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Title: Phase I/II Trial of Letrozole ([redacted] and Sorafenib [redacted] as First-Line Therapy in Postmenopausal Women with Hormone Receptor-Positive Locally Advanced or Metastatic Breast Cancer

Principal Investigator: [redacted]

*Role is non-clinical, no 1572 required

[redacted]

[redacted] ealthcare

Drug(s) Under Investigation	Company	IND#	Drug Supply
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute neutrophil count
BUN	Blood urea nitrogen
CBC	Complete blood count
CINJOG	Cancer Institute of New Jersey Oncology Group
CT	Computer Tomography
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IRB	Institutional Review Board
Kg	Kilograms
mL	Milliliters
mcg/μg	Micrograms
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRS	Office of Human Research Services
OHRP	Office of Human Research Protection
PD	Progressive disease
PHI	Protected health information
PI	Principal Investigator
PR	Partial response
RWJUH	Robert Wood Johnson University Hospital
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
ULN	Upper limit of normal

1. Purpose/Specific Objectives

1.1 Primary Endpoint

1.1.1 Determine the recommended phase II dose of sorafenib in combination with a fixed daily dose of 2.5 mg of letrozole in patients with hormone receptor-positive locally advanced or metastatic breast cancer.

1.1.2 Determine the clinical benefit rate (proportion of patients who achieve a complete response, partial response, or stable disease ≥ 6 months) of letrozole and sorafenib in the first-line treatment of postmenopausal patients with hormone receptor-positive locally advanced or metastatic breast cancer.

1.2 Secondary Endpoints

1.2.1 Determine time to progression and overall survival of patients treated with this combination.

1.2.2 Assess the safety and tolerability of this combination.

1.2.2 Evaluate components in the Ras-Raf-MAPK and vascular endothelial growth factor (VEGF) pathways in tumor samples before and after treatment (if available) with letrozole and sorafenib.

1.2.3 Evaluate the change in circulating tumor cells in peripheral blood before and after treatment with letrozole and sorafenib.

2. Background and Significance

2.1 Introduction

In 2007, over 178,480 women will be diagnosed with invasive breast cancer and 40,460 women will die of this disease.[1] Although the last two decades have witnessed significant advances in systemic therapies, metastatic breast cancer still remains an incurable disease. Once metastases are discovered, median survival for all patients is only two to three years. Given the lack of curable treatment, the major goals of therapy include palliation of symptoms, maintenance of quality of life, and improvement in overall and progression-free survival. When choosing the optimal therapy for metastatic breast cancer, one must take into account a number of factors, such as the likelihood of response with a particular therapy, its side effect profile, and ease of administration. In addition, consideration of an individual tumor's biology allows the tailoring of therapy to optimize resources and outcomes.

Hormonal therapy, such as selective estrogen receptor modulators, aromatase inhibitors, and estrogen antagonists, is a major treatment option for women with hormone receptor-positive metastatic breast cancer. Approximately 75% of breast cancers are positive for the estrogen receptor (ER), the progesterone receptor (PR), or both.[2] About 50 to 60% of patients with hormone receptor-positive tumors respond to hormonal therapy. Approximately 20 to 35% of patients with hormone receptor-positive metastatic breast cancer will experience an objective response to initial hormone therapy. However, a portion of hormone receptor-positive patients will not respond.

Data are evolving in preclinical models demonstrating that estrogen modulates angiogenesis, in part through effects on VEGF.[3-6] Data also suggest that estrogen (E_2) modulates VEGF-induced angiogenesis in physiologic and pathologic conditions. One study in an androgen-dependent male mouse model of breast cancer demonstrated that castration resulting in the removal of androgen causes tumor regression. There was also a reduction in tumor vasculature in response to castration and androgen deprivation that correlated with a decrease in VEGF at the molecular level, particularly 7 days after castration.[7]

Therefore, one way to enhance endocrine sensitivity and delay disease progression in patients with hormone receptor-positive metastatic breast cancer is to add an anti-VEGF therapy, such as an oral tyrosine kinase inhibitor of VEGF, to standard anti-hormonal treatment for patients with breast cancer. In this trial, we will test the hypothesis that adding an anti-angiogenic agent might delay the onset of resistance to endocrine therapy, specifically estrogen deprivation with an aromatase inhibitor.

2.1.1 Aromatase inhibitors in postmenopausal metastatic breast cancer

Aromatase inhibitors (AIs) block the cytochrome P450 enzyme aromatase (CYP19), thereby preventing the conversion of androstendione to estrone and testosterone to estradiol. Lower estrogen levels deprive the tumor of its growth stimulus. This property makes AIs in particular suitable for postmenopausal women whose main source of active estrogen is the result of peripheral aromatization of androgen precursors.

The first-generation compounds, such as aminoglutethimide, were associated with significant toxicity. Subsequently, second and third-generation compounds have been developed and include anastrozole, letrozole, and exemestane. These agents have shown exquisite specificity and are highly selective in targeting the aromatase enzyme. Second-generation AIs are either steroidal or nonsteroidal. The nonsteroidal compounds (i.e., letrozole, anastrozole) competitively inhibit the aromatase enzyme while the steroidal compounds, such as exemestane, irreversibly inactivate the enzyme.

In the last few years, AIs have shown to be equivalent or superior in efficacy to tamoxifen (and also of similar or better tolerability) in the first-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer as well as in the adjuvant setting.[8-11]

2.1.2 [redacted]

2.1.2.1 General comments: [redacted]e (4,4'-(1H-1,2,4-triazol-1-ylmethylene)bis-benzonitrile) is a synthetic achiral benzydryltriazole derivative. It is an orally active highly selective nonsteroidal competitive inhibitor of the aromatase enzyme system.[12] Letrozole effectively inhibits the conversion of androgens to estrogens in vitro and in vivo. Letrozole is up to 150 to 250 times more potent than the first-generation AI, aminoglutethimide, in vitro and more than 10,000 times as potent as aminoglutethimide in inhibiting aromatase in vivo.[13] The high potency of letrozole is not accompanied by any significant effect on adrenal steroidogenesis in vitro or in vivo over its maximally effective dose range.[12,13]

Thus, it is also a highly selective inhibitor of aromatase. The high potency and selectivity of letrozole explains its favorable pharmacological profile and high therapeutic index. In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg letrozole suppressed plasma levels of estradiol, estrone and estrone sulfate by 75-95% from baseline.[14]

2.1.2.2 Clinical Information: A Phase III global, multicenter, randomized clinical trial evaluated letrozole (2.5 mg/day) as a first-line hormonal therapy as compared to the present standard of treatment tamoxifen (20 mg/day).[8] This trial accrued 907 postmenopausal women with ER and/or PR positive or unknown receptor breast cancer and locally advanced disease, metastatic disease, or loco-regional recurrence not amenable to treatment by surgery or radiotherapy. Patients received treatment until disease progression or discontinuation for any other reason. The primary endpoint was time to progression (TTP). Letrozole was superior to tamoxifen and reduced the risk of progression by 28% (hazard ratio 0.72, $P < .0001$). The median TTP was prolonged by 57%: 6.0 months for tamoxifen vs. 9.4 months for letrozole. The secondary endpoints included overall tumor response rate, clinical benefit, and time to treatment failure. Overall tumor response rate (complete and partial response) was significantly higher with letrozole (32% vs. 21%, $P = .0002$), irrespective of dominant site of disease. Clinical benefit (complete response, partial response or stabilization of disease) lasting at least 24 weeks was 50% for letrozole vs. 38% for tamoxifen ($P = .0004$). Time to treatment failure was significantly better for letrozole compared to tamoxifen (9.0 months vs. 5.7 months respectively, $P = .0001$.) The median overall survival was slightly prolonged for letrozole vs. tamoxifen (34 months vs. 30 months, respectively). This difference is not significant. However, the study design included a crossover to the other treatment arm at the discretion of the investigator. An analysis was done in the patients who did not crossover, which demonstrated a 15-month survival advantage in the letrozole treatment group.[15] The data cutoff for this analysis was September 2001 when median follow-up was 32 months with a maximum observation period of 57 months. Tolerability was similar in both arms of the trial, with 2% of patients on letrozole and 3% of patients on tamoxifen discontinuing therapy due to adverse events.

2.1.2.3 Summary: Letrozole has a highly favorable toxicity profile and is superior to tamoxifen in terms of TTP and complete response in patients with locally advanced and metastatic breast cancer. Based on this study and other supportive data, the FDA approved letrozole for first-line hormonal therapy in locally advanced or metastatic breast cancer in January 2001.

2.1.3 [redacted]

2.1.3.1 General Comments: The Ras-Raf-Mitogen activated protein kinase (MAPK) pathway is a critical signaling pathway involved in cell proliferation.[16] Increased activation and overexpression of MAPK have been observed in breast tumors.[17] Moreover, a significant positive association has been shown between activated MAPK and the presence of lymph node metastases.[18] There also appears to be significant cross-talk between the MAPK and ER pathways, with activation of MAPK resulting in ER phosphorylation and activation in a steroid-independent manner.[19] In fact, endocrine-resistant ER-positive breast

cancer cells show increased dependence on MAPK-mediated signaling. Inhibition of the critical Ras-Raf-MAPK pathway thus is an attractive potential treatment for breast cancer.

Sorafenib (4-{4-[3-(4-chloro-3-trifluoromethyl-phenyl)ureido]-phenoxy}-pyridine-2 carboxylic acid methylamide-4-methylbenzensulfonate), a bi-aryl urea, is a potent inhibitor of wild-type and mutant b-Raf kinase isoforms in vitro. It also inhibits the tyrosine kinase of VEGFR-1, VEGFR–2, VEGFR-3, PDGFR, and c-KIT.[20] By inhibiting Raf, which interacts at the plasma membrane with activated Ras and initiates the MAPK cascade, this drug suppresses the signaling events required for tumor proliferation. Sorafenib is currently approved for the treatment of patients with advanced renal cell carcinoma.[21]

Angiogenesis has been shown to be essential to the growth of solid tumors.[22] Vascular endothelial growth factor (VEGF) is the dominant growth factor controlling angiogenesis. Levels of VEGF are markedly elevated in the vast majority of tumors and vascular growth and formation are key components in promoting and sustaining tumor survival. In breast carcinoma, tumor angiogenesis has been reported to have prognostic significance.[23] Specifically, a statistically significant correlation between microvessel density and lymph node status as well as incidence of metastases has been demonstrated in patients with breast cancer.[24] By targeting the VEGF receptor, sorafenib also inhibits tumor angiogenesis and deprives the tumor of the neovascularization required to sustain its growth. Sorafenib is therefore an attractive therapeutic agent given its potential to prevent tumor growth by inhibiting both tumor cell proliferation and tumor angiogenesis.

2.1.3.2 Clinical Information: The safety and clinical activity of sorafenib, alone or in combination with chemotherapy, has been examined in a series of phase I studies conducted in patients with solid tumors.[25-30] In a multi-center, randomized, placebo-controlled, double-blind phase III trial of 906 patients with advanced renal cell carcinoma (RCC) who had received one prior systemic therapy, sorafenib-treated patients had a median PFS of 24 weeks versus 12 weeks for the placebo group (hazard ratio 0.44; $p<0.00001$).[21,31] The 12-week progression-free rate was 79% for sorafenib versus 50% for placebo. Based on these results, in May 2005 the study was unblinded and patients in the placebo group allowed to cross over and receive sorafenib. At the time of cross over, an interim analysis of overall survival was conducted based on 220 events. Median overall survival in the placebo group was 14.7 months and had not been reached in the sorafenib group. The hazard ratio (sorafenib over placebo) was 0.72 with a p-value of 0.018. The threshold for statistical significance for this interim analysis was not reached ($p < 0.0005$). Final analysis of OS was reported at the American Society of Clinical Oncology (ASCO) Annual Session in 2007.[31] Overall survival in the sorafenib group was 17.8 months and 15.2 months in the placebo group (HR 0.88, p=0.146). For this study, however, OS was likely confounded by the fact that approximately half of the placebo patients crossed over at the time of unblinding to receive sorafenib. To illustrate that point, overall survival analysis with placebo patients censored at the time of cross over indicated that sorafenib treated patients had a statistically significant 22% reduction in mortality risk compared to placebo patients (OS 17.8 mo vs 14.3 mo, HR 0.78, p=0.287). Based in part on these findings, the

US FDA approved sorafenib for the treatment of patients with advanced renal cell carcinoma in December 2005.

A multi-center, randomized, placebo-controlled, double-blind phase III trial was also conducted for patients with advanced hepatocellular carcinoma (HCC) and was reported at ASCO in 2007.[32] In this study 602 patients with advanced HCC, Child Pugh class A, having not received prior systemic therapy were randomized to receive either sorafenib (n=299) at 400 mg bid or placebo (n=303). In February 2007, based on a planned interim analysis of overall survival, the data safety monitoring board recommended unblinding and closure of the study. OS in the sorafenib group was 46.3 wks versus 34.4 wks in the placebo-treated group. This represented a 44% increase in relative OS (HR 0.69, p=0.00058). PFS was also significantly increased in the sorafenib group (24 wks) vs the placebo group (12.3 wks); HR 0.58, p=0.000007.

Sorafenib as a single agent has been evaluated in patients with metastatic breast cancer in the phase II setting. In one phase II trial, 54 patients were treated with sorafenib 400 mg twice daily in 4-week cycles until toxicity, disease progression, or death.[33] All patients had received at least one prior chemotherapy regimen and had progressed on adjuvant hormone therapy (if hormone receptor-positive) or trastuzumab (if HER2 positive). The median treatment duration was 58 days (range 1-402). Analysis of the study's primary endpoint of best response, according to World Health Organization criteria, revealed a partial response in one patient (2%). Twenty (37%) women had stable disease, including 22% and 11% of patients disease stabilitzation for 4 months and 6 months, respectively. Sorafenib was well-tolerated with one grade 4 drug-related adverse event which was an increase in GGT. The most common side effects were rash/desquamation, anorexia, and hand/foot skin reactions. These toxicities were mild-to-moderate and clinically manageable. Another phase II study primarily conducted in the United States enrolled patients with metastatic breast cancer who were candidates for first or second-line chemotherapy and had previously received an anthracycline and/or a taxane in the neoadjuvant, adjuvant, or metastatic setting.[34] Patients were treated with sorafenib 400 mg twice daily on days 1-28 of each 4-week cycle. In this study, 20 pts were eligible for efficacy analysis. One pt (5%; 95% CI 0.5-20.5%) achieved a PR with duration of 3.6 months and one patient achieved stable disease for at least 6 months. The 6-month overall survival rate was 81% and the progression-free survival rates were 53% at 2 months, 24% at 4 months and 6% at 6 months. Median time to progression was 2 months.

2.1.3.3 Summary: Although studies demonstrate limited activity of sorafenib as a single-agent in heavily pre-treated metastatic breast cancer populations, there is potential for efficacy in combining sorafenib with other agents, such as chemotherapy, hormone therapy and other targeted drugs. There are several ongoing trials being conducted with sorafenib in patients with metastatic breast cancer. This includes a phase II trial of sorafenib and anastrozole in previously treated patients with hormone receptor-positive disease, a randomized phase II trial of paclitaxel with or without sorafenib as first-line therapy in locally recurrent or metastatic breast cancer, and a double-blind, randomized

phase II trial of sorafenib versus placebo in combination with chemotherapy after progression on bevacizumab.

2.1.4 Biologic and imaging correlates

Since sorafenib is a potent c-Raf and B-Raf kinase inhibitor and inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, and c-KIT tyrosine kinases, components of the Ras-Raf-MAPK and angiogenesis pathways will be evaluated in tumor specimens of patients enrolled on study if available. We propose to measure tissue expression of mitogen-activated protein kinase (MAPK), phosphorylated-MAPK, VEGFR-2, and phosphorylated VEGR-2. Effect on tumor proliferation will be measured by assessing Ki67 in tumor samples.

The development of new treatments for cancer could be facilitated if tumor cells could be sampled directly at multiple time points following the administration of a new drug or drug combination. It is very desirable to have direct access to relevant target cells to learn about a drug's effect. Although we will try to directly sample solid tumor masses and evaluate the end points described above, this will be difficult. In this trial, we will collect peripheral blood for circulating tumor cells before treatment and after two cycles of treatment. In 2004, it was shown that the use of circulating tumor cells (CTCs) for the management of metastatic breast cancer patients undergoing systemic therapy was a strong independent predictor of progression-free survival and overall survival.[35]

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) has been used extensively with novel anti-angiogenic agents in clinical studies to monitor their effect on tumor vasculature through parameters reflecting both tumor perfusion and permeability. Other modalities such as perfusion CT (pCT) may serve as a noninvasive tool to monitor tumor response to therapy via quantification of blood flow parameters. Perfusion CT techniques have demonstrated decreasing effects of different angiogenesis inhibitors on tumor blood flow parameters.[36-38] In this trial, patients undergoing imaging studies at Robert Wood Johnson University Hospital will have a perfusion CT performed before treatment and after two cycles of treatment to assess tumor perfusion.

Correlation between serial CTC values and blood flow measurements from serial perfusion CT will be performed as an exploratory analysis.

2.1.5 Rationale for study

Metastatic breast cancer is not curable. However, in patients with hormone receptor-positive disease, quality of life and duration of remission are important parameters of their treatment. Due to its relatively low toxicity, hormonal therapy is usually the first line therapy for women for initial recurrence or low burden of metastatic disease.

Therapy directed at angiogenesis and tumor proliferation pathways in addition to aromatase represents a potentially novel approach. We hypothesize that sorafenib, a potent inhibitor of angiogenesis as well as the MAPK signaling pathway, could inhibit the signaling events required for tumor proliferation while letrozole inhibits aromatase activity.

It is not expected that there will be a pharmacokinetic interaction for this combination because neither drug inhibits or induces the metabolic pathway of the other at clinical concentrations. There is also detailed pharmacokinetic data available for both drugs. For these reasons, we will not perform detailed pharmacokinetics as part of the trial, however, this trial will include a short phase I component with dosing outlined in section 7.4.

We chose letrozole as our AI because it is the only AI to date to show superiority to tamoxifen in the first-line treatment of metastatic postmenopausal breast cancer, although there has been no head-to-head comparison of a nonsteroidal AI to a steroidal AI in the treatment setting. We chose a nonsteroidal inhibitor because it has no androgenic properties, unlike exemestane, a steroidal agent, which has some weak androgenic side effects, such as weight gain, acne, and hypertrichosis. In terms of suppression of estrogen and its metabolites, letrozole appears to suppress plasma estradiol, estrone and estrone sulfate levels to a greater extent than exemestane (90.1 – 97.6% vs. 72.9 - 89%), although this was not determined in a comparative study.[39,40]

In addition, in aromatase-expressing cellular models, including human breast fibroblasts, MCF-7Ca cancer cells and JEG-3 human choriocarcinoma cell lines, letrozole has been compared with other AIs, such as anastrozole and formestane, a steroidal AI, and shown to be consistently more potent.[40] Another study that examined the activity of aromatase in placental microsomes and mammary fibroblast cultures with letrozole, anastrozole, or exemestane showed that for each tissue, letrozole had the lowest IC_{50} and the highest potency, which suggests that it has the best capability of inhibiting aromatase in vitro.[44] Furthermore, letrozole has also been shown to exhibit the lowest residual aromatase activity at 1.1% versus anastrozole at 3.3% and exemestane at 2.1%.[39,41] Although the clinical relevance of these differences needs to be further investigated, these studies provide further support for using letrozole as the AI of choice for our study.

We propose using the combination of letrozole and sorafenib as first-line therapy in postmenopausal hormone receptor-positive patients with locally advanced or metastatic breast cancer. We postulate that depriving hormone-dependent breast cancer cells of estrogen in addition to interfering with the tumor's proliferation signals and vascular supply will be an effective strategy in the treatment of advanced breast cancer and may result in more activity than what has been reported with letrozole as a single agent.

3. Participating Institutions

The [redacted]

4. Experimental Design and Methods

This is an open-label phase I/II trial to determine the clinical benefit rate of combining letrozole and sorafenib in postmenopausal women with previously untreated hormone receptor-positive locally advanced or metastatic breast cancer.

Patients will receive oral letrozole once daily at 2.5 mg/day in combination with oral sorafenib at a daily dose to be determined based upon the phase of study that patient is enrolled. Letrozole and sorafenib will be taken continuously on Days 1 through 28 (a cycle). The phase II dose of sorafenib will be determined from the phase I portion of the study. Treatment will be administered until disease progression or withdrawal from study due to unacceptable toxicity or other reasons (i.e., consent withdrawal, non-compliance, etc.).

5. Patient Selection Criteria

5.1 Inclusion Criteria

A patient is eligible for enrollment if all of the following inclusion criteria are met.

5.1.1 Histologically confirmed invasive breast cancer

5.1.2 Stage IIIB, IIIC with T4 lesion or Stage IV disease

5.1.3 ER-positive and/or PR-positive of primary or secondary tumor tissue

5.1.4 Women age ≥ 18 years

5.1.5 Postmenopausal status defined by one of the following criteria:

- Age 56 or older and history of at least 12 months without spontaneous menstrual bleeding prior to study entry, or
- Age 55 or younger with a history of at least 12 months without menstrual bleeding, whether spontaneous or from a prior hysterectomy, with a documented estradiol level within the institutional/laboratory postmenopausal range, or
- Prior documented bilateral oophorectomy or
- Ovarian suppression by a luteinizing hormone-releasing hormone (LHRH) agonist. Medical ovarian suppression can be initiated any time prior to or at the start of protocol therapy, and continued throughout the duration of the trial.

5.1.6 Patients must have an ECOG performance status 0, 1, or 2 (Appendix A).

5.1.7 Patients must have normal organ and marrow function as defined below:

- ANC count ≥ 1200/μL
- Platelets ≥ 100,000 /μL
- Total bilirubin ≤ 1.5 X institutional ULN
- AST(SGOT)/ALT(SGPT) ≤ 2.5 X institutional ULN, (≤ 5 X ULN if liver metastases present)
- Creatinine ≤ 1.5 X institutional ULN

5.1.8 Patients can have non-measurable disease or measurable disease according to RECIST (Section 9).

5.1.10 Life expectancy of 3 months or longer

5.1.11 Able to swallow and retain oral medication
5.1.12 Written informed consent

5.2 Exclusion Criteria

A patient will not be eligible for this study if any of the following exclusion criteria are met.

5.2.1 Prior hormonal therapy for metastatic disease (prior adjuvant tamoxifen or aromatase inhibitor will be allowed)
5.2.2 Prior chemotherapy for metastatic disease
5.2.3 Prior treatment with sorafenib
5.2.4 Patients with a history of brain metastases or leptomeningeal metastases.
5.2.5 Second primary malignancy except most situ carcinoma (e.g. in situ carcinoma of the cervix, adequately treated non-melanomatous carcinoma of the skin) or other malignancy treated at least 5 years previously with no evidence of recurrence
5.2.6 Cardiac disease: Congestive heart failure > class II NYHA (see Appendix B). Patients must not have unstable angina (anginal symptoms at rest) or new onset angina (began within the last 3 months) or unstable coronary artery disease within the past 6 months
5.2.7 Serious concomitant systemic disorders (including symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia requiring therapy, myocardial infarction within the past 6 months, or active infections or severe hepatic impairment) that would compromise the safety of the patient or compromise the patient's ability to complete the study, at the discretion of the investigator
5.2.8 Uncontrolled hypertension defined as systolic blood pressure > 150 mm Hg or diastolic pressure > 100 mm Hg, despite optimal medical management
5.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to letrozole or sorafenib
5.2.10 History of allergic reaction to sulfonamides
5.2.11 Thrombolic or embolic events such as a cerebrovascular accident including transient ischemic attacks within the past 6 months
5.2.12 Serious non-healing wound, ulcer, or bone fracture
5.2.13 Evidence or history of bleeding diathesis
5.2.14 Major surgery, open biopsy or significant traumatic injury within 4 weeks of first study drug
5.2.15 Use of cytochrome P450 enzyme inducing antiepileptic drugs (phenytoin, carbamazepine, or phenobarbital), or St. John's Wort or rifampin (rifampicin)
5.2.16 History of malabsorption syndrome
5.2.17 Patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy, therefore, known HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with sorafenib.

5.3 Inclusion of Women and Minorities

Women from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. Males will not be eligible for this study. Breast cancer in men is rare and the efficacy of aromatase inhibitors in males is limited.

5.4 Participation of Children

Only patients 18 years of age or older will be enrolled on this study, since postmenopausal breast cancer does not occur in children.

5.5 Sources or Methods of Recruitment

Patients will be recruited through screening of patients being followed in the [redacted]

5.6 Study Enrollment Procedures

A copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol must be on file at the [redacted] before any participating institution may enter patients. Consent forms proposed for use at a participating institution must be reviewed and approved by the OHRS Regulatory Affairs Manager and all documents must be received (i.e., IRB approved documentation, IRB approved consent form, See Section 15.2 for a complete list of regulatory items).

Participating institutions will register patients through the OHRS Registration Desk [redacted]. Patient demographic information, the signed and dated study-specific eligibility checklist and completed signature page of the consent form and additional source documents if requested by OHRS must be sent to the registration desk. Once the OHRS Registration Desk verifies eligibility, a unique patient study number will be issued. The patient will not be identified by name. This is the point that the patient is considered on study. Patients must <u>not</u> start protocol treatment prior to registration.

If a patient does not receive any protocol therapy, baseline data will be collected and submitted on the pre-study and follow-up electronic case report forms (eCRF). The reason for not starting protocol therapy will be documented in the "follow-up eCRF". Case report form completion instructions and training will be provided to each participating institution prior to study activation at the participating institution.

6. Study Parameters

The following tests and evaluations will be performed according to the schedule below. Baseline (i.e., pre-study) evaluations must be performed no longer than 4 weeks (+/- 3 days) prior to therapy, unless otherwise indicated in one of the footnotes below the table.

Evaluations	Pre-study	Every 4 weeks (prior to each cycle beyond cycle 1)	After the first 8 weeks (after first 2 cycles)	Every 12 Weeks	End of Treatment
Initial History and Physical	X[10]				
Interim History and Physical[1]		X			X
Toxicity Assessment		X			X
ECOG Performance Status	X	X			X
Weight and Height[2]	X	X			
CBC, differential, platelets	X[10]	X[11]			X[12]
Serum Chemistries[3]	X[10]	X[11]			X[12]
Liver Enzymes[4]	X[10]	X[12]			X[12]
EKG	X				
Radiographic Assessments[5]	X			X	
Circulating Tumor Cells[6]	X		X		
Correlative Blood Studies[6]	X		X		
Archived Tumor Tissue[7]	X				
Tumor Biopsy (if accessible)	X	X[8]			
Pill Diary		X			X
Record concomitant medications	X	X			X
Compliance Assessment		X			X
Survival[9]					X

1. Blood pressure should be monitored weekly during the first cycle. Measurements maybe obtained outside of the treating physician's office, however, must be documented in the patient's diary. Measurements should be made using a calibrated electronic device, unless performed in a doctor's office where a manual blood pressure measurement is acceptable.
2. Height to be measured only at baseline.
3. Serum chemistries include: Sodium, Potassium, Chloride, Bicarbonate, Calcium, Glucose, BUN and Creatinine.
4. Includes: total bilirubin, AST, ALT, alkaline phosphatase, albumin and total protein.
5. Radiographic assessments will be selected by the attending physician as clinically indicated and in accordance with the criteria for tumor measurement assessments. Confirmatory scans should be obtained ≤ 4 weeks following initial documentation of response. Response will be evaluated every 3 cycles.
6. See Section 11 for sample collection and analysis methods.
7. Obtain archived tumor tissue (from time of original diagnosis) for immunohistochemical analysis; can be obtained at anytime after enrollment. Send to Cancer Institute of New Jersey (see Section 11).
8. If biopsy is done, it should be performed prior to receiving study therapy and prior to start of Cycle 2. Send to [redacted] (see Section 11).

9. Follow every 3 months to determine status. A telephone call can be made for survival follow-up.
10. ≤ 14 days prior to treatment
11. ≤ 7 days prior to re-treatment
12. As clinically indicated.

6.1 Efficacy Assessments

The primary efficacy endpoint is the clinical benefit rate of letrozole and sorafenib in this patient population. Clinical benefit rate (CR + PR + SD ≥ 6 months) will be determined for each patient using definitions in RECIST to evaluate response. [redacted] will require copies of radiological scans performed during the study for all patients, and preferably on CD. A review of all radiological scans will be performed to verify or question the qualitative nature of the apparent response. For subjects with skin lesions, photographs should also be sent for review as well. Films and/or CDs should be mailed to:

[redacted]

7. Treatment Plan

7.1 General Considerations

Treatment will be administered on an outpatient basis. Patients will be instructed to start study drugs on Day 1 of each 28-day treatment period. One cycle is defined as 28 days of treatment. Prior to starting a cycle, all patients must continue to meet all inclusion criteria (see Section 5.1). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Patients will receive treatment until it is no longer of benefit to them. Patients may discontinue therapy at any time for any reason.

7.2 Dose Determination

Doses of sorafenib will be determined by the phase of the study in which the patient is enrolled. Letrozole is given at a fixed dose of 2.5 mg daily for both the phase I and phase II portions of the study.

7.3 Treatment Administration

Treatment will require daily oral administration of medications on an outpatient basis.

Treatment may be delayed for up to two weeks for recovery from Grade 3 or 4 adverse events. If patients do not recover within two weeks, the patient will be removed from study.

7.3.1 Letrozole

Patients will take letrozole orally at a daily dose of 2.5 mg/day on Days 1 through 28.

Letrozole may be taken with or without food. Tablets should be swallowed whole with 8 ounces or 250 ml of water.

Patients will be provided with a Medication Diary for letrozole, instructed in its use, and asked to bring the diary with them to each appointment.

7.3.2 Sorafenib

Patients will also take sorafenib orally at a daily dose to be determined based upon the phase of the study that patient is enrolled (See Section 7.4). Sorafenib will be taken on Days 1 through 28.

Sorafenib should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal. Tablets should be swallowed whole, not crushed or chewed, with 8 ounces or 250 ml of water. Sorafenib should not be taken with grapefruit juice.

Patients will be provided with a Medication Diary for sorafenib, instructed in its use, and asked to bring the diary with them to each appointment.

7.3.3 Missed Doses

If patients vomit after taking letrozole or sorafenib, patients should be instructed not to retake the dose. Patients should take the next scheduled dose of letrozole or sorafenib therapy.

If a scheduled dose is missed, patients should be instructed to take the dose as soon as remembered. If it is near the time of their next dose they should be instructed to skip the dose and resume their usual dosing schedule. Patients should not double their dose to catch up missed doses.

7.4 Phase I Dose Modifications or Escalations

7.4.1 Phase I Component

For the Phase I dose escalation portion of the trial, patients will be enrolled in two cohorts (Level 0 and 1) with the following dose escalation rules:

Dose Level 0

The first three patients will start at Level 0:

- If 0 patients experience dose-limiting toxicity (DLT) during cycle 1, the dose will be escalated to Level 1.
- If 1 of the first 3 patients experience DLT in cycle 1, we will expand the cohort and 3 more patients will be treated at Level 0 for a total of 6 patients.

- If 1 of these 6 patients experiences DLT in cycle 1, the dose will be escalated to Level 1.
- If 2 or more of the patients in this cohort experience DLT in cycle 1, we will have exceeded the maximum tolerated dose (MTD) and will de-escalate to Level –1 and enroll 3 patients. If no patients experience DLT during cycle 1, this will be the recommended phase II dose.

Dose Level 1

The second cohort of three patients will be started according to the rules above and enrolled as follows:

- If 0 patients experience DLT at Level 1 in cycle 1, this will be our recommended phase II dose.
- If 1 of the first 3 patients experience DLT in cycle 1, we will expand the cohort and 3 more patients will be treated at Level 1 for a total of 6 patients.
- If 1 of these 6 patients experiences DLT in cycle 1, this will be our recommended phase II dose.
- If 2 or more of the patients in this cohort experience DLT in cycle 1, we will have exceeded the MTD and Level 0 will be the recommended phase II dose.

Each of the two dose levels of sorafenib will be given with letrozole at 2.5 mg orally daily as outlined in the dose escalation schedule listed in the following table:

Does Escalation Schedule	
Dose Level	**Dose of Sorafenib**
Level 1	400 mg po twice a day
Level 0	400 mg po daily
Level -1	400 mg po every other day

Intrapatient dose escalation will be allowed for patients enrolled at Level 0 and if they do not experience DLT during Cycle 1, they can escalate to Level 1 for Cycle 2.

DLT will be evaluated in the first cycle of therapy and defined as: Grade 3 or 4 non-hematologic toxicity (except alopecia, nausea, emesis that resolves to ≤ Grade 1 with symptomatic treatment) or Grade 4 hematologic toxicity that is thought to be related to sorafenib.

7.5 Phase II Toxicity and Dose Modifications

7.5.1 Phase II:

Patients will take letrozole 2.5 mg orally daily along with sorafenib at the maximum tolerated dose to be determined from the Phase I results.

7.5.2 Sorafenib Dose Modifications

Sorafenib specific modifications are outlined in the following tables:

Table 7.5.2.1 Dose Modifications for Sorafenib for Hand-Foot Skin Reaction

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patients normal activity	Any occurrence	Institute supportive measures immediately and continue sorafenib treatment
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Institute supportive measures and consider a decrease of sorafenib by 1 dose level. • If toxicity returns to grade 0–1 after dose reduction, increase sorafenib to full dose (per original dosing schedule) after 28 days • If toxicity does not return to grade 0-1 despite dose reduction, interrupt sorafenib treatment for a minimum of 7 days, until toxicity has resolved to grade 0–1 When resuming treatment after dose interruption, resume sorafenib at the next lower dose level for 28 days • If toxicity is maintained at grade 0–1 at reduced dose, increase sorafenib to full dose (per original dosing schedule) after 28 days
	2nd or 3rd occurrence	As for first occurrence, but upon resuming sorafenib treatment, decrease dose to the next lower dose level indefinitely
	4th occurrence	Decision whether to discontinue sorafenib treatment should be made based on clinical judgement and patient preference
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st occurrence	Institute supportive measures and interrupt sorafenib treatment for a minimum of 7 days and until toxicity has resolved to grade 0–1 • When resuming treatment after dose interruption, resume sorafenib at the next lower dose level for 28 days • If toxicity is maintained at grade 0–1 at reduced dose, increase sorafenib to full dose (per original dosing schedule) after 28 days
	2nd occurrence	As for first occurrence, but upon resuming sorafenib treatment, decrease dose to the next lower dose level indefinitely
	3rd occurrence	Decision whether to discontinue sorafenib treatment should be made based on clinical judgement and patient preference

*Patients who develop grade 3 fever/chills, grade 3 elevation of hepatic transaminases with ALT and AST < 10X ULN, grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, grade 3 leukopenia, or grade 3/grade 4 lymphopenia may continue study treatment without interruption at the discretion of the investigator.

Table 7.5.2.2 Dose Modification for Sorafenib Associated Non- HematologicToxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤ 1, then resume treatment at the same dose level. If patient experiences a second grade 3 toxicity, withhold dose until toxicity is grade ≤ 1, then reduce dose the next lower dose level and resume treatment. If toxicity does not resolve within 2 weeks patient will discontinue treatment.	Withhold dose until toxicity is grade ≤ 1, then reduce dose to the next lower dose level and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor. If toxicity does not resolve within 2 weeks patient will discontinue treatment. If a second toxicity occurs the patient will discontinue treatment.

Table 7.5.2.3 Dose Modification for Sorafenib Associated HematologicToxicity

Day 1 of Any Cycle	ANC < 1200/μL and/or platelets < 100,000 /μL	Hold Treatment
* CBCs should be repeated weekly until recovery	If count recovers within 1 week	Resume treatment at full dose
	If count recovers within 2 weeks	Reduce 1 dose level for all subsequent cycles
	If count does not recover within 2 weeks	Discontinue protocol treatment
Anytime during treatment	Febrile episode (> 38.5°C) accompanied by ANC count < 1200/μL	Reduce 1 dose level for all subsequent cycles.
	A subsequent febrile neutropenic event	Discontinuation of protocol therapy

Table 7.5.2.3.A Dose Modification for Sorafenib Associated HematologicToxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicities not listed above	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤ 2, then resume treatment at the same dose level. If patient experiences a second grade 3 toxicity, withhold dose until toxicity is grade ≤ 2, then reduce dose to the next lower dose level and resume treatment.	Withhold dose until toxicity is grade ≤ 2, then reduce dose to the next lower dose level and resume treatment, or discontinue at the discretion of the principal investigator.

Table 7.5.2.4 Management of Treatment Emergent Hypertension

Grade	Management/Next Dose
Grade 1	Consider increased BP monitoring
Grade 2 asymptomatic and diastolic BP < 110 mm Hg	Begin anti-hypertensive therapy and continue agent.
Grade 2 symptomatic and/or persistant OR Diastolic BP ≥ 110 mm Hg OR Grade 3	Agent should be held until symptoms resolve and diastolic BP ≤ 100 mm Hg; also treat patient with anti-hypertensives and when agent is restarted reduce by 1 dose level. If diastolic BP is not controlled (≤ 100 mm Hg) on therapy reduce another dose level.
Grade 4	Discontinue therapy.

7.6 Concomitant Medications

A preexisting condition is one that is present at the start of the study. Any medications (including but not limited to prescription medicines, over-the-counter medications, and herbal supplements) required for a patient's pre-existing condition must be approved by study personnel. Any medication proven to have side effects with either letrozole or sorafenib will not be approved while the patient is participating in the study.

7.7 Supportive Care Guidelines

No other chemotherapy, hormonal therapy (other than letrozole), radiation therapy or experimental medications will be permitted while patients are participating on this study.

Symptomatic anemia should be treated with appropriate red blood cell support and transfusion is recommended if the hemoglobin falls below 8 g/dl. Alternately recombinant erythropoietin may be used if desired by the patient's physician.

Thrombocytopenia should be treated conservatively. In the absence of bleeding or a planned invasive procedure, platelet transfusions should only be given for a platelet count below 10,000 cells/mm^3. If invasive procedures are planned or the patient develops bleeding, platelet transfusions should be administered in accordance with standard of practice, usually maintaining a platelet count greater than 50,000 cells/mm^3.

Nutritional assessment and psychological support: Refractory neoplasms are commonly complicated by malnutrition. Patients with weight loss or evidence of wasting syndrome should have a nutritional consult. Patients who are having emotional difficulties dealing with their treatment, and disease, or those patients who request assistance, will be referred to a Social Worker for evaluation and support.

Hand-foot skin reaction (palmar-plantar erythrodysaesthesia) and rash represent the most common adverse drug reactions with sorafenib. Rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib (see Section 7.5.3). Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 3 of 451 sorafinib patients.

An increased incidence of hypertension was observed in sorafenib-treated patients. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was amenable to management with standard antihypertensive therapy. Blood pressure should be monitored monitored weekly for the first 6 weeks of therapy and then on a regular basis and treated, if required, in accordance with standard medical practice. In cases of severe or persistent hypertension, or hypertensive crisis despite adequate antihypertensive therapy, permanent discontinuation of sorafenib should be considered. Permanent discontinuation of therapy due to hypertension occurred in 1 of 451 sorafinib patients.

An increase in the risk of bleeding may occur following sorafenib administration. The incidence of severe bleeding events is uncommon. If any bleeding event necessitates medical intervention, it is recommended that permanent discontinuation of sorafenib be considered.

Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia and/or infarction.

Sorafenib therapy should be discontinued in patients with gastointestinal perforation.

7.8 Adherence/Compliance

Patient compliance in daily self-administration of the oral tablets will be assessed at each clinic visit. Patients will be given a medication diary and instructed to fill out how many tablets (letrozole and sorafenib) were taken each day and the time of day the drug was taken. At the end of each cycle of treatment, the actual amount of unused drug will be compared to the anticipated amount of unused drug and the patient's medication diary.

8. Toxicity Monitoring and Adverse Event Reporting

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to each cycle the treating physician will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record.

Adverse events will be recorded on electronic case report forms in accordance with a study-specific data capture plan.

8.1 Definitions and Reporting Requirements of Adverse Events/Reactions

8.1.1 Definition of Related

There is a reasonable possibility that the drug caused the adverse experience. That is, the event is judged by the investigator to be possibly, probably or definitely related to the treatment.

8.1.2 Definition of Unexpected

Any adverse drug experience and/or specificity, that is not included in the current investigator's brochure and/or package insert.

8.1.3 Definition of Adverse Events (AE)

An adverse event is any event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

8.1.4 Definition of Serious Adverse Event (SAE)

A serious adverse event includes any event that:

Results in death.

Is life-threatening.

NOTE: The term 'life-threatening' refers to an event during which the subject was at risk of death. It does not refer to an event which hypothetically might have caused death if it had been more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization means that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment planned prior to study enrollment is neither an SAE nor an AE.

Results in persistent or significant disability or incapacity.

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated

headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly or birth defect.

Is an important medical event.

An event may be considered an important medical event when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.5. Definition of Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means in view of the investigator and/or company that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility and that the adverse event is associated with the use of the drug.

8.1.6. Definition of Serious Adverse Drug Reaction (SADR)

A Serious Adverse Drug Reaction is an event that meets any of the criteria for seriousness as previously defined and has a possible causal relationship to the study drug.

8.1.7 Requirements for Reporting of Serious Adverse Events:

All SAEs occurring after a [redacted] product has been utilized must be reported to [redacted] within 24 hours of the Principal Investigator's awareness and must include the following minimum information:

1. The name and contact information of the reporter
2. The name of the study drug(s)
3. A description of the reported SAE
4. A patient identified by one or more of the following:
    a. Name or initials
    b. Patient number
    c. Knowledge that a patient who experienced the adverse event exists
    d. Age
    e. Sex

5. An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug.

Additional data which would aid the review and causality assessment of the case include but are not limited to:

The date of onset

The severity

The time from administration of study drug(s) to start of the event

The duration and outcome of the event

Any possible etiology for the event

The final diagnosis or syndrome, if known

Action(s) taken, if any

For blinded studies, the Principal Investigator will provide the treatment assignment upon request for patients who experience SAEs. The Principal Investigator will provide the final treatment assignment immediately after the end of the study.

8.1.8 Expedited Reporting of Other Safety Information to B[redacted]

All participating institutions will report all SAEs to the OHRS at the [redacted] The OHRS will be responsible for forwarding SAE reports to all appropriate groups as needed as described in Section 8.1.9.

The OHRS will be responsible for forwarding SAE reports tot he study supporter, [redacted]

The Investigator/ Sponsor shall report to Bayer within 24 hours of the investigator's awareness of other events such as:

An adverse event related to study specific procedures

Any new and important event related to treatment with the study drug(s).

Any pregnancy during which a female patient was exposed to the study drug(s)

Any pregnancy in the partner of a male patient, where the male patient was exposed to study drug at the time of conception or conception occurred within two weeks of the last dose of study drug(s).

When follow-up information becomes available for a previously submitted safety report, the report form should be updated with the new information and sent to Bayer.

The Investigator/Sponsor may report SAEs using either:

An ADEERS form (Adverse Event Expedited Reporting System) available at http://ctep.cancer.gov/reporting/adeers.html OR

A MedWatch form available at http://www.fda.gov/medwatch/

[redacted]

The Principal Investigator commits to respond promptly to any query from [redacted] regarding SAE reports.

8.1.9 Reporting Unexpected and/or Serious Adverse Events to the [redacted]

All "unexpected"(defined below) and/or "serious" (defined below) adverse events occurring during the active portion of therapy, or up to 30 days after the last dose of [redacted]

8.1.10 Reporting Unexpected and/or Serious Adverse Events to Institutional Review Board

Events will be promptly reported, in writing, to the local IRB in accordance with IRB policy. If a death occurs the IRB will be notified within 24-hours of initial receipt of information. All unexpected and/or serious adverse events must be reported to the [redacted] Sciences Institutional Review Board within five (5) days of discovery of the adverse event. Written follow-up reports are required when additional information is needed to fully characterize the event.

[redacted]

8.1.11 Reporting Serious Adverse Events to the Food and Drug Administration

8.1.11.1 Sorafenib

The PI is responsible for notifying the FDA of any adverse experience associated with the use of sorafenib that is both serious and unexpected *(i.e., not listed in the lapatinib investigators brochure*), as soon as possible and in no event later than 15 calendar days after the PI's discovery of the event. Each written notification may be submitted on FDA Form MedWatch 3500A http://www.fda.gov/medwatch/safety/3500a.pdf (fax # 1-800-FDA-0178).

The PI shall also notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experiences associated with the use of the drug, as soon as possible but no later than 7 calendar days from the PI's discovery of the event information.

8.1.11.2 Letrozole

The PI is responsible for notifying the FDA of any unexpected (*not listed in the package insert*) serious adverse events that are **associated** (definitely, probably or possibly related) with the use of letrozole, must be reported to the FDA within 10 business days using a FDA Form MedWatch 3500 form http://www.fda.gov/medwatch/safety/3500.pdf (fax # 1-800-FDA-0178).

9. Treatment Evaluation/Criteria for Response

For the purposes of this study, patients should be reevaluated for response following every third cycle of therapy. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.[42] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

9.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.2 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial

effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

9.3 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response. There may be occasions when progressive disease is suspected but cannot be fully characterized. In these cases the treating physician may decide to continue treatment for one or two cycles before reassessment, if he/she feels it is in the patient's best interest and the patient agrees to continue treatment.

9.4 Non-Target Lesions

All other lesions (or sites of disease) will be identified as non-target lesions and will be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

9.5 Guidelines for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique will be used whenever possible to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

9.5.1 Clinical lesions- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion.

9.5.2 Chest x-ray- Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

9.5.3 Conventional CT and MRI- These techniques will be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT will be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

9.5.4 Ultrasound (US)- Because one of the endpoints of the study is objective response evaluation, US will not be used to measure tumor lesions. US might be used, at the discretion of the investigator, to confirm the complete disappearance of superficial lesions assessed by clinical examination.

9.5.6 Tumor markers- Tumor markers alone will not be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.5.7 Cytology, histology- These techniques may be used to differentiate between partial responses (PR) and complete responses (CR) if necessary and determined by the investigator. Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

9.6 Response Criteria

9.6.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

9.6.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and *normalization of tumor marker level.
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.
Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the investigator will prevail.	
*Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.	

9.6.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Notes:
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort will be made to document the objective progression.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, the residual lesion will be investigated (fine needle aspirate/biopsy if possible) before confirming the complete response status.

9.7 Confirmatory Measurement/Duration of Response

9.7.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that will be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 8 weeks.

9.7.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

9.7.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10. Removal of Patients from Study/Off Study Criteria

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

a) Disease progression/relapse during active treatment,
b) Intercurrent illness that prevents further administration of treatment,
c) Unacceptable adverse event(s).
d) In the event of any drug-related life-threatening toxicity or laboratory abnormality the patient will be withdrawn from further treatment,
e) Patient decides to withdraw from the study,
f) Noncompliance with treatment plan,
g) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
h) Protocol violation - any patient found to have entered this study in violation of the protocol might be discontinued from the study at the discretion of the Principal Investigator.

11. Laboratory Evaluations and Procedures/Correlative Studies

11.1 Tissue biopsies

11.1.1 In patients with disease that can be safely biopsied, an attempt will be made to obtain tissue before the start of treatment and prior to the start of Cycle 2. At time of biopsy, an attempt will be made to remove the equivalent of two cores or two punch biopsies. The first biopsy is to be formalin-fixed and paraffin-embedded. The second sample and other additional cores if obtained are to be flash-frozen using liquid nitrogen and then stored at –70°C to –80°C for future studies (see Study Operations Manual).

11.1.2 For patients who are registered at affiliate sites, patients will be given the option of traveling to The Cancer Institute of New Jersey to have a tumor biopsy performed and/or correlative blood studies drawn. Patients may opt not to have

these studies done yet remain on the study. These tests can only be performed at the [redacted]. As stated, patients may choose to come to the [redacted] and have these tests performed at no cost to them.

11.1.3 Biopsies will be obtained only if they can be performed under local anesthesia. General anesthesia will not be used to obtain biopsies that are to be used only for research purposes. These biopsies may be obtained with the assistance of either a surgical consultant or a member of the interventional radiology staff.

11.1.4 Biopsies performed for research purposes will only be obtained after the procedure has been explained to the patient and informed consent has been secured per institution policy. Patients will have the opportunity to consent or refuse the use of their tumor samples for additional unplanned studies.

11.2 Immunohistochemistry Analysis

11.2.1 Tumor tissue samples (from time of original diagnosis or if not available, metastatic diagnosis, or if collected on study) will be collected for each patient on-study to evaluate the expression of MAPK, phosphorylated MAPK, VEGFR-2, phosphorylated VEGFR-2, and Ki67 by immunohistochemistry.

11.2.2 Paraffin blocks containing embedded tissue samples are preferred; however if a paraffin block is not available 10 unstained slides should be submitted to Dr. Tan C/O Julie Friedman at the [redacted] Biospecimen Repository Service (BRS).

11.3 Circulating Tumor Cells

In several studies it has been shown that circulating tumor cells (CTCs) can be found in the peripheral blood of patients with a variety of metastatic carcinomas. The presence of CTCs has been associated with poor prognosis in patients with metastatic breast cancer,[46] and similar conclusions are likely true for other types of carcinomas. Recent studies have also identified both the prognostic and predictive utility for determining the number of CTCs in patients with metastatic breast cancer.[43,44] In addition to quantitating CTCs, these cells may provide an opportunity to characterize molecular changes in the tumor, thereby helping to guide targeted therapy. In this study, analysis of changes in the number of CTCs, pre-treatment and after 2 cycles of treatment, will be performed and compared to radiological studies obtained at similar time points. Details regarding collection, handling, storage, and shipping of blood samples will be provided in the Study Operations Manual.

11.4 Imaging Studies

The potential role of dynamic contrast-enhanced computed tomography, or perfusion CT (pCT) in monitoring treatment with anticancer agents that affect tumor angiogenesis is evolving. pCT is a non-invasive functional imaging technique capable of assessing tumor microvasculature clinically.[45] The pCT technique is based on the continuous acquisition of 3D CT images during the distribution of an intravenously administered iodinated contrast

agent bolus. The contrast agent is FDA-approved and is used in routine clinical practice. The total contrast administered to each patient is within the FDA-approved limits. Perfusion CT does not involve the use of an investigational device.

In this study, pCT will be performed before treatment and after two cycles of treatment in patients who are undergoing their radiographic assessments at [redacted] University Hospital. A metastatic site will be selected to assess the rate of blood flow to the tumor. All pCT examinations will be performed on the dual-source Siemens Somatom Definition CT. pCT will be performed 5 minutes following the acquisition of the standard-of-care contrast-enhanced CT. The pCT will be acquired following an additional injection of 40 ml of iodinated contrast at a rate of 4 ml/sec. The dynamic acquisition will take place at 6 time points at 3 second intervals following the contrast injection. Each image acquisition will consist of 6 slices of 5-mm thickness. Images will be transferred to a scientific workstation for analysis using the DICOM protocol. Blood flow to the lesion will be measured using the maximum-slope model. Measurement of the blood flow will include manual segmentation to exclude large blood vessels from the region of interest.

Due to resource constraints, perfusion CT (pCT) testing will not be performed on any patient in the study. As of 01/23/2013 perfusion CT (pCT) testing has been removed from the study evaluations table (see Section 6).

11.5 Optional and Future Studies (only for Cancer Institute of New Jersey patients)

11.5.1 All study participants at the [redacted] will be invited to provide a blood sample for retrospective genotyping. Participation in pharmacogenetic studies will be optional for all patients entering the study. A patient's acceptance of pharmacogenetic analyses will not be a requirement of their participation in the main study. See Study Operations Manual for details of sample labeling, collection, transport, and storage.

11.5.2 All study participants at the [redacted] will be invited to provide a blood sample for future unplanned studies before treatment and after two cycles of treatment. Participation will be optional for all patients entering the study. A patient's acceptance of unplanned future analyses will not be a requirement of their participation in the main study. Patients will have the opportunity to consent or refuse the use of these samples for additional unplanned studies. See Study Operations Manual for details of sample labeling, collection, transport, and storage.

11.4 Shipping Instructions

All samples are to be identified with the patient's assigned registration number and shipped with reference to Breast study [redacted]. Slides and Tissue blocks are to be sent by overnight express to the [redacted] (BRS).

Paraffin Blocks
Please wrap paraffin blocks in bubble wrap or some material that will cushion them. During spring and summer months paraffin blocks must be shipped with a cooler pack inside the shipping container or the wax will melt and the specimen will be compromised.

Glass Slides
Glass slides must be mailed/shipped in appropriate protective slide containers. These can be made of cardboard (flat slide holder) or plastic (slide box or slide shipper).

Documentation
Please have the name, address and the appropriate laboratory or office phone number of the institution that the patient specimens were shipped from. For any questions relating to shipment of samples please call [redacted]

[redacted]

12. Pharmaceutical Information

12.1 Sorafenib [redacted]

Name: Sorafenib. Sorafenib tosylate [redacted] is the tosylate salt of sorafenib [redacted]). Its chemical name is [redacted]{4-[3-(4-chloro-3-trifluoromethyl-phenyl) ureido]-phenoxy}-pyridine-2 carboxylic acid methylamide-4-methylbenzensulfonate and its molecular formula is $C_{12}H_{16}ClF_3N_4O_3XC_7H_8O_3S$. Molecular weight of sorafenib (free base) is 465 Daltons and sorafenib tosylate is 637 Daltons.

How Supplied: BAY 43-9006 sorafenib 200 mg is supplied as round, biconvex, red-film-coated tablets, debossed with the 'Bayer cross' on one side and '200' on the other side. The tablets contain BAY 43-9006 tosylate equivalent to 200 mg of the free base BAY 43-9006, and the excipients croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, and magnesium stearate. The film-coat consists of hypromellose, polyethylene glycol, titanium dioxide and red iron oxide. The film coating has no effect on the rate of release of the active BAY 43-9006 tosylate.[46]

Sorafenib will not be provided and is commercially available. Patients will be given assistance on how to obtain sorafenib. Patients may have to pay for it or be responsible for any co-pays associated with obtaining drug supply.

Storage requirements/ Stability: Tablets are stable at room temperature. Do not store above 25°C (77°F). Store in the original package.. The current shelf life is 36 months.

Route of administration: The dose of sorafenib to be taken by patients will be determined from the phase I component of the trial. Sorafenib is available in immediate-release preparations and thus the active ingredient is completely dissolved in a short period of time after oral administration of film-coated tablets. Sorafenib should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal. Tablets should be swallowed whole, not crushed or chewed, with 8 ounces or 250 ml of water. It should not be taken with grapefruit juice.[46]

Expected toxicities: Adverse Drug Reactions in patients in multiple clinical trials (MedDRA coded)

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%
Infections and infestations			Folliculitis infection
Blood and lymphatic system disorders	Lymphopenia	Leucopenia Neutropenia Anemia Thrombocytopenia	
Immune system disorders			Hypersensitivity reactions (including skin reactions and urticaria)
Endocrine disorders			Hypothyroidism
Metabolism and nutrition disorders	Hypophosphatemia	Anorexia	Hyponatremia Dehydration
Psychiatric disorders		Depression	
Nervous system disorders		Peripheral sensory neuropathy	Reversible posterior leukoencephalopathy*
Ear and labyrinth disorders		Tinnitus	
Cardiac disorders			Myocardial ischemia and infarction* Congestive heart failure*
Vascular disorders	Hemorrhage (including gastrointestinal* and respiratory tract* and cerebral hemorrhage*) Hypertension		Hypertensive crisis*
Respiratory, thoracic and mediastinal disorders		Hoarseness	Rhinorrhea
Gastrointestinal disorders	Diarrhea Nausea	Constipation Stomatis (including dry	Gastro esophageal reflux disease

System Organ Class	Very Common ≥ 10%	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%
	Vomiting	mouth and glossodynea) Dyspepsia Dysphagia	Pancreatitis Gastritis Gastrointestinal perforation*
Hepato-biliary disorders			Increase in bilirubin and jaundice
Skin and subcutaneous tissue disorders	Rash Alopecia Hand-foot reaction** Pruritis Erythema	Dry skin Dermatitis exfoliative Acne Skin desquamation	Eczema Erythema multiforme minor
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia	
Reproductive system and breast disorders		Erectile dysfunction	Gynaecomastia
General disorders and administration site conditions	Fatigue Pain (inc. mouth, abdominal, bone pain, headache and tumor pain)	Asthenia Fever Influenza-like illness	
Investigations	Increased amylase Increased lipase	Weight decreased Transient increase in transaminases	Transient increase in blood alkaline phosphatase INR abnormal, prothrombin level abnormal

* Events may have a life-threatening or fatal outcome. Such events are uncommon.
** Palmar plantar erythrodysaethesia syndrome in MedDRA

In combination with cytotoxic agents, myelosuppression leading to febrile neutropenia has also been observed. Such events may have a life-threatening or fatal outcome.

Drug Interactions: Based on numerous Phase I oxidative and Phase II glucuronidation metabolic pathway in vitro trials, the potential of sorafenib to interact with other drugs is low. The sorafenib tosylate is metabolized by the CYP P450 enzymatic pathway (specifically CYP3A) and therefore may interact with other drugs that utilize this pathway. Close monitoring is suggested in patients taking medications such as warfarin, carbamazepine, phenytoin, quinidine, phenobarbital, and digoxin, which are metabolized by the liver and have small therapeutic ranges. Sorafenib has been seen to increase levels of doxorubicin, docetaxel, and irinotecan, but the clinical importance of these elevations is unclear and currently being studied.[49]

12.2 Letrozole [redacted]

How supplied: Letrozole will be supplied to patients at no cost by [redacted] It will be supplied as 2.5 mg tablets and one bottle will contain 30 tablets. Letrozole is available as a 2.5 mg dark yellow film-coated tablet. It is a synthetic achiral benzhydroltriazole derivative of the chemical name 4,4'[(1H-1,2,4-triazol-1-yl)methylene]bisbenzonitrile (MW 285.31). The compound formula $C_{17}H_{11}N_5$ is odorless, white to yellowish crystalline material, freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water.

Storage and stability: Very stable at room temperature; shelf life is 2 years.

Route of administration: Patients will take one 2.5 mg tablet by mouth once a day. Letrozole is rapidly absorbed and completely bioavailable after oral administration of film-coated tablets.

Toxicities: The most frequently reported adverse events were headache, nausea, vomiting, peripheral edema, hot flashes, fatigue, hair thinning, bone pain, back pain, arthralgia, and dyspnea.

Drug interactions: Based on two pharmacokinetic drug interaction studies (warfarin, cimetidine), review of data from large Phase III trials, and the in vitro results on cytochrome P450 enzymes, the potential of letrozole to interact with other drugs is low. No dose adjustments are recommended nor required for patients with renal or liver impairment.

12.3 Drug Accountability

The investigator is required to maintain adequate records of receipt, dispensing and final disposition of study drug. This responsibility has been delegated to the pharmacy. Include on receipt record (e.g. packing slip) from and to whom study drug was shipped, date, quantity, and batch or lot number. On dispensing record, note quantities and dates study drug was dispensed to and returned by each subject.

12.4 Drug Destruction/Disposal

Empty and partially empty containers of study drug will be disposed of in accordance with institutional policies and procedures. Unused containers of study drug will be returned to the study sponsor following completion of the study.

13. Data Collection and Records to be Kept

13.1 Electronic Case Report Forms

The PIat each institution will be responsible for assuring that all data specified in the study-specific data capture plan is collected and entered onto the electronic case report forms (eCRFs).

Data submission guidelines are in concordance with those expected by the National Cancer Institute, i.e.: Baseline data is to be entered onto eCRFs within 2 weeks of initiation of treatment. Subsequent eCRFs are to be completed within 2 weeks of the date in which the previous cycle was completed. All e-CRFs will be submitted to the OHRS at the [redacted] via its secure web-based data management system. The e-CRFs are found in the study specific calendar that has been created in the data management system. The system will prompt the user to the forms that are required based upon the patient's enrollment and treatment dates.

Periodically, monitoring and/or auditing visits will be conducted by the [redacted] monitoring/auditing staff for the purpose of verifying data entered onto eCRFs with source documentation. The participating institution will provide access to the patient's original records to permit verification data entry.

13.2 Research Charts

A research chart (i.e., shadow chart) is maintained at OHRS for each patient enrolled. Copies of the most significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment and documents that verify Grade 3-4 adverse events and response. This information will be updated on a prospective basis and will be confidentially maintained at the OHRS.

13.3 Reports

Publications and annual reports for submission to the IRB and FDA will be written by the [redacted] PI using the data captured on the CRFs. Study progress reports will be provided to participating institutions for submission to local IRBs.

14. Data and Safety Monitoring

Monitoring of this study will occur in accordance with the [redacted] NCI approved Data and Safety Monitoring Plan (DSMP). An "initiation audit" will be conducted by OHRS Quality Assurance staff in accordance with the DSMP following enrollment of the first two (2) or three (3) patients. Subsequent audits will occur on an annual basis if the findings from the initiation audit were satisfactory. More frequent audits of patient data and study conduct will occur if necessary. All [redacted] centers will be monitored at least quarterly and audited annually. Prior audit findings and/or situations that may arise during the course of the study will determine the need for more frequent auditing. All audit findings will be reported to the PI, Human Research Oversight Committee (HROC) and to the [redacted] Institutional Review Board.

15. Multi-Institutional Guidelines

15.1 IRB Approvals

As the Coordinating Center for a trial, it is the coordinating center's responsibility to ensure that no patients are entered on the trial at a participating institution without full IRB approval. Thus, OHRS will approve the addition of each participating institution to the

study. A copy of the IRB approval document from each participating institution will be obtained prior to activation of the study at the participating institution.

15.2 Other Pre-Study Documents

Each participating center is required to have the following documents on file at the OHRS:

- Curricula Vitae of all physician Investigators
- Signed FDA form 1572 of all physician Investigators
- Rutgers Financial Disclosure of all physician Investigators if site is under the Rutgers IRB of record. If a site utilizes their local IRB, their approval covers this and would not applyDocumentation of Human Subjects Protection training from all Investigators
- Medical license from each Investigator

15.3 Initiation Site Visit/Meeting

A study initiation meeting will be conducted with each participating institution prior to enrollment of patients from the institution. OHRS staff will conduct the study initiation meeting in close proximity to IRB approval of the study at the participating center. In most situations the study initiation meeting will be conducted via teleconference.

15.4 IRB Continuing Approvals

Investigators from participating institutions must provide a copy of the institution's approved continuing review documentation. Registration will be halted at any participating institution in which a current continuing approval is not on file at OHRS. Centers who are approved to utilize the [redacted] Board will not be required to file continuing review documentation.

15.5 Amendments and Consents

The OHRS will maintain a copy of all amendments, consent forms and approvals from each participating institution. Consent forms will be reviewed and approved by OHRS to ensure consistency with the [redacted] Institutional Review Board approved consent. Should changes to the protocol become necessary, protocol amendments will be submitted in writing to the [redacted] PI and local IRB for approval prior to implementation; unless the patient's best interest is endangered. In that case, notification to [redacted] PI and local IRB will be made as soon as possible.

15.6 Patient Registration

All patients from participating institutions must register patients with the OHRS central registration desk, as described in Section 5.7 of this protocol.

15.7 Data Collection and Toxicity Reporting

The PI at each institution will be responsible for assuring that all the required data is collected and entered onto the eCRFs accurately and completed eCRFs submitted as described in Section 13.

15.8 Data Monitoring and Source Document Verification

Each site participating in the accrual of patients to this protocol will be audited for protocol and regulatory compliance, data verification and source documentation.

The [redacted] staff will conduct remote monitoring on a continual basis of participating institutions with monitoring visits occurring as necessary. The monitoring visits will focus on verifying data with source documents. Adherence to the protocol(s), including the prompt reporting of serious adverse events, will be assessed. Findings of all monitoring visits are recorded on a Monitors Report, which is kept in the OHRS regulatory file. Issues concerning study compliance are reviewed at regular meetings with the HROC.

15.9 Data and Center Audits

[redacted] staff will conduct annual audits to participating centers in accordance with OHRS Standard Operating Procedures (SOPs). The audit guidelines are in accordance with the [redacted] and Safety Monitoring Plan.

16. Statistical Considerations

16.1 Primary and Secondary Hypotheses

The study will require a short run-in phase I portion to determine the recommended phase II dose. The primary objective of the single arm single-stage phase II portion of the study is to determine the clinical benefit rate (proportion of patients who achieve a complete response, partial response, or stable disease $\geq$ 6 months) of letrozole and sorafenib as first-line therapy in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer. The secondary objectives are to determine the safety and tolerability of sorafenib in combination with letrozole and evaluate time to progression and overall survival.

16.2 Sample Size Justification

A historical study showed that single-agent letrozole in the first-line treatment of patients with hormone receptor-positive metastatic breast cancer had a clinical benefit rate of 50% compared to tamoxifen.[8] The combination therapy of letrozole and sorafenib will not be considered of further interest if the true clinical benefit rate is less than or equal to 50%. We assume that this study will target a clinical benefit rate of 67% for identifying the combination therapy as active and worthy of further investigation. With these settings, the null hypothesis is that the clinical benefit rate of the combination therapy is less than or equal to 50%, and the alternative hypothesis is that the clinical benefit rate of 67% or more is of considerable interest. For the phase II part of the study, the sample size was calculated according to a single-stage design.[47] The study will accrue a total of 58 patients, and the combination therapy will be accepted if there are at least 35 responders out of 58 patients. The design will have a 4.3% (< 5%) type-I error (false positive) rate and a power of 82.7% (> 80%) (i.e., 17.3% type-II error or false negative rate). The total number of evaluable patients to be accrued to this study is not expected to exceed 64 patients.

The patients accrued in the Phase I dose escalation will be included in the Phase II portion if they receive the same dose. Evaluable patients for the phase I portion are defined as study-eligible patients who have received at least one cycle of treatment. Evaluable patients for the phase II portion are those who have received at least two cycles of treatment.

16.3 Outcome Measures

Patients will be evaluated based on clinical benefit rate, as described in Sections 6 and Section 7. The rate of clinical benefit is defined as the proportion of patients who achieve a complete response, partial response, or stable disease $\geq$ 6 months. Time to progression will be calculated based on the time between the first day of treatment and the date of disease progression. Overall survival will be calculated based on the time between the first day of treatment and the date of death from any cause.

16.4 Analysis

Time to progression and overall survival will be summarized using the standard Kaplan-Meier method. The frequency of serious adverse events as outlined in Section 8 will be described by summary statistics. Biological end points obtained from biopsy specimens are likely to be assessed semi-quantitatively, and compared using nonparametric methods to determine correlations with tumor response and disease progression.

17. Human Subjects

17.1 Subject Population

Postmenopausal women with previously untreated hormone receptor-positive locally advanced or metastatic breast cancer may participate in this trial if they meet the eligibility criteria. The inclusion and exclusion criteria detailed in this protocol are designed to exclude patients solely for medical reasons. Study participants will be patients who are receiving care for their disease at the [redacted] or at [redacted] affiliated medical oncology practices and community hospitals. The Principal Investigator and OHRS research personnel will closely monitor the status of the study (and individual patient data) at all centers. Males will not be eligible for this study. Breast cancer in men is rare and the efficacy of aromatase inhibitors in males is limited.

17.2 Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. Reported side effects of letrozole include headache, nausea, vomiting, peripheral edema, hot flashes, fatigue, hair thinning, bone pain, back pain, arthralgia, and dyspnea. Most of these side effects that were observed in patients who received letrozole in clinical studies were not considered serious and were generally mild to moderate. Reported side effects of sorafenib include hand-foot syndrome, diarrhea, fatigue, hypertension, pain and rash and were noted to be mainly mild to moderate. Grade 3 and 4 reactions were noted to be uncommon and seen as elevations in serum amylase and lipase levels (with corresponding symptoms of pancreatitis) and hand-foot syndrome.[49]

This study may involve risks to patients that are currently unforeseeable. Patients enrolled in this trial will receive their treatment in an outpatient setting. In addition, monthly blood work will be taken to monitor side effects. Evaluations at each cycle to monitor the treatment of patients will be performed and recorded in the patient chart. For patients at the [redacted] or at the affiliated sites who do not customarily receive their care at the affiliated institution, a local oncologist should be identified to monitor for complications and to improve long term care. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

17.3 Consent Procedures

Informed consent must be obtained prior to commencing any research procedures. The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the patient or representative. The informed consent document may not include any exculpatory language through which the patient or representative is made to waive any of the patient's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks, discomforts, and potential benefits will be carefully explained to the patient. This process will include a general description of the disease process, as well as a description of the patient's expected clinical course. Alternative therapies will be fully described, and outlined in the consent document. The patient will be asked to read the consent at his/her convenience and will be encouraged to ask questions. Enrollment on this study will only occur if the patient meets all eligibility criteria, is judged by the Principal Investigator or participating investigator to potentially benefit from the therapy, is willing to provide consent, and has signed the consent document. Moreover, any experimental invasive procedure will require a separate consent form (standard procedure consent form).

17.4 Potential Benefits

It is likely that a significant proportion of patients who participate in this clinical trial will receive direct clinical benefit because they will be receiving a drug that is commonly used for their disease. This benefit may be reduction in the size of their tumor, stability in the size of their tumor, and/or improvement in symptoms related to their disease.

As a result of participating in this trial, patients will receive evaluation and treatment of their tumor at the [redacted] or at the enrolling [redacted] affiliated institution. The study drugs, sorafenib and letrozole, will be provided at no charge to enrolled patients. However, additional medical services will be billed to the patients and/or their insurance carriers in the customary way. The cost of correlative pharmacodynamic studies will not be billed to the patient or insurer.

17.5 Risk-Benefit Ratio

The potential benefit that may result from this study balances the potential risks to the patients. A multicenter Phase III trial indicates that letrozole is superior in efficacy to tamoxifen in the first-line treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer.[8] However, it is not clear whether the combination of letrozole and sorafenib is superior to letrozole alone, but the theoretical approach of targeting two pathways of tumor progression simultaneously is encouraging. This protocol may or may not be helpful to a specific patient, but the results may help the investigators learn about the administration and effectiveness of letrozole and sorafenib in breast cancer and may aid in the treatment of other patients. This research treatment is not curative, but may offer temporary control of the disease. Benefit cannot be promised nor can the chance of benefit be accurately predicted.

17.6 Gender and Minorities

The National Institute of Health and NCI have stressed the importance of gender and minority inclusion in clinical services and research. African Americans make up 11%, Hispanics 6%, and Asians 5% of the patients, respectively. The percentage of minority patients enrolled onto clinical research trials were 12% African-American, 6% Hispanic, and 6% Asian, respectively.

No person shall on the grounds of race, color or national origin, be excluded from participation in, be denied the benefits of, enrollment in this study. There is a restriction regarding the sex of the patient. Minorities are prevalent in the area.

18. Economic/Financial Considerations

Patients and/or their insurance carriers will be expected to pay for costs related to monitoring and follow-up. Patients will be expected to pay for any costs not paid by their insurance carrier. The cost of correlative studies will not be billed to the patient or insurer. Patients will not be expected to pay for the cost of letrozole and sorafenib.

19. Publication of Research Findings

The policies and procedures of that the results of this trial will be submitted for publication in a timely manner following the conclusion. PI, and all co-authors prior to submission or use, must review any abstract or manuscript.

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Appendix A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B

New York Heart Association Criteria

Class	
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, palpitation or anginal pain.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. With any physical activity, increased discomfort is experienced.

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 9th ed. Boston, Little, Brown and Co, 1994:253-6.