DF/HCC Protocol #: 17-318

TITLE: A Phase 2 Study of Neratinib with or without Fulvestrant in HER2-Positive, ER-Positive Metastatic Breast Cancer

Coordinating Center: Dana-Farber Cancer Institute

***Principal Investigator (PI):**

Jose Pablo Leone, MD

[redacted]

Statistician:

[redacted]

Project Manager:

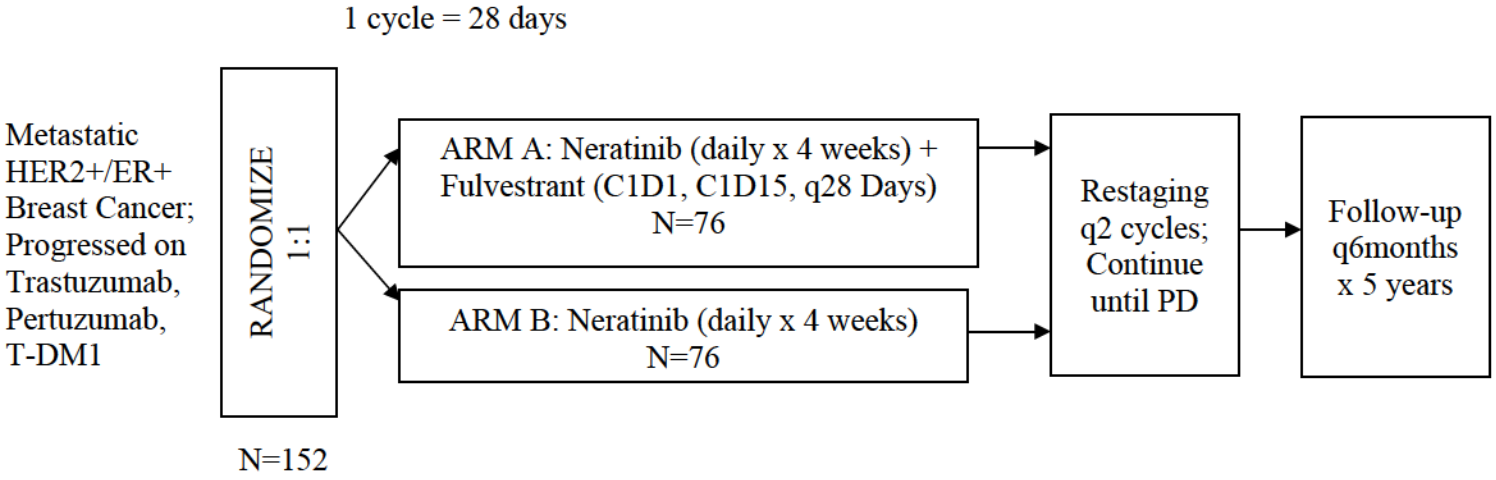
[redacted]

IND #: 135557

IND Sponsor: [redacted]

Protocol Type / Version # / Version Date: Amendment / Version 4 / 02/14/2022

SCHEMA



Stratification by:

- Prior lines of therapy (≤3, ≥4)
- Prior Use of Fulvestrant (Yes v No)

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is a randomized, two-arm phase II study of neratinib with or without fulvestrant in patients with metastatic, ER-positive/HER2-positive breast cancer. We hypothesize that crosstalk between HER2 and ER signaling pathways provides escape mechanisms for tumor growth, and therefore tumors that are both HER2-positive and ER-positive can be effectively treated with neratinib in combination with fulvestrant, and that the combination will be more effective than neratinib alone.

1.2 Primary Objective

To estimate the efficacy, as measured by progression free survival (PFS), of neratinib combined with fulvestrant compared with neratinib alone in patients with inoperable locally advanced or metastatic HER2-positive, ER-positive breast cancer.

1.3 Secondary Objectives

1.3.1 To estimate the efficacy, as measured by overall survival (OS) of neratinib combined with fulvestrant compared with neratinib alone in patients with inoperable locally advanced or metastatic HER2-positive, ER-positive breast cancer. (ENDPOINT: OS)

1.3.2 To estimate the clinical activity, as measured by overall response rate (ORR) of neratinib combined with fulvestrant compared with neratinib alone in patients with inoperable locally advanced or metastatic HER2-positive, ER-positive breast cancer. (ENDPOINT: ORR)

1.3.3 To estimate the clinical activity, as measured by duration of response, of neratinib combined with fulvestrant compared with neratinib alone in patients with inoperable locally advanced or metastatic HER2-positive, ER-positive breast cancer. (ENDPOINT: duration of response)

1.4 Correlative Objectives

1.4.1 To determine the proportion of patients with ESR1 gene mutations in baseline tumor tissue

1.4.2 To determine the proportion of patients with PIK3CA gene mutations and loss of PTEN expression in baseline tumor tissue

1.4.3 To determine the proportion of patients with PIK3CA gene mutations in circulating tumor DNA (ctDNA) from blood obtained at study baseline

1.4.4 To determine concordance of PIK3CA mutation status assessed in circulating free tumor DNA and distant metastasis specimens (i.e. liquid and solid biopsies)

1.4.5 To determine concordance of ESR1 mutation status assessed in circulating free tumor DNA and distant metastasis specimens (i.e. liquid and solid biopsies)

1.4.6 To perform molecular characterization of potential resistance mechanisms, predictive biomarkers, and immunological function by collecting blood and tumor specimens.

2. BACKGROUND

2.1 Metastatic HER2-Positive, ER-Positive Breast Cancer

Breast cancer is the most common malignancy in women in the United States. Every year, more than 230,000 women are diagnosed, and more than 40,000 women die of breast cancer.[1] Most of these deaths are due to metastatic breast cancer. Though existing treatments may effectively control disease for a period of time, nearly all tumors will acquire resistance to therapy, leading to tumor growth and eventually death. More effective treatments are needed. Approximately two-thirds of breast cancers express the estrogen receptor (ER), and hormone-directed treatment has been a mainstay of therapy for such cancers for decades. Human epidermal growth factor receptor-2 (HER2) overexpressing tumors account for 20-25% of breast cancers, and are associated with high grade tumors, higher rates of recurrence, and higher rates of brain metastases. Anti-HER2 therapies have transformed the trajectory of HER2-positive disease, improving patients' outcomes dramatically. Approximately 10% of all breast cancers co-express HER2 and ER2. Though these HER2+/ER+ tumors make up a significant portion of metastatic breast cancers, they have historically been studied together with HER2+/ER- disease, meaning that patients with HER2+/ER+ disease usually receive HER2-directed treatment in combination with chemotherapy. There is reason to believe, however, that because of crosstalk between HER2 and ER signaling pathways, blockade of both may be more effective.

2.2 Neratinib

Neratinib is a potent, oral, irreversible-binding inhibitor of the erbB family of receptor tyrosine kinases that inhibits signal transduction through erbB1 (EGFR), erbB2 (HER2), and erbB4. The irreversible binding of these receptors by neratinib results in sustained inhibition of growth pathways (autophosphorylation, signal transduction, and cell proliferation) and ultimately cell cycle arrest at the gap 1/DNA synthesis (G1/S) phase transition of the division cycle. This agent has demonstrated promising clinical activity in patients with HER2-positive breast cancers.[2]

In a phase II trial of neratinib for patients with HER2-positive, metastatic de-novo or pre-treated breast cancer, the ORR (defined as complete or partial responses) was 51% (95% Confidence Interval [CI] 16% to 39%) and 26% (95% CI 38% to 64%), respectively. At 16 weeks, 75% of first-line patients and 61% of previously treated patients were progression-free.[3] In a subsequent, randomized phase two study comparing neratinib monotherapy to lapatinib plus capecitabine in previously treated metastatic breast cancer, the ORR was 29% in the neratinib arm.[4] The major

toxicity of neratinib in all studies has been diarrhea, which is most common during the first cycle of treatment.

2.3 Fulvestrant

Fulvestrant is a selective estrogen receptor degrader (SERD), which binds to ER and leads to its degradation. It is FDA approved for patients who have disease progression on other anti-estrogen agents in the advanced breast cancer setting. In two phase III trials, fulvestrant 250 mg monthly was found to be as effective as anastrozole with respect to disease progression and overall survival.[7,8] In the CONFIRM trial, high-dose fulvestrant at 500 mg monthly was found to be more effective compared to the previous dosing of 250 mg monthly, which prompted the FDA's subsequent approval of fulvestrant 500 mg every 28 days, following a loading dose of 500 mg on days 1 and 15 during the first month of therapy for refractory metastatic breast cancer.[9]

Overall, fulvestrant demonstrated an overall response rate of approximately 10% in aromatase inhibitor resistant, fulvestrant naive ER+ HER2- breast cancers.[9] In a retrospective study of patients with HER2+/ER+ breast cancer, fulvestrant demonstrated an overall response rate of 9% and clinical benefit rate of 42% (43/101 patients), with anti-tumor activity observed in up to the fourth line of endocrine therapy and seventh line of overall therapy.[10]

2.4 Rationale

HER2 is a member of the HER/EGFR family of plasma membrane-bound receptor tyrosine kinases. HER2 dimerizes with itself or other members of the HER family, leading to its activation and subsequent downstream growth-promoting signaling via a number of pathways. Investigation of mechanisms of resistance to hormone-directed therapy in breast cancer has demonstrated significant crosstalk between the HER2 and ER pathways. In HER2-positive cell lines, addition of estrogen or tamoxifen induces activation of HER2 signaling.[11] In ER+ cell lines that develop resistance to tamoxifen, HER2 expression increases significantly.[12] And in HER2+ xenografts resistant to HER2-directed therapies, ER expression is upregulated.[13] These data suggest that ER-mediated signaling may provide an important mechanism of resistance to anti-HER2 therapy, and conversely, that HER2-signaling promotes endocrine therapy resistance. Dual blockade of HER2 and estrogen pathways could be an effective method of treating HER2+/ER+ disease.

Data from clinical studies supports what has been seen in the laboratory. Rimawi and colleagues evaluated the efficacy of neoadjuvant lapatinib, trastuzumab and hormonal therapy in a single-arm, phase II study of 66 women with stage II to III HER2+/ER+ breast cancer.[14] They found that this combination, targeting both the HER2 and ER pathways, was effective, resulting in a pathologic complete response (pCR) rate of 21%.[14] In 2015, Chan et al. presented 2 year follow up data from the ExteNET trial, a phase III, randomized, placebo-controlled trial of neratinib after completion of trastuzumab in the adjuvant setting in HER2+ breast cancer. In this study, early stage breast cancer patients with HER2+ disease who had completed adjuvant trastuzumab were randomized to receive either one year of neratinib or placebo. Of the 2841 patients enrolled in this study, 57% in each arm had HER2+/ER+ disease. Though the improvement in invasive disease-free survival (IDFS) was statistically significant in the overall study population, in a pre-

planned subset analysis, the strongest benefit was seen in the centrally confirmed HER2+, ER+ subgroup, In this group, patients receiving neratinib had an IDFS of 97.0% at 2 years, while IDFS in patients receiving placebo was 88.4%, corresponding to a hazard ratio of 0.25 (95% CI 0.12-0.48).[15] In contrast, the hazard ratio for patients with centrally confirmed HER2+, ER- cancers was 0.96 (0.53–1.74). Importantly, nearly all patients with HER2+/ER+ disease were also taking adjuvant hormonal therapy. One potential mechanistic explanation of these results is that targeting both the HER2 and ER pathways simultaneously may overcome resistance mediated by the cross-talk between the two pathways. If true, this approach may be an effective method for treating HER2+/ER+ breast cancer. We plan to investigate this further in this trial.

Rationale for Prior Fulvestrant (Amendment 2, Protocol Version 2 update)

The protocol was updated with Version 2 to allow for prior fulvestrant, a revision to the original eligibility criteria (3.2.3) for the study. Internal data from [redacted] in mouse models and additional pre-clinical data from Sudhan et al. in Clinical Cancer Research suggests that even in fulvestrant resistant HER2+ models, the addition of fulvestrant to neratinib provides benefit.[16] Allowing prior fulvestrant will increase the eligible patient population and study accrual and will not significantly impact the therapeutic signal in the experimental arm.

2.5 Correlative Studies Background

2.5.1 Circulating Tumor DNA (ctDNA)

For a number of reasons that include discomfort to the patient, logistics, and lack of clinical indication, serial tumor biopsies in individual patients in the metastatic setting are infrequently done. It has therefore been challenging to study the molecular evolution of tumors over time and through progression on serial treatment regimens. Both normal and malignant cells secrete cell-free DNA into plasma, generating an easily accessible repository of each cell's genetic signature. Emerging technology now permits whole exome sequencing from circulating tumor DNA (ctDNA) isolated from plasma. We aim to examine the utility of this approach for detecting molecular changes in individual patients' tumors over time by collecting and analyzing ctDNA.

2.5.2 Tissue Samples

We will collect new metastatic biopsies before treatment begins from all enrolled patients unless there is no safe, accessible site to biopsy. (Please see eligibility criteria). We will also collect primary, archived tumors and archived biopsies of metastases for additional correlative testing. These samples will be banked for future research using state-of-the-art technologies to correlate findings with clinical response.

3. PARTICIPANT SELECTION

Laboratory tests required for eligibility must be completed within 4 weeks prior to registration. Scans and x-rays must be done $\leq$4 weeks prior to registration. MUGA or echo must be done within 60 days prior to registration.

3.1 Eligibility Criteria

Participants are eligible to be included in the study only if they meet all of the following criteria:

3.1.1 Participants must have histologically or cytologically confirmed inoperable locally advanced or metastatic ER+ breast cancer. To fulfill the requirement for ER+ disease, a breast cancer must express, by immunohistochemistry (IHC), ER in ≥10% of cells, on the most recent biopsy. If ER quantification is not available, a determination of ER+ by IHC will suffice. Central confirmation of ER status is not required.

3.1.2 Participants must have documented HER2+ disease by overexpression and/or gene amplification on the most recent biopsy, per current ASCO-CAP (American Society of Clinical Oncology – College of American Pathologists) guidelines. Central confirmation of HER2 status is not required.

3.1.3 Participants must have received prior therapy with the following agents in any combination, and in setting (i.e., neoadjuvant, adjuvant, metastatic, etc.). These therapies do not need to be the most recent line of therapy.

- Trastuzumab
- Pertuzumab
- Ado-trastuzumab emtansine (T-DM1)

3.1.4 Participants must agree to undergo a research biopsy of a reasonably accessible metastatic lesion (chest wall, skin, subcutaneous tissue, lymph nodes, skin, breast, bones, lung, and liver metastases). If a reasonably accessible metastatic lesion is not available, the patient may go on study provided that archived tissue is available. However, if a reasonably accessible site is available for biopsy, the patient must agree to biopsy. Any patients not undergoing biopsy must be approved for study enrollment by the Overall Principal Investigator at DFCI. Biopsies may be done with local anesthesia or intravenous conscious sedation, according to institutional guidelines. If a biopsy requires general anesthesia, then it is only allowed if acquisition of tissue is clinically indicated, and excess tissue may be collected for research purposes. Patients without sites available for biopsy must have available tissue [archived formalin-fixed paraffin embedded blocks (FFPB), blocks from which slides can be created, or fresh frozen tissue from original diagnosis or metastatic setting] for correlative studies. Tissue needs to be located and available at the time of registration See Section 9.3 for more details.

3.1.5 Women ≥ 18 years of age. Men are not eligible.

3.1.6 Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see Appendix A).

3.1.7 Participants must have normal organ and marrow function as described below:

- Absolute neutrophil count ≥1,000/uL
- Platelets ≥75,000/uL
- Hemoglobin ≥8g/dL

- Total bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) ;in case of known Gilbert's syndrome, <2 x ULN is allowed
- AST(SGOT)/ALT(SGPT) ≤3X institutional ULN without liver metastases, or ≤5X institutional ULN with liver metastases
- Creatinine clearance ≥ 50 mL/min
- Left ventricular ejection fraction ≥50%, as determined by RVG (MUGA) or echocardiogram (ECHO) within 60 days prior to initiation of protocol therapy

3.1.8 Participants may have received any number of prior therapies as long as they have adequate performance status and meet all other eligibility criteria.

3.1.9 Women of childbearing potential (including premenopausal women and women less than 12 months after menopause) must have a negative β-human chorionic gonadotropin (hCG) urine pregnancy test within 4 weeks of registration.

3.1.10 The effects of neratinib and fulvestrant on the developing human fetus are unknown. For this reason and because SERD agents are known to be teratogenic, women of child-bearing potential must agree to be abstinent, or to use a highly effective double barrier method of contraception (e.g, a combination of male condom with an intravaginal device such as the cervical cap, diaphragm, or vaginal sponge with spermicide) or a non-hormonal method, while enrolled in the study, until at least 28 days after the last dose of neratinib or 1 year after the last dose of fulvestrant. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately. If a woman is of childbearing potential, she must agree to use adequate contraception prior to the study, for the duration of study participation, and for one year after completion of the study drug.

3.1.11 Ability to understand and willingness to sign a written informed consent document.

3.2 Exclusion Criteria

A patient will be excluded from this study if she meets any of the following criteria:

3.2.1 Participants who have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to neratinib or fulvestrant.

3.2.2 Participants who have known hypersensitivity to any component of loperamide or colestipol.

3.2.3 Participants who have received previous therapy with neratinib.

3.2.4 Participants who have received anti-cancer therapy (including chemotherapy, biological therapy, investigational agents, hormonal therapy, or other anti-cancer therapy) or radiotherapy within ≤14 days prior to the planned initiation of investigational products, or those who have not recovered to grade ≤1from adverse events due to their most recent therapy (excepting alopecia).

3.2.5 Participants who have had any major surgery ≤28 days prior to the planned initiation of study therapy, or those who have not recovered from adverse events due to agents/surgery administered more than 4 weeks earlier.

3.2.6 Participants who are receiving any other investigational agents.

3.2.7 Known brain metastases that are untreated, symptomatic, or require therapy to control symptoms. Participants with a history of treated central nervous system (CNS) metastases are eligible. Treated brain metastases are defined as those without ongoing requirement for corticosteroids, as ascertained by clinical examination and/or brain imaging (magnetic resonance imaging or CT scan) completed during screening. Any corticosteroid use for brain metastases must have been discontinued without the subsequent appearance of symptoms for ≥ 7 days prior to registration. Treatment for brain metastases may include whole brain radiotherapy, radiosurgery, surgery or a combination as deemed appropriate by the treating physician. Radiation therapy must be completed at least 14 days prior to registration, as specified in Section 3.2.4..

3.2.8 Participant has active, uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2), unstable angina, myocardial infarction within 12 months of enrollment, or ventricular arrhythmia.

3.2.9 Participant has a QTc interval >470 ms or known history of QTc prolongation or Torsade de Pointes. Note: correction may be made using any method of QTc calculation (i.e. QTcF)

3.2.10 Participant has an active infection or unexplained fever >38.5°C (101.3°F).

3.2.11 Participant has had another malignancy within the past 5 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the breast, cervix or vulva; or c) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder, or benign tumors of the adrenal or pancreas.

3.2.12 Participant has significant chronic gastrointestinal disorder with diarrhea as a major symptom (e.g., Crohn's disease, malabsorption, or Grade ≥2 (NCI CTCAE v.4.0) diarrhea of any etiology at screening).

3.2.13 Participant has known active infection with hepatitis B or hepatitis C virus. Hepatitis B and C serology testing is not required, unless active infection is suspected.

3.2.14 Participant is unable or unwilling to swallow tablets.

3.2.15 Participant has evidence of significant medical illness, abnormal laboratory finding, or psychiatric illness/social situations that would, in the Investigator's judgment, limit compliance with study requirements.

3.2.16 Pregnant women are excluded from this study because fulvestrant is a SERD agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with neratinib and/or fulvestrant, breastfeeding should be discontinued if the mother is treated with neratinib and/or fulvestrant.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial. Men are not eligible, as no data exist to our knowledge on the effect of fulvestrant in male breast cancer.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore via the Office of Data Quality. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Coordinating Center through the Study Coordinator or Project Manager. The list of required forms can be found in Section 4.4.

It is recommended that participants begin protocol treatment within 7 business days, and no more than 30 days from registration. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and faxed [redacted] or e-mailed [redacted] to the Project Manager:

- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist
- Baseline exam note including medical/surgical history, ECOG, vital signs
- EKG report
- MUGA or echocardiogram report
- Laboratory report including results for CBC, Chemistries, Urinalysis, and Urine Pregnancy Test
- Tumor Evaluation (MRI or CT and clinical assessment of visible of palpable lesions) Report
- Pathology Report and documentation of ER/PR and HER2 status
- Bone Scan Report (if done)
- Documentation of tissue availability (per eligibility criteria 3.1.8)

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol.
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

5. TREATMENT PLAN

5.1 Treatment Regimen

Neratinib and fulvestrant will be administered in 4 week cycles, with 28 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. There is no specific order of administration for neratinib and fulvestrant. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
ARM A					
Neratinib	Loperamide and Colestipol (see Section 5.3.3)	240mg (six 40mg tablets)	Orally	Neratinib: once daily, continuous Loperamide: Days 1-28, continuous Colestipol: Days 1-28, continuous	28 days (4 weeks)
Fulvestrant		500mg (two injections of 250mg each)	Intramuscularly	Cycle 1: Day 1, 15 Cycle 2 and all subsequent cycles: Day 1	
ARM B					
Neratinib	Loperamide and Colestipol (see Section 5.3.3)	240mg (six 40mg tablets)	Orally	Neratinib: once daily, continuous Loperamide: Days 1-28, continuous Colestipol: Days 1-28, continuous	28 days (4 weeks)

5.2 Ovarian Suppression

Ovarian suppression with LHRH agonists (goserolin or leuprolide) per standard institutional or regional practices should be followed in pre-menopausal and peri-menopausal patients (i.e start on LHRH agonist at time of study treatment start). Postmenopausal patients are defined as no spontaneous menses over 12 consecutive months or post bilateral surgical oophorectomy.

5.3 Pre-Treatment Criteria

5.3.1 Cycle 1, Day 1

- Absolute neutrophil count ≥1,000/uL
- Platelets ≥75,000/uL
- Hemoglobin ≥8g/dL
- Total bilirubin ≤ 1.5 X upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤3X institutional ULN without liver metastases, or ≤5X institutional ULN with liver metastases
- Creatinine clearance ≥ 50 mL/min
- Left ventricular ejection fraction ≥50%, as determined by RVG (MUGA) or echocardiogram(ECHO) within 60 days prior to initiation of protocol therapy

5.3.2 Subsequent Cycles

- Absolute neutrophil count ≥1,000/uL
- Platelets ≥75,000/uL
- Hemoglobin ≥8g/dL
- Total bilirubin ≤ 3 X upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤5X institutional ULN without liver metastases, or ≤8X institutional ULN with liver metastases
- Creatinine clearance ≥ 50 mL/min

5.4 Agent Administration

5.4.1 Neratinib

Neratinib is administered orally once daily, continuously with no breaks, on days 1-28 of a 4- week (28-day) cycle, +/- 3 days. Neratinib is dosed as 240 mg once daily (six 40 mg tablets). Dosing is not weight-based. Patients should take neratinib at approximately the same time of day every day, preferably in the morning, with food. The dose is considered "missed" if not taken within approximately 12 hours of the usual administration time. Doses should not be retaken if skipped, missed, or vomited. Tablets must be swallowed whole; they may not be crushed, chewed, or dissolved.

Neratinib requires the use of anti-diarrheal prophylaxis with loperamide and colestipol (see Sections 5.3.3). Investigators must ensure that participants have loperamide and colestipol on hand when starting to take the investigational product. Loperamide and colestipol are the standard anti-diarrheal therapies in this study. If alternative anti-diarrheal medication is used, the reason must be documented in the source documents. Acceptable reasons are non-tolerance of standard therapies or lack of efficacy. Loperamide and colestipol will be dispensed directly by the site on day 1 of each cycle.

Dose modifications are delineated in section 6. If significant treatment–related toxicities have not recovered to Grade ≤1 or baseline grade, the patient may skip up to 28 days from the last scheduled dose. Patients should be re-evaluated weekly during the delay whenever possible. Patients randomized to the fulvestrant arm (Arm A) may continue

fulvestrant dosing while neratinib is held, as long as the toxicity is felt to be unrelated to fulvestrant.

Dosing may also be suspended for up to 28 days for unanticipated intercurrent medical events that are not associated with study treatment toxicity or disease progression.

Patients are to fill out a pill diary for every cycle (Appendix B) and return it to clinic staff at the end of each cycle.

5.4.2 Fulvestrant

Fulvestrant is administered intramuscularly on Cycle 1 Day 1, Cycle 1 Day 15, and then on Day 1 of each subsequent 4-week (28-day) cycle +/- 3 days. Fulvestrant is dosed as 250 mg/5mL (x2) for a total of 500 mg via intramuscular injection. Administer intramuscularly slowly in the buttock. (NOTE: 500 mg dose will require one 250 mg injection in each buttock). Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until needle tip is fully covered. Visually confirm that the lever arm has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps container.

No dose modifications are allowed. If a patient has an intolerable toxicity felt to be related to fulvestrant, fulvestrant dosing can be held for up to 28 days (1 cycle) to allow the toxicity to recover to baseline or grade ≤1. Neratinib dosing can continue while fulvestrant is held. Commercial supply of fulvestrant will be used.

5.4.3 Mandatory Diarrhea Prophylaxis

Diarrhea is the major dose-limiting toxicity of neratinib, with onset typically occurring early in the course of treatment (during the first few days of the first cycle of treatment). Primary prophylactic use of antidiarrheal medication is mandatory for all patients taking neratinib. Loperamide and colestipol are the required standard therapies to treat diarrhea. Second-line antidiarrheal treatments and adjunctive therapies (i.e., octreotide [SANDOSTATIN®]) (or equivalent)) are also recommended for use when appropriate. The Investigator must review with the patient the Patient Instructions for the management of diarrhea in Appendix C.

The patient should be given clear instructions to contact the Investigator in the event of persistent Grade ≥2 diarrhea to discuss the appropriate course of treatment. Loperamide and colestipol should be dispensed directly with neratinib. It is very important to initiate treatment with loperamide and colestipol concomitantly with the first dose of neratinib to minimize occurrence and severity of diarrhea.

Refer to protocol Section 6.1.2, Table 2 for Dose Adjustment of Neratinib as applicable.

The Investigator or suitably trained and qualified delegate (e.g., MD, RN, NP, etc.) must

contact the patient by phone on Cycle 1 Day 2, Cycle 1 Day 3, and Cycle 1 Day 4 after the first dose of neratinib to inquire about compliance with loperamide and colestipol, diarrhea or any other adverse events. (These phone calls are very important and should be recorded in the clinical records together with response from the patient and action taken.)

Patients should be instructed to promptly report diarrhea symptoms and to report the number of stools per day and the dose of any anti-diarrheal medication taken each day for the first 28 days of therapy.

5.4.3.1 Loperamide (Imodium ®)

For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally 3 times a day (total 12 mg a day). The initial dose of loperamide will be administered orally with the first dose of neratinib. After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be administered orally twice a day (total 8 mg a day) through the first cycle of therapy (Day 28) from start of neratinib dosing, whether the patient is experiencing diarrhea or not. Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day) per the investigator's discretion. Commercial supply of loperamide will be used and provided by research pharmacies (cost covered by [redacted]

Loperamide Dosing

Day	Loperamide Dose
1-14	Daily dose of 12 mg in 3 divided doses of 4 mg
15-28	Daily dose of 8 mg in 2 divided doses of 4 mg
>28	Daily dose as needed (not to exceed 16 mg per day)

Loperamide Dose Adjustment

Patients are expected to take loperamide prophylaxis as directed. However, patients may require individualization of loperamide prophylaxis dose (up to a maximum dose of 16 mg per day) with the goal of titrating to 1-2 bowel movements a day.

- For patients who develop diarrhea during Cycle 1, loperamide should be increased up to a maximum of 16 mg a day.
- If a patient is unable to tolerate loperamide due to symptomatic constipation, loperamide should be held until after the first bowel movement and then resumed at a dose reduced by one level from their current level.
- For recurrent symptomatic constipation events, hold loperamide until after the first bowel movement and then resume at a dose reduced to the next lower dose level.
- If a patient is unable to tolerate once-daily loperamide due to constipation, hold loperamide and discuss subsequent loperamide dosing with the Investigator or suitably trained and qualified delegate.
- Neratinib dosing should continue if loperamide is held.

Recommended dose reductions for loperamide are listed in the table below.

Loperamide Dose Reduction Levels for Constipation.

Dose Level	Loperamide Dose	Tablets/Capsules per day
0	4 mg TID	6 tablets/capsules a day
-1	4 mg BID	4 tablets/capsules a day
-2	2 mg TID	3 tablets/capsules a day
-3	2 mg BID	2 tablets/capsules a day
-4	2 mg once a day	1 tablet/capsule a day

Abbreviations: BID = twice daily; mg=milligrams; TID= three times daily.

5.4.3.2 Colestipol (colestid)

Loperamide in combination with twice daily colestipol is required for 28 days at the initiation of neratinib. It is very important to initiate antidiarrheal medications (loperamide and colestipol) with the first dose of neratinib and should continue throughout the first cycle unless patients have trouble tolerating these medications. In that case, providers have the discretion to make changes in these medications. . Beyond Cycle 1, ongoing prophylaxis is discretionary per the treating provider.

Patients will self-administer oral colestipol at a dose of 2g twice daily, for the first treatment cycle (28 days).

**** NOTE: During Cycle 1: Patients should take colestipol 2 gm twice daily for 28 days, with the first dose taken at least 4 hours before neratinib and loperamide prophylaxis, and the second dose to be taken at least **2 hours after neratinib** and loperamide prophylaxis****

Commercial supply of colestipol will be used and provided by research pharmacies (cost covered by [redacted]

Prior to protocol version 2, diarrhea prophylaxis consisted of loperamide in combination with daily budesonide for the first 28 days. Active patients who are taking diarrhea prophylaxis at the time of protocol version 2 activation can either complete budesonide treatment or start colestipol per the treating investigator's discretion.

5.4.3.3 Additional Anti-Diarrheal Instructions

Treatment of diarrhea (Days 1-28)

- Follow dietetic measures:
  - Stop all lactose-containing products.
  - Drink 8 to 10 large glasses of clear liquids per day.
  - Eat frequent small meals.
  - Recommend low fat regimen enriched with bananas, rice, applesauce and toast until resolution of diarrhea.
- For patients with persistent Grade 1 diarrhea (<4 stools per day above baseline) despite maximal loperamide use, Lomotil® (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent).
- For Grade 2 diarrhea during the first 28 days (4 to 6 stools per day above baseline, despite intensive anti-diarrheal therapy), consider adding octreotide (short-acting) 150

μg subcutaneous [SC] injection 3 times a day, or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg by intramuscular (IM) injection (or equivalent).
- After resolution of diarrhea, loperamide prophylaxis can be decreased in 2-mg decrements with the goal of titrating to 1-2 bowel movements a day.

For new onset uncomplicated Grade 1 or Grade 2 diarrhea (>28 Days and beyond)

Dietetic measures
- Stop all lactose-containing products.
- Drink 8 to 10 large glasses of clear liquids per day.
- Eat frequent small meals.
- Recommend low fat regimen enriched with bananas, rice, applesauce and toast until resolution of diarrhea.

Pharmacological Treatment
- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours.
- For patients with persistent Grade 1 diarrhea on a maximum dose of loperamide (16 mg per day) Lomotil (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 hours to 8 hours may be added (or equivalent).
- For Grade 2 diarrhea during the first 28 days of treatment (4 to 6 stools per day above baseline, despite intensive antidiarrheal therapy), consider adding octreotide (short acting) 150 μg SC TID; or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg IM (or equivalent medication).

For Grade 3 or Grade 4 diarrhea with complicating features (dehydration, fever, and/or Grade 3-4 neutropenia)

Dietetic measures (same as above)

Pharmacologic treatment
- Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (<4 stools/day).
- Administer octreotide (100-150 μg SC BID or intravenously (IV) (25-50 μg/h) if dehydration is severe, with dose escalation up to 500 μg SC TID).
- Use IV fluids as appropriate.
- Consider prophylactic antibiotics as needed (e.g., fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia.
- Stool cultures should be done to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or Grade 3 or 4 neutropenia) per the Investigator's discretion. Results from occult blood, fecal

leukocyte stain, Clostridium difficile, Campylobacter, Salmonella, and Shigella testing, when performed, should be recorded in the clinical records.
- Patients with significant diarrhea who are unresponsive to medical treatment may require treatment interruption or dose reduction.

Patient instructions for the management of diarrhea are provided in Appendix C.

5.5 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications and concomitant nonpharmacological treatments/therapies will be recorded in the medical record from 30 days prior to the signing of the informed consent form (ICF) until the Safety Follow-up Visit occurring 28 days after the last dose of neratinib. This will include the start date, stop date, generic name, and indication for treatment.

At screening, patients will be asked what medications they have taken during the previous 30 days, which medications are ongoing at the time of screening, any medical conditions that require medication, and all prior cancer therapies. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

5.5.1 Permitted Concomitant Treatment

Any palliative and/or supportive care for cancer-related symptoms, which are not otherwise specified in the list of prohibited medications below, is permitted at the Investigator's discretion.
Specifically, the following treatments are permitted during the study:

- Standard therapies for preexisting medical conditions and for medical and/or surgical complications.
- Ovarian suppression is allowed.
- Bisphosphonates and RANK (receptor activator of nuclear factor kappa-B) ligand inhibitors (e.g., denosumab), are allowed regardless of indication.

5.5.2 Prohibited Concomitant Treatment

The following treatments are prohibited throughout the duration of the active (treatment) stage/phase of the study: Any concurrent chemotherapy, hormonal therapy (except ovarian suppression which is permitted), surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents by oral or parenteral route.

Patients who have demonstrated control of their extra-cranial disease (defined for this purpose as objective response or SD maintained for at least 2 cycles) from study therapy, but who have developed isolated brain metastases that are felt to be treatable with radiation will be allowed to receive radiation therapy and then continue their assigned study therapy until they either experience systemic progression of their disease and/or further progression in the brain. Patients should have their study therapy held until radiation is completed. Patients can restart study therapy once clinically stable as deemed

by the investigator.

Any treatment required during the first 2 months of the Program Treatment Phase that might have an interaction with loperamide (refer to loperamide package insert) or colestipol (refer to colestipol package insert) is prohibited.

5.5.3 Potential Drug-Drug Interactions

Because there is a potential for interaction of neratinib and fulvestrant with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix D presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

The solubility of neratinib is pH dependent and treatments that alter gastrointestinal pH such as proton pump inhibitors (PPIs), H2-receptor antagonists, and antacids may lower the solubility of neratinib. It has been observed that a single 240-mg dose of neratinib combined with lansoprazole may decrease neratinib AUC by up to 65%. The potential PK interaction of H2-receptor antagonists with neratinib has not been evaluated. It is unknown whether separating PPI and neratinib doses reduces the interaction. If antacids are necessary, the antacid dose and the neratinib dose should be separated by 3 hours.

When taking colestipol with neratinib and loperamide during the first 28 days (Cycle 1) there should be close monitoring during the concomitant administration with ketoconazole (and itraconazole, ritonavir, saquinavir, or erythromycin), or any other CYP3A4 inhibitor for increased signs and/or symptoms of hypercorticism. Refer to the colestid package insert for contraindications, warnings, and precautions for colestipol.

Patients taking digoxin, a P-glycoprotein (P-gp) substrate with a narrow therapeutic window, should be monitored closely. The digoxin dose should be adjusted as needed, since neratinib is an inhibitor of P-gp. Co-administration of neratinib with digoxin could result in increased digoxin levels and associated digoxin toxicity.

Patients taking oral coumarin-derivative anticoagulants (ie, warfarin and phenprocoumon) should be monitored closely and their anticoagulant dose adjusted as needed.

Avoid grapefruit juice, which is a known CYP3A4 inhibitor.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant. No crossover from neratinib (Arm B) to neratinib plus fulvestrant (Arm A) will be allowed.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, [redacted]

5.7 Duration of Follow Up

Participants will be followed for up to 5 years after removal from protocol therapy or until death, whichever occurs first. During follow up, participants will be called every 6 months for survival assessment and to report any further anti-cancer treatment. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the Coordinating Center.

6. DOSING DELAYS/DOSE MODIFICATIONS

General guidelines for dose delay and dose reduction are outlined below. Management guidelines for specific (e.g. diarrhea, pulmonary toxicity, hepatic toxicity,) and clinically-relevant toxicities are provided in Section 6.1. The dose delay and reduction instructions provided in these sections are intended to serve as guidelines to allow ongoing treatment for patients without signs or symptoms of progression while ensuring patient safety. In addition to the guidelines provided below, drug holds and dose reductions for the management of adverse events are permitted at the discretion of the treating physician.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Neratinib dose modifications

Neratinib dose delays and modifications should be made as indicated in the following table(s). Dose re-escalation is not allowed after a dose reduction.

If significant treatment–related toxicities have not recovered to Grade ≤1 or baseline grade, the patient may skip up to 28 days from the last scheduled dose. Patients should be re-evaluated weekly during the delay whenever possible. In patients randomized to the fulvestrant arm (Arm A), fulvestrant dosing can continue while neratinib is held or if neratinib is discontinued, as long as the toxicity is felt to be unrelated to fulvestrant. Cycles will not be delayed in the event neratinib is held, but will resume as originally scheduled. The missed dose(s) will not be made up.

Dosing may also be suspended for up to 28 days for unanticipated intercurrent medical events that are not associated with study treatment toxicity or disease progression.

Dose Reduction Table

Dose Reduction Level	Neratinib Dose
Starting Dose	240mg, daily
Dose level -1	160mg, daily
Dose level -2	120mg, daily

If a patient develops a toxicity requiring a dose reduction below Dose level -2 (120mg), neratinib should be permanently discontinued.

6.1.1 General Toxicity

Guidelines for dose adjustments of neratinib for general toxicities that are clinically significant and felt to be drug related are shown in Table 1. For dose modifications for known toxicities (diarrhea, pulmonary toxicity, and hepatic toxicity) please see tables 2, 3, and 4.

Table 1: General Toxicities Requiring Dose Adjustment of Neratinib

NCI CTCAE v. 4.0	**Action**
Grade 2 adverse reaction*	
1st appearance	Hold neratinib until event resolves to Grade ≤1; then resume neratinib at the same dose level.
2nd appearance	Hold neratinib until event resolves to Grade ≤1; then resume neratinib at one dose level lower.
3rd appearance	Hold neratinib until event resolves to Grade ≤1; then resume neratinib at one additional dose level lower.
4th appearance	Discontinue neratinib permanently.
Grade 3 adverse reaction	
1st appearance	Hold neratinib until event resolves to Grade ≤1; then resume neratinib at one dose level lower.
2nd appearance	Hold neratinib until event resolves to Grade ≤1; then resume neratinib at one additional dose level lower.
3rd appearance	Discontinue neratinib permanently.
Grade 4 adverse reaction	
1st appearance	Discontinue neratinib permanently

Grade 2 ANC (neutrophil count decrease ≥1000/uL), Grade 2 Anemia (Hemoglobin <10-8.0g/dL), and Creatinine Clearance that is ≥50 mL/min (Grade 2 Chronic Kidney Disease is creatinine clearance 59-30mL/min) are acceptable values for treatment as indicated in pre-treatment criteria, section 5.2.* ***Do not hold neratinib for Grade 2 ANC, Grade 2 Anemia, or Creatinine Clearance that is ≥50mL/min.*

Based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v.4.0)

6.1.2 Gastrointestinal Toxicity:

Guidelines for adjusting doses of neratinib in the event of gastrointestinal toxicity of diarrhea are shown in Table 2. Refer to Section 5.3.3 for additional dietetic measures and pharmacological treatment.

Table 2: Gastrointestinal Toxicities Requiring Dose Adjustment of Neratinib

NCI CTCAE V4.0	**Action**
Grade 1 Diarrhea [Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.] OR Grade 2 Diarrhea [Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline;] *lasting <5 days* OR Grade 3 Diarrhea [Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline limiting self-care activities of daily living (ADL);] *lasting < 2 days*	• Continue neratinib at the current dose level. • Adjust anti-diarrheal treatment, as per the guidelines for management of diarrhea at the first onset of diarrhea. • Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea. • Fluid intake of ~2L/day should be maintained to avoid dehydration. • Once the event resolved to Grade ≤ 1 or baseline, start loperamide 4 mg with each subsequent neratinib administration

Persisting and intolerable **Grade 2 Diarrhea** lasting >5 days despite being treated with optimal medical therapy, or associated with fever, dehydration, or **Grade 3-4 neutropenia**
 	
OR
 	
Grade 3 Diarrhea lasting > 2 days despite being treated with optimal medical therapy, or associated with fever, dehydration, or **Grade 3-4 neutropenia**
 	
OR
 	
Any **Grade 4 diarrhea** [Life-threatening consequences; urgent intervention indicated]
	• Hold neratinib until recovery to Grade ≤ 1 or baseline.
	
	• Adjust anti-diarrheal treatment, as per the guidelines for management of diarrhea at the first onset of diarrhea.
	
	• Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea.
	
	• Fluid intake of ~2L should be maintained, intravenously if needed.
	
	• If recovery occurs:
	  • ≤1 week after withholding treatment, resume same dose of neratinib.
	  • Within 1-3 weeks after withholding treatment, resume neratinib at one dose level lower.
	  • If event occurs a 2nd time and the neratinib dose has not already been decreased, reduce neratinib dose to the next lower dose level.
	• If subsequent events occur, resume at an

NCI CTCAE V4.0	Action
	additional dose level lower once resolved to Grade ≤ 1 or baseline • Once the event resolved to Grade ≤ 1 or baseline, start loperamide 4 mg with each subsequent neratinib administration

Based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

6.1.3 Pulmonary Toxicity

Guidelines for adjusting doses of neratinib in the event of pulmonary toxicities are shown in Table 3. Interstitial lung disease, which can sometimes be fatal, has been reported with other oral tyrosine kinase inhibitors that target ERBB receptor kinases, including lapatinib, gefitinib, and erlotinib. Rare cases of pneumonitis (0.6%) and lung infiltration (0.4%) have been reported in patients treated with neratinib monotherapy, and considered drug-related. Patients receiving neratinib should be monitored for acute onset or worsening of pulmonary symptoms such as dyspnea, cough, and fever and treated appropriately.

Table 3: Pulmonary Toxicities Requiring Dose Adjustment of Neratinib

NCI CTCAE V4.0	Action
Grade 2 Pneumonitis/Interstitial Lung Disease [Symptomatic; medical intervention indicated; limiting instrumental ADL]	• Hold neratinib until recovery to Grade ≤ 1 or baseline. • Reduce neratinib one dose level or discontinue neratinib as per Investigator's best medical judgment.
Grade ≥3 Pneumonitis/Interstitial Lung Disease [Severe symptoms; limiting self-care ADL; oxygen indicated]	• Discontinue neratinib permanently.

6.1.4 Liver Toxicity

Guidelines for adjustment of neratinib in the event of liver toxicity are shown in Table 4.

Abnormal values in ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

Patients who experience Grade ≥ 3 diarrhea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia should be evaluated for changes

in liver function tests. Bilirubin and prothrombin time must also be collected during hepatotoxicity evaluation.

Table 4: Liver Function Test Abnormalities Requiring Dose Adjustment of Neratinib

NCI CTCAE V4.0	Action
Grade 2 AST/ALT (>3.0 - 5.0 x ULN) **OR** **Grade 2 bilirubin** (>1.5 - 3.0 x ULN)	• Continue neratinib at same dose.
Grade 3 AST/ALT (>5 – 20x ULN) OR **Grade 3 bilirubin** (>3-10x ULN)	• For participants with AST/ALT <grade 1 at baseline, resume neratinib at one dose level lower if recovery to baseline occurs within 21 days. • If grade 3 AST, ALT or bilirubin recurs despite one dose reduction, resume neratinib at a further dose reduction if recovery to baseline occurs within 21 days. • If grade 3 AST/ALT or bilirubin occurs despite this second dose reduction, permanently discontinue neratinib. Report as SAE. • Evaluate alternative causes.
Grade 4 AST/ALT (>20x ULN) OR **Grade 4 Bilirubin** (>10x ULN)	• Permanently discontinue neratinib. • Evaluate alternative causes.
ALT > 3x ULN AND **Total bilirubin** > 2x ULN AND **Alkaline phosphatase** < 2x ULN (potential Hy's law indicators of drug-induced liver damage)	• Hold neratinib. The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. Laboratory assessment must include: repeat AST and ALT, albumin, total bilirubin, direct bilirubin, PT, PTT and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, concomitant medications, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic

NCI CTCAE V4.0	Action
	disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the criteria mentioned above (i.e., ALT > 3 x ULN associated with bilirubin >2 x ULN and alkaline phosphatase <2 x ULN), with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases, irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. •Contact [redacted] immediately to discuss next steps, including evaluation of alternative causes, and management of investigational product(s). •These events must be reported as SAEs.

NOTE: During evaluation of hepatotoxicity, bilirubin must be fractionated, prothrombin time must be measured, and liver imaging should be considered.

6.2 Fulvestrant dose modifications

No dose modifications are permitted for fulvestrant. If a patient has an intolerable toxicity felt to be related to fulvestrant, fulvestrant dosing can be held for up to 28 days to allow the toxicity to recover to baseline or grade ≤1. Neratinib dosing can continue while fulvestrant is held.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events Lists

7.1.1.1 Adverse Event List(s) for Neratinib

A list of the adverse events and potential risks associated with neratinib appears below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting in addition to routine reporting. For

toxicity management of diarrhea please refer to Table 2.

Table 5: Neratinib Toxicity [Adapted from 14-JUL-2017 Investigator's Brochure, version 5.0]

Table 73. Adverse Drug Reactions Occurring in Subjects Receiving Neratinib Monotherapy (N = 1408)

System Organ Class	All Causality Frequency	Preferred Term	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations	Common	Urinary tract infection	5.1	0.1	0
Metabolism and nutrition disorders	Very common	Decreased appetite	12	0.2	0
	Common	Dehydration	3.6	0.9	0.1
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	5	0	0
Gastrointestinal disorders	Very common	Diarrhoea	95.4	39.8	0.1
		Nausea	43	1.8	0
		Vomiting	26.2	3.3	0
		Abdominal pain	24	1.7	0
		Abdominal pain upper	15.1	0.8	0
		Stomatitis[a]	10.8	0.6	0
	Common	Dyspepsia	9.8	0.4	0
		Abdominal distension	5.2	0.3	0
		Dry mouth	3.3	0.1	0
Hepatobiliary disorders	Common	Alanine aminotransferase increased	8.5	1.1	0.2
		Aspartate aminotransferase increased	7.4	0.5	0.2
	Uncommon	Blood bilirubin increased	0.3	0	0
Skin and subcutaneous tissue disorders	Very common	Rash[b]	15.8	0.4	0
	Common	Nail disorder[c]	8	0.3	0
		Dry skin	6	0	0
		Skin fissures	2	0.1	0
Musculoskeletal and connective tissue disorders	Very common	Muscle spasms	11.2	0.1	0
Renal and urinary disorders	Common	Blood creatinine increased	1	0.1	0.1
	Uncommon	Renal failure	0.3	0.2	0
General disorders and administration site conditions	Very common	Fatigue	27.1	1.6	0
Investigations	Common	Weight decreased	4.8	0.1	0

MedDRA (Version 17) coding dictionary applied. Toxicity graded using NCI CTCAE version 3.0; each patient counted only once in the worst grade category.
[a] Includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering, and mucosal inflammation.
[b] Includes rash, rash erythematous, rash follicular, rash generalized, rash pruritic, and rash pustular.
[c] Includes nail disorder, paronychia, onychoclasis, and nail discolouration.

7.1.1.2

Diarrhea

Diarrhea is the most frequent TEAE reported with neratinib, both as monotherapy and in combination with other drugs, and may be severe, and associated with dehydration, particularly in subjects with concomitant nausea and vomiting.

As diarrhea represents the most prevalent TEAE with neratinib, both as monotherapy and in combination with other drugs, an intensive diarrhea management plan with prophylactic use of loperamide and colestipol is part of this and all ongoing and future neratinib clinical studies (Ustaris et al, 2015). Guidelines for dose adjustment of neratinib in the event of diarrhea are also provided. Among subjects receiving loperamide prophylactic antidiarrheal medication, 11-28% of subjects experienced Grade 3 diarrhea; no Grade 4 diarrhea were reported to date. In contrast, in studies without diarrhea prophylaxis, 26-40% of subjects experienced Grade 3 diarrhea.

Stomatitis

Dermatologic toxicities associated with EGFR inhibitors include dryness of the skin and mucus membranes (Nanney et al, 1990; Dunne and Sumner, 2008). Oral mucositis is the more specific term that is used to describe oral mucosal inflammation and ulceration induced by cancer therapies (Lalla et al, 2008). Stomatitis was reported by 10.8% of neratinib-treated subjects versus 3.2% of placebo-treated subjects with early stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy. The majority of the events were Grade 1 (neratinib, 7.5%; placebo, 2.6%) and Grade 2 (neratinib, 2.8%; placebo, 0.6%) with a few Grade 3 events (neratinib, 0.6%; placebo, 0.1%). There were no Grade 4 events. Other event terms included are mucosal inflammation, stomatitis, aphthous stomatitis, mouth ulceration, and oral mucosal blistering.

Hepatotoxicity

Hepatotoxicity with asymptomatic elevations of transaminases and hyperbilirubinemia are commonly associated with oral TKIs (Cabanillas et al, 2011). The risk is usually manageable by dose adjustment or a switch to a suitable alternative TKI. All subjects enrolled in this and other neratinib clinical trials have their liver function tests assessed routinely. Abnormal values in ALT concurrent with abnormal elevations in total bilirubin in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always considered important medical events. Symptoms of multiple loose bowel movements in a day or any worsening of fatigue, nausea, vomiting, abdominal pain or tenderness, fever or rash may indicate changes in liver function tests.

Dermatologic Toxicities

Dermatologic toxicities associated with EGFR inhibitors include rash, dryness of the skin and mucus membranes, hair changes and alopecia, nail changes, and hand and foot reactions. Rash was reported more frequently by neratinib-treated subjects than placebo-treated subjects (16.3% versus 7.9%, respectively). There were 0.4% of neratinib-treated subjects who experienced Grade 3 events. Rash led to treatment discontinuation in 8

(0.6%) neratinib-treated subjects. Nail changes are believed to result from skin thinning afflicting up to 15% of subjects (Dunne and Sumner, 2008).

7.1.1.3 Adverse Event List for Fulvestrant

The most common, clinically significant adverse reactions occurring in ≥ 5% of patients receiving Fulvestrant 500 mg were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation. Increased hepatic enzymes (ALT, AST, ALP) occurred in >15% of FASLODEX patients and were not dose-dependent. Please see the package insert for complete information regarding adverse events:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021344s019s020lbl.pdf

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators must report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 toxicity with a possible, probable or definite attribution, any grade 4 and grade 5 (death) toxicity regardless of study phase or attribution.

7.4 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	**DF/HCC Reportable AEs**				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.4.1 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the only event that does not required expedited reporting to the Overall PI or the DFCI IRB is disease progression. However, this still must be reported through the routine reporting mechanism (i.e. case report form).

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event

that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Reporting to [redacted]

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

All serious adverse events, in addition to being reported to the FDA by the investigator, must be reported by email to [redacted] as follows:

For expedited reports, DFCI will send the MEDWATCH report to the Company no later than seven (7) days for initial life-threatening and death reports, and fifteen (15) days for all other initial or follow-up serious and unexpected suspected adverse reaction (SUSAR) as assessed by the investigator for causality and by the Investigator-Sponsor for causality and expectedness based on the adverse reaction table in the most current Investigator Brochure, from the time of receipt of the SAE by the DFCI Principal Investigator. For non-expedited SAE reports (i.e., unrelated to study drugs or listed/expected event), DFCI will send a completed MEDWATCH report [redacted] no later than thirty (30) days from the time of receipt of the SAE by DFCI.

By e-mail to [redacted]

SAEs brought to the attention of the investigator at any time after cessation of neratinib and considered by the investigator to be related or possibly related to neratinib must be reported to [redacted] if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged from the study.

Pregnancy

All initial reports of pregnancy must be reported to the Overall PI and [redacted] by the investigational staff within 24 hours of their knowledge of the event.

For investigational medicinal products and for marketed products used as study drug in neratinib studies, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational medicinal product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational medicinal product (maternal exposure);
- A male has been exposed, either due to treatment or environmental, to the investigational medicinal product prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational medicinal product, the investigator must submit this information to the Overall PI and [redacted]

Follow-up and additional information may be requested.

7.7 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.8 Routine Adverse Event Reporting

Grade ≥1 diarrhea and all grade 2 or higher Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and other agent administered in this study can be found in Section 7.1.

8.1 Neratinib

8.1.1 Description

The chemical name is: 2-Butenamide, N-[4-[[3-chloro-4-(2-pyridinylmethoxy)phenyl]amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-, (2E)-, (2Z)-2-butenedioate (1:1). Neratinib is also known as PB-272, HKI-272, and HKI-272 maleate and is an irreversible inhibitor of the HER family of receptor tyrosine

kinases. The molecular formula is C30H29ClN6O3-C4H4O4. The molecular weight is 673.11.

Clinical pharmacokinetic (PK) results from the first-in-human study with ascending single and multiple doses in subjects with cancer showed that absorption of neratinib was slow with Tmax ranging from 3-6.5 hours post dose. After single or multiple daily oral doses of neratinib with food, the peak exposure (Cmax) and the area under the plasma concentration-versus-time curve (AUC) increased with increasing dose. Furthermore, no major accumulation was observed when comparing Day 14 exposure with Day 1 exposure following once-daily dosing of neratinib 240 mg and 360 mg with food. The mean half-life following a single dose on Day 1 ranged from 8 to 17 hours, which supports once-daily dosing of neratinib.

8.1.2 Form

Neratinib (40mg tablets) will be supplied by [redacted] and will be packaged into bottles for patient administration (28 day supply + 7 days to allow for +/- 3 days on each end of the cycle and one additional day). The color of the tablets is reddish-brown.

8.1.3 Storage and Stability

Neratinib tablets should be stored at 25°C (77°F) or below with desiccant. Do not freeze. Excursions up to 30°C (86°F) are permitted.

8.1.4 Handling

Neratinib tablets require no specific handling precautions. Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.5 Availability

Neratinib is an investigational agent and will be supplied free-of-charge to the study team and patients from [redacted] investigational supply of Neratinib.

8.1.6 Preparation

Neratinib will be pre-prepared and packaged by [redacted] and shipped directly to participating institution pharmacies. Drug orders will be placed by each participating center once [redacted] has received the site information required to ship drug to each site. Study drug will be distributed to each center. Once a patient meets criteria to continue therapy, he/she will receive study drug (after each study visit).

8.1.7 Administration

Neratinib will be packaged in bottles containing a maximum of 210 tablets (40 mg) (This is equal to a 28 day supply + 7 days to allow for +/- 3 days on each end of the cycle and one additional day). Tablets will be self-administered orally by patients once daily as six 40 mg tablets (total 240 mg). Further doses will be determined at each cycle, depending on toxicities and need for dose adjustment. Labeling of the bottles containing tablets will be done in accordance with local procedures (as required by law). Patients will return any unused pills at next protocol visit.

8.1.8 Ordering

The investigator or those named as sub-investigators agree to supply study drug (neratinib) only to those subjects who are enrolled in the study. The investigator or designee will keep a current and accurate inventory of all clinical drug supplies provided by [redacted] The study site will maintain a dispensing log and compliance with the treatment regimen will be calculated at the site from this information at each visit. Each participating center will order its own inventory of neratinib. Drug will be shipped directly to that participating site by [redacted] A new prescription will be provided to each patient for each cycle of therapy.

8.1.9 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.10 Destruction and Return

At the end of the study, unused supplies of neratinib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8.2 Fulvestrant

8.2.1 Description

Fulvestrant injection for intramuscular administration is an estrogen receptor antagonist. The chemical name is 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17 beta-diol. The molecular formula is C32H47F5O3S and its structural formula is: OH OH (CH2)9SO(CH2)3CF2CF3 Fulvestrant is a white powder with a molecular weight of 606.77. The solution for injection is a clear, colorless to yellow, viscous liquid.

Fulvestrant is commercially available and considered standard-of-care for patients with hormone receptor positive, metastatic breast cancer. The dose, schedule, and mode of administration used in this trial are identical to the dose, schedule, and mode of administration approved for use for this indication by the U.S. FDA.

Fulvestrant will be charged to the patient and/or insurance company as it is considered standard-of-care.

8.2.2 Form

Fulvestrant injection is commercially available as a sterile, single patient, prefilled syringe containing 250 mg at a concentration of 50 mg/mL. The solution is a clear, colorless to yellow, viscous liquid. In addition to the fulvestrant, each injection contains as inactive ingredients alcohol, USP, benzyl alcohol, NF, and benzyl benzoate, USP, as co-solvents and castor oil, USP, as a co-solvent and release rate modifier.

8.2.3 Storage and Stability

Syringes of fulvestrant should be stored in the original container and refrigerated at 2-8°C.

8.2.4 Handling

Fulvestrant requires no specific handling precautions. Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.5 Preparation

Remove syringe from tray and check that it is not damaged. Peel open the safety needle outer packaging. Break the seal of the white plastic cover on the syringe luer connector to remove the cover with the attached rubber tip cap. Twist to lock the needle to the luer lock connector. Remove needle sheath. Remove excess air from the syringe (a small bubble may remain).

8.2.6 Administration

Fulvestrant will be administered at a dose of 500 mg (2 x 250 mg injections) IM on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, and on Day 1 of each subsequent cycle. Cycle length = 28 days.

Fulvestrant will be administered slowly into each buttock. Immediately upon withdrawal of syringe from patient activate needle protection device by pushing lever arm forward until needle tip is fully covered. Visually confirm that the needle arm has advanced and that the needle tip is fully covered. If unable to activate, discard immediately into an

approved sharps container.

8.2.7 Ordering

Fulvestrant is commercially available and will be ordered by each prescribing provider for the duration for the study.

8.2.8 Accountability

Fulvestrant is commercially available and therefore accountability should be performed as standard policy in the investigational site.

8.2.9 Destruction

Fulvestrant is commercially available and therefore destruction should be performed as standard policy in the investigational site.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Table 6: Specimen Collection Schedule

Specimen	Screening	Cycle 1		Subsequent Cycles	End of treatment/ Progression	Shipping Condition	Ship to
		Day 1 (± 1 Day)	Day 15	Day 1 (± 3 Days)			
ctDNA Collection (Section 9.1)		x	x	x	x	Ambient	DF/HCC Core Blood and Tissue Bank
Archival tumor tissue (blocks or slides) [a] (Section 9.2)	x					Ambient	DFCI BOC study team
Required Fresh tumor tissue biopsy [b] (Section 9.3)	x	x				Frozen in OCT	DF/HCC Core Blood and Tissue Bank
Optional Fresh tumor tissue biopsy (Section 9.3)					x	Frozen in OCT	DF/HCC Core Blood and Tissue Bank

a. If archival tumor tissue is not available, fresh tissue biopsy must be performed prior to treatment start. Biopsy may be done as part of screening or on C1D1 before treatment begins. **For external site patients**, biopsy should be done after registration or on C1D1 prior to treatment start. See section 9.3 below.
b. Fresh tumor biopsy of accessible metastatic lesion is mandatory before treatment begins. The biopsy may be performed at screening or on Cycle 1 Day 1 prior to dosing. **For external site patients**, biopsy should be done after registration or on C1D1 prior to treatment start. See section 9.3 below.

9.1 ctDNA Collection

9.1.1 Collection of Blood Specimen(s)

For ctDNA analyses, two 10 mL blood samples will be drawn into two Streck Tubes. Streck Tubes will be supplied to sites. Blood will be collected at:

- Cycle 1 Day 1 (prior to treatment start)
- Cycle 1 Day 15
- Subsequent Cycles Day 1
- End of Treatment

Every effort will be made to coordinate study blood draws with clinically-indicated blood tests to minimize additional venipuncture. Research coordinators will track participants closely and make every effort to collect blood at required timepoints. Some blood draws

will be missed or fall outside timeframe window due to the following circumstances and will not be considered deviations from the protocol:

- Unanticipated changes in treatment regimens and last minute clinic visits,
- The serial ctDNA blood draws may not occur as scheduled, depending on the participant's clinical schedule and visits at their participating institution. We do not plan to bring participants back to clinic solely for the purpose of a research blood draw and will make every attempt to coordinate it with a clinically indicated blood draw. Missed ctDNA draws due to these reasons will not be considered deviations or violations.

It is anticipated that future studies will include evaluation of genetic, immunologic, hormonal, and/or other issues related to breast cancer. We will inform participants in the informed consent document that we will use their specimens for research related to breast cancer and other cancers. If investigators wish to obtain identifiable information as part of their biomarker research, they will be required to submit such plans for IRB approval.

9.1.2 Handling of Blood Specimens(s)

Blood will be processed and banked in the DF/HCC Core Blood and Tissue Bank for future research purposes or until sent to the Broad Institute for sequencing.

Blood collected in Streck tubes at non-DFCI sites is to be shipped to DFCI within 24 hours of collection as per instructions below. Upon receipt at DFCI, Streck Tubes will be kept at room temperature and processed within 7 days.

Tube precautions:

- Fill the Streck tube completely and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate results.
- If samples cannot be shipped within 24 hours of collection, contact DFCI. DO NOT FREEZE OR REFRIGERATE TUBES as this could cause issues with sample integrity.
- Do not use tubes after expiration date.
- Fill the tube completely.

9.1.3 Shipping of Blood Specimen(s)

Complete a Specimen Requisition Form (Appendix F) to be sent with the tubes; make a copy of the requisition for the participant's research chart prior to sending.

Ship Monday through Thursday within 24 hours of collection at ambient temperature overnight to:

Brigham and Women's Hospital
DF/HCC Core Blood and Tissue Bank
20 Shattuck Street
Thorn Building – Room 428
Boston, MA 02215

DO NOT FREEZE OR REFRIGERATE STRECK TUBES. Streck tubes must be stored at room temperature to preserve the sample.

If blood specimens must be collected on Friday, the specimens should be stored over the weekend and shipped on Monday. When storing tubes over a weekend, Streck tubes should be stored at room temperature until shipment.

Email the assigned study coordinator and [redacted] with the sample information and tracking information the day before shipping specimens. Please include UPS or FedEx tracking information for the sample.

9.2 Archival Tissue

9.2.1 Collection of Archival Tissue Specimen(s)

Archival tissue (either paraffin blocks or unstained slides) will be collected for molecular characterization including potential resistance mechanisms, predictive biomarkers, and immunological function. Tumor (breast and/or lymph node) tissue from the initial breast cancer surgery is preferred. For participants diagnosed with de novo metastatic disease then tissue from the initial diagnostic biopsy should be collected. Additionally, available archival tissue from surgery or biopsy for metastatic disease will be collected.

This material should be provided preferably as paraffin blocks, if not, at least ten 5micron sections on charged or coated slides and ten 5-7 micron sections on regular non-coated slides should be submitted (20 slides total with 10 from primary and 10 from metastatic sites). For those patients that do not undergo a baseline biopsy, 20 slides from the metastatic site and 10 slides from the primary should be submitted (30 slides total).

Tissue needs to be located and availability must be confirmed at the time of registration, as indicated in eligibility criterion 3.1.4. If archival tissue is not available, patients will be required to undergo a tumor biopsy prior to treatment start. This biopsy can be done during screening or on C1D1 before treatment begins. **For external site participants,** biopsy should be performed after registration or on C1D1 prior to dosing. Details for this biopsy including collection, processing, and shipping are outlined below in Section 9.3.

Patients will not be able to start study drugs without confirmation of tissue availability or biopsy. Tissue needs to be submitted to DFCI within 3 weeks of study initiation (treatment start).

9.2.2 Handling of Archival Tissue Specimens(s)

Label all blocks or slides with the participants Study ID number, Initials, Date of Birth and surgical site (site of disease from which sample was obtained). Include a copy of the associated de-identified pathology report labeled with the participant's Study ID number, Initials, and Date of Birth with blocks/slides.

9.2.3 Shipping of Archival Tissue Specimen(s)

Include a copy of the Specimen Requisition Form (Appendix F) with your shipment. Keep a copy of the requisition in the participant's research chart. Tissue needs to be submitted to DFCI within 3 weeks of study initiation (treatment start).

Ship at ambient temperature to the DFCI study team:

Dana Farber Cancer Institute
Breast Oncology
450 Brookline Avenue, Dana-157
Boston, MA 02215

Email the assigned study coordinator with the sample and tracking information the day before shipment. Blocks will be returned to sites after the completion of the specimen analysis. Please include UPS or FedEx tracking information for the sample.

9.3 Fresh Tissue Biopsy Collection

9.3.1 Collection of Pre-treatment Biopsy Specimen(s)

Participants will undergo a required research biopsy of a reasonably accessible metastatic lesion (chest wall, skin, subcutaneous tissue, lymph nodes, skin, breast, bones, lung, and liver metastases) before treatment begins. The biopsy may occur during screening or on Cycle 1 Day 1 before treatment begins. **For external site participants,** biopsy should be performed after registration or on C1D1 prior to dosing. If the biopsy is done prior to registration, please store the sample in a -80°C freezer until the time of shipment (once the participant is registered). If a reasonably accessible metastatic lesion is not available, the patient may go on study provided that archived tissue is available. However, if a reasonably accessible site is available for biopsy, the patient must agree to biopsy. Any patients not undergoing biopsy must be approved for study enrollment by the Overall Principal Investigator at DFCI.

Biopsies may be done with local anesthesia or intravenous conscious sedation, according to institutional guidelines. If a biopsy requires general anesthesia, then it is only allowed if acquisition of tissue is clinically indicated, and excess tissue may be collected for research purposes. Patients without sites available for biopsy must have available tissue [archived formalin-fixed paraffin embedded blocks (FFPB), blocks from which slides can be created, or fresh frozen tissue from original diagnosis or metastatic setting] for correlative studies. Tissue needs to be located and available at the time of registration. Tissue specimens will be collected from tumor lesions using standard institutional procedures.

9.3.2 Collection of Post-Progression Biopsy Specimen(s)

Patients will be asked at the time of consent if they would like to provide an optional biopsy at the time of progression. If patients agree to participate in the optional progression biopsy at the time of consent, they may refuse at the time of progression if they wish, without resulting in a deviation or violation. This tissue will be used for molecular characterization including potential resistance mechanisms, predictive biomarkers, and immunological function.

Tissue specimens will be collected from tumor lesions using standard institutional procedures.

9.3.3 Tissue Biopsy Guidelines

- **The cost of the biopsies will be covered by the study if they are being done for research only.** However, it is recognized that biopsies might be considered to aid in clinical management (for example, to re-assess ER, PR, and HER2 status). In the case of a clinically indicated biopsy (with an additional "research pass"), the cost of the biopsy will be charged to the patient and/or her insurance company.
- Patients who undergo an attempted research biopsy procedure for the purpose of this protocol, and in whom inadequate tissue is obtained, are not required to undergo a repeat biopsy in order to continue on protocol.

The amount of tissue collected will follow the guidelines listed below. If a patient has more than one site of disease, only one site needs to be biopsied, and the site is left to the discretion of the patient and her treating physician. Core biopsies are preferred; punch biopsies may be done when necessary, but fine needle aspirates are not allowed.

Breast:
- A goal of 3-6 core biopsy will be obtained using standard institutional guidelines for a diagnostic core biopsy of a breast mass

Skin/Chest wall:
- A goal of two 5-mm punch biopsies will be obtained

Lymph node/Soft tissue:
- A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle.

Liver:
- A goal of 3-6 core biopsy specimens will be obtained using an 18-gauge needle.

Lung:
- Because of the risk of pneumothorax associated with core needle biopsies of lung nodules, no core biopsies of lung nodules will be performed on this protocol; unless if they are clinically indicated.

Bone:

- Because the yield of malignant tissue from bone biopsies tends to be relatively low, if a patient has another accessible site of disease (e.g., skin, lymph node, liver), that site should be biopsied preferentially. If bone is the only biopsy-accessible site, then a goal of 1-3 core biopsy specimens will be obtained using an 11 to 13-gauge needle.

Please note that the above are guidelines for the amount of tissue to be obtained and are not meant to replace clinical judgment at the time the procedure is performed. Less than the goal quantity of tissue is accepted for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure. If ascites or pleural fluid is to be used as the investigational biopsy specimen, consideration should be given to confirming the malignant nature of the ascites or pleural fluid prior to study entry.

In order to minimize the risk of a biopsy, only qualified personnel will perform these procedures. Prior to the procedure, the physician performing the procedure will discuss the risks with each study participant, answer any questions, and obtain a separate procedure consent. Patients will be evaluated for co-morbidities or concomitant medications that may increase the risk of potential complications. For biopsies of lesions that are not superficial and clearly palpable, imaging studies such as CT or ultrasound will be used to guide the biopsy in order to minimize the risk of damage to adjacent structures. After lymph node biopsies, patients will be observed a minimum of 2 hours (range 2-4 hours) after the procedure, or according to standard institutional guidelines. After liver biopsies, patients will be observed a minimum of 4 hours (range 4-6 hours) after the procedure, or according to standard institutional guidelines. Less than the goal quantity of tissue is accepted for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure.

9.3.4 Handling of Fresh Tissue Biopsy Specimens(s)

Following the biopsy of a specimen, all tissue cores will be snap-frozen in OCT compound intra-operatively. After the biopsy is performed, the tissue mass is placed on a dry sterile gauze and the tumor tissue is separated using forceps. Two pieces (cores) of tumor tissue are placed on a pre-frozen bed of OCT in each cassette, typically ending up with 3 cassettes per biopsy (the last cassette will contain many small pieces of tumor tissue). Cassettes are then filled with OCT, completely covering the tissue and limiting the amount of bubbles (forceps can be used to pop any bubbles). Tissue must be frozen immediately by placing cassettes on dry ice in a biohazard cooler; freezing of samples in OCT with dry ice takes about 10 minutes freezing time. Once samples are frozen, place in plastic bag; label bag with date, protocol number, patient number, patient initials, and number of biopsy samples included. Store in -80ºC freezer until the time of shipment.

All samples will be anonymized by assigning a unique sample ID number prior to use. Tissue biopsy collection and processing materials are not provided by the study. Coded laboratory specimens will be stored in the Tumor Bank of the DF/HCC. These specimens will become the property of DF/HCC. In cases where the research sample is forfeited for clinical purposes, this sample will be flagged in spreadsheet to indicate it can be used for research purposes if there is any left over after clinical use.

9.3.5 Shipping of Biopsy Specimen(s)

Complete the Specimen Requisition Form (Appendix F) to be sent with the biopsy samples. Make a copy of the requisition for the participant's research chart prior to sending.

Ship biopsy samples overnight Monday – Thursday to:

[redacted]

Email the assigned study coordinator and [redacted] with the sample information and tracking information the day before shipping specimens. Please include UPS or FedEx tracking information for the sample.

9.4 Sites Performing Correlatives

Brigham and Women's Hospital
Dana Farber Cancer Institute (DF/HCC Core Blood and Tissue Bank, Functional Cancer Epigenetics)
The Broad Institute of MIT

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 4 weeks prior to registration. Scans and x-rays must be done ≤4 weeks prior to registration. MUGA or echo must be done within 60 days prior to registration. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted. ECHO/MUGA assessments should be performed within 7 days of the protocol-specified date; scans performed +/- 7 days from the protocol-specified date. Subjects who discontinue study therapy but have responsive or stable disease will be followed approximately every 3-6 months for progression and overall survival. Minor deviations in scheduling of procedures (i.e. cycle 1 procedures, +/- 3 days; from cycle 2 forward treatment schedule, -3 days to +7 days; from Cycle 3 forward, +/- 7 days) are allowed to accommodate for vacation, holidays, or patient convenience.

Table 7: Study Calendar

	Baseline	Cycle 1			Subsequent Cycles			End of therapy or Progression	Follow up (every 6 months)
	≤ 4 Weeks prior to registration	Day 1	Day 2, 3, 4 (In person or by phone)	D15	Day 1	Every 2 cycles	Every 3 cycles		
Informed consent	X								
Patient Education for Diarrhea	X	X							
Demographics	X								
Medical/surgical history	X								
Concomitant medications (See Section 5.4)	X	X			X			X	
Height	X								
Vital Signs (Weight, Blood Pressure)	X	X		X	X				
Physical examination, ECOG PS	X	X			X			X	
12-lead EKG	X								
MUGA or echocardiogram [A]	X						X		
Urine Pregnancy test	X								
Urinalysis	X								
CBC, including differential and platelets[B]	X	X			X			X[F]	
Serum chemistries [B]	X	X			X				
Research Collection: Blood or Tissue [C]	X[C]	X		X	X			X	
Tumor Evaluation (MRI or CT and clinical assessment of visible of palpable lesions) [D]	X					X			
Bone scan [E]	X					X			
Adverse event evaluation		X	X		X			X	
Phone call to assess for diarrhea (See Sections 5.3.3.)			X						
Phone call for survival assessment and subsequent therapies (See Section 5.6)									X

A. Baseline MUGA or ECHO within 60 Days prior to registration. It is strongly recommended to us the same method of cardiac evaluation at each time point. ECHO/MUGA assessment will be completed at the end of every 3 cycles and should be completed within 7 days of the subsequent cycle. If ECHO/MUGA completed on Day 1 of the applicable cycle, a preliminary read of the test will be needed before the patient can be dosed on Day 2 of the cycle. If a preliminary read is not available, the patient should be told to hold neratinib until the result becomes available.
B. Hematology: PTT and PT/INR drawn at baseline for all patients and at end of therapy/progression for patients who undergo the optional biopsy. Chemistries: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, total protein, albumin, total bilirubin, SGOT(AST), SGPT(ALT), Alkaline Phosphatase
C. See Section 9.
D. Patients should have imaging of the Chest-Abdomen-Pelvis at baseline. After completion of 12 cycles, scans can decrease in frequency to every 3 cycles. If there are no pelvic lesions or abnormalities identified, future imaging may include chest and abdomen only, as appropriate. For alternative imaging options (non-CT), please see 11.1.3. Window around imaging is +/- 7 days.
E. Bone scan not required for study but may be done at baseline and every 2 cycles (+/- 7 days), if clinically indicated.
F. PTT and PT/INR only, for patients who undergo the optional biopsy

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 2 cycles (or 8 weeks). After completion of 12 cycles, scans can decrease in frequency to every 3 cycles. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

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 by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease,

abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should 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 should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as

assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm

short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: 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. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 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.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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, including the baseline measurements.

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category;

summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix E.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12.4 Collaborative Research and Future Use of Data and Samples

Tissue, blood, stool, bodily fluids, and other materials derived from these will be collected in this study to analyze genes, DNA, RNA, proteins and cells for the study's correlative endpoints and potential future research, utilizing new types of biomarker testing as it becomes available.

These samples and any data generated as a part of these clinical trials may be used for future research studies and may be provided to collaborating investigators both within and outside of the DF/HCC for either correlative endpoints or secondary use. Samples and data may be shared with outside non-profit academic investigators, as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate. When samples or data are sent to collaborators and when any research is performed on them, all information will be identified with a code, and will not contain any PHI, such as name, birthday, or MRNs.

In order to allow the greatest amount of research to be performed on the specimens and information generated as a part of this trial, researchers in this study may share results of genetic sequencing with other scientists. De-identified specimen or genetic data may be placed into one of more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). The results from the correlative research on this study will be shared with these public databases. Through such databases, researchers from around the world will have access to de-identified samples or data for future research. More detailed information, beyond the public database, may only be accessed by scientists at other research centers who have received special permission to review de-identified data.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a randomized two-arm phase II study of neratinib +/- fulvestrant in patients with metastatic ER+/HER2+ breast cancer. The primary objective is to compare the progression-free survival between neratinib monotherapy versus neratinib plus fulvestrant. The endpoint is progression-free survival (PFS) defined as the interval from the date of randomization to progression or death. Patients who are alive and progression-free will be censored at the date of last disease assessment. Randomization will be 1:1 within stratum defined by the number of prior lines of therapy (≤ 3 versus ≥ 4) and prior use of fulvestrant (yes or no). Prior to Version 2 of the protocol, participants were stratified by the number of prior lines of therapy (≤ 3 versus ≥ 4) and PR expression (0-10% vs. 11% or more).

13.2 Sample Size, Accrual Rate and Study Duration

The total planned sample size is 152 patients (76 patients on each arm), which is calculated based on the number of randomized patients and defines the intention-to-treat population for efficacy analysis. The study is sized to have 82.3% power to detect improvement of median PFS from 4 months with neratinib monotherapy to 6 months with neratinib + fulvestrant (HR=0.67) using a stratified logrank test with a one-sided alpha level of 0.1, and final analysis to occur when 125 PFS events are observed. This assumes that the total planned sample size is enrolled at a constant accrual over 18 months with 6 months of additional follow-up, and a constant hazard of PFS and dropout such that 5% of patients are lost-to-follow-up at 1 year. One futility analysis is planned at 50% information (63 PFS events) and will stop early if the Z-statistic from the logrank test is less than 0 (i.e. observed HR from a Cox model > 1.0). No early stopping for efficacy will be considered. Power and sample size were calculated using East v6.4 (Cytel Inc., Cambridge MA).

We anticipate enrollment of approximately 8.5 patients per month. Patients will be followed for up to five years after removal from study or until death, whichever occurs first.

13.3 Stratification Factors

We will stratify patients based on two factors: number of prior lines of therapy (≤ 3 versus ≥ 4) and prior use of fulvestrant (yes or no).

13.4 Analysis of Primary Endpoints

The primary analysis of the study will be the comparison of PFS per RECIST 1.1 between neratinib monotherapy versus neratinib plus fulvestrant using a stratified logrank test with a overall one-sided Type I error rate at 0.1.

All inferences will be conducted in the intent-to-treat manner with all randomized patients

evaluated according to treatment assignment that was given, and the survival function will be summarized using the Kaplan-Meier methods according to randomized treatment assignment. Final analysis will be performed after 126 PFS events are observed or at least 12 months after the last patient is enrolled on study, whichever occurs first.

13.5 Analysis of Secondary Endpoints

13.5.1 We will estimate the clinical activity, as measured by overall survival (OS) of neratinib combined with fulvestrant compared with neratinib alone in patients with inoperable locally advanced or metastatic HER2-positive, ER-positive breast cancer. OS is defined as the length of time from randomization until death from any cause.

13.5.2 We will estimate the clinical activity, as measured by objective response rate (ORR) of neratinib combined with fulvestrant compared with neratinib alone in patients with inoperable locally advanced or metastatic HER2-positive, ER-positive breast cancer. ORR is defined as the proportion of patients with CR or PR according to RECIST v1.1.

13.5.3 We will estimate the clinical activity, as measured by duration of response (DoR), of neratinib combined with fulvestrant compared with neratinib alone in patients with inoperable locally advanced or metastatic HER2-positive, ER-positive breast cancer. DoR is defined as the time from the date of first evidence of CR or PR to the date of objective progression (according to RECIST v1.1) or death from any cause, whichever is earlier.

The hazard ratio for each secondary time-to-event endpoint will be estimated with 95% confidence intervals derived from the Cox proportional hazard model, but no hypothesis testing will be conducted. Objective response per RECIST 1.1 will be reported with 95% exact confidence intervals using a Pearson chi-squared test for difference in proportions with a one-sided alpha of 0.1.

13.6 Analysis of Correlative Endpoints

13.6.1 The proportion of patients with *ESR1* gene mutations, *PIK3CA* gene mutations, and loss of PTEN expression in baseline tumor tissue, and the proportion of patients with *PIK3CA* and *ESR1* gene mutations in circulating tumor DNA (ctDNA) from blood obtained at study baseline will be summarized using 95% binomial exact tests and exploratory analyses will characterize the association of molecular phenotypes with other patient and disease characteristics using Fisher exact tests.

13.6.2 The concordance of *PIK3CA* mutation status and *ESR1* mutation status assessed in circulating free tumor DNA and distant metastasis specimens (i.e. liquid and solid biopsies) will be assessed using kappa statistics with 95% confidence intervals obtained from bootstrap resampling. Operating characteristics including sensitivity, specificity, PPV and NPV will be used to summarize the performance of the liquid biopsy against solid biopsy as the 'gold standard'. For any quantitative assessments of mutation status in the liquid biopsy, we will use ROC analysis to explore thresholds to optimize the linear combination of sensitivity and specificity (i.e. Youden index) for either absolute counts or estimates of the allele frequency. The following table provides the levels of precision in estimating sensitivity for varying failure rates of the paired assays and anticipated prevalence of 40% (PIK3CA) and 20% (ESR1) gene mutations.

		Maximum Width of CI for Sensitivity	
Failure rate	Number of evaluable pairs	40% prevalence	20% prevalence
10%	137	0.39	0.28
20%	122	0.41	0.29
30%	106	0.44	0.31

13.6.3 All other molecular characterization of potential resistance mechanisms, predictive biomarkers, and immunological function by collecting blood and tumor specimens will be exploratory and descriptive-only.

13.7 Reporting and Exclusions

All eligible participants included in the study will be evaluable for analysis.

13.7.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment.

13.7.2 Evaluation of the Primary Efficacy Endpoint

All eligible participants included in the study will be assessed for response/outcome to therapy for the primary endpoint, even if there are major protocol therapy deviations.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

15. REFERENCES

1. Estimated Cancer Deaths by Sex and Age Group, 2015. 2015; http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044509.pdf. Accessed June 10, 2015.
2. Rabindran SK, Discafani CM, Rosfjord EC, et al. Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. *Cancer research.* 2004;64(11):3958-3965.
3. Burstein HJ, Sun Y, Dirix LY, et al. Neratinib, an Irreversible ErbB Receptor Tyrosine Kinase Inhibitor, in Patients With Advanced ErbB2-Positive Breast Cancer. *J Clin Oncol.*
4. A phase two randomised trial of neratinib monotherapy versus lapatinib plus capecitabine combination therapy in patients with HER2+ advanced breast cancer ☆. 2013;49(18):3763–3772.
5. Awada A, Dirix L, Beck HL, et al. Safety and Efficacy of Neratinib (HKI-272) in Combination with Vinorelbine in ErbB2+ Metastatic Breast Cancer. Presented at the San Antonio Breast Cancer Symposium, December 2009. .
6. Chow LW-C, Xu B, Gupta S, et al. Combination neratinib (HKI-272) and paclitaxel therapy in patients with HER2-positive metastatic breast cancer. *British Journal of Cancer.* 2013;108(10):1985-1993.
7. Howell A, Robertson JF, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(16):3396-3403.
8. Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2002;20(16):3386-3395.
9. Leo AD, Jerusalem G, Petruzelka L, et al. Final Overall Survival: Fulvestrant 500mg vs 250mg in the Randomized CONFIRM Trial. 2013.
10. Robertson JFR, Steger GG, Neven P, et al. Activity of fulvestrant in HER2-overexpressing advanced breast cancer. 2010.
11. Arpino G, Wiechmann L, Osborne CK, Schiff R. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. *Endocrine reviews.* 2008;29(2):217-233.
12. Massarweh S, Osborne CK, Creighton CJ, et al. Tamoxifen Resistance in Breast Tumors Is Driven by Growth Factor Receptor Signaling with Repression of Classic Estrogen Receptor Genomic Function. 2008.
13. Giuliano M, Hu H, Wang Y-C, et al. Upregulation of ER Signaling as an Adaptive Mechanism of Cell Survival in HER2-Positive Breast Tumors Treated with Anti-HER2 Therapy. 2015.
14. Rimawi MF, Mayer IA, Forero A, et al. Multicenter Phase II Study of Neoadjuvant Lapatinib and Trastuzumab With Hormonal Therapy and Without Chemotherapy in Patients With Human Epidermal Growth Factor Receptor 2–Overexpressing Breast Cancer: TBCRC 006. 2013.

15. Chan A, Delaloge S, Holmes FA, et al. Neratinib after adjuvant chemotherapy and trastuzumab in HER2-positive early breast cancer: Primary analysis at 2 years of a phase 3, randomized, placebo-controlled trial (ExteNET). *Journal of Clinical Oncology*. 2015;33(suppl; abstr 508).
16. Sudhan DR, Schwartz LJ, et al. Extended Adjuvant Therapy with Neratinib Plus Fulvestrant Blocks ER/HER2 Crosstalk and Mainatins Complete Responses of ER+/HER2+ Breast Cancers: Implications to the ExteNET Trial. *Clinical Cancer Research*: 2018

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 Neratinib Pill Diary

Name_____ **Subject #** _____ **Dose** _____ **Cycle** _____

Day	Date (DD-MM-YY)	Time Taken	No. of neratinib capsules taken
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			

*Please take your neratinib capsules at the same time every day with food. Avoid grapefruit, grapefruit juice, grapefruit hybrids and starfruit.

*Please do not make up any missed doses (or vomited doses). If you forget to take your neratinib dose within 12 hours of the usual time, do not take it that day. Restart taking neratinib the next day.
*Neratinib can be stored at ambient temperature. If you are taking an acid-reducing medication (such as lansoprazole or ranitidine) please consult with your doctor.

Please contact your study team with any questions.

Subject Signature _____ Date _____
Reviewed by _____ Date _____
(Study staff)

APPENDIX C Patient Instructions for Management of Diarrhea

Please review these instructions with your study doctor/team. Once all of your questions are answered, sign at the bottom and make sure you are given a copy of these instructions to take home.

Diarrhea is the most common side effect you may have while participating in this study. Diarrhea usually starts within a few hours to a few days of the first dose of study drug. In order to reduce or even prevent diarrhea as far as possible, you will be supplied with anti-diarrheal medicines called loperamide and colestipol to take at the start of the study. **Use of anti-diarrheal medication is required for all enrolled subjects to help reduce or prevent diarrhea.** Loperamide and colestipol will be dispensed directly by your study doctor/team on day 1 with the instruction to initiate treatment with loperamide and colestipol on the same day as you take your first dose of neratinib.

The first dose of colestipol should be taken at least 4 hours before neratinib and loperamide. The second dose of colestipol should be taken at least 2 hours after neratinib and loperamide.

Your study doctor/team will call you on Cycle 1 Day 2, Cycle 1 Day 3, and Cycle 1 Day 4 after your first dose of study drug to find out if you are experiencing diarrhea and to provide further treatment instructions and advice if necessary.

If you are having new-onset diarrhea, persistent diarrhea or diarrhea with increase of 7 or more stools per day over usual, call your study doctor/team at phone number _____ to let them know so they can work with you to control the diarrhea. If you are dizzy or weak because of diarrhea, go to the study doctor's office or go to the hospital immediately.

Please record the number of stools and any anti-diarrheal medication taken during all cycles of the study along with the daily dose of study medication.

<u>Information to provide when talking to your doctor</u>

When talking to the study doctor/team I will provide as much of the information below as possible, in order to help my study doctor/team to assess my diarrhea and decide on the best treatment:

- Number of stools per day as compared to my normal bowel habits
- Presence of diarrhea during the night
- Presence of fever, dizziness, abdominal pain/cramping, or weakness
- What the stool looks like, that is, watery stools, blood, or mucus
- When I took my last study drug
- Any other information that could explain my diarrhea (food, recent travel, contact with other people with diarrhea).

1. Medications to treat diarrhea

My study doctor/team will provide me with loperamide and colestipol on day 1 with the instruction to start treatment with loperamide and colestipol along with the first dose of neratinib. I need to take the medications as directed by my study doctor/team.

Loperamide:

- I will start loperamide with the first dose of neratinib
- I will take 2 tablet/capsule (4 mg) three times a day for the first two weeks; if I get constipated, I should contact my study doctor/team who will instruct me on how often and how much loperamide to take but I should not stop taking loperamide.
- After the first two weeks, I will take 2 tablets (4 mg) twice a day onwards through the first cycle of therapy (28 days) from the start of neratinib regardless of whether I have diarrhea or not.
- If I continue to have diarrhea while taking loperamide, I should contact my study doctor/team for additional anti-diarrheal medication and consult.
- If I have diarrhea with increase of up to 6 stools per day over usual any time after completing the first cycle of therapy and I am not taking any anti-diarrheal medication, I will take 2 tablets/capsules (4 mg) immediately after the first loose stool and then 1 tablet (2 mg) every 4 hours or after each loose stool to a maximum dose of 8 tablets/capsules (16 mg) in any 24 hour period until I haven't had any loose stool for at least 12 hours.

Colestipol:

- I will take 2g of colestipol twice a day for the first 28 days of treatment along with the neratinib and loperamide.
- **I will take the first dose of colestipol at least 4 hours before neratinib and loperamide prophylaxis, and I will take the second dose at least 2 hours after neratinib and loperamide prophylaxis.**
- Take colestipol with plenty of water or other appropriate liquid. Do not cut, crush, or chew tablets.
- Other medication (Study doctor/team to write in name of medication and instructions):

_____

_____

In case of more severe diarrhea and any diarrhea associated with fever, pain, infection, or dehydration, I may receive IV fluids, antibiotics and/or other medications.

2. Changes to my diet to treat diarrhea

If I have diarrhea, I will:

- Stop all lactose-containing products (milk, yogurt, cheese, etc)
- Drink 8 to 10 large glasses of clear liquids per day
- Eat frequent small meals
- Eat low fat foods such as the BRAT diet that includes **b**ananas, **r**ice, **a**pplesauce, and/or **t**oast:

- The BRAT diet is a bland diet that is low in fat and fiber and will not irritate the stomach;
- Bananas are high in potassium and can cause constipation which can help alleviate the diarrhea
- Other similar foods are crackers, cooked cereals and pasta
- This diet is not complete in nutrients and should only be taken for a short period of time and only upon the doctor's advice.

My study doctor/team may have other suggestions for me. (Study doctor/team to write in any suggestions).

_____

_____

3. <u>Study Medication adjustments</u>

If I am experiencing loose stools or diarrhea and cannot reach my study doctor/team immediately, I will start taking anti-diarrheal medication per the instructions above until further advice is given by my study doctor/team. If I have more than 4-6 stools per day compared to normal despite taking anti-diarrheal medication for 24 hours, and I cannot reach my study doctor/team, I will stop taking the study medication and wait for further instructions from my study doctor/team.

My signature below indicates I have reviewed this information and have received the following medications:

- Neratinib Tablets
- Loperamide
- Colestipol

_____

Study participant name Study participant Signature and Date

_____

Investigator delegate name Investigator delegate Signature and Date

OR

_____

Investigator name Investigator Signature and Date

APPENDIX D Medications to use with caution while on study

List of Cytochrome P450 Inhibitors and Inducers (updated list also available at http://medicine.iupui.edu/clinpharm/ddis/table.aspx)

INHIBITORS

Norfloxacin (3A4)
Ritonavir (3A4)
Clarithromycin (3A4)
Erythromycin (3A4)
Fluconazole (3A4)
Fluvoxamine (3A4)
Grapefruit juice (3A4)
Grapefruit-containing products (3A4)
Indinavir (3A4)
Itraconazole (3A4)
Ketoconazole (3A4)
Mibefradil (3A4)
Miconazole (3A4)
Nefazodone (3A4)
Nelfinavir (3A4)
Saquinavir (3A4)
Troleandomycin (3A4)
Voriconazole (3A4)

Amiodarone
Cannabinoids
Fluoxetine
Lopinavir
Metronidazole
Quinine
Sertraline
Zafirlukast

INDUCERS

Barbiturates
Cotrimoxazole
Efavirenz
Ethosuximide
Methadone
Metyrapone
Mexiletine
Nevirapine
Oral contraceptives
Rifabutin (3A4)
Rifampin (3A4)
St. John's wort (3A4)
Troglitazone

In boldface are identified strong CYP3A4 inducers/inhibitors.

From: Tatro BO. *Drug Interaction Facts 2003: The Authority on Drug Interaction;*.2003.

APPENDIX E MULTICENTER GUIDELINES

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: Dana-Farber Cancer Institute (DFCI) is responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (Food and Drug Administration (FDA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA, etc.). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution or Project Manager) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible for ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, [redacted] will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials).
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.

- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center

Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

Refer to protocol Section 4.3 and 4.4 of the protocol for the participant registration process.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. This number is unique to the participant on this trial and must be used for CRF/eCRF completion and correspondence. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the

IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol Section 7.0.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

The DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC CTRIO provides a web based training for all eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

Neratinib will be ordered from [redacted] The ordering of investigational agent is specified in the protocol Section 8.1.8.

Fulvestrant is commercially available. Check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution with the aid of the ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will be required to submit participant source documents to the DF/HCC Lead Institution or designee for monitoring. Participating Institutions may also be subject to on-site monitoring conducted by the DF/HCC Lead Institution.

The DF/HCC Lead Institution will implement on-site and virtual monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. At minimum, the DF/HCC Lead Institution, or designee, will monitor each participating site twice a year while patients are receiving study treatment. Should a Participating Institution be monitored once and then not accrue any additional participants or participant visits, then a second monitoring visit may not be necessary.

Monitoring practices may include but are not limited to: source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management. Additionally, ongoing communication will occur through regularly scheduled teleconferences and by email. Source documents from Participating Institutions, will be collected at specific timepoints to support the primary and/or secondary endpoints.

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. Participating

Institutions will be required to provide access to participants' complete medical record and source documents for verification during on-site visits. Upon request, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the Participating site. If there are protocol compliance concerns, issues that impact subject safety or the integrity of the study, or trends identified based on areas of need, additional monitoring visits may occur.

Virtual Monitoring: On-site monitoring visits will be supplemented with virtual monitoring visits. The DF/HCC Lead Institution will request source documentation from Participating Institutions as needed to complete virtual monitoring activities. Participating Institutions will be asked to forward de-identified copies of participants' medical record and source documents to the DF/HCC Lead Institution to aid in the source documentation verification process.

In addition to monitoring performed by the Coordinating Center, the DF/HCC ODQ may monitor data for timeliness of submission, completeness, and adherence to protocol requirements. The DF/HCC Lead Institution or designee and, if applicable, the ODQ Data Analysts will perform ongoing protocol data compliance monitoring with the support of the Participating Institution's Coordinators, the Principal Investigators, and the Protocol Chair.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting accrual expectations may be subject to termination. Sites are expected to accrue at least 3 patients per year.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ).

Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or external) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and the DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX F SPECIMEN REQUISITION

Complete this form and include with the specimen shipment (make a copy for the participant's research chart). Label ALL materials with participant initials, DFCI participant study ID, and the date and time the specimen was obtained. Include a pathology report with any archival tissue specimens being submitted. Refer to Section 9 for additional details.

Ship BLOOD and BIOPSY specimens to:
DF/HCC Core Blood & Tissue Bank
Brigham and Women's Hospital
20 Shattuck Street
Thorn Building-Room 428
Boston, MA 02215

Ship archival BLOCKS and SLIDES to:
Dana Farber Cancer Institute
Breast Oncology
450 Brookline Avenue, Dana 157
Boston, MA 02215

Specimen Information

Participant Initials (FML): _____ DFCI Participant Study ID Number: _____ Date specimen(s) shipped: _____

Time Point:
- ☐ Screening
- ☐ Cycle 1 Day 1
- ☐ Cycle 1 Day 15
- ☐ Cycle ____ (fill in) Day 1
- ☐ End of Treatment

Specimen Type *(indicate inclusion in shipment by checking box)*	**Pathology Number(s) or Serial Coding (if applicable)**	**Quantity submitted**	**Date specimen obtained**	**Time specimen obtained** (24 Hour Clock)
☐ Streck Tubes (Circulating Tumor DNA)				
☐ Archival tissue block				
☐ Slides				
☐ Biopsy core(s) frozen in OCT				
☐ Biopsy core(s) frozen in OCT				

Site information for block/tissue return if collected: _____
_____