every time you take your medicine on a calendar we provide. Please also record any symptoms you are experiencing. The dose of vandetanib (300 mg, once per day by mouth) is based on previous studies that showed this dosage was generally well-tolerated.

You will take doses of vandetanib or placebo once a day for 7 to 14 days, up to and including the day of your breast cancer surgery. At the time of surgery, we will take a small piece of the cancer tissue and send it to our lab. No additional tissue will be removed because of this study. We will compare the diagnostic biopsy taken to diagnose your cancer and compare it to the resection specimen from your operation to learn about whether the vandetanib impacted the cancer. After the study is over, you can contact the research coordinator if you would like to know whether you took the vandetanib or the placebo.

Tissue Storage for Future Use

As part of this study, we are obtaining breast cancer tissue from you. Collection of tissue is standard of care at the time of diagnosis and surgical treatment. We would like to study your tissue in the future, after this study is over.

The tests we might want to use to study your tissue may not even exist at this time. Therefore, we are asking for your permission to store your tissue so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding breast cancer, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your tissue might be used to develop products or tests that could be patented and licensed. There are no plans

to provide financial compensation to you should this occur.

Please place your initials in the blank next to Yes or No for the statement below:
My tissue may be stored and used in the future for breast cancer research.

_____ Yes _____ No

If you agree now to future use of your tissue, but decide in the future that you would like to have it removed from future research, you should contact Dr Ronald Weigel at 319-353-7474. However, if some research with your tissue has already been completed, the information from that research may still be used.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

The study medication may cause some side effects. Any side effect you experience will be assigned a grade 1-4 depending upon how severe it is. The study doctor will grade it based upon criteria that were developed by the National Institutes of Health, National Cancer Institute and are called the Common Terminology Criteria for Adverse Events. This ensures all study doctors follow the same guideline for rating the severity of side effects. If you experience a side effect that is graded severe by the study doctor and he/she thinks it is related to the study drug, then the study drug will be stopped and you will be removed from the study. The following side effects were observed in patients receiving 300mg Vandetanib alone (with no other treatment). You may experience none, some, or all of the following:

Very Common (experienced by more than 10% of patients taking vandetanib)

- Headache
- diarrhea
- nausea
- vomiting
- constipation
- decreased appetite
- skin rash
- dry skin
- elevated blood pressure
- trouble sleeping
- weakness
- fatigue

Patients taking vandetanib may develop a skin rash, which may become severe, but is manageable with proper treatment. Vandetanib may also make your skin more sensitive to the sun. It is recommended that you take preventative action to prevent the rash from occurring while receiving study medication and for 3 to 4 weeks after stopping medicine by using the following guidelines:

- Avoiding direct sunlight
- Covering sun exposed skin with clothing (long trousers, long sleeve shirts, and hats)
- Using a sun protection factor (SPF) 45 or higher sun protection cream
- Notifying the study doctor when the first sign of a rash occurs so he/she may take the appropriate steps in preventing the rash from becoming severe.

Common (Experienced by 1 – 10% of patients taking vandetanib)

- Changes in heart function (called QTc prolongation),
- abnormal taste in mouth
- abdominal pain
- swelling in your mouth
- dry mouth
- decrease in thyroid hormone
- weight loss
- elevated blood levels of certain proteins produced by the liver
- anorexia (loss of appetite)
- low potassium in the blood
- low calcium in the blood
- dehydration
- low magnesium in the blood
- changes in your skin (sensitivity to the sun, itchy skin, redness)
- acne
- hair loss
- nail disorders
- mild nose bleeding
- protein or blood in the urine
- kidney stone
- changes in your eyes (vision problems, swollen, dry or irritated eyes)
- feeling depressed
- anxiety

The manufacturer of the drug has observed changes in EKGs in some patients being treated with vandetanib. These changes in the EKG may be drug-related and usually occur without symptoms; accordingly, frequent safety follow-up visits have been built into all studies. Similar changes in the EKGs of patients receiving other medications have led to heart rhythm changes, some of which have been life threatening. It is estimated that between 0.1 to 1% of patients receiving vandetanib 300 mg have developed heart rhythm changes linked to life-threatening arrhythmia called Torsades de Pointes. Torsades de Pointes has been associated with sudden death. If any such changes are noted on your EKGs, you may need to attend additional visits for further safety assessments.

The risk of developing changes in the EKG and serious heart rhythm changes will be greater if you have diarrhea, blood electrolyte imbalance (imbalance of minerals in your blood), vomiting, high fever, faintness or dizzy spells, or are unable to maintain a normal diet. You should report any of these symptoms to your study doctor immediately. You should review your medications and diet with your study doctor at each visit while you are continuing to receive study drug.

Changes in the heart rhythm may cause rapid or irregular heart beat, dizziness, light-headedness, chest discomfort, shortness of breath, or losing consciousness. We will be monitoring your heart function with an electrocardiogram. If significant changes occur, we may need to stop therapy. These or other new symptoms or possible side effects should be reported immediately to your study doctor.

Uncommon (Experienced by fewer than 1% of patients taking vandetanib)

- Certain heart conditions (heart failure – a weakening of the heart's ability to pump blood, a fast heart beat that can be dangerous),
- chest pain,
- inflammation in the pancreas,
- decrease in platelets in the blood which could cause bleeding because platelets help your blood clot,
- small bluish/purple spots on the skin,
- increase in haemoglobin in the blood,
- severe skin disorders.

Some patients have had seizures while taking vandetanib, which can be a result of swelling in the brain. This can be seen on an MRI scan, and is expected to improve after vandetanib has been stopped. If you develop seizures, dizziness, headache, changes in your vision, or confusion, you should let your study doctor know as soon as possible. These may be symptoms of reversible posterior leukoencephalopathy syndrome (RPLS) which is expected to be uncommon.

A very small number of patients with lung cancer receiving vandetanib have developed shortness of breath and cough because of an inflammation of scar tissue formation in the lungs, although this symptom could also be due to the underlying lung cancer.

You should not drink grapefruit juice or eat grapefruit during your participation in this study. It may make the amount of vandetanib in your blood increase to a harmful level.

Reproductive risks: Because the drugs in this study can harm an unborn baby, you should not become pregnant while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

If you are a woman of child-bearing potential:

- We will ask you to confirm to the best of your knowledge that you are not pregnant now and you do not intend to become pregnant during this study

- A pregnancy test will be done to confirm that you are not pregnant before you take part in this study

- You must avoid becoming pregnant and use a highly effective method of birth control during your participation in this study. Acceptable methods of birth control are defined as a barrier method in conjunction with a spermicide (i.e., condom with spermicide, diaphragm with spermicide), approved contraceptive implants, long-term injectable contraception, intrauterine devices, or tubal ligation. The oral contraceptive pill is acceptable, but it must be combined with a barrier method in conjunction with a spermicide. You should avoid becoming pregnant for 4 months following the last dose of vandetanib.

If at any time during this study you think you might be pregnant, or later learn that you were pregnant during the study, you must contact the study doctor immediately for further instructions about your participation in this study and follow-up. You will be asked about the results of the pregnancy/birth and may need to have follow up visits.

WHAT ARE THE BENEFITS OF THIS STUDY? You will not benefit from being in this study. However, we hope that, in the future, other people might benefit from the knowledge that is gained about treating breast cancer.

WHAT OTHER OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you have the following options:
* Biopsy and surgery for breast cancer without being in this study.
* No therapy at this time
* Treatment with commonly used chemotherapy or experimental chemotherapy.

WILL IT COST ME ANYTHING TO BE IN THISSTUDY?
You will not have any additional costs for being in this research study. The vandetanib will be paid by the study. You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You will need to provide your social security number (SSN) in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. You may also need to provide your address if a check will be mailed to you. If your social security number is obtained for payment purposes only, it will not be retained for research purposes.

You will be paid $50 for completing your first study visit (consultation visit), an additional $50 for completing your second study visit (pre-operative assessment visit) and an additional $100 on completion of your participation in the study (post-operative visit 7-14 days after surgery). You will

receive payment only for the visits you complete for the research study.

WHO IS FUNDING THIS STUDY?

The National Institutes of Health (NIH) is providing some funding for this research study. This means that the University of Iowa is receiving payments from the NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from NIH for conducting this study. Vandetanib for this study is being provided by the manufacturer, AstraZeneca Pharmaceuticals, LP.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If you are injured by or become ill from participating in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.

- The sponsor will reimburse your reasonable and necessary medical costs for treatment for a research-related illness or injury through the University of Iowa if the injury or illness :
  - is a direct result of the drug being studied or the properly performed study procedures
  - is not a medical condition that you had when you started the study;
  - is not the direct result of a failure to follow the study plan; and
  - is not the direct result of proven negligence of the University of Iowa.

- The sponsor does not plan to provide any other form of compensation to you for any illness or injury resulting from this study.

- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

* federal government regulatory agencies,
* The U.S. Food and Drug Administration, AstraZeneca and its related companies located throughout the world
* auditing departments of the University of Iowa, and
* the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality, we will keep paper records of your participation in the study in

coded files, in locked file cabinets, within locked office, and electronic records on password-protected computer workstations that only research personnel will have access to. Samples collected will be given a unique subject identifier. Only the study staff will know the unique subject identifier. The name that belongs to the unique subject identifier will be kept in a locked file or in a computer with a password. The results of any research will not be placed in your medical record. In the event of any report or publication from this study, your identity will not be disclosed. Results will be reported in a summarized manner in such a way that you cannot be identified.

The University of Iowa Hospitals and Clinics generally requires that we document in your medical record chart that you are participating in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires your health care provider to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study. Once your health care provider has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, the U.S. Food and Drug Administration, and UIHC laboratories.

You cannot participate in this study unless you permit us to use your protected health information. If you choose not to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes your health care provider to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to:

Ronald J. Weigel, MD, PhD
1509 JCP
200 Hawkins Dr.
Iowa City, IA 52242

However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, or have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I Decide to Drop Out of the Study?

If you decide to leave the study early, we will ask you to allow us to contact you and follow-up with your health one time regarding your reaction to the study drug and your overall health. Of course, care will continue to be available to you in the clinic, and there will be no consequences to you should you decide to withdraw from the study.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because, in our judgment, it would not be safe for you to continue, or if your condition has become worse.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself or experience a research-related injury, please contact: Michelle Arnold, RN at 319-356-2778. If you are calling during non-business hours, please call 319-356-1616 and ask the operator to page the surgery resident on-call. Tell the operator you are a research subject in one of Dr. Weigel's studies.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://research.uiowa.edu/hso. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this

Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed): _____

Do not sign this form if today's date is on or after EXPIRATION DATE: 08/23/19.

_____ _____
(Signature of Subject) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)