MD Anderson IND Sponsor Cover Sheet

Protocol ID	2016-0537
Protocol Title	A phase 1b study of neratinib, pertuzumab and trastuzumab with taxol (3HT) in metastatic and locally advanced breast cancer, and phase II study of 3HT followed by AC in HER2 + primary IBC, and neratinib with taxol (NT) followed by AC in HR+ /HER2- primary IBC
Protocol Version	21
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IND Sponsor	MD Anderson Cancer Center
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1.0 TRIAL SUMMARY

Abbreviated Title	Combination of neratinib in metastatic and locally advanced (stage III) HER2+ breast cancer in phase Ib Combination of neratinib in locally advanced (stage III) HER2+ IBC and HER2-/HR+ IBC in phase II
Trial Phase	Ib/II
Clinical Indication	3HT (neratinib, pertuzumab, trastuzumab: triple HER2 targeting therapy in combination with paclitaxel) in metastatic or locally advanced breast cancer in phase Ib 3 HT follwed by AC in HER2 positive primary IBC, and NT (neratinib with paclitaxel) followed by AC in HER2 negative/ HR positive primary IBC in phase II
Trial Type	Open label, non- randomized, single center
Type of control	None
Route of administration	neratinib: PO pertuzumab, trastuzumab, paclitaxel, doxorubicin, cyclophosphamide : IV
Trial Blinding	Open label
Treatment Groups	Three cohorts
Number of trial subjects	Maximum 99
Estimated duration of trial	5 years. Expected to start: March 2017, and end February 2022
Duration of Participation	6 months

2.0 OBJECTIVES & HYPOTHESES

2.1 Primary Objectives & Hypotheses

2.1.1 Cohort I:

- Phase Ib: To determine the maximum tolerated dose (MTD) of neratinib in combination with paclitaxel, pertuzumab, and trastuzumab in HER2-positive (HER2+) metastatic or locally advanced (stage III) breast cancer within 2 cycles.

- Phase II: To determine the pathologic complete response (pCR) rate of neratinib in combination with paclitaxel, pertuzumab, and trastuzumab followed by doxorubicin and cyclophosphamide (AC) in HER2+ metastatic or locally advanced (stage III) inflammatory breast cancer (IBC) patients.

2.1.2 Cohort II:

To determine the pCR rate of neratinib in combination with paclitaxel followed by AC in HER2-negative/HR-positive (HER2-/HR+) metastatic or locally advanced (stage III) IBC patients.

Hypothesis: The addition of neratinib will improve the pCR rate in both HER2+ and ER+/HER2- primary IBC by pan-HER activity that enhances the effective suppression of HER2, EGFR and possibly via suppression of HER2 mutation.

2.2 Secondary Objectives

- To estimate 2 years progression free survival (PFS) rate of HER2+ metastatic or locally advanced (stage III) IBC patients, and HER2-/ HR+ IBC patients treated with neratinib plus anthracycline and taxane based chemotherapy (Cohort I Phase II and Cohort II).

- To determine toxicity and safety of the combination therapy.

2.3 Exploratory Objective

- To determine the adaptive target and downstream changes in pan-HER family members induced by one-week window period of neratinib based on tissue and blood based biomarkers.

- To determine the correlation between positive/negative changes in EGFR, HER2 and HER4 and the occurrence of pCR.

- To determine the rate of HER2 mutation in HER2+ IBC and HER2-/ HR+ IBC.

- To determine the association between HER2 mutation and pCR achieved by study combination therapy.

- To determine the correlation between tumor tissue based pharmacodynamic marker changes in association with CTC and ctDNA.

3.0 BACKGROUND & RATIONALE

3.1 Inflammatory Breast Cancer (IBC)

Inflammatory breast cancer (IBC) is rare, but the most aggressive form of primary breast carcinoma and has distinctive biological features, and confers poor prognosis by local and distant metastasis and frequent recurrence[1]. IBC is defined by a rapid onset of diffuse skin erythema, edema, involving more than 2/3 of the breast resulting in a pitted appearance (peau d'orange), as well as tenderness, induration and warmth of the involved breast[2].

The outcome for patients with IBC is bleak despite multimodality treatment approaches; 3-OS rates after combined chemotherapy, surgery, and radiation are only 40% compared to 80% for non-inflammatory breast cancer [3, 4]. At the time of initial diagnosis, most IBC patients have lymph node involvement and approximately 30% have distant metastases [5].

At this time, combined-modality treatment (neoadjuvant anthracycline-taxane-based chemotherapy, mastectomy, adjuvant chemotherapy, and radiotherapy) is considered to be a standard of care for IBC[3].

3.2 Preclinical Data and Clinical data of Neratinib

- **Preclinical Data of Neratinib**

Neratinib (HKI-272), an orally administered small molecule, is an irreversible inhibitor of pan ErbB receptor tyrosine kinases, by binding to the cysteine residue in the ATP-binding pocket of the receptor. Neratinib inhibits tyrosine kinase activity of dimers such as HER1:1, HER1:2, HER1:3 and HER2:3. Both inhibitors bind to the ATP sites of these enzymes and prevent phosphorylation and activation of downstream signaling pathways. Neratinib has shown to be highly active *in vitro* against cell lines overexpressing ErbB2 or ErbB1[6]. And neratinib effectively inhibits the proliferation of EGFR and HER2 expressing cells that are resistant to treatment with first-generation ErbB receptor tyrosine kinase inhibitors such as gefitinib[7].

In BT474 cell lines, HKI-272 effectively repressed phosphorylation of MAPK and Akt signal transduction pathways, whereas trastuzumab failed to completely inhibit HER2 receptor phosphorylation or downstream signaling events. The Ras-Raf-MAPK pathway and the phosphotidylinositol-3-kinase (PI3K)/Akt pathway are the two major downstream pathways initiated as a consequence of HER2 receptor activation. Consistent with erbB-2 inactivation, neratinib results in inhibition of downstream signal transduction events and cell cycle regulatory pathways. As a consequence, neratinib treatment of BT474 cells results in the inhibition of MAPK and Akt phosphorylation, down-regulation of cyclin D1 levels, and induction of p27. Actually, neratinib was shown to be more effective compared to trastuzumab as a single agent. Moreover the combination treatment of neratinib and trastuzumab significantly reduced tumor size compared to trastuzumab alone ($P<0.001$) or neratinib alone ($P<0.05$)[8].When compared to trastuzumab, inhibition of these pathways was more complete with neratinib[6].

Given the highly specific and potent tyrosine kinase inhibition of neratinib, it is postulated that breast cancer cells resistant to trastuzumab on the basis of enhanced signaling through alternative pathways (i.e. HER2/HER3 heterodimerization) or mechanisms preventing antibody binding to HER2 would retain sensitivity to neratinib. Neratinib shows activity in some cell lines which are innate and acquired trastuzumab resistance, and innate lapatinib resistance in HER2 positive breast cancer as an irreversible inhibitor of EGFR, HER2 and HER4 tyrosine kinase activity [9]. In preclinical studies, neratinib has shown to inhibit HER2/HER2, EGFR/HER2, and HER2/HER3 homo- and hetero-dimers and downstream signaling effectors (RAF, ERK, AKT) regardless of trastuzumab resistance or ligand association[6, 10-12]. The specificity, potency and irreversibility of neratinib may be even more effective at promoting complete inhibition of HER pathway signaling and bypassing resistant mechanisms. Neratinib also showed to increase ADCC responses of trastuzumab by stabilizing and accumulating inactive HER2 receptor dimers (HER2/HER2, HER2/EGFR, HER2/HER3) at the cell surface, thereby, increasing trastuzumab binding and immune-mediated action[13, 14]. In tumor xenografts with HER2 overexpressed cell lines, neratinib shown to suppress tumor growth in a dose-dependent manner, that further support efficacy induced by neratinib itself [6].

The other interesting data regarding neratinib includes the anti-HER2 mutation activity. Seven activating HER2 mutations were detected in HER2 gene amplification negative breast cancer, and all of these mutations were sensitive to neratinib. Other HER2 targeted drugs were less potent and not effective in reducing the growth of cells bearing HER2 mutations.

- **Clinical Data of Neratinib**

Neratinib has demonstrated its antitumor activity in phase I and II clinical studies in patients with HER2 positive breast cancer, including ones with or without prior exposure to trastuzumab, as well as in patients with other solid tumors.[15, 16]

In a Phase I clinical trial of neratinib, the dose-limiting toxicities (DLT) were diarrhea, nausea and vomiting, anorexia, and rash. DLT was reached at 320 mg orally per day. The MTD was 240 mg/day. The overall response rate observed in breast cancer patients in the Phase I study was 32% (8/25), and within 18 patients with HER2+ by IHC (3+) was 39% (7/18).

A Phase II study evaluated neratinib as monotherapy at a dose of 240 mg per day in patients with HER2+MBC. Response rate was 24% in 63 patients who had previous treatment with trastuzumab and 56% in 64 patients who were trastuzumab-naïve. The most common adverse events, all grades, in both cohorts included diarrhea 89% to 97% (grade 3-4 43%), nausea 30% to 42%, and rash/dermatitis 13% to 27%. Hand-foot syndrome was not observed [16].

In adjuvant setting, sequential therapy with 1 year of trastuzumab followed by 1 year of neratinib—ExteNET study showed improved disease-free survival. In this study, stage 2–3 HER2-positive breast cancer who had completed trastuzumab therapy up to 1 year previously. Patients were randomly assigned (1:1) to receive oral neratinib 240 mg per day or matching placebo, and the PFS was 93.9% in neratinib group vs 91.6%. While further longer follow up is warranted to confirm this early signal, this study proved the benefit of additional use of neratinib in HER2 positive breast cancers [17].

3.3 Rationale for Selected Subject Population

- **Cohort I phase Ib: HER2+ metastatic and locally advanced breast cancer**

This phase Ib is performed to determine MTD and recommended phase 2 dose (RP2D) of neratinib, pertuzumab, trastuzumab and paclitaxel combination.

- **Cohort I phase II: HER2+ in IBC**

HER2+ subtype is higher in IBC (40%) than non-IBC [18], Table 1 shows, HER2+ IBC patients have worse prognosis compared with HER2+ non-IBC. Therefore, it is of significant importance to develop new effective HER2 therapies for this subgroup of patients with IBC. In the US, pertuzumab in combination with trastuzumab and chemotherapy has rapidly gained acceptance as the new standard of care for stage II and III HER-2+ non-IBC and IBC based in NeoSphere[19] and TRYPHAENA[20] studies. The pCR rates were 45.8% and 66.2%, respecetively. In the NeoSphere study (n=417), trastuzumab and pertuzumab, either alone or combined or added to docetaxel, were evaluated preoperatively in women with locally advanced and inflammatory breast cancer. The pCR were as follows: trastuzumab plus docetaxel (TH), 29%; trastuzumab,

pertuzumab plus docetaxel (THP), 46%; trastuzumab and pertuzumab (HP), 17%; and pertuzumab plus docetaxel (TP), 24%. pCR with THP was significantly higher (p=0.014) than with TH which was significantly higher than with HP (p=0.020)[19]. However, the resistance to first and second generation HER2 targeted therapy still occurs. Given the higher proportion among molecular subtypes, and the lower pCR rate compared to non-IBC patients, our question is whether simple double HER2 targeting therapy in HER-2+ IBC is sufficient (e.g., pertuzumab and trastuzumab). Therefore additional HER family blockade by a irreversible inhibitor of pan ErbB receptor tyrosine kinase, neratinib, may induce additional or synergistic benefit. In breast cancer, HER2/HER3 dimerization promotes the strongest mitogenic signaling, primarily through the PI3K/AKT pathway, which is critical in maintaining cell proliferation and survival[21]. Resistance to targeted therapies is a result of constitutive activation of the PI3K/AKT pathway through upregulation of the HER3 receptor that directly binds and activates PI3K via ligand-dependent and ligand-independent mechanisms [22, 23]. Pertuzumab enhances the efficacy of anti-HER2 inhibition especially with antibody-dependent cell mediated cytotoxicity (ADCC)[8, 24, 25]. Pertuzumab prevents the heterodimerization of HER2: HER3. In HER2 overexpressing cells and tumors that are ligand-independent, enhanced downstream signaling is inhibited by trastuzumab whereas ligand-dependent signaling can be blocked by the addition of pertuzumab to disrupt HER2 homo- and heterodimers [26, 27]. However, small molecule inhibitor also has its own benefit. Neratinib showed a higher response rate than lapatinib in phase non-randomized II trials in HER-2+ MBC. Lapatinib and neratinib response rates in trastuzumab-refractory patients was 5.1% vs. 24%, respectively and in trastuzumab-naïve patients 24% vs. 56%, respectively[16, 28, 38] This data support the rationale that a small molecule TKI may add to the efficacy of trastuzumab and pertuzumab in the neoadjuvant setting. Pertuzumab, another antibody to HER2, binds to domain II and prevents the heterodimerization of HER2:HER3.

Cohort II: HER2-/HR+ in IBC

From our previous study, the pCR rate in IBC patients was worse than non-IBC patients. IBC patients' pCR rate of ER+/HER2-is worse compared with other subtypes. (ER+/HER2+:13.6%; N=96, ER+/HER2-:8.2%; N=231, ER-/HER2+: 31.7%; N=180, ER-/HER2-: 15.2%; N=224; Table 1). Therefore, we need new drug combinations to improve pCR[29] across all molecular subtypes, especially, in ER +/HER2- IBC.

The rate of HER2 mutation in overall breast cancer has previously shown to be approximately 1.6%[9], however from our unpublished data (Matsuda et al), HER2 mutation was found in 4/28 patients in hormone receptor positive IBC patients (14%), which is significantly higher than previously reported rate of mutation. This finding suggests that ER+ IBC patients have more frequent HER2 mutation compared to ER- IBC patients. As shown in above section, neratinib also has activity against HER2 mutated breast cancer cells, offering the second rationale of utilizing neratinib in HER2 negative but hormone receptor positive IBC patients.

More interestingly, our preclinical analysis of IBC cell lines shows that ER+ IBC cell lines over-expressing p-EGFR. EGFR was overexpressed in 30% of IBC, and has been clearly correlated with worse prognosis in patients with IBC [30]. In our ongoing single-arm phase II study in patients with primary HER2- IBC treated with panitumumab, nab-paclitaxel, and carboplatin and FEC preoperative systemic chemotherapy, panitumumab, EGFR tyrosine kinase inhibitor, has antitumor activity against IBC, and supports the role of EGFR aberration in IBC. In this study, 3

out of 15 ER+/HER2- patients (20%) achieved pCR. So an EGFR targeted therapy using neratinib may have a promising role in this sub-type of IBC.

Table1: Summary for pCR rate in IBC (N=731, MDACC data; from 1989 to 2011) and non-IBC (historic data)

	TNBC	ER+/HER2-	ER+/HER2+	ER-HER2+
pCR in IBC	15%	8.2%	14%	32%
pCR in non-IBC	30-40%	7-16%	35%	40-60%

* Most recent small data set HER2 + IBC pCR rate: 39%

We hypothesize that in HR +/HER2- IBC patients, neratinib improve the pCR possibly via: 1) EGFR targeting, 2) HER2 mutation targeting despite lack of clinical amplification of HER2. To test both hypotheses in HR+/HER2- IBC population, we propose a phase II study using neratinib in HR+ HER2- IBC patients, and design a cohort that has expansion criteria for HER2 mutation patients. While the data is accumulating after introduction of trastuzumab and pertuzumab, MDACC's most recent collection of HER2 positive IBC patients showed 9/23 patients achieving pCR (39%), still not optimal and less compared to non-IBC patients.

Taken together, these provide the rationale for adding neratinib, irreversible tyrosine kinase inhibitor of the ErbB family of receptors (epidermal growth factor receptor (EGFR)/HER1, HER2, and HER4), which covalently binds to the cytoplasmic domain of ErbB receptors and prevents downstream signaling [6, 31], for HER2+ and HER2-/HR+ IBC patients. Using neratinib combination therapy is a promising approach for these patients for whom more effective agents have been needed to achieve pCR.

3.4 Rationale for the Dose Selection/Regimen/Modification

Anthracycline-containing regimens (e.g., AC, FAC, EC or FEC) and taxanes (paclitaxel or docetaxel) are the most effective cytotoxic agents in the management of early and advanced breast cancer including IBC[2]. However, with best available chemotherapy combination, the pCR rate among IBC patients is still limited as shown in table 1. This is why targeted agents should be introduced to standard anthracycline (AC) and taxane regimen. However, novel combination should also be safe, and able to be tolerated in breast cancer patients.

The feasibility of safe combination of neratinib and paclitaxel/ neratinib with trastuzumab has been tested in a previous clinical trial, allowing to safely launch of our phase II study. Neratinib dosing of 200 mg/day was chosen as the maximal tolerated dose of NSABP FB-8, a Phase I dose escalation study evaluating the combination of weekly paclitaxel with neratinib and trastuzumab in women with metastatic HER2+ MBC, based on the results of this phase I study, this dose was later evaluated in phase II trial in HER-2+ stage II/III BC, NSABP B-7. The analysis of this phase Ib study showed grade 2 or greater diarrhea occurred in 7 of 17 patients with most patients experiencing diarrhea within 1 to 3 days of starting therapy. Typically, after the first two weeks of therapy, diarrhea diminished and was easily managed. During the course of this study, the diarrhea management was intensified from the recommendation to start anti-diarrheal at the first loose stool to initiation of anti-diarrheal with the first dose of neratinib. Taken together, we selected neratinib 200mg/day in cohort II when only paclitaxel is combined with neratinib.

There are no data of safety and tolerability of four-drug combination, neratinib, pertuzumab, trastuzumab and paclitaxel. Therefore we will perform a phase Ib dose escalation study evaluating the combination of neratinib with pertuzumab, trastuzumab and paclitaxel in women with metastatic and locally advanced HER2+ breast cancer in cohort I. The Bayesian modified Toxicity Probability Interal (mTPI) dose-escalation algorithm will be used to estimate the MTD from the five doses.

3.5 The Rationale for Adaptive Response Change Assessment utilizing Tissue/Blood based Biomarkers – Window period and screening HER2 mutation

The primary setting provides a unique opportunity to discover candidate predictive markers of response to study drugs since pretreatment tissue can be obtained as core biopsy samples. The molecular profile obtained from the core biopsy samples can be correlated with pathologic and clinical response without the need for long-term follow-up. One of our main exploratory questions in this study is whether we can identify tumors that have higher efficacy of neratinib via molecular profiling. Molecular profiling can be done from both tissue and blood based analysis. The answer could be as simple as the level of gene amplification or expression of HER2 itself or as complex as co-expression levels of other members of the EGFR family of receptors, presence of HER2 mutation, or the activation profile of a downstream signaling pathway. We will use various molecular profiling techniques to test and discover markers that can identify tumors that are selectively responsive to neratinib. To achieve this goal, it is critical to find what exact panel of biomarkers change after neratinib, a pan-HER inhibitor will be introduced as an adaptive response. Here are supportive reasons why this is critical.

First, to date, no biomarkers have been established to identify patients who might benefit from dual inhibition of HER2 and EGFR. In phase I and II clinical studies in patients with HER2-positive breast cancer, neratinib has demonstrated antitumor activity, but we do not know the selective biomarker of patients who had additional benefit [15, 16]. Secondly, while neratinib has shown to be more potent irreversible HER2 inhibitor, subsequent downstream changes that are different from other HER2 inhibitors related changes have not been investigated further. Thirdly and more importantly, the core biology of cancer that can potentially associated with eventual achievement of pCR and longer PFS that are induced by HER pathway suppression have not been well established in clinical setting, and need to be further elucidated. Well-designed patient tissue and blood sample analysis comparing before and after neratinib treatment will enlighten such important biological questions, and thus mandated in at least 20 patients per cohort, in our protocol.

Specifically in cohort II, HER2 somatic mutations in HER2 gene-amplification negative breast cancer patients through cancer genome sequencing have been identified, and Rose R., et al (2013)[9] found seven activating HER2 mutation and neratinib was a very potent inhibitor for all of these HER2 mutations. Therefore, we like to enroll a minimum of 18 patients with HER2 mutation confirmed with in house platform PCR based mutation testing to discover the rate, and different efficacy to induce pCR of neratinib containing regimen.

In terms of EFGR expression, in the results of a phase II trial in patients with advanced non-small-cell lung cancer, neratinib showed significant and durable response among the small cohort of patients with G719X mutation in EGFR [32], and therefore justifying the rationale to study the association between EGFR mutation or over expression with clinical outcome.

Plasma RNA seq

As we aim to identify other new biomarkers by employing a novel approach, that allows serial monitoring over the course of the combination treatment. Thermostable group II intron reverse transcriptases (TGIRT)-seq is a new strand-specific RNA-seq method based on technology developed by our collaborator Dr. Alan Lambowitz at UT Austin exploits the beneficial properties of TGIRTs to obtain more comprehensive RNA-seq libraries [1,2]. TGIRT enzymes have higher processibility and fidelity compare to retroviral reverse transcriptases, and a novel template-switching activity that enables addition of RNA-seq adapters without RNA ligation, an inefficient and bias-inducing step in other RNA-seq methods [3]. TGIRT-seq offer additional advantage of the ability to comprehensively profile mRNAs and long non-coding (nc) RNAs in the same RNA-seq as small ncRNAs [1]. The latter include not only miRNAs but also structured small ncRNAs, including tRNAs and tRNA fragments, which are potential cancer biomarkers and have been suggested to play a key role in breast cancer etiology and metastasis [1,2,4]. TGIRT-seq is the only method that can readily distinguish tRNA fragments from strong stops to reverse transcription during RNA-seq library preparation [5]. TGIRT-seq will allow us to completely annotate and quantify a larger number of gene transcripts than other methods, provide information on alternative and novel splicing events relevant to chemotherapy resistant IBC, and detect known as well as novel mRNA. Furthermore, this novel assay can be conducted on multiple blood based samples, allowing serial monitoring on the whole RNA information.

Circulating Tumor DNA

The ability to detect cancer mutations in blood provides a possible solution to these and many other challenges that arise from multiple tumor biopsies. Advanced-stage tumors often shed cell-free DNA (cfDNA)[6], or circulating tumor DNA (ctDNA) into the bloodstream, which can be isolated from a non-invasive blood draw and detected by polymerase chain reaction (PCR)-based assays or next-generation sequencing (NGS)-based testing. ctDNA sequencing have benefit of easy access to the sample, less invasiveness, and cost effectiveness, and has shown its value in breast cancer as well[7]. More recently, with advancement of field, now ctDNA detection can be employed in the early detection, or monitoring of the therapeutic response. ctDNA approach is the ability to monitor the quantities and identities of tumor-derived genetic lesions over time via routine and minimally invasive blood draws. Taking advantage of benefit from ctDNA as available technique, we will collect serial blood sample that can monitor the different genomic population for the patients with IBC, at baseline and throughout the course of treatment. We expect to see the change in the downstream molecules, e.g., Akt and mTOR with different existence of sub-population and emergence of new subpopulation over the course of treatment using neratinib and others we use in this protocol.

3.6 Study Endpoint

3.6.1 Primary endpoint:

- pCR rate after study combination that is determined by pathological complete response in breast and axillary lymph nodes (pCR breast & nodes) in HER2+ and HER2-/ HR+ IBC treated with neratinib-based treatment. The determination of pCR will be performed by one of our breast pathologist.

- To determine MTD in neratinib, pertuzumab, trastuzumab and paclitaxel treatment..

3.6.2 Secondary endpoints:

- Two years progression-free survival (PFS) rate of HER2+, and HER2-/ HR+ IBC subgroups.
- Toxicity profile of combination therapy

3.6.3 Correlative endpoints:

- To determine the rate of HER2 mutation in HER2+ IBC and HER2-/ HR + IBC
- To determine the association between HER2 mutation and pCR achieved by combination therapy
- To determine one week window period of neratinib induced changes of pEGFR, EGFR by mRNA and protein assay and correlation with pCR
- To determine neratinib induced EGFR and HER2 downstream pathway molecules, e.g., Akt, STAT, Foxm1 and correlation with pCR
- To determine the correlation between tumor tissue based pharmacodynamic marker changes in association with CTC and ctDNA

4.0 METHODOLOGY

4.1 Entry Criteria

In order to be eligible for study participation, subject must meet the following criteria.

4.1.1 Common Inclusion Criteria

1. Histological confirmation of breast cancer
2. 18 years of age or older
3. Able to provide written informed consent for the trial.
4. Performance status of ≤1 on the ECOG performance scale.
5. Able to swallow oral medication.
6. LVEF assessment by 2-D echocardiogram or MUGA scan performed within 90 days prior to registration must be ≥ 50%.
7. Adequate organ function as determined by the following laboratory values:
   - Absolute neutrophil count ≥ 1,500 /μL
   - Platelets ≥ 100,000 / μL
   - Hemoglobin ≥ 9 g/dL
   - Creatinine clearance ≥ 50 ml/min
   - Total bilirubin ≤ 1.5 X ULN. For patients with congenital unconjugated hyperbilirubinemia (Crigler-Najjar syndrome type 1 and 2, Gilbert syndrome) that transient hyperbilirubinemia can occur due to physiological condition, as long as there is clear documentation of diagnosis, allowed to be enrolled if direct (conjugated) bilirubin is ≤ 1.5 X ULN

- Alanine aminotransferase and aspartate aminotransferase ≤ 2.5 X ULN except in patients with AST/ALT elevation that is declared to be caused due to liver metastasis, they are allowed to be enrolled as long as <5 x ULN.

8. Subject of childbearing potential should be willing to use effective methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through at least 4 months after the last dose of study drug. Subject of childbearing potential is defined as has not been surgically sterilized or free from menses for > 1 year.
   Effective methods of birth control include:
   1) Use of hormonal birth control methods: pills, shots/injections, implants (placed under the skin by a health care provider), or patches (placed on the skin);
   2) Intrauterine devices (IUDs);
   3) Using 2 barrier methods (each partner must use 1 barrier method) with a spermicide. Males must use the male condom (latex or other synthetic material) with spermicide. Females must choose either a Diaphragm with spermicide, or Cervical cap with spermicide, or a sponge (spermicide is already in the contraceptive sponge). Female patients of childbearing potential must have a negative urine pregnancy test no more than 7 days prior to starting study drug.
   4) For male participant, they must agree and commit to use a barrier method of contraception while on treatment and for 3 months after the last dose of investigational product.

4.1.2 Cohorts I and II specific Inclusion Criteria

Cohort I:
Phase Ib: Patient must have HER2 + (regardless of hormonal receptor status) metastatic or locally advanced breast cancer (IBC or Non-IBC).

Phase II: Patient must have HER2+ (regardless of hormonal receptor status) stage III IBC or Stage IV IBC if the metastatic sites are amenable for local therapy (i.e. radiation and/ or surgery) and will have breast surgery.

Cohort II
Patient must have HER2-/ HR+ stage III IBC or Stage IV IBC if the metastatic sites are amenable for local therapy (i.e. radiation and/ or surgery) and will have breast surgery.

Definition:

HER2 positive status is defined as strongly positive (3+) staining score by IHC, or gene amplification using FISH, if performed. If IHC is equivocal (2+), please refer to Appendix H for current ASCO guidelines algorithm for evaluation of HER2.

HER2 negative status, which is determined by assays using IHC require negative (0 or 1+) staining score. If IHC is equivocal (2+) staining score, please refer to Appendix H for current ASCO guidelines algorithm for evaluation of HER2.

Hormone receptor (HR) positivity is determined by ER ≥10% and /or PR ≥10% by IHC staining. If patients have paraffin blocks or unstained slides from outsides the institution, the material can be used for baseline biomarker tissue as validation.

IBC is determined by using international consensus criteria:

- Onset: Rapid onset of breast erythema, edema and/or peau d'orange, and/or warm breast, with/without an underlying breast mass
- Duration: History of such findings no more than 6 months
- Extent erythema occupying at least 1/3 of whole breast
- Pathology: Pathologic confirmation of invasive carcinoma

4.1.3 Exclusion Criteria:

1. Excisional breast biopsy or lumpectomy for the current breast cancer.
2. Any other previous malignancies (except for cervical in situ cancers treated only by local excision, and basal and squamous cell carcinomas of the skin) within 5 years.
3. Any other previous antitumor therapies for the current cancer diagnosis event. This exclusion does not apply to phase Ib part of cohort I.
4. Breast-feeding at screening or planning to become pregnant during the course of therapy.
5. History of active or known autoimmune disease that can cause diarrhea like (but not limited to) Addison's Disease, Celiac Disease/Gluten Intolerance/Irritable Bowel Syndrome, Scleroderma.
6. Active infection or chronic infection requiring chronic suppressive antibiotics.
7. Known hepatitis B or hepatitis C with abnormal liver function tests.
8. Malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, resection of the stomach or small bowel, or other disease or condition significantly affecting gastrointestinal function.
9. Persistent ≥ grade 2 diarrhea regardless of etiology.
10. Sensory or motor neuropathy ≥ grade 2
11. Conditions that would prohibit intermittent administration of corticosteroids for paclitaxel premedication. However, corticosteroid can be dropped after confirming of no asthma like reaction to paclitaxel after 3 doses.
12. Uncontrolled hypertension defined as a systolic BP > 150 mmHg or diastolic BP > 90 mmHg, with or without anti-hypertensive medications.
13. Cardiac disease (history of and/or active disease) that would preclude the use of any of the drugs included in the treatment regimen. This includes but is not confined to:
    ---Active cardiac diseases including:
    • symptomatic angina pectoris within the past 180 days that required the initiation of or increase in anti-anginal medication or other intervention;
    • ventricular arrhythmias except for benign premature ventricular contractions;
    • supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication;
    • conduction abnormality requiring a pacemaker;
    • valvular disease with documented compromise in cardiac function; and
    • symptomatic pericarditis.
    ---History of cardiac disease:
    • myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function;
    • history of documented CHF; and
    • documented cardiomyopathy.

14. If you are pregnant, you will not be enrolled on this study

4.2 Treatment Plan

4.2.1 Treatment procedures

After obtaining informed consents, all eligible patients will be registered in the Clinical Oncology Research system. Based on biomarker status (HER2 and hormonal receptor), patients will be assigned to Cohort I and Cohort II.

In Cohort I, patients will receive Neratinib, Paclitaxel, Pertuzumab and Trastuzumab (for both Cohort I phase Ib and Cohort I phase II), then followed by doxorubicin/cyclophosphamide (Cohort I Phase II only)

- Cohort I Phase Ib: We will enroll patients in phase Ib first until maximum tolerated dose is reached, and recommended phase II dose (RP2D) is determined. A maximum of 20 patients will be treated in this group.

- Cohort I Phase II: Upon determination of RP2D, maximum of 31 patients will be treated in this cohort.

In Cohort II, 31 patients will receive neratinib and paclitaxel. We will enroll additional up to 17 ER+ HER2- patients with a HER2 mutation for the expansion cohort until we have total 18 such patients (See 11.1cohort II).

Post–neoadjuvant chemotherapy patient treatment who are enrolled in this trial will follow standard of care for IBC patients, as summarized in our review paper Yamauchi et al. Oncologist 2012[37].

4.2.2 Dosage of combination agents (Table 2 & 3)

Table 2: Cohort I Phase II Patients will receive 4 cycles of neratinib, pertuzumab, trastuzumab and paclitaxel followed by 4 cycles of doxorubicin and cyclophosphamide

	Premedications	Dose	Route	Schedule Each cycle is 3 weeks
Neratinib	Loperamide and budesonide (see section **5.2.1.2**)	Phase Ib: starting dose at 80 mg, see Figure 5 for Dose-Escalation Rules and Table 8 for dose modification, no dose escalation in the same patient phase II: recommended phase II dose	oral	single agent daily during window period C1-4 daily

Pertuzumab	Use institutional guideline	840 mg loading dose, followed by 420 mg	IV over approx.. 60 min If no reaction to the first dose of pertuzumab, approx..30 min for subsequent dose	C1-4 every 3 weeks
Trastuzumab	Use institutional guideline	8 mg/kg loading dose, followed by 6 mg/kg	IV over approx 90 min If no reaction to the first dose of trastuzumab, approx..30 min for subsequent dose	C1-4 every 3 weeks
Paclitaxel	Use institutional guideline	80 mg/m^2	IV over approx.. 60 min	C1-4 (weekly x 12)
Doxorubicin	Use institutional guideline	60 mg/m^2	IV, follow institutional guideline	C5-8 every 2-3 weeks
Cyclophosphamide	Use institutional guideline	600 mg/m^2	IV, follow institutional guideline	C5-8 every 2-3 weeks

Note: Doxorubicin and cyclophosphamide are per standard of care, administration of dose dense will be permitted per physician's discretion.

Table 3. Cohort II Patients will receive 4 cycles of neratinib and paclitaxel followed by 4 cycles of doxorubicin and cyclophosphamide

	Premedications	Dose	Route	Schedule
Neratinib	Loperamide and budesonide (see section **5.2.1.2**)	200mg	oral	C1-4 daily
Paclitaxel	Use institutional guideline	80 mg/m^2	IV over approx.. 60 min	C1-4 (weekly x 12)
Doxorubicin	Use institutional guideline	60 mg/m^2	IV, follow institutional guideline	C5-8 every 2-3 weeks
Cyclophosphamide	Use institutional guideline	600 mg/m^2	IV, follow institutional guideline	C5-8 every 2-3 weeks

Note: Doxorubicin and cyclophosphamide are per standard of care, administration of dose dense will be permitted per physician's discretion.

Infusion reactions during Pertuzumab and Traztuzumab administration is per institutional policy, instructions present in treatment plan.

4.2.3 Phase Ib dose escalation management

The Phase Ib portion of the trial will be restricted to cohort I patients only. MTD will be determined from the five doses listed below, starting at Dose Level 0 (neratinib at 80mg/day).

Dose Level	Neratinib Dose
-1	40 mg
0	80 mg
1	120 mg
2	160 mg
3	200 mg

Definition of DLT

DLT includes any of the following possibly, probably, or definitely due to study therapy, assessed during the first 2 cycles [*42 days*]:

- Any death not clearly due to the underlying disease or extraneous causes
- Non- hematologic toxicity
  - Grade 3 or higher non-hematologic toxicity, except grade 3 diarrhea is a DLT if it lasts ≥ 2 days despite prophylactic medication
  - Grade 2 diarrhea lasting ≥ 5 days despite prophylactic medication
  - Hy's Law case, defined as a patient meeting all of the following criteria:
    a. ALT or AST ≥ 3 x Upper Limit of Normal (ULN)
    b. Total bilirubin >2 x ULN
    c. Little or no evidence of cholestasis (alkaline phosphatase <2 x ULN)
    d. No other identified explanation for the injury (such as hepatitis A, B, C, or other viral hepatic injury, alcohol ingestion, congestive heart failure).
  - Neutropenic fever
- Hematologic toxicity
  - Grade 4 neutropenia or thrombocytopenia >7 days
  - Grade 3 thrombocytopenia with bleeding

The targeted maximum DLT rate is 20%, and we will enroll patients in cohorts of size 2. A maximum of 20 patients will be treated at the five dose levels. The Figure 5 in section 11.2 provides the rules for escalation and de-escalation once each cohort of patients has been assessed.

The MTD is defined as the highest dose for which the posterior probability of toxicity is closest to 20%. Once MTD is determined, Phase Ib is completed and eligible patients will start to be enrolled to Cohort I phase II part.

4.3 Study Schema and Flow Chart

Figure 1. Schema of Cohort I phase Ib Upon completion of 4 cycles of paclitaxel, neratinib, pertuzumab and trastuzumab (continuing the same regimen is allowed if clinically indicated), further treatment of choice will be determined by the treating physician.

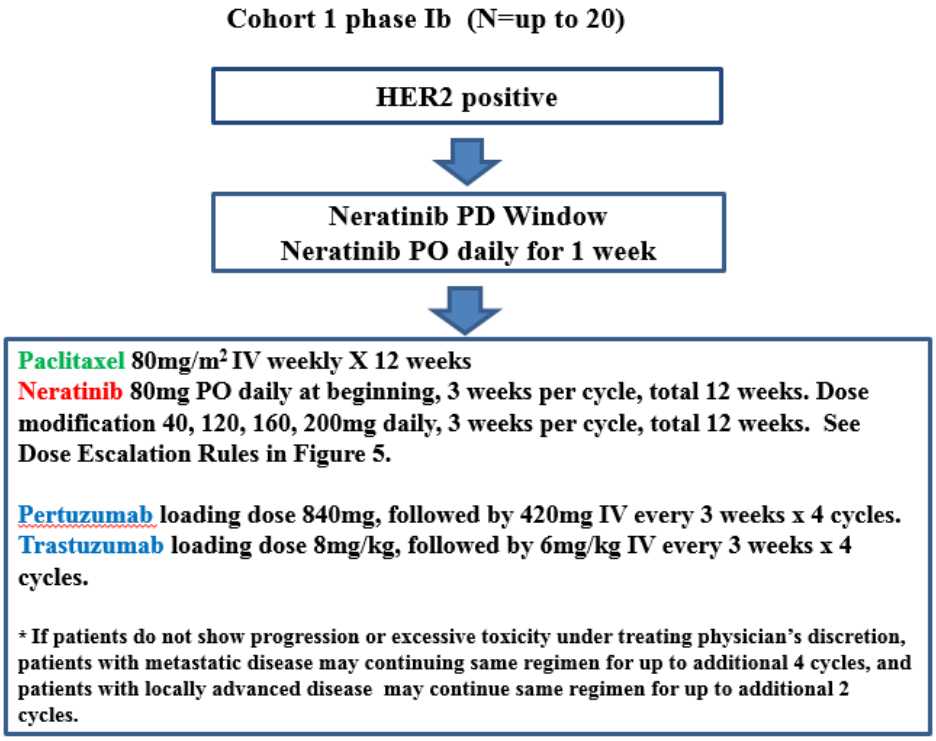


Figure 2. Schema of Cohort I Phase II

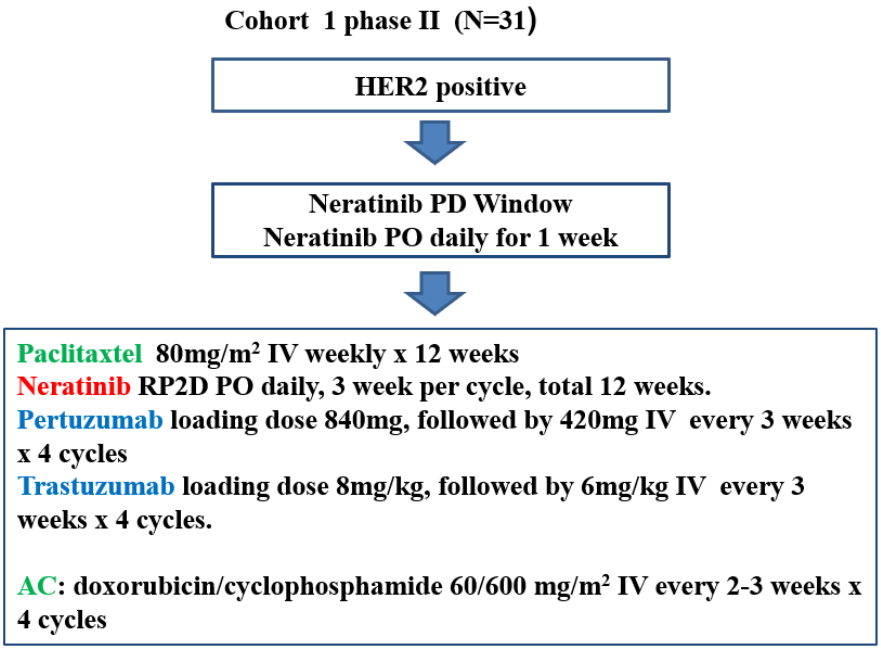


Figure3. Schema of Cohort II Phase II

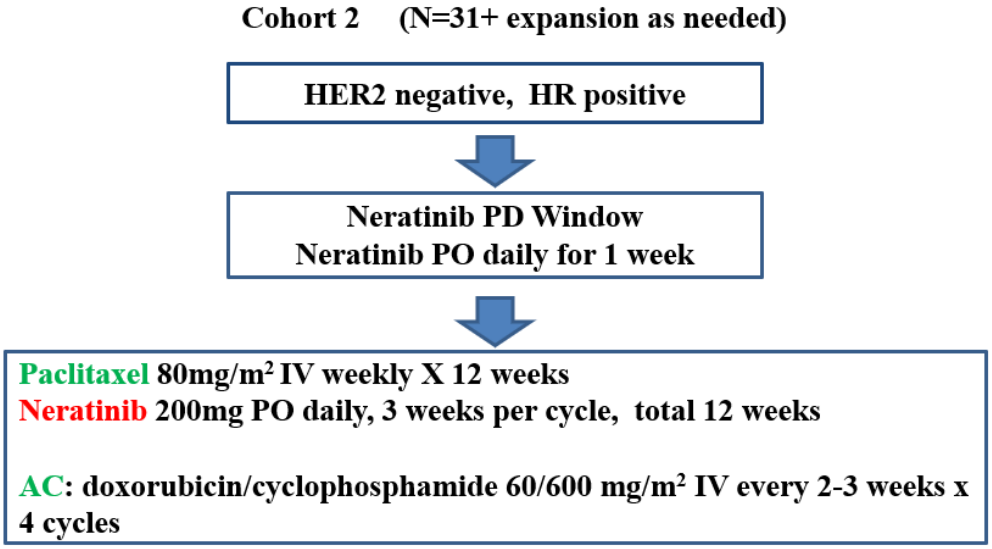


Table 4. Cohort I Phase Ib

	Pre-Study (within 4 weeks)	Wk 1	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Before next treatment (continue on the same regimen [h] or treatment of physician's choice) ±7D
			Wk 2±1D	Wk 3±1D	Wk 4±1D	Wk 5±1D	Wk 6±1D	Wk 7±1D	Wk 8±1D	Wk 9±1D	Wk 10±1D	Wk 11±1D	Wk 12±1D	Wk 13±1D	
Neratinib(daily)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Paclitaxel			X	X	X	X	X	X	X	X	X	X	X	X	
Pertuzumab			X			X			X			X			
Trastuzumab			X			X			X			X			
Informed consent	X														
AEs	X		X			X			X			X			X
Physical exam, PS	X		X			X			X			X			X
Photography of bilateral breasts[k]	X		X												X
CBC w/diff, Platelet [a,j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
SMA (serum chemistry) [b,j]	X		X			X			X			X			X
ECGECHO or MUGA (within 90 days)	X														X[g]
Urine/Blood pregnancy test for childbearing potential (within7 days prior to starting treatment)	X														
PET/CT or chest and abdominal CT scan plus bone scan, chest X-ray (SOC as clinical indicated)	X	Every 3 cycles as clinical indicated													
Bilateral mammography, breast MRI, involved breast ultrasound with	X[c]														X[d]

axillary(SOC as clinical indicated)															
Tissue collection [e]	X[f]		X												
Liquid Biopsy [i]	X		X												X

a. Before each cycle, may repeat until recovery (absolute neutrophil count≥1.5, Platelets ≥100,000 per mm^3). Only WBC, platelets, ANC and hemoglobin will be captured in RedCap database
b. Na, K, Cl, CO2, BUN, creatinine, magnesium, calcium, SGOT [AST], SGPT [ALT], glucose, LDH, total bilirubin,
c. Bilateral mammography, breast MRI involved breast, involved breast and ipsilateral nodal basin ultrasound as SOC as clinical indicated.
d. Mammography of involved breast, ultrasound of involved breast with regional lymphatic chains, or breast MRI as clinically needed as SOC as clinical indicated.
e. For patients with untreated newly diagnosed locally advanced disease or de novo metastatic disease only, up to 20 patients' breast core needle biopsy (3-6 cores) for frozen section will be obtained.
f. 1) If patient is consented for both 2006-1072 (IBC registry) and this protocol, core biopsy (7cores) will be performed in one setting. 4) If patient is only consented for this protocol, core biopsy (3-4 cores) will be performed. Core biopsy tissue can be collected any time before therapy.
g: Echocardiogram or MUGA scan will be performed every 3 monthly as following standard of care for anti-HER2 regimen during study time
h. If patients do not show progression or excessive toxicity under treating physician's discretion, Patients with metastatic disease may continue same regimen for up to an additional 4 cycles per physician discretion, and patients with locally advanced disease only may continue same regimen for up to an additional 2 cycles, per physician discretion All Labs (except research blood collections) / imaging/ physical exams will continue as in C1-C4,
i. Research blood collection- One 10 ml EDTA and one 10 ml Streak tube at baseline, after the pharmacodynamics window and after Cycle 4 (Wk 13).
j. For patients with metastatic disease, in the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.
k. If applicable.

Table 5. Cohort I Phase II

	Pre-Study (within 4 weeks)	Wk 1	Cycle 1			Cycle 2			Cycle 3			Cycle 4			AC	
			Wk 2±1D	Wk 3±1D	Wk 4±1D	Wk 5±1D	Wk 6±1D	Wk 7±1D	Wk 8±1D	Wk 9±1D	Wk 10±1D	Wk 11±1D	Wk 12±1D	Wk 13±1D	Every 2-3 wks ±3D x 4 cycles	Before surgery
Neratinib(daily)		X	X	X	X	X	X	X	X	X	X	X	X	X		
Paclitaxel			X	X	X	X	X	X	X	X	X	X	X	X		
Pertuzumab			X			X			X			X				
Trastuzumab			X			X			X			X				
Informed consent	X															
AEs	X		X			X			X			X			X	X
Physical exam, PS	X		X			X			X			X			X	X
Photography of bilateral breasts	X		X												X[h]	X
CBC w/diff, Platelet [a,]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
SMA (serum chemistry) [b,]	X		X			X			X			X			X	X
ECG, ECHO or MUGA (within 90 days)	X														X[j]	
Urine pregnancy test for childbearing potential (within7 days prior to starting treatment)	X															
PET/CT or chest and abdominal CT scan plus bone scan, chest X-ray (SOC)	X															
Mammography, breast MRI, breast ultrasound with axillary	X[c]														X[d]	X[d]
Tissue collection [e]	X[f]		X													X[g]

Liquid Biopsy [i]	X		X											X	

a: Before each cycle, may repeat until recovery (absolute neutrophil count≥1.0, Platelets ≥100,000 per mm^3 per physician discretion, growth factor support can be given per physician's discretion). Only WBC, platelets, ANC and hemoglobin will be captured in RedCap database
b: Na, K, Cl, HCO3, BUN, creatinine, Mg, calcium, SGOT [AST], SGPT [ALT], glucose, LDH, total bilirubin
c: Bilateral mammography, breast MRI involved breast, involved breast and ipsilateral nodal basin ultrasound..
d: Mammography of involved breast, ultrasound of involved breast with regional lymphatic chains, or breast MRI as clinically needed.
e. Breast core needle biopsy (3-4 cores) for frozen section and paraffin block collection are mandatory for the primary site that obtained for all patients. 10 slides are needed for each patient.
f. 1) If patient is consented for both 2006-1072 (IBC registry) and this protocol, core biopsy (7 cores) will be performed in one setting. . 4) If patient is only consented to this protocol, core biopsy (3-4 cores) will be performed. Core biopsy tissue can be collected any time before therapy.
g. Surgical sample collections.
h. Only one time before Cycle 1 of AC treatment.
i. Research blood collection- One 10 ml EDTA and one 10 ml Streak tube at baseline, after the pharmacodynamics window and prior to Cycle # 1 of AC.
j. Echocardiogram or MUGA scan will be performed every 3 monthly as following standard of care for anti-HER2 regimen during study time

Table 6. Cohort II

	Pre-Study (within 4 weeks)	Wk 1	Cycle 1			Cycle 2			Cycle 3			Cycle 4			AC	
			Wk 2±1D	Wk 3±1D	Wk 4±1D	Wk 5±1D	Wk 6±1D	Wk 7±1D	Wk 8±1D	Wk 9±1D	Wk 10±1D	Wk 11±1D	Wk 12±1D	Wk 13±1D	Every 2-3 wks±3D x 4 cycles	Before surgery
Neratinib(daily)		X	X	X	X	X	X	X	X	X	X	X	X	X		
Paclitaxel			X	X	X	X	X	X	X	X	X	X	X	X		
Informed consent	X															
AEs	X		X			X			X			X			X	X
Physical exam, PS	X		X			X			X			X			X	X
Photography of bilateral breasts	X		X												X[h]	X
CBC w/diff, Platelet [a,]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
SMA (serum chemistry) [b,]	X		X			X			X			X			X	X
ECG, ECHO or MUGA (within 90 days)	X														X[j]	
Urine/Blood pregnancy test for childbearing potential (within 7 days prior to starting treatment)	X															
PET/CT or chest and abdominal CT scan and bone scan, chest X-ray (SOC)	X															
Mammography, breast MRI, involved breast and nodal basin ultrasound	X[c]														X[d]	X[d]
Tissue collection [e]	X[f]		X													X[g]

Liquid Biopsy [i]	X		X											X	

a: Before each cycle, may repeat until recovery (absolute neutrophil count≥1.0, Platelets ≥100,000 per mm^3 per physician discretion, growth factor support can be given per physician's discretion). Only WBC, platelets, ANC and hemoglobin will be captured in RedCap database
b: Na, K, Cl, HCO3, BUN, creatinine, Mg, calcium, SGOT [AST], SGPT [ALT], glucose, LDH, total bilirubin,
c: Bilateral mammography, breast MRI involved breast, involved breast and ipsilateral ultrasound.
d: Mammography of involved breast, ultrasound of involved breast with regional lymphatic chains, or breast MRI as clinically needed as SOC.
e. Breast core needle biopsy (3-4 cores) for frozen section and paraffin block collection are mandatory for the primary site that obtained for all patients. 10 slides are needed for each patient.
f. At baseline, if a patient is consented for both 2006-1072 (IBC registry) and this protocol, core needle biopsy (up to 7 cores) will be performed in one setting and tissues will be collected separately for both studies. If core biopsy is already performed for protocol 2006-1072, and patient is subsequently consented for this study, core biopsy (3-4 cores) will be performed. 1 core biopsy will be collected for Whole Exome Sequencing for IPCT. Core biopsy tissue can be collected any time before therapy.
g. Surgical sample collections.
h. Only one time before Cycle 1of AC treatment
i. Research blood collection-. One 10 ml EDTA and one 10 ml Streak tube at baseline, after the pharmacodynamics window and prior to Cycle # 1 of AC. An additional one 10 ml Streak tube for IPCT at baseline only.
j. Echocardiogram or MUGA scan will be performed every 3 monthly as following standard of care for anti-HER2 regimen during study time

4.4 Outside Physician Participation During Treatment

1. MDACC physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to participate in the patient's care (Appendix D in PDOL).
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5. All decisions regarding dose adjustments and treatment interruptions or re-initiation of treatment, grading and attribution of adverse events and assessment of efficacy will be done by MDACC investigators. The home physician will not make any decisions regarding dose adjustments and/or treatment interruptions or resumption of treatment, grading and/or attribution of adverse events, or assessment of efficacy. These will all be done by the MDACC investigators.
6. Only routine, standard-of-care laboratory assessments will be done by the home physician. All protocol-specific tests will be done at MDACC.
7. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
8. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies, and documentation of any hospitalizations.
9. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
10. Patients will return to MDACC every 3 weeks during the first 4 cycles, before the first dose of AC (phase II) or other regimens (phase Ib) and before surgery for evaluation.

5.0 COMMON TOXICITY AND DOSE MODIFICATION

In this study, neratinib and paclitaxel must be fundamentally reduced for drug-related toxicities and severe or life-threatening adverse events (AEs). However, if AEs still remain in spite of neratinib and paclitaxel reduction or discontinuation, pertuzumab and trastuzumab should be discontinued. Patient will be taken off from the study.

If there is overlapping toxicity from two drugs, e.g., diarrhea – which can be caused by both neratinib and pertuzumab, neratinib dose will first be reduced. Pertuzumab, without flexibility of dose modification will be continued. However even after proper supportive management, and dose reduction of neratinib still does not control significant level of toxicity (grade 3 or above for non-hematologic and hematologic), treatment combination will be stopped and patient will be taken off from the study.

5.1 Dose modification of each drug

5.1.1 Pertuzumab:

Loading dose 840 mg, followed by 420 mg every 3 weeks. No dose reduction allowed.

5.1.2 Trastuzumab:

Loading dose 8 mg/kg, followed by 6 mg/kg every 3 weeks. No dose reduction allowed.

5.1.3 Paclitaxel:

There are total 3 levels of dose down for paclitaxel as in table 7. Standard of care for paclitaxel administration will be used.

Table 7. Dose modification levels of paclitaxel

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Paclitaxel	80 mg/m2	70 mg/m2	60 mg/m2	Discontinue

5.1.4 Neratinib:

There are total 4 levels of dose modification for neratinib in phase Ib in cohort1as in table 8 and RP2D is decided.

RP2D is taken in phase II cohort I.

There are total 3 levels of dose modification for neratinib in phase II as in table 9. With the use of mandated primary diarrheal prophylaxis, the RP2D was determined to be 200 mg/day in neratinib, trastuzumab and paclitaxel combination therapy.[33]

Table 8. Dose escalation levels of neratinib for phase Ib in cohort I

	Dose Level -1	Dose Level 0	Dose Level 1	Dose Level 2	Dose Level 3
Neratinib	40 mg	80 mg	120 mg	160 mg	200mg

Table 9. Dose modification levels of neratinib for cohort II

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Neratinib	200 mg	160 mg	120 mg	Discontinue

5.2 Common toxicity and management

5.2.1 Management of Diarrhea, and Dose Modification of Neratinib

5.2.1.1 Patients Education

Diarrhea is a commonly occurring toxicity. Monotherapy with neratinib has a median time of 3 days to onset of diarrhea. With combination therapy, it is anticipated that diarrhea may occur earlier. For the majority of patients, diarrhea subsides after about 2 weeks.

Therefore it is critical that intensive prophylactic measures begin at the start of therapy.

- *Inform patients that they will experience diarrhea while taking neratinib.*
- Patients **must** be instructed to:
  - start prophylactic antidiarrheal therapy (see below) on day 1, with the first dose of neratinib
  - continue prophylactic therapy as directed
  - promptly report diarrhea symptoms
  - record the number of stools per day
  - record each dose of antidiarrheal medicine taken each day
  - report constipation *before* taking any laxatives or stopping antidiarrheal medication.

5.2.1.2 Intensive primary prophylaxis

Antidiarrheal medication **(loperamide, budesonide)** must begin with the first dose of neratinib. Patients must take an initial dose of loperamide **(Imodium®)** 4 mg p.o. with the first dose of neratinib, then followed by 4 mg TID for the first 14 days. After two weeks on study, patients will take 4 mg twice a day (BID) for the remainder of the first two cycle of neratinib. Thereafter, loperamide will be administered as needed throughout neratinib treatment (Table 10).

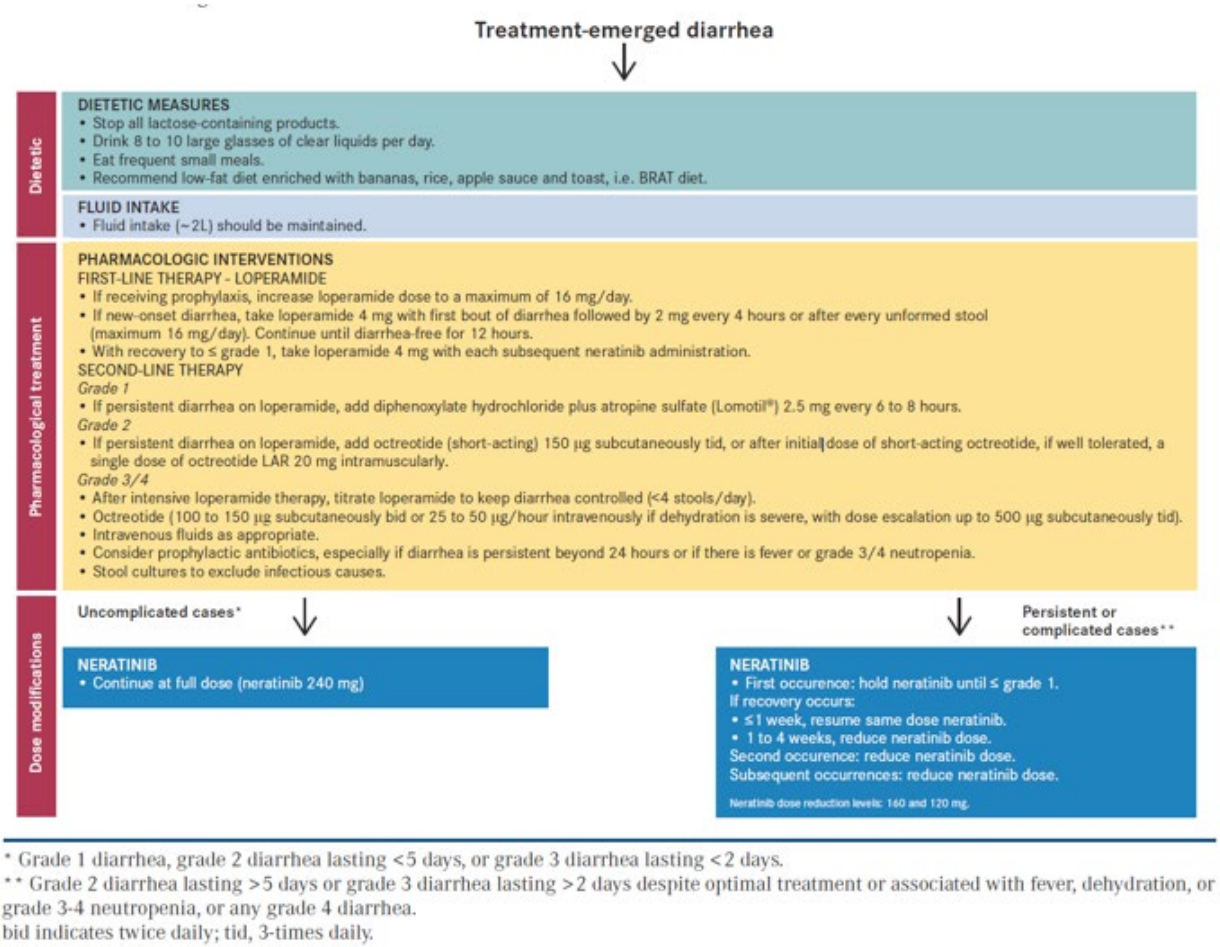
Budesonide will be taken with neratinib and intensive loperamide prophylaxis at a dose of 9 mg once daily during week 1 and cycle 1 for 28 days.

Table 10: Loperamide Dosing for Neratinib Treatment

Loperamide Dose	Day
4 mg TID with a total daily dose of 12 mg	Days 1-14 (Cycle 1)
4 mg BID with a total daily dose of 8 mg	Days 15-49 (Cycle 1-2)
Daily dose as needed (not to exceed 16 mg per day)	Days 50+ (Cycle 3 and beyond)

For Grade 2 diarrhea lasting ≥ 5 days despite prophylactic medication, and higher grade (Grade 3 and 4), we recommend to follow the guideline as noted in below figure 4 (focusing on the yellow box). This figure also contains other adjunctive measures that can help patients to manage the diarrhea related issues, e.g., hydration, diet changes:

Figure 4. Management Guideline for Neratinib-related Diarrhea



* Grade 1 diarrhea, grade 2 diarrhea lasting <5 days, or grade 3 diarrhea lasting <2 days.
** Grade 2 diarrhea lasting >5 days or grade 3 diarrhea lasting >2 days despite optimal treatment or associated with fever, dehydration, or grade 3-4 neutropenia, or any grade 4 diarrhea.
bid indicates twice daily; tid, 3-times daily.

5.2.2 Cardiac Left Ventricular Dysfunction and Dose Modification of Neratinib, Pertuzumab, and Trastuzumab

Neratinib, doxorubicin, pertuzumab and trastuzumab must be discontinued for patients who have a symptomatic decrease in LVEF.

- Congestive heart failure (grade 3):

Patients should be monitored for signs and symptoms of CHF (e.g., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema). If the patient develops any of these signs and symptoms, neratinib, and/or pertuzumab, doxorubicin, and trastuzumab must be held. The investigator must confirm the diagnosis of CHF with either an echocardiogram or a MUGA scan. Once the diagnosis of CHF is confirmed, trastuzumab and neratinib must be permanently discontinued.

- Severe refractory/poorly controlled CHF (grade 4):

Neratinib, pertuzumab, doxorubicin, and trastuzumab should be discontinued if patient develops severe refractory/poorly controlled CHF.

For asymptomatic patients, the decision to continue or stop doxorubicin, neratinib, pertuzumab and trastuzumab is based on two factors, the value of the measured ejection fraction and the change in ejection fraction from baseline, which was performed at the time of registration. Investigators should reference the pertuzumab and trastuzumab labels (see Appendix E and F in PDOL).

5.2.3 Musculoskeletal Pain, Neuropathy and Paclitaxel Dose Modification.

The treatment management instructions for neuropathy is in Table 11. If symptoms are in greater degree, dose modification is warranted as below.

Table 11. Dose modification of paclitaxel for neuropathy

Paresthesias/Dysesthesias	1 – 7 Days Duration	Persistent for > 7 Days or Caused a Dose Delay
Grade 1 Paresthesias/dysesthesias that do not interfere with function	Maintain paclitaxel dose	
Grade 2 Paresthesias/dysesthesias interfering with function, but not activities of daily living	Maintain paclitaxel dose[a]	Decrease paclitaxel one dose level[b]
Grade 3 Paresthesias/dysesthesias with pain or with function impairment that also interfere with activities of daily living	First episode: Decrease paclitaxel one dose level[a] Second episode: Discontinue paclitaxel	Discontinue paclitaxel
Grade 4 Persistent paresthesias/dysesthesias that are disabling or life-threatening	Discontinue paclitaxel	
a. Must be resolved to ≤ grade 1 on Day 1 of the next treatment cycle. b. Hold paclitaxel for persistent grade 2 neuropathy. When ≤ grade 1, resume treatment with dose modification. If grade 2 toxicity persists after 2 weeks of delay, discontinue paclitaxel.		

The treatment management instructions in Table 12 apply to patients with musculoskeletal pain not controlled by analgesics. Use of narcotics and NSAIDs is encouraged to maintain the paclitaxel dose if possible.

Table 12. Dose modification of paclitaxel for muscular pain

Musculoskeletal Pain	1 – 7 Days Duration	Persistent for > 7 Days *or* Caused a Dose Delay
Grade 1 *(despite analgesics)*	Maintain paclitaxel dose	
Grade 2 *(despite analgesics)*	Maintain paclitaxel dose	Maintain paclitaxel dose or Decrease paclitaxel one dose level*

Grade 3 *(despite analgesics)*	First episode: Decrease paclitaxel one dose level Second episode: Discontinue paclitaxel	First episode: Decrease paclitaxel one dose level* or Discontinue paclitaxel Second episode: Discontinue paclitaxel
Grade 4 *(despite analgesics)*	Discontinue paclitaxel	
* Hold paclitaxel for persistent grade 2 or 3 musculoskeletal pain. (Targeted therapy should be continued while paclitaxel is held.) When ≤ grade 1, resume treatment with paclitaxel dose modification. If grade 2 or grade 3 toxicity persists after 2 weeks of delay, discontinue paclitaxel.		

5.3 Other Toxicity Management

Table 13. Other toxicity management

Dose level management • Refer to dose level table for paclitaxel and neratinib (Table 3). • If paclitaxel is discontinued, neratinib must be discontinued; if neratinib is discontinued, paclitaxel must be discontinued.			
Adverse Event	**CTCAE Ver 4.0 Grade**	**Paclitaxel**	**Neratinib**
Allergy/immunology Allergic reaction/hypersensitivity (including drug fever) Investigator must determine attribution of AE and only follow instructions for the causal agent.	1	Treat as per institutional policy and re-challenge (maintain dose)	Maintain dose with no delay
	2		Hold until ≤ grade 1; may re-challenge (maintain dose) or D/C
	3	Treat as per institutional policy; may re-challenge (maintain dose) or D/C	Treat as per institutional policy; may re-challenge (maintain dose) or D/C
	4	D/C	D/C
Platelets	2, 3, 4	Only if present on the scheduled treatment day: Hold until ≥ 75,000/mm3. If recovery takes: 1-2 weeks – ↓ one dose level > 2 weeks – D/C	Continue with no delay (Platelets do NOT need to be ≥ 75,000/mm3 to continue neratinib.)
Cardiac arrhythmia •Conduction abnormality • Supraventricular and nodal arrhythmia • Ventricular arrhythmia • Other	2	Hold until rhythm is controlled; then resume and maintain dose	
	3	Hold until rhythm is controlled, then resume (maintain dose) or D/C	Hold until rhythm is controlled, then resume (maintain dose) or D/C
	4	D/C	D/C
Cardiac general Cardiac ischemia/infarction	2	Hold study therapy and conduct a cardiac evaluation. Based on this evaluation, continuation of paclitaxel and/or neratinib is at the investigator's discretion.	
	3,4	D/C	D/C
Left ventricular dysfunction	2, 3, 4	Refer to Section 4.2.2	

Dose level management • Refer to dose level table for paclitaxel and neratinib (Table 3). • If paclitaxel is discontinued, neratinib must be discontinued; if neratinib is discontinued, paclitaxel must be discontinued.			
Adverse Event	**CTCAE Ver 4.0 Grade**	**Paclitaxel**	**Neratinib**
<u>Dermatology/Skin</u> • Rash/desquamation • Rash: acne/acneiform Note: Clinical management of acne/acneiform rash is at the investigator's discretion.	2	Management, dose holding, and dose reduction per treating physician's discretion per SOC.	1st appearance: Continue without delay or hold until improvement; maintain dose 2nd appearance: If recurrent or intolerable, hold until improving and ↓ one dose level 3rd appearance: ↓ one dose level or D/C if intolerable
	3		Hold until ≤ grade 2 1st appearance: ↓ one dose level 2nd appearance: D/C
	4		D/C
Nail changes (Paronychia) Note: See Section 9.8.2 for neratinib-related nail change instructions.	2	Maintain dose with no delay unless medically contraindicated	1st appearance: Continue without interruption or hold until improvement and maintain dose 2nd appearance: If recurrent or intolerable, hold until improving and ↓ one dose level 3rd appearance: ↓ one dose level or D/C if intolerable
	3		Hold until ≤ grade 2 1st appearance: Maintain dose or ↓ one dose level 2nd appearance: ↓ one dose level or D/C
<u>Gastrointestinal</u> Diarrhea attributed to therapy (see Sections 5.2.1.2 Table 10 and Figure 4 for important instructions regarding diarrhea management).	1	Management, dose holding, and dose reduction per treating physician's discretion per SOC.	Maintain dose without delay; continue antidiarrheal medication management
	2		Hold until ≤ grade 1 1st appearance: Maintain dose 2nd appearance: ↓ one dose level 3rd appearance: ↓ one dose level or D/C Note: If anti-diarrheal medication use was not maximized, maintain dose when ≤ grade 1
	3		Hold until ≤ grade 1 1st appearance: ↓ one dose level 2nd appearance: D/C Note: If anti-diarrheal medication use was not maximized, maintain dose when ≤ grade 1
	4	D/C	D/C
•Mucositis/stomatitis •Vomiting (despite antiemetics)	2	Management, dose holding, and dose reduction per treating physician's discretion per SOC.	Hold until ≤ grade 1 1st appearance: Maintain dose 2nd appearance: ↓ one dose level 3rd appearance: ↓ one dose level or D/C

Dose level management • Refer to dose level table for paclitaxel and neratinib (Table 3). • If paclitaxel is discontinued, neratinib must be discontinued; if neratinib is discontinued, paclitaxel must be discontinued.			
Adverse Event	**CTCAE Ver 4.0 Grade**	**Paclitaxel**	**Neratinib**
	3		Hold until ≤ grade 1 1st appearance: ↓ one dose level 2nd appearance: D/C
	4		D/C
Hepatic Function • Total bilirubin • ALT • Alkaline phosphatase • AST	2	Management, dose holding, and dose reduction per treating physician's discretion per SOC.	Hold until ≤ grade 1 1st appearance: ↓ one dose level 2nd appearance: D/C
	3		Hold until ≤ grade 1 1st appearance: ↓ one dose level 2nd appearance: D/C
	4		D/C
Infection • Febrile neutropenia • Infection with grade 3 or 4 neutropenia • Infection with normal ANC or grade 1 or 2 neutrophils Note: If adding G-CSF, only filgrastim on Days 2-6, 9-13, and 16-20 may be used; pegfilgrastim is prohibited.	3	Hold until clinically stable 1st appearance: Maintain dose and add G-CSF 2nd appearance: ↓ one dose level 3rd appearance: ↓ one dose level or D/C	1st appearance: Maintain dose with no delay (unless it is in the patient's best interest to hold neratinib) 2nd appearance: Maintain dose with no delay (unless it is in the patient's best interest to hold neratinib) 3rd appearance: ↓ one dose level or D/C
	4	Hold until clinically stable 1st appearance: ↓ one dose level and add G-CSF 2nd appearance: D/C	Hold until clinically stable 1st appearance: Resume neratinib and ↓ one dose level 2nd appearance: D/C
Pulmonary/Upper Respiratory Dyspnea	2,3,4	Hold study therapy until ≤ grade 1 and CHF and interstitial pneumonitis have been ruled out. • If caused by CHF or interstitial pulmonary toxicity, D/C therapy. • If caused by infection or asthmatic process, resume paclitaxel and neratinib therapy when symptoms have resolved to ≤ grade 1.	
Pneumonitis/pulmonary infiltrates/other pulmonary events • Hypoxia • Pulmonary fibrosis	2,3	If a patient develops symptoms suggestive of interstitial pneumonitis, ARDS, or non-cardiogenic pulmonary edema, hold paclitaxel and neratinib and conduct a pulmonary evaluation. • If pulmonary infection is documented, paclitaxel and neratinib may be resumed when pulmonary AE has resolved to ≤ grade 1. • If non-infectious interstitial lung disease is confirmed, D/C therapy.	
	4	D/C	D/C
Other AEs requiring dose modification per investigator Note: Investigator must determine attribution of AE and only follow dose modifications for the causal agent	3	Hold until ≤ grade 1 Modify only if the AE is attributed to paclitaxel. 1st appearance: ↓ one dose level 2nd appearance: ↓ one dose level 3rd appearance: D/C	Hold until ≤ grade 1 Modify only if the AE is attributed to neratinib: 1st appearance: ↓ one dose level 2nd appearance: ↓ one dose level 3rd appearance: D/C
	4	D/C	D/C

5.4 Unanticipated Dose Interruptions

Dosing interruptions are permitted in the case of logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3-5 days of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's medical record.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. .

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Concomitant medication will be recorded as standard of care inthe patient's EMR. .

Monitoring will be needed if the medications listed are taken with neratinib:

1. Patients taking anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin) should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes. The dose of anticoagulant should be adjusted as needed.

2. Patients taking concomitant digoxin should have digoxin levels monitored closely and their digoxin dose adjusted as needed.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the study.

1. Any other anti-cancer agents.

2. Radiation therapy for curative purpose.

3. Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

Medications listed are **prohibited** from concomitant use with neratinib.

4. Agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors. Refer to Table 14 for a list of selected inhibitors and inducers of the cytochrome P450 CYP3A4, 5, 7 isoenzymes. Patients should also avoid grapefruit and herbal remedies, including St John's Wort as well.

5. Chronic immunosuppressive therapies including systemic corticosteroids. Steroids given for physiological replacement, as premedication for paclitaxel, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

Table 14. List of selected inhibitors and inducers of the Cytochrome P450 CYP3A,5,7 isoenzymes

INHIBITORS*		INDUCERS*	
3A4	**OTHER**	**3A4**	**OTHER**
Clarithromycin	Amiodarone	**Carbamazepine**	Barbiturates
Erythromycin	Cannabinoids	Dexamethasone**	Cotrimoxazole
Fluvoxamine	Fluoxetine	Phenobarbital	Efavirenz
Grapefruit juice	Lopinavir	Phenytoin	Ethosuximide
Grapefruit-containing products	Metronidazole	Primidone	Methadone
Indinavir	**Quinine**	Rifabutin	Metyrapone
Ketoconazole	**Sertraline**	Rifampin	Mexiletine
Mibefradil	**Zafirlukast**	St John's Wort	**Nevirapine**
Miconazole			Oral contraceptives
Nefazodone			Troglitazone
Nelfinavir			
Norfloxacin			
Ritonavir			
Saquinavir			
Troleandomycin			
Voriconazole			

* In **boldface** are identified strong CYP3A4, 5, 7 inducers/inhibitors. This list is not meant to be considered all inclusive. Extracted from: Tatro BO. *Drug Interaction Facts 2003: The Authority on Drug Interactions, 2003.*
** Dexamethasone is permitted when given as premedication for paclitaxel

6.0 SUBJECT WITHDRAWAL/DISCONTINUATION CRITERIA

Disease progression

Disease progression is defined as rapid growth of multiple measurable, non-measurable, or new lesions, or at least a 20% increase in the sum of diameters of target (measurable) 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 progression).

Noncompliance

If the patient is not able to be compliant with the treatment schedule in the absence of toxicity, the study treatment should be discontinued for the patient.

Sustained toxic effects

Study treatment will be discontinued for patients who have sustained toxic effects that are attributed to the study drug and require a dose interruption lasting more than 12 weeks.

Initiation of new anticancer treatment

In patients for whom the investigator, in his or her judgment, determines new treatment for breast cancer is warranted, the study treatment may be discontinued.

Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria, section 5.2.4 and Table 14 are not allowed during the ongoing trial. If there is a clinical indication for one of these medications or vaccinations specifically prohibited during the trial, discontinuation from trial is required.

Patient withdraws consent

In the event that a patient withdraws consent, the reason(s) for withdrawal must be documented. Patients must be informed that their participation in the study is voluntary and that they may choose not to take part in the study or to stop taking part at any time. If a patient chooses not to take part in the study or to stop at any time, his/her future medical care or medical benefits will not be affected.

7.0 FOLLOW UP

Duration of follow-up

Cohort I, Phase Ib

Patients will be followed for safety for 30 days (+/-10 days) following the last dose of study drug, or until initiation of another anticancer therapy, whichever comes first via telephone calls, patient medical records, and/or clinic visits.

Patients who have an ongoing major study treatment–related AE upon study completion or at discontinuation from the study will be followed up to 4 weeks until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

Cohort I Phase II and Cohort II

Patients will be monitored until 1 month after surgical resection of the tumor. The date of the last follow-up visit should be within 30 days (+/-10 days) of surgical resection via telephone calls, patient medical records, and/or clinic visits.

For patients who discontinue protocol therapy early, they will be followed for safety for 30 days (+/-10 days) following the last dose of study drug, or until initiation of another anticancer therapy, whichever comes first.

Patients who have an ongoing major study treatment–related AE upon study completion or at discontinuation from the study will be followed up to 4 weeks until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months for 2 years (unless the patient withdraws consent or the study is terminated).

8.0 DISEASE ASSESSMENT

Cohort I Phase II and Cohort II

For patients in Cohort I Phase II and Cohort II, treatment response is determined by the surgical pathology report.

Pathologic response will be assessed by RCB criteria according to the American Joint Committee on Cancer (AJCC) guidelines per MDACC Department of Pathology policy.

9.0 CORRELATIVE RESEARCH

To further understand the biological effect of neratinib as a single agent and to discover novel biomarkers, we will collect tumor samples at baseline, post neratinib window study and during breast surgery.

9.1 Tumor Sample Collection / Research Blood Collection

Correlative research will be performed on biologic specimens from each 20 patients in Cohort 1 phase Ib, Cohort I phase II and Cohort II. Pharmacodynamic markers to be measured in this proposed study. The pEGFR, HER2 expression changes induced by neratinib will be analyzed and compared between dose levels.

- mRNA sequencing at baseline, after pharmacodynamics window, at the time of surgery if viable tissue available. This will assess the adaptive changes, downstream changes, and if remnant disease – can investigate the predictor of resistance markers.

- Plasma RNA, PBMC and Circulating tumor DNA collection at baseline, after the pharmacodynamics window and after cycle 4 (week 13).

Table 15. Correlative studies

Correlative Studies	Baseline	Cycle 1 Week 2 (Post neratinib window)	After Cycle 4 (Week 13)
Biopsy - Up to 20 patients, (Each cohort*) • Using RNA seq to assess EGFR and additional HER 2 pathway related genomic landscape change. RNA seq will be performed at IPCT or core facility at MD Anderson. **(For cohort I phase Ib locally advanced patients only, baseline and Cycle I, Week 2 only)*	x	x	
Blood- (Each cohort) • Plasma RNA sequencing, PMBC (UT Austin Collaboration) • Circulating tumor DNA to be stored in Core Facility	x	x	x
Biopsy- Up to 48 patients, (Cohort II) Using Whole Exome Seq to check HER2 mutation and other associated mutations in IPCT	x		
Blood- Up to 48 patients, (Cohort II) • Normal control by Whole Exome Seq (WES) in IPCT	x		

9.2 HER2 Expression and HER2 Mutation

HER2 expression level is detected by immunohistochemical (IHC) staining or fluorescence in situ hybridization (FISH) per most recent ASCO CAP guideline. HER2 mutation level is detected by the RNA sequencing data (RNA-seq). All techniques for measuring HER2 expression and HER2 mutation level have been standardized at M. D. Anderson.

9.3 EGFR Expression and downstream pathways

EGFR expression level, as well as its putative downstream including nodal-Axl pathway is detected by IHC staining and FISH. Both techniques (IHC, FISH) for measuring EGFR expression level have been standardized at M. D. Anderson. All tissues and blood based samples will be bio-banked for further analysis upon our ongoing EGFR targeting based preclinical and clinical studies.

10.0 SAFETY MONITORING AND REPORTING

10.1 Adverse Event

Adverse events will be assessed according to the CTCAE version 4.0. All study patients who have received neratinib as a single agent and as combination therapy will be evaluable for safety. The ongoing review of safety data will include review of clinical AEs and SAEs. The Study PI or designee will be responsible for assigning attribution of adverse events to the study agent and signing the case report form.

AEs (>/=2 non-hematological and >/=3 hematological AEs) occurring after first protocol intervention signing observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be documented in the medical record and recorded in RedCap. Abnormal laboratory values will not be reported as AEs; however, any clinical consequences of the abnormality should be reported as AEs. Baseline toxicities will be captured in the medical record/ RedCap.

10.2 Serious Adverse Event Reporting (SAE)

10.2.1 Internal SAE reporting to Investigational New Drug (IND) Office

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

10.2.2 Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

10.2.3 Investigator Communication with Supporting Company:

The MDACC Internal SAE Report Form will be used for reporting to Puma Biotechnology Inc., and reporting timeline is as below:

- Death that is unanticipated and definitely, probably or possibly related to study intervention that occur during and within 30 days after the last day of active study intervention will be reported to Puma Biotechnology Inc. within 24 working hours.

- All other SAEs that are serious, unanticipated, and definitely, probably or possibly related to study drugs will be reported to Puma Biotechnology Inc. within 24 hours.

- Investigator will report Serious Adverse Events (as such term is defined in the Protocol) requiring expedited reporting to Puma using MDACC Internal SAE Report Form. For expedited reports, Investigator will send the MDACC Internal SAE Report Form to Puma no later than seven (7) days for initial life-threatening reports, and fifteen (15) days for all other initial or follow-up serious and unexpected suspected adverse reaction (SUSAR), from the time of receipt of the SAE by Investigator. For non-expedited reports (i.e., unrelated to study drugs or listed/expected event), Investigator will send the MDACC Internal SAE Report Form to Puma no later than thirty (30) days from the time of receipt of the SAE by Investigator. Investigator shall send all MDACC Internal SAE reports to Puma via email to PumaSAE@parexel.com

11.0 STATISTICAL CONSIDERATIONS

11.1 Overview

There will be two cohorts in this trial, as defined in Section 3.3.

Cohort I:

For Cohort I, the primary objectives of this phase Ib/II trial are to determine the MTD of neratinib in combination with paclitaxel, pertuzumab, trastuzumab, and doxorubicin/cyclophosphamide or other regimens in HER2-positive metastatic or locally advanced breast cancer patients (phase Ib) and to assess the efficacy of neratinib in combination with paclitaxel, pertuzumab, trastuzumab, and doxorubicin/cyclophosphamide in metastatic or locally advanced HER2-positive IBC patients (phase II). Secondary objectives include assessing progression-free survival, the association between pCR and HER2 and EGFR expression, and toxicity and safety.

The phase Ib portion of the trial uses the Bayesian modified Toxicity Probability Interal (mTPI)[34] dose-escalation algorithm to determine the MTD of neratinib from among five dose levels. Up to 20 HER2-positive metastatic breast cancer and locally advanced IBC and non-IBC patients will be included. In the phase II portion, enrollment will be for the same population, metastatic or locally advanced HER2-positive IBC patients. Patients will be treated at the MTD of neratinib chosen during the phase Ib portion in combination with the other drugs. The primary endpoint is the pCR rate at the end of neoadjuvant chemotherapy. For the phase II portion, a maximum of 31 patients will be treated, although we expect the actual number to be less (see below). Toxicity will be monitored in the Phase II portion by the monitoring rule described below.

Cohort II:

For cohort II, the primary objective is to assess the efficacy of neratinib in combination with paclitaxel followed by AC in stage III or IV HER2-/ HR+ IBC patients. Secondary objectives include assessing progression-free survival, the association between pCR and HER2 and EGFR

expression, and toxicity and safety. A maximum of 31 patients will be included in this cohort. Response is monitored by using Simon's two-stage design [35] (details below).

For the expansion cohort, we will enroll additional HER2- patients with a HER2 mutation until we have total 18 such patients. Eighteen patients will provide reasonable power for secondary biomarker endpoints. We expect that 5-20% of the 31 Cohort II patients will have the HER2 mutation; thus, we will need to enroll between 12 and 17 additional patients for expansion cohort to meet our target of 18. Toxicity will be monitored in the Phase II portion by the monitoring rule described below.

11.2 Phase Ib Design

The Phase Ib portion of the trial will be restricted to cohort I patients only. The mTPI approach of Ji et al will be used to estimate the MTD from the five doses listed in Table 16, starting at Dose Level 0 (neratinib at 80mg/day). Dose -1 is included in case Dose 0 is too toxic. DLT will be evaluated within the first 2 cycles.

Table 16. Dose levels

Dose Level	Neratinib Dose	Pertuzumab Dose#	Trastuzumab Dose#	Paclitaxel*
-1	40 mg	loading dose 840 mg, followed by 420 mg	loading dose 8 mg/kg, followed by 6 mg/kg	80mg/kg
0	80 mg	loading dose 840 mg, followed by 420 mg	loading dose 8 mg/kg, followed by 6 mg/kg	80mg/kg
1	120 mg	loading dose 840 mg, followed by 420 mg	loading dose 8 mg/kg, followed by 6 mg/kg	80mg/kg
2	160 mg	loading dose 840 mg, followed by 420 mg	loading dose 8 mg/kg, followed by 6 mg/kg	80mg/kg
3	200 mg	loading dose 840 mg, followed by 420 mg	loading dose 8 mg/kg, followed by 6 mg/kg	80mg/kg

This is current standard treatment dose, dose modification is not recommended.
* Dose reduction allowed as needed per standard treatment guideline at all levels

DLT includes any of the following possibly, probably, or definitely due to study therapy, assessed during the first 2 cycles [*42 days*]:

- Any death not clearly due to the underlying disease or extraneous causes
- Non- hematologic toxicity
  - Grade 3 or higher non-hematologic toxicity, except grade 3 diarrhea is a DLT if it lasts ≥ 2 days despite prophylactic medication
  - Grade 2 diarrhea lasting ≥ 5 days despite prophylactic medication
  - Hy's Law case, defined as a patient meeting all of the following criteria:
    a. ALT or AST ≥ 3 x Upper Limit of Normal (ULN)
    b. Total bilirubin >2 x ULN
    c. Little or no evidence of cholestasis (alkaline phosphatase <2 x ULN)
    d. No other identified explanation for the injury (such as hepatitis A, B, C, or other viral hepatic injury, alcohol ingestion, congestive heart failure).

  - Neutropenic fever
- Hematologic toxicity
  - Grade 4 neutropenia or thrombocytopenia >7 days
  - Grade 3 thrombocytopenia with bleeding

The targeted maximum DLT rate is 20%, and we will enroll patients in cohorts of size 2. We assume a prior distribution of Beta (1,1) for the toxicity rate at each dose level, and we also assume an equivalence interval around the toxicity rate of 5% in either direction; i.e., (15%, 25%). A maximum of 20 patients will be treated at the dose levels shown in Table 16. Figure 5 provides the rules for escalation and de-escalation once each cohort of patients has been assessed.

Figure 5. Dose-Escalation Rules

Number of Patients in Cohort

Number of dose limiting toxicities (DLT's)	2	4	6	8	10	12	14	16	18	20
0	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	E	E	E	E	E	E
2	DU	D	S	S	S	S	S	S	E	E
3		DU	DU	S	S	S	S	S	S	S
4		DU	DU	DU	D	S	S	S	S	S
5			DU	DU	DU	DU	S	S	S	S
6			DU	DU	DU	DU	DU	DU	S	S
7				DU	DU	DU	DU	DU	DU	DU
8				DU	DU	DU	DU	DU	DU	DU
9					DU	DU	DU	DU	DU	DU
10					DU	DU	DU	DU	DU	DU
11						DU	DU	DU	DU	DU
12						DU	DU	DU	DU	DU
13							DU	DU	DU	DU
14							DU	DU	DU	DU
15								DU	DU	DU
16								DU	DU	DU
17									DU	DU
18									DU	DU
19										DU
20										DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
DLT = Maximum 20%
Sample Size = 20
Epsilon1 = 0.05
Epsilon2 = 0.05

The MTD is defined as the highest dose for which the posterior probability of toxicity is closest to 20%. The table below summarizes the operating characteristics of the proposed design for this trial for 6 scenarios defined by different toxicity rates for the 5 doses. These operating characteristics are based on 2000 simulations of the trial.

Table 17. Operating Characteristics of Phase Ib Study Design

Dose Level	-1	0	1	2	3	No Dose Chosen
Scenario 1						
True Toxicity Rate	0.010	0.025	0.05	0.10	0.15	
Selection Probability	0.001	0.016	0.065	0.199	0.719	0
Avg. # of Patients Treated	0.1	2.8	3.5	4.3	9.3	
Total Patients		20.0				
Overall Toxicity		0.10				
Scenario 2						
True Toxicity Rate	0.025	0.05	0.15	0.25	0.35	
Selection Probability	0.006	0.106	0.362	0.355	0.172	0
Avg. # of Patients Treated	0.3	4.5	6.7	5.3	3.2	
Total Patients		20.0				
Overall Toxicity		0.18				
Scenario 3						
True Toxicity Rate	0.025	0.05	0.20	0.35	0.45	
Selection Probability	0.011	0.199	0.505	0.229	0.058	0
Avg. # of Patients Treated	0.4	5.5	8.3	4.3	1.6	
Total Patients		20.0				
Overall Toxicity		0.21				
Scenario 4						
True Toxicity Rate	0.25	0.35	0.45	0.55	0.65	
Selection Probability	0.581	0.158	0.067	0.006	0	0.190
Avg. # of Patients Treated	7.5	7.8	2.4	0.5	0.1	
Total Patients		18.2				
Overall Toxicity		0.33				
Scenario 5						
True Toxicity Rate	0.30	0.35	0.45	0.55	0.65	
Selection Probability	0.51	0.142	0.057	0.009	0.001	0.282
Avg. # of Patients Treated	7.3	7.3	2.2	0.5	0.1	
Total Patients		17.4				
Overall Toxicity		0.35				
Scenario 6						
True Toxicity Rate	0.01	0.03	0.06	0.09	0.12	
Selection Probability	0.001	0.025	0.07	0.160	0.746	0
Avg. # of Patients Treated	0.1	2.9	3.6	3.9	9.4	
Total Patients		20.0				
Overall Toxicity		0.09				

11.3 Phase II Design

In both cohorts, the primary endpoint will be the pCR rate at the end of neoadjuvant chemotherapy. Patients evaluable for efficacy are those who have completed the course of treatment per protocol and have surgery. Non-evaluable patients will be replaced.

In cohort I, HER2-positive patients, we will use Simon's optimum two-stage design to monitor the pCR rate. We will target a maximum one-sided alpha of 5% and a beta of 20%. The historical pCR rate in these patients is 40%, which we hope to increase to 65% with the introduction of neratinib. We will enroll 11 patients in the first stage, and if at least 6 have a pCR, we will enroll an additional 20. If at least 17 patients of the total of 31 respond, we will be able to conclude that the pCR rate in the HER2+ cohort is significantly higher than the historical rate of 40%. If the true pCR rate in this group is 40% or lower, the probability that the study stops after the first look is at least 75%.

In cohort II, HER2-negative/ HR-positive patients, we will also use Simon's minimax two-stage design to monitor the pCR rate. We will also target a maximum one-sided alpha of 5% and a beta of 20%. The historical pCR rate in these patients is 8.2%, which we hope to increase to 25% with neratinib. We will enroll 16 patients in the first stage, and if at least 2 have a pCR, we will enroll an additional 15. If at least 6 patients of the total of 31 have a pCR, we will be able to conclude that the pCR rate in HER2-/HR+ patients is significantly higher than the historical rate of 8.2%. If the true pCR rate in this group is 8.2% or lower, the probability that the study stops after the first look is at least 61%.

11.4 Toxicity Monitoring in Phase II

Toxicity in Phase II will be monitored separately by cohort by the method of Thall and Sung [36]. We wish to assure that the DLT rate in the Phase II portion is no higher than 30% in either cohort. DLT will be assessed at the same time as in the Phase I portion of the design; i.e., at the end of 2 cycles of treatment.

In Cohort I, we will denote the probability of DLT as P_{DLT1} and assume a Beta (0.6, 1.4) prior distribution for this probability, which has a mean of 0.3, corresponding to the target rate of 30%. We will monitor DLT in this cohort by using the following rule: stop accrual into the cohort if at any time

$$\Pr(P_{DLT1} > 0.30 \mid \text{data from patients in cohort}) > 0.95$$

This rule leads to the stopping boundaries found in Table 18.

Table 18. Stopping Boundaries for DLT Monitoring Rule for Cohort I

If there are this many patients with DLT	Stop accrual if this many patients have been evaluated for DLT
3	3
4	4-5
5	5-8
6	6-10
7	7-12

8	8-15
9	9-18
10	10-20
11	11-23
12	12-25
13	13-27
14	14-30
15	Always Stop

This rule was simulated using the program MultcLean Desktop, version 2.1.0. The operating characteristics are found in Table 19 below. If Cohort I is stopped, Cohort II may continue.

Table 19. Operating Characteristics of DLT Monitoring Rule for Cohort I

		Sample Size		
True P_{DLT}	**Early Stopping Probability**	**25th**	**Median**	**75th**
10%	0.001	31	31	31
20%	0.017	31	31	31
30%	0.151	31	31	31
40%	0.473	12	31	31
50%	0.822	7	12	23

In Cohort 2, we will denote the probability of DLT as P_{DLT2} and assume a Beta (0.6, 1.4) prior distribution for this probability, which has a mean of 0.3, corresponding to the target rate of 30%. Accounting for up to 17 additional patients with a HER2 mutation, we may enroll up to 48 patients in this cohort. We will monitor DLT by using the following rule: stop accrual into Cohort 2 if at any time

$$\Pr(P_{DLT2} > 0.30 \mid \text{data from patients in cohort}) > 0.975$$

This rule leads to the stopping boundaries found in Table 20.

Table 20. Stopping Boundaries for DLT Monitoring Rule for Cohort II

If there are this many patients with DLT	Stop accrual if this many patients have been evaluated for DLT
3	3
4	4-5
5	5-7
6	6-9
7	7-11
8	8-13
9	9-16
10	10-18
11	11-21
12	12-23
13	13-26
14	14-29
15	15-31
16	16-34
17	17-37

18	18-39
19	19-42
20	20-45
21	21-47
22	Always Stop

This rule was simulated using the program MultcLean Desktop, version 2.1.0. The operating characteristics are found in Table 21 below. If Cohort II is stopped, Cohort 1 may continue.

Table 21. Operating Characteristics of DLT Monitoring Rule for Cohort II

		Sample Size		
True P_{DLT}	**Early Stopping Probability**	**25th**	**Median**	**75th**
10%	0.001	48	48	48
20%	0.017	48	48	48
30%	0.118	48	48	48
40%	0.488	18	48	48
50%	0.888	7	16	31

11.5 Secondary Objectives and Analyses

Secondary and exploratory analyses include assessing progression-free survival, toxicity, safety, determining the adaptive target and downstream changes in pan-HER family members, assessing the association between changes in EGFR, HER2, and HER4 and pCR, assessing the rate of HER2 mutations and the association with pCR, and assessing the association between pharmacodynamic markers and circulating tumor cells (CTC) and ctDNA.

Adaptive target and downstream changes will be measured by the change in PI3K and Akt phosphorylation from baseline.

Progression-free survival (PFS) will be estimated by the Kaplan-Meier method, and distributions will be compared using the log-rank test. Cox proportional hazards regression models may be fit to assess the relationship between PFS and disease, clinical, and demographic covariates of interest.

Adverse events will be summarized using standard methods; i.e., mean, median, quartiles, and standard deviation for continuous parameters and frequency summaries for categorical parameters.

Logistic regression will be used to assess the association between the probability of pCR and disease, clinical, and demographic covariates of interest, including changes in EGFR, HER2, and HER4, and HER2 mutations.

The assocation between changes in adaptive targets, changes in pharmacodynamic marker changes, and changes in CTC and ctDNA will be assessed using linear regression.

11.6 Toxicity/Efficacy Report to IND Office

Phase Ib

A Toxicity/Efficacy Summary will be submitted to the IND Office Medical Monitor after the first 2 evaluable patients complete the first 2 cycles of study therapy, and every 2 evaluable patients thereafter, prior to dose modification or initiation of Phase 2.

Phase II

Cohort I

- A toxicity summary will be submitted to the IND Office Medical Monitor after 3 evaluable patients complete 2 cycles of treatment and every 2 evaluable patients thereafter. An Efficacy Summary will be submitted after the first 11 evaluable patients have been treated at the RP2D, and after the total treated population of 31 patients have completed the study therapy.

Cohort II

- A toxicity summary will be submitted to the IND Office Medical Monitor after 3 evaluable patients complete 2 cycles of treatment and every 2 evaluable patients thereafter. An Efficacy Summary will be submitted after the first 16 evaluable patients have been treated, and after the total treated population of 31 patients have completed the study therapy.

12.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

12.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Puma Biotechnology Inc. as summarized in the table below.

Product Descriptions

Product Name & Potency	Dosage Form
Neratinib : 40mg/tablet	Oral Drug

12.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

12.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

12.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

12.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Puma Biotechnology Inc or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

13.0 DATA MANAGEMENT

The Principal Investigator is responsible for assuring that the data entered into the database are complete and accurate and that data entry is performed in a timely manner. CORe/RedCap will be used as the electronic case report form for this protocol and protocol specific data will be entered into CORe/RedCap.

13.1 Data collection for this study including:

- Demographic information (sex, race, and date of birth)
- Date of initial breast cancer diagnosis, pathology report of primary breast cancer, biomarker status, and date and location of distant metastases at disease progression
- History of breast cancer surgery, and radiation therapy, if applicable
- Date and type of chemotherapy and/or hormonal therapy for metastatic disease

All AEs will be collected, however only >/=2 non-hematologic AEs and >/=3 hematological AEs will be recorded. Other abnormal laboratory values will not be reported as AEs; however, any clinical consequences of abnormality should be reported as AEs.

Concomitant medication will be recorded per standard of care in clinic database, and will not be recorded in the study database.

13.2 Data confidentiality plan

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity will be possible only after accessing a password-protected database. Access to the database will be available only to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

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