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Protocol B-07

A Multicenter, Open Label, Randomized Phase II Trial of Presurgical Treatment with Single-Agent Trastuzumab (H) or Lapatinib (Ty) or the Combination of Trastuzumab and Lapatinib (H+Ty), Followed by Six Cycles of Docetaxel (T) and Carboplatin (C) with Trastuzumab (TCH) or Lapatinib (TCTy) or the combination of Trastuzumab and Lapatinib (TCHTy) in Patients with HER2/neu-Amplified Breast Cancer

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Study Summary

Title	A Multicenter, Open Label, Randomized Phase II Trial of Presurgical Treatment with Single-Agent Trastuzumab (H) or Lapatinib (Ty) or the Combination of Trastuzumab and Lapatinib (H+Ty), Followed by Six Cycles of Docetaxel (T) and Carboplatin (C) with Trastuzumab (TCH) or Lapatinib (TCTy) or the combination of Trastuzumab and Lapatinib (TCHTy) in Patients with HER2/neu-Amplified Breast Cancer
Objectives	Primary • To investigate the clinical efficacy of TCH, TCTy and TCH-Ty by estimating the Pathologic Complete Response (pCR) rate in the breast and axilla. Secondary • To estimate the molecular effects of lapatinib alone, trastuzumab alone and lapatinib combined with trastuzumab on tumor tissue by assessing changes in gene expression using serial gene microarray analysis. • To assess for gene expression and/or biomarker changes that may be correlated with or predict pCR and clinical response to lapatinib and/or trastuzumab. • To evaluate the safety and tolerability of the three treatment arms • To evaluate the clinical efficacy of the three treatment arms by estimating the clinical objective response rate (CR + PR) • To estimate the rate of CHF or drop in LVEF (>10% points from baseline and below lower limits of normal) in each of the three treatment arms
Sample Size	140 subjects
Study Design	Open label, randomized phase II trial. First twenty (20) eligible participants will be assigned to Arm 3 (TCHTy) to assess the safety of the combination of the 4 agents: Arm 3 (TCHTy): 20 subjects Run in cycle: Trastuzumab (H) 8 mg/kg IV x 1 cycle (loading dose) Lapatinib (Ty) 1000 mg PO QD days 1-21 Treatment cycles: TCH IV q3 weeks x 6 cycles plus Ty 1000 mg PO QD D1-21 x 6 cycles After first twenty (20) participants have been enrolled to Arm 3(TCHTy), one-hundred twenty (120) participants will be randomized (40:40:40) to one of three treatment arms: Arm 1 (TCH): 40 subjects Run in cycle: Trastuzumab (H) 8 mg/kg IV x 1 cycle (loading dose) Treatment cycles: TCH IV q3 weeks x 6 cycles Arm 2 (TCTy): 40 subjects Run in cycle: Lapatinib (Ty) 1000 mg PO QD days 1-21

	Treatment cycles: TC IV q3 weeks x 6 cycles plus Ty 1000 mg PO QD D1-21 x 6 cycles <u>Arm 3 (TCHTy):</u> 40 subjects Run in cycle: Trastuzumab (H) 8 mg/kg IV x 1 cycle (loading dose) Lapatinib (Ty) 1000 mg PO QD days 1-21 Treatment cycles: TCH IV q3 weeks x 6 cycles plus Ty 1000 mg PO QD D1-21 x 6 cycles <u>Drug Doses & Administration</u> Arm 1 (TCH): Trastuzumab (H) 8 mg/kg IV loading dose (run-in) followed three weeks later by Docetaxel (T) (75 mg/m2 IV q3 wk), carboplatin (C) (AUC 6 IV q3 wk), trastuzumab (6 mg/kg IV q3week) x 6 cycles, followed by definitive breast cancer surgery, followed by standard-of-care therapy. Arm 2 (TCTy): Lapatinib (Ty) 1000 mg/day days 1-21 then on day 22: docetaxel (T) (60 or 75 mg/m2 IV q3 wk), carboplatin (C) (AUC 5 or 6 IV q3 wk, **depending on the outcomes of below-described Dose Escalation of Carboplatin in Arm 3*), lapatinib (1000 mg/day days 1-21 continuously throughout cycle) x 6 cycles, followed by definitive breast cancer surgery, followed by standard-of-care therapy. Arm 3 (TCHTy): Trastuzumab (H) 8 mg/kg IV loading dose plus lapatinib 1000 mg/day days 1-21 then on day 22: docetaxel (T) (60 or 75 mg/m2 IV q3 wk), carboplatin (C) (AUC 5 or 6 IV q3 wk, **see below Dose Escalation of Carboplatin*), trastuzumab (6 mg/kg IV q3 wk) and lapatinib (Ty) (1000 mg/day days 1-21 continuously throughout 21-day cycle) x 6 cycles, followed by definitive breast cancer surgery, followed by standard-of-care therapy. Arm 1 is the control arm. All participants will undergo biopsy of tumor for biomarker analysis (1) after consenting and prior to starting any treatment, (2) after run in phase with biologic agent (Ty monotherapy, Ty + H or H monotherapy), before starting chemotherapy portion and (3) at the time of definitive breast surgery. **<u>*Dose escalation of carboplatin</u>** Due to lack of established safety with the combination of TC and H-Ty, the first 6-12 participants randomized to Arm 3 will be part of a dose escalation evaluation of carboplatin. Dose escalation will proceed in 2 cohorts of 6-12 participants in Arm 3. <u>Cohort 1</u> • If no DLT is observed in first three participants enrolled in Cohort 1, continue to Cohort 2 with the next 3 participants. • If 1 DLT is observed in the first 3 participants in Cohort 1, Cohort 1 will be expanded up to 6 participants.

- If no further DLT (1 of 6), continue to Cohort 2 with the next 3 participants.

- Note: Participants enrolled in Cohort 1 will receive the first dose level (carboplatin AUC 5 and docetaxel 75 mg/m2) for all cycles of their therapy, even if a different dose level is defined as the dose to be used for the remainder of participants on the trial.
- If 2 or more participants have a DLT at the first dose level (2/3 or 2/6), then the maximum tolerated dose (MTD) has been exceeded and the remainder of participants enrolled in this arm (and Arm 2) will receive carboplatin AUC 5 and ***docetaxel 60*** mg/m2 with lapatinib 1000 mg/d +/- trastuzumab 6 mg/kg.

Cohort 2

- If no DLT is observed in the 3 participants enrolled in Cohort 2, this will be the dose used for the remainder of participants enrolled in this treatment arm and in arm 2.
- If 1 DLT is observed (1/3), Cohort 2 will be expanded up to 6 participants.
  - If no further DLT (1 of 6), the remainder of participants enrolled in this arm and in arm 2 will receive carboplatin at this dose level.
- Note: Participants enrolled in Cohort 2 will receive the second dose level (carboplatin AUC 6 and docetaxel 75 mg/m2) for all cycles of their therapy, even if a different dose level is defined as the dose to be used for the remainder of participants on the trial.
- If 2 or more participants have a DLT at the dose level 2 (2/3 or 2/6), then the maximum tolerated dose (MTD) has been exceeded and the remainder of participants enrolled in this arm and in Arm 2 will receive carboplatin AUC 5 and docetaxel 75 mg/m2 with lapatinib 1000 mg/d +/- trastuzumab 6 mg/kg.

Doses of carboplatin and docetaxel for Arms 2 and 3

The doses of carboplatin and docetaxel will be determined by the outcomes of the above dose escalation for arm 3 as well as for arm 2.

Definition of Cohorts – Drug Doses

Arm	Cohort	Doses of Drugs
3	1	Carboplatin AUC 5, lapatinib 1000 mg/d, docetaxel 75 mg/m2, trastuzumab 6 mg/kg
3	2	Carboplatin AUC 6. lapatinib 1000 mg/d, docetaxel 75 mg/m2 trastuzumab 6 mg/kg

Dose limiting toxicity (DLT) is defined as any NCI CTCAE v3 (see Appendix B) Grade 4 toxicity or any Grade 3 toxicity lasting more than 1 week. Participants who have experienced Grade 3 toxicity will be assessed 1 week after Grade 3 toxicity noted to determine if event is DLT.

	Prior to enrollment of the first patient in Cohort 2, all participants in the previous cohort should reach at least day 14 of protocol therapy and at least one participant shall have reached day 21 of protocol therapy. Clinical tumor assessments will be performed by physical examination at baseline, before each cycle of therapy, and at the completion of all prescribed protocol therapy. Clinical tumor assessment may also be performed by imaging tests at baseline, at the end of chemotherapy/prior to surgery, and at the end of study visit. Participant visits will take place q3weeks during treatment phase. Treatment will continue until completion of all prescribed protocol therapy, or until disease progression, unacceptable toxicity, or withdrawal of participant consent. At the conclusion of chemotherapy*, subjects who are candidates for surgery and/or radiotherapy will receive surgery and/or radiotherapy at the discretion of the treating investigator. The tumor pCR rate will be determined in subjects who complete the study-defined pre-surgical therapy and undergo a mastectomy or breast conserving surgery. The study will conclude at surgery. Post-surgical therapy will be administered according to standard of care at the discretion of the treating physician. Tissue specimens (core biopsies and/or tumor specimens) will be obtained serially for the performance of exploratory molecular analyses. * Note: “Chemotherapy” refers to Taxotere and Carboplatin for this study.

Inclusion Criteria

1. Women aged 18 to 70 years, inclusive
2. Histologically or cytologically proven adenocarcinoma of the breast
3. Stage I, II or III breast cancer. If stage I, tumor size must be at least 1 cm and must be (1) grade > 1, (2) estrogen and progesterone receptor negative, or (3) patient 35 years of age or younger.
4. Inflammatory breast cancer, defined as the presence of erythema or induration involving one-third or more of the breast is allowed on study
5. Tumor HER2/neu positive by fluorescence in situ hybridization (FISH) or Silver (Chromogenic) In Situ Hybridization (SISH). (Results from a local lab is sufficient).
6. Estrogen and progesterone receptor status known prior to study entry
7. ECOG performance status score ≤1
8. No prior chemotherapy, radiotherapy, or endocrine therapy for currently diagnosed invasive or noninvasive breast cancer
9. Normal cardiac function (ejection fraction ≥ lower limit of normal) as determined by MUGA or echocardiogram
10. If female of childbearing potential, pregnancy test is negative and willing to use effective contraception while on treatment and for at least 3 months after the last dose of study therapy
11. Patient is accessible and willing to comply with treatment, tissue acquisition and follow up
12. Patient is willing to provide written informed consent prior to the performance of any study-related procedures
13. Adequate organ function as defined by the following laboratory values
    a. Absolute neutrophil count ≥ 1.5 x 10^9/L
    b. Hemoglobin ≥ 9.0 g/dL
    c. Platelet count ≥ 100 x 10^9/L
    d. Creatinine < 1.5 mg/dL
    e. Total bilirubin ≤ 1.0 x upper limit of normal (ULN). Subjects with Gilbert's syndrome, confirmed by genotyping or Invader UGTIA1 molecular assay prior to study entry must have total bilirubin <3X ULN.
    f. Alkaline phosphatase and AST/ALT within the following parameters. In determining eligibility, the more abnormal of the two values (AST or ALT) should be used.

	AST or ALT (whichever higher)			
Alk Phos	≤ ULN	>1x but ≤1.5x	>1.5x but ≤2.5x	>2.5x ULN
≤ULN	Eligible	Eligible	Eligible	Ineligible
>1x but ≤2.5x	Eligible	Eligible	Ineligible	Ineligible
>2.5x but ≤5x	Eligible	Ineligible	Ineligible	Ineligible
>5x ULN	Ineligible	Ineligible	Ineligible	Ineligible

Exclusion Criteria	1. Bilateral invasive breast cancer 2. Metastatic breast cancer 3. Concurrent therapy with any other non-protocol anti-cancer therapy 4. History of any other malignancy within the past 5 years, with the exception of non-melanoma skin cancer or carcinoma-in-situ of the cervix 5. Prior chemotherapy, radiotherapy or endocrine therapy for currently diagnosed invasive or noninvasive breast cancer. 6. Prior ipsilateral radiation therapy for invasive or non-invasive breast cancer or any radiotherapy to the ipsilateral chest wall for any malignancy. 7. Current therapy with raloxifene, tamoxifen, or other selective estrogen receptor modulators (SERMs), either for osteoporosis or prevention of breast cancer. Subjects must have discontinued prior to first baseline biopsy. 8. Concurrent treatment with ovarian hormonal replacement therapy. Prior treatment must be stopped prior to first baseline biopsy. 9. Pre-existing motor or sensory neurotoxicity of a severity $\geq$Grade 2 by NCI-CTCAE version 3.0. 10. Cardiac disease including myocardial infarction within 6 months, unstable angina, or New York Heart Association (NYHA) Grade II or greater congestive heart failure. 11. Inflammatory bowel disease or other bowel condition causing chronic diarrhea, requiring active therapy. 12. Active, uncontrolled infection requiring parenteral antimicrobials 13. The presence of any other medical or psychiatric disorder that, in the opinion of the treating physician, would contraindicate the use of the drugs in this protocol or place the subject at undue risk for treatment complications 14. Male subjects. 15. Pregnant or lactating subjects 16. Subjects with known hypersensitivity to Chinese hamster ovary products or other recombinant human or humanized antibodies and/or known hypersensitivity to any of the study drugs or their ingredients (eg, polysorbate 80 in docetaxel)
Efficacy Assessments	• Pathologic complete response (pCR) at the time of surgery. • Clinical objective response rate will be determined by physical examination or imaging tests (CR + PR) at visit prior to surgery • Safety will be evaluated q3 weeks during chemo/biological agent • Biomarker analysis: See above tumor biopsy assessments.
Molecular Analyses	The tissue acquisition component of this study is aimed at better understanding the molecular effects of trastuzumab and/ or lapatinib

	in human breast cancer tissue and correlating these with molecular and clinical responses. The molecular analyses proposed in the study are based on evaluating tumor tissue from participants participating in the study. *Tumor tissue*: Global gene expression changes between the baseline (pre-treatment) and post-treatment core biopsies will be performed using mRNA microarray analysis (Agilent). Molecular changes after treatment will be correlated with baseline expression profiles to identify molecular subsets of participants that might be more likely to benefit from lapatinib and/or trastuzumab. In addition, these changes will be correlated with pathologic response. There are two objectives of the molecular analysis: 1) To identify a set of genes that respond differentially across the treatment arms; 2) To identify a set of genes correlated with pathological response. The above molecular studies are not powered for statistical changes between treatment arms but are rather meant to be hypothesis-generating for further studies.
Statistical Analyses	Safety Analysis The safety analysis will be conducted on all participants who received all or any portion of any study drug. Descriptive statistics will be used to summarize the number and types of adverse events, serious adverse events, clinically relevant laboratory data, and number of participants in whom study treatment had to be stopped, dose-reduced, or delayed. Adverse events will be compared using chi-squared (χ^2) tests or, when expected counts are low, Fisher's exact test or one of its generalizations. Efficacy and Molecular Analyses This trial is a pilot study to define estimates and do exploratory treatment comparisons. Section 10.0 describes the statistical calculations to be used in this study.

1.0 INTRODUCTION AND SCIENTIFIC RATIONALE

1.1 BACKGROUND

Breast cancer remains a highly significant cause of morbidity and mortality worldwide. There are nearly 1,000,000 cases of breast cancer diagnosed globally each year. In the U.S. alone in 2007, it is estimated that nearly 180,000 new cases of breast cancer will be diagnosed and over 40,000 women will die from breast cancer [1]. It is clear that better therapies are required for the treatment of this disease. Cytotoxic chemotherapy and endocrine agents have been the mainstays of systemic treatment for women with early and late breast cancer for more than three decades. Chemotherapeutic agents from a wide variety of classes, including alkylators, vinca alkaloids, antimetabolites, anthracyclines, and platinum compounds have demonstrated activity in the treatment of early and advanced breast cancer. The introduction of new chemotherapeutic and endocrine agents, such as taxanes and aromatase inhibitors, have lead to incremental improvements in clinical outcomes for women with breast cancer. The treatment of breast cancer was revolutionized, however, by the discovery that approximately 25% of breast tumors overexpress the human epidermal growth factor-2 (HER2/neu), a transmembrane receptor tyrosine kinase, and this overexpression denotes a particularly aggressive form of breast cancer [2, 3]. This finding lead to the development of the anti-Her2/neu humanized monoclonal antibody, trastuzumab. As detailed below, this antibody has activity as both a single agent and in combination with chemotherapy and now is FDA approved for the treatment of both metastatic and early breast cancer. The development of trastuzumab represented a milestone in oncology, since it validated the concept of targeting a specific molecular alteration in the tumor cell, and demonstrated the feasibility of translating laboratory observations into approved new anti-cancer therapeutics. Since that time, lapatinib, a small molecule tyrosine kinase inhibitor that targets both Her2/neu and EGFR (Her1) has earned FDA approval for Her2/neu overexpressing metastatic breast cancer.

This Phase II clinical study proposes to explore the safety and efficacy of lapatinib and/or trastuzumab for HER2-overexpressing early breast cancer in combination with standard chemotherapy. This study seeks to obtain preliminary efficacy and safety data that would serve as a basis for evaluation in a larger Phase III study of each of the treatment stratum.

1.2 HER2/NEU OVEREXPRESSION AND CARCINOGENESIS IN BREAST CANCER

The HER family of receptor tyrosine kinase couples binding of extracellular growth factor ligands to intracellular signal transduction pathways, contributing in this fashion to the ability of the cell to respond correctly to its environment [4]. The HER family and its ligands are critically involved in the carcinogenesis of the mammary gland. Abnormal function of members of the HER family resulting from receptor hyperactivation (due to gene amplification, protein over expression, or abnormal transcriptional regulation) has been linked with breast cancer prognosis. Clinical indications support the concept that none of these receptors (EGFR, HER2, HER3, and HER4) can be considered as the stand-alone receptor in breast cancer development and clinical course of disease.

Increasingly, evidence suggests that it is the cooperation between them that contributes to more aggressive tumor phenotype and influences the response to therapy [4].

Her2/neu is over-expressed in 20% to 25% of breast cancers and 8% to 11% of ovarian cancers, suggesting a role for over-expression in transformation and tumorigenesis [2, 3, 5]. Women with primary breast cancers that contain HER2 gene amplification and/or over-express HER2 protein have a poor prognosis that includes a greater risk of relapse and shortened survival compared with women whose cancers are negative for the HER2 alteration [2, 3, 5-8]. Her2 over-expression in retrospective analyses of adjuvant studies was also associated with resistance to cyclophosphamide, methotrexate, and fluorouracil chemotherapy [9, 10].

1.3 CHEMOTHERAPY IN THE TREATMENT OF EARLY BREAST CANCER

The standard of care for patients with node-positive or high-risk node-negative breast cancer involves administering a predefined course of chemotherapy (in the absence of clinically significant comorbid conditions) either before or after primary surgery. Today, most North American patients with a breast t[1]umor 1 cm or greater at presentation are offered some form of chemotherapy, which typically contains drugs such as anthracyclines and taxanes [11]. This standard of care for the adjuvant treatment of breast cancer is the result of intense investigation during the last 20 years and is continually evolving.

1.3.1 Docetaxel-containing regimens for breast cancer

Docetaxel (Taxotere®, Sanofi-Aventis) is a semi-synthetic antineoplastic agent of the taxoid family that acts by disrupting the microtubular network in cells essential for mitotic and interphase cellular functions. It binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells [12]. Docetaxel has been demonstrated to inhibit angiogenesis by suppressing the proliferation, migration, and capillary formation of endothelial cells mainly through inhibitory effects on VEGF in both *in vitro* and *in vivo* models [13]. It has become clear over the past 10 years that docetaxel is among the most promising compounds to have been developed in the 1990s for the treatment of breast cancer. More recently, docetaxel also became one of the standard therapies in the adjuvant and neoadjuvant settings, and a promising partner for novel biologic therapies, such as those that target HER2 [14].

1.4 TRASTUZUMAB FOR HER2/NEU POSITIVE BREAST CANCER

In the last decade, the targeted anti-Her2/neu monoclonal antibody, trastuzumab (Herceptin®, Genentech) has been tested in conjunction with chemotherapy for subjects with HER2 positive breast cancer in the adjuvant and metastatic settings.

1.4.1 Trastuzumab: Initial clinical studies in metastatic breast cancer

Trastuzumab is a recombinant, humanized, monoclonal antibody directed against the extracellular domain of the Her2/neu tyrosine kinase receptor. It was approved by the United States Food and Drug Administration (FDA) in 1998 for the treatment of chemotherapy-refractory advanced breast cancers that overexpress the Her2/neu protein or have the Her2/neu gene amplified. Approval was based on results from a multinational study which enrolled 222 women with metastatic breast cancer that had

progressed following one or two regimens for metastatic disease [15]. The overall response rate (ORR) from the independent review was 15% with 8 (4%) complete responses (CR) and 26 (11%) partial responses (PR). The median duration of response was 9.1 months and the median duration of survival was 13 months. The median time to disease progression (TTP) was 3.1 months (range 0 - >28 months).

Trastuzumab was also approved in the first-line setting in combination with paclitaxel. A pivotal phase III trial enrolled 469 chemotherapy-naïve subjects with metastatic breast cancer whose tumors overexpressed Her2/neu [16]. Subjects were randomized to receive either standard chemotherapy (doxorubicin plus cyclophosphamide or paclitaxel) alone or in combination with trastuzumab. Subjects who received trastuzumab plus chemotherapy had a longer median TTP (7.4 months versus 4.6 months, $p < 0.001$), a higher ORR (50% versus 32%, $p < 0.001$), a longer median duration of response (9.1 months versus 6.1 months, $p < 0.001$), longer median survival (25.1 months versus 20.3 months, $p = 0.046$) and a 20% lower risk of death than subjects who received chemotherapy alone. Subjects who received combination treatment also had better gains in quality of life than those that received chemotherapy alone. The most serious adverse event seen with trastuzumab therapy was cardiac toxicity. This toxicity was seen more frequently when trastuzumab was combined with anthracyclines. Given the level of activity demonstrated in metastatic disease, studies in the adjuvant setting were initiated and accrued.

1.4.2 Trastuzumab: Clinical studies in early breast cancer

Four large studies that evaluated the role of trastuzumab in the adjuvant setting in early stage breast cancer have been reported recently. In the Herceptin Adjuvant (HERA) study, patients who had completed neoadjuvant (5%) and/or adjuvant chemotherapy were randomized to observation, 1 year or 2 years of trastuzumab [17]. In June 2006, Smith, *et al* reported the updated results for this study, including data only from the observation and 1-year of trastuzumab therapy arms [18]. At a median follow up of 23 months, 1 year of trastuzumab was associated with a statistically significant absolute disease free survival benefit of 6.3% (HR 0.64). Importantly, patients treated in the trastuzumab arm had a statistically significant 34% relative reduction in their risk of death (HR=0.66 p=0.0115). This benefit was seen in patients with both lymph node positive and lymph node negative disease. A combined analysis of the NSABP B-31 study and the NCCTG 9831 study were reported by Romond, *et al* [19]. The B-31 study studied doxorubicin/cyclophosphamide (AC) followed by paclitaxel (T) administered every 3 weeks with and without 52 weeks of trastuzumab therapy. The NCCTG 9831 compared 3 regimens: AC followed by weekly T, AC followed by weekly T followed by trastuzumab (H) for 52 weeks, and AC followed by a combination of weekly TH for 52 weeks. The authors reported an absolute benefit in 3-year survival of 12% at 3 years. The cumulative incidence of class III or IV CHF or death from cardiac causes was 4.1% in the B-31 study and 2.9% in the NCCTC 9831 study in the trastuzumab treated arms. The fourth large study that evaluated the adjuvant use of trastuzumab combined with chemotherapy was the BCIRG006 study (discussed in detail below in section 1.5.2).

Trastuzumab has also been evaluated in the *preoperative* setting combined with a variety of chemotherapeutic agents. One of the first of these trials was a pilot study that evaluated the safety and efficacy of paclitaxel combined with trastuzumab. This regimen yielded a pCR rate of 18% and clinical response rate of 85% [20]. A more recent trial reported that patients who received neoadjuvant polychemotherapy plus trastuzumab achieved a remarkable pCR rate of 65%, compared to only 26% of patients who received chemotherapy alone (p=0.016) [21]. Preoperative treatment of locally advanced

breast cancer with the combination of trastuzumab and docetaxel has also been shown to be reasonably well-tolerated with a pCR of 47% [22].

1.5 RATIONALE FOR USE OF DOCETAXEL (T), CARBOPLATIN (C), TRASTUZUMAB (H) (TCH) COMBINATION THERAPY AS CONTROL ARM

One of the newest chemotherapy regimens being investigated today for the treatment of early breast cancer combines docetaxel with a platinum salt and trastuzumab.

1.5.1 Phase II trials of TCH

Based on biologic data demonstrating pharmacologic synergy between trastuzumab and both docetaxel and platinum analogs in terms of anti-tumor activity [23], and on the cardiac toxicity associated with anthracycline-trastuzumab based combination regimens, the Breast Cancer International Research Group (BCIRG) conducted 2 pilot TCH Phase II studies, one combining docetaxel/trastuzumab and carboplatin (TCH1 or BCIRG 102) and one combining docetaxel/trastuzumab and cisplatin (TCH2 or BCIRG 101) in the metastatic breast cancer setting were conducted [24]. These phase II multi-center studies in the metastatic Her2/neu positive patient population showed these regimens to be feasible, active and safe and provided compelling evidence that TCH limits the potential cardiac toxicity seen with an anthracycline-trastuzumab combination therapy.

1.5.2 Phase III trial of adjuvant TCH

Given this data, the BCIRG conducted a Phase III, randomized, controlled, multi-center study that evaluated the safety and efficacy of standard chemotherapy versus 2 trastuzumab-containing chemotherapy regimens for the treatment of node positive and high risk node negative HER2-positive early, operable breast cancer [25]. It was designed to determine if the introduction of trastuzumab in early stage HER2 breast cancer significantly improves clinical outcomes and if the increased cardiotoxicity observed with trastuzumab when used with anthracyclines could be avoided by using a novel regimen of docetaxel without anthracyclines. 3,222 eligible subjects were randomly assigned to 1 of 3 treatment arms: doxorubicin and cyclophosphamide followed by docetaxel (AC→T); doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH); or docetaxel, platinum salt, and trastuzumab (TCH). Trastuzumab was infused weekly during chemotherapy and then every 3 weeks thereafter for a total of 52 weeks. The second interim efficacy and safety analysis of this study (based on 185 events) showed at a 3-year median follow-up a reduction in the risk of death of 41% ($p = 0.004$) and 34% ($p = 0.017$) for patients in the AC→TH and TCH arms, respectively when compared with the non-trastuzumab containing control arm. The relative reduction in the risk of relapse was 39% ($p < 0.0001$) and 33% ($p = 0.0003$) for AC→TH and TCH respectively versus the control arm. At 4 years 92% and 91% of patients in the trastuzumab/docetaxel-containing arms (AC→TH and TCH) respectively were alive compared to 86% in the AC→T arm. In addition, there were fewer grade 3 or 4 CHF events in the TCH arm when compared to the anthracycline/trastuzumab arm (4 versus 20 respectively, $p = 0.0015$). The BCIRG presented this second interim efficacy and safety results, as well as updated cardiac analyses, during the San Antonio Breast Cancer Symposium in December 2006 [25]. This data showed that trastuzumab combined with docetaxel-based regimens significantly improved disease-free and overall survival for women with early HER2-positive breast cancer.

1.5.3: Trials evaluating TCH as neoadjuvant therapy

Systemic anti-cancer therapy may also be given prior to surgery (i.e. neoadjuvant therapy, see section 1.8). The triplet regimen of docetaxel, carboplatin with or without trastuzumab (T/C +/- H) has been investigated in the neoadjuvant setting [26, 27]. One study [26] reported on 12 patients with Her2/neu positive disease who completed neoadjuvant therapy with either T/C (n=6) or T/C/H (n=6). The pCR rate was 16% (1/6) in the T/C/H group versus 0 in the T/C group. No patient developed cardiac symptoms or had a drop in LVEF below the lower limits of normal, underscoring the relative safety of this combination. A 70-patient phase II trial of neoadjuvant TCH was recently reported with a pCR rate of 43% (24/56) for tumors that were Her2/neu 3+ by immunohistochemistry and/or FISH positive [27].

1.6 LAPATININB FOR HER2/NEU POSITIVE BREAST CANCER

While trastuzumab-based therapy has yielded impressive results in both the early and advanced disease settings, some patients do not respond to the treatment and others will experience disease relapse. New agents are therefore still needed. Lapatinib (GW572016, Tykerb®, Glaxo-Smith-Klein) is a novel, orally active small molecule, reversible tyrosine kinase inhibitor (TKI) of both HER1 (epidermal growth factor receptor, EGFR, or ErbB1) and HER2/neu. It has been shown to inhibit growth and block the phosphorylation and activation of Erk1/2 (p-Erk1/2) and Akt (p-Akt) in ErbB1- and/or ErbB2-expressing tumor cell lines and mouse xenografts [28-31] and is not cross-resistant with trastuzumab [32].

1.6.1 Phase I/II studies of lapatinib

A phase I study of lapatinib combined with capecitabine in patients with HER2-positive breast cancer that progressed during trastuzumab therapy showed this combination to be active and to have an adverse event profile similar to that of each drug individually [33]. Results of the interim analysis of a phase II study of lapatinib in the first-line setting in subjects with locally advanced or metastatic breast cancer with HER2 amplification by FISH were presented at ASCO 2005 [34]. Independently reviewed data on the first 40 subjects randomized to receive oral lapatinib as either a single daily dose of 1500 mg, or 500 mg twice daily showed that confirmed PRs were demonstrated in 14/40 (35%) subjects. An additional 14/40 (35%) subjects had stable disease (SD) for at least eight weeks, and 5/40 (12.5%) had progressive disease (PD). No grade 3/4 treatment-related adverse events (AEs) were reported. Twenty-eight (40%) subjects experienced grade 1/2 treatment-related AEs with pruritis (15; 38%), diarrhea (10; 25%), rash (5; 13%), acne (5;13%), dry skin (4; 10%), dyspepsia (4; 10%) and abnormal hepatic function (4; 10%) reported as the most frequent. No interstitial pneumonitis events were reported and no decrease in left ventricular ejection fraction (LVEF) events reported met serious adverse event (SAE) criteria. One subject had a grade 2 decrease in LVEF on echocardiogram that did not drop below institution's lower limit of normal. These data provide evidence that lapatinib is well tolerated and shows activity in the first-line setting in FISH positive chemotherapy-naïve subjects with advanced or metastatic breast cancer.

1.6.2 Phase III studies of lapatinib

Recently, data was reported from a phase III, randomized, open-label study comparing lapatinib (1250 mg/day) plus capecitabine (2000 mg/m^2/day days 1-14) with capecitabine alone (2500 mg/m^2/day days 1-14) in 324 women with progressive, HER2-positive, locally advanced or metastatic breast cancer who had previously been treated with a minimum of an anthracycline, a taxane, and trastuzumab [35]. Treatment in the lapatinib

arm was associated with a 51% reduction in the risk of disease progression compared to patients in the chemotherapy-alone arm. The median time to progression was 8.4 months for patients in the lapatinib combination arm compared to 4.4 months in the monotherapy group. Patients in the combination arm did not have an increase in serious toxicity compared to those in the capecitabine-alone arm. The most common adverse events were diarrhea, hand–foot syndrome, nausea, vomiting, fatigue and rash. Importantly, there were no withdrawals from treatment due to declines in LVEF, no cases of congestive heart failure, and no decreases in the mean LVEF values in the group receiving lapatinib.

In June 2007, data from a phase III randomized trial of lapatinib plus paclitaxel versus paclitaxel plus placebo for the first-line treatment of metastatic breast cancer were presented [36]. In this study, 580 patients with Her2/neu negative or Her2/neu untested breast cancer were randomized to receive paclitaxel 175 mg/m2 IV q3 weeks with lapatinib 1500 mg PO daily or paclitaxel 175 mg/m2 IV q3 weeks with placebo. There was an increase in the number of grade 3/4 diarrhea in the combination arm (16% in the lapatinib arm vs 1% in the placebo arm) and three fatal adverse events related to diarrhea and septic shock. The presenting investigator noted that the number of these fatal AEs declined significantly as early aggressive management of lapatinib-induced diarrhea was implemented. Her2/neu status was centrally determined by FISH. 91 patients were found to have Her2/neu positive tumors. In the Her2/neu positive population, patients treated with lapatinib-paclitaxel had a statistically significantly improved response rate (60%) compared to those who received placebo-paclitaxel (36%, odds ratio 2.9, p=0.027). In contrast, there was no significant difference in response rates between the two treatment arms in patients who had Her2/neu negative tumors. Also, in patients with Her2/neu positive tumors, the combination of paclitaxel-lapatinib was associated with a statistically significantly increased time to progression compared with the placebo-arm (8.1 mos vs. 5.8 mos, HR 0.57 95% CI (0.34, 0.93) p=0.011). In the Her2/neu negative population, the time to progression did not differ between the two treatment arms [HR=1.04, 95% CI (0.83, 1.30), p=0.747].

1.6.3 Trial evaluating lapatinib as neoadjuvant therapy

Lapatinib has also been evaluated in the neoadjuvant setting in inflammatory breast cancer (IBC) [37]. 35 patients with newly diagnosed HER2-overexpressing or EGFR-expressing IBC were treated with lapatinib (1500 mg/day weeks 1-2) followed by lapatinib (1500 mg/day) plus paclitaxel (80 mg/m2/week). At the interim analysis presented in December 2006, 3 of the 18 patients (17%) with HER2 overexpressing tumors who had completed surgery achieved a pCR at week 14 of therapy. Preliminary results from the biomarker analysis showed that response to lapatinib occurred in patients with insulin-like growth factor-I receptor (IGFR-1) expression or PTEN deficiency.

1.7 RATIONALE FOR COMBINING LAPATINIB/TRASTUZUMAB

Combining non-cross resistant Her2/neu targeted therapy that acts at different sites of the receptor may enhance the efficacy of both drugs. Indeed, *in vitro* data supports the synergistic effects of combining lapatinib with trastuzumab therapy in breast cancer cell lines [32]. Based on this, a phase I study evaluating the safety, tolerability and optimal dosing of the combination of lapatinib and trastuzumab for metastatic breast cancer was conducted [38]. The combination showed promising activity with a response rate of 15% in a heavily pretreated population who had all progressed on prior trastuzumab. The most common adverse events with the combination were diarrhea, fatigue, nausea and

anorexia. The optimally tolerated dosing regimen was defined as 1000 mg/day of Lapatinib with standard dosed trastuzumab.

1.8 RATIONALE FOR PREOPERATIVE (NEOADJUVANT) SYSTEMIC TREATMENT

The rational development of targeted agents in breast cancer will require elucidation of the molecular effects of these agents on tumor. In this regard, the presurgical (neoadjuvant) setting provides a unique opportunity to investigate the biologic effects of new treatments and new combinations of therapies. Neoadjuvant therapy permits serial sampling of tumor tissue, allowing the molecular characterization of tumor tissue and tumor microenvironment in response to treatment with specific agents. Furthermore, correlation of these molecular and functional data with clinical outcome (e.g., pathologic complete response rate) will help validate potential surrogate markers of clinical efficacy. In essence, this setting provides an *in vivo* laboratory for the investigation of novel breast cancer therapeutics.

A number of observations support the use of neoadjuvant therapy in early breast cancer. First, neoadjuvant therapy provides immediate systemic treatment, potentially eradicating micrometastases that would otherwise proliferate if the standard sequence of surgery followed by adjuvant systemic therapy were followed, due either to altered tumor cell growth kinetics or alterations in the balance of circulating pro- and anti-angiogenic factors [39, 40]. In addition, neoadjuvant therapy permits an in vivo assessment of drug efficacy (clinical response), which may guide the choice of subsequent treatments. Finally, the likelihood that breast-conserving surgery can be performed is increased with the use of neoadjuvant therapy [41].

The use of presurgical systemic therapy for breast cancer has been studied in several large randomized trials that have compared neoadjuvant chemotherapy to standard adjuvant treatment [42-47]. By far the largest phase III study is the NSABP B-18 trial, which randomized 1,523 patients with operable breast cancer to preoperative or postoperative doxorubicin-cyclophosphamide (AC) chemotherapy [45]. There was no significant difference in disease-free or overall survival between the groups. Compared with those who received postoperative therapy, more patients receiving neoadjuvant chemotherapy underwent breast-conserving surgery (68% vs 60%). Importantly, among those who received neoadjuvant therapy, patients who experienced a pathologic complete response (pCR) had improved outcome compared with those achieving partial responses or who did not respond to preoperative chemotherapy. This latter finding was also reported in most of the other randomized trials [48, 49]. In light of the above data, the concept of neoadjuvant therapy is now well established, with this approach being considered a standard treatment option for patients with early breast cancer.

1.9 STUDY DESIGN RATIONALE

This Phase II clinical study proposes to explore the safety and efficacy of lapatinib and/or trastuzumab for HER2-overexpressing early breast cancer in combination with standard chemotherapy. This study seeks to obtain preliminary efficacy and safety data that would serve as a basis for evaluation in a larger Phase III study of each of the treatment stratum.

Neoadjuvant studies represent the optimal setting for testing new and promising chemotherapy combinations because the subjectiveness of response rate assessment

seen in metastatic studies is replaced by the objectiveness of outcome parameters (eg, pCR, DFS and OS) and the time needed to measure a patient's response is relatively short (pathologically measured at surgery), compared to that of adjuvant studies (DFS, OS). The results from the BCIRG 006 study justify the use of TCH as the control regimen for the treatment of HER2-overexpressing breast cancer. As detailed above, there is mounting evidence supporting the use of lapatinib in combination with chemotherapy in patients with locally advanced and metastatic breast cancer and safety data has been presented for the combination of trastuzumab and lapatinib. Thus, the proposed trial will combine lapatinib with a very efficacious combination chemotherapy regimen for the treatment of early primary breast cancer. Should this trial demonstrate acceptable safety for the TC combination, it will provide a rationale to further evaluate lapatinib with TC or TCH in the neoadjuvant setting as well as in the adjuvant setting in patients with early breast cancer.

In addition, the study design incorporates an initial cycle of lapatinib, trastuzumab or lapatinib and trastuzumab. Assessing the isolated effects of HER2-targeted therapy in a setting where pre- and post-treatment tissue specimens can be obtained will provide essential information about the mechanisms by which HER2 and EGFR inhibition affects tumor growth, and represents an ideal opportunity to evaluate the molecular effects of lapatinib and trastuzumab on breast tumor tissue by evaluating whether changes in gene expression, or the expression of specific biomarkers, are predictive of response to trastuzumab and/or lapatinib. In this study, serial microarray studies will be performed on tumor tissue to characterize markers that may correlate with response or resistance to trastuzumab and/or lapatinib.

1.9.1 Selection of Study Population

This study is designed to investigate treatment options for all women with breast cancer who are appropriate for consideration of adjuvant and/or neoadjuvant therapy (e.g., node positive or high risk node negative breast cancer). Subjects will be stratified based on baseline tumor size ($\leq$3 cm and > 3 cm) and hormone receptor status (ER and/or PR positive versus ER and PR negative).

1.9.2 Rationale for Molecular Investigations

In addition to assessing the safety and efficacy of the TCTy and TCH-Ty regimens, another principal aim of this study is to investigate whether changes in gene expression, or the expression of specific biomarkers, are either predictive of response to anti-HER2 and/ or anti-EGFR therapy or indicative of response. Given the sample size, the molecular data obtained in this trial will be considered hypothesis-generating, with the ultimate goal being to develop additional trials to validate which patients have a greater likelihood of benefiting from HER2 and/or EGFR targeted therapy. The ability to identify markers that can predict response, or are indicative of response, will allow more rational use of these therapies in breast cancer and potentially other solid tumors. In addition, there is little data evaluating the effects of anti-HER2 and/ or anti-EGFR therapy in human tissue. These data will be important in developing therapies and regimens in the future.

Microarray analysis is now a widely used technique to assess gene expression. With the use of an oligonucleotide-based microarray platform, we are able to reliably detect 1.5-fold differences in gene expression in tumors before and after exposure to investigational agents [50]. In this study, serial biopsies will be obtained during treatment with lapatinib and/ or trastuzumab. Microarray analysis (Agilent) will be performed on tumor tissue to characterize markers that may correlate with response or resistance to

lapatinib and/ or trastuzumab. We have successfully performed these analyses with EGFR directed therapies in the past [51]. In addition, tumor tissue will be used for immunohistochemistry of proteins of interest. Additional material will be available for further validation and exploratory studies as well (i.e. rt-PCR).

1.10 SAFETY PLAN

In addition to routine assessments and treatment modifications as described in Sections 5 and 6 of this protocol, a number of measures will be taken to ensure the safety of subjects participating in this trial. These measures will be addressed through exclusion criteria (see Section 3.5) and routine monitoring as follows. Participants enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, assessing or monitoring of adverse events, physical examinations, blood pressure, echocardiography (or MUGA) and laboratory measurements (performed by local laboratories). Participants will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. All AEs should be graded using the NCI-CTCAE, Version 3.0. Participants discontinued from the treatment phase of the study for any reason will be evaluated within 30 days after the decision to discontinue treatment. In addition to the standard monitoring procedures, the following special safety procedures and monitoring will take place in this trial:

- This study will be monitored by the Jonsson Comprehensive Cancer Center Data Safety Monitoring Board (DSMB).
- Carboplatin dose escalation cohorts will be used to test the safety of TCHTy (see section 4.1.1)
- Doses of carboplatin and docetaxel that will be determined for TCHTy will be used for TCTy.
- Limiting the TCTy and TCHTy arms to 1000 mg lapatinib
- Mandatory growth factors, antiemetics and steroid prophylaxes
- Mandatory diarrhea guidelines
- Mandatory training of center personnel to increase awareness regarding potential complications
- Mandatory phone follow up on day 8 and 15 in the first 6-12 participants enrolled in the Dose Escalation cohorts on the TCHTy arm by study personnel
- Cardiac dysfunction will be reported as an SAE and will be defined as any signs or symptoms of deterioration in left ventricular cardiac function that are Grade 3 (NCI CTCAE) or a drop in left ventricular ejection fraction of more than 10 points from baseline **and** to below the institutional lower limits of normal. Refer to NCI CTCAE grading of left ventricular cardiac function (Appendix B) and to section 7.0.
- Any signs or symptoms of pneumonitis that are $\geq$Grade 3 (NCI CTCAE) (defined as radiographic changes and requiring oxygen) will be reported as an SAE. Refer to NCI CTCAE grading of pneumonitis/pulmonary infiltrates and to section 6.3.4.
- Subjects with an NCI CTCAE Grade 3 or 4 left ventricular systolic dysfunction or interstitial pneumonitis must be withdrawn from investigational product (lapatinib) and taken off study.

2.0 OBJECTIVES

This is a neoadjuvant study designed to study the short-term efficacy, safety and molecular effects of TCH, TCTy and TCHTy in a defined breast cancer population.

2.1 PRIMARY OBJECTIVE

To investigate the clinical efficacy of TCH, TCTy and TCH-Ty by estimating the Pathologic Complete Response (pCR) rate in the breast and axilla.

2.2 SECONDARY OBJECTIVES

- Both pre- and post-treatment tissue specimens will be obtained in this neo-adjuvant setting to evaluate the molecular effects of lapatinib and trastzumab on tumor tissue. This analysis is designed to:
- Estimate the molecular effects of lapatinib alone, trastuzumab alone and lapatinib combined with trastuzumab on tumor tissue by assessing changes in gene expression using serial gene microarray analysis.
- Assess for gene expression and/or biomarker changes that may be correlated with or predict pCR and clinical response to lapatinib and/or trastuzumab.
- To evaluate the safety and tolerability of the three treatment arms
- To evaluate the clinical efficacy of the three treatment arms by estimating the clinical objective response rate (CR + PR)
- To estimate the rate of CHF or drop in LVEF (>10% points from baseline and below lower limits of normal) in each of the three treatment arms

3.0 SELECTION OF PARTICIPANTS

3.1 TARGET POPULATION

The target population includes women with early (Stage I or II) or locally advanced (Stage III), HER2-positive breast cancer who have not received prior therapy.

3.2 NUMBER OF SUBJECTS

As calculated in Section 10.2, 140 subjects should be enrolled and treated in this study. It is planned to recruit this sample in approximately 24 centers in the U.S. Enrollment into the screening or registration phase of the study will be stopped when the anticipated or actual subject numbers have been achieved across all study sites.

Enrollment was closed on 12/21/2012 after the 130th participant was enrolled. We plan on combining data from up to an additional 80 women who participated in a nearly-identical trial in Ireland, bringing the total sample size up to approximately 210.

3.3 RECRUITMENT ARRANGEMENTS

Investigators may enroll subjects from their existing or incoming patients, ask other physicians for referrals of suitable patients.

3.4 INCLUSION CRITERIA

1. Women aged 18 to 70 years, inclusive
2. Histologically or cytologically proven adenocarcinoma of the breast
3. Stage I, II or III breast cancer. If stage I, tumor size must be at least 1 cm and must be (1) grade > 1, (2) estrogen and progesterone receptor negative, or (3) patient 35 years of age or younger.
4. Inflammatory breast cancer, defined as the presence of erythema or induration involving one-third or more of the breast is allowed
5. Tumor HER2/neu positive by fluorescence in situ hybridization (FISH) or Silver (Chromogenic) In Situ Hybridization (SISH). (Results from a local lab is sufficient).
6. Estrogen and progesterone receptor status known prior to study entry
7. ECOG performance status score ≤1
8. No prior chemotherapy, radiotherapy, or endocrine therapy for currently diagnosed invasive or noninvasive breast cancer
9. Normal cardiac function (ejection fraction ≥ lower limit of normal) as determined by MUGA or echocardiogram
10. If female of childbearing potential, pregnancy test is negative and willing to use effective contraception while on treatment and for at least 3 months after the last dose of study therapy
11. Patient is accessible and willing to comply with treatment, tissue acquisition and follow up
12. Patient is willing to provide written informed consent prior to the performance of any study-related procedures
13. Adequate organ function as defined by the following laboratory values
    a. Absolute neutrophil count ≥ 1.5 x 10^9/L
    b. Hemoglobin ≥ 9.0 g/dL
    c. Platelet count ≥ 100 x 10^9/L
    d. Creatinine < 1.5 mg/dL
    e. Total bilirubin ≤ 1.0 x upper limit of normal (ULN). Subjects with Gilbert's syndrome, confirmed by genotyping or Invader UGTIA1 molecular assay prior to study entry must have total bilirubin <3X ULN.
    f. Alkaline phosphatase and AST/ALT within the following parameters. In determining eligibility, the more abnormal of the two values (AST or ALT) should be used.

	AST or ALT (whichever higher)			
Alk Phos	≤ ULN	>1x but ≤1.5x	>1.5x but ≤2.5x	>2.5x ULN
≤ULN	Eligible	Eligible	Eligible	Ineligible
>1x but ≤2.5x	Eligible	Eligible	Ineligible	Ineligible
>2.5x but ≤5x	Eligible	Ineligible	Ineligible	Ineligible
>5x ULN	Ineligible	Ineligible	Ineligible	Ineligible

3.5 EXCLUSION CRITERIA

1. Bilateral invasive breast cancer
2. Metastatic breast cancer
3. Concurrent therapy with any other non-protocol anti-cancer therapy
4. History of any other malignancy within the past 5 years, with the exception of non-melanoma skin cancer or carcinoma-in-situ of the cervix
5. Prior chemotherapy, radiotherapy or endocrine therapy for currently diagnosed invasive or noninvasive breast cancer.
6. Prior ipsilateral radiation therapy for invasive or non-invasive breast cancer or any radiotherapy to the ipsilateral chest wall for any malignancy.
7. Current therapy with raloxifene, tamoxifen, or other selective estrogen receptor modulators (SERMs), either for osteoporosis or prevention of breast cancer. Subjects must have discontinued prior to first baseline biopsy.
8. Concurrent treatment with ovarian hormonal replacement therapy. Prior treatment must be stopped prior to first baseline biopsy.
9. Pre-existing motor or sensory neurotoxicity of a severity ≥Grade 2 by NCI-CTCAE version 3.0.
10. Cardiac disease including myocardial infarction within 6 months, unstable angina, or New York Heart Association (NYHA) Grade II or greater congestive heart failure.
11. Inflammatory bowel disease or other bowel condition causing chronic diarrhea, requiring active therapy.
12. Active, uncontrolled infection requiring parenteral antimicrobials
13. The presence of any other medical or psychiatric disorder that, in the opinion of the treating physician, would contraindicate the use of the drugs in this protocol or place the subject at undue risk for treatment complications
14. Male subjects.
15. Pregnant or lactating subjects
16. Subjects with known hypersensitivity to Chinese hamster ovary products or other recombinant human or humanized antibodies and/or known hypersensitivity to any of the study drugs or their ingredients (eg, polysorbate 80 in docetaxel)

3.6 SUBJECTS OF REPRODUCTIVE POTENTIAL

Female subjects of childbearing potential (i.e., ovulating, pre-menopausal, not surgically sterile) must use a medically accepted non-estrogen, non-progesterone containing contraceptive regimen while on treatment and for a minimum of three (3) months following the last dose of trastuzumab and/or lapatinib. The contraceptive method(s) chosen should be medically, culturally, and geographically acceptable as well as proven to have an acceptably low failure rate. If a subject becomes pregnant while enrolled in the study, the investigational product should be discontinued, the subject must be withdrawn from the study and the sponsor (TORI) must be immediately notified. Further treatment should be addressed on a case-by-case basis with the treating invesigator and the study prinicipal investigator. Both the detection and the outcome of the pregnancy must be reported to the sponsor. If a female subject becomes pregnant during the study, she must be followed up until the outcome of the pregnancy is known.

Subjects should be advised not to breast feed for at least three months following the last dose of trastuzumab and/or lapatinib.

4.0 STUDY DESIGN

This trial will be a multicenter, randomized, open-label phase II study to evaluate the relative safety, clinical efficacy, and molecular effects of TCH (docetaxel, carboplatin, trastuzumab) v*ersus* TC-lapatinib (TC-Ty) *versus* TCH-Ty. A run-in cycle of trastuzumab and/or lapatinib alone will also permit an evaluation of the effects of these targeted therapies on molecular parameters. One-hundred forty (140) participants will be enrolled in this trial locally, and data from approximately 80 additional women will be included from a nearly-identical study in Ireland.

4.1 STUDY TREATMENT

1 cycle = 21 days

First twenty (20) eligible participants will be assigned to Arm 3 (TCHTy) to assess the safety of the combination of the 4 agents:

Arm 3 (TCHTy):	20 subjects
Run in cycle:	Trastuzumab (H) 8 mg/kg IV x 1 cycle (loading dose)
	Lapatinib (Ty) 1000 mg PO QD days 1-21
Treatment cycles:	TCH IV q3 weeks x 6 cycles plus
	Ty 1000 mg PO QD D1-21 x 6 cycles

After first twenty (20) participants have been enrolled to Arm 3 (TCHTy), one-hundred twenty (120) participants will be randomized (40:40:40) to one of three treatment arms:

Arm 1 (TCH):	40 subjects
Run in cycle:	Trastuzumab (H) 8 mg/kg IV x 1 cycle (loading dose)
Treatment cycles:	TCH IV q3 weeks x 6 cycles

Arm 2 (TCTy):	40 subjects
Run in cycle:	Lapatinib (Ty) 1000 mg PO QD days 1-21
Treatment cycles:	TC IV q3 weeks x 6 cycles plus
	Ty 1000 mg PO QD D1-21 x 6 cycles

Arm 3 (TCHTy):	40 subjects
Run in cycle:	Trastuzumab (H) 8 mg/kg IV x 1 cycle (loading dose)
	Lapatinib (Ty) 1000 mg PO QD days 1-21
Treatment cycles:	TCH IV q3 weeks x 6 cycles plus
	Ty 1000 mg PO QD D1-21 x 6 cycles

Arm 1 is the control arm.

All participants will undergo biopsy of tumor for biomarker analysis (1) after consenting and prior to starting any treatment, (2) after run in phase with biologic agent (Ty monotherapy, Ty + H or H monotherapy), before starting chemotherapy portion and (3) at the time of definitive breast surgery.

4.1.1 Drug Doses & Administration

Arm 1 (TCH): Trastuzumab (H) 8 mg/kg IV loading dose (run-in) followed three weeks later by Docetaxel (T) (75 mg/m2 IV q3 wk), carboplatin (C) (AUC 6 IV q3 wk), trastuzumab (6 mg/kg IV q3week) x 6 cycles, followed by definitive breast cancer surgery, followed by standard-of-care therapy.

Arm 2 (TCTy): Lapatinib (Ty) 1000 mg/day days 1-21 then on day 22: docetaxel (T) (60 or 75 mg/m2 IV q3 wk), carboplatin (C) (AUC 5 or 6 IV q3 wk, **depending on the results of below-described Dose Escalation of Carboplatin for Arm 3*), lapatinib (1000 mg/day days 1-21 continuously throughout cycle) x 6 cycles, followed by definitive breast cancer surgery, followed by standard-of-care therapy.

Arm 3 (TCHTy): Trastuzumab (H) 8 mg/kg IV loading dose plus lapatinib 1000 mg/day days 1-21 then on day 22: docetaxel (T) (60 or 75 mg/m2 IV q3 wk), carboplatin (C) (AUC 5 or 6 IV q3 wk, **see below Dose Escalation of Carboplatin*), trastuzumab (6 mg/kg IV q3 wk) and lapatinib (Ty) (1000 mg/day days 1-21 continuously throughout 21-day cycle) x 6 cycles, followed by definitive breast cancer surgery, followed by standard-of-care therapy.

4.1.1.1 Dose Escalation of Carboplatin

Due to lack of established safety with the combination of TC and H-Ty, the first 6-12 participants randomized to Arm 3 will be part of a dose escalation evaluation of carboplatin. Dose escalation will proceed in 2 cohorts of 6-12 participants in Arm 3.

Cohort 1

- If no DLT is observed in first three participants enrolled in Cohort 1, continue to Cohort 2 with the next 3 participants.
- If 1 DLT is observed in the first 3 participants in Cohort 1, Cohort 1 will be expanded up to 6 participants.
  - If no further DLT (1 of 6), continue to Cohort 2 with the next 3 participants.
- Note: Participants enrolled in Cohort 1 will receive the first dose level (carboplatin AUC 5 and docetaxel 75 mg/m2) for all cycles of their therapy, even if a different dose level is defined as the dose to be used for the remainder of participants on the trial.
- If 2 or more participants have a DLT at the first dose level (2/3 or 2/6), then the maximum tolerated dose (MTD) has been exceeded and the remainder of participants enrolled in this arm (and in Arm 2) will receive carboplatin AUC 5 and *docetaxel 60* mg/m2 with lapatinib 1000 mg/d +/- trastuzumab 6 mg/kg.

Cohort 2

- If no DLT is observed in the 3 participants enrolled in Cohort 2, this will be the dose used for the remainder of participants enrolled in this treatment arm and in Arm 2.
- If 1 DLT is observed (1/3), Cohort 2 will be expanded up to 6 participants.
  - If no further DLT (1 of 6), the remainder of participants enrolled in this arm and in Arm 2 will receive carboplatin at this dose level.
- Note: Participants enrolled in Cohort 2 will receive the second dose level (carboplatin AUC 6 and docetaxel 75 mg/m2) for all cycles of their therapy, even if a different dose level is defined as the dose to be used for the remainder of participants on the trial.

- If 2 or more participants have a DLT at the dose level 2 (2/3 or 2/6), then the maximum tolerated dose (MTD) has been exceeded and the remainder of participants enrolled in this arm (and in Arm 2) will receive carboplatin AUC 5 and docetaxel 75 mg/m2 with lapatinib 1000 mg/d +/- trastuzumab 6 mg/kg.

Doses of carboplatin and docetaxel for Arms 2 and 3

The doses of carboplatin and docetaxel used in Arms 2 and 3 will be determined by the outcomes of the above dose escalation for arm 3.

Table 1: Definition of Cohorts - Drug Doses

Arm	Cohort	Doses of Drugs
3	1	Carboplatin AUC 5, lapatinib 1000 mg/d, docetaxel 75 mg/m2, trastuzumab 6 mg/kg
3	2	Carboplatin AUC 6. lapatinib 1000 mg/d, docetaxel 75 mg/m2 trastuzumab 6 mg/kg

Dose limiting toxicity (DLT) is defined as any NCI CTCAE v3 (see Appendix B) Grade 4 toxicity or any Grade 3 toxicity lasting more than 1 week. Participants who have experienced Grade 3 toxicity will be assessed 1 week after Grade 3 toxicity noted to determine if event is DLT.

Prior to enrollment of the first participant in Cohort 2, all participants in the previous cohort should reach at least day 14 of protocol therapy and at least one participant shall have reached day 21 of protocol therapy.

4.1.2 Treatment Assignment

One-hundred forty (140) participants in total will be enrolled. First twenty (20) eligible participants will be assigned to Arm 3 (TCHTy). Then 40 participants per arm will be enrolled in Arms 1, 2 and 3. Randomization of participants to treatments will be carried out by the method of random permuted blocks; the adaptive randomization of Zelen will not be used. Participants will be stratified based on baseline tumor size ($\leq$ 3 cm and > 3 cm) and hormone receptor status (ER and/or PR positive versus ER/PR negative).

4.1.3 Treatment Duration

Treatment will continue until one of the following criteria is met:

- Completion of all prescribed protocol therapy (run in cycle plus 6 cycles of chemotherapy plus trastuzumab and/or lapatinib) followed by definitive breast cancer surgery
- Disease progression
- Unacceptable toxicity (defined as toxicity necessitating the discontinuation of study drug, as outlined in Section 6.0)
- Withdrawal of participant consent
- Continuation would, in the judgment of the investigator, not be in the best interests of the subject

4.1.4 Response Assessments

Clinical tumor assessments by physical examination will be performed at baseline, before each cycle of therapy, and at the completion of all prescribed protocol therapy. At the conclusion of chemotherapy, participants who are candidates for surgery will receive surgery. The tumor pCR rate will be determined for both the intent to treat population

(which includes all participants who receive a dose of study drug, regardless of whether they complete all protocol-specified therapy) and for the evaluable participant population (which includes only those participants who complete the protocol-specified pre-surgical therapy and undergo mastectomy or a breast-conserving procedure). Pathology reports from definitive surgery will be centrally reviewed for all participants enrolled on study who received at least one dose of study drug regardless of whether patient completes protocol-specified therapy. Tissue specimens (core biopsies and/or tumor specimens) will be obtained serially as described in Section 4.2 below.

4.2 TISSUE COLLECTION AND MOLECULAR STUDIES

A principal aim of this study is to explore whether changes in gene expression, or the expression of specific biomarkers, are either predictive of response to lapatinib and/or trastuzumab or indicative of response.

There are two objectives of the molecular analysis:
1) To identify a set of genes that respond differentially across the treatment arms;
2) To identify a set of genes correlated with pathological response.

Given the sample size, the molecular data obtained in this trial will be considered hypothesis-generating, with the ultimate goal being to develop additional trials that will identify which participants have a greater likelihood of benefiting from this therapy.

4.2.1 Tissue Collections

To perform the molecular studies on tumor cells, tumor tissue will be obtained serially at the following time points:

Core Biopsies (Baseline)
Tumor samples must be collected after consenting and prior to run-in cycle either by core needle or incisional biopsy. Excisional biopsy will not be allowed. Please note that a clip may be placed in the site of the tumor during the baseline biopsy procedure to help identify the site of disease at the time of definitive surgery in case of complete response. There is no need to place another clip if a clip has been placed at time of diagnosis or prior to baseline biopsy procedure. A minimum of 4 core biopsies, using a 14-gauge needle (or the equivalent amount of tissue with an incisional biopsy), is required to perform the molecular analyses identified below. Once the core biopsies have been removed, three of the samples must be immediately snap-frozen using the procedure outlined in Appendix C or an equivalent technique, then stored in liquid nitrogen or at –70 to -80 °C at the site. The fourth sample should undergo formalin fixation and embedding in paraffin according to standard institutional guidelines. Samples will be batch shipped to the UCLA laboratory within 60 days of collection.

Core Biopsies (After the Start of Run-In Cycle)
A second tumor sample must be collected 14-21 days after the start of run-in cycle of trastuzumab and/or lapatinib, either by core needle or incisional biopsy. Excisional biopsy will not be allowed. A minimum of 4 core biopsies, using a 14-gauge needle (or the equivalent with an incisional biopsy), is required to perform the molecular analyses identified below. Once the core biopsies have been removed, three of the samples must be immediately snap-frozen using the procedure outlined in Appendix C or an equivalent technique, then stored in liquid nitrogen or at –70 to -80° Celsius at the site. The fourth

sample should undergo formalin fixation and embedding in paraffin according to standard institutional guidelines. Samples will be batch shipped to the UCLA laboratory within 60 days of collection.

Definitive Surgery

A third tumor sample must be collected at the time of the participant's definitive surgery in the same manner as above. Please refer to Appendix C for further details on the procedure. If no tumor is found during the surgery, tissue should be taken from the site of the tumor. For a participant who comes off of study prior to definitive surgery, tumor should be collected for this study if the participant proceeds to definitive surgery in the future. This holds true even for participants who receive subsequent systemic therapy off study prior to surgery. Alternatively, in participants whose tumors remain inoperable after the completion of chemotherapy, repeat core biopsies or an incisional biopsy may be obtained and prepared as described in Appendix C or using an equivalent technique. The biopsies may be obtained 4 weeks ± 1 week after the last chemotherapy is administrated with full recovery from the toxicity of chemotherapy and prior to the administration of additional therapy. Once the biopsies have been obtained, three of the samples must be immediately snap-frozen using the procedure outlined in Appendix C or an equivalent technique, then stored in liquid nitrogen or at –70 to -80 °C at the site. The fourth sample should undergo formalin fixation and embedding in paraffin according to standard institutional guidelines. Samples will be batch shipped to the UCLA laboratory within 60 days of collection.

In the event that a sentinel node biopsy procedure is performed, the dye can either be:

1. Injected near the site of the tumor **after** tumor removal. (The dye should not be injected into the tumor itself as this may alter the tissue and affect the molecular analyses); OR,
2. Injected into the periareolar region distant from tumor **prior to** removal of tumor (as long as it is not injected directly into the tumor).

4.2.2 Molecular Studies

One aim of this study is to investigate whether changes in gene expression, or the expression of specific biomarkers, are either predictive of response to anti-HER2 and/ or anti-EGFR therapy or indicative of response. Given the sample size, the molecular data obtained in this trial will be considered hypothesis-generating, with the ultimate goal being to develop additional trials to validate which participants have a greater likelihood of benefiting from HER2 and/or EGFR targeted therapy. The ability to identify markers that can predict response, or are indicative of response, will allow more rational use of these therapies in breast cancer and potentially other solid tumors. In addition, there is little data evaluating the effects of anti-HER2 and/ or anti-EGFR therapy in human tissue. These data will be important in developing therapies and regimens in the future.

Microarray analysis is now a widely used technique to assess gene expression. With the use of an oligonucleotide-based microarray platform, we are able to reliably detect 1.5-fold differences in gene expression in tumors before and after exposure to investigational agents [50]. In this study, serial biopsies will be obtained during treatment with lapatinib and/ or trastuzumab. Microarray analysis (Agilent) will be performed on tumor tissue to characterize markers that may correlate with response or resistance to lapatinib and/ or trastuzumab. We have successfully performed these analyses with EGFR directed therapies in the past [51]. In addition, tumor tissue will be used for immunohistochemistry of proteins of interest. Additional material will be available for

further validation and exploratory studies as well (i.e. rt-PCR). Refer to section 10.4 for details of molecular analyses.

4.3 STUDY DURATION AND DATES

The duration of this study is expected to be approximately 26 months, beginning with the first subject's first visit anticipated to occur in approximately November 2008 and ending in approximately May 2013 with the last subject's final visit. The actual overall study duration may vary.

5.0 TREATMENT REGIMENS

5.1 INVESTIGATIONAL PRODUCT: LAPATINIB

5.1.1 Description

Lapatinib will be provided by the study for the purposes of this study. Lapatinib (GW572016) is a novel compound being developed for the treatment of various cancers. Lapatinib ditosylate monohydrate tablets, 250 mg, are oval, biconvex, orange, film-coated tablets with one side of the tablet plain and other side of the tablet debossed with FG HLS. Lapatinib may also be supplied as oval, biconvex, tan tablets, with no markings. The tablets contain 410 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base per tablet. Refer to the lapatinib (GW572016) IB for information regarding the physical and chemical properties of the drug substance and list of excipients.

5.1.2 Packaging and Labeling

Lapatinib will be provided in HDPE bottles with a child-resistant closure. Each bottle will be labeled with participant name, the protocol number, dosing instructions, storage instructions, and sponsor name and address. The contents of the label will be in accordance with all applicable regulatory requirements. 90 tablets will be provided per bottle.

5.1.3 Handling and Storage

The investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive the investigational product, in accordance with all applicable regulatory requirements. Only the site pharmacist or authorized site personnel may supply or administer the investigational product. The investigational product(s) will be dispatched to the site only after receipt of required documents in accordance with applicable regulatory requirements and TORI procedures.

The investigational product will be dispensed to the subject on Day 1 after it has been confirmed that the subject meets all eligibility criteria and all screening assessments have been completed and the results reviewed. Subjects are to return to the site approximately every 3 weeks for re-supply of investigational product(s). Lapatinib should be stored in a secure, limited-access area at the study site. The recommended storage conditions, and expiry date where required, are stated on the product label.

5.1.4 Product Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or the head of the medical institution (where applicable), or designated site staff (e.g., research staff, storage manager, where applicable) must maintain investigational product accountability records throughout the course of the study. The responsible person(s) will document the amount of investigational product received from TORI, the amount supplied and/or administered to and returned by subjects. All unused lapatinib will be inventoried and destroyed at the site per the institutional SOPs. Copies of all forms, documenting drug receipt at the study site together with drug accountability records, will be retained and reviewed according to the regulations governing record retention.

5.1.5 Assessment of Compliance

Using the Lapatinib Patient Administration Log (see Appendix F), a record of the number of tablets dispensed to and taken by each subject must be maintained and reconciled with the 'Investigational Product' page in the CRF.

5.1.6 Treatment of Investigational Product Overdose

Subjects with suspected overdose of lapatinib should be monitored until drug can no longer be detected systemically (at least 5 half-lives) and a follow-up physical examination with laboratory test taken between 10 and 14 days after drug concentrations are undetectable and before being discharged from the investigator's care. Any AEs that occur as a result of an overdose should be reported to the sponsor (TORI). There is no specific antidote for lapatinib in case of an overdose. Treatment should be based on subject signs and symptoms.

5.1.7 Dosage and Administration

Subjects on the lapatinib arms will receive 1000 mg (4x250mg tablets) of oral Lapatinib daily, continuously starting on Day 1 of each cycle through day 21. Subjects will be instructed to take medication either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. A record of the number of tablets dispensed and taken by each subject must be maintained (see Appendix F, Lapatinib Patient Drug Log).

Note: Lapatinib is not to be taken with grapefruit or grapefruit juice. Grapefruit and grapefruit juice should not be taken at anytime during the study. If a subject vomits after taking study medication(s), the subject should be instructed not to retake the dose. Subjects should take the next scheduled dose of study medication(s). If vomiting persists then the subject should contact the investigator.

5.1.8 Lapatinib Dose Delays and Dose Modifications

Refer to Section 6.3 for dose reductions and delays for management of lapatinib-related toxicity. Treatment may be delayed up to 3 weeks for toxicity. If greater than a 3 week delay is required for toxicity, the participant must come off study. If treatment is delayed for reasons other than toxicity (i.e., unplanned travel or vacation, or lack of transportation to the site) and the subject has insufficient investigational product available, the subject should resume the usual dosing schedule once drug supply has been made available.

5.1.10 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Permitted Medications

All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is that drug name, indication, and the dates of administration are to be recorded. The following will be recorded on the appropriate CRF pages:

- A complete list of prescription and over-the-counter medications that have been taken within 2 weeks prior to the first dose of study medication(s).
- All concomitant medications taken while participants are receiving study medication(s) (to the End of Study visit) will also be recorded in the CRF.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

Prohibited Medications

Retrospective analysis of pharmacokinetic data from Phase I patient studies suggests that concomitant use of proton pump inhibitors and histamine H2-antagonists to elevate gastric pH does not significantly decrease lapatinib absorption. Prior to obtaining this information, prohibition of these agents was based on *in vitro* data demonstrating a significant decline in lapatinib solubility at pH values greater than 4. Based on this new information, concomitant use of these agents appears unlikely to diminish systemic exposure to lapatinib.

Lapatinib is a substrate for CYP3A4. Inducers and inhibitors of CYP3A4 may alter the metabolism of lapatinib. The following list of CYP3A4 inducers and inhibitors are prohibited from screening through discontinuation from study. Additionally, medications that modify gastric pH are included in Table 2 below:

Table 2: CYP3A4 Inducers & Inhibitors

Drug Class	Agent	Washout
Cyp3A4 Inducers		
Antibiotics	All rifamycin class agents (e.g. rifampicin, rifabutin, rifapentin)	14 days
Anticonvulsants	Phenytoin, carbamezepine, barbiturates (e.g. Phenobarbital)	
Antiretrovirals	Efavirenz, nevirapine	
Glucocorticoids	Prolonged use of prednisone (>10 mg), methylprednisolone (>8 mg), hydrocortisone (>40 mg), dexamethasone (>1.5 mg) (Note: premedication for chemotherapy allowed and temporary use of steroids for asthma or COPD exacerbations or allergic reactions allowed)	
Other	St. John's wort, modafinil	
CYP3A4 Inhibitors		
Antibiotics	Clarithromycin, erythromycin, troleandomycin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
Antiretrovirals, protease inhibitors	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinivir	
Calcium channel blockers	verapamil, diltiazem	
Antidepressants	nefazodone, fluvoxamine	
GI Agents	cimetidine, aprepitant	
Other	Grapefruit, grapefruit juice	

	Amiodarone	6 months
Miscellaneous		
Antacids	Mylanta, Maalox, Tums, Rennies	1 hr before and after dosing
Herbal or Dietary Supplements	All	14 days

At the time of screening, if a participant is receiving any of the above listed medications/substances, the medication or substance must be discontinued (if clinically appropriate) for the period of time specified prior to administration of the first dose of lapatinib and throughout the study period in order for the participant to be eligible to participate in the study

If the participant wishes to continue to take a supplement (e.g., a multivitamin), then a Memo-To-File signed by the treating physician must be filed in the participant's chart to indicated that the herbal or dietary supplement she was/is taking have no known dangerous interations with lapatinib.

5.2 CHEMOTHERAPY: DOSE CALCULATIONS AND ADMINISTRATION

Note: The doses administered for Docetaxel, Carboplatin and Trastuzumab may be rounded up or down, but it should be within +/- 10 mg from the calculated dose.

5.2.1 Docetaxel (Taxotere®)

Docetaxel will be obtained from commercial sources for the purposes of this study. The drug should be stored, prepared, and administered according to the manufacturer's guidelines and institutional practice (see Appendix E). The dose administered will be 75 mg/m2 every three weeks by IV infusion per institutional guidelines.

Docetaxel dose will be calculated according to the baseline BSA for all cycles. The BSA at the time of the Run-in Cycle may also be used as the baseline BSA. If there is a 10% or greater decrease or increase in body weight compared to baseline, the BSA will be recalculated. If the BSA for a subject is >2.0 m^2, the dose to be administered to the subject will be calculated according to a BSA of 2.0 m^2. Ideal body weight should not be used for the calculation of BSA. Docetaxel will be administered as an intravenous infusionper the institutional guidelines.

5.2.2 Carboplatin

Carboplatin will be obtained from commercial sources for the purposes of this study. The drug should be stored, prepared, and administered according to the manufacturer's guidelines and institutional practice.

Carboplatin dose is calculated using a modified Calvert formula (creatinine clearance is substituted for glomerular filtration rate) as follows:

Total dose (mg) = (target AUC) $\times$ (creatinine clearance + 25)

Carboplatin dose is calculated in mg, not mg/m^2

Creatinine clearance can either be measured or estimated using the Cockroft-Gault formula, as follows:

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight in kg}) \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

For the dosing of carboplatin using the Calvert formula, the calculation of the creatinine clearance will be done according to baseline or run-in cycle weight. If there is a 10% or greater *increase or* decrease in body weight compared to baseline or run-in (depending on which weight is used), the calculation should be revised according to the new actual weight *at each cycle during chemotherapy treatment.* For participants who are obese, an adjusted ideal body weight may be used at investigator's discretion. Carboplatin will be administered as an intravenous infusion per institutional guidelines.

For participants whose creatinine is < 1.0 mg/dL, creatinine 1.0 mg/dL may be used at investigator's discretion to calculate carboplatin dose, allowing for administration of a lower dose for participant safety if deemed necessary.

Based on new FDA safety information, the following carboplatin dosing caps should be followed:

For a target AUC = 6, the maximum dose is 6 x 150 = **900** mg.
For a target AUC = 5, the maximum dose is 5 x 150 = **750** mg.

For Arm 1, Target AUC= 6 mg/mL/min. This may be decreased due to toxicity.

For Arm 3, the first 6-12 participants randomized to Arm 3 will be part of a dose escalation evaluation of carboplatin. Please refer to section 4.1.1.1 for dose escalation rules.

For Arm 2, the dose used will be that dose that is determined to be the MTD during the dose escalation phase for Arm 3.

5.3 TRASTUZUMAB

Trastuzumab will be obtained from commercial sources for the purposes of this study. The drug should be stored, prepared, and administered according to the manufacturer's guidelines and institutional practice.

Trastuzumab dosing will be based on the baseline or run-in cycle weight. Weight will be measured prior to each infusion. In case of a 10% *or greater* increase or decrease in weight, the trastuzumab dose should be recalculated using the new weight. No dose reductions are allowed for trastuzumab for toxicity (refer to section 6.2). Trastuzumab will be administered as an intravenous infusion. The first dose (run-in cycle) will be a loading dose of 8 mg/kg administered over 90 minutes. Subsequent infusions (with chemotherapy) will be given at 6 mg/kg per cycle and may be administered over 30 minutes (+/- 10 minutes).

5.4 TREATMENT SCHEDULES

5.4.1 Run-In Cycle

5.4.1.1 Arm 1: TCH

One dose of trastuzumab (8 mg/kg) will be administered intravenously after randomization and second tumor sample will be collected 14-21 days after the start of run-in cycle for molecular studies. The initial dose of trastuzumab will be administered over 90 minutes. Trastuzumab dosing will be based on the baseline weight.

5.4.1.2 Arm 2: TCTy

One cycle of lapatinib (1000 mg) will be administered orally daily days 1-21 after randomization and second tumor sample will be collected 14-21 days after the start of run-in cycle for molecular studies.

5.4.1.3 Arm 3: TCHTy

One dose of trastuzumab (8 mg/kg) will be administered intravenously and one cycle of lapatinib (1000 mg per day days 1-21) will be administered orally after randomization and second tumor sample will be collected 14-21 days after the start of run-in cycle for molecular studies. The initial dose of trastuzumab will be administered over 90 minutes.

5.4.2 Cycles 1-6: Chemotherapy plus trastuzumab and/or lapatinib

On day 22, subjects will start treatment with chemotherapy cycles as below in Table 3. The exact dose, date, and time of administration of medication will be documented in the case report form. Docetaxel and carboplatin (TC) will be administered every three weeks (21 days). Each 3-weekly administration of TC will constitute one cycle of TC.

For Arm 3, due to lack of established safety with the combination of TC and H/Ty, a dose escalation of carboplatin will take place for the first 6-12 participants enrolled in this arm. Please refer to section 4.1.1.1 for specific dose escalation rules and definitions.

Table 3: Treatment Arms

Treatment Arm	Treatment Regimen
Arm 1	Docetaxel (75 mg/m2 IV q3 wk), Carboplatin (AUC 6 IV q3 wk), Trastuzumab (6 mg/kg IV q3week) x 6 cycles, followed by definitive breast cancer surgery
Arm 2	Docetaxel (60 or 75 mg/m2 IV q3 wk), Carboplatin [AUC 5 or 6 IV q3 wk (see above Dose Escalation of Carboplatin, section 4.1.1.1)], Lapatinib (1000 mg/day daily throughout cycle) x 6 cycles, followed by definitive breast cancer surgery
Arm 3	Docetaxel (60 or 75 mg/m2 IV q3 wk), Carboplatin [AUC 5 or 6 IV q3 wk (see above Dose Escalation of Carboplatin, section 4.1.1.1)], Trastuzumab (6 mg/kg IV q3 wk) and Lapatinib (1000 mg/day daily throughout 21-day cycle) x 6 cycles, followed by definitive breast cancer surgery

5.5 PROPHYLACTIC MEDICATIONS FOR CHEMOTHERAPY

5.5.1 Antiemetic Prophylaxis

A prophylactic antiemetic premedication regimen utilizing a 5-HT3 antagonist plus a corticosteroid (eg, dexamethasone) is mandatory prior to chemotherapy. Treating investigators should also consider providing participants with a standard antiemetic regimen for the treatment of delayed or breakthrough nausea and/or vomiting.

5.5.2 Steroid Prophylaxis for Docetaxel

Dexamethasone decreases the incidence and severity and delays the onset of late-occurring fluid retention and also may decrease the incidence and severity of acute hypersensitivity reactions.

All subjects must receive a prophylactic steroid regimen prior to each dose of docetaxel. The steroid dosage and regimens are at the discretion of the investigator, based on the subject's concomitant medical conditions (e.g. diabetes). The following are suggested prophylactic steroid regimens:

Dexamethasone 8 mg, orally, 12 hours prior to docetaxel, dexamethasone 10 mg IV just prior the docetaxel infusion, and 8 mg orally 12 hours after docetaxel administration.

> * If a subject has not taken their oral dexamethasone the evening prior to receiving docetaxel, increase the dose of the pre-docetaxel infusion of dexamethasone from 10 mg IV to 15 mg IV.

Dexamethasone 8 mg equivalent may be used (dexamethasone 8 mg = methylprednisolone 40 mg = prednisone 50 mg = prednisolone 50 mg)

5.5.3 Use of prophylactic antibiotics

Primary prophylactic use of antibiotics is *not* mandated but is permitted at the investigator discretion. Prophylactic use of antibiotics ***must*** be used in subsequent chemotherapy cycles for those subjects who have experienced a serious or life-threatening infection only.

5.5.4 Use of prophylactic growth factors

All subjects must receive G-CSF as primary prophylaxis of febrile neutropenia. Peg-filgrastin (Neulasta®) is the recommended product. However, filgrastin (Neupogen®) may be substituted for peg-filgrastin (Neulasta®). The **suggested** doses and schedules for these G-CSF products are as follows:

- Neulasta® 6 mg subcutaneously 24 hours following each cycle of chemotherapy (not to be given greater than 72 hours after chemotherapy dose)
- Neupogen® 300 μg subcutaneously for 5 to 10 days beginning on Day 2 after chemotherapy.

Erythropoietic agents may be used at the discretion of the treating investigator for participants with anemia, according to institutional guidelines.

5.6 CONCOMITANT TREATMENT

Concomitant medications are any prescription medications or over-the-counter preparations used by the patient from 2 weeks preceding run-in cycle until the study completion or early termination visit. All concomitant medications will be recorded in the CRF with indication and dates of administration. The following will be permitted during the study:

• Antiemetics
• Steroid prophylaxis
• Growth factors
• Loperamide for diarrhea
• Diuretics for fluid retention
• Common immunizations, such as influenza vaccine

The following will not be permitted:

• Amifostine

• Dexrazoxane
• Any other investigational agent
• Any other non-protocol anti-tumor therapy

In addition, refer to 5.1.10 for therapies not permitted with lapatinib (Arms 2 and 3)

6.0 DOSE REDUCTIONS AND DELAYS

In general, as detailed below:

- **Treatment may not be delayed greater than 21 days.**
- **Cycles may be delayed for therapy, but not skipped.**
- **When a cycle is held for toxicity, all drugs (chemotherapy, H and Ty) are held to maintain concurrent dosing.**

A dose modification table can be found as Appendix H on page 83 of protocol. Please note that this table is provided as a quick reference tool only and should be used **with** the protocol, and not **instead of** it.

6.1 TC CHEMOTHERAPY DOSE REDUCTIONS & DELAYS

All toxicities will be graded utilizing the NCI Common Toxicity Criteria for Adverse Events (CTCAE), v 3.0 (Appendix B). If toxicity occurs, it will be graded and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Chemotherapy dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity or for conflicting recommendations, follow the most conservative dose adjustment recommended.

All dose modifications and/or reductions will be based on the planned dose, with a maximum allowable treatment delay of 3 weeks or 1 cycle (21 days). Any toxicity necessitating a treatment delay greater than 3 weeks will result in discontinuation of study treatment. Subjects will be evaluated a minimum of weekly when chemotherapy is held due to toxicity.

Chemotherapy doses, which have been reduced due to toxicity, will not be re-escalated with the exception of liver function tests (LFTs) that improve within acceptable treatment ranges.

Table 4 Chemotherapy Dose Modifications

Dose Level	Docetaxel	Carboplatin
0	75 mg/m^2	AUC 6 mg/mL/min
-1	60 mg/m^2	AUC 5 mg/mL/min

Only one dose reduction (of each agent) will be permitted. No dose re-escalations will be permitted except for hepatic toxicity (see 6.1.8)

NOTE: If the dose level for Arm 2 or Arm 3 is determined in the dose escalation cohorts to be carboplatin AUC 5 or docetaxel 60 mg/m2 and a dose reduction is mandated by the development of toxicity, no further dose reductions beyond those doses is allowed and the participant must come off study.

6.1.1 Neutropenia and its complications

6.1.1.1 Neutropenia without fever

On Day 1 of each treatment cycle, subjects must have an ANC $\geq 1.0 \times 10^9$/L. If subject has an ANC less than 1.0 x 10^9/L on Day 1, treatment must be held until ANC has recovered, up to 21 days (1 cycle). If neutropenia has recovered to an ANC $\geq 1.0 \times 10^9$/L by Day 21, decrease docetaxel –1 dose level and continue prophylactic G-CSF support for all subsequent cycles. If neutropenia has not recovered to an ANC of $\geq 1.0 \times 10^9$/L by day 21, the participant should come off study.

6.1.1.2 Febrile Neutropenia

Febrile neutropenia is defined as an oral or tympanic fever of $\geq$ 38.5°C or 101.3°F in the presence of neutropenia (where neutropenia is defined as ANC $<1.0 \times 10^9$/L). See NCI CTCAE, version 3.0 (Appendix B). Hold chemotherapy and immediately initiate appropriate supportive care following the diagnosis of febrile neutropenia. Subjects may require hospital admission if clinically indicated. Recommended therapeutic interventions include:

- CBC with differential and blood cultures
- Initiate empirical antibiotic therapy
- CBC with differential should be done at least every 3 days until recovery of ANC $\geq 1.0 \times 10^9$/L or temperature <38.5°C and must be documented in the CRFs.
- Decrease docetaxel –1 dose level, continue prophylactic G-CSF, and add prophylactic antibiotic support for all subsequent cycles
- Prophylactic Antibiotic Therapy: Oral fluoroquinolone (eg, ciprofloxacin 500 mg, orally, every 12 hours, beginning on Day 5 of each cycle and continue for 5 to 7 days) or alternate antibiotic therapy at the discretion of the investigator. Note: fluoroquinolone is an acceptable antibiotic therapy for participants taking lapatinib. Please refer to Table 2 for prohibited medications while on lapatinib.

6.1.1.3 Second Incidence of Febrile Neutropenia

In the case of a second febrile neutropenia event:
Decrease carboplatin –1 dose level and continue prophylactic G-CSF and antibiotic support for all subsequent cycles

6.1.1.4 Third Incidence of Febrile Neutropenia

In the case of a third event, there will be no further chemotherapy dose reductions. Subject will be taken *off study* and further neoadjuvant therapy will be given at the discretion of the investigator.

6.1.2 Infection with (or without) Neutropenia

For severe (Grade 3) or life-threatening (Grade 4) infection during chemotherapy, with or without neutropenia, all chemotherapy drugs will be reduced one dose level and prophylactic antibiotic therapy with an oral fluoroquinolone will be added for all subsequent cycles (e.g., ciprofloxacin 500 mg, orally, every 12 hours, beginning on Day 5 and continue for 5 to 7 days) or alternate antibiotic therapy at the discretion of the investigator. (Note: fluoroquinolone is an acceptable antibiotic therapy for participants taking lapatinib. Please refer to Table 2 for prohibited medications while on lapatinib.) Treatment must be delayed (up to 3 weeks, 1 cycle/21 days) until subject has recovered from infection. If infection has not recovered after 3 week treatment delay, subject will be taken *off study* and further neoadjuvant therapy will be given at the discretion of the

investigator. Subjects who develop two episodes of grade 3 or grade 4 infection despite G-CSF prophylaxis will not receive further study drug treatment.

6.1.3 Thrombocytopenia

Platelet count must be at least 100,000/mm^3 on Day 1 of a treatment cycle. For platelet count of <100,000/mm^3 on Day 1 of a treatment cycle, hold therapy for up to 3 weeks (21 days, 1 cycle) to allow recovery to platelet count ≥100,000/mm^3. If recovered, reduce chemotherapy dosage(s) by – 1 dose level for this and all subsequent cycles of chemotherapy (see below). If not recovered, participant will be taken off study and further neoadjuvant therapy will be given at the discretion of the treating physician.

6.1.3.1 First incidence of thrombocytopenia – grade 1-3

- Decrease carboplatin –1 dose level

6.1.3.2 Second incidence of thrombocytopenia – grade 1-3

- Decrease docetaxel –1 dose level (and continue carboplatin at –1 dose level)

6.1.3.3 Grade 4 thrombocytopenia

- For first incidence of Grade 4 thrombocytopenia (platelet count <25,000/mm^3) occurring during a cycle, treatment must be held (a maximum of 3 weeks) until platelets have recovered to at least 100,000.
- If after 3 weeks (1 cycle, 21 days) the platelets have not recovered to at least 100,000, participant must be taken off study.
- If *platelets recover to at least 100,000 within 3 weeks, docetaxel and carboplatin must be reduced –1 dose level for all subsequent cycles.*
- Note: platelet count must be at least 100,000 to give next cycle of chemotherapy. If next treatment cycle has been delayed greater than 3 weeks and platelets have not yet recovered to 100,000, participant is taken off study and further further neoadjuvant therapy will be given at the discretion of the treating physician.

6.1.4 Anemia

Recombinant erythropoietin agents for proactive treatment of asymptomatic anemia as evidenced by declining hemoglobin may be administered according to institutional guidelines. For acute symptomatic issues, a blood transfusion may be utilized to maintain a minimum hemoglobin of >9.0 g/dL. For participants developing grade 3 or grade 4 anemia, all chemotherapy drugs should be reduced one dose level and the participant may receive an erythropoietic agent at the investigator's discretion.

6.1.5 Nausea and Vomiting

A prophylactic antiemetic premedication regimen utilizing a 5-HT3 antagonist plus a corticosteroid (eg, dexamethasone) is mandatory prior to chemotherapy (see Section 5.3.1). Subjects experiencing delayed nausea and vomiting should receive an antiemetic therapy based on institutional guidelines.

For ≥Grade 3, clinically significant nausea and vomiting occurring despite an aggressive antiemetic prophylaxis for both acute and delayed emesis, reduce carboplatin by – 1 dose level. For participants in Arms 2 and 3 (lapatinib-arms), refer also to section 6.3.1.1.

6.1.6 Diarrhea (TCH Arm 1 ONLY)

(This section is for management of diarrahea for participants on TCH Arm 1 ONLY. Refer to section 6.3.1.2 for participants on TCTy or TCHTy Arms (Arms 2 and 3) for management of diarrhea)

No prophylactic treatment for diarrhea is recommended. However, in case of ≥Grade 2 diarrhea, the subject should receive treatment with an antidiarrheal regimen, such as loperamide. During subsequent cycles, loperamide should be administered immediately upon the development of diarrhea of any grade. If grade 2 or 3 diarrhea recurs in subsequent cycles despite loperamide use, docetaxel should be reduced one dose level for all subsequent cycles. If grade 3 diarrhea persists despite loperamide use and docetaxel dose reduction, study drug treatment will be discontinued. The development of grade 4 diarrhea will result in the discontinuation of study drug treatment.

6.1.7 Stomatitis, Mucositis, and/or Esophagitis

If ≥ grade 2 stomatitis is present on day 1 of any cycle, treatment should be withheld until stomatitis has resolved to ≤ grade 1. If grade 2 stomatitis and/or esophagitis develops during anytime of the treatment cycle, docetaxel will be reduced one dose level in all subsequent cycles. If grade 3/4 stomatitis and/or esophagitis develops during any time of the treatment cycle, all drugs will be reduced one dose level in all subsequent cycles. The development of grade 3/4 stomatitis and/or esophagitis after a dose reduction will necessitate the discontinuation of study drug treatment.

Table 5 Stomatitis, Mucositis or Esophagitis Dose Modifications

Grade	Chemotherapy Cycle Day 1
Grade 1	No chemotherapy dose reduction is required
Grade 2	Hold chemotherapy for up to 3 weeks until resolved to Grade ≤1. Reduce docetaxel by -1 dose level for all subsequent cycles.
Grade 3/4	Hold chemotherapy for up to 3 weeks until resolved to grade ≤ 1. Reduce carboplatin and docetaxel –1 dose for all subsequent cycles. If Grade 3/4 recurs despite dose reduction, discontinue study treatment.

6.1.8 Hepatotoxicity (Bilirubin and Impaired Liver Function Tests)

Subjects who develop abnormal ALT, AST and/or alkaline phosphatase (Alk Phos) for any reason while receiving docetaxel will have the following dose adjustments:

Table 6 Docetaxel dose modification for elevated LFT results:

	AST or ALT :			
ALK PHOS:	**≤ULN[1]**	**>1x but ≤1.5x ULN**	**>1.5x but ≤5x ULN**	**>5x ULN**
≤ULN[1]	Full Dose	Full Dose	Full Dose	Hold[2]
>1x but ≤2.5x	Full Dose	Full Dose	Reduce Dose[3]	Hold[2]
>2.5x but ≤5x	Full Dose	Reduce Dose[3]	Hold[2]	Hold[2]
>5x ULN[1]	Hold[2]	Hold[2]	Hold[2]	Hold[2]

1. ULN: upper limit of normal
2. Hold chemotherapy for elevated liver function for up to 21 days, if recovered resume therapy with a -1 dose level reduction of docetaxel. If LFTs have not recovered within 21 days, the subject will be taken off all chemotherapy. *("Recovered" is defined as meeting the study baseline eligibility criteria.)*
3. Reduce dose by –1 dose level

In case of recovery of LFTs on the following cycle, the dose may be re-escalated to the previous dose-level at investigator's discretion.

6.1.8.1 Bilirubin

Docetaxel will not be administered to subjects with serum total bilirubin >ULN. Subjects with Gilbert's syndrome, confirmed by genotyping or Invader UGTIA1 molecular assay prior to study entry must have total bilirubin <3X ULN.

6.1.8.1.1 First Incidence of elevated bilirubin

- If serum total bilirubin is >ULN on treatment day, hold chemotherapy until serum total bilirubin is ≤ULN (maximum 21 days) and resume chemotherapy with a docetaxel –1 dose level reduction. If bilirubin has not recovered to within normal limits by day 21, the subject will be taken off study.

6.1.8.1.2 Second Incidence of elevated bilirubin

For a second incidence of serum total bilirubin >ULN on treatment day, hold chemotherapy until serum total bilirubin is ≤ULN for a maximum 21 days.

- If bilirubin has not recovered to within normal limits, the subject will be taken off study. If recovers to within normal limits, resume treatment (continue docetaxel – 1 dose level). If bilirubin is elevated a third time, participant will be taken off study.

6.1.9 Neurotoxicity (peripheral neuropathy) – Docetaxel

No dose modifications are necessary for grade 1 neuropathy. If grade 2 neuropathy (motor or sensory) develops, docetaxel should be reduced (without treatment delay) one dose level for all subsequent cycles. If grade 3/4 peripheral neuropathy (motor or sensory) develops, hold chemotherapy for up to 3 weeks to allow recovery to Grade ≤1. If neurotoxicity has not recovered, the subject will be taken off study treatment. If recovered, decrease docetaxel by -1 dose level for all subsequent cycles

Table 7 Neurotoxicity dose modifications

Neurologic	Grade	Chemotherapy Cycle Day 1
Neuropathy-Sensory *OR* Neuropathy-Motor	Grade 0-1	No docetaxel dose reduction required
Neuropathy-Sensory *OR* Neuropathy-Motor	Grade 2	Reduce docetaxel by -1 dose level for all subsequent cycles, may dose on schedule based on the physician's clinical judgment
Neuropathy-Sensory *OR* Neuropathy-Motor	Grade ≥3	Hold chemotherapy for up to 3 weeks to allow recovery to Grade ≤1, if not off study treatment[1]. If recovered, decrease docetaxel by -1 dose level for all subsequent cycles

[1] If neurotoxicity has not recovered to Grade ≤1, the subject will be taken off study .

6.1.10 Cutaneous Reactions (Arm 1, TCH ONLY)

(Refer to section 6.3.2 for subjects on Arms 2 or 3 (TCTy or TCHTy)

No dose modifications will occur for grade 0-2 cutaneous reactions (such as pruritus, rash, dermatitis, erythema, desquamation or hand-foot syndrome). For grade 3 reactions, TC chemotherapy should be delayed for up to 3 weeks (1 cycle), until recovery to ≤ grade 1. Docetaxel should be reduced one dose level for all subsequent cycles. If the cutaneous reaction does not resolve to ≤ grade 1, study drug treatment will be discontinued. Study drug treatment will be discontinued for all grade 4 cutaneous reactions. Nail changes do not require chemotherapy dose modification.

Table 8 Cutaneous Reaction Dose Modifications

Grade	Chemotherapy Cycle Day 1
Grade 1	No chemotherapy dose reduction is required. Continue treatment as scheduled.
Grade 2	Hold chemotherapy for up to 3 weeks until resolved to Grade ≤1. No chemotherapy dose reduction is required
Grade 3	Hold chemotherapy for up to 3 weeks until resolved to Grade ≤1. Reduce docetaxel by -1 dose level for all subsequent cycles. If cutaneous toxicity has not recovered to ≤Grade 1 within 3 weeks, subject will come off study treatment.
Grade 4	Discontinue study treatment

6.1.11 Fluid retention (peripheral edema and/or effusions)

Docetaxel dose reduction is not required for fluid retention. Subjects developing new onset edema, progression of existing edema, or other signs of fluid retention (e.g., ≥2-pound weight gain) are to be treated with oral diuretics.

Suggested regimens found to be effective in the management of fluid retention due to docetaxel include:

- HCTZ/Triamterene (Dyazide®) 1 capsule, orally, once daily, up to 3 times a day.
- Furosemide (Lasix®) 40 mg, orally, daily if edema progresses despite Dyazide (or generic equivalent) therapy. Potassium supplementation should be given as needed.
- If after a 2-week trial, furosemide 40 mg, orally, once daily, is ineffective, the subject may be treated with furosemide 20 mg, orally, daily plus metolazone (Zaroxolyn®) 2.5 mg, orally, daily with potassium supplementation as needed.

Further docetaxel therapy should be dependent upon the clinical situation. The clinical tolerance of the subject and the medical judgment of the treating investigator will determine if it is in the subject's best interest to continue or discontinue docetaxel treatment.

6.1.12 Medullary Bone Pain - pegfilgrastim (Neulasta)

For Grade ≥3 severe medullary bone pain resulting in uncontrolled pain and/or analgesic usage interfering with activities of daily living: Discontinue pegfilgrastim and utilize an alternative prophylactic G-CSF therapy (eg, filgrastim [Neupogen®] or sargramostim [Leukine®, GM-CSF]) for all subsequent cycles.

6.1.13 Acute Hypersensitivity Reactions (AHR) – Docetaxel

All participants treated with docetaxel must receive steroid prophylaxis to prevent hypersensitivity reactions and fluid retention. Please refer to section 5.5.2 for recommended regimen.

There are no chemotherapy dose reductions for acute hypersensitivity reactions. In the event that a hypersensitivity reaction occurs despite premedication, it is very likely to occur within a few minutes of start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusions, the infusion must be given drop by drop for the first 5 minutes, and a careful evaluation of general sense of well being and whenever possible blood pressure and heart rate monitoring will be performed so that immediate intervention would occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation will be immediately available including: antihistamine, corticosteroids, aminophylline, epinephrine. If a reaction occurs, the specific treatment that is medically indicated will be instituted. In addition, it is recommended to take the measures listed below:

Table 9 Management of docetaxel acute hypersensitivity reactions

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	• Consider decreasing the rate of the docetaxel infusion until recovery from symptoms, stay at bedside and monitor subject • then, complete docetaxel infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	• **Hold** docetaxel infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor subject until resolution of symptoms • resume docetaxel infusion after recovery of symptoms; depending on the physician's assessment of the subject, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, *(e.g., infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, then finally, resume at the initial planned rate.* • depending on the intensity of the reaction observed, additional oral or IV pre-medication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to initial planned rate, *(eg, infuse at a 4-hour rate for 3 minutes, then at a 2-h rate for 3 minutes, then at a 1-h rate for 3 minutes, and finally, administer at the initial planned rate.)*
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	• **immediately discontinue docetaxel infusion** • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor subject until resolution of symptoms • the same treatment guidelines outlined under moderate symptoms (ie, the third and fourth bullets) should be followed.
Anaphylaxis (NCI Grade 4 reaction)	• **NO further docetaxel therapy should be infused**[1]

[1] If Grade 4 anaphylaxis occurs the subject will be off study treatment

6.1.14 Other Non-Hematologic Toxicities

Other clinically significant adverse effects should be managed symptomatically as medically appropriate. For other clinically significant Grade 3 toxicities (except anemia or nail changes), further treatment should be withheld for a maximum of 3 weeks (1 cycle) until the toxicity resolves to Grade ≤1, then reinstituted as medically appropriate. If the toxicity does not resolve to ≤ grade 1, study drug treatment will be discontinued. The offending chemotherapy agent(s) should be reduced -1 dose level for all subsequent cycles. Study drug treatment will be discontinued for all grade 4 toxicities.

6.2 DOSE REDUCTIONS AND DELAYS FOR TRASTUZUMAB (ARMS 1 & 3)

6.2.1 Dose Reductions and Dose Delays

No dose reductions will be permitted for the assigned dose of trastuzumab *(except for recalculation of dose in cases of significant weight change, as per section 5.3)*.

In the event the administration of TC chemotherapy is delayed, the administration of trastuzumab should be delayed to maintain a concurrent dosing schedule for all agents, i.e. trastuzumab should be delayed and administered on the day chemotherapy is administered. If trastuzumab is held, no reloading dose is necessary when treatment is resumed. Participants discontinuing TC therapy will be removed from study and will not receive further trastuzumab on study.

6.2.2 Treatment Modification Due to Adverse Events

Study drug treatment will be modified, and toxicities managed, according to the guidelines in Table 11. Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment delay is 3 weeks.

6.2.3 Trastuzumab Infusion Related Adverse Events

During the first infusion with trastuzumab, chills, and/or fever are commonly observed. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity and occur infrequently with subsequent trastuzumab infusions. These infusion-related symptoms may be treated with an analgesic/antipyretic such as meperidine/pethidine or acetaminophen/paracetamol, or an antihistamine such as diphenhydramine. Some adverse reactions to trastuzumab infusion, including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress, can be serious and potentially fatal. The majority of these events occur during or shortly after of the start of the first infusion. Subjects who experience severe or moderate infusions symptoms may be managed by slowing or stopping the trastuzumab infusion and supportive therapy with oxygen, beta agonists, antihistamines, and corticosteroids.

If a Grade 3 or 4 toxicity occurs during the post-infusion observation period, the subject must be evaluated for a minimum of 1 hour from the time the toxicity was first noticed until resolution of any observed severe symptoms.

Sometimes subjects will experience symptoms after the infusion is complete. Subjects should be warned of the possibility of delayed reactions and should be instructed to contact their physicians if they experience any symptoms throughout the study.

Subjects who experience a trastuzumab infusion-related adverse event should receive prophylactic treatment with antihistamines and/or corticosteroids prior to all subsequent trastuzumab infusions (refer to the trastuzumab/Herceptin® package insert for specific prophylactic premedication recommendations).

6.2.4 Cardiac dysfunction

Refer to Section 7.0

6.2.5 Pneumonitis
Refer to section 6.3.4

6.3 DOSE REDUCTIONS AND DELAYS FOR LAPATINIB (ARMS 2 & 3)

6.3.1 Gastrointestinal adverse events
If GI adverse events are not appropriately managed, they may be associated with the development of dehydration. Management of gastrointestinal adverse events is discussed in detail in below.

6.3.1.1 Nausea, vomiting, or both
In subjects who have emesis and are unable to retain lapatinib, every attempt should be made to obtain control of nausea and vomiting.

6.3.1.2 Diarrhea
Diarrhea can be debilitating, and on rare occasions, it is potentially life-threatening. Based on experience with lapatinib alone or in combination with taxanes and/or trastuzumab, diarrhea should be managed proactively to avoid complications or worsening of the participant's condition. Guidelines developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea are abstracted below. These broad general management principles are recommended to avoid more serious complications. Guidelines such as these should never replace sound clinical judgment. These general management principles do not address comprehensive management of more serious or protracted diarrhea syndromes.

6.3.1.2.1 Uncomplicated grade 1-2 diarrhea
- Advise subject to stop all lactose containing products, drink 8-10 large glasses of clear liquids a day and eat frequent small meals;
- Grade 2 diarrhea consider dose reduction of lapatinib (discuss with study principal investigator);
- Administer standard dose of loperamide:
    - Initial dose 4mg followed by 2mg every 4 hours or after every unformed stool.
    - Continue loperamide until diarrhea free for 12 hours.

6.3.1.2.2 Grade 3 or 4 diarrhea or complicated grade 1 or 2 diarrhea
(Complicating features: severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, grade 3 or 4 neutropenia, frank bleeding, dehydration):
- Intravenous fluids as appropriate, consider hospital admission;
- Prophylactic antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or grade 3-4 neutropenia (Note: fluoroquinolone is an acceptable antibiotic therapy for participants taking lapatinib. Please refer to Table 2 for prohibited medications while on lapatinib);
- Hold next dose of TC chemotherapy [next cycle may be delayed up to three weeks (21 days, 1 cycle)] and stop lapatinib until diarrhea ≤ grade 1.
- If diarrhea resolves to ≤ grade 1, resume lapatinib on Day 1 of next cycle at dose of 750 mg po QD and reduce docetaxel by –1 dose level for next and all subsequent cycles.

- If subject has already had dose reduction in lapatinib and docetaxel and has recurrent complicated grade 1/2 diarrhea or grade 3/4 diarrhea, participant must come off study treatment.

- Other pharmacological approaches include the following:
- Loperamide, administered as an initial 4-mg dose, followed by 2-mg doses every 4 hours. This dose and regimen are moderately effective.
- Clonidine, non-steroidal anti-inflammatory drugs, and the serotonin antagonist cyproheptadine have been shown to be effective in controlling diarrhea associated with inflammation of the bowel.
- The synthetic octapeptide, octreotide, has been shown to be effective in the control of diarrhea induced by fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered at doses ranging from 100 μg twice daily to 500 μg 3 times daily, with a maximum-tolerated dose of 2000 μg 3 times daily in a 5-day regimen.

6.3.2 Cutaneous Reactions

Significant skin adverse events (Grade 3 or more) resulting from lapatinib are rare (1-3%).

For NCI-CTCAE v3.0 Grade 4 rashes, such as those manifested as toxic epidermal necrolysis (i.e. Stevens-Johnson's Syndrome etc) lapatinib must be permanently discontinued and participant should come off study.

For grade 3 reactions, lapatinib and chemotherapy should be delayed for up to 3 weeks (1 cycle), until recovery to ≤ grade 2. If recovery to ≤ grade 2, lapatinib may be resumed with next cycle at same dose. If the cutaneous reaction does not resolve to < grade 3, study drug treatment should be discontinued.

No dose modifications will occur for grade 0-2 cutaneous reactions (such as pruritus, rash, acne, dry skin, dermatitis, erythema, desquamation or hand-foot syndrome). Subjects with poorly tolerated skin adverse events may be successfully managed by providing a brief (up to 14 days) therapy interruption at the investigator's discretion; the daily dose of lapatinib should then be reinstated. However, the rash may improve without the need for interrupting therapy with lapatinib. Of note in current studies, many subjects were able to resume lapatinib therapy at the same dose after resolution of rash, and they then had less extensive and/or severe rashes. A variety of agents can be used to manage skin rashes. These include mild-to-moderate strength steroid creams, topical or systemic antibiotics, topical or systemic antihistamines, and occasionally, retinoid creams

There is no standard, known, or established treatment proven effective for drug-related skin rashes or changes due to lapatinib. If the rash is severe (1-3%) then most commonly, a papular/pustular rash has been observed, which frequently improves even though the same dose of lapatinib therapy is continued uninterrupted. The need for oral or topical antibiotics is a clinical decision of the investigator and should be preceded by a culture of affected areas and, if indicated, a dermatology consultation. Oral retinoids should not be given because of theoretical concerns about negatively affecting the lapatinib mechanism of action. Oral steroids are also strongly discouraged. Other

options for treatment of significant rashes may be determined upon consultation with dermatologist.

Table 10 Cutaneous Reaction Dose Modifications

Grade	Chemotherapy Cycle Day 1
Grade 1	No lapatinib or chemotherapy dose reduction is required. Continue treatment as scheduled.
Grade 2	Symptomatic management, lapatinib may be held at investigator discretion for up to 3 weeks.
Grade 3	Hold lapatinib and chemotherapy for up to 3 weeks until resolved to Grade ≤2. If cutaneous toxicity has not recovered to ≤Grade 2 within 3 weeks, subject will come off study treatment.
Grade 4	Discontinue study treatment

6.3.3 Cardiac dysfunction
Refer to section 7.0

6.3.4 Pneumonitis
If a participant develops symptoms suggestive of interstitial pneumonitis, adult respiratory distress syndrome (ARDS), or non-cardiogenic pulmonary edema, lapatinib and/or trastuzumab therapy should be interrupted and a thorough evaluation performed. If NCI-CTCAE v3.0 Grade 3 or 4 pneumonitis/fibrosis or pulmonary infiltrate is confirmed (and the relationship to lapatinib and/or trastuzumab cannot be excluded), lapatinib and/or trastuzumab must be permanently discontinued and subject taken off study. All incidences of grade 3 or 4 interstitial lung disease/ interstitial pneumonitis must be reported as serious adverse events (SAEs).

6.3.5 Other toxicities possibly related to lapatinib
For any other toxicity where causality related to the administration of lapatinib is uncertain, the investigator should contact the study prinicipal investigator to determine the possibility of any modifications of lapatinib.

7.0 CARDIAC SAFETY

7.1 CARDIAC MONITORING

- All participants must have a baseline evaluation of cardiac function including a measurement of LVEF by either MUGA or echo a maximum of 14 days prior to run in cycle. Only subjects with a normal (no less than lower limits of normal for institution) LVEF should be enrolled in the study.
- Echocardiography must be performed under the supervision of a cardiologist. The guidelines of the American Society of Echocardiography will be used.
- The method used for LVEF assessment in an individual participant should be the same throughout the trial.
- Subsequent scheduled LVEF assessments must be performed between cycle 3 and 4 of chemotherapy (at approximately week 13 of study) and then 28 days prior to surgery.

- During the course of trastuzumab and/or lapatinib therapy, subjects should be monitored for signs and symptoms of CHF (ie, dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain).
- In addition, any participant who develops clinical signs or symptoms of cardiac failure should undergo an LVEF assessment and an ECG;

7.2 DEFINITIONS OF CARDIAC ENDPOINTS

7.2.1. Primary cardiac endpoint

- **Cardiac death** defined as either:
  - Cardiac death due to heart failure, myocardial infarction or arrhythmia;
  - Probable cardiac death defined as sudden, unexpected death within 24 hours of a definite or probable cardiac event.
- **Severe symptomatic congestive heart failure** defined as NYHA Class III or IV (Class III defined as being not capable of climbing one flight of stairs and Class IV defined as having symptoms at rest) and a drop in left ventricular ejection fraction (LVEF) of more than 10 points from baseline **and** to below the institutional lower limit of normal. In these cases, there is NO need to perform a confirmatory second LVEF assessment. The method used for LVEF assessment should be the same method as used for the baseline assessment. (See management below, section 7.4)

7.2.2 Secondary cardiac endpoints

- Defined as an asymptomatic (NYHA I) or mildly symptomatic (NYHA II) significant drop in LVEF, confirmed by a second LVEF assessment within approximately three weeks showing also a significant drop. A significant LVEF drop is defined as an absolute decrease of more than 10 points below the baseline LVEF **and** to below the institutional lower limit of normal. The method used for LVEF assessment should be the same method as used for the first (baseline) assessment.

7.3 HOLDING AND DISCONTINUATION RULES

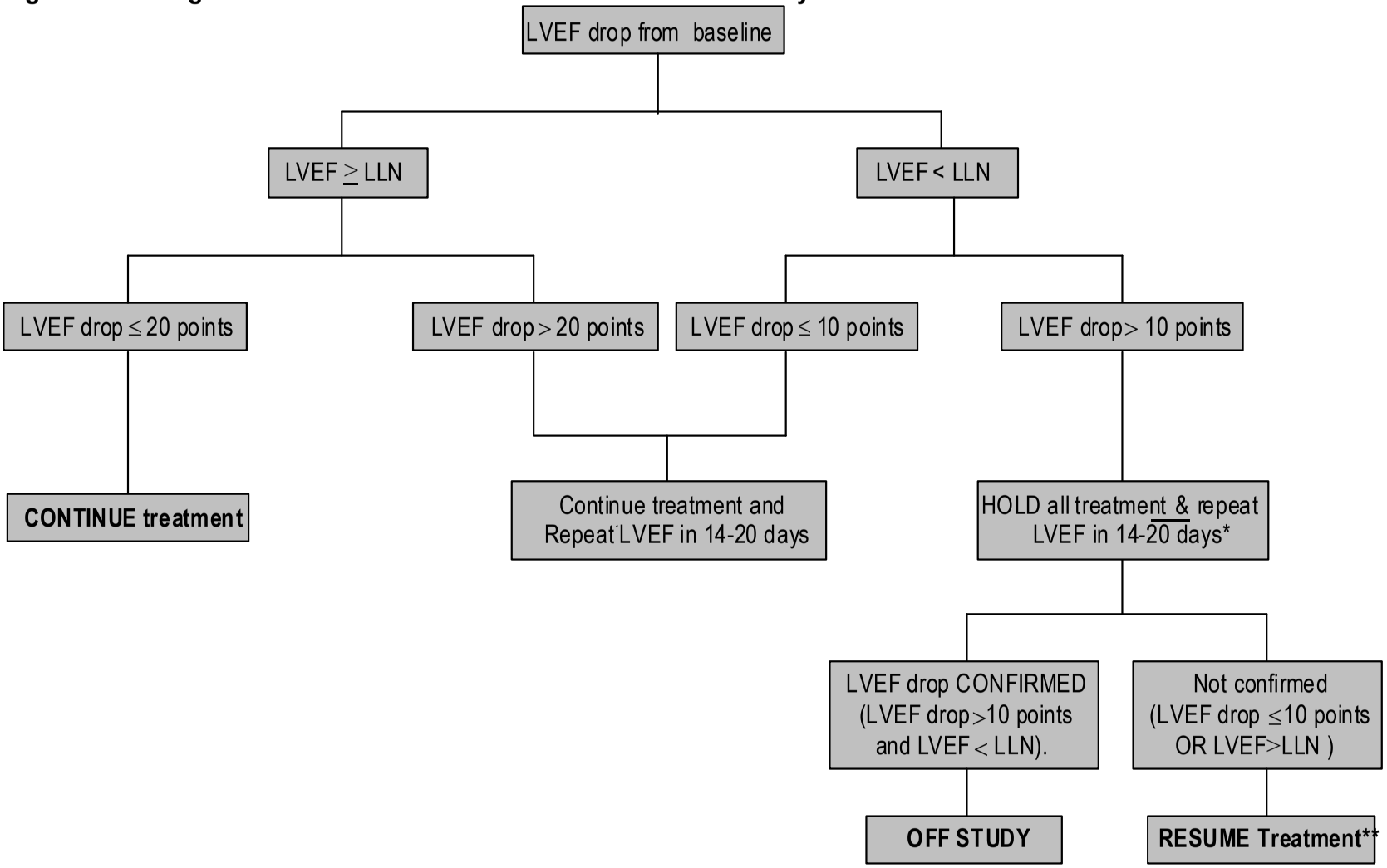
- Treatment with trastuzumab, lapatinib or both will be permanently stopped if a participant develops a **primary cardiac event** or a **secondary cardiac event** confirmed.
- The result of an LVEF assessment must be available prior to subsequent administration of cancer treatments. The decision to administer or to hold is based on the algorithm on Figure 1.

Note: LVEF results from ECHO or MUGA should be obtained and reviewed within 24 hours of assessment so treatment can be held if significant drop in EF is detected. Because participants on Arms 2 and 3 are taking Lapatinib daily, obtaining results should not be postponed until just prior to the next scheduled clinic visit as this delay may pose a safety risk to the participant.

7.4 MANAGEMENT OF SYMPTOMATIC CARDIAC CHANGES

Subjects who develop signs and symptoms of CHF should have trastuzumab and/or lapatinib stopped (see section 7.3) and should receive treatment for CHF following established medical guidelines such as the Heart Failure Society of America (HFSA), Recommendations for Pharmacological Therapy for Left Ventricular Systolic Dysfunction. Potential medical interventions include therapy with ACE inhibitors, angiotensin-II receptor blockers, β-blockers, diuretics, and cardiac glycosides, as required. It is strongly recommended that participants who have symptomatic decreases in LVEF or those who meet the criteria for stopping treatment seek cardiologic consultation for advice on potential treatment for their cardiac dysfunction.

Figure 1 Algorithm for continuation and discontinuation of study treatment based on interval LVEF assessments



LLN: Institutional lower limits of normal
*** Refer to page 24. This drop must be reported as an SAE.**
****If treatment resumed after hold, LVEF must be rechecked day 17-20 after next treatment given. If LVEF again drops and algorithm requires a second hold, patient must come OFF STUDY.**
Note: There is no data supporting routine cardiac monitoring of LVEF as a predictor of eventual development of cardiac toxicity for trastuzumab or lapatinib.

8.0 STUDY ASSESSMENTS AND PROCEDURES

8.1 REGISTRATION, RANDOMIZATION, AND STUDY TIMELINES

A signed, written informed consent form must be obtained prior to screening assessments and any study specific procedures are initiated. All eligible participants must be registered with Translational Oncology Research International (TORI) in Los Angeles, CA, USA prior to the start of therapy. Registration forms must be faxed to the TORI offices and will include the following information:

- Protocol number
- Investigator's name and center
- Participant identifiers (initials and date of birth)
- Checklist verifying inclusion and exclusion criteria
- Confirmation of HER2 status by FISH or SISH

Each investigator will be responsible for enrolling only those participants who have met protocol eligibility criteria.

First twenty (20) eligible participants will be assigned to Arm 3 (TCHTy) to assess the safety of the combination of the 4 agents. After first twenty (20) participants have been enrolled to Arm 3(TCHTy), one-hundred twenty (120) participants will be randomized through the sponsor (TORI) according to a pre-specified randomization algorithm to receive either docetaxel, carboplatin, trastuzumab (TCH, Arm 1) or TC plus lapatinib (TCTy, Arm 2) or TCHTy (Arm 3). The randomization will be stratified by baseline tumor size ($\leq$ 3 and > 3 cm) and by hormone receptor status (ER and/or PR positive versus ER and PR negative).

All study procedures/treatments must occur within the following time periods (also refer to the Study Schema):

- All cycles are 21 days (3 weeks) with a +/- 3 days window, in duration.
- Run-In Cycle will be followed by six cycles of TCH, TCTy or TCHTy (Cycles 1 to 6).
- All screening studies and procedures must be performed within the window listed in Table 11.
- Definitive surgery should occur 28-42 days after Day 1 of Cycle 6 with full recovery from the toxicity of chemotherapy.
- The end of study/withdrawal visit should occur 28 days ± 7 days after study drug completion or treatment discontinuation.

8.2 SCREENING ASSESSMENTS

The following will be obtained at screening:

Table 11 Screening Assessments

Assessment	Explanation	Timing
Informed consent	Signed	Within 30 days prior to run-in cycle
Medical history	General medical history including prior and concomitant conditions and medications; tumor history including date of diagnosis, histology, stage, all prior therapy, hormone receptor status, and HER2 status (if known); history of all baseline toxicities	Within 28 days prior to run-in cycle
Physical examination	Complete physical exam including vital signs, Height, weight, BSA determination, NYHA, and ECOG performance status	Within 14 days prior to run-in cycle
Echocardiogram or MUGA	Evaluation of ejection fraction Using the same method throughout the entire study	Within 28 days prior to run-in cycle

Hematology	Complete blood count including differential	Within 14 days prior to run-in cycle
Standard chemistry	Sodium, potassium, chloride, bicarbonate, creatinine, total bilirubin, AST, ALT, alkaline phosphatase	Within 14 days prior to run-in cycle
Pregnancy test	Serum or urine, for women of childbearing potential	Within 14 days prior to run-in
Her2/neu status	By FISH or SISH	Prior to run-in cycle
Hormone receptor status	By immunohistochemistry	Prior to run-in cycle
Tumor status	Documentation of clinical tumor status by physical examination (unidimensional measurements) at time of entry including all measurable or evaluable disease	Within 14-days prior to run-in
Radiologic assessment to exclude metastases	Not-mandatory. To be performed as clinically indicated	Prior to run-in cycle
Core biopsies	Snap frozen & paraffin embedded, See Appendix C for collection requirements.	Prior to run-in cycle
Concomitant medications	See concomitant medications 5.1.10 and 5.6	14 days prior to run-in cycle

8.3 ASSESSMENTS DURING RUN-IN CYCLE

The following assessments and procedures will be performed during the run-in cycle:

Table 12 Assessments during Run-In Cycle

Assessment	Explanation	Timing
Medical history	History since prior exam	Day of infusion or up to 7 days prior to infusion. (If screening history done within 7 days prior to run-in cycle, no need to repeat.)
Physical examination	Limited physical exam, including vital signs, weight, and ECOG performance status	Day of infusion or up to 7 days prior to infusion. (If screening physical done within 7 days prior to run-in cycle, no need to repeat.)
Tumor status	Documentation of clinical tumor status by physical examination (unidimensional measurements)	Day of infusion or up to 7 days prior to infusion. (If tumor status assessed within 7 days prior to run-in cycle, no need to repeat.)
Core biopsies	Snap frozen and paraffin embedded See Appendix C for collection requirements	14-21 days after run-in cycle started
Concomitant medications	See concomitant medications 5.1.10 and 5.6	Day of infusion or up to 7 days prior to infusion (If concomitant medications recorded at screening visit within 7 days prior to run-in cycle, no need to repeat, as long as no change in meds.)
Lapatinib and/or trastuzumab administration	See Study Treatment	Day 1 of run-in cycle for trastuzumab Day 1 through Day 21 of run-in cycle for Lapatinib

8.4 ASSESSMENTS DURING CHEMOTHERAPY

Table 13 Assessments During Chemotherapy (Cycles 1-6)

Assessment	Explanation	Timing
Medical history	History since prior exam	Every 21 days (day of infusion or up to 10 days prior to infusion)
Physical examination	Limited physical exam, including vital signs, BSA determination, and ECOG performance status	Every 21 days (day of infusion or up to 10 days prior to infusion)
Echocardiogram or MUGA	Evaluation of ejection fraction to be performed MANDATORY between cycle 3 and 4, and to be performed during the cycles if clinically indicated otherwise, using the same method throughout the entire study	MANDATORY Between cycle 3 and 4 of chemotherapy and During the cycles if clinically indicated
Hematology	Complete blood count, including differential	Day of infusion or within 10 days prior. If done on same day, **infusion must not be given until lab results are reviewed.**
Standard chemistry evaluation	Sodium, potassium, chloride, bicarbonate, creatinine, total bilirubin, AST, ALT, alkaline phosphatase	Day of infusion or within 10 days prior. If done on same day**, infusion must not be given until lab results are reviewed.**
Tumor status	Documentation of clinical tumor status by physical examination (unidimensional measurements)	Every 21 days (day of infusion or up to 10 days prior to infusion)
Concomitant medications	See concomitant medications 5.1.10 and 5.6	Every 21 days (day of infusion or up to 2 days prior to infusion)
Adverse events	See Safety	Every 21 days (day of infusion or up to 10 days prior to infusion)
TCH or TCTy or TCHTy administration	See Study Treatment	Day 1 of each cycle for T, C and H Day 1 through Day 21 of each cycle for Ty

8.5 ASSESSMENTS AT END OF CHEMOTHERAPY/PRESURGICAL VISIT

The following assessments and procedures will be performed at the conclusion of chemotherapy, prior to definitive surgery (if surgery is to be performed) or radiotherapy. Cycle 6 data may be used if it is within window:

Table 14 Assessments at End of Chemotherapy/Presurgical Visit

Assessment	Explanation	Timing
Medical history	History since prior exam	Within 28 days prior to surgery
Physical examination	Limited physical exam, including vital signs, weight and ECOG performance status	Within 28 days prior to surgery
Echocardiogram or MUGA	Evaluation of ejection fraction Using the same method throughout the entire study	Within 28 days prior to surgery

Hematology	Complete blood count including differential	Within 28 days prior to surgery
Standard chemistry evaluation	Sodium, potassium, chloride, bicarbonate, creatinine, total bilirubin, AST, ALT, alkaline Phosphatase	Within 28 days prior to surgery
Tumor status	Documentation of clinical tumor status by physical examination.	Within 28 days prior to surgery
Tumor Tissue	Snap frozen & paraffin embedded. See Appendix C for collection requirements	At the time of definitive surgery
Pathologic assessment**	Evaluation of tumor specimen in participants undergoing mastectomy or breast conserving procedure to determine response (pCR)	At the time of definitive surgery
Concomitant medications	See Concomitant Medications	Within 28 days prior to surgery
Adverse Events	See Safety	Within 28 days prior to surgery

*For participants whose tumors remain inoperable, repeat core biopsies or an incisional biopsy may be obtained 4 weeks $\pm$ 1 week after the last chemotherapy is administrated with full recovery from the toxicity of chemotherapy and prior to the administration of additional therapy.

**For participants who need to come off study prior to completion of 6 cycles of chemotherapy (e.g., for toxicity or PD), we will still obtain 4 tumor tissue samples (3 snap frozen and 1 parrafin block) as well as a copy of the pathology report.

8.6 ASSESSMENTS AT POST-SURGICAL VISIT/END OF STUDY/EARLY WITHDRAWAL

The following assessments will be performed at 28 days ± 7 days after surgery (if surgery is performed) or from the time of study withdrawal/discontinuation for any reason.

Table 15. Assessments at Post-Surgical or EOS Visit

Assessment	**Explanation**
Medical history	History since prior exam
Physical examination	Limited physical exam, including vital signs, weight, wound assessment and ECOG performance status
Hematology	Complete blood count & differential
Standard chemistry evaluation	Sodium, potassium, chloride, bicarbonate, creatinine, total bilirubin, AST, ALT, alkaline phosphatase
Concomitant medications	See Concomitant Medications, including treatment initiated post surgery, e.g. radiotherapy or endocrine therapy, if applicable
Adverse events	See safety

8.7 CLINICAL EFFICACY ASSESSMENT

The response to treatment will be determined by evaluating both the clinical objective response rate and, in those who undergo mastectomy or a breast-conserving procedure, the pathologic complete response rate.

8.7.1 Assessment of Response by Physical Examination or an Imaging Test

The RECIST criteria will be used to evaluate the clinical objective response to therapy. A summary of the RECIST criteria is found in Appendix D.

8.7.2 Assessment of Pathologic Response

A pathologic complete response will be defined as the absence of viable tumor cells in the resected specimen, including axillary lymph node sample, as determined by standard histologic examination. The pathology report of definitive surgery will be centrally reviewed to confirm the response. The tumor pCR rate will be determined for both the intent to treat population (which includes all participants who receive a dose of study drug, regardless of whether they complete all protocol-specified therapy) and for the evaluable participant population (which includes only those participants who complete the protocol-specified pre-surgical therapy and undergo mastectomy or a breast-conserving procedure). Pathology reports from definitive surgery will be centrally reviewed for all participants enrolled on study who received at least one dose of study drug regardless of whether participant completes protocol-specified therapy.

9.0 SAFETY

The investigator is responsible for the detection and documentation of events meeting the criteria and definitions of an Adverse Event (AE) or Serious Adverse Event (SAE).

9.1 DEFINITION OF AN ADVERSE EVENT (AE)

An AE is any undesirable sign, symptom, or medical condition occurring after starting study treatment, even if the event is not considered to be related to study treatment. This can include any physical or clinical change experienced by the participant whether or not considered related to the use of the study drug. An adverse event can therefore be any unfavorable or unintended sign, symptom or disease (including the onset of new illness and the exacerbation of pre-existing conditions) temporally associated with the use of the study treatment. In this protocol, study treatment refers to TCH, TCTy or TCHTy.

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

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition
- New conditions diagnosed or detected after study treatment administration, even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose

Examples of an AE do not include:

- Medical or surgical procedure (the condition that leads to the procedure is an AE)
- Anticipated day-to-day fluctuations of pre-existing diseases or conditions present or detected at the start of the study that do not worsen
- Progression of the disease/disorder being studied, unless more severe than expected for the subject’s condition

9.1.1 Definition of an abnormal laboratory value adverse event

Investigators must document their review of each laboratory report by signing or initialing and dating each report page. The abnormal laboratory values that are clinically significant should be indicated on the report by the investigator.

If the abnormal values are clinically relevant, the values will be considered as adverse events and are to be recorded on the Adverse Events Case Report Form page. The values:

- Require dose modification or interruption of study drug
- Require discontinuation from study;
- Lead to clinical symptoms/signs;
- Require therapeutic intervention
- Are related to study drug/concomitant medications or therapies.

9.2 DEFINTION OF A SERIOUS ADVERSE EVENT (SAE)

In the event of a serious adverse event (SAE) the first concern will be for the safety of the subject. Investigators are required to report to TORI Central Administration ANY SAE or serious treatment emergent adverse event (STEAE) as soon as possible.
An SAE or STEAE is any sign, symptom or medical condition that emerges during study drug treatment or during a post-treatment follow-up period that (1) was not present at the start of study drug treatment and it is not a chronic condition that is part of the participant's medical history, OR (2) was present at the start of study drug treatment or as part of the participant's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening (subject was at immediate risk of death at the time of the event)
- Requires in-patient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly or birth defect
- Is medically significant, in that is may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

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

9.3 REPORTING OF ADVERSE EVENTS

MedWatch/IND Alert Safety reports are required to be immediately distributed to all investigators by the study sponsors. These Safety Reports, as well as any participant adverse event which meets the requirements of a **serious adverse event** must be reported to TORI and to appropriate Health Regulatory Authorities, the appropriate Institutional Review Board/Ethics Committee and/or reported in accordance with local law/regulations. The Investigator is required to keep documentation of such notification/submission at the trial site and must provide copies to TORI.

All **serious adverse events**, whether or not deemed drug-related or expected, must be reported to TORI by the Investigator immediately or within 24 hours (one working day) by telephone for US sites. A written report must follow within 10 working days, which includes a full description of the event and any sequelae. This includes SAEs that occur anytime while enrolled in the active phase of study treatment or 30 days past the end of therapy or withdrawal visit. All SAE's should be recorded on a MedWatch 3500 form (www.fda.gov/medwatch/getforms.htm) in English and faxed to:

TORI Central Administration
ATTN: Protocol TRIO TORI B-07
Fax: 1-310-794-5517
Phone: 1-310-794-6500

In addition, all MedWatch 3500 form should be submitted to the appropriate IRB/EC for those participating sites that are not using Western Institutional Review Board.
TORI will immediately forward reports to

1) Sanofi-Aventis by **FAX** or **EMAIL** to Sanofi-Aventis Pharmaceuticals Global Pharmacovigilance and Epidemiology Department
   Fax: (908-231-4827) **FAX transmission will include the following on the provided IIT SAE REPORT, fax cover form (below):**
   Investigator-Initiated (IIT #) study number:_____
   Study Title:_____
   Name of Principal Investigator:_____

   E-mail: GPEmailbox@sanofi-aventis.com **E-Mail transmission should include the following:**
   Investigator-Initiated (IIT #) study number:_____
   Study Title:_____
   Name of Principal Investigator:_____

And to:

2) GlaxoSmithKline by **EMAIL**
   E-mail: loren.h.nakamura@gsk.com **E-Mail transmission should include the following:**
   Investigator-Initiated (IIT #) study number:_____
   Study Title:_____
   Name of Principal Investigator:_____

3) For TORI Clinical Research Specialist, not for participating sites:

sanofi-aventis Pharmaceuticals
Global Pharmacovigilance and Epidemiology
200 Crossing Boulevard
P.O. Box 6890
Mailstop BX4 – 412-i
Bridgewater, NJ 08807
Fax: 908-231-4827

sanofi-aventis Pharmaceuticals Inc.

Fax IST SAE REPORT

To: Global Pharmacovigilance and Epidemiology

Fax: 908-231-4827	
Date:	Pages:
From:	Phone:

IIT#: Insert IIT study #	
Study Title: Insert study title	
PI Name: Insert PI name	
Causality:	*All serious, related adverse events will be reported and documented on MedWatch Form FDA 3500A (www.fda.gov/medwatch/getforms.htm) and forwarded directly to sanofi-aventis Pharmaceuticals. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.* **For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.**
Check one:	
	Unrelated: The adverse event is clearly NOT related.

	Unlikely to be related: The adverse event is doubtfully related.
	Possibly related: The adverse event may be related.
	Probably related: The adverse event is likely related.
	Definitely related: The adverse event is clearly related.

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.

9.4 GRADING OF ADVERSE EVENTS

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0 (Appendix B).
For AEs which are not covered by the NCI CTCAE grading system, the following terminology will be used:

- Mild – awareness of sign, symptom, or event, but easily tolerated
- Moderate – discomfort severe enough to cause interference with usual activity and which may warrant intervention
- Severe - incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention such as hospitalization
- Life-threatening – immediate risk of death

9.5 MONITORING OF ADVERSE EVENTS

Participants having adverse events will be monitored with relevant clinical assessments and laboratory tests as determined by the Investigator. All adverse events must be followed to satisfactory resolution or stabilization of the event(s). Any actions taken and follow-up results must be recorded on the appropriate page of the Case Report Form, as well as in the participant's source documentation. Follow-up laboratory results should be filed with the participant's source documentation.

9.6 IMMEDIATE REPORTING TO THE SPONSOR

Adverse Events and Serious Adverse Events that meet criteria for immediate reporting, as defined by TORI must be immediately reported to TORI.

9.7 REPORTS OF PARTICIPANT DEATH

The death of any participant during the active treatment phase of study or within 30 days of last dose of study drug, regardless of the cause, must be reported within 24 hours by telephone and fax to TORI. A written report must follow as soon as possible. If an autopsy is performed, the report must be provided. Reports of these events must also be made to the appropriate Institutional Review Board and/or reported in accordance with local law/regulations. The Investigator must keep documentation of such notification/submission at the trial site and must provide copies to the sponsor.

9.8 PERIOD OF OBSERVATION

The period of observation for collection and reporting of adverse events for this study is the interval between when the subject starts study treatment and 30 days after the last receipt of any study treatment (TCH, TCTy or TCHTy) or a protocol-specified follow-up visit. If an SAE occurs after the period of observation

expires, the Investigator should contact TORI to determine how the SAE should be reported. In general, late fatal complications or conditions of medical importance should be documented and reported as an SAE.

10.0 STATISTICAL METHODS AND CONSIDERATIONS

10.1 GENERAL CONSIDERATIONS

This trial is a pilot study to define estimates and do exploratory treatment comparisons, thus it is designed to assess each treatment arm independently, as the purpose of randomization is mostly administrative to avoid selection bias with no intent on comparing the arms directly. The small sample size typical for phase II studies likely precludes the viability of inferential statistics, but the descriptive information may provide valuable insights that will receive additional evaluation if larger studies are conducted. The arms administering only the single biological agent will be used to help confirm a range of interesting response rates for the TC-H treatment or screen for activity the TC-Ty treatment.

10.2 SAMPLE SIZE DETERMINATION

We plan to combine the data from our trial (N=130) with the data from a nearly-identical trial (Ireland, n=80); the statistical plan will remain unchanged. Before combining the two data sets, patients' characteristics and pCR for the two trials will be compared. If there has no significant difference, the two sets of data will be combined.

The primary endpoint is pathologic complete response (pCR) rate. Based on literature, the pCR rate is about 40% for single biological agent treatment (trastuzumab) combined with multi-agent chemotherapy (TCH) [21, 22 26, 27]. We anticipate that the combination biological arm TCHTy (trastuzumab-lapatinib combined with multi-agent chemotherapy) will improve the pCR rate by incremental 20%. The primary objective of this trial is to confirm that such a difference truly exist using historical data as a reference. A sample size of 56 evaluable participants is required to detect an absolute 20% difference in the pCR rate between the experimental treatment (with hypothesized 60% pCR rate) and the historical-control pCR rate (of ~ 40%) with a nominal one-sided 0.05 significance and 90% power using the exact binomial method [52]. Assuming a 5-10% non-evaluability rate typical for such pilot studies, 60 participants are planned to be enrolled for the experimental TCH-L arm of this study. 40 participants will be randomized to each of the single biological agent arm, thus 140 participants total will be enrolled into this study. An unbalanced randomization is implemented in this study (with twenty additional participants in the TCH-L arm vs. the single biological agent arms) to gather safety information and perform biomarker analysis on the most interesting combination biological treatment.

As a consequent secondary efficacy analysis, the pCR rates will be also compared between the arms using Chi-square test in a pairwise setting with a two-sided type I error rate of 20%. With 60 participants in the combination arm and 40 participants in the single biological arm, this test would have 75% power for testing a difference in the pCR rates of 40% vs. 60% between the two arms (TC-H or TC-Ty vs. combination TCHTy treatment) [53]. Another exploratory pairwise comparison of combined groups TC-H &.TC-Ty vs. TCHTy might be performed in a similar fashion. These comparisons are considered hypothesis generating, as the trial design only allows assessment of each arm of treatment independently, as noted above.

10.3 RANDOMIZATION

After written informed consent has been obtained and eligibility has been established, the study site will obtain the subject's identification number from the sponsor (TORI). First twenty (20) eligible participants will be assigned to Arm 3 (TCHTy) to assess the safety of the combination of the 4 agents. After first twenty

(20) participants have been enrolled to Arm 3(TCHTy), one-hundred twenty (120) subjects will be randomized to the three treatment arms. The randomization will be stratified by baseline tumor size (≤ 3 and > 3 cm) and by hormone receptor status (ER and/or PR positive versus ER and PR negative). One-hundred forty (140) participants in total will be enrolled. 40 participants per arm will be enrolled in Arms 1 and 2. 60 participants will be enrolled in Arm 3. Randomization of participants to treatments will be carried out by the method of random permuted blocks; the adaptive randomization of Zelen will not be used.

10.4 EVALUATION OF GENE EXPRESSION BY MICROARRAY ANALYSIS

10.4.1 Population to be analyzed

All of the following criteria must be satisfied in order to consider a participant as evaluable for the interim molecular analyses:

Prior to interim biopsy:

- Participant meets eligibility criteria.
- Participant has received at least 10 consecutive days of lapatinib and/ or all prescribed trastuzumab immediately prior to the collection of the frozen tumor post study treatment initiation.
- Frozen tumor collected as specified and sent to the UCLA laboratory.
- Adequacy for molecular assessment of the tissue specimens collected before and after the study treatment initiation. The adequacy will be evaluated by the UCLA laboratory according to the following criteria:
    - sufficient tissue to perform a core for tissue array and immuno-histochemistry
    - 3-5 ug of total RNA available
    - RNA quality confirmed by Agilent 2100 Bioanalyzer, with a rRNA ratio (28S/18S) of 1.8-2.4

All of the following criteria must also be satisfied for participants in order to consider a participant as evaluable for the final molecular analyses:

Prior to definitive surgery:

- Participant meets eligibility criteria.
- Frozen tumor collected as specified and sent to the UCLA laboratory.
- Adequacy for molecular assessment of the tissue specimens collected before and after the study treatment initiation. The adequacy will be evaluated by the UCLA laboratory according to the following criteria:
    - sufficient tissue to perform a core for tissue array and immuno-histochemistry
    - 3-5 ug of total RNA available
    - RNA quality confirmed by Agilent 2100 Bioanalyzer, with a rRNA ratio (28S/18S) of 1.8-2.4

10.4.2 Molecular Analyses

The molecular analyses will be conducted on tumor specimens obtained from those participants having received one of the prescribed study treatments. Descriptive statistics will be used to compare the pre-and post molecular findings.

There are two objectives of the molecular analysis:
1) To identify a set of genes that respond differentially across the treatment arms;
2) To identify a set of genes correlated with pathological response.

A correlation analysis between the molecular alterations from the baseline tumor sample and the sample collected at the time of the interim biopsy and definitive surgery following administration of the assigned study drug(s) will be conducted. A correlation analysis between the molecular alterations observed in tumor tissue versus the pathological response to study treatment will be performed.

10.4.3 Statistical methods
The molecular correlate studies in this protocol are intended to be hypothesis-generating.
Descriptive statistics will be used to compare the pre-and post-treatment molecular findings.
A detailed Statistical Analysis Plan (SAP) is forthcoming. It will be finalized at the latest prior to database lock.

10.5 SAFETY EVALUATION

10.5.1 Population to be Analyzed
The safety analysis will be conducted on all participants who received all or any portion of one infusion of any study drug.

10.5.2 Statistical Methods
Descriptive statistics will be used to summarize the number and types of adverse events, serious adverse events, abnormal laboratory values that are clinically relevant (defined on 9.1.1), and number of participants in whom study treatment had to be stopped, dose-reduced, or delayed. Adverse events will be compared using chi-squared χ^2 tests or, when expected counts are low, Fisher's exact test or one of its generalizations. Significant differences will only be used to highlight areas worthy of further inquiry.

10.6 RATE OF CARDIAC EVENTS IN EACH ARM

A secondary objective of this study is to estimate the rate of CHF or drop in LVEF (>10% points and below lower limits of normal) in each of the three treatment arms. The rate of CHF with a 95% CI will be estimated for each treatment group.

10.7 CLINICAL EFFICACY

A secondary objective of this trial is to estimate the clinical response rate to therapy. All participants who complete the run-in cycle plus six cycles of chemotherapy plus trastuzumab and/or lapatinib will be evaluated clinically (by physical exam) to assess the participant's clinical response (See Appendix D). The clinical complete response rate (cCR) and clinical partial response rate (cPR) with 95% CIs for each will be estimated for each treatment group.
A pathologic complete response will be defined as the absence of viable tumor cells in the resected specimen, including axillary lymph node sample, as determined by standard histologic examination. The pathology report of definitive surgery will be centrally reviewed to confirm the response. The tumor pCR rate will be determined for both the intent to treat population (which includes all participants who receive a dose of study drug, regardless of whether they complete all protocol-specified therapy) and for the evaluable participant population (which includes only those participants who complete the protocol-specified pre-surgical therapy and undergo mastectomy or a breast-conserving procedure). Pathology reports from definitive surgery will be centrally reviewed for all participants enrolled on study who received at least one dose of study drug regardless of whether participant completes protocol-specified therapy.

10.8 STUDY DISCONTINUATION

Criteria for removal from the study include the following:
- Completion of all prescribed protocol therapy
- Disease progression
- Unacceptable toxicity (defined as toxicity necessitating the discontinuation of study drug, as outlined in Section 5)
- Withdrawal of participant consent

- Continuation would, in the judgment of the investigator, not be in the best interests of the subject

10.9 DATA SAFETY MONITORING BOARD

The Jonsson Comprehensive Cancer Center Data Safety Monitoring Board (DSMB) will be constituted prior to the randomization of the first participant. The role of the DSMB will be to review the study from a safety perspective and to make recommendations regarding the continuation of the trial. The DSMB will meet at least twice yearly to review the incidence and severity of all AEs and SAEs. Prior to each meeting, members of the DSMB will be provided with all relevant data, according to the statistical analysis plan of the study. In the event of unanticipated severe AEs or SAEs, the DSMB will convene immediately to review the event(s) and ensure the safety of participants on the trial. After each meeting, the DSMB will issue one of three recommendations:
• Continue with the trial as planned
• Continue with the trial, with modifications to the protocol
• Discontinue the trial due to serious safety concerns
The deliberations of the DSMB are confidential and must not be disclosed to any individuals, including project management personnel, not responsible for making decisions regarding the scientific and ethical conduct of the trial.

11.0 REGULATORY AND ETHICAL CONSIDERATIONS

11.1 REGULATORY AUTHORITY APPROVAL

The sponsor (TORI) will be responsible for obtaining approval, in accordance with all specific regulatory requirements, to conduct the study from appropriate regulatory agencies in which the trial is performed.

11.2 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with Good Clinical Practice (GCP) and ICH guidelines, the Declaration of Helsinki (Edinburgh, Scotland Amendment, 2000), and all applicable local regulatory requirements.

11.3 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

The protocol, informed consent form, and all other required documents will be reviewed and approved by a properly constituted Institutional Review Board (IRB) or Ethics Committee (EC). A signed and dated statement that the IRB/EC has approved the study must be forwarded to TORI prior to the initiation of the trial. Any amendments to the protocol must also be approved by the IRB/EC, according to applicable regulations. If modifications are made according to local requirements, the new version has to be approved by TORI. Each investigator will be responsible for enrolling only those participants who have met protocol eligibility criteria.

11.4 INFORMED CONSENT

Prior to the performance of any study-related procedures or assessments, each subject must sign an IRB/EC-approved informed consent form. The investigator must explain to each subject the nature of the study, its purposes, the procedures involved, the expected duration, potential risks and benefits, and any discomfort it may entail. Each subject must be informed that participation is voluntary, and that she may withdraw from the study at any time without prejudicing further medical treatment or her relationship with the

treating physician. The Investigator and/or a legally approved designee, and the subject, must sign and date the informed consent form. The subject must receive a copy of the signed and dated form, and the original must be retained in the site's records. The informed consent is considered part of the study protocol, and any changes to the informed consent must be approved by the sponsor (TORI) prior to submission to the IRB/EC.

11.5 STUDY MONITORING

How frequent the study is monitored at a participating site will be based on enrollment rates and other relevant considerations. The monitor will check the completeness of participant records, determine the accuracy of entries on the Case Report Forms, verify adherence to the protocol and Good Clinical Practice, evaluate the pace of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specification. The Investigator must provide access to all relevant source documents during monitoring visits. In addition, site personnel must be available to assist the monitor during these visits.

11.6 RECORDING OF DATA AND RETENTION OF RECORDS

The investigator must complete the Case Report Forms and transmit the data as instructed, and must store copies of the Case Report Forms with other study documents in a secure location in accordance with all regulatory requirements. All entries to the Case Report Forms must be made as described in the completion guidelines.
Essential documents must be retained by the investigator for as long as necessary to comply with national regulations. The sponsor (TORI) will notify the Investigator when essential documents are no longer required; otherwise, essential documents must be retained for 15 years.
Essential documents include:

- IRB/EC approvals for the protocol, informed consent, and all amendments
- Protocols and amendments
- All source documents and laboratory records, and investigational drug accountability records
- CRF paper copies
- Informed consent forms
- FDA Form 1572 (as required)
- Any other pertinent study documents

11.7 AUDITING

In addition to routine monitoring procedures, TORI and/or the industry supporters may wish to conduct an audit for the purposes of quality assurance, and to ensure compliance with GCP, ICH, and other applicable guidelines. Regulatory authorities may also wish to conduct an audit at any time during or after the completion of the study. If an audit is requested by a regulatory agency, the Investigator must notify TORI immediately.

11.8 MODIFICATION OF THE PROTOCOL

Any substantive modifications of the protocol that may affect the conduct of the study, participant safety, or scientific validity of the study require a protocol amendment. Such amendments will be agreed upon by TORI, and must be approved by the IRB/EC prior to implementation at a site.

11.9 DATA MANAGEMENT

Data will be collected using the designated Case Report Forms. Subject data necessary for analysis and reporting the results of the study will be entered into a validated, secure database. Clinical data management and data validation will be performed in accordance with defined procedures. Access to the data will be strictly controlled.

11.10 INFORMATION DISCLOSURE AND PUBLICATIONS

All information provided by TORI and/or the industry supporters relating to this study or the investigational agent, and not previously published, is considered confidential and proprietary. This confidential information shall remain the sole property of TORI and/or the industry supporters, and shall not be disclosed or used (except in the performance of this study) without prior written authorization. No publication, abstract, or presentation of any aspect of the study shall be made without the approval of TORI. A prespecified procedure will be used to determine the authorship list of any publication or presentation, taking into account participation in the leadership, design and conduct of the trial as well as participant accrual.

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APPENDIX A: ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: National Cancer Institute Common Terminology Criteria for Adverse Events

(NCI CTCAE, version 3.0)

NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0
The complete text can be obtained at:
http://ctep.cancer.gov/forms/CTCAEv3.pdf

APPENDIX C: Tumor Tissue Collection and Preparation

CONTACTS

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SUPPLIES NEEDED TO PERFORM FROZEN SPECIMEN COLLECTION

- Cryo-Gel® or OCT
- Deep-waffled large face blockholder or rubber mold
- Gentle Jane® or CryoJane® system
- Portable liquid nitrogen tank
- Nunc 2.0 mL cryotubes with rounded bottoms and screw caps (one for each biopsy specimen) prelabeled with freezerproof (permanent) marker
- Cryotube holder
- Dry ice in a suitable container, or a portable liquid nitrogen container
- Metal 'straw' for placing cryotubes in portable liquid nitrogen container
- Tumor Specimen Shipping Form
- Freezerproof (permanenent) marker

PROCEDURES

1. Prepare the Gentle Jane apparatus by filling the well 4 times with liquid nitrogen from the plastic thermos. Place the plastic thermos in the well, ensuring that it is covered by liquid nitrogen.
2. In the Gentle Jane System, place the Heat Extractor in the plastic thermos containing liquid nitrogen. This will chill the Heat Extractor to -196°C.
3. Place a small amount of Cryo-Gel into the blockholder or rubber mold. Then place the blockholder or rubber mold containing the Cryo-Gel on the Gentle Jane device. Alternatively, the blockholder or rubber mold may be placed on the base of the Gentle Jane, and then Cryo-Gel may be added to the blockholder or rubber mold.
4. Now place the heat extractor in its holder over the blockholder or rubber mold containing the Cryo- Gel. This will form a frozen base for the specimen in 5 – 10 seconds. The base should form a flat surface.
5. Remove the heat extractor from the blockholder or rubber mold and return it to the plastic thermos containing liquid nitrogen.
6. After obtaining informed consent, the patient should be prepared according to institutional guidelines for the biopsy procedure(s).
7. Tumor collection should be performed as follows:

Core Biopsies:

Prior to the administration of the run-in cycle of lapatinib and/or trastuzumab, and after the run-in cycle, four core needle biopsy samples (or an equivalent amount of tissue from an incisional biopsy) should be obtained from the area anticipated to have the largest tumor volume. Ultrasound guidance should be used as clinically indicated. These procedures should be performed according to institutional guidelines and the specimens subsequently processed according to the protocol outlined in steps 8-13 below. Care should be taken during the collection of all specimens to minimize crush injury, and the specimens should be

processed immediately after collection. Note that three core biopsy specimens should be snap-frozen using the methods outlined in steps 8-13 below. The fourth specimen should undergo formalin fixation and embedding in paraffin according to standard institutional guidelines.

Definitive Surgery:

At the time of definitive surgery, a portion of the resected tumor (at least 200 mg of tissue) should be obtained and immediately processed according to the protocol outline in steps 8-14 below. One specimen will undergo formalin fixation and embedding in paraffin (same as for the core biopsies)..

8. As quickly as possible, and at least within 5 minutes of devitalization, each biopsy sample should be placed on top of the blockholder or rubber mold. Forceps should be used at all times at this point when handling the tissue specimens
9. The chilled heat extractor is then removed from the plastic thermos containing liquid nitrogen, placed in its holder, and released. When the heat extractor contacts the specimen, the tissue is snap-frozen. The heat extractor should remain in contact with core biopsy specimens for 5 seconds and in contact with larger specimens for 15-20 seconds.
10. Return the heat extractor to the plastic thermos containing liquid nitrogen.
11. Immediately transfer the specimen to a pre-labeled Nunc tube that is on dry ice. Alternatively, the Nunc tube may be placed in a metal straw designed for use with portable liquid nitrogen tanks and transferred in liquid nitrogen.
12. The number recorded on the Nunc tube with the freezerproof permanent marker must be recorded on the Tissue Specimen Shipping Form. This form identifies the sample and the patient, and records the time and details of the tissue sample collection.
13. Once snap frozen, specimens should be stored immediately at -70 to -80°C or in liquid nitrogen prior to shipping. Specimens can be stored at the site for a maximum of 60 days.
14. Tumor specimen shipping should be done as follows:

    For shipping, cryotubes will be sealed in the provided container, placed in dry ice, and shipped by courier service to Dr. Dennis Slamon's laboratory at the following address:

    Lillian Ramos c/o Slamon Laboratory
    MacDonald Research LaboratorRoom 5-535
    UCLA School of Medicine
    Los Angeles, CA 90095
    USA
    Tel: +1-310-206-1408

APPENDIX D: RECIST CRITERIA

Definitions

- **Measurable disease** – the presence of at least one measurable lesion
- **Measurable lesions** – lesions that can be accurately measured in at least one dimension with longest diameter >20 mm using conventional techniques or >10 mm using spiral CT
- **Non-measurable lesions** – all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and abdominal masses that are not confirmed and followed by imaging techniques

Baseline Documentation of Target and Non-Target Lesions

All measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as Target Lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor.

All other lesions (or sites of disease) should be identified as Non-Target Lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence or worsening of each should be noted throughout follow-up.

Response Criteria

Tables 1 and 2 summarize the criteria to be used to evaluate response.

Appendix D Table 1. Response Criteria for Target Lesions

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

Appendix D Table 2. Response Criteria for Non-Target Lesions

Response Criteria	Evaluation of Non-Target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response or stable	Persistence of one or more non-target lesions and/or

disease (SD)	maintenance of tumor marker level above normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of non-target lesions
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a less sensitive technique than at baseline

Table 3 summarizes the assessment of overall response, which is a composite of target lesion response, non-target lesion response, and presence of new lesions.

Appendix D Table 3. Evaluation of Overall Response

Target Lesions	Non-target lesions	New Lesion	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR
SD	Non-PD and not UNK	No	SD
UNK	Non-PD and/or UNK	No	UNK
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document objective progression after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

APPENDIX E: DOCETAXEL PREPARATION & ADMINISTRATION

Recently, the manufacturer of Taxotere (Sanofi Aventis) released a new single-vial formulation that is replacing the 2-vial Taxotere packaging. This new formulation does not require reconstitution.

Docetaxel is considered standard of care for these study participants and is not supplied by the study sponsor. We recommend the use of the 2-vial formulation (Sanofi Aventis) as stated in the approved study protocol. However, due to the availability of the drug as a generic, the use of the recently released 1 vial formulation (Sanofi Aventis) as well as the generic docetaxel will be considered acceptable for the purposes of this study. All investigative sites should proceed with the infusion of docetaxel following the package insert guidelines provided by the manufacturer.

TAXOTERE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing TAXOTERE solutions. The use of gloves is recommended. Please refer to **Handling and Disposal** section.

If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If TAXOTERE Injection Concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the TAXOTERE concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final TAXOTERE dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TAXOTERE Injection Concentrate requires <u>two</u> dilutions prior to administration. Please follow the preparation instructions provided below. **Note:** Both the TAXOTERE Injection Concentrate and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the **<u>entire</u>** contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL docetaxel.

The table below provides the fill range of the diluent, the approximate extractable volume of diluent when the entire contents of the diluent vial are withdrawn, and the concentration of the initial diluted solution for TAXOTERE 20 mg and TAXOTERE 80 mg.

Product	Diluent 13% (w/w) ethanol in water for injection Fill Range (mL)	Approximate extractable volume of diluent when entire contents are withdrawn (mL)	Concentration of the initial diluted **solution** (mg/mL docetaxel)
Taxotere® 20 mg/0.5 mL	1.88 – 2.08 mL	1.8 mL	10 mg/mL
Taxotere® 80 mg/2 mL	6.96 - 7.70 mL	7.1 mL	10 mg/mL

Preparation and Administration

A. Initial Diluted Solution

1. TAXOTERE vials should be stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of TAXOTERE Injection Concentrate and diluent (13% ethanol in water for injection) vials to stand at room temperature for approximately 5 minutes.

2.Aseptically withdraw the **entire** contents of the appropriate diluent vial (approximately 1.8 mL for TAXOTERE 20 mg and approximately 7.1 mL for TAXOTERE 80 mg) into a syringe by partially inverting the vial, and transfer it to the appropriate vial of TAXOTERE Injection Concentrate. **If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.**

3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.

4.The initial diluted TAXOTERE solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Final Dilution for Infusion

1.Aseptically withdraw the required amount of initial diluted TAXOTERE solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.

If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded.

2.Thoroughly mix the infusion by manual rotation.

3.As with all parenteral products, TAXOTERE should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the TAXOTERE initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

Stability: TAXOTERE infusion solution, if stored between 2 and 25°C (36 and 77°F) is stable for 4 hours. Fully prepared TAXOTERE infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour i.v. administration).

HOW SUPPLIED

TAXOTERE Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, Diluent (13% ethanol in water for injection) vial. The following strengths are available:

TAXOTERE 80 MG/2 ML (NDC 0075-8001-80)

TAXOTERE (docetaxel) Injection Concentrate 80 mg/2 mL: 80 mg docetaxel in 2 mL polysorbate 80 and Diluent for TAXOTERE 80 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

TAXOTERE 20 MG/0.5 ML (NDC 0075-8001-20)

TAXOTERE (docetaxel)) Injection Concentrate 20 mg/0.5 mL: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for TAXOTERE 20 mg (13% (w/w) ethanol in water for injection). Both items are in a blister pack in one carton.

Storage: Store between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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APPENDIX F: LAPATINIB PATIENT DRUG LOG

Patient Initials: ☐☐☐

Site: **Patient Study #:** ☐☐☐☐

IRB #: **Cycle#:**_____

Day	Study Drug Taken?	Date Study Drug Taken	Time Study Drug Taken	Dose Taken (mg)	If NO Study Drug Taken, Please check the reason
Day __1__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __2__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __3__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __4__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __5__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __6__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __7__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __8__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __9__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day _10__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day _11__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day _12__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day _13__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day _14__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day _15__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __16_	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __17_	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day _18__	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __19_	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __20_	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor
Day __21_	☐Yes ☐ No	___/___/___ (mm/dd/yy)	_____:_____ ☐AM ☐PM	☐1000 ☐750	☐ Dose missed ☐ Dose stopped by your doctor

APPENDIX G: TRIO TORI B-07 Study Flow Sheet

	Screening				Run-in Cycle		Cycles 1-6	Between Cycles 3 and 4 (around wk 13)	Between Cycles 1-6 if clinically indicated	End of Chemo/ Pre-Surgical		**End of Study/ Post-Surgical**
	Prior to run-in cycle	Day -30 to -1	Day -28 to -1	Day -14 to -1	Day -7 to 1	Day 14-21	Day -2 to 1			Day -28 to 1 of surgery	At time of definitive surgery	**28 days ± 7 after surgery or study withdrawal/ discontinuation**
Informed Consent		X										
HER2/neu status	X											
Hormone Receptor Status	X											
Radiological Assessment to exclude metastases	X[1]											
Medical History			X		X[5]		X			X[8]		X
Physical Examination				X	X[5]		X			X[8]		X
ECHO/MUGA				X[6]				X	X	X[8]		
Hematology				X			X[7]			X[8]		X
Chemistry				X			X[7]			X[8]		X
Pregnancy Test				X								
Tumor Status				X[3]	X[3,5]		X[3]			X[3,8]		
Core Biopsy		X[2]				X[2]					X[2]	
Pathologic Response											X[4]	
Concomitant Meds				X	X[5]		X			X[8]		X
Adverse Events							X			X[8]		X

1 Not-mandatory. To be performed as clinically indicated.

2 Snap frozen and paraffin embedded. All core biopsies performed for purposes of this study must be collected after consenting patient. (See Appendix C for collection requirements)

3 Documentation of clinical tumor status by physical examination (unidimensional measurements). RECIST criteria will be used to evaluate the clinical objective response to therapy.(See Appendix D)

4 Evaluation of tumor specimen in patients undergoing mastectomy or breast conserving procedure to determine pathologic complete response (pCR).

5 If screening assessment performed within 7 days prior to run-in cycle, no need to repeat.

6 B/L ECHO or MUGA show be done within 28 days prior to run-in cycle. Use same method throughout study.

7 Should be done on day of infusion or within 10 days prior. If done on same day, **infusion must not be given until labs are reviewed.**

8 Cycle 6 data may be used it it is within window.

APPENDIX H: DOSE MODIFICATION QUICK REFERENCE TABLE

Dose Reductions and Delays	Docetaxel	Carboplatin	Trastuzumab	Lapatinib	Page#
Common Symptoms					
Acute Hypersensitivity Reactions (AHR)	See page 45 in protocol				45
Cardiac dysfunction	See pages 50-52 in protocol				50-52
Cutaneous reactions (Arm1) (Gr2)	**Hold**	**Hold**	**Hold**	**N/A**	44
Cutaneous reactions (Arm1) (Gr3)	**Hold / Reduce**	**Hold**	**Hold**	**N/A**	44
Cutaneous reactions (Arm1) (Gr4)	**Off Study**	**Off Study**	**Off Study**	**N/A**	44
Cutaneous reactions (Arm2&3) (Gr3)	**Hold**	**Hold**	**Hold**	**Hold**	49-50
Cutaneous reactions (Arm2&3) (Gr4)	**Off Study**	**Off Study**	**Off Study**	**Off Study**	49-50
Diarrhea	See page 42 and 48-49 in protocol				42, 48
Fluid retention (per. edema and/or effusions)	See page 44-45 in protocol				44-45
Medullary bone pain	See page 44 in protocol				45
Nausea/Vomiting (≥ Gr3)	**No Change**	**Reduce**	**No Change**	**No Change**	42
Neurotoxicity (peripheral neuropathy)-Gr2	**Reduce**	**No Change**	**No Change**	**No Change**	44
Neurotoxicity (peripheral neuropathy)-Gr3/4	**Hold / Reduce**	**Hold**	**Hold**	**Hold**	44
Pneumonitis	**Hold**	**Hold**	**Hold**	**Hold**	50
Stomatitis/Mucositis/Esophagitis (G2)	**Hold / Reduce**	**Hold**	**Hold**	**Hold**	42-43
Stomatitis/Mucositis/Esophagitis (G3/4)-1st	**Hold / Reduce**	**Hold / Reduce**	**Hold**	**Hold**	43
Stomatitis/Mucositis/Esophagitis (G3/4)-2nd	**Off Study**	**Off Study**	**Off Study**	**Off Study**	43
Labs					
Anemia (Gr3-4)	**Reduce**	**Reduce**	**No Change**	**No Change**	42
Bilirubin > UNL (1st)	**Hold / Reduce**	**Hold**	**Hold**	**Hold**	43
Bilirubin > UNL (2nd)	**Hold**	**Hold**	**Hold**	**Hold**	43
Bilirubin > UNL (3rd)	**Off Study**	**Off Study**	**Off Study**	**Off Study**	43
Febrile neutropenia (1st)	**Hold / Reduce**	**Hold**	**Hold**	**Hold**	40-41
Febrile neutropenia (2nd)	**No Change**	**Reduce**	**No Change**	**No Change**	41
Febrile neutropenia (3rd)	**Off Study**	**Off Study**	**Off Study**	**Off Study**	41
Hepatotoxicity (AST, ALT, Alk P)	See page 43 in protocol				43
Infection w or w/o neutropenia (Gr3-4)	**Reduce**	**Reduce**	**No Change**	**No Change**	41
Neutropenia w/o fever (ANC < 1.0 on Day1)	**Hold / Reduce**	**Hold**	**Hold**	**Hold**	40
Thrombocytopenia (1st-Gr1-3)	**No Change**	**Reduce**	**No Change**	**No Change**	41
Thrombocytopenia (2nd-Gr1-3)	**Reduce**	**No Change**	**No Change**	**No Change**	42
Thrombocytopenia (1st-Gr4)	**Hold / Reduce**	**Hold / Reduce**	**Hold**	**Hold**	42

*** Treatment may not be delayed greater than 21 days.**

*** Cycles may be delayed for therapy, but not skipped.**

*** When a cycle is held for toxicity, all drugs (chemotherapy, H & Ty) are held to maintain current dosing.**

*** No dose re-escalations with the exception of LFTs that improve within acceptable ranges.**

Chemotherapy Dose Modifications

Dose Level	Docetaxel	Carboplatin
0	75 mg/m^2	AUC 6 mg/mL/min
-1	60 mg/m^2	AUC 5 mg/mL/min

Note: Only one dose reduction (of each agent) permitted.