A Phase II Randomized Trial Evaluating Neoadjuvant Dose-Dense Doxorubicin/ Cyclophosphamide Followed by Paclitaxel/Trastuzumab/Pertuzumab (AC THP) and Docetaxel/Carboplatin/Trastuzumab/Pertuzumab (TCHP) For Early Her2Neu Positive Breast Cancer

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1. SYNOPSIS

A Phase II Randomized Trial Evaluating Neoadjuvant Dose-Dense Doxorubicin/Cyclophosphamide followed by Paclitaxel/Trastuzumab/Pertuzumab (ACTHP) and Docetaxel/Carboplatin/Trastuzumab/Pertuzumab (TCHP) For Early Her2Neu Positive Breast Cancer

(34-74 patients)

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Objectives

Primary Objective:

- Determination of pathologic complete response (pCR) rates, (i.e., ypT0 ypN0 in the current AJCC system).

Secondary Objective:

- Determination of cardiac toxicity as measured by: composite of LVEF, longitudinal strain and troponin.
- Breast conservation rates
- Overall survival

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Patient Population (*Accrual 34 -74*):

Inclusion criteria:

- ECOG performance status of 0 or 1
- Eligible tumors must meet one of the following criteria:
  - Operable (T1c, T2-3, N0-1, M0)
  - Locally advanced (T1c or greater or any N)
  - Inflammatory breast cancer (T4d, any N, M0)
- Breast cancer determined to be:
  - Confirmed HER2-positive (IHC 3+ or 2+ and ISH positive)
  - any ER or PR receptor status
- LVEF assessment by echocardiogram within 30 days of initiation; EF of ≥55% considered normal.
- Normal troponin I level at baseline

Exclusion criteria:

1. Patients with a history of decompensated congestive heart failure or an EF < 55% will be excluded
2. Active or history of cardiac disease that would preclude the use of the drugs
3. Definitive clinical or radiologic evidence of metastatic disease or bilateral breast cancer
- Previous therapy with anthracylines, taxanes, or trastuzumab for any malignancy

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Study Design

- Approximately 34-74 patients with Her2 positive, Stage I-regional IV breast cancer will be enrolled.
- Patients will be stratified by ER status.
- They will be randomized to ddACTHP vs TCHP.
  - Initially, 17 patients will be randomly assigned to each treatment arm.

- If 3 or fewer patients have a pCR, then that arm will be terminated and no further patients will be entered on that treatment arm.
- If 4 or more patients obtain a pCR, 20 additional patients (total of 37 patients) will be randomized to that treatment arm.
- If 11 or more patients out of 37 have a pCR, the treatment will be of interest for further study.

- After completion of neoadjuvant therapy, each patient will be evaluated for definitive treatment by their breast surgeons. Surgical management and radiation oncology management as per institutional guidelines.
- After completion of chemotherapy and surgical and/or radiation therapy, patients with estrogen receptor (ER) –positive and/or progesterone receptor–positive tumors will be offered adjuvant endocrine therapy.

Evaluations

- **Physical examination** of breasts and regional lymph node basins will be performed before each cycle of chemotherapy.
- **Cardiac: Echocardiogram**s to evaluate for EF, longitudinal strain will be performed every 3 months.
- **Blood Sample: Troponin measurements** will be performed as per protocol at regular intervals.

TABLE OF CONTENTS

1.0 Summary

Breast cancer is the second leading cause of death amongst women in the western world.[1] For those patients with localized disease who could become surgical candidates, the standard of care is to offer neoadjuvant systemic chemotherapy as part of multimodality therapy. It has been shown that adding trastuzumab and more recently pertuzumab to chemotherapy improves outcomes in the neoadjuvant setting for Her2neu positive cancers, yet it is not known which chemotherapy regimen is best to combine with these two biologic agents. The NOAH trial has confirmed adding trastuzumab to chemotherapy in the neoadjuvant setting prolonged 3yr DFS by 15% and doubles the rate of pCR. [2]Dose dense doxorubicin (A), cyclophosphamide (C) followed by paclitaxel (T) with trastuzumab (H) (ddAC→TH) has been widely accepted as the standard regimen which is an extrapolation from the adjuvant literature. More recently it has been shown that the addition of pertuzumab (P) to chemotherapy significantly increases the pCR rate thus making the case for dual blockade of Her2Neu in the neoadjuvant setting [3,4] which lead to the recent FDA approval of pertuzumab in the neoadjuvant setting. Both studies of dual Her2Neu blockade used to support the FDA's decision: TRYPHAENA [3] and NEOSPHERE [4] lack long-term cardiotoxicity data so more studies are needed to investigate cardiotoxicity using novel measurements. We aim to determine which of two regimens (anthracycline containing and anthracycline-free) will provide both a high pCR rate and less cardiotoxicity. Via a prospective Phase II randomized trial, we aim to compare an FDA approved regimen (with the addition of carboplatin) (TCHP) with a commonly used doxorubicin based regimen with the addition of pertuzumab (ddAC→THP), not previously explored for locally advanced Her2neu positive breast cancer. The primary objective will be to evaluate efficacy as measured by pCR rates and the secondary objective will be to evaluate cardiac toxicities using a definition that includes changes in LVEF, longitudinal strain and troponin values.

2.0 Background and Rationale

Over 200,000 new cases of invasive breast cancer are expected to be diagnosed in the United States each year and 40,000 will die from disease.[1,5] Locally advanced breast cancer has not always been consistently defined but usually includes tumors that are inoperable/large and/or have extensive lymph node involvement.[6]

2.1 Rationale for Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is used for locally advanced breast cancer to increase the likelihood of breast conservation outcomes. A benefit of preoperative chemotherapy is that it allows the oncologist to evaluate tumor response in vivo[6] and is therefore a model

for more efficient drug development strategies. Studies have shown that when neoadjuvant chemotherapy is administered to operable breast cancer patients, that there is no difference in survival as compared to giving the same chemotherapy adjuvantly.[7] Previous RCTs have shown that pCR may predict DFS and OS. In the NSABP-18 trial which compared preoperative versus postoperative delivery of 4 cycles of doxorubicin plus cyclophosphamide (AC), patients in the preoperative AC arm who attained pCR had a markedly reduced risk of death (hazard ratio (HR) 0.32, $p<0.0001$) at 16 years of follow-up compared with those who did not.[7] A Cochrane meta-analysis of 14 trials of preoperative versus postoperative chemotherapy enrolling 5,500 patients with a median follow-up of 18 to 124 months reported that the risk of death in patients who attained pCR was reduced by almost half compared with patients who had residual tumor present at the time of surgery (HR 0.48; 95 percent CI 0.33, 0.69).[8] The NSABP-B27 was a phase III, randomized trial designed to evaluate whether adding preoperative docetaxel to neoadjuvant doxorubicin/cyclophosphamide, and noted a strong, statistically significant correlation between pCR and DFS and OS. [9]

2.2 Defining pCR as a an endpoint

Based on the above studies, the FDA recognized pCR as a surrogate endpoint for DFS and OS and created in May, 2012 a guidance for industry regarding using pathologic CR as an endpoint for neoadjuvant trials to support accelerated approval of novel therapeutics.[10] There has not always been a uniform definition of pCR making reporting and interpretation of these trials difficult.[10] The FDA proposed the following definition: the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypN0 in the current AJCC system).[10]As per these guidelines presence of residual DCIS should not be used to judge the effectiveness of systemic neoadjuvant chemotherapy. [10]

2.3 Trastuzumab

Historically, women with breast cancers that overexpress Her2neu were at greater risk for disease progression and death than women whose tumors do not overexpress Her2neu prior to the development of Trastuzumab.[11] Trastuzumab, a recombinant humanized monoclonal antibody against the extracellular domain of the Her2neu protein blocks downstream signaling of Her2neu and substantially improves the efficacy of chemotherapy in women with metastatic and early-stage Her2neu-positive breast cancers. Neoadjuvant therapy may be most appropriate for patients likely to have good locoregional response such as patients with Her2neu-positive or triple negative disease (ER-/PR-/Her2-). [12] The addition of trastuzumab for Her2neu positive locally advanced breast cancer in the neoadjuvant setting further increased pCR rates. The NOAH (Neoadjuvant Trastuzumab) trial compared 1 year of treatment with

trastuzumab (given as neoadjuvant and adjuvant treatment; n=117) with no trastuzumab (n=118), in women with HER2-positive locally advanced or inflammatory breast cancer treated with a neoadjuvant chemotherapy regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and fluorouracil and found pCR doubled from 19 to 38% (p=0.001) and 3 year DFS increased from 56 to 71% (p=.0013)with the addition of trastuzumab.[2] The GeparQuattro (epirubicin and cyclophosphamide followed by capecitabine and docetaxel with trastuzumab) showed a pCR rate of 31.7% compared to 15.7% with the addition of trastuzumab. [13] Preliminary results from the NSABP-41 (which will complete accrual in 2015) of neoadjuvant AC→T (paclitaxel) H showed a pCR rate of 49.1%.[14] The results of the trial have not been published, yet this regimen is used routinely in the clinical setting.

2.4 Dual Her2Neu Blockade

Dual Her2Neu blockade was the next logical step of exploration. The CLEOPATRA trial was a randomized, double-blind, placebo-controlled, phase 3 trial involving patients with HER2-positive metastatic breast cancer who had not received chemotherapy or biologic therapy for their metastatic disease. Pertuzumab is a humanized anti-HER-2 monoclonal antibody that binds to the extracellular dimerization subdomain of the HER-2 receptor thereby preventing herterodimer formation most notably with HER3 and reduces intracellular signaling. Pertuzumab and trastuzumab bind to different sites on the HER-2 receptor and have complementary anti-tumor activities. [2, 3] Patients were randomized to trastuzumab plus docetaxel plus pertuzumab or placebo. [15] Pertuzumab prolonged PFS by 6 months and OS by more than 15 months at 3 yrs. HR of 0.66, resulting in a 34% reduction in risk of death. Median overall survival was 37.6 months (95% CI 34·3—NE [not estimable]) in the placebo group but had not been reached (95% CI 42·4—NE) in the pertuzumab group (hazard ratio 0·66, 95% CI 0·52- 0·84; p=0·0008). [15]

2.5. Neoadjuvant Pertuzumab

Studies using pertuzumab in the neoadjuvant setting such as TRYPHAENA and NEOSPHERE both have shown significant increases in pCR rates secondary to the addition of pertuzumab to various trastuzumab based regimens. NeoSphere is a multicentre, open-label, phase 2 study, of treatment-naive women with HER2-positive operable, locally advanced or inflammatory breast cancer randomly assigned to receive four neoadjuvant cycles of: trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) plus docetaxel (75 mg/m², escalating, if tolerated, to 100 mg/m² every 3 weeks; group A) or pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks) and trastuzumab plus docetaxel (group B) or pertuzumab and trastuzumab (group C) or pertuzumab plus docetaxel (group D). All patients went on to definitive treatment and adjuvant F (5-flourouracil) E (epirubicin) C (cyclophosphamide)

chemotherapy. The primary endpoint was pCR in the breast. This study showed that treatment with pertuzumab, trastuzumab and docetaxel chemotherapy significantly improved the rate of total pCR by 17.8% compared to trastuzumab and docetaxel alone (39.3 vs. 21.5%, p=0.0063). [4] However in this study the most recent definition of pCR including no evidence of disease in sampled lymph nodes was not used but was described. The TRYPHAENA study was a multicenter, open-label phase II study, of patients with operable, locally advanced, or inflammatory breast cancer who were randomized to receive six neoadjuvant cycles every 3 weeks of Arm A: 5-fluorouracil, epirubicin, cyclophosphamide [FEC] + H + P ×3 → docetaxel [T] + H + P ×3; Arm B: FEC ×3 → T + H + P ×3; Arm C: T + carboplatin + H [TCH]+P ×6). pCR was assessed at surgery and adjuvant therapy given to complete 1 year of H. The primary endpoint was cardiotoxicity and the secondary endpoint was pCR. It showed a pCR of 63.6% in the anthracycline-free arm which contained pertuzumab, trastuzumab, docetaxel and carboplatin chemotherapy vs. a pCR of 54.7% in the anthracycline based arm which contained pertuzumab, trastuzumab and docetaxel. [3] However it is important to note that this study was not powered to compare the pCR rates across arms because it was a secondary endpoint.

2.6 Investigating Cardiac Toxicity

However neither of these studies explored doxorubicin-containing regimens and more investigation regarding long-term cardiotoxicity is needed. Cardiac toxicity is an important side effect of trastuzumab. Although no added cardiac toxicity with pertuzumab has been observed in the metastatic setting, more long-term data is needed in the neoadjuvant setting. The NeoSphere trial which contained non-anthracycline based regimens was not powered to detect cardiotoxicity but was positive in showing no appreciable difference was detected when pertuzumab was added to trastuzumab. [4] The mean maximum decrease in LVEF was low (4-5%) and was balanced across treatment groups. [4] The TRYPHAENA study which was powered for cardiotoxicity and included anthracyclines showed that the combination of pertuzumab with trastuzumab resulted in low rates of symptomatic LVSD and low rates of significant declines in LVEF (≥ 10% points from baseline to < 50%). A slightly higher percentage of patients (yet statistically insignificant) experienced asymptomatic declines in LVEF in the anthracycline arms compared to the anthracycline free arm (5.6% and 5.3% compared to 3.9%) and the only 2 patients that experienced symptomatic LVSD were in the anthracycline based arm.

It has been shown that other cardiac measures may be useful for predicting development of cardiotoxicity. Myocardial deformation indices have been shown to identify subclinical dysfunction in a variety of diseases.[16,17] In recent studies, longitudinal strain (deformation of the left ventricle along the long axis) is a parameter which is most predictive of development of cardiotoxicity.[18] In a recent clinical study,

longitudinal strain has been shown to be an independent and incremental early predictor of later reduction in EF in patients at risk for trastuzumab-induced cardiotoxicity.[18] In a study of 43 patients with breast cancer treated with anthracyclines followed by trastuzumab and paclitaxel a drop of more than 10% in peak global longitudinal strain from baseline to 3 month could predict later development of cardiotoxicity at 6 months while LVEF and parameters of diastolic dysfunction did not. [19] A change in longitudinal strain was the strongest predictor of subsequent decrease in EF (GLS (global longitudinal peak systolic strain): AUC, 0.84, $P < .001$). [20] Additionally circulating blood markers such as troponins and others may be predictive of identifying clinically relevant cardiotoxicity.[19] As the myocardium undergoes volume of pressure stress, cardiac myocytes release measurable substances that may or may not correlate with patient characteristics, echocardiographic findings, and clinical signs and symptoms. Troponin measurements have been used to measure myocardial injury and predict incident LV dysfunction in patients receiving high doses of anthracyclines but their role in patients receiving low to moderate doses of anthracyclines is not well established.[21] In a study of patients with breast cancer treated with dose-dense chemotherapy incorporating trastuzumab and lapatinib cardiac troponin I (cTnI) were commonly detected and these elevations may precede changes in LVEF but do not predict LVEF. [21] Longitudinal strain and troponin I warrant further study in the neoadjuvant setting.

2.7 Our Study

There is no standard neoadjuvant regimen for Her2Neu positive breast cancer. Often we extrapolate from the adjuvant setting and use regimens like ACTH and TCH in the neoadjuvant setting. Based primarily on data from NeoSphere and secondarily from TRYPHAENA, the FDA approved of pertuzumab and trastuzumab and docetaxel for the neoadjuvant treatment of patients with Her2Neu-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer on Sept 30th 2013. This was the first neoadjuvant regimen approved in breast cancer and the first treatment approved based on pCR. [23] The addition of pertuzumab to trastuzumab and docetaxel and carboplatin chemotherapy results in a pCR of 63.6% with minimal cardiac toxicity. [3] Thus, TCHP has amongst the highest reported pCRs with no reported significant cardiotoxicity so further study of the TCHP regimen is warranted. BCIRG 006 compared TCH (docetaxel, carboplatin, trastuzumab) with ACTH (doxorubicin, cyclophosphamide, docetaxel, trastuzumab) in the adjuvant setting and showed that there was no statistical advantage of ACTH over TCH but a slight improvement in DFS in the ACTH treatment arm. This numeric advantage comes at the cost of 21 CHFs (5X more than in TCH 2% vs. 0.4%).[24] This study compared ACTH and TCH, but used docetaxel not paclitaxel for the "T" in ACTH and therefore did not use a dose dense

regimen, which is not our current standard of care. Dose dense AC→TH with paclitaxel has the most evidence for improved outcomes in the adjuvant setting and it is widely accepted.[25] There is lingering doubt that TCH may not be as effective in comparison. Perhaps the additional benefit of pertuzumab may obviate the need for anthracycline based chemotherapy. ACTH with P has not been investigated in the neoadjuvant setting and TCHP has not yet been compared with a doxorubicin-containing regimen. Also the cardiac safety of pertuzumab as part of a doxorubicin-containing regimen has not yet been established. Moreover, since we do not yet have data for pertuzumab in the adjuvant setting, providing pertuzumab in the neoadjuvant setting to operable tumors may be the only chance to give these patients the added benefit of pertuzumab. We propose a randomized Phase 2 study to evaluate neoadjuvant ddAC→THP and TCHP in patients with Stage II-IIIA, (including T1c tumors) breast cancer with Her2 positive breast cancer. The primary outcome will be efficacy as measured by pCR rates and the secondary outcome will be cardiac toxicity, as defined by changes in LVEF, longitudinal strain, and biomarkers of cardiac injury (troponin) as described above. We propose to measure longitudinal strain and Troponin I as a preclinical marker of cardiotoxicity and determine if they are predictive of cardiotoxicity in addition to measuring LVEF.

3.0 Hypothesis:

We aim to determine which of 2 treatments TCHP or ACTHP shows adequate efficacy and expect TCHP to be less cardiotoxic than ACTHP because of the lack of anthracyline-based chemotherapy.

4.0. Objectives:

4.1 Primary Objective:

- Determination of pathologic complete response (pCR) rates, defined by the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypN0 in the current AJCC system).

4.2 Secondary Objectives:

4.2.1 Determination of cardiac toxicity as measured by: composite of LVEF, longitudinal strain and troponin.

- Changes in LVEF from regularly scheduled echocardiograms, every 3 months
- A change in longitudinal strain combined with an abnormally elevated value of troponin should provide about a 90% sensitivity to predict early cardiotoxicity. Peak systolic longitudinal strain is calculated by averaging the values of peak systolic strain in the basal, mid and apical segments of

the LV in 4-, 3- and 2-chamber views on echocardiograms. A value of <-18% or a >15% decline in strain from patient's baseline value will be used as a cut-off value. Similarly a value of troponin I > 0.08 ng/ml [21, 30,31] will be considered elevated.

- Determination of non-cardiac toxicities as measured by frequencies of adverse events categorized using CTCAE v4.03.

4.2.2 Breast Conservation Rates

Breast conservation rates: rate of breast-conserving surgery for patients for whom mastectomy was planned before treatment. It would be based on surgical opinion at time of surgery if the tumor was appropriately "downstaged" to perform breast conserving surgery on patients previously recommended to have a mastectomy

4.2.3 Overall survival

5.0. Patient Selection:

5.1. Inclusion criteria:

- The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.
- Female
- 18 years or older
- ECOG performance status of 0 or 1
- Eligible tumors must meet one of the following criteria:
  - Operable (T1c, T2-3, N0-1, M0)
  - Locally advanced (T1c or greater or any N)Inflammatory breast cancer (T4d, any N, M0)
- Staging evaluation:
  - History and physical exam, cbc, chemistry profile
  - CT Chest/Abdomen/Pelvis and a bone scan or PET/CT as needed
- Diagnosis of invasive adenocarcinoma made by core needle biopsy
- Breast cancer determined to be:
  - Confirmed HER2-positive : (ASCO CAP guidelines, 10/7/2013)
    - IHC 3+ based on circumferential membrane staining that is complete, intense
    - ISH positive based on:
    - Single probe average HER2 copy number $\geq$ 6 signals/cell

- Dual probe HER2/CEP 17 ratio ≥ 2.0 with an average HER2 copy number ≥ 4.0 signals/cell
- Dual probe HER2/CEP 17 ratio ≥ 2.0, with an average HER2 copy number of < 4.0 signals/cell
- Dual probe HER2/CEP17 ratio <2.0 with the average HER2 copy number of ≥6.0 signals/cell

- any ER or PR receptor status

- LVEF assessment by echocardiogram within 30 days of initiation; EF of ≥ 55% considered normal.
- Normal troponin I level at baseline
- Blood counts must meet the following criteria:
  - ANC greater than or equal to 1500/mm^3
  - Platelet count greater than or equal to 100,000/mm^3
  - Hemoglobin greater than or equal to 10 g/dL
- Serum creatinine less than or equal 2.5 mg/100ml
- Adequate hepatic function by these criteria: total bilirubin must be less than or equal to 1.5 x the ULN for the lab unless the patient has a bilirubin elevation great than the ULN to 1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin; and alkaline phosphatase must be less than or equal to 2.5 x ULN for the lab; and AST must be less than or equal to 1.5 x ULN for the lab. Both alkaline phosphatase and AST may not both be greater than the ULN.
- Patients with AST or alkaline phosphatase > ULN are eligible for inclusion in the study if liver imaging (CT, MRI, PET-CT or PET scan) performed within 90 days prior to randomization does not demonstrate metastatic disease and the requirements are met as above
- Patients with alkaline phosphatase that is > ULN but less than or equal to 2.5 x ULN or unexplained bone pain are eligible for inclusion in the study if a bone scan, PET-CT scan, or PET scan performed within 90 days prior to randomization does not demonstrate metastatic disease.

5.2. Exclusion criteria:

- Patients with a history of decompensated congestive heart failure or an EF < 55% will be excluded
- Cardiac disease that would preclude the use of the drugs included in the above regimens This includes but is not confined to:
  - Active cardiac disease:
    - angina pectoris requiring the use of anti-anginal medication;

        - ventricular arrhythmias except for benign premature ventricular contractions controlled by medication;
        - conduction abnormality requiring a pacemaker;
        - supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication; and
        - clinically significant valvular disease
        - symptomatic pericarditis
        - pulmonary hypertension
    - History of cardiac disease:
        - myocardial infarction;
        - congestive heart failure; or
        - cardiomyopathy
- Definitive clinical or radiologic evidence of metastatic disease or bilateral breast cancer (excluding DCIS (Ductal Carcinoma In Situ)
- History of non-breast malignancies (except for in-situ cancer treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior to randomization
- Previous therapy with anthracylines, taxanes, or trastuzumab for any malignancy
- Pregnant or refusing to use contraception

6.0. Treatment Plan (Please see Appendix A: schema)

6.1. Treatment Regimens

Approximately 54-74 patients with Her2 positive, Stage II-regional IV breast cancer will be enrolled. Patients will be stratified by ER status. They will be randomized to:

6.1.1. Dose Dense AC → THP[22]

- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1
- Pegfilgastrim 6mg SC, day 2 of AC

Cycled every 14 days for 4 cycles, followed by,

- Paclitaxel 80 mg/m^2 IV x 1 hour infusion on days 1, 8, and 15*
- Trastuzumab 8 mg/kg IV day 1, followed by 6mg/kg
- Pertuzumab loading dose 840 mg IV followed by 420 mg IV every 3 weeks

Cycled every 21 days for 4 cycles, or

6.1.2. TCHP (regimen as per references [3, 4] and NCCN guidelines) [22]

- Docetaxel 75mg/m^2 IV, day 1
- Carboplatin AUC 6 IV, day 1
- Trastuzumab 8mg/kg IV initial dose, followed by 6mg/kg IV , day 1
- Pertuzumab 840 mg IV initial dose followed by 420 mg IV, day 1
- Pegfilgastrim 6mg SC, day 2
- Cycled every 21 days for 6 cycles

  * Our institutional practice is to titrate the infusion rate on the initial Paclitaxel dose (40 ml/hr x 5 min, then 80 ml/hr x 5 min, then 120 ml/hr x 10 min, then 200 ml/hr). Subsequent Paclitaxel doses are given over 1 hour.
- Supportive care (including antiemetics, premedications and anaphylactic medications) as per institutional guidelines at each site.

6.2. Randomization

Each site (Mount Sinai, Beth Israel/ and St Lukes/Roosevelt) will randomize treatment groups 1:1 stratifying by ER status (<1% and ≥ 1% of tumor cell nuclei are immunoreactive.%). The ER category will be provided on the patient registration form in order for the pharmacy personnel or coordinator—depending on location to randomize patients appropriately. At Mount Sinai Hospital the research pharmacist will implement randomization. At Beth Israel and St Luke's/Roosevelt, the clinical research coordinator will implement randomization to each arm. The stratification by site will ensure that we have balanced numbers in the two arms for each site.

6.3. Dose Determinations:

Recalculation of BSA and drug doses is required if the patient has a 10% of greater change in weight from baseline or, if the dose has already been adjusted due to weight change, from the weight at the time of the most recent dose adjustment.

6.4. Treatment Course

6.4.1. Physical examination of breasts and regional lymph node basins will be performed before each cycle of chemotherapy.

Bidimensional tumor measurements of breast and/or axilla if clinically involved are to be performed at every medical oncology visit. If the Product of the lesion dimensions increase by >25% would defer to managing medical oncologist and surgical oncologist to determine if interim imaging is recommended to verify progression vs stability vs response and if chemotherapy must be altered for progression of disease or if patient will be recommended to go to surgery directly and thus be removed from the trial.

6.4.2. Bloodwork: CBCs, differential counts, and platelet counts will be done weekly to monitor the myelotoxicity of chemotherapy in the first cycle, and subsequently, blood counts will be performed on day 1 of each cycle. (CBC weekly for weekly paclitaxel). Comprehensive panel to be ordered as per standard EPIC Beacon chemotherapy protocols.

6.4.3. Cardiac evaluation:

- via echocardiograms to detect LVEF and longitudinal strain at baseline and every 3 months. See LVEF requirements for initiation of trastuzumab after AC above. [10] (see Appendix B regarding cardiologist's documentation of longitudinal strain).
- Troponin I serum measurements will be performed at screening for baseline (within 7 days of first infusion), right before chemotherapy is administered (time "0"), 24 hours after start of chemotherapy, within 1 month of time "0" and within 3 months of time "0" for duration of both regimens until surgery. Most of these scheduled troponin measurements will be performed within 24 hours of chemotherapy administration (see Study Calendar and Appendix C regarding appropriate collection of specimen for troponin measurement).

6.4.4 Definitive Treatment:

After completion of neoadjuvant therapy, each patient will be evaluated for definitive treatment by their breast surgeon. As per standard of care, this will include breast specific imaging as determined by their surgeon as well as any systemic imaging that may be required to follow up any prior equivocal findings. Surgical management and radiation oncology management as per institutional guidelines. pCR will be determined by the pathologist. (See Appendix D for pathologist's documentation of pCR).

6.4.5. Eligibility for Adjuvant Treatment:

- Adjuvant therapy including continuation of Trastuzumab 6mg/kg every 21 days to complete 1 year vs other anti-Her2 based adjuvant treatment options will be at the discretion of the treating MD given evolving treatment strategies/evidence.

- After completion of chemotherapy and surgical and/or radiation therapy, patients with estrogen receptor (ER) –positive and/or progesterone receptor–positive tumors will be offered adjuvant endocrine therapy.

6.4.6. Surveillance Phase

- Patients will be evaluated at 3-month intervals during the initial year and then at 6-month intervals thereafter for total of 2 years
- Follow up echocardiograms will be performed annually for 2 years or earlier if there is a change in patient's symptom status.

7.0 Dose Modifications and Management of Toxicity

- The CTCAE v4.03 must be used to grade the severity of AEs. Refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
- All doses must be based on the AE requiring the greatest modification.
- Chemotherapy doses that have been reduced may not be escalated.
  unless specified otherwise in the treatment management sections/tables.

7.1. Management of anemia for AC→THP and TCHP

Chemotherapy should not proceed with greater than or equal to grade 4 anemia. Chemotherapy can resume when anemia less than or equal to grade 2. Transfusion is acceptable for improving the hemoglobin value to allow therapy to continue without delay. The patient should be assessed to rule out other causes of anemia. *Use of erythropoiesis-stimulating agents is prohibited.*

7.2. Adverse Event Management during AC→THP

7.2.1 Cardiac AEs during AC→ THP

- If the patient develops any of the following cardiac AEs during AC (please see table 1 below), study therapy should be discontinued and further therapy is at the investigator's discretion.

Table 1. Cardiac A/E

CARDIAC DISORDERS – CTCAE v4.03	
Adverse Event	**Grade 2 Criteria**
Acute coronary syndrome	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable
Atrioventricular block complete	Non-urgent intervention indicated
Chest pain - cardiac	Moderate pain; limiting instrumental ADL
Heart failure	Symptoms with mild to moderate activity or exertion
Mobitz (type) II atrioventricular block	Symptomatic; medical intervention indicated
Mobitz type I	Symptomatic; medical intervention indicated
Myocardial infarction	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes
Myocarditis	Symptoms with mild to moderate activity or exertion
Pericarditis	Symptomatic pericarditis (e.g., chest pain)
Right ventricular dysfunction	Symptoms with mild to moderate activity or exertion
Sick sinus syndrome	Non-urgent intervention indicated
Sinus bradycardia	Symptomatic, medical intervention indicated
Ventricular arrhythmia	Non-urgent medical intervention indicated
Ventricular tachycardia	Non-urgent medical intervention indicated

- Any greater than or equal to grade 3 AE listed in the Cardiac Disorders section of the CTCAE v.4.03

7.2.2 Non-cardiac AEs during AC

- If AC is discontinued due to non-cardiac toxicity, paclitaxel, trastuzumab and pertuzumab should be initiated.
- If AEs occurring during dose-dense AC have resulted in treatment delays, the AC therapy should be converted to the every-3-week treatment schedule. If in three weeks toxicity has not resolved or is not less than grade 1 (except ANC $\geq$ 1200 mm^3 and bilirubin $\leq$ the baseline grade or anemia $\leq$ grade 2) then discontinue AC and move on to THP.
- All dose modifications defined below: **(see Table 2)**

Table 2: Treatment Management of Non-Cardiac A/E for AC		
Dose modification must be based on AEs that occurred during the cycle (column 2) AND AEs present on the scheduled Day 1 of Cycles 2-4 (column 3)		
All dose modifications apply to both AC		
Dose modification must be based on the AE requiring the greatest modification		
CTCAE v4.03 Adverse Event/Grade	**Modifications for AEs that occurred during a cycle but RESOLVE PRIOR TO THE NEXT TREATMENT CYCLE (See footnote a)**	**Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE TREATMENT CYCLE (See footnote b)**
Hematologic		
Neutrophil count decreased	Maintain dose	ANC: Hold until $\geq$ 1200 mm^3. If recovery takes: 1 week:

Grade 2 (<1500-1000/mm3)		maintain dose; 2-3 weeks-decrease one dose level(footnote c)
Grade 3,4		
Platelet count decreased	Maintain dose	Hold until ≥ 75,000 mm^3.If recovery takes:
Grades 2,3		1 week: maintain dose; 2-3 weeks: decrease one dose level
Grade 4	Decrease dose one level	Hold until ≥ 75,000 mm3. Decrease one dose level
Anemia		
Grade 2	Maintain Dose	Maintain Dose
Grade 3	Maintain Dose	Maintain Dose
Grade 4	Hold	Hold, Resume when Grade ≤ 2
GI (if related to chemotherapy)		
Diarrhea		
Grade 2	Maintain dose	Maintain dose or decrease one level
Grade 3	Decrease dose one level	Decrease dose one level
Grade 4	Decrease dose one level or D/C	D/C
Mucositis-oral		
Grade 2	Maintain dose	Maintain dose or decrease one level
Grade 3	Decrease dose one level	Decrease dose one level
Grade 4	Decrease dose one level or D/C	D/C
Vomiting (despite antiemetics)		
Grade 2	Maintain dose or decrease one level	Maintain dose or decrease one level
Grade 3, 4	Decrease dose one level or D/C	D/C
Hepatic (Bilirubin, AST, alk phos)		
Grade 2	Decrease dose one level	Hold until bilirubin returns to the baseline grade and AST and alk phos have returned to ≤ grade 1; decrease one dose level
Grade 3	Decrease dose one level or D/C	Hold until bilirubin returns to the baseline grade and AST and alk phos have returned to ≤ grade 1; decrease one dose level or D/C
Grade 4	D/C	D/C
Infection or febrile neutropenia		
Grade 2 (N/A)	Decrease dose one level	
Grade 3	Decrease dose one level	
Grade 4	Decrease dose one level or D/C	
Other clinically significant AEs (footnote d)		
Grade 2	Maintain dose or decrease one level	
Grade 3	Decrease dose one level	Decrease dose one level
Grade 4	Decrease dose one level or D/C	D/C
a. Resolved means that all clinically significant AEs are ≤ grade 1 (except ANC ≥ 1200 mm^3 and bilirubin ≤ the baseline grade or anemia ≤ grade 2) on Day 1 of the next scheduled cycle (i.e. treatment can be given without delay)		
b. Hold and check weekly. With exception of neutrophils and bilirubin and anemia resume treatment when toxicity is ≤ grade 1. If toxicity has not resolved after 3 weeks of delay D/C AC and proceed to THP		
c. Doxorubicin Dose Levels: *0*:60mg/m^2; *1*:50mg/m^2; *2*:40 mg/m^2; *3*: D/C		

Cyclophosphamide Dose Levels: *0: 600mg/m^2;1*:500mg/m^2;*2:400 mg/m^2; 3:* D/C
d. Determination of clinically significant AEs is at the discretion of the investigator
Adapted from NSABP-47 protocol

7.2.3 Treatment Management of Trastuzumab for AC→THP

- Use the CTCAE v4.03 to grade the severity of AEs
- Treatment decisions should be based on the AE requiring the greatest modification
- There are no reductions in the trastuzumab dose. If trastuzumab is held, the loading dose followed by the maintenance dose for the remaining doses may be administered, at the investigator's discretion, when resuming therapy.
- Trastuzumab must end 1 year (52 weeks) following the first trastuzumab dose regardless of any missed doses
- When weekly paclitaxel is delayed for reasons not requiring a delay in trastuzumab/pertuzumab, investigators are encouraged to continue trastuzumab/pertuzumab. However, at the discretion of the investigator, trastuzumab/pertuzumab may also be held.
- With the exception of cardiac toxicity, pulmonary toxicity, or severe allergic or anaphylactic reaction (related to trastuzumab), trastuzumab/pertuzumab therapy should continue even if chemotherapy has been discontinued before completion of all chemotherapy cycles.

7.2.4 Cardiac Safety criteria for initiation of Trastuzumab therapy following AC:

Please see table 3 below regarding LVEF requirements for initiation of trastuzumab following AC. If the patient develops any of the following cardiac AEs during AC (Table 1), protocol therapy should be discontinued and further therapy will be personalized per investigators discretion. *Initiation of* ***trastuzumab is prohibited***

Table 3: LVEF for initiation of trastuzumab therapy after AC

LVEF assessed 10-21 days after last AC dose	Change in LVEF percentage points from baseline [a]		
	Increase or no change	Decrease of < 10 percentage points	Decrease of ≥ 10 percentage points
≥55%	Initiate trastuzumab therapy		
50-54%	N/A	Initiate trastuzumab therapy	Initiate trastuzumab therapy and repeat echo in 6 weeks [b]
≤ 49%	N/A	Do NOT initiate trastuzumab therapy; Initiate paclitaxel as per protocol [c]	
a. The baseline LVEF is the LVEF measured prior to randomization.			

b. If repeat echo/MUGA was required, the LVEF value for the 2nd assessment must meet criteria as stated above for initiation of trastuzumab.
c. Cardiac follow-up as per protocol.
d. Adapted from NSABP-47 protocol

-Any grade 2 AE

-Any grade 3 AE listed in cardiac disorders of CTCAE 4.03

7.2.5 Cardiac AEs during Trastuzumab treatment

Any greater than or equal to grade 2 cardiac AE listed below (table 4):
Trastuzumab will not be continued following any **grade 2** cardiac AE listed in table 4. (Trastuzumab should be administered following any of the other grade 2 AEs listed in the Cardiac Disorders section of the CTCAE v4.03 but not listed below.

Table 4: Cardiac Disorders CTCAE criteria

CARDIAC DISORDERS – CTCAE v4.03	
Adverse Event	**Grade 2 Criteria**
Acute coronary syndrome	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable
Atrioventricular block complete	Non-urgent intervention indicated
Chest pain - cardiac	Moderate pain; limiting instrumental ADL
Heart failure	Symptoms with mild to moderate activity or exertion
Mobitz (type) II atrioventricular block	Symptomatic; medical intervention indicated
Mobitz type I	Symptomatic; medical intervention indicated
Myocardial infarction	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes
Myocarditis	Symptoms with mild to moderate activity or exertion
Pericarditis	Symptomatic pericarditis (e.g., chest pain)
Right ventricular dysfunction	Symptoms with mild to moderate activity or exertion
Sick sinus syndrome	Non-urgent intervention indicated
Sinus bradycardia	Symptomatic, medical intervention indicated
Ventricular arrhythmia	Non-urgent medical intervention indicated
Ventricular tachycardia	Non-urgent medical intervention indicated

7.2.6 Trastuzumab management based on LVEF assessments: Patients with asymptomatic decrease in LVEF: For patients who do not develop symptoms related to LV dysfunction or

other cardiac AEs as stated above will depend on the absolute LVEF value and absolute change in percentage points between the baseline LVEF and LVEF serial measurements. [32,33] **(Table 5)**

Table 5: Trastuzumab Management Based on LVEF assessments

Relationship of LVEF to LLN	Asymptomatic Decrease in LVEF from baseline		
	< 10 Percentage points	10-15 Percentage Points	> 15 Percentage Points
Within Normal Limits	Continue trastuzumab	Continue trastuzumab	Hold Trastuzumab and repeat ECHO after 4 weeks
1-5 Percentage Points below LLN	Continue trastuzumab [b]	Hold trastuzumab and repeat ECHO after 4 weeks [b, c]	Hold trastuzumab and repeat ECHO after 4 weeks [c,d]
≥ 6 percentage points below LLN	Continue trastuzumab and repeat ECHO after 4 weeks[d]	Hold trastuzumab and repeat ECHO after 4 weeks [c,d]	Hold trastuzumab and repeat ECHO after 4 weeks [c]
< Normal	Symptomatic: HOLD TRASTUZUMAB		

[a] Based on NSABP-31 protocol [32]; Modified to include recommendations for cardiology consultation or treatment of cardiac dysfunction (or both) when appropriate

[b] Consider cardiac assessment and initiation of angiotensin converting-enzyme inhibitor therapy.

[c] After 2 holds (> 8 weeks), consider permanent discontinuation of trastuzumab or for >3 incidents of treatment interruptions for cardiomyopathy

[d] Initiate angiotensin converting-enzyme inhibitor therapy and refer to cardiologist

LLN: lower limit of normal; ECHO: echocardiography

7.2.7 Table 6. All AEs during trastuzumab treatment

Treatment Management for Trastuzumab (H) related adverse events		
Dose modification must be based on the AE requiring the greatest modification		
CTCAE v4.03 Adverse Event/Grade	**CTCAE Grade v4.03**	**Action to be Taken**
Cardiac AEs as listed in CTACE v4.03	1	Continue trastuzumab at investigator's discretion
	2	Hold trastuzumab and conduct cardiac evaluation. See above (under initiation of trastuzumab after AC) regarding which grade 2 AEs require trastuzumab discontinuation. For other cardiac grade 2 AEs, trastuzumab should be held during evaluation of AE and until ≤ grade 1; continue or discontinue at investigator's discretion.
	3, 4	Discontinue trastuzumab
Gastrointestinal Disorders		

Diarrhea	2	Maintain dose without delay or hold until resolved to ≤ grade 1 and resume
	3	Hold trastuzumab until resolved to ≤ grade 1, then resume
	4	D/C trastuzumab
Immune System Disorders		
Allergic reaction	1	Slow the infusion and assess the patient; management is at the investigator's discretion
	2	Stop infusion and administer support medications per investigator's discretion. When symptoms resolve to ≤ grade 1, infusion may be resumed later that day at a slower rate or on the next day at a slower rate with pre-meds. Pre-meds should be used for all subsequent treatments.
	3	Follow instructions for grade 2; trastuzumab may be discontinued at the investigator's discretion.
	4	D/C trastuzumab
Anaphylaxis	3	Follow instructions for grade 3 allergic reactions or, at investigator's discretion, discontinue trastuzumab
	4	D/C trastuzumab
Respiratory, Thoracic and Mediastinal Disorders		
ARDS	3,4	D/C trastuzumab
Cough	2,3	Hold trastuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
Dyspnea	1,2,3	Hold trastuzumab; rule out heart failure and non-infectious lung disease. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
	4	D/C trastuzumab
Hypoxia	2,3	Hold trastuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
	4	D/C trastuzumab
Pneumonitis	2	Hold trastuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
	3,4	D/C trastuzumab
Pulmonary Edema	2,3	Hold trastuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
	4	D/C trastuzumab
Pulmonary Fibrosis	1	If fibrosis was present at baseline, trastuzumab may be continued at the investigator's discretion. If new or worsening fibrosis, D/C trastuzumab
	2,3,4	D/C trastuzumab

Pulmonary Hypertension	2,3,4	D/C trastuzumab
Other Clinically Significant AE's as determined by the investigator	2	Hold trastuzumab until ≤ grade 1 or D/C trastuzumab
	3,4	D/C trastuzumab

7.2.8 Management of Pertuzumab during AC→ THP Regimen

7.2.8.1 Cardiac A/E

The only guidelines for management of pertuzumab cardiotoxicity are derived from CLEOPATRA [15] a randomized controlled trial for Stage IV breast cancer that included a pertuzumab containing regimen. Currently there are insufficient data available to determine cardiac toxicity risk factors for the combination of pertuzumab and trastuzumab. Because current preliminary data suggest that the incidence of clinical cardiac toxicity in patients receiving combination pertuzumab/trastuzumab-based treatments is similar to that reported for trastuzumab-based treatments, this study will include regular cardiac LVEF monitoring of all patients, and will implement the treatment delay/stopping algorithm for LVEF decline as is the standard for patients receiving trastuzumab-based chemotherapy as described above. Specifically there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF for pertuzumab containing regimens. Please refer to 7.2.3-7.2.7 for guidelines for trastuzumab management which we will follow for pertuzumab management. Similar to trastuzumab there are no dose modifications for pertuzumab. Pertuzumab therapy finishes when chemotherapy completes as per regimens described above (See section 6.1) and does not continue onwards with trastuzumab monotherapy. Pertuzumab and trastuzumab will be discontinued in any patient who develops clinical signs and symptoms suggesting congestive heart failure, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA. Congestive heart failure should be treated and monitored according to standard medical practice

7.2.8.2 Non-Cardiac A/E

The most common adverse events observed when pertuzumab is given with trastuzumab include diarrhea, nail changes, allergic reactions, anemia, and thrombocytopenia.

Loperamide recommended for Grade 2 diarrhea. Management at discretion of treating physician.

7.2.9 Management of Paclitaxel (T) of AC→THP Regimen

7.2.9.1 Treatment Guidelines

Paclitaxel should be completed in 12 weeks. If delays for medical or non-medical reasons occur, every effort should be made to administer all 12 doses of paclitaxel within 15 weeks after initiation of paclitaxel. No dose of paclitaxel may be given beyond the 15th week from the start of paclitaxel therapy as per NSABP-31 [32].

7.2.9.2 Initiation of Paclitaxel Therapy

Since AC and paclitaxel are substantially different in toxicity and mechanism of action, any toxicity that occurs during AC administration and resolves prior to paclitaxel administration does not require dose reduction or delay during paclitaxel therapy. In addition, a patient who discontinues AC therapy due to toxicity should still proceed with paclitaxel according to the protocol.

7.2.9.3 Paclitaxel Administration when Trastuzumab is Delayed or Discontinued

When trastuzumab is delayed because of conditions related to LVEF, cardiac ischemia, or arrhythmia, paclitaxel administration may also be delayed at the investigator's discretion. If trastuzumab is delayed for reasons other than those cited above, paclitaxel administration should continue.

When trastuzumab is permanently discontinued because of conditions related to LVEF, cardiac ischemia, arrhythmia, or severe allergic reactions, Paclitaxel administration may also be permanently discontinued at the investigator's discretion. If trastuzumab is permanently discontinued for reasons other than those cited above, paclitaxel administration should continue.

7.2.9.4 Table 7 A/E Management of Weekly Paclitaxel

Unless otherwise specified, paclitaxel that is held due to toxicity will not resume until the toxicity has resolved to ≤ grade 1.

Treatment Management for Weekly Paclitaxel		
Dose modification must be based on AEs that occurred between treatments (column 2) AND AEs present on the scheduled treatment day (column 3)		
Dose modification must be based on the AE requiring the greatest modification		
CTCAE v4.03 Adverse Event/Grade	Modifications for AEs that occurred between treatments BUT DID NOT REQUIRE A DELAY IN TREATMENT (See footnote a)	Modifications for AEs that REQUIRE A DELAY IN ADMINISTRATION OF THE NEXT TREATMENT (See footnote b)
Hematologic		
Neutrophil count decreased	Maintain dose	ANC: Hold until ≥ 1000 mm^3. Decrease one dose level
Grade 3,4		
Platelet count decreased		Hold until ≥ 75,000 mm^3.If recovery takes: 1 wk: maintain dose; 2-3 weeks: decrease one dose level
Grades 2,3	Maintain dose	

Grade 4	Decrease one dose level	Hold until ≥ 75,000 mm3. Decrease one dose level
Hemoglobin Decreased		
Grade 2	Maintain Dose	Maintain Dose
Grade 3	Maintain Dose	Maintain Dose
Grade 4	Hold	Hold, Resume when Grade 2
GI (if related to chemotherapy)		
Diarrhea		
Grade 2	Maintain dose	Maintain dose or decrease one level
Grade 3	Decrease dose one level	Decrease dose one level
Grade 4	Decrease dose one level or D/C	Decrease dose one level or D/C
Mucositis-oral		
Grade 2	Maintain dose	Maintain dose or decrease one level
Grade 3	Decrease dose one level	Decrease dose one level
Grade 4	D/C	D/C
Vomiting (despite antiemetics)		
Grade 2	Maintain dose or decrease one level	Maintain dose or decrease one level
Grade 3, 4	Decrease dose one level or D/C	D/C
Hepatic (Bilirubin, AST, alk phos)		
Grade 2	Decrease dose one level	Hold until bilirubin returns to the baseline grade and AST and alk phos have returned to ≤ grade 1; decrease one dose level
Grade 3	Decrease dose one level	Hold until bilirubin returns to the baseline grade and AST and alk phos have returned to ≤ grade 1; decrease one dose level or D/C
Grade 4	D/C	D/C
Infection or febrile neutropenia		
Grade 2 (N/A)	Decrease dose one level	
Grade 3	Decrease dose one level	
Grade 4	Decrease dose one level or D/C	
Other clinically significant AEs (footnote d)		
Grade 2	Maintain dose or decrease one level	
Grade 3	Decrease dose one level	Decrease dose one level
Grade 4	Decrease dose one level or D/C	D/C
a. Treatment may not proceed until clinically significant AEs are ≤ grade 1 (except ANC ≥ 1000 mm^3 and bilirubin ≤ the baseline grade or anemia ≤ grade 2) on Day 1 of the next scheduled cycle (i.e. treatment can be given without delay)		
b. Hold and check weekly. With exception of neutrophils and bilirubin and anemia resume treatment when toxicity is ≤ grade 1. If toxicity has not resolved after 3 weeks of delay D/C paclitaxel, see specific instructions for continuing trastuzumab (VII-6C)		
c. Paclitaxel Dose Levels: *0*:80mg/m^2; *1*:60mg/m^2; *2*:45 mg/m^2; *3*: D/C		
d. Determination of clinically significant AEs is at the discretion of the investigator (Adapted from NSABP-47 protocol)		

Table 8.Treatment management for paclitaxel-related neuropathy

Nervous System Disorders • Paresthesias • Peripheral sensory neuropathy	1 – 7 Days Duration	Persistent for > 7 Days or Caused the Next Treatment to be Delayed
Grade 1	Maintain dose	
Grade 2	Maintain dose[a]	Decrease dose one level [b]
Grade 3	First episode: Decrease paclitaxel one dose level [a] Second episode D/C Paclitaxel	D/C paclitaxel
Grade 4	D/C paclitaxel	
a Must be resolved to ≤ grade 1 on the next treatment day. b Hold paclitaxel for persistent grade 2 neuropathy. When ≤ grade 1, resume treatment with dose modification for paclitaxel. If grade 2 toxicity persists after 3 weeks of delay, discontinue paclitaxel (Adapted from NSABP-47 protocol)		

Table 9.Treatment management for paclitaxel-related musculoskeletal pain

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

Musculoskeletal and Connective Tissue Disorders • Arthralgia • Myalgia	1 – 7 Days Duration	Persistent for > 7 Days or Caused the Next Treatment to be Delayed
Grade 1 (despite analgesics)	Maintain dose	
Grade 2 (despite analgesics)	Maintain 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
* Hold paclitaxel for persistent grade 2 or 3 musculoskeletal pain. (Trastuzumab/Pertuzumab should be continued while paclitaxel is held.) When ≤ grade 1, resume treatment with dose modification. If grade 2 or grade 3 toxicity persists after 3 weeks of delay, discontinue paclitaxel. (Adapted from NSABP-47 protocol)		

7.3 Adverse Event Management during TCHP

7.3.1 Treatment Management of Non-Cardiac A/E of TC of TCHP Regimen

Table **10. Treatment Management of Non-Cardiac A/E of TC of TCHP Regimen**

Adverse Event	**CTACE v4.03 Grade**	**Docetaxel**	**Carboplatin**
Hematologic			
ANC	Grade 3,4	ANC: Defer dose if ANC< 1000 mm^3 Delay one week and repeat cbc for recovery to ANC 1000 If despite GCSF, febrile neutropenia occurs or dose delay is required, consider dose reduction by 25% for docetaxel and reduce to AUC 5 mg/mL/min for carboplatin	
Platelet count decreased	Grade 2,3,4	Defer dose if platelets < 100,000 mm^3 and repeat cbc for recovery of platelets ≥ 100,000 If dose delay is required, consider dose reduction by 25% for docetaxel and reduce to AUC 5 mg/mL/min for carboplatin	
Anemia	Grade ≥ 2	Consider blood transfusion, administer for Hg > 10 g/dL	
	Grade ≥ 3,4	Consider blood transfusion and docetaxel should be reduced to 60mg/m2 and carboplatin to AUC 5 mg/mL/min	
Non-Hematologic Toxicities			
Renal Impairment: Adjust Carboplatin dose using Calvert formula. Dose = AUC (25+GFR)			
Cr Cl <20 ml/min		No dose adjustment required	CONTRAINDICATED
Hepatic Impairment: patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5X ULN AND alkaline phosphatase greater than 2.5X the ULN, the recommended docetaxel dose is 60mg/m2			
Bilirubin			
> ULN		Not recommended	No dose reduction necessary
Nausea (despite optimal antiemetics)	Grade 4	D/C therapy	D/C therapy
Diarrhea	Grade 2	Loperamide recommended	
	Grade ≥ 3	Optimally treat with antidiarrheals and Reduce docetaxel dose to 60mg/m2. If continues despite dose reduction, consider D/C docetaxel	
Stomatitis	Grade 3	Reduce to 60 mg/m2. If despite dose reduction, it persists, further	

		reduce to 50mg/m2	
Other Toxicities	Grade 0-2	Delay treatment by one or more weeks until recovery to grade 0 or 1	
	Grade 3,4	Reduce to 60 mg/m^2	Reduce to AUC 5
Infection or Febrile Neutropenia (neutrophil < 500cells/mm^3 for more than one week)	Grade 3,4	Reduce to 60 mg/m^2	Reduce to AUC 5
Neuropathy	Grade 2	Delay carboplatin and docetaxel by maximum of 2 weeks As soon as patient recovers to Grade 1, decrease docetaxel to 60mg/m2 If grade ≥ 2 persists for ≥ 2 weeks, patient can continue on carboplatin and trastuzumab alone or come off therapy In case of second episode, reduce docetaxel dose from 60 to 50 mg/m2	
Cutaneous Reactions	Grade 1	No change	
	Grade 2	Consider dose reduction to 60mg/m2	
	Grade 3	Delay maxiumum 2 weeks until ≤ Grade 1 and then for subsequent cycles Reduce docetaxel to 60 mg/m2 and if occurs again, second reduction allowed of 50 mg/m2	
(Adapted from BCIRG 006 protocol [24])			

7.3.2 Management of docetaxel-related edema

Suggested interventions include:

- Hydrochlorothiazide/triamterene (Dyazide®) 1 capsule by mouth daily; dose can be increased to twice daily.
- Furosemide (Lasix®) 40 mg by mouth daily if edema progresses despite Dyazide (or equivalent) therapy. Potassium supplementation should be given as needed

7.3.3: Management of Trastuzumab for the TCHP Regimen

- Use the CTCAE v4.03 to grade the severity of AEs
- Treatment decisions should be based on the AE requiring the greatest modification
- There are no reductions in the trastuzumab dose. If trastuzumab is held, the loading dose followed by the maintenance dose for the remaining doses may be administered, at the investigator's discretion, when resuming therapy.
- Trastuzumab must end 1 year (52 weeks) following the first trastuzumab dose regardless of any missed doses
- When docetaxel + carboplatin is delayed, investigators are encouraged to continue trastuzumab/pertuzumab
- With the exception of cardiac toxicity, pulmonary toxicity, or severe allergic or anaphylactic reaction (related to trastuzumab), trastuzumab therapy should continue

even if chemotherapy has been discontinued before completion of all chemotherapy cycles.

Please see 7.2.5-7.2.7 for management of cardiac and non-cardiac A/E related to trastuzumab

7.3.4 Management of Pertuzumab for the TCHP Regimen

7.3.4.1 Cardiac A/E

The only guidelines for management of pertuzumab cardiotoxicity are derived from CLEOPATRA [15] a randomized controlled trial for Stage IV breast cancer that included a pertuzumab containing regimen. Currently there are insufficient data available to determine cardiac toxicity risk factors for the combination of pertuzumab and trastuzumab. Because current preliminary data suggest that the incidence of clinical cardiac toxicity in patients receiving combination pertuzumab/trastuzumab-based treatments is similar to that reported for trastuzumab-based treatments, this study will include regular cardiac LVEF monitoring of all patients, and will implement the treatment delay/stopping algorithm for LVEF decline as is the standard for patients receiving trastuzumab-based chemotherapy as described above. Specifically there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF for pertuzumab containing regimens. Please refer to 7.2.3-7.2.7 for guidelines for trastuzumab management which we will follow for pertuzumab management. Similar to trastuzumab there are no dose modifications for pertuzumab. Pertuzumab therapy finishes when chemotherapy completes as per regimens described above (See section 6.1) and does not continue onwards with trastuzumab monotherapy. Pertuzumab and trastuzumab will be discontinued in any patient who develops clinical signs and symptoms suggesting congestive heart failure, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA. Congestive heart failure should be treated and monitored according to standard medical practice

7.3.4.2 Non-Cardiac A/E

The most common adverse events observed when pertuzumab is given with trastuzumab include diarrhea, nail changes, allergic reactions, anemia, and thrombocytopenia.

Loperamide recommended for Grade 2 diarrhea. Management at discretion of treating physician.

7.4 Management of Trastuzumab Monotherapy following completion of chemotherapy ACTHP and TCHP

7.4.1 Treatment Management of Trastuzumab Monotherapy

- Use the CTCAE v4.03 to grade the severity of AEs
- Treatment decisions should be based on the AE requiring the greatest modification
- There are no reductions in the trastuzumab dose. If trastuzumab is held, the loading dose followed by the maintenance dose for the remaining doses may be administered, at the investigator's discretion, when resuming therapy.
- Trastuzumab must end 1 year (52 weeks) following the first trastuzumab dose regardless of any missed doses
- With the exception of cardiac toxicity, pulmonary toxicity, or severe allergic or anaphylactic reaction (related to trastuzumab), trastuzumab therapy should continue even if chemotherapy has been discontinued before completion of all chemotherapy cycles.

7.4.2 Cardiac AEs during Trastuzumab treatment

Any greater than or equal to grade 2 cardiac AE listed below (table 4):
Trastuzumab will not be continued following any **grade 2** cardiac AE listed in table 4. (Trastuzumab should be administered following any of the other grade 2 AEs listed in the Cardiac Disorders section of the CTCAE v4.03 but not listed below.

Table 4: Cardiac Disorders CTCAE criteria

CARDIAC DISORDERS – CTCAE v4.0 3	
Adverse Event	**Grade 2 Criteria**
Acute coronary syndrome	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable
Atrioventricular block complete	Non-urgent intervention indicated
Chest pain - cardiac	Moderate pain; limiting instrumental ADL
Heart failure	Symptoms with mild to moderate activity or exertion
Mobitz (type) II atrioventricular block	Symptomatic; medical intervention indicated
Mobitz type I	Symptomatic; medical intervention indicated
Myocardial infarction	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes
Myocarditis	Symptoms with mild to moderate activity or exertion
Pericarditis	Symptomatic pericarditis (e.g., chest pain)
Right ventricular dysfunction	Symptoms with mild to moderate activity or exertion
Sick sinus syndrome	Non-urgent intervention indicated
Sinus bradycardia	Symptomatic, medical intervention indicated
Ventricular arrhythmia	Non-urgent medical intervention indicated
Ventricular tachycardia	Non-urgent medical intervention indicated

7.4.3 Trastuzumab management based on LVEF assessments: Patients with asymptomatic decrease in LVEF: For patients who do not develop symptoms related to LV dysfunction or other cardiac AEs as stated above will depend on the absolute LVEF value

and absolute change in percentage points between the baseline LVEF and LVEF serial measurements. [32,33] **(Table 5)**

Table 5: Trastuzumab Management Based on LVEF assessments

Relationship of LVEF to LLN	Asymptomatic Decrease in LVEF from baseline		
	< 10 Percentage points	10-15 Percentage Points	>15 Percentage Points
Within Normal Limits	Continue trastuzumab	Continue trastuzumab	Hold Trastuzumab and repeat ECHO after 4 weeks
1-5 Percentage Points below LLN	Continue trastuzumab [b]	Hold trastuzumab and repeat ECHO after 4 weeks [b, c]	Hold trastuzumab and repeat ECHO after 4 weeks [c,d]
≥ 6 percentage points below LLN	Continue trastuzumab and repeat ECHO after 4 weeks[d]	Hold trastuzumab and repeat ECHO after 4 weeks [c,d]	Hold trastuzumab and repeat ECHO after 4 weeks [c]
< Normal	Symptomatic: HOLD TRASTUZUMAB		

[a] Based on NSABP-31 protocol [32]; Modified to include recommendations for cardiology consultation or treatment of cardiac dysfunction (or both) when appropriate

[b] Consider cardiac assessment and initiation of angiotensin converting-enzyme inhibitor therapy.

[c] After 2 holds (> 8 weeks), consider permanent discontinuation of trastuzumab or for >3 incidents of treatment interruptions for cardiomyopathy

[d] Initiate angiotensin converting-enzyme inhibitor therapy and refer to cardiologist

LLN: lower limit of normal; ECHO: echocardiography

7.4.4 Table 6. All AEs during trastuzumab treatment

Treatment Management for Trastuzumab (H) related adverse events		
Dose modification must be based on the AE requiring the greatest modification		
CTCAE v4.03 Adverse Event/Grade	**CTCAE Grade v4.03**	**Action to be Taken**
Cardiac AEs as listed in CTACE v4.03	1	Continue trastuzumab at investigator's discretion
	2	Hold trastuzumab and conduct cardiac evaluation. See above (under initiation of trastuzumab after AC) regarding which grade 2 AEs require trastuzumab discontinuation. For other cardiac grade 2 AEs, trastuzumab should be held during evaluation of AE and until ≤ grade 1; continue or discontinue at investigator's discretion.
	3, 4	Discontinue trastuzumab
Gastrointestinal Disorders		

Diarrhea	2	Maintain dose without delay or hold until resolved to ≤ grade 1 and resume
	3	Hold trastuzumab until resolved to ≤ grade 1, then resume
	4	D/C trastuzumab
Immune System Disorders		
Allergic reaction	1	Slow the infusion and assess the patient; management is at the investigator's discretion
	2	Stop infusion and administer support medications per investigator's discretion. When symptoms resolve to ≤ grade 1, infusion may be resumed later that day at a slower rate or on the next day at a slower rate with pre-meds. Pre-meds should be used for all subsequent treatments.
	3	Follow instructions for grade 2; trastuzumab may be discontinued at the investigator's discretion.
	4	D/C trastuzumab
Anaphylaxis	3	Follow instructions for grade 3 allergic reactions or, at investigator's discretion, discontinue trastuzumab
	4	D/C trastuzumab
Respiratory, Thoracic and Mediastinal Disorders		
ARDS	3,4	D/C trastuzumab
Cough	2,3	Hold trastuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
Dyspnea	1,2,3	Hold trastuzumab; rule out heart failure and non-infectious lung disease. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
	4	D/C trastuzumab
Hypoxia	2,3	Hold trastuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
	4	D/C trastuzumab
Pneumonitis	2	Hold trastuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
	3,4	D/C trastuzumab
Pulmonary Edema	2,3	Hold trastuzumab and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume trastuzumab when grade 0 if secondary to dyspnea AE or when AE ≤ grade 1.
	4	D/C trastuzumab
Pulmonary Fibrosis	1	If fibrosis was present at baseline, trastuzumab may be continued at the investigator's discretion. If new or worsening fibrosis, D/C trastuzumab
	2,3,4	D/C trastuzumab

Pulmonary Hypertension	2,3,4	D/C trastuzumab
Other Clinically Significant AE's as determined by the investigator	2	Hold trastuzumab until ≤ grade 1 or D/C trastuzumab
	3,4	D/C trastuzumab

7.5 Management of Infusion Reactions

7.5.1 Management of Trastuzumab Infusion Reaction

Infusion reactions consist of a symptom complex, such as fever and chills, and on occasion nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. Infusion reactions should be managed by standard clinical practice. Stop infusion and give antipyretics if fever occurs within 24 hours of trastuzumab infusion. Once the temperature is < 38°C, resume infusion at a slower rate and monitor the patient according to institutional standard practice. Chills triggered by trastuzumab infusion can be treated with acetaminophen and/or diphenhydramine hydrochloride. Meperidine may be given at the investigator's discretion.

Pulmonary toxicity including dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis can occur as sequelae of infusion reactions. Management of pulmonary toxicity should follow clinical standard practice.

Trastuzumab should be discontinued for anaphylaxis or angioedema.

7.5.2 Management of Pertuzumab Infusion Reaction

Infusion reactions (either during or on the day of infusion) have been associated with pertuzumab; commonly described as fever, chills, fatigue, headache, weakness, myalgia, hypersensitivity, abnormal taste or vomiting. The incidence of hypersensitivity/anaphylaxis was slightly higher in the group receiving pertuzumab (compared to placebo) in combination with trastuzumab and docetaxel. Monitor for 1 hour after the first infusion and for 30 minutes after subsequent infusions. For significant infusion reactions, interrupt or slow infusion rate; for severe infusion reactions, consider permanently discontinuing. Medications and equipment for the treatment of hypersensitivity should be available for immediate use during infusion.

7.5.3. Management of Paclitaxel Infusion Reaction

Hypersensitivity reactions with Paclitaxel**.** There will be no dose modifications for hypersensitivity reactions. Management of mild
to moderate hypersensitivity reactions is at the discretion of the

investigator. Severe reactions (Grade 3 or 4), such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria, require immediate and permanent discontinuation of Taxol and aggressive symptom management. If a grade 3 or 4 hypersensitivity reaction occurs during or after trastuzumab administration, following paclitaxel, both trastuzumab and paclitaxel mustbe permanently discontinued.

7.5.4 Management of Docetaxel Infusion Reaction

Patients should be observed closely for hypersensitivity reactions, especially during the first and second docetaxel infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel; thus, facilities for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and administration of appropriate therapy. These patients should not be re-challenged with the docetaxel. Docetaxel must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Minor symptoms such as flushing or localized cutaneous reactions generally do not require interruption of therapy.

7.6 Extravasation Management

7.6.1 Doxorubicin

Extravasation of doxorubicin can result in severe local tissue injury and necrosis requiring wide excision of the affected area and skin grafting. Immediately terminate the drug and apply ice to the affected area. Doxorubicin must not be given by the intramuscular (IM) or subcutaneous route. If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; elevate extremity. Initiate antidote (dexrazoxane or dimethyl sulfate [DMSO]). Apply dry cold compresses for 20 minutes 4 times daily for 1 to 2 days ; withhold cooling beginning 15 minutes before dexrazoxane infusion; continue withholding cooling until 15 minutes after infusion is completed. Topical DMSO should not be administered in combination with dexrazoxane; may lessen dexrazoxane efficacy. See institutional guidelines regarding use of dexrazoxane and DMSO

7.6.2 Paclitaxel

Paclitaxel is an irritant with vesicant-like properties; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation. Injection-site reactions are generally mild (skin discoloration, tenderness, erythema, or swelling) and occur more commonly with an extended infusion duration (eg, 24 hours); injection-site reactions may be delayed (7 to 10 days). More severe reactions (phlebitis, cellulitis, skin exfoliation, necrosis, fibrosis, and induration) have also been reported. Recall skin reactions may occur despite administering through a different IV site.

7.6.3 Docetaxel

If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; elevate extremity. Information conflicts regarding the use of warm or cold compresses

8.0 Adverse Events Reporting

8.1 Adverse Events: List and Reporting Requirements (See Appendix E)

An Adverse Event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Adverse events will be monitored from the time the subject signs informed consent. Subjects will be instructed to report all AEs during the study and subjects will be assessed for the occurrence of AEs throughout the study. All AEs (serious and nonserious) must be recorded on the source documents and case report forms regardless of the assumption of a causal relationship with the study drug.

Adverse Events that begin or worsen after informed consent should be recorded in the Adverse Events section of the case report form (CRF). Conditions that were already present at the time of informed consent should be recorded in the baseline symptoms section of the CRF. Adverse Event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse Events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

8.1.1

The following list of AEs (Table 10) and the characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

Comprehensive Adverse Events and Potential Risks List

Table 11: Adverse Event List for Trastuzumab and Pertuzumab

Adverse Events with Possible Relationship to Trastuzumab or Pertuzumab (CTCAE 4.03 Term)		
Likely (> 20%)	**Less Likely (⩽e20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	1. Anemia 2. Febrile neutropenia[2]	
CARDIAC DISORDERS		
	1. Cardiomyopathy 2. Left ventricular systolic dysfunction 3. Pericardial effusion 4. Pericarditis 5. Sinus tachycardia 6. Supraventricular tachycardia	
GASTROINTESTINAL DISORDERS		
	1. Abdominal pain 2. Diarrhea 3. Mucositis oral 4. Nausea 5. Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	1. Chills 2. Fatigue 3. Fever 4. Flu like symptoms 5. Infusion related reaction 6. Non-cardiac chest pain 7. Pain	
IMMUNE SYSTEM DISORDERS		
	1. Allergic reaction[3] 2. Anaphylaxis	
INFECTIONS AND INFESTATIONS		
	1. Infection[4]	
INVESTIGATIONS		
	1. Alkaline phosphatase increased 2. Aspartate aminotransferase increased 3. GGT increased	

	4. Neutrophil count decreased[2]	
METABOLISM AND NUTRITION DISORDERS		
	1. Anorexia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	1. Arthralgia 2. Back pain 3. Bone pain 4. Myalgia	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
	1. Tumor pain	
NERVOUS SYSTEM DISORDERS		
	1. Headache 2. Peripheral sensory neuropathy	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	1. Allergic rhinitis 2. Cough 3. Dyspnea[3] 4. Hypoxia[3] 5. Pneumonitis[3] 6. Pulmonary edema 7. Pulmonary fibrosis	1. Adult respiratory distress syndrome[3] 2. Bronchospasm[3] 3. Pneumonitis[3] 4. Pulmonary edema 5. Pulmonary fibrosis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	1. Rash acneiform 2. Rash maculo-papular 3. Urticaria	***Rash acneiform (Gr. 3)*** ***Rash maculo-papular (Gr. 3)*** ***Urticaria (Gr. 3)***
VASCULAR DISORDERS		
	1. Hypertension[5] 2. Hypotension[5]	

[1]This table will be updated as the toxicity profile of the agent is revised.
[2]Fatal event when given in combination with Xeloda® (capecitabine) and Taxotere® (docetaxel).
[3]Severe hypersensitivity reactions including angioedema and pulmonary adverse events (e.g., hypoxia, dyspnea, pulmonary infiltrates, pleural effusion, and acute respiratory distress syndrome) have been reported.
[4]Infection may include any of the 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.
[5]Associated with infusion reactions.

8.1.2 Additional adverse events:

The following are adverse events which have been reported on trastuzumab and pertuzumab trials; however, **the relationship to trastuzumab is currently undetermined**.

Cardiac Disorders – acute coronary syndrome, atrial fibrillation, cardiac arrest, myocardial infarction; ventricular arrhythmia; ventricular fibrillation; ventricular tachycardia
Ear and Labyrinth Disorders - hearing impaired
Endocrine Disorders – hypothyroidism
Eye Disorders - blurred vision; extraocular muscle paresis
Gastrointestinal Disorders - colitis; dyspepsia; enterocolitis; esophageal ulcer; gastritis; pancreatitis; upper gastrointestinal hemorrhage
General Disorders and Administration Site Conditions - sudden death NOS
Immune System Disorders - immune system disorders - Other (autoimmune thyroiditis)

Investigations - alanine aminotransferase increased; blood bilirubin increased; cardiac troponin-I; creatinine increased; platelet count decreased
Metabolism and Nutrition Disorders - hypomagnesemia; hyponatremia
Musculoskeletal and Connective Tissue Disorders - avascular necrosis; generalized muscle weakness; muscle weakness left-sided; muscle weakness lower limb; muscle weakness right-sided; muscle weakness trunk; muscle weakness upper limb; musculoskeletal and connective tissue disorder - Other (myopathy)
Nervous System Disorders - ataxia; cognitive disturbance; depressed level of consciousness; dizziness; hydrocephalus; ischemia cerebrovascular; neuralgia; seizure; syncope
Psychiatric Disorders - anxiety; confusion; depression; psychosis
Renal and Urinary Disorders - acute kidney injury; hematuria; proteinuria; urinary tract obstruction
Reproductive System and Breast Disorders - fallopian tube obstruction; prostatic obstruction; spermatic cord obstruction; uterine obstruction; vaginal obstruction
Respiratory, Thoracic and Mediastinal Disorders - apnea; laryngeal edema; pharyngolaryngeal pain; pleural effusion; pneumothorax; pulmonary hypertension; voice alteration
Skin and Subcutaneous Tissue Disorders - nail loss; pruritus; skin ulceration
Vascular Disorders - thromboembolic event

Note: Trastuzumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

8.1.3. Additional adverse events from the FDA-approved October 2010 Prescribing Information for Herceptin® (Trastuzumab)

General Disorders – edema limbs, edema trunk
Infections and Infestations – pharyngitis
Nervous System Disorders – dizziness
Psychiatric Disorders – depression, insomnia
Renal and Urinary Disorders – other (glomerulopathy)

8.2. Common Terminology Criteria for Adverse Events (CTCAE) version

Adverse events should be reported according to CTCAE version 4.03

8.2.1 Adverse Event Definitions

8.2.1.1 Adverse events

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

8.2.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalization, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require

medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

8.2.1.3 Intensity of Event

Intensity of the events will be graded according to the CTCAE version 4.03 and reported in the CRF/eCRF.

8.2.1.4 Causal Relationship

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms:

- Yes: There is a reasonable causal relationship between the investigational drug administered and the AE.
- No: There is no reasonable causal relationship between the investigational drug administered and the AE.

8.3. Reporting Requirements

The study must be conducted in compliance with FDA regulations and local safety reporting requirements.

All adverse events, serious and non-serious, will be fully documented on the appropriate case report form (CRF)/electronic case report form (eCRF). For each adverse event, an investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs. Worsening of the underlying disease or of other pre-existing conditions will be recorded as an AE in the CRF/eCRF. Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an AE in the CRF/eCRF, if they are judged clinically relevant by the investigator.

The investigator has the obligation to report AEs during the specified observational phase. If defined in the personalized treatment plan, the investigator also has the responsibility to report AEs occurring in a certain period after a patient completes the trial. Any AEs reported by the investigator during this phase must be documented in the appropriate CRF/eCRF.

Documentation of SAEs must include a causal relationship assessment and provide as much detail regarding the SAE as possible. With receipt of follow-up information, the SAE documentation and CRF/eCRF must be updated accordingly.

8.4. Reporting to the Institutional Review Board (IRB)

Investigators will report SAEs according to IRB policies and procedures. Expedited reporting to the IRB of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), will be done according to local regulatory requirements.

8.5. Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the investigator assesses them as stable, or the investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form as required and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report). Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Investigators should notify the IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

8.6. Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. Second malignancies require ONLY routine reporting unless otherwise specified.

9.0. Data Reporting/Regulatory Requirements

9.1 Data Collection:

Demographic data, ascertained either directly from the patient or from the subject's medical chart, will be entered into eRAP, a secure, password-protected, computerized research database. Health information reported by the subject will be corroborated by the subject's medical records

9.2 Data Reporting

Investigators must record the information required by the protocol. Case Report Forms will be completed for each subject enrolled into the clinical study. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

10.0 Data Safety and Monitoring Board

The Data Safety and Monitoring Board (DSMB) of Tisch Cancer Institute at Mount Sinai (TCI) will monitor the trial at periodic intervals to ensure the safety of subjects enrolled in the trial as determined by the DSMB charter. The TCI DSMB is composed of clinical specialists from oncology and hematology, nursing, pharmacy and biostatistics with experience in oncology and who have no direct relationship with the study. The PI will submit data and safety monitoring reports to the DSMB at a frequency (every three to six months) to be determined by the TCI DSMB based on accrual rate and risks to the subjects. At the time of renewal, the study team will submit the most recent DSMB approval for safety review to the MSMC IRB. All protocol deviations, violations, and eligibility waivers will be reported to the DSMB and IRB.

The Coordinating Site will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMB's conclusion with respect to progress or need for modification of the protocol.

11.0 Provisions to Protect the Privacy Interests of Subjects

Written Informed consent will be obtained in the Investigators' private offices in order to maintain confidentiality**.** If patients find any procedures, tests or questionnaires uncomfortable they may speak with the investigator and can decline to get the test done. Patients will be informed about health information and confidentiality. Subjects will be informed that certain parties will have access to confidential health information including the treating team, research team and also possibly IRB, governmental regulatory agencies and the sponsor. Patients will be made aware that participation in the study is purely voluntary and should they wish to withdraw their consent at any point, the subjects will not be penalized at any point.

All members who will have access to subjects' private information will have HIPPAA training. The study team will ask permission and obtain authorization from each participant regarding access to personal health information including demographics,

past and present medical records, research records, records about phone calls made as part of the study and records about study visits.

12.0 Statistical Data management and analysis

12.1 Primary Outcome:

The primary objective of the study is to evaluate pCR rates in the two arms. A Simon two-stage design will be used for each of the two treatment arms. In each treatment arm the null hypothesis will be H0: $p \leq 0.20$ (treatment uninteresting) and the alternative hypothesis will be HA: $p \geq 0.40$ (treatment interesting), where p is the pCR rate. Initially, 17 patients will be randomly assigned to each treatment arm. If 3 or fewer patients have a pCR, then that arm will be terminated and no further patients will be entered on that treatment arm. If 4 or more patients obtain a pCR, 20 additional patients (total of 37 patients) will be randomized to that treatment arm. If 11 or more patients out of 37 have a pCR, the treatment will be of interest for further study. This design has a type I and type II error rate of 0.10. Efficacy will be analyzed by an intent to treat analysis. All patients who stop chemotherapy early due to progressive disease would count as treatment failures and would be included in both efficacy and safety analyses.

12.2 Interim Analysis

One interim analysis for efficacy is planned after accrual and follow-up of 17 patients in each treatment arm as described above.

12.3 Secondary Outcome: Cardiac Toxicity

Cardiac toxicity rates will be compared between the two treatment arms. The proportion of patients experiencing a $\geq$10% decline in peak systolic longitudinal strain from baseline will be compared between the treatment arms by the chi-square test or Fisher's exact test. The proportion of patients having an elevated value of troponin I (defined as >0.08 ng/ml) will be compared between treatment arms by the chi-square test or Fisher's exact test. Echocardiograms will measure LVEF at baseline and every 3 months. These measures over time will be compared between treatment arms by a mixed effects model for longitudinal data. Assumptions underlying mixed models will be investigated and checked before use of an appropriate model. Safety data will be analyzed for all patients having at least one dose of a study drug.

The TRYPHAENA study discussed in section 2 showed that the combination of pertuzumab with trastuzumab resulted in low rates of asymptomatic decline in LVEF. Only 3.9%-5.6% of patients had asymptomatic declines in LVEF for the three treatment arms studied and only 2 patients experienced symptomatic LVSD. However, the

cardiac safety of pertuzumab as part of a doxorubicin-containing regimen has not yet been established and is a focus of the present study. Our study of 37 patients in each arm will allow detection of a difference between a 4% and a 25% proportion of patients with >10% declines in LVEF with 75% power for a two-sided test at the 0.10 level.

12.4 Stopping Rule for Safety/Toxicity

A treatment arm will be suspended pending further review due to safety if there is sufficient evidence to suggest that the true probability of a Grade 2 or more cardiac adverse event or a Grade 3 or worse non-cardiac adverse event exceeds 10%. Sufficient evidence will be taken to be an observed toxicity rate whose lower one-sided 90% confidence limit exceeds 10%. The observed toxicity rates will be examined after every 10^{th} enrolled patient in a treatment arm becomes evaluable. Operationally this limit will be met if the following is observed, Grade 2 or worse cardiac or Grade 3 or worse non-cardiac AE: If 3 of first 10 patients develop cardiac toxicity grade 2 or above or non-cardiac toxicity grade 3 or above then suspend or if 5 of the first 20 patients develop grade 2 or above cardiac toxicity or grade 3 or above non-cardiac toxicity then suspend or if 6 of the first 30 patients develop grade 2 cardiac toxicity or above or grade 3 or above non-cardiac toxicity then suspend the trial and re-evaluate

13.0 STUDY CALENDAR

Scans, including CT scans and/or PET, ECHO, and x-rays must be done < 30 days prior to the start of therapy.

13.1 Arm 1 ddAC →THP

	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5	Surgery		End of Study (Adjuvant anti-Her2 therapy and endocrine therapy as per protocol)	Follow-up
Visit Day		Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78				Q 3 months for first year and q 6 months for second year
Medication Administration														
Doxorubicin		X		X		X		X						
Cyclophosphamide		X		X		X		X						
Pegfilgastrim			X		X		X		X					
Paclitaxel										X				
Trastuzumab										X (day 1,22,43, 64)				
Pertuzumab										X(day 1,22,43, 64)				
LABS														
cbc	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)				
Comprehensive panel	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)				
Imaging														
Staging: CT C/A/P and bone scan or PET scan	X (SOC)													

Echo (q 3 months)	X (SOC)									X (Around Day 29) (SOC)				X (for 1st year)
Echo annually														X For 2 years
Pathology Assessments														
Pre-chemotherapy biopsy, Her2 status confirmed	X (SOC)													
Assessment of pCR by pathologists											X (SOC)			
Visit Assessments														
Informed consent	X													
Inclusion/Exclusion Criteria	X													
Demographics	X (SOC)													X (SOC)
Medical history	X (SOC)													X (SOC)
Concurrent meds	X (SOC)													X (SOC)
History and Physical exam	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)				X (SOC)
Vital signs	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)				X (SOC)
Height	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)				X (SOC)
Weight	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)				X (SOC)
BSA	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)				X (SOC)
Performance status	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)				X (SOC)
Adverse event evaluation	X	X		X		X		X		X				
Study Assessments														

Troponin I	X	X (time "0")	X				X			X (Day 29)				

13.2 Arm 2: TCHP

	Pre Study	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Surgery		End of Study	Follow-up
Visit Day		Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2				Q 3 months for first year and q 6 months for second year
Medication Administration																	
Docetaxel		X		X		X		X		X		X					
Carboplatin		X		X		X		X		X		X					
Trastuzumab		X		X		X		X		X		X					
Pertuzumab		X		X		X		X		X		X					
Pegfilgastrim			X		X		X		X		X		X				
Labs																	
cbc	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)					
Comprehensive panel	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)					
Imaging																	
Staging: CT C/A/P and bone scan or PET scan	X (SOC)																

Echo (q 3 months)	X (SOC)									X (SOC)							X (for 1st year)
Echo annually																	For 2 years
Pathology Assessments																	
Pre-chemotherapy biopsy, Her2 status confirmed	X (SOC)																
Assessment of pCR by pathologists														X (SOC)			
Visit Assessments																	
Informed consent	X																
Inclusion/Exclusion Criteria	X																
Demographics	X (SOC)																X (SOC)
Medical history	X (SOC)																X (SOC)
Concurrent meds	X (SOC)																X (SOC)
History and Physical exam	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)					X (SOC)
Vital signs	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)					X (SOC)
Height	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)					X (SOC)
Weight	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)					X (SOC)
BSA	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)					X (SOC)
Performance status	X (SOC)	X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)		X (SOC)					X (SOC)
Adverse event evaluation	X	X		X		X		X		X		X					
Study Assessments																	
Troponin I	X	X	X		X						X						

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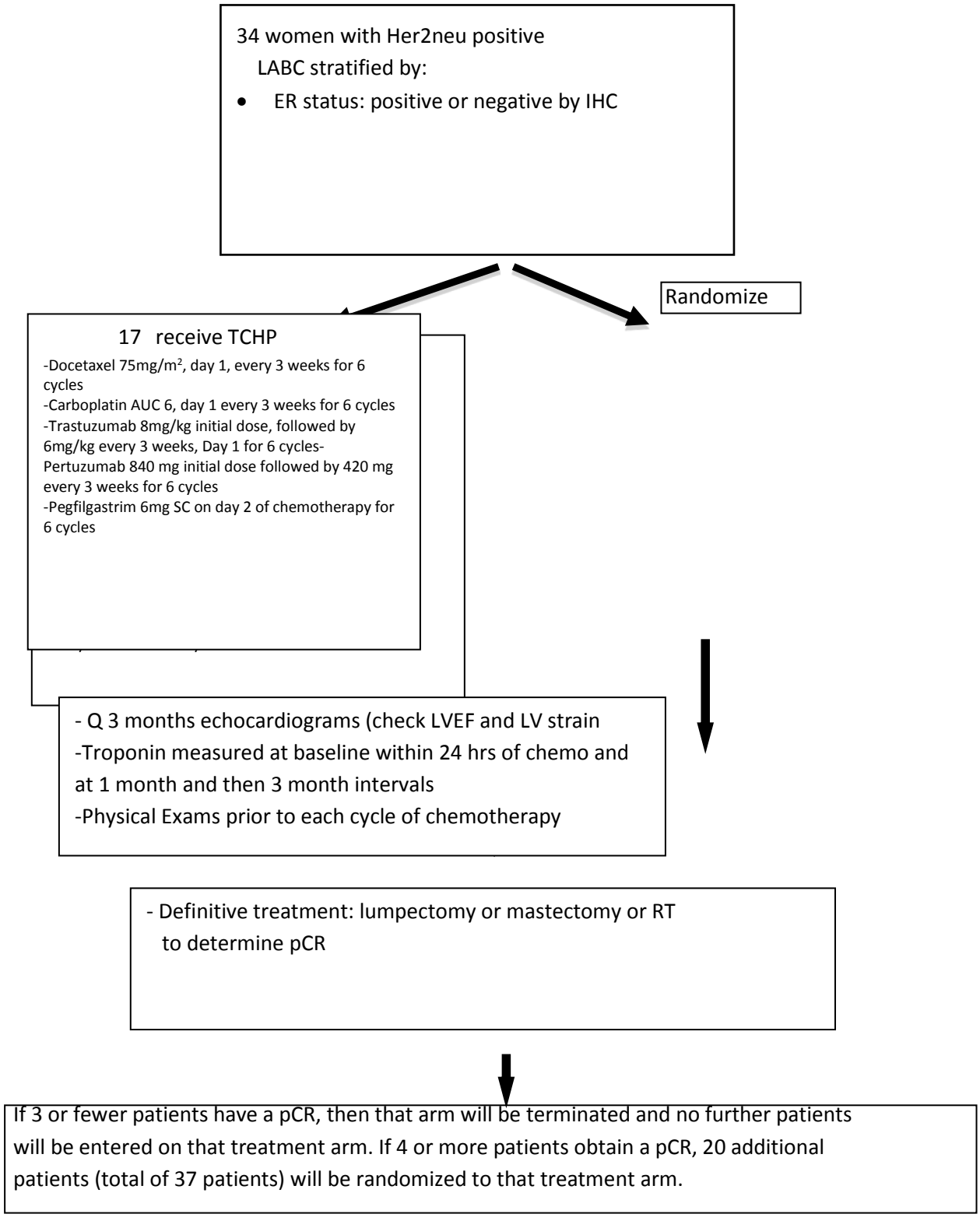
Appendix A: Protocol Schema



Appendix B: Notification to Cardiology to Calculate Longitudinal Strain with Echocardiograms

To Cardiologist:

Please note: this patient is on a study as above. Please calculate patient's Ejection Fraction (EF) as well as longitudinal strain and document it here and in the report.

Patient Name:

Patient MRN:

Local Protocol ID#

(*A Phase II Randomized Trial Evaluating Neoadjuvant Dose-Dense Doxorubicin/Cyclophosphamide followed by Paclitaxel/Trastuzumab/Pertuzumab Compared with Docetaxel/Carboplatin/Trastuzumab/Pertuzumab For Early Her2Neu Positive Breast Cancer)*

Documentation: : (or attach report) Patient's EF:

Patient's calculated longitudinal strain:

*please return completed form to Dr. Aarti Bhardwaj MD via email with subject "protocol EF and longitudinal strain"

Appendix C: Blood Serum Troponin Collection

- Samples should be obtained at protocol specified time points [1] using supplies available onsite, specifically a green top tube.
- The minimum amount of sample required is 0.15cc of blood.
- All specimens should be sent to the institution's central lab immediately for processing as per their standard of practice.

1. Troponin I serum measurements will be performed at screening for baseline, right before chemotherapy is administered (time "0"), 24 hrs after start of chemotherapy, within 1 month of time "0" and within 3 months of time "0" for duration of both regimens until surgery. Most of these scheduled troponin measurements will be done within 24 hours of chemotherapy administration See Study calendar.

Appendix D: Pathology Form: Determination of pCR status

Patient Name:

Patient MRN:

Local Protocol ID#:

(*A Phase II Randomized Trial Evaluating Neoadjuvant Dose-Dense Doxorubicin/Cyclophosphamide followed by Paclitaxel/Trastuzumab/Pertuzumab Compared with Docetaxel/Carboplatin/Trastuzumab/Pertuzumab For Early Her2Neu Positive Breast Cancer)*

Documentation:

1.Please circle one

Total pCR or Residual disease

Appendix E. Serious Adverse Event Reporting Form

SERIOUS ADVERSE EVENT REPORTING FORM

1 – Trial Information	
SPONSOR	
OVERALL PRINICPAL INVESTIGATOR	
LOCAL PRINCIPAL INVESTIGATOR	
IRB NUMBER	
STUDY TITLE	

2 – About the event				
Are you reporting a UP? (Unanticipated Problem)	Yes	☐	No	☐

3 – SAE report type				
Report type	Initial notification	☐	Follow up	☐

4 – About the time of the event					
Date Investigator informed		Date of report			
Date of Onset		Date Resolved			

5 – Participant information								
SUBJECT ID NUMBER		**Age**		**Gender**	Male	☐	Female	☐

6 – Description of Event					
	Seriousness		**Causality**		**Expectedness**
Death	☐	Not related	☐	Expected	☐
Life threatening	☐	Unlikely	☐	Not expected	☐
Hospitalization or prolongation of hospital stay	☐	Possibly	☐		
Persistent or significant disability or incapacity	☐	Probably	☐		

Congenital abnormality or birth defect	☐	Definitely	☐	
Otherwise considered serious	☐			

Brief description of event
[] Check if Cardiac Event
Diagnosis
Outcome

Fatal	☐	On-going	☐	Recovered with sequelae	☐	Recovered	☐

If *recovered* (or *recovered with sequelae*) selected, enter date of recovery	
If *fatal* enter date of death	
Cause of death:	

7 – Medication details						
Information about the CHEMOTHERAPY/ STUDY DRUG						
Drug (please specify action taken next to the agent) Legend is in the last column		Dose	Route	Start date	Stop date	Action Taken
						1- Dose stopped 2- Dose reduced 3- Dose unchanged 4- Dose increased
Relevant Concomitant Medication						
Drug (please specify action taken)	Indication	Dose	Route	Start date	Stop date	Action Taken
						1- Dose stopped 2- Dose reduced 3- Dose unchanged 4- Dose increased 5- N/A
Other clinical information, including relevant tests (laboratory, CT, ECG etc.) **Please include relevant redacted source documentation.						