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

Principal Investigator
Ronald J. Weigel, MD, PhD
EA Crowell Jr Professor and Head
Department of Surgery
1509 JCP
Phone: 319-353-7474
Fax: 319-356-8378
ronald-weigel@uiowa.edu

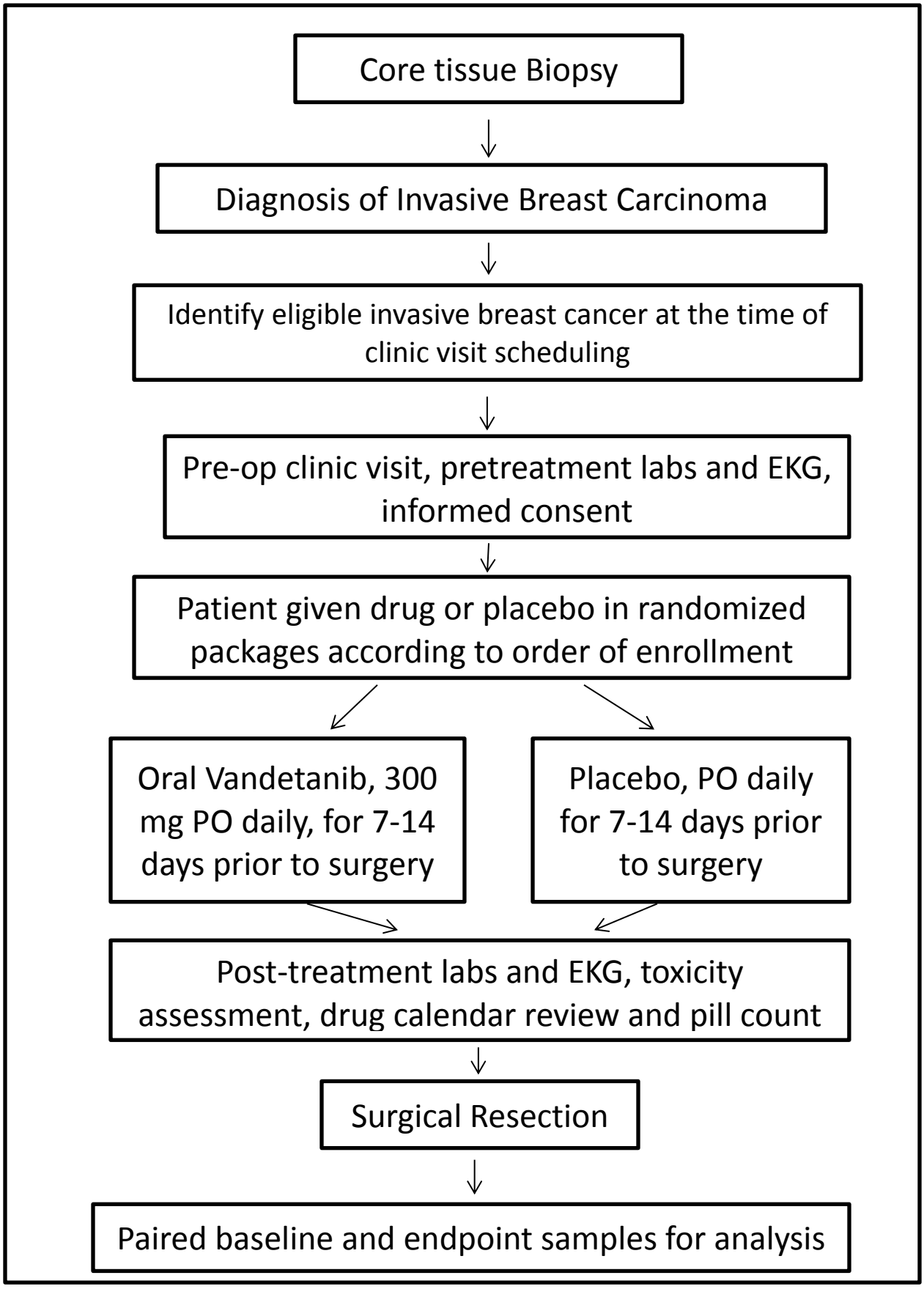
Co-Investigators
Lillian Erdahl, MD Department of Surgery
Sonia Sugg, MD Department of Surgery
Ingrid Lizarraga, MD Department of Surgery
Mark Karwal, MD Department of Internal Medicine
Amani Bashir, MD Department of Pathology

Biostatistician
Gideon Zamba, Ph.D

Protocol Version: 7 Date: 4/5/2017

TABLE OF CONTENTS

Figure 1: Study Design



1.0 Introduction

1.1 Breast Cancer Background

In 2012, an estimated 227,000 women in the US were expected to be diagnosed with invasive breast cancer, with breast cancer remaining second only to lung cancer as the most common cause of cancer related death in women [1]. Diagnosis is made by core needle biopsy of a palpable mass or abnormality on mammogram. Definitive treatment consists of surgical resection with staging of the axilla. Chemotherapy is reserved for advanced cases and can be administered in the adjuvant or neoadjuvant setting. Patients with estrogen receptor positive breast cancer have relatively worse neoadjuvant specific outcomes in terms of clinical and pathologic response compared to other types of breast cancer, making this an important group for receptor targeted therapy [2].

1. 2 Tyrosine Kinase Inhibitor Background

The receptor tyrosine kinases (RTK) are a family of molecules involved in receiving hormonal and chemokine signals and starting signal transduction pathways often involved in growth, cell survival, and proliferation. Activating mutations of RTK's have been identified in a wide variety of cancers including gastrointestinal stromal tumors (GIST), chronic myelogenous leukemia (CML) and medullary thyroid cancer (MTC), among others. Tyrosine kinase inhibitor (TKI) therapy has provided promising new targeted treatments for cancers driven by RTK activation.

The tyrosine kinase expression profile of breast cancers is a relatively new field. Since bevacizumab was developed, study of tyrosine kinase inhibition has focused on VEGFR antagonism and EGFR. More recently, expression of RET has been discovered in breast cancers with an association with estrogen receptor expression [3-6]. Mutations of the RET proto-oncogene are well described in MTC and the multiple endocrine neoplasia (MEN) 2 syndromes. Trials have been conducted in breast cancer with multiple TKI's without significant efficacy [7, 8]. However, these trials have focused primarily on ER negative cancers which express low levels of RET relative to estrogen receptor positive tumors, and metastatic tumors which are more likely to be ER negative.

In vitro, blocking RET activation, either by reducing protein levels, or with pharmacologic inhibition, leads to decreased activation of cellular mediators of proliferation and growth including ERK1/2 and AKT [9, 10]. Further it has been shown that inhibiting RET activation can restore sensitivity to Tamoxifen, prevent Tamoxifen resistance, and decrease cell proliferation in an ER and RET expressing breast cancer cell line [6]. Further, RET expression is a negative prognostic indicator in breast cancer [11]. We hypothesize that Vandetanib will be more efficacious in treating RET expressing breast cancers compared to breast cancers expressing lower levels of RET. Although there is a subset of ER-negative RET expressing tumors, most expression is associated with ER, making that the most likely phenotype to benefit from RET antagonist therapy.

1.3 Rationale of Proposed Trial

Our unpublished data show that *in vitro* activation of RET by its ligand, GDNF, leads to phosphorylation of ERK1/2 and AKT and leads to an increase in proliferation. Pharmacologic inhibition with Sunitinib, a small molecule tyrosine kinase inhibitor with activity against RET, abrogates GDNF/RET dependent ERK1/2 and AKT activation. Further it results in decreased proliferation, which FACS analysis for Ki-67 and cleaved caspase 3 demonstrate is the result of a modest reduction in proliferation and a large induction of apoptosis. Oral treatment with Sunitinib reduces human luminal breast cancer tumorigenesis in a xenograft model and immunohistochemistry analysis demonstrates a similar effect of a small reduction in Ki-67 positivity with a large induction of apoptosis. Vandetanib, another TKI with higher activity on RET than Sunitinib, similarly

reduces tumorigenesis and slows growth of previously formed xenograft tumors. Additionally, effects on proliferation are additive when combined with tamoxifen treatment, with the additional effect of inducing apoptosis compared to Tamoxifen treatment alone, indicated a separation of pathways and a role for combination therapy. In fact, treatment with the antiestrogen fulvestrant has been shown enhance Vandetanib effects in non-small cell lung cancer indicating a role for TKI and antiestrogen dual treatment to prevent pathway cross talk [12]. To corroborate these data in primary tumors we have obtained tissue samples and have shown that TKI treatment can decrease activated ERK1/2 in primary breast cancers with an increased effect in ER positive tumors. Our further study will include determining a more specific receptor expression profile that will predict TKI responsiveness (Unpublished data).

In the proposed trial women will be offered enrollment after core breast biopsy demonstrates invasive breast cancer, for which subsequent surgical resection typically occurs several weeks after the initial biopsy. Patients will be evaluated in the surgery clinic per normal protocol and if eligible and consenting enrolled in this trial. They will proceed with the normal course of treatment, with the only modification due to study enrollment being randomization to take either Vandetanib, 300 mg by mouth once daily, or placebo for 7 to 14 days prior to surgery. Paired baseline (diagnostic core biopsy) and endpoint tumor samples (surgical resection) will then be available for analysis. Randomization and blinding protocol is described in section 7.0.

Tissue markers would be analyzed on each of these samples allowing for rapid assessment of *in vivo* response to TKI treatment. In this initial evaluation, tissue levels of RET, Ki-67, TUNEL, phosphorylation specific levels of ERK1/2, AKT, and mTOR will be assessed. This will provide information on the primary endpoint of down regulation of Ki-67 expression. Additionally, proliferation and apoptosis markers were selected to assess the *in vivo* impact of TKI treatment on these carcinogenic mechanisms. Ki-67, a proliferation gene is weighted heavily in the multi-gene assay described by Paik et al which is used with increasing frequency clinically [13]. TUNEL is an apoptosis marker. Our pre-clinical studies indicate an effect of tyrosine kinase inhibition on both Ki-67 and TUNEL in luminal breast cancer.

Evaluation of paired tumor samples following a brief treatment course has been described in multiple studies and is appealing for several reasons.[14-18] Trials using mortality or disease progression as endpoints often require long follow-up, large study enrollment and significant resources. The proposed design, in contrast, permits relatively rapid evaluation of a drug's *in vivo* mechanism of action and impact. Promising agents could then be studied in larger, longer term trials. Paired baseline-to-endpoint samples can also be analyzed for their impact on individual patients and smaller subgroups. Evaluation of these subgroups and comparison with their counterparts might provide biochemical clues to support these observations. Tissue samples may be saved and used for subsequent unplanned analysis, should other studies support reevaluation using different markers. Finally, patients enrolled in this study would not need additional invasive procedures, as these samples will be obtained as part of standard treatment for invasive breast cancer.

The treatment dose will be Vandetanib 300 mg orally, one time each day. Currently, the FDA has approved 300 mg orally for treatment of medullary thyroid cancer, which also has been determined to be a safe dose in breast cancer [19]. Vandetanib, at this dose, was selected to demonstrate tumor change in the brief interval between diagnostic biopsy and surgical resection. AstraZeneca has agreed to provide Vandetanib and placebo at no cost for this trial.

2.0 Study Objectives

2.1 Determine the change in Ki-67 expression on paired samples obtained before and after Vandetanib treatment.

2.2 Compare TUNEL levels and phosphorylation specific levels of ERK1/2, AKT, and mTOR levels in paired samples obtained before and after Vandetanib treatment.

2.3 Evaluate any differences in analyses 2.1 and 2.2 based on level of RET expression as well as between ER-positive and ER-negative tumors.

3.0 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy and, therefore, only enroll patients for which the agents administered are appropriate. Although they will not be considered as formal eligibility criteria, as part of this decision-making process physicians should recognize that the following may increase the risk to the patient entering this protocol:

3.0.1 A psychiatric condition which would prevent compliance with treatment or informed consent.

3.0.2 Liver disease, diabetes, pulmonary disease, or infection, which in the opinion of the treating physician would make this protocol treatment unreasonably hazardous for the patient.

3.0.3 Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and considered by their physician to be at less than 30% risk of relapse within one year.

3.0.4 Patients who have received any investigational agent within the prior 4 weeks.

4.0 Eligibility Criteria:/Definitions of Disease:

4.0.1. Patients with core breast biopsy that, on pathology review, demonstrates invasive breast cancer and are determined to need surgical excision of the lesion. All subtypes of invasive breast cancer will be enrolled. Core biopsy specimens of enrolled patients will be stained for RET by immunohistochemistry and scored, however, patients will not be excluded according to RET expression.

4.1 Eligibility Criteria:

4.1.1 Inclusion Criteria

- Female gender. There is an incidence of male breast cancer, but it is unclear if the etiology is the same and inclusion of males could confound results.
- Age ≥ 18. Breast cancer, while not restricted only to adult women, is rare in the younger population.
- ECOG performance status ≤ 2.
- Life expectancy of greater than 6 months.
- Ability and willingness to provide informed consent to participate in this study.

4.1.2 Exclusion Criteria

- Prolonged QT interval (QTc > 480 milliseconds) on screening EKG or congenital long QT syndrome
- Any concomitant medications that are known to be associated with Torsades de Pointes or QT elongation (see appendix 2).
- Hypertension not controlled by medical therapy (systolic BP greater than 160 millimeters of mercury [mmHg] or diastolic blood pressure great than 100 mmHg).
- Patients taking metformin or digoxin.

- History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication are permitted.
- Significant cardiac event (e.g., myocardial infarction), superior vena cava syndrome, New York Heart Association (NYHA) classification of heart disease ≥2 within 12 weeks, or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia.
- Serum calcium or magnesium outside the institutional range of normal.
- Serum Potassium < 4.0 mmol/L or above 5.0 mmol/L
- Creatinine clearance < 50 ml/min
- PT > 12 seconds or PTT > 31 seconds
- Platelet count of < 100,000
- Serum bilirubin greater than 1.5 mg/dl
- Alanine aminotransferase (ALT) > 50 U/L, aspartate aminotransferase (AST) > 65 U/L, or alkaline phosphatase (ALP) > 250 U/L
- Any cytotoxic treatments, such as neoadjuvant chemotherapy, planned before subsequent surgical procedure.
- Previous exposure to Vandetanib
- Previous enrollment or randomization in this study
- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and staff at UIHC).
- Previous or current malignancies of other histologies within the last 5 years, with the exception of in situ carcinoma of the cervix, and adequately treated basal cell or squamous cell carcinoma of the skin.
- Patients who have received prior surgical site radiation.
- Patients on CYP3A4 inhibitors or inducers (see appendix 1).
- Inability to test core biopsy for study markers
- Pregnancy or lactation at the time of study entry. ***(Note: Pregnancy testing must be performed within 2 weeks prior to randomization according to institutional standards for women of childbearing potential.)***

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the Investigator should inform the Study Physician, Dr. Weigel, immediately.

4.2 Inclusion of Minorities

Although there is no evidence to suggest that the outcome will differ by ethnicity and there is insufficient power to detect small or moderate effects, we will, in a secondary analysis, report the results by ethnicity.

4.3 Sample Size

This study will aim to accrue a total of 40 subjects with invasive breast cancer into both the placebo and treatment arms (80 patients in total). The diagnosis will be based on histopathological evidence. The number of subjects was chosen based on the estimated ability to provide meaningful information on breast cancer. For discussion of statistics and power analyses, please see Section 12.

4.4 Informed Consent

Signed informed consent for enrollment in this protocol will be obtained from eligible subjects by a member of the research team before the start of the study. Subjects will be fully informed of the purpose and potential risks and benefits of participating in the study. Subjects will have the opportunity to have questions answered to their satisfaction before signing the consent.

4.5 Contacting Subjects for Consent

Patients will be identified for potential study enrollment at the time they are scheduled for a surgery clinic visit for a preoperative evaluation for invasive breast cancer. The study will be reviewed and patients enrolled at the time of their preoperative visit. Some patients will be seen in clinic before they receive the information regarding the study. These patients will be given the opportunity to participate and will have a study related discussion at their clinic visit. All patients seen in breast surgery clinic will be screened by the providing surgeon for potential involvement in this study.

5.0 Schedule of Assessments and Procedures

Tests & Observations	**Baseline (Pre-operative clinic visit)**	**Day 7-14**	**Post-Treatment safety assessment visit (Day 13 or 14)**	**Post-treatment sample**	**Follow-up visit POD 7-14**
History	X				X
Age/ECOG PS	X				
Physical Examination	X				X
Pulse, Blood Pressure	X		X		X
Weight/Height	X				
Drug Toxicity Evaluation		X	X		X
Study Drug Calendar		X	X		
EKG	X		X		
Pregnancy test within 2weeks of treatment (urine or serum)	X				
Laboratory Studies					
Ca, Mg, K, Cr, PT, PTT, Bilirubin, AST, ALT, Alk Phos, CBC	X				
Ca, Mg, K, platelets			X		
Treatment					
Placebo/Vandetanib 300 mg daily		X			
Staging Evaluations					
Pathologic Tumor Size				X	
Histology	X			X	
Tumor markers[1]	X			X	
Elston-Ellis Grade[2]	X			X	
Lymph node status[3]	X (CLINICAL)			X (PATHOLOGIC)	

Note: Staging determinants can be obtained on the baseline or post-treatment sample. They do not need to be obtained on both, but should reflect the final conclusions of the pathologist.
[1] Tumor markers are Estrogen Receptor, Progesterone Receptor and Her2/neu. See Section 9.2.
[2] Eliston-Ellis Grade is a pathological term for tumor aggression.
[3] Lymph node status will be recorded in accordance with preoperative (clinical) and postoperative (pathologic) staging.

6.0 Treatment Plan

Subjects meeting the eligibility requirements in Section 4.1 and who have given signed informed consent will start the treatment dose of Vandetanib 300 mg or placebo orally, daily, starting such time as to allow 7 to14 doses with the 7th or 14th dose given on the morning of the operation. Patients will return to clinic the day before the scheduled operation or the morning of surgery for repeat laboratory studies and EKG. Costs of the post-treatment labs and EKG will be covered by the PI. The results will be reviewed and safety to proceed documented prior to the operation. The study calendar (which will be provided at the pretreatment office visit to document administration of the study drug and any side effects associated with treatment) will be reviewed, pill counts performed, and an adverse events assessment performed at that time. Any concerns related to toxicities and safety to proceed to surgery will be addressed with the attending surgeon at that time. Common induction anesthetics (isoflurane, desflurane and sevoflurane) can cause QTc prolongation. Any QTc (>440 ms) on EKG should be discussed with the attending anesthesiologist prior to induction, and these induction agents should not be used if QTc > 480 ms. A flow chart of the preoperative screening procedure is shown in appendix 3. Subjects will be instructed to take their medication at the same time each day. In general subjects should take their dose every day even if it is not at the recommended time. Specific questions regarding timing and doses can be directed to Dr Weigel (319-353-7474, pager 1529). Patients will be removed from the study for failure to take at least 80% of the study doses. Patients will not be replaced if they are removed from the trial.

Women of Childbearing Potential (WOCBP) must use *highly effective* methods of birth control (one method or a combination of methods that results in a less than 1% failure rate per year) throughout therapy and must maintain full contraception for at least 95 days after the last dose of Vandetanib.

7.0 Drug Formulation, Availability and Preparation

7.1 Vandetanib

Availability

AstraZeneca Pharmaceuticals Investigational Products will pack, label, and supply the investigational product (IP) for this study. Tablets will be packed into white high-density polythene bottles with child resistant, tamper evident closures. Study drug must be kept out of the reach of children. Each bottle will contain 100 tablets. Patients will be supplied with sufficient amounts of tablets at each dispensing visit plus overage (2 week supply with 2 additional doses). Drug and placebo will be sent to the Investigational Drug Service (IDS) in the Department of Pharmaceutical Care at the University of Iowa. The IDS will perform randomization using randomization.com and provide identical packages of drug or placebo for distribution by the pharmacist in the cancer center. Randomization will not be stratified and will be performed in groups of eight patients and for the entire cohort. Packages will be sequentially numbered and distributed as patients are enrolled, such that when a patient is enrolled they will be given the lowest numbered package remaining. Package number and patient identification number will be recorded in the study database, and the package key will held by the IDS and released to the investigator on completion of the trial.

Vandetanib tablets must be taken whole or dispersed in water, without crushing. If tablets cannot be taken whole, the tablets can be dispersed in a glass containing 60 mL of non-carbonated water and stirred for approximately 10 minutes until the tablets are dispersed (will not completely dissolve). No other liquids should be used. The mixture should be swallowed immediately. To ensure the full dose is received, the patient should refill the glass with an additional half glass of water and mix with any remaining drug and drink it.

There are no food restrictions for the administration of Vandetanib tablets. Vandetanib tablets should be taken in the morning at about the same time each day with a glass of water.
The first dose of Vandetanib tablets will be taken only after all the assessments assigned have been performed. Patients should take study drug in the morning. If a patient inadvertently misses a dose and the next dose is in 12 hours or more, the patient should take the missed dose immediately and the next dose at the normal time. If it is less than 12 hours before the next dose, the patient should take the next dose at the normal time and the missed dose should not be taken. The missed dose must be documented in the CRF, where appropriate, with a comment indicating the patient missed the dose. The dose of study treatment may be repeated if vomiting occurs within 30 minutes of taking the study treatment. If vomiting occurs after 30 minutes of taking the study treatment, the dose will not be repeated.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling.
Information on the bottle labels for Vandetanib will indicate the study number, contents, caution, and storage conditions and will have blank spaces for the patient number, visit number, and dispensing date (to be written in by the site personnel at the center at the time of dispensing). Instruction that study drug should be taken as directed will be included on the label. Patients will be supplied with a study participation card where the dosing instruction will be described for a patient by Investigator or delegate. All study drugs should be kept in a secure place under appropriate storage conditions

Administration
Subjects will be asked to take Vandetanib as a single oral daily dose of 300 mg or placebo. Patients will discontinue the drug and be removed from the study for toxicity. A patient may withdraw from the study at any time for any reason without prejudice for future treatment. Patients will be removed from the study for failure to comply with greater than 80% of scheduled doses.

Toxicity
The major toxicities of Vandetanib are nausea/vomiting/diarrhea, hypertension, thrombocytopenia, prolonged QT interval, Torsades de pointes, and ventricular tachycardia. The patients will be carefully screened for any conduction abnormalities, arrhythmia, electrolyte/coagulation/platelet abnormalities, and medications in Appendix 2 associated with QT prolongation. The short duration of treatment, two weeks, should limit toxicity. Detailed description of toxicities is provided in sections 11.2.3 and 11.2.4.

8.0 Ancillary Therapy

Because Vandetanib is metabolized by P450 CYP3A4 enzyme, drugs that affect metabolism by this enzyme may alter Vandetanib levels and enhance toxicity. Agents that inhibit CYP3A4 include: erythromycin, cyclosporine, fluconazole, itraconazole, ketoconazole, and grapefruit juice. For these reasons these drugs and foods should be avoided, if at all possible, during the Vandetanib treatment. See List of CYP3A4 inhibitors in Appendix 1. Vandetanib can also cause prolongation of the QTc and Torsades de Pointes. Medications that cause prolonged QTc are listed in Appendix 2 and should be avoided while on study, and patients will be excluded if they take any of the listed medications. Patients will also be instructed to avoid initiation of any of these compounds while on study. Concomitant medications will be reviewed at the time of study entry and at the time of scheduled assessments and procedure, to assess use of agents to avoid, but ongoing documentation is not required in this study.

9.0 Criteria for Response

The primary study end point will be down regulation of proliferative index measured by Ki-67 expression.

9.1 Ki-67

Tissue samples from the paired baseline and endpoint samples will be sent to the Histology Research Laboratory and percentage of cells expressing K-67 will be determined by immunohistochemical staining. The FFPE tissue blocks from core biopsies performed at other hospitals will be obtained and analysis for study data points will be performed and interpreted in the pathology laboratory at UIHC.

9.2. Other tumor markers

ER, PR, and HER2 levels will be assessed per normal procedure by the department of pathology, which is standard of care for the diagnosis and treatment of breast cancer. RET, TUNEL, and phosphorylation specific levels of ERK1/2, AKT, and mTOR will also be assessed on the paired samples using immunohistochemical staining. If alternative assays are found to be more effective at evaluating the levels of these markers in the paired samples, they could be employed on these tissue samples as well. All costs of analysis not considered standard of care will be covered by the PI. Laboratory testing will be performed in the department of pathology histology lab 5225 RCP. Cost for assays will be covered by the PI through a HCC MOG grant. All specimens will be processed in the histology lab per standard of care with formalin fixation and paraffin embedding followed by routine clinical testing (ER, PR, HER2).

9.3 Follow-up Post Surgery

After surgery, the subject will return to clinic for a post-operative visit. This will involve a final drug toxicity evaluation. This is also the standard of care post-operative follow-up visit.

10.0 Removal of Subjects from Protocol Therapy

10.1 Duration of Treatment

Subjects will continue vandetanib or placebo up to and including the morning of surgery for a total of 7 to14 days. The time frame from preoperative clinic visit until definitive surgery will be a minimum of 2 weeks and the maximum of 4 weeks. Subjects with an adverse reaction of CTCAE grade III or higher will discontinue the study drug. Subjects can voluntarily discontinue the drug at any time during the trial, be removed from the drug at the discretion of their treating physician, or be discontinued by the study investigators. In previous trials with vandetanib, surveillance labs and toxicity assessment has been performed at two weeks of treatment, which will be done in this trial with the preoperative safety assessment. Because subjects will have already discontinued the study drug at that time it will not be possible to discontinue the study drug early based on that assessment. Due to the short duration of treatment in this trial and the low incidence of adverse reactions over that time frame in previous phase I and II trials we do not expect a significant number of severe adverse reactions. Subjects will be evaluated for study withdrawal if noncompliant with requirement for therapy, or if they are experiencing drug related toxicity. If the date of surgery is unexpectedly changed after initiation of treatment, the patient will continue treatment, including the morning of surgery, for not more than 28 total days.

10.2 Extraordinary Medical Circumstances:

If at any time the constraints of this protocol are detrimental to the subject's health and/or the subject no longer wishes to continue protocol therapy, remove the subject from the protocol treatment. In this event:

- Document the reason(s) for ending treatment on the follow-up form.
- The primary outcomes of response of down regulation of Ki-67 and secondary outcomes of evaluation of tumor markers in the baseline and endpoint tissue samples will be analyzed unless the subject withdraws consent to do so.

11.0 Data Management, Quality Control and Data Security

Data management for the optimal entry, processing, storage, and retrieval for this protocol's data will be accomplished by the PI. The data base will be located on a computer or in a locked cabinet in a locked office. This computer will be secured, accessible only by the research team. There will be more than one copy of the database. The second, secured, copy of the protocol data will be stored in a locked room accessible only by the research team. For quality control, auditing, and checking data for integrity, there will be a regular accounting date periodically performed.

11.1 Data and safety monitoring

1.1.1. **Purpose:** The Data Safety Monitoring Plan for this study (see Appendix 5) is written to ensure the safety of subjects and to verify the validity and integrity of the data.

1.1.2. **Assessment of risk:** This investigation involves risk-level 3 out of 4 (see appendix 5) procedures, in a population that is at risk of death or severe morbidity because of existing illness or disease.

1.1.3. **DSMC audits:** The CRSO will perform biannual audits of the research charts, case report forms and the corresponding primary source documents. Safety audits will be conducted to validate eligibility of patients accrued to study, check for the presence of informed consent, determine compliance with protocol, determine whether AE/SAE are being reported to internal and external regulatory agencies, and compare veracity of data in the research record with the primary source documents. As part of the ongoing monitoring of this study, the PI will maintain an AE summary table to be reviewed during the audits.

The results of each audit will be reviewed by the DSMC Chair and/or the study monitor. A final report for the audit will be sent to the PI, PRMC Chair, and the IRB, along with any resulting recommendations or required actions.

1.1.4. **Expedited reports:** All expedited adverse event reports will be reviewed by the DSMC.

1.1.5. **Continuing reviews:** All DSMC audit reports must be attached to continuing review submissions for the IRB approval.

11.2 Adverse Event (AE and Serious Adverse Event [SAE])

11.2.1 Definitions

An **adverse event** (AE) is defined in the *CTEP, NCI Guidelines* [2005] as "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure (attribution of unrelated, unlikely, possible, probably or definite)."

A **serious adverse event** (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is a congenital anomaly / birth defect. Hospitalization for planned surgical treatment of breast cancer does not constitute an SAE.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The definition of "**related**" is that there is a reasonable possibility that the drug caused the adverse experience.

Investigators are required by Federal regulations to report serious adverse events as defined in the tables below. If a subject has a reportable serious adverse event, the Study Chair and the Institutional Review Board follow guidelines of this table. This study will utilize the Common Toxicity Criteria version 4.0 to determine the severity of the reaction for adverse event reporting.

11.2.2 Assessment of Risk Level

The Data Safety Monitoring Plan (DSMP) can be found in Appendix 5 of this protocol.
This investigation involves a risk-level 3 procedure, in a population that should not be at any increased risk for complications.

11.2.3 Assessing Toxicity:

Toxicity will be graded according to NCI's Common Toxicity Criteria (CTCAE v4). The investigator will determine relationship of toxicity to the investigational drug as unrelated, unlikely related, possibly related, probably related, or definitely related using standard criteria for clinical trials. All grades of toxicity will be noted and reported as directed in Table I: Clinical Data Update System (CDUS) Guidelines for Routine Adverse Event Reporting.

Patients who experience a CTCAE (version 4) Grade 3 or 4 toxicity that is considered related to Vandetanib will have their study drug stopped. If a patient discontinues treatment, safety follow-up visits will be performed according to the schedule of assessments and procedures. In addition, a 30 day follow up visit will occur if AEs have not resolved by the time of the post op safety visit. SAEs and study drug-related AEs must be followed until resolution unless in the Investigator's opinion, the event is unlikely to resolve due to the patient's underlying condition.

Cardiac toxicity - QTc prolongation
Electrocardiograms will be evaluated by suitably qualified personnel for the presence of QTc prolongation or other abnormalities, in particular, any changes in the T-wave morphology that would suggest a higher likelihood for the development of any arrhythmia. Any clinically significant abnormal findings or QTc prolongations will be recorded as AEs.
In addition to scheduled ECG, additional ECGs should also be performed in the event of QTc prolongation, both during and post the prolongation period.

- During the QTc prolongation period: For a single QTc value of >500 ms, Vandetanib must be withheld and patients will be removed from the study. Electrocardiograms will be followed at least once per week (done at the same day each week) along with electrolytes, until QTc falls ≤480 ms.

Gastrointestinal toxicity
Nausea, vomiting, or both may be controlled with anti-emetic therapy. The use of somatostatin or a somatostatin analogue is allowed to control diarrhea.
Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits and prevent an increased risk of QTc prolongation.
If CTCAE Grade 3 or 4 diarrhea develops, patients will be removed from the study. Any electrolyte imbalance must be promptly corrected since hypokalemia and hypomagnesaemia are potential risk factors for drug-induced arrhythmia.

Cutaneous toxicity
It is strongly recommended that all patients follow a program of sun protective measures (wearing additional clothing and/or sunscreen) while receiving study treatment and for 3 to 4 weeks after discontinuing study treatment. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study therapy.
If a patient develops a skin rash, the following actions are recommended to the Investigator for the management of this reaction:

- A variety of agents can be used to manage skin rashes. These include mild to moderate strength steroid creams or systemic glucocorticoids, either topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams.

- The rash should be graded as soon as possible according to the CTCAE cutaneous toxicity criteria.

- If a rash of CTCAE Grade 2 or higher is detected, immediate symptomatic treatment should be provided.

- If a rash of CTCAE Grade 3 or 4 is detected, patients will be removed from the study

Hypertension
Patients who develop CTCAE Grade 3 hypertension may continue on therapy if blood pressure is controlled on increased anti-hypertensive medication (to CTCAE Grade 1 or baseline). If blood pressure cannot be stabilized with increased anti-hypertensive medication, patients will be removed from the study.
Patients with CTCAE Grade 4 hypertension must be removed from the study.

11.2.4 Adverse Event Reporting:

Table I:

Clinical Data Update System (CDUS) Guidelines for Routine Adverse Event Reporting

Attribution	Adverse Event				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Not required	Not required	CRSO	CRSO	CRSO
Unlikely	Not required	Not required	CRSO	CRSO	CRSO
Possible	CRSO	CRSO	CRSO	CRSO	CRSO
Probable	CRSO	CRSO	CRSO	CRSO	CRSO
Definite	CRSO	CRSO	CRSO	CRSO	CRSO

Reports are collected by the CRSO or DSMB and communicated to the DSMC

For Hospitalization Only — Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements of Phase of Study, expected or unexpected grade and attribution.

All adverse events related to the experimental procedures will be reported to the Data Safety Monitoring Committee (DSMC) via the Clinical Research Safety Officer (CRSO) as well as the appropriate regulatory authority. Annual progress reports will be sent to the CRSO, who will enter this into OnCore and report findings to the DSMC. Only

Grade 4 and 5 events that are unexpected with at least possible attribution to Vandetanib will require an **expedited report**. The investigator will continue to follow or obtain documentation of the resolution course of such an event. The event may also require reporting to the IRB, as determined by current policies (http://research.uiowa.edu/hso/downloads/policies/Guide_Human_Subjects_Research.pdf).

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32., and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (#ISS64740032)

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-866-984-7229

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Overdose

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.
The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

Maternal exposure

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. Should pregnancy occur during a female subject's trial participation, the female subject will immediately be discontinued from the trial and followed-up.
All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be followed-up, documented and reported to AstraZeneca. The following information must be reported to AstraZeneca:

- DOB, Occupation
- Relevant medical history (pregnancy risk factors, smoking alcohol, etc.)
- Relevant family history
- Previous pregnancies (overall number, deliveries, spontaneous miscarriage, etc)
- Current pregnancy (LMP, expected delivery date, any amniocentesis, chorionic villus sampling, in-vitro fertilization)
- Concomitant medications taken during pregnancy (name, total daily dose, therapy duration, indication)
- Outcome of pregnancy (i.e., full-term, premature birth, spontaneous miscarriage, elective termination. If premature birth, specify gestational age in weeks. If elective abortion, specify if any medical reason.)
- Details of birth (i.e., DOB, weight, sex, healthy baby, sick baby, congenital anomaly/birth defect, still birth, multiple births, sickness manifestations, etc.)
- Any complications, infections, illness during pregnancy

The most common side effects seen in patients treated with Vandetanib included the following:

Risks for Vandetanib

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

Headache
Diarrhea
Nausea/vomiting
Constipation
Decreased appetite,
Rash
Dry skin
Hypertension
Trouble sleeping
Weakness
Fatigue

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

QTc prolongation
Abnormal taste in mouth
Abdominal pain
Mouth swelling
Dry mouth
Weight loss
Elevated liver function tests
Anorexia
Hypokalemia
Hypocalcemia
Dehydration
Hypomagnesemia
Skin changes
Acne
Hair loss
Nail disorders
Mild nose bleed
Proteinuria
Kidney stone
Visual problems
Depression
Anxiety

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

Heart failure
Chest pain
Pancreatitis
Thrombocytopenia
Severe skin disorder
Seizure
Shortness of breath
Hypokalemia

12.0 Statistical Analysis

In this study, women will be enrolled after core breast biopsy demonstrates invasive breast cancer. Baseline tissue sample will be obtained on study participants, after which, subjects will take Vandetanib or placebo until the time of a definitive surgical procedure, at which point the resection specimen will serve as a paired tissue sample. In vivo response Vandetanib will be assessed through analyses of the change in tissue levels of KI67, TUNEL, and changes in activation of ERK1/2, AKT, and mTOR and compared to placebo treated patients. All data points will be evaluated as paired continuous data points.

Descriptive statistics (means, medians, standard deviations, percentages, and confidence intervals) will be reported for all baseline and follow-up variables as well as for their changes over time. Statistical comparisons of the changes will be performed with paired t-test for continuous variables. Power analysis for comparisons of

continuous variables was based on published results for Ki-67 [20]– the only readily available results for the proposed treatment and study population. Based on a published standard deviation of 10%, the planned enrollment of 35 subjects will ensure 90% power to detect a decrease of 5% in Ki-67. The power drops to 82% if a two-sided alternative is considered. We will enroll 40 patients in each arm to account for non-compliance and withdrawal.

With a total of 70 evaluable patients (i.e. 35 in control and 35 in treatment group), we can achieve 70% power to detect 6% difference in Ki-67 between the two arms, from the null hypothesis that both arms have equal expression of Ki-67. In this case, we operate under the assumption that both arms have similar standard deviation of 10%, that the significance level is 5%, and that a two-sided two-sample t-test has been used. The power is 80% if a one-sided two-sample t-test is used under the same assumptions. We will enroll 80 patients (40 per arm) to account for potential patient dropouts and ineligibility for analysis due to missed doses.

Power in subgroup comparisons is likely to be low and, thus, the results are most useful for generating hypotheses to be tested in future studies. All statistical tests will be one-sided and assessed for significance at the 5% level.

13.0 References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10-29.
2. Spanheimer PM, Carr JC, Thomas A, Sugg SL, Scott-Conner CEH, Liao J, Weigel RJ. The Response to Neoadjuvant Chemotherapy Predicts Clinical Outcome and Increases Breast Conservation in Advanced Breast Cancer. The American Journal of Surgery 2013; In press.
3. Spanheimer PM, Woodfield GW, Cyr AR et al. Expression of the RET Proto-oncogene Is Regulated by TFAP2C in Breast Cancer Independent of the Estrogen Receptor. Ann Surg Oncol 2012.
4. Tozlu S, Girault I, Vacher S et al. Identification of novel genes that co-cluster with estrogen receptor alpha in breast tumor biopsy specimens, using a large-scale real-time reverse transcription-PCR approach. Endocr Relat Cancer 2006; 13: 1109-1120.
5. Kao J, Salari K, Bocanegra M et al. Molecular profiling of breast cancer cell lines defines relevant tumor models and provides a resource for cancer gene discovery. PLoS One 2009; 4: e6146.
6. Plaza-Menacho I, Morandi A, Robertson D et al. Targeting the receptor tyrosine kinase RET sensitizes breast cancer cells to tamoxifen treatment and reveals a role for RET in endocrine resistance. Oncogene 2010; 29: 4648-4657.
7. Gucalp A, Sparano JA, Caravelli J et al. Phase II trial of saracatinib (AZD0530), an oral SRC-inhibitor for the treatment of patients with hormone receptor-negative metastatic breast cancer. Clin Breast Cancer 2011; 11: 306-311.
8. Boer K, Lang I, Llombart-Cussac A et al. Vandetanib with docetaxel as second-line treatment for advanced breast cancer: a double-blind, placebo-controlled, randomized Phase II study. Invest New Drugs 2012; 30: 681-687.
9. Boulay A, Breuleux M, Stephan C et al. The Ret receptor tyrosine kinase pathway functionally interacts with the ERalpha pathway in breast cancer. Cancer Res 2008; 68: 3743-3751.
10. Esseghir S, Todd SK, Hunt T et al. A role for glial cell derived neurotrophic factor induced expression by inflammatory cytokines and RET/GFR alpha 1 receptor up-regulation in breast cancer. Cancer Res 2007; 67: 11732-11741.
11. Wang C, Mayer JA, Mazumdar A, Brown PH. The rearranged during transfection/papillary thyroid carcinoma tyrosine kinase is an estrogen-dependent gene required for the growth of estrogen receptor positive breast cancer cells. Breast Cancer Res Treat 2011.
12. Siegfried JM, Gubish CT, Rothstein ME et al. Combining the multitargeted tyrosine kinase inhibitor vandetanib with the antiestrogen fulvestrant enhances its antitumor effect in non-small cell lung cancer. J Thorac Oncol 2012; 7: 485-495.
13. Paik S, Shak S, Tang G et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004; 351: 2817-2826.
14. Dowsett M, Bundred NJ, Decensi A et al. Effect of raloxifene on breast cancer cell Ki67 and apoptosis: a double-blind, placebo-controlled, randomized clinical trial in postmenopausal patients. Cancer Epidemiol Biomarkers Prev 2001; 10: 961-966.
15. Dowsett M, Dixon JM, Horgan K et al. Antiproliferative effects of idoxifene in a placebo-controlled trial in primary human breast cancer. Clin Cancer Res 2000; 6: 2260-2267.
16. Burcombe R, Wilson GD, Dowsett M et al. Evaluation of Ki-67 proliferation and apoptotic index before, during and after neoadjuvant chemotherapy for primary breast cancer. Breast Cancer Res 2006; 8: R31.
17. Mohsin SK, Allred DC, Osborne CK et al. Morphologic and immunophenotypic markers as surrogate endpoints of tamoxifen effect for prevention of breast cancer. Breast Cancer Res Treat 2005; 94: 205-211.
18. Arpino G, Ciocca DR, Weiss H et al. Predictive value of apoptosis, proliferation, HER-2, and topoisomerase IIalpha for anthracycline chemotherapy in locally advanced breast cancer. Breast Cancer Res Treat 2005; 92: 69-75.
19. Miller KD, Trigo JM, Wheeler C et al. A multicenter phase II trial of ZD6474, a vascular endothelial growth factor receptor-2 and epidermal growth factor receptor tyrosine kinase inhibitor, in patients with previously treated metastatic breast cancer. Clin Cancer Res 2005; 11: 3369-3376.

20. Garwood ER KA, Baehner FL, Moore DH, Au A, Hylton N, Flowers CI, Garber J, Lesnikoski BA, Hwang ES, Olopade O, Port ER, Campbell M, Esserman LJ. . Fluvastatin reduces proliferation and increases apoptosis in women with high grade breast cancer. Breast Cancer Res Treat 2010; Jan;119: 137-144.

Appendix 1
List of Drugs with Potential Interactions
Examples of inducers & inhibitors of isoenzyme CYP3A4

Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampicin
Nafcillin	Rofecoxib
Nevirapine	St John's wort
Oxcarbazepine	Sulfadimidine
Phenobarbital	Sulfinpyrazone
Phenylbutazone	
	Troglitazone

Inhibitors	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Aprenavir	Mibefradil
Azithromycin	Miconazole
Bromocriptine	Nefazodone
Cannabinoids	Nelfinavir
Cimetidine	Nevirapine
Cisapride	Norfloxacin
Clarithromycin	Norfluoxetine
Clotrimazole	Omeprazole
Cyclosporine	Oxiconazole
Danazol	Paroxetine
Delavirdine	Propoxyphene
Dexamethasone	Quinidine
Diethyldithiocarbamate	Quinine
Diltiazem	Quinupristin and dalfopristin
Dirithromycin	Ranitidine
Disulfiram	Ritonavir
Entacapone (high dose)	Saquinavir
Erythromycin	Sertindole
Ethinyl estradiol	Sertraline
Fluconazole	Telithromycin
Fluoxetine	Troglitazone
Fluvoxamine	Troleandomycin
Gestodene	Valproic acid
Grapefruit juice	Verapamil
lndinavir	Zafirlukast
Isoniazid	Zileuton
ltraconazole	

Appendix 2
List of Drugs with Potential Interactions
Examples of medications known to prolong the QT interval and/or induce Torsades De Pointes (TDP)

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. The drugs that prolong the QT interval and/or have a risk of inducing Torsades de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP:

A. Group 1: Drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes

Concomitant use of these drugs is not allowed during the study or within 2 weeks of randomization (at least four weeks for levomethadyl). These drugs should also be avoided for **up to 4 weeks following discontinuation of study treatment:**

Table 1 Group 1 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Amiodarone	Anti-arrhythmic/abnormal heart rhythm	Females>Males,TdP risk regarded as low
Arsenic trioxide	Anti-cancer/Leukemia	
Astemizole	Antihistamine/Allergic rhinitis	No Longer available in U.S.
Azithromycin	Antibiotic/bacterial infection	
Bepridil	Anti-anginal/heart pain	Females>Males
Chloroquine	Anti-malarial/malaria infection	
Chlorpromazine	Anti-psychotic/Anti-emetic/schizophrenia/ nausea	
Cisapride	GI stimulant/heartburn	No longer available in U.S.
Citalopram	Anti-depressant/depression	
Clarithromycin	Antibiotic/bacterial infection	
Disopyramide	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Dofetilide	Anti-arrhythmic/abnormal heart rhythm	Females > Males
Domperidone	Anti-nausea/nausea	Not available in U.S.
Droperidol	Sedative;Anti-nausea/anesthesia adjunct, nausea	
Erythromycin	Antibiotic;GI stimulant/bacterial infection; increase GI motility	Females>Males
Flecainide	Anti-arrhythmic/abnormal heart rhythm	
Halofantrine	Anti-malarial/malaria infection	Females>Males
Haloperidol	Anti-psychotic/schizophrenia, agitation	TdP risk with I.V. or excess dosage
Ibutilide	Anti-arrhythmic/abnormal heart rhythm	Females>Males

Table 1 Group 1 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Levomethadyl	Opiate agonist/pain control, narcotic dependence	Not available in U.S.
Mesoridazine	Anti-psychotic/schizophrenia	
Methadone	Opiate agonist/pain control, narcotic dependence	Females>Males
Moxifloxacin	Antibiotic/bacterial infection	
Pentamidine	Anti-infective/pneumocystis pneumonia	Females>Males
Pimozide	Anti-psychotic/Tourette's tics	Females>Males
Probucol	Antilipemic/Hypercholesterolemia	No longer available in U.S.
Procainamide	Anti-arrhythmic/abnormal heart rhythm	
Quinidine	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Sotalol	Anti-arrhythmic/abnormal heart rhythm	Females>Males
Sparfloxacin	Antibiotic/bacterial infection	No longer available in U.S.
Terfenadine	Antihistamine/Allergic rhinitis	No longer available in U.S.
Thioridazine	Anti-psychotic/schizophrenia	
Vandetanib (*Does not apply to this study)	Anti-cancer/Thyroid cancer	

[a] Source: www.QTdrugs.org. Last revised: 17 May 2012

B. Group 2: Drugs that in some reports may be associated with Torsades de Pointes but at this time lack substantial evidence of causing Torsades de Pointes.

Concomitant use of these drugs is not allowed within 2 weeks of randomization or during the study. These drugs will be allowed during the study, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes (reference Section 5.6.2 of the protocol).

Table 2 Group 2 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Alfuzosin	Alpha1-blocker/Benign prostatic hyperplasia	
Amantadine	Dopaminergic/Anti-viral/Anti-infective/ Parkinson's Disease	
Artenimol + piperaquine	Anti-malarial/	Not available in U.S.
Atazanavir	Protease inhibitor/HIV	
Chloral hydrate	Sedative/sedation/ insomnia	
Clozapine	Anti-psychotic/schizophrenia	
Dolasetron	Anti-nausea/nausea, vomiting	

Table 2 Group 2 Drugs[a]

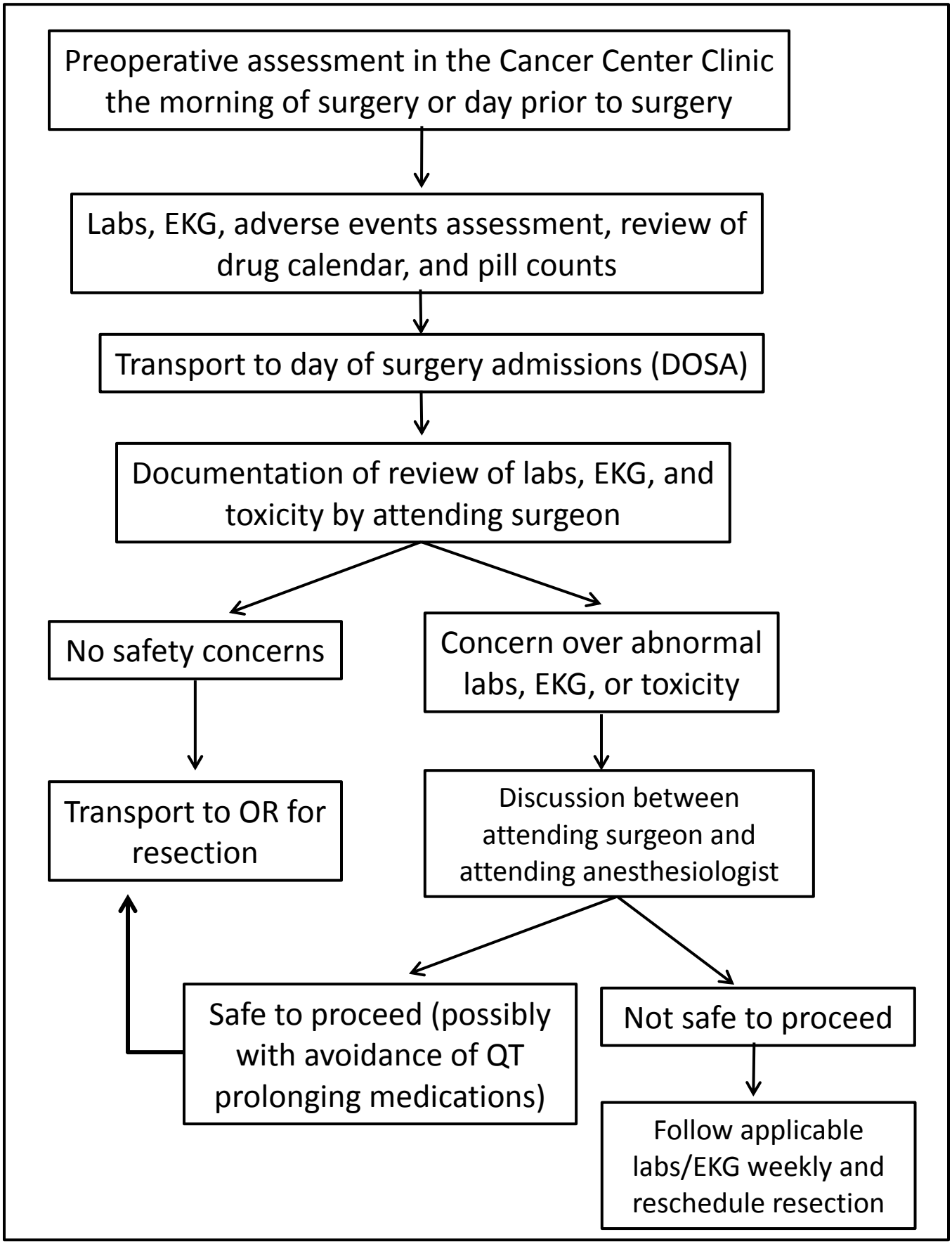
Generic Name	Class/Clinical Use	Comments
Dronedarone	Anti-arrhythmic/Atrial Fibrillation	
Eribulin	Anti-cancer/metastatic breast neoplasias	
Escitalopram	Anti-depressant/Major depression/Anxiety disorders	
Famotidine	H2-receptor antagonist/Peptic ulcer/ GERD	
Felbamate	Anti-convulsant/seizure	
Fingolimod	Immunosuppressant/Multiple Sclerosis	
Foscarnet	Anti-viral/HIV infection	
Fosphenytoin	Anti-convulsant/seizure	
Gatifloxacin	Antibiotic/bacterial infection	Oral/I.V. forms no longer available in U.S. and Canada, only ophthalmic
Gemifloxacin	Antibiotic/bacterial infection	
Granisetron	Anti-nausea/nausea and vomiting	
Iloperidone	Antipsychotic, atypical/Schizophrenia	
Indapamide	Diuretic/stimulate urine & salt loss	
Isradipine	Anti-hypertensive/high blood pressure	
Lapatinib	Anti-cancer/breast cancer, metastatic	
Levofloxacin	Antibiotic/bacterial infection	
Lithium	Anti-mania/bipolar disorder	
Moexipril/HCTZ	Anti-hypertensive/high blood pressure	
Nicardipine	Anti-hypertensive/high blood pressure	
Nilotinib	Anti-cancer/Leukemia	
Octreotide	Endocrine/acromegaly, carcinoid diarrhea	
Ofloxacin	Antibiotic/bacterial infection	
Ondansetron	Anti-emetic/nausea and vomiting	
Oxytocin	Oxytocic/Labor stimulation	
Paliperidone	Antipsychotic, atypical/Schizophrenia	
Perflutren lipid microspheres	Imaging contrast agent/Echocardiography	
Quetiapine	Anti-psychotic/schizophrenia	
Ranolazine	Anti-anginal/chronic angina	
Risperidone	Anti-psychotic/schizophrenia	
Roxithromycin*	Antibiotic/bacterial infection	*Not available in U.S.
Sertindole	Antipsychotic, atypical/Anxiety, Schizophrenia	Not available in U.S.

Table 2 Group 2 Drugs[a]

Generic Name	Class/Clinical Use	Comments
Sunitinib	Anti-cancer/RCC, GIST	
Tacrolimus	Immunosuppressant/Immune suppression	
Tamoxifen	Anti-cancer/breast cancer	
Telithromycin	Antibiotic/bacterial infection	
Tizanidine	Muscle relaxant/	
Vardenafil	phosphodiesterase inhibitor/vasodilator	
Venlafaxine	Anti-depressant/depression	
Voriconazole	Anti-fungal/anti-fungal	
Ziprasidone	Anti-psychotic/schizophrenia	

[a] Source: www.QTdrugs.org. Last revised: 17 May 2012

Appendix 3: Preoperative toxicity visit flowchart



Appendix 4
Randomized, Controlled, Double-Blinded Trial Investigating the Effect of Vandetanib on Cellular Markers of Proliferation and Apoptosis in Breast Cancer

Ronald J. Weigel, MD, PhD

INSTRUCTIONS FOR THE PATIENT: This is a monthly calendar on which you are to record which days you have taken your Vandetanib. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the pill, mark this on the calendar.
Bring the unused pills and your calendars with you at your next appointment
This diary is for your **Vandetanib** only

If you have any questions contact:_____
Telephone:_____
Your next appointment is:_____

VANDETANIB DIARY 300 mg daily

Week of	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week of	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week of	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week of	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week of	**Sunday**	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**

Patient's signature: _____date:_____

Appendix 5
Data and Safety Monitoring Plan

HCCC Clinical Trial Data and Safety Monitoring Plan (DSMP)

Date: 2/19/2013

IRB#: 201301763

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

Principal Investigator: Ronald J. Weigel, MD, PhD

Co-Investigators:
Sonia Sugg, MD Department of Surgery
Ingrid Lizarraga, MD_Department of Surgery
Mark Karwal, MD Department of Internal Medicine
Amani Bashir, MD Department of Pathology
Gideon Zamba, Ph.D Biostatistician

All investigator-initiated protocols will be subject to ongoing monitoring of accrual, subject eligibility, protocol modifications and continuing reviews. Active studies will be audited for the DSMC by the CRSO, following guidelines based on level of risk to subjects. Audits will be conducted by reviewing subject files provided by clinical research coordinators, as well as original source documentation provided by online medical records and research pharmacists. The CRSO will review adverse events, eligibility of subjects, and adherence to the IRB- and PRMC-approved protocol. Protocols found to have discrepancies will be require a response from the PI and an action plan for correcting identified deficiencies. The DSMC will provide a schedule of audit and report dates if requested. **Type of Clinical Trial (check all that apply):**

__X___ Investigator-initiated (Iowa)

_____ Investigator-initiated, multi-center (non-Iowa)

- Is this study monitored by an outside DSMB? Yes_____ No_____

_____ Compassionate-use drug protocol

_____ Pilot study

_____ Phase I

_____ Phase I/II

__X___ Phase II

_____ Phase III

_____ Phase IV

Study risk-level (refer to attached risk-level assessment for this study):

_____ Level 1—low risk of morbidity or death, * <<1% of death or any adverse event

_____ Level 2—risk of death* <1% or any adverse event 1% – 5%

__X___ Level 3—risk of death* 1% – 5% or grade 4 – 5 SAE 1% – 5%

_____ Level 4—risk of death* >5% or grade 4 – 5 SAE >15%

_____ Drugs being used on a "compassionate" basis

***** *Risk of death" refers specifically to 100-day treatment-related mortality*

The following additional documents will be included in the DSMP for this study:

- A subject eligibility check-list (inclusion / exclusion criteria), which will be available in OnCore, the HCCC CTMS
- A list of expected toxicities and stopping rules for suspension of accrual secondary to adverse events and safety parameters
- A signed and dated statement from the Principal Investigator(s) declaring any conflict of interest (or lack thereof) with a description of how a conflict of interest will be monitored to enhance transparency
- The Human Subjects application will be obtained from HawkIRB
- Future Continuing Review and/or Modification forms will be obtained from HawkIRB
- For multi-centered trials, a detailed description of the procedures in place at each center that enable communication between participating centers such that the PI is aware of the status of participating subjects including the immediate (<24hours – week day) awareness of grade 4 – 5 SAE / death

Risk Level 3

- An independent Study Monitor, or the DSMC Chair (or his designee), will review study data (provided by the PI and CRSO) and communicate with the PI at least twice yearly. The proceedings of this meeting will be summarized by the CRSO in a brief letter to the PI, a copy of which will be forwarded to the DSMC.
- Principal Investigator will provide a QUARTERLY report to the Study Monitor and the CRSO for the DSMC, or data may be obtained from OnCore:
    - Quarterly patient accrual data
- Copies of all Serious Adverse Events will be reported to the CRSO as per DSMC reporting guidelines.
- CRSO will conduct a BIANNUAL audit of at least 25% of the subjects' research charts, and will report the results to the DSMC. Audits will:
    - Validate eligibility of patients accrued to the study
    - Check for the presence of a signed informed consent
    - Determine compliance with protocol methodology
    - Determine whether SAEs are being reported to internal and external regulatory agencies
    - Compare veracity of data in the research record with the primary source documents
    - Review investigational drug processing and documentation.

Assess cumulative AE/SAE reports for trends and compare to study stopping rules.

Routine Adverse Event Reporting

Routine reporting of adverse events to the DSMC via the CRSO is described in Table 1:

Table I: Routine Reporting of Adverse Events

Attribution	Adverse Event				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Not required	Not required	CRSO	CRSO	CRSO
Unlikely	Not required	Not required	CRSO	CRSO	CRSO
Possible	CRSO	CRSO	CRSO	CRSO	CRSO
Probable	CRSO	CRSO	CRSO	CRSO	CRSO
Definite	CRSO	CRSO	CRSO	CRSO	CRSO

Eligibility Criteria:

- Patient with core biopsy, pathology demonstrating invasive breast cancer, with planned surgical excision
- Female gender. There is an incidence of male breast cancer, but it is unclear if the etiology is the same and inclusion of males could confound results.
- Age ≥ 18. Breast cancer, while not restricted only to adult women, is rare in the younger population.
- ECOG performance status ≤ 2.
- Life expectancy of greater than 6 months.
- Patient able to willingly provide informed consent to participate

4.1.2 Exclusion Criteria

- Prolonged QT interval (QTc > 480 milliseconds) on screening EKG or congenital long QT syndrome
- Any concomitant medications that are known to be associated with Torsades de Pointes or QT elongation (see appendix 2).
- Hypertension not controlled by medical therapy (systolic BP greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg.
- Patients taking metformin or digoxin. History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication are permitted.
- Significant cardiac event (e.g., myocardial infarction), superior vena cava syndrome, New York Heart Association (NYHA) classification of heart disease ≥2 within 12 weeks, or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia.
- Serum calcium or magnesium outside the institutional range of normal.
- Serum Potassium < 4.0 mmol/L or above 5.0 mmol/L
- Creatinine clearance < 50 ml/min
- PT > 12 seconds or PTT > 31 seconds
- Platelet count < 100,000
- Serum bilirubin greater than 1.5 mg/dl
- Alanine aminotransferase (ALT) > 50 U/L, aspartate aminotransferase (AST) > 65 U/L, or alkaline phosphatase (ALP) > 250 U/LAny cytotoxic treatments, such as neoadjuvant chemotherapy, planned before subsequent surgical procedure.
- Previous exposure to Vandetanib
- Previous enrollment or randomization in this study.
- Involvement in the planning and /or conduct of the study (applies to both Astra Zeneca staff and staff at UIHC).
- Previous or current malignancies of other histologies within the last 5 years, with the exception of in situ carcinoma of the cervix, and adequately treated basal cell or squamous cell carcinoma of the skin.
- Patients who have received prior surgical site radiation.
- Patients on CYP3A4 inhibitors or inducers (see appendix 1).
- Inability to test core biopsy for study markers
- Pregnancy or lactation at the time of study entry. ***(Note: Pregnancy testing must be performed within 2 weeks prior to randomization according to institutional standards for women of childbearing potential.)***

Toxicities

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

Headache
Diarrhea
Nausea/vomiting
Constipation
Decreased appetite,
Rash
Dry skin
Hypertension
Trouble sleeping
Weakness
Fatigue

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

QTc prolongation
Abnormal taste in mouth
Abdominal pain
Mouth swelling
Dry mouth
Weight loss
Elevated liver function tests
Anorexia
Hypokalemia
Hypocalcemia
Dehydration
Hypomagnesemia
Skin changes
Acne
Hair loss
Nail disorders
Mild nose bleed
Proteinuria
Kidney stone
Visual problems
Depression
Anxiety

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

Heart failure
Chest pain
Pancreatitis
Thrombocytopenia
Severe skin disorder
Seizure
Shortness of breath
Hypokalemia

Stopping Rules

Subjects will continue Vandetanib up to and including the morning of surgery. The time frame from clinic visit until definitive surgery will be a minimum of 2 weeks and the maximum of 4 weeks. Subjects will be evaluated for study withdrawal if noncompliant with requirement for therapy (at least 80% of doses), or if they are experiencing drug related toxicity. Patients may withdraw from the study at any time for any reason without effecting treatment of their breast cancer.