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DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

TITLE: Phase II prospective open label study of pertuzumab, trastuzumab, and nab-paclitaxel in patients with HER-2 positive advanced breast cancer.

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TITLE: **Phase II prospective open label study of pertuzumab, trastuzumab, and nab-paclitaxel in patients with HER-2 positive advanced breast cancer.**

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Experimental Design Schema

- Identification of patients with advanced (metastatic [MBC], or stage II-III locally advanced -including inflammatory [LABC]) breast cancer
- Consent

- Work-up, including validation of HER2 positive tumor status, and, if feasible, procurement of archival tumor tissue and blood samples. Once eligibility criteria met : registration for treatment
- Cycle length is 21 days. Therapy: Pertuzumab, Day 1 of each cycle; Nab-paclitaxel and trastuzumab, weekly. Total planned duration for patients with MBC: until progression; for patients with LABC: 6 cycles, followed by definitive surgery.
- Staging studies/imaging for patients with MBC: every 9 weeks for surveillance and monitoring progression/response; for patients with LABC: breast/lymph node imaging and staging studies prior to initiating therapy, and as indicated prior to surgery.
- Primary analysis of clinical data after progression (MBC) or completion after of neoadjuvant therapy (LABC).

Protocol Synopsis

Protocol Title
Phase II prospective open label study of pertuzumab, trastuzumab, and nab-paclitaxel in patients with HER-2 positive advanced breast cancer
Brief Protocol Title for the Lay Public (if applicable)
N/A
Study Phase
Phase II
Participating Sites
City of Hope
Rationale for this Study
Overexpression of HER2 occurs in 20-25% of breast cancers and has historically been associated with poorer prognosis.[1] The addition of the monoclonal antibody trastuzumab to chemotherapy has significantly impacted progression free survival and overall survival both in the adjuvant and metastatic setting.[2-6] Unfortunately, in patients with MBC, disease progression on trastuzumab therapy generally occurs within approximately one year. Multiple molecular mechanisms of trastuzumab resistance have been identified.[7-10] One of the identified mechanisms is the development of heterodimerization between HER2 and EGFR or less importantly, HER2 and IGFR.[11-13] Pertuzumab is a monoclonal antibody that inhibits ligand-activated signaling and interfers with the dimerization process ofHER2 And other HER family members. In order to overcome trastuzumab resistance, studies have combined pertuzumab with trastuzumab to gain synergistic inhibition of breast cancer cells with overexpression of HER2, with subsequent confirmation of clinical synergy.[14-19] The results of a Phase III study (CLEOPATRA) compairing docetaxel, pertuzumab, and trastuzumab versus docetaxel and trastuzumab revealed that the combination of pertuzumab, trastuzumab, and docetaxel had increased progression free survival to 18.4 months compared to trastuzumab and docetaxel a at 12.4 months, with no increase in cardiotoxicity when given as first line treatment, for metastatic breast cancer. Overall survival at a median follow-up of 30 months has also favored the combination, with the

median not reached, vs. 37.6 months with docetaxel and trastuzumab.[20,21]
Recent data suggest activity and safety when pertuzumab and tarstuzumab are combined with weekly paclitaxel.[22]
Nab-paclitaxel at the 100 mg/m^2 wekly dose was chosen as the chemotherapeutic agent in our study because it demonstrated improved acceptable safety profile and better response rate and progression free survival particularly in subsets of patients wih visceral metastasis when compared with docetaxel in phase II studies. Also a Phase III study showed improved PFS with every 3 week nab-paclitaxel compared to every 3 week paclitaxel, with less neurotoxicity and hypersensitivity.[23,24] Furthermore, the ION 04-012 randomized phase II study compared nab-paclitaxel with or without trastuzumab in first line treatment of metastatic breast cancer. This study demonstrated an overall response rate of 52.4% in HER-2 overexpressing patients with median PFS of 14.5 months, which includes HER2 non-overexpressing patients.[25].

A combination therapy that can improve PFS with less toxicity in patients with HER-2 overexpressing MBC would be a step forward in the treatment of this disease. The addition of pertuzumab to nab-paclitaxel and trastuzumab has the potential to be such a combination therapy.

More recently, a series of trials tested the feasibility and efficacy (as defined by complete pathologic response rate at surgery) of dual targeting neoadjuvant therapies in HER2+ locally advanced breast cancer. Based on the positive outcome of such trials including the Neosphere trial, the FDA recently approved the use of neoadjuvant dual targeting therapy with trastuzumab, pertuzumab, and a docetaxel.[26] Recently updated NCCN guidelines allow for administration of any of the taxanes in such setting, in combination with dual HER2-targeting therapies [27]. Since the complete pathological response rate with pertuzumab, trastuzumab, and docetaxel has been reported in the Neosphere trial at 39.3%, (a quite high pCR rate considering that both estrogen receptor positive and negative tumors were included, and this pCR included only patients whose breast and lymph node tissues were void of evidence of cancer) the eligibility criteria for this trial will now allow to test the proposed pertuzumab, trastuzumab, nab-paclitaxel regimen in the first line metastatic, AND neoadjuvant settings focusing on locally advanced breast cancer

Objectives

The primary objective of this study is to determine (1) efficacy of administration of pertuzumab in combination with trastuzumab with nab-paclitaxel in subjects with HER-2 overexpressing breast cancer (MBC) as measured by progression free survival (PFS), and (2) the efficacy as neoadjuvant treatment of the regimen in locally advanced HER2+ breast cancer (LABC) as measured by pathologic complete response (pCR).

Secondary Objectives

1) To evaluate the safety of pertuzumab when added to trastuzumab and nab-paclitaxel in MBC and HER-2 overexpressing LABC as assessed by the frequency and severity of adverse events (AEs), abnormal treatment-related findings on physical examination,

laboratory tests, and vital signs;
2) To evaluate the objective response rate (RECIST 1.1.) and duration of response in MBC
3) To evaluate the response as assessed by residual cancer burden (RCB) score in LABC.
4) To assess the progression free survival (MBC), relapse-free survival (LABC) and the overall survival in all patients.
5, To perform exploratory circulatory gene, microRNA and exosome profiling as well as protein and glycomic profiling.
6, To assess the feasibility of molecular profiling in both primary and metastatic tumor samples
7, To assess numerical and qualitative aspects of circulating tumor cells and circulating tumor-derived DNA.

Study Design

Phase II First line Advanced Breast Cancer Treatment Trial; Single-site; type of study: safety, preliminary efficacy.

Endpoints

Progression Free Survival, Objective Response Rate, Clinical Benefit Rate in the stage IV setting; Complete Pathologic Response and Relpase-free survival in the locally advanced setting; overall survival in all patients.

Sample Size

The sample size is to be 65 patients. All patients are to receive all study medications, and patients treated will be counted towards analysis.

Estimated Duration of the Study

Study duration is expected to be 48 months; first patient to enroll in mid-2013, last patient to enroll by 12/2016.

Summary of Subject Eligibility Criteria

Inclusion Criteria:

Disease Status

Cytologically or histologically documented adenocarcinoma of breast; HER-2 positive biology only. At least one measurable site required for patients with MBC; Patients with LABC are accrued if they present with ≥ 2 cm primary, or any T size with documented lymph node involvement, or with inflammatory breast cancer (Stages II and III)

Age Criteria and Life Expectancy

Greater than 18 years of age, female patients

Child Bearing Potential

The effects of the proposed therapeutic agents (pertuzumab, nab-paclitaxel) on the developing fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for six months following duration of study participation. Should a woman become pregnant or suspect that she is pregnant while participating on the trial, she should inform her treating physical immediately.

Protocol-Specific Criteria

1) HER2 by IHC (3+), or in case of IHC of 2+, positive by FISH (≥2.0) or by alternative gene testing.
2) ECOG ≤ 1
3) Organ function:

   Liver enzymes ≤ 2 x upper limit of institutional normal.
   Calculated or measured creatinine clearance of > 50 ml/min
   Left ventricular ejection fraction > 50%
   Absolute neutrophil count ≥ 1,500/μl; platelets ≥ 100,000/μl

Informed Consent/Assent

All subjects must have the ability to understand and the willingness to sign a written informed consent.

Prior Therapy

No prior therapies are allowed for the treatment of locally advanced or newly diagnosed metastatic breast cancer. Prior adjuvant therapy for preceeding stages II-III breast cancer more than 12 months prior to enrollment into study is allowed.

Exclusion Criteria

Study-Specific Exclusions

1) Known active Hepatitis B, or C
2) Known active HIV (necessitating therapy)
3) Pregnancy
4) Neuropathy > grade 1
5) Any other intercurrent medical/psychological problem deemed exclusionary by the treating physician or investigators/PI

Non-Compliance
Subjects will be excluded who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

Investigational Product Dosage and Administration

Pertuzumab administered as 840 mg IV during cycle 1 followed by 420 mg IV every three weeks starting cycle 2.

Trastuzumab loading dose of 4mg/kg for week one followed by 2 mg/kg IV weekly.

Nab-paclitaxel 100 mg/m^2 IV weekly.

Clinical Observations and Tests to be Performed

Laboratory studies will be required to be performed within a week prior to initiating therapy. Other diagnostic assessments should be performed within 28 days prior to initiating therapy (exception Echo/MUGA may be done within 42 days).

Statistical Considerations

To evaluate the combination of pertuzumab, trastuzumab and nab-paclitaxel in HER2+ breast cancer, we can combine the ability of this regimen to shrink/control the tumor in untreated breast cancer cases whether it is in a metastatic patient or in the neoadjuvant setting, as both are untreated HER2+ breast cancers. The assumption is that a promising result in one setting would translate into a promising result in the other. To combine these two, we note that the Cleopatra trial[20,21] observed a median PFS of 18.5 months in metastatic breast cancer with pertuzumab, trastuzumab and docetaxel. As a result, a success for an individual patient with MBC can be defined as PFS $\geq$ 18.5 months, with an observed success rate of 50%. In the neoadjuvant setting, a pCR rate (success rate) of 39.3% was observed with the pertuzumab, trastuzumab and docetaxel[26]. As a result, this study will be designed to declare the study successful if it at least matches response rate in the Cleopatra and Neosphere trials due to the presumed lower toxicity and possibly improved efficacy over other taxanes such as docetaxel or paclitaxel when using nab-paclitaxel on the proposed dose and schedule. 65 patients will be accrued, with 25 metastatic breast cancer (MBC) patients and 40 LABC patients who are to receive neoadjuvant therapy. At the final analysis, the matching target success rate would be (0.393*40+0.5*25)/65=43.4% or 28 successes. If the true success rate is 10% above the matching success rate this design has 94% power to declare a success. If the true success rate is 10% below the matching success rate, this design has a type I error less than 5% (one sided). This design is equivalent to testing the null hypothesis H0: success rate is 33.4% against an alternative H1: success rate is 53.4%, with a type I error (one-sided) of 5% and a type II error of 6% (94% power). These error estimates are conservative due to the slight underdispersion resulting from the combination of two binomials.

In addition to the combined endpoint, each strata will be evaluated independently. With 25 metastatic cancer patients, the median PFS will be estimated. If accrual is within 24 months, and follow-up is approximately 24 months after accrual completes, the probability of a true median survival of 24 months being less than 18.5 months is less than 20% (80% power), and the probability of a true median survival of 13 months exceeding 18.5 months is approximately 13.4% (type I error, one sided). This is assuming a non-parametric estimate of the median survival and uses the Brookmeyer-Crowley method. This design is equivalent to testing the null hypothesis H0: median survival is 13 months against an alternative H1: median survival of 24 months, with a type I error (one-sided) of 13.5% and a type II error less than 20% (80% power). If accrual is longer, with follow-up after the last accrual unchanged, the type I and type II error are reduced.

With 40 neoadjuvant cases, the probability of a true discouraging neoadjuvant pCR rate of 29.3% exceeding the benchmark of 39.3% (16 or more) is 10% (type I error), and the probability of a true neoadjuvant pCR rate of 49.3% resulting in a observation below 39.3% (15 or less) is less than 10% (>90% power). This design is equivalent to testing the null hypothesis H0: pCR rate is 29.3% against an alternative H1: pCR rate is 49.3%, with a type I error (one-sided) of 10% and a type II error less than 10% (at least 90% power).

The study is likely to accrue 2 patients per months in the locally advanced cohort , the 40 patient LABC accrual should be met by the end of 2016.

For interim analysis, no formal analysis is planned due to the time required to assess the PFS endpoint and the expected rapidity of accrual. However, a report will be generated after 29 patients have been accrued to review with the Sponsor and PI, with a report to the COH DSMB. At the final analysis, the PFS (for stage IV cases), the pathological complete response rate (for neoadjuvant cases) and toxicity/tolerability may refine the decision to pursue the combination, or may suggest restricting this combination to more fragile patients less able to receive more aggressive chemotherapy combinations.

There will be interim analysis for toxicity. Specifically, if dose limiting toxicity (grade 3 or higher treatment-related non-hematologic toxicity other than readily reversible electrolyte abnormalities or diarrhea/ nausea/vomiting that lasts less than 24 hrs after treatment or any treatment related grade 4 toxicity) is observed in 2 of the first 6 patients treated during the first cycle of treatment (28 days), or in more than 30% of the patients thereafter, the study will hold accrual pending review by the COH DSMC, PI and Sponsor.

Sponsor

City of Hope/Genentech/Celgene Corporation

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Abbreviation	**Meaning**
AE	Adverse Event
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
SAE	Serious Adverse Event

1.0 Goals and Objectives (Scientific Aims)

1.1 The primary objective of this study is to determine (1) Efficacy of administration of pertuzumab in combination with trastuzumab with nab-paclitaxel in subjects with stage IV HER-2 overexpressing metastatic breast cancer (MBC) as measured by progression free survival (PFS), and (2) the efficacy as neoadjuvant treatment of the regimen in HER2+ locally advanced breast cancer (LABC) as defined by pathologic complete response (pCR).

1.2 The secondary objectives of this study are:
1) To evaluate the safety of pertuzumab when added to trastuzumab and nab-paclitaxel in HER-2 overexpressing MBC and LABC cancer as assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, and vital signs;
2) To evaluate the objective response rate (RECIST 1.1.) and duration of response in MBC.
3) To evaluate efficacy of the regimen by assessing tumor response including assessment of residual cancer burden (RCB) scores in LABC.
4) To assess the progression free survival (MBC), relapse-free survival (LABC) and overall survival in all patients.
5) To perform exploratory circulatory gene, microRNA and exosome profiling as well as protein and glycomic profiling
6) To assess the feasibility of molecular profiling in both primary and metastatic tumor samples
7) To assess numerical and qualitative aspects of circulating tumor cells and circulating tumor-derived DNA.

2.0 Background and Rationale

2.1 Introduction/Rationale for Study

Overexpression of HER2 occurs in 20-25% of breast cancers, and its over-expression has historically been associated with poorer prognosis.[1] The addition of monoclonal antibody trastuzumab to chemotherapy has significantly impacted progression free survival and overall survival in the adjuvant and metastatic setting.[2-6] Unfortunately, disease progression after trastuzumab therapy generally occurs within approximately one year. Thus, there is a need for a combination therapy that can overcome trastuzumab resistance. The rationale for this study proposal is to overcome trastuzumab resistance via the addition of pertuzumab in the treatment of HER2 positive metastatic breast cancer.

2.2 Mechanisms of trastuzumab resistance:

Trastuzumab activity is aimed at the subdomain IV of HER2 receptor extracellular domain where it blocks HER2 cleavage; stimulates antibody-dependent, cell-mediated cytotoxicity; and inhibits ligand-independent, HER2-mediated mitogenic signaling. Multiple molecular mechanisms of trastuzumab resistance have been identified.[7-10] These mechanisms include activation of downstream PI3K-signaling pathway, accumulation of a constitutively

activated HER2, and cross talk of HER2 with other growth factor receptors. One of the proposed mechanisms to overcome HER2 resistance is to block heterodimerization between HER2 and other growth factor receptors to inhibit cross talk.[11-13]

2.3 Pertuzumab

Pertuzumab is a monoclonal antibody that binds to subdomain II of the extracellular domain of HER2 receptor. Pertuzumab prevents the dimerization of HER2 with other ligand-activated HER receptors, particularly HER2/EGFR and HER2/HER3 heterodimers. Although the HER2 binding site is different, the mechanism of action is similar to trastuzumab in that it stimulates antibody-dependent cytotoxicity and inhibits ligand-independent signaling. Due to this similar mechanism of action and unique binding sites, in order to overcome trastuzumab resistance, studies have combined pertuzumab with trastuzumab to gain synergistic inhibition of breast cancer cells with overexpression of HER2. As a result, there is a more comprehensive blockade of HER2 signaling and greater antitumor activity than either agent alone as demonstrated in the preclinical and phase II clinical setting.[14-20]

A randomized phase III study (CLEOPATRA) showed that the combination of docetaxel, pertuzumab, and trastuzumab had increased progression free survival at 18.5 months compared to trastuzumab and docetaxel alone at 12.4 months with no increase in cardiotoxicity in first line metastatic breast cancer.[20],[21]

Recent data suggest activity and safety when pertuzumab and trastuzumab are combined with weekly paclitaxel as first line therapy.[22]

Nab-paclitaxel at the 100 mg/m^2 wekly dose was chosen as the chemotherapeutic agent in our study because it demonstrated improved acceptable safety profile and better response rate and progression free survival particularly in subsets of patients wih visceral metastasis when compared with docetaxel in phase II studies. Also a Phase III study showed improved PFS of every 3 week nab-paclitaxel compared with every 3 week paclitaxel with less neurotoxicity and hypersensitivity.[22-24] Furthermore, the ION 04-012 randomized phase II study compared nab-paclitaxel with or without trastuzumab in first line treatment of metastatic breast cancer. This study demonstrated an overall response rate of 52.4% in HER-2 overexpressing patients with median PFS of 14.5 months, with the study including HER2 non-overexpressing patients.[25].

In the neoadjuvant setting , both the NeoSphere trial combining pertuzumab and trasstuzumab[26] and the NeoAltto study testing the EGFR and HER-2 dual tyrosin kinase-targeting agent lapatinib with trastuzumab [28] proved that dual-biologic HER2 targeting is superior to single HER2 targeting, particularly when combined with chemotherapy.

Partly based on mature analysis of neoadjuvant trial outcomes,[29,30] and particularly based on the positive outcome in the Neosphere trial, the FDA recently approved the use of neoadjuvant dual targeting therapy with trastuzumab, pertuzumab, and a docetaxel. NCCN guidelines allow for administartion of any of the taxanes in such setting, in combination with dual HER2-targeting therapies [27]. Since the complete pathological response rate with pertuzumab, trastuzumab, and docetaxel has been reported in the Neosphere trial at 39.3%, (a quite high pCR rate considering that both estrogen receptor positive and negative tumors were included, and this pCR rate included only patients whose breast and lymph node tissues were both void of evidence of invasive cancer) the eligibility criteria for our trial will now allow to test the proposed pertuzumab, trastuzumab, nab-paclitaxel regimen in the

first line metastatic, AND neoadjuvant settings. To provide a potentially sensitive tool for pathologic response, assessment of residual cancer burden (RCB) scores have been proposed as a predictor of long-term outcome, in the neoadjuvant setting.[31] We will perform this assay and the results of such scoring will now be included in the exploratory analysis.

2.4 Nab-paclitaxel

Nab-paclitaxel is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition allows for a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intralumminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium. A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane.[32-34]

Following a series of phase I and II trials and demonstration of efficacy in the phase III setting, weekly nab-paclitaxel was chosen as the chemotherapeutic agent in this study because it demonstrated significantly improved progression free survival when compared with docetaxel in first line metastatic breast cancer with the benefit over 5 months.[23,24,35-37] Weekly nab-paclitaxel compared with every 3 week paclitaxel has also been shown to have less neurotoxicity and hypersensitivity based on randomized trials.[23] While earlier trials showed that nab-paclitaxel at 150mg/m^2 weekly was superior to nab-paclitaxel 100mg/m^2, a more recent trial suggested that toxicities associated with such dosing in comparison to weekly paclitaxel given at 90 mg/m^2 were worse.[38] Hence, we chose the dosing of 100 mg/m^2 in hopes to maintain the efficacy while minimizing toxicity.

2.5 Overview of Proposed Study

A combination therapy that can improve PFS with less toxicity in patients with stage IV HER-2 overexpressing MBC would be a step forward in the treatment of HER2 overexpressing metastatic breast cancer. We hypothesize that the addition of pertuzumab to weekly nab-paclitaxel and weekly trastuzumab is an effective treatment in metastatic breast cancer with less toxicity.

The FDA recently approved the use of neoadjuvant dual targeting therapy with trastuzumab, pertuzumab, and a docetaxel, based on the assumption that the high pathologic complete response rate may be a surrogate marker for improved overall survival.[26, 29, 30] NCCN guidelines allow for administration of any of the taxanes in such setting, in combination with dual HER2-targeting therapies[27]. Since the complete pathological response rate with pertuzumab, trastuzumab, and docetaxel has been reported in the Neosphere trial at 39.3%, we put forward that trastuzumab, pertuzumab, and weekly nab-paclitaxel may improve the pathologic complete response rate further.

Hence, the elgibility criteria for this trial will now allow to test the proposed pertuzumab, trastuzumab, nab-paclitaxel regimen in the first line metastatic, AND neoadjuvant settings.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Because all three drugs are approved for used in advanced breast cancer, but the three have never been studied together, an IND exemption has been provided by the FDA for this study.

2.6 Translational Research Component

Serum samples procured prior to, during, and at the completion (on progression) of protocol therapy will be spun at 1,000 x g to remove tissue debris, and treated in one of several ways to optimize potential biomarker recovery.

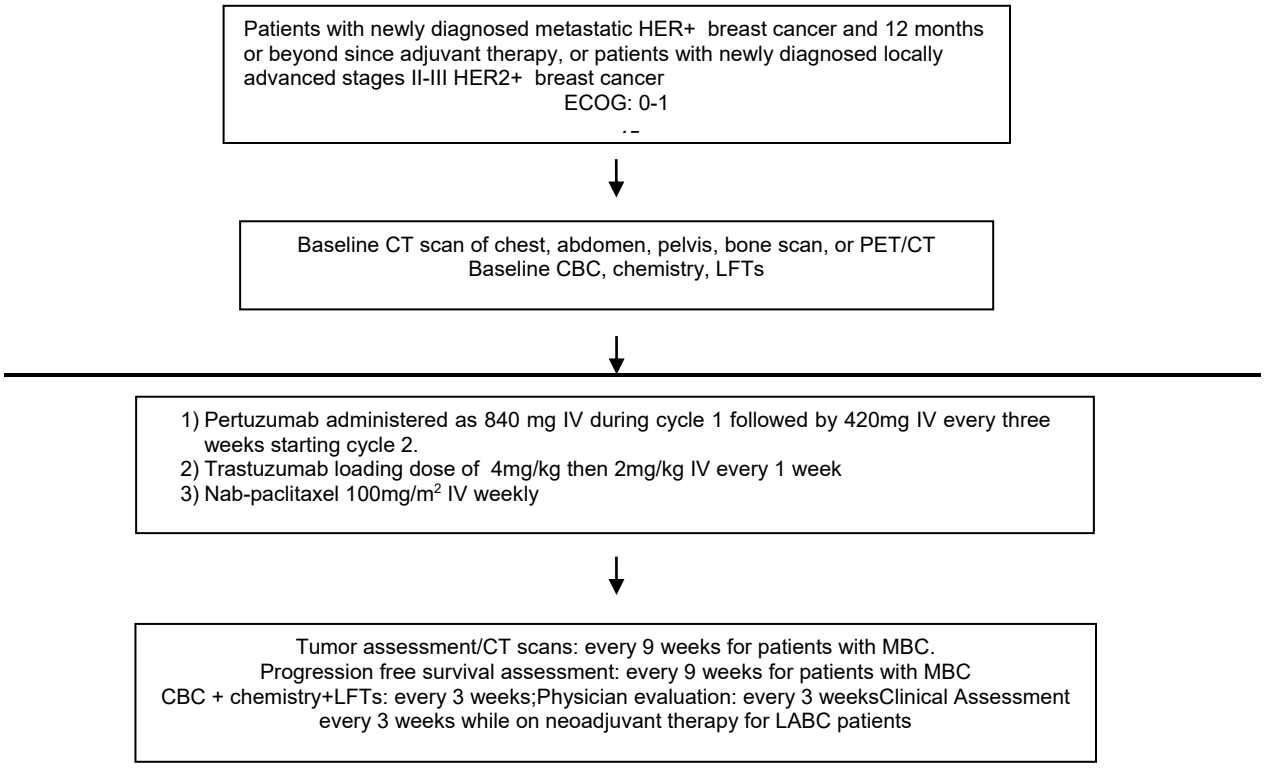
a) For protein biomarker discovery: protein recovery in the supernatant will be determined using a BCA protein analysis kit (Pierce Scientific) to obtain protein concentration, and 1ul and 5ul of supernatant will be examined by mass spectrometry to determine the mass profile of the fluid sample. This will be done by spotting the fluid directly onto a target plate, (consisting of one or more of the following materials: stainless steel, an anionic (WCX-10), cationic (CM-10), neutral phase, metal ion binding(IMAC) or hydrophobic (H50) SELDI chip surface under detergent extraction conditions, washing the surfaces with the appropriate buffers, overlaying the bound proteins with an energy absorbing material (i.e., matrix) such as but not limited to: Sinapinic acid, CHCA, DHB, or super DHB, etc.,) and then analyzing the proteins bound to the target plate surface by matrix assisted laser desorption ionization (MALDI) mass spectrometry in both the negative ion and positive ion mode to maximize the type of protein signature identified. The chromatography-like surfaces (e.g., WCX-10, etc.,) present a way for performing solid-state chromatography, and is an ideal methodology for fractionating small volumes of patient fluid into several fractions that permit enrichment of specific classes of proteins within the available patient samples.

b) For glycomic biomarker discovery: the patient samples will be digested with MS grade trypsin, and the resulting glycopeptides/peptides will be treated with PNGase F to release N-linked glycosidic linkages. The glycosidic linkages will be captured by micro-lectin chromatography, permethylated, and analyzed by electrospray ionization (ESI) mass spectrometry or by MALDI mass spectrometry. The resulting mass spectra will then be "deconvoluted" against a Bruker supplied database containing the masses for intact sugars and fragments of sugars expected after laser induced fragmentation of these known sugars, (e.g., glucose, fructose, galactose, glucosamine, fucose, mannose, etc.), as well as branched chains of sugars common to mammalian cells. PCA analysis will then be run on the various branched chain sugars identified in the fluid, to initially see if the relative abundance of one sugar isoform vs. another isoform can be predictive of the presence of cancer, or whether the node is free of cancer cells. O-linked glycans will be isolated and analyzed by collection of the peptides passing through the first lectin column, and subjecting these peptides/glycopeptides to chemical cleavage followed by capture of the 0-glycan on an alternate lectin affinity chromatography matrix, then subjecting the glycans eluted from the matrix to permethylation, and analysis by mass spectrometry as described for the N-linked glycans. This part of the study will be carried out under the guidance of Robert Hickey Ph.D, pending availability of funding.

2.7 Exploratory Analysis of Cancer-associated MicroRNAs and Exosomes:
Exploratory analysis of microRNA and exosome expression profile from serum samples procured prior to, during protocol treatment, and at progression, will be carried out in collaboration with Emily Wang, Ph.D., as part of an already approved and NIH-grant-supported collaboration (IRB 09147). Cancer-secreted exosomes and miRNAs can be internalized by other cell types in the primary tumor microenvironment and pre-/metastatic niches. MiRNAs loaded in these exosomes, which to a certain extent reflect the dysregulated miRNA profile in cancer cells, can thus be transferred to recipient niche cells to exert genome-wide regulation of gene expression. Cancer-derived miRNAs have been detected in the blood of cancer patients, where their levels distinguish cancer patients from healthy controls[39,40]. Previous studies from our and other groups have identified circulating miRNAs associated with the histopathological features of breast tumors and clinical outcomes in BC patients [41-45]. Therefore, cancer-associated microRNAs and exosomes are novel non-invasive circulating biomarkers for breast cancer. This collaboration is supported by NIH grant (R01CA166020) and Breast Cancer Research Foundation-AACR Grant (12-60-26-WANG).

2.8 Exploratory Analysis of Cancer-associated gene profiling of tumors, serum DNA analysis, and circulating tumor cell analysis:
Additional components include exploratory analysis of gene expression profile of tissue, circulating tumor cells, and serum DNA, which is pending availability of funding.[46-50] Profiling will be carried out in the setting of various internal and external collaborations (all MTA supported, or grant supported). Collaborators include Hua Yu, Peter Lee, Shiuan Chen, various COH cores. External collaborators with MTAs in place include TGEN (J. Trent and laboratory), The Jackson Laboratory (F. Mengi and Ed Liu), Agendia, Emily Wang (UC San Diego-R0-1 joint PI-ship).

Study Schema



3.0 Patient Eligibility

3.1Inclusion Criteria: To be eligible, patients must meet all of these criteria.

3.1.1 Disease Status

Patients must be diagnosed with metastatic cytologically or histologically confirmed adenocarcinoma of the breast with HER2 over-expression or with newly diagnosed locally advanced (including inflammatory) breast cancer (LABC) with stage II-III disease. Patients with metastatic (stage IV) disease (MBC) must have measurable lesions.

3.1.2 Age Criteria and Life Expectancy

Greater than 18 years of age

3.1.3 Child Bearing Potential

The effects of the proposed therapeutic agents (pertuzumab, nab-paclitaxel, trastuzumab) on the developing fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for six months following duration of study participation. Should a woman become pregnant or suspect that she is pregnant while participating on the trial, she should inform her treating physical immediately.

3.1.4 Protocol-Specific Criteria

- Tumor positive or negative for expression of hormone receptors (< 1% or >1%) and overexpressing HER2 by IHC (3+), or, HER2-amplified by FISH or by alternative gene testing as per the latest ASCO/CAP guideline update.[51]
- For patients with LABC, no prior therapy is allowed
- For patients with MBC, prior adjuvant chemotherapy and trastuzumab more than or equal to 12 months prior to enrollment are allowed
- No prior chemotherapy or trastuzumab for treatment of metastatic breast cancer
- LVEF ≥50% (determined by echocardiogram or multigated acquisition scan) within 42 days of treatment
- Eastern Oncology Group Performance Status of 0 or 1.
- Patients must have normal organ and marrow function as defined below (within 7 days prior to start of study treatment):
  - Hemoglobin ≥ 9g/dl
  - Leukocytes ≥ 3.0 x 10^9/L
  - Absolute Neutrophil Count ≥ 1.5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Total Bilirubin ≤ 1.3 mg/dl (institutional upper limit of normal)
  - AST (SGOT)/ALT (SGPT) ≤2 x institutional upper limit of normal

- Creatinine within normal institutional limits
- Or creatinine clearance >50 mL/min/1.73m^2 for patients with creatinine levels above institutional normal (using Crockcroft-Gault Formula)

- All radiology studies(study required staging) must be performed within 35 days prior to the start of therapy.
- No serious medical conditions such as myocardial infarction within 6 months prior to entry, congestive heart failure, unstable ventricular arrhythmia, uncontrolled hypertension, uncontrolled diabetes mellitus, uncontrolled psychotic disorders, serious infections, active peptic ulcer disease, psychiatric illness, or any other medical conditions that might be aggravated by treatment or limit compliance
- Currently, no active second malignancy other than non-melanoma skin cancer. Note: Patients are not considered to have a "current active" malignancy if they have completed anti-cancer therapy and are considered by their physicians to have a less than 30% chance of relapse.
- All patients must have the ability to understand and the willingness to sign an informed consent
- Negative serum or urine Beta-hCG pregnancy test at screening for patients of child-bearing potential.

3.1.5 Informed Consent/Assent

All subjects must have the ability to understand and the willingness to sign a written informed consent.

3.1.6 Prior Therapy

No prior therapies (except for anti-estrogen therapy) are allowed for the treatment of the newly diagnosed metastatic breast cancer. Patients are allowed to have had prior chemotherapy for breast cancer in the adjuvant setting at least 12 months prior to enrollment into this study. Patients with a prior diagnosis of malignancy treated ≥ 5 years ago are eligible, provided that they have not received prior nab-paclitaxel as part of their prior treatment regimen, and that they meet all eligibility criteria.

3.2 Exclusion Criteria: A patient is rendered ineligible if any of these criteria applies.

3.2.1 Study-Specific Exclusions

1) Known active Hepatitis B or C (due to the potential for disease/treatment-related pharmacological and liver function-specific interactions).
2) Known active HIV (due to the complexity and potential pharmacological interactions between the standard neoadjuvant therapeutic agents, and HAART).
3) Prior breast cancer or other invasive malignancy treated within 5 years.
4) Pregnancy
5) Neuropathy > grade 1
6) Any other intercurrent medical/psychological problem deemed exclusionary by the treating physician or investigators/PI.
7) Cumulative dose of doxorubicin or equivalent of >360mg/m^2 during prior adjuvant therapy

8) LVEF <50% during previous trastuzumab therapy
9) Central nervous system metastases
10) Another malignancy excluding basal cell skin cancer
11) Pregnant women

3.2.2 Non-Compliance

Subjects will be excluded who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

3.3 Inclusion of Women and Minorities

The study is open to women regardless of ethnicity. Female subjects of all racial/ethnic groups are eligible for this study if they meet the eligibility criteria specified in sections 3.1 and 3.2. To address disparities in healthcare and breast cancer treatment among women from underserved populations, all efforts will be made to accrue subjects from ethnically diverse, underserved and minority populations. While efforts will be made to extend the accrual to a representative population, in a trial which will accrue 40 fully evaluable subjects, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to racial or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Table 1.0

City of Hope Breast Patients, 2009								
		By Sex		**By Ethnicity**				
Site	Total	Female	Male	White	Hispanic	Black	Asian	Other
Breast	477	476(99%)	1 (1%)	255 (53%)	120 (25%)	38 (8%)	63 (13%)	1 (1%)

Table 2.0

Accrual Goal for Women and Minorities on this Study								
		By Sex		**By Ethnicity**				
Site	Accrual Goal	Female	Male	White	Hispanic	African-American	Asian	Other
Breast	45	45 (100%)	0 (0%)	20 (44%)	12 (27%)	4 (9%)	8 (18%)	1 (2%)

4.0 Registration Procedures

4.1 Registration Process

To register a patient, the treating physician should contact the responsible Clinical Research Associate (CRA) in Clinical Trial Office (CTO) or the protocol nurse to determine whether the patient meets all of the eligibility criteria, and to assist with the informed consent process. After verifying the eligibility and receiving the signed informed consent, the CRA will confirm the drug dose, and register the patient onto the study.

4.2 Registration Process

1. CRA assigned to this study will register patient for this protocol.

2. A patient failing to meet all protocol requirements may not be registered.

3. Pre-study laboratory tests, scans and x-rays must be completed prior to registration according to study calendar.

4. Patients must sign an informed consent prior to registration.

5. Confirm that the patient meets all inclusion and exclusion eligibility criteria for this protocol.

6. Complete the eligibility checklist.

7. Verify that all required pre-study tests were performed.

8. If the patient qualifies, the City of Hope coordinator will assign the patient's study ID number.

5.0 Informed Consent

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were for clinical indications (not exclusively to determine study eligibility but consistent with good medical practice [GMP]) may be used for baseline values, even if the studies were done before informed consent was obtained. Reference is made to Section 10.0 – Study Calendar. The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the subject's research chart and medical record.

6.0 Dose Assignment

Pertuzumab administered as 840 mg IV during cycle 1 followed by 420 mg IV once every three weeks starting with cycle 2.
Trastuzumab administered with loading dose of 4mg/kg IV for week one followed by 2mg/kg IV given weekly.
Nab-paclitaxel 100mg/m^2 IV given weekly
Dose reductions can occur as medically necessary as described below in section 9.2.1

7.0 Treatment Plan

7.1 Treatment Administration

Treatments are planned to be delivered in the outpatient setting.
Management and dose modification associated with adverse events are outlined in Section 9.0
Off Label: This proposal includes commercial agents for use in an investigational setting/trial.

7.2 Dose Summary:

- Pertuzumab administered as 840 mg IV during cycle 1 followed by 420 mg IV once every three weeks starting cycle 2.
- Trastuzumab loading dose of 4mg/kg IV for week one followed by 2mg/kg IV weekly.
- Nab-paclitaxel 100 mg/m^2 IV weekly.
- Treatment is scheduled to continue until:
  - Disease progression for patients with MBC, and for a planned 6 cycles for patients with LABC
  - Unmanageable toxicity
  - Primary physician or patient request to discontinue therapy
  - Study termination by the sponsors

7.3 Details:

7.3.1 Pertuzumab

IV administration of pertuzumab should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. Patients should be monitored during and following completion of each pertuzumab infusion for any adverse effects. Since there is the potential for delayed onset infusion-associated reactions, patients should be warned of this possibility and instructed to contact the treating physician with any concerns.

The initial pertuzumab dose should be administered over 60 minutes (± 10 minutes). Patients should be observed for fever, chills, and other infusion-associated symptoms for at least 60 minutes after the first infusion and for 30 minutes after subsequent infusions. If prior infusions were well tolerated, subsequent doses may be administered over 30 minutes (± 10 minutes). If symptoms occur, the infusion should be slowed, interrupted, or discontinued. When the patient's symptoms have completely resolved,

the infusion may be continued at 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full dose during the next cycle. Patients who experience pertuzumab infusion-associated symptoms may be premedicated for subsequent.

7.3.2 Nab-paclitaxel

Nab-paclitaxel will be administered as an IV infusion over 30 minutes.
Administration: Abraxane® is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line liter is not recommended.

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of Abraxane®. In any event, filters of pore-size less than 15 micrometers must not be used.

Dose: Abraxane® will be reconstituted by appropriate study personnel and administered to the patient in the study site setting at 1-week intervals. The investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount of nab-paclitaxel to be administered.
Reconstitution and use of Abraxane®:

1. Calculate the patient's body surface area at the beginning of the study and if the weight changes by >10%.
2. Calculate the total dose (in mg) to be administered by:
   Total Dose (mg) = BSA x (study dose mg/m^2)
3. Calculate the total number of vials required by:
   Total Number of Vials = $\frac{\text{Total Dose (mg)}}{\text{100 (mg/vial)}}$
4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Reconstitute each Abraxane® vial by using a sterile syringe to inject 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than 1 minute (Note: Change the syringes after reconstituting every 3 vials).
   - **Slowly** inject the 20mL of 0.9% Sodium Chloride Injection, USP,, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a **minimum of 5 minutes** to ensure proper wetting of the lyophilized cake/power.
   - **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. **Avoid** generation of foam.
   - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

- Each mL of reconstituted product will contain 5 mg of Nab-paclitaxel.

7. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient:
   Dosing volume (mL) = Total dose (mg)/5 (mg/mL)
8. The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be **gently** inverted again to ensure complete resuspension, prior to use.
9. Once the exact volume of reconstituted Abraxane® has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Inject the calculated dosing volume of reconstituted Abraxane® suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag. Repeat steps 10 and 11 until the patient's entire required dose is injected into the IV bag.
11. Administer the calculated dosing volume of reconstituted Abraxane® suspension by IV infusion over 30 minutes. The use of in-line filters is not necessary. If used, in-line filters with pore sizes of <15µ should not be used.

7.3.3 Trastuzumab

Information provided here is mostly from the Herceptin® package insert.[52]

Administration: Herceptin® will be administered intravenously over 30 minutes. The inital dose is a loading dose of 4mg/kg over 90 minutes, but subsequent weekly maintenance dose is 2mg/kg administered over 30- minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.**

Dose: Herceptin® will be reconstituted by appropriate study personnel and administered to the patient in the study site setting at 1-week intervals.

Reconstitution and use of Herceptin®:

The diluent provided has been formulated to maintain the stability and sterility of Herceptin® for up to 28 days. Other diluents have not been shown to contain effective preservatives for Herceptin®. Each vial of Herceptin® should be reconstituted with **ONLY 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied**, to yield a multi-dose solution containing 21 mg/mL Trastuzumab. Use of all 30 mL of diluent results in a lower-than-intended dose of Herceptin®. THE REMAINDER (approximately 10 mL) OF THE DILUENT SHOULD BE DISCARDED. Immediately upon reconstitution with BWFI, the vial of Herceptin® must be labeled in the area marked "Do not use after:" with the future date that is 28 days from the date of reconstitution.
If the patient has known hypersensitivity to benzyl alcohol, Herceptin® must be reconstituted with Sterile Water for Injection (see PRECAUTIONS).

Herceptin® WHICH HAS BEEN RECONSTITUTED WITH SWFI MUST BE USED IMMEDIATELY AND ANY UNUSED PORTION DISCARDED. USE OF OTHER RECONSTITUTION DILUENTS SHOULD BE AVOIDED.
Shaking the reconstituted Herceptin® or causing excessive foaming during the addition of diluent may result in problems with dissolution and the amount of Herceptin® that can be withdrawn from the vial.
Use appropriate aseptic technique when performing the following reconstitution steps:

1. Calculate the dose in milligram based on patients weight and adjust if the weight changes by > 10 %
2. Calculate the total number of vials required by:

   Total Number of Vials = $\frac{\textbf{Total Dose (mg)}}{\textbf{440 (mg/vial)}}$
3. Using sterile technique, prepare the vials for reconstitution.
4. Swab the rubber stoppers with alcohol.
5. Using a sterile syringe, slowly inject **21 mL** of the diluent into the vial containing the lyophilized cake of Trastuzumab. The stream of diluent should be directed into the lyophilized cake.
6. Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. **DO NOT SHAKE**.
7. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The solution should be essentially free of visible particulates, clear to slightly opalescent, and colorless to pale yellow.
8. Determine the number of mg of Trastuzumab needed, based on a loading dose of 4 mg Trastuzumab/kg body weight or a maintenance dose of 2 mg Trastuzumab/kg body weight.
9. Calculate the volume of 21 mg/mL Trastuzumab solution and withdraw this amount from the vial and added it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP.
10. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. No incompatibilities between Herceptin® and polyvinylchloride or polyethylene bags have been observed.

11. Patients should be observed for fever and chills or other infusion-associated symptoms (see ADVERSE REACTIONS). If prior infusions are well tolerated, subsequent weekly doses of 2 mg/kg Trastuzumab may be administered over 30 minutes.

12. **Herceptin® should not be mixed or diluted with other drugs. Herceptin® infusions should not be administered or mixed with Dextrose solutions.**

8.0 Criteria for Starting Subsequent Cycles

Patients should meet the laboratory parameters and the performance status as outlined in section 3.0 before initiation of each cycle of therapy. All toxicities (except alopecia and lymphopenia, anemia, hyperglycemia, hypoalbuminemia, elevated serum alkaline phosphatase) should have resolved to grade 1 or lesser severity before initiation of next cycle of therapy.

Qualifying laboratory tests and procedures can be obtained up to 72 hours before planned initiation of therapy from cycle #2 and onwards.

8.1 Planned Duration of Therapy

Therapy will continue until:

- Disease progression for patients with MBC
- 6 cycles for patients with LABC
- Unmanageable toxicity
- Primary physician or patient request to discontinue therapy
- Study termination by the sponsors

8.2 Criteria for removal from Treatment

Criteria for removal

Removal of a patient from treatment will be based upon the following: unacceptable toxicities as assessed by the treatment team, based on the grade, duration, need for dose adjustment/modification of treatment; patient desires; or disease progression.

Subject Follow up

All patients having been enrolled and having received at least one dose of therapy will be evaluated for toxicity. Patients will be followed for an indefinite amount of time after enrollment. Subsequent to the 5-year mark, standard follow-up measures per tumor registry guidelines will apply.

8.3 Supportive Care and other concomitant therapy:

Supportive care will be at the treating physician's discretion, and in line with standard practice. For usage of antiemetics, granulocyte and erythrocyte growth factors, physicians are advised to follow ASCO and NCCN guidelines, as appropriate.

9.0 Dose Delays/Modifications for Adverse Events

9.1 Modifications due to toxicity during second and subsequent cycles

Dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
Therapy can be held until initiation of the next cycle of therapy. Treatment delay of > 6 weeks will require reloading of pertuzumab and trastuzumab.

9.2 Nab-paclitaxel (Abraxane) dose modifications

Refer to section 7.0 for dose calculation of nab-paclitaxel

ABRAXANE dosing should not be administered at the start of each cycle until the absolute neutrophil count returns to $\geq 1.5 \times 10^9$ cells/L and the platelet count returns to $\geq 100 \times 10^9$ cells/L. For patients receiving weekly ABRAXANE, for each subsequent dose of ABRAXANE within a cycle (Days 8, 15), patients must have an ANC $\geq 1.0 \times 10^9$ cells/L and platelets $\geq 75 \times 10^9$ cells/L. If the ANC and platelets are not adequate for treatment on Day 8, 15, and/or 22, the dose will be omitted and the total cycle length remains the same. Administration of granulocyte growth factors are allowed according to institutional guidelines.

9.2.1 Administration of ABRAXANE to Patients with Abnormal Hepatic Function

ABRAXANE should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

9.2.2 Dose Modification Table

Use this table as a guideline to determine any necessary dose modifications. The modification is dependent on the starting dose for the study.

Table 3.0: Dose Modification

Dose Level	ABRAXANE (mg/m^2)	Schedule
0	100	Weekly
-1	90	Weekly
-2	80	Day 1,8, every 21 days
-3	60	Day 1,8 every 21 days

Dose Reductions and guidelines for optional use of Growth Factors for Hematologic Toxicity

The table below provides a guideline for implementing dose reductions and optional use of growth factor treatment for hematologic toxicity:

Table 4.0: Use of G-CSF and Dose reductions for Hematologic Toxicity

Adverse Event	**Occurrence**	**Action to be Taken**
ANC < 500 cells/mm^3 (nadir count) with neutropenic fever > 38° OR Delay of next cycle due to persistent neutropenia (ANC < 1500 cells/mm^3) OR For patients on weekly treatment whose next treatment within the cycle (Day 15) is omitted due to persistent neutropenia (ANC < 1000 cells/mm^3). OR Neutropenia < 500 cells/mm^3 for > 1 week	Any Occurrence	At the first occurrence of a hematological toxicity (as outlined in the Adverse Event column), the same dose is maintained and G-CSF can be given as outlined below per discretion of primary oncologist. In the event that a hematological toxicity re-occurs in the face of G-CSF, dose reduction to the next lower level will be required for subsequent cycles once ANC is ≥ 1500 cells/mm^3. If G-CSF is given concurrently with weekly ABRAXANE, administration may begin the day after ABRAXANE is given and should stop at least 48 hours prior to when ABRAXANE is given the following week.
Thrombocytopenia Grade 3 or Grade 4*	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level

*See NCI Toxicity Criteria Scale for definition of Grade 3 and Grade 4 events.

G-CSF Administration
G-CSF administration is at the discretion of the primary oncologist and may be initiated prior to dose reduction. For QW study drug administration administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per investigator/institution's standard of care) 24 hours after chemotherapy and hold 48 hours prior to the next dose

Sensory Neuropathy
ABRAXANE should be withheld in patients who experience ≥ Grade 2 sensory neuropathy. Treatment may be resumed at the next lower dose level (see Table 3) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. The time to

resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting. In those patients who experience Grade 4 sensory neuropathy, study drug should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Level -2; see Table 3) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1.

Hypersensitivity Reactions
Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged. It is not recommended to administer ABRAXANE to patients with prior hypersensitivity to a taxane.

Other Toxicities
If toxicities are ≥ grade 3, except for anemia, and skin pain, treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Table 3). Patients with skin pain ≥ grade 2 may have their dose decreased one dose level.

9.3 Trastuzumab Dose Modifications:

The trastuzumab dose will not be modified.

9.3.1 Infusion-associated symptoms
During the first infusion, a symptom complex of fever and/or chills may occur. These are usually mild to moderate and may be accompanied by nausea, vomiting, headache, dizziness, rigors, pain, hypotension, rash, and asthenia. These symptoms occur infrequently during subsequent infusions.

a) Fever:

- For Grade 1-2 fever (38º-40ºC), stop infusion and give antipyretics. Once temperature is <38ºC, resume infusion at a slower rate.
- For Grade 3-4 (>40ºC), stop infusion and give antipyretics. If temperature falls to <38ºC within 3 hours, resume infusion at a slower rate. If fever does not fall to <38ºC within 3 hours, inpatient monitoring and assessment for other possible causes of fever, such as infection, is advised. If temperature falls to <38ºC within 3 days, and the patient has no apparent sequelae of the febrile episode, she may be rechallenged at a slower rate. If temperature >38ºC persists for >3 days, and no other cause of the fever can be identified, treatment with trastuzumab will be permanently discontinued.

b) Chills:
Treat with acetaminophen and/or diphenhydramine. Meperidine may be given at the investigator's discretion.

c) Hypersensitivity reaction (any grade):
Stop infusion and administer diphenhydramine. If symptoms resolve within 3 hours, administer the next scheduled dose of trastuzumab at a slower rate. If symptoms take longer than 3 hours to resolve, further treatment with trastuzumab is at the discretion of the investigator. Patients experiencing CTC grade 3 allergic/hypersensitivity reactions may be re-treated if, in the opinion of the investigator, the reaction was characteristic of an infusion reaction. These patients will receive appropriate premedications (steroids and antihistamines), will be closely monitored while receiving their next dose of trastuzumab (infused initially at a much slower rate), and must also be monitored for at least 8 hours after completion of the trastuzumab infusion, to make sure that they do not experience a delayed reaction after their premedications wear off. Treatment with trastuzumab will be permanently discontinued in any patient who experiences either an anaphylactic reaction (a CTC Grade 4 allergic/hypersensitivity reaction) or a grade 3 reaction that is consistent with an allergic reaction (most often with the first dose of trastuzumab, characterized by bronchospasm and/or urticaria) to this agent.

9.4 Pertuzumab Dose Modifications:

The Pertuzumab dose will not be modified.

As of 10 November 2010, data are available for 1327 patients with cancer and treated with pertuzumab in all company-sponsored trials (this number excludes ongoing blinded trials). Gastrointestinal toxicities (diarrhea, nausea, vomiting, abdominal pain) and fatigue are the most frequently reported adverse events (AEs) with single-agent therapy. Diarrhea and rash are common events increased with pertuzumab in combination with chemotherapy compared with chemotherapy alone in one ongoing and one completed study in patients with ovarian cancer (Studies BO17931, TOC3258g). The most common AEs during dual therapy with pertuzumab and trastuzumab in MBC (based on Study BO17929) were diarrhea, fatigue, nausea and rash. The majority of these AEs were National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 1 or 2 in severity.

The mechanisms behind diarrhea and rash are unknown, similar side effects are seen with other agents that cause HER1 inhibition. The most frequently occurring AEs during neoadjuvant treatment of patients with EBC (based on Study WO20697) with pertuzumab with/without trastuzumab in combination with docetaxel were alopecia, neutropenia, diarrhea, nausea, fatigue, rash and mucosal inflammation. Addition of pertuzumab to the trastuzumab plus docetaxel regimen did not notably affect the overall safety profile, and the tolerability of pertuzumab plus docetaxel was also broadly comparable to the triple regimen. Patients receiving trastuzumab and pertuzumab without docetaxel in the neoadjuvant setting reported notably fewer AEs across most body systems compared to patients receiving chemotherapy-containing treatment. Serious adverse events (SAEs) assessed as compatible with infusionrelated/ hypersensitivity/anaphylactic reactions have been rarely identified in patients

(<1%) receiving pertuzumab. A low level of cardiac toxicities, predominantly asymptomatic declines in left ventricular ejection fraction (LVEF), has been reported. A total of eight patients (<1%) have experienced symptomatic cardiac failure across all studies to date. Of these eight patients, four were receiving pertuzumab in combination with trastuzumab. No clear association between the frequency, nature, and severity of pertuzumab-related toxicities and dose level has been observed, however the majority of trials have been performed with a schedule of 840 mg loading dose followed by 420 mg every 3 weeks thereafter.

Dose will be held or not based on cardiac monitoring as described under the heading for trastuzumab dose modification above.

9.5 Cardiac Toxicity with pertuzumab and trastuzumab:

All patients must have a baseline LVEF ≥ 50%. LVEF will be monitored regularly. If an investigator is concerned that an AE may be related to cardiac dysfunction, an additional LVEF measurement should be performed. Pertuzumab and trastuzumab will be discontinued in any patient who develops clinical signs and symptoms suggesting CHF, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA. CHF should be treated and monitored according to standard medical practice.

At present, there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF. However, to ensure the safety of patients in the trial, pertuzumab and trastuzumab must be interrupted in all patients for whom a drop of LVEF by ≥ 10 points to a value lower than 50 % is documented and must be discontinued if a repeat assessment within 3 weeks of the first assessment, using the same assessment method, confirms the drop of LVEF by ≥ 10 points to a value lower that 50%

Withhold pertuzumab and Herceptin dosing for at least 3 weeks for either:

- a drop in LVEF to less than 40%
- a LVEF of 40% – 45% associated with a fall of ≥ 10% points below pretreatment values or lower

Pertuzumab may be resumed if the LVEF has recovered to > 45% or 40% – 45% associated with < 10% points below pretreatment values.

If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of pertuzumab and Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Pertuzumab should be withheld or discontinued if Herceptin treatment is withheld or

discontinued.

10.0 Monitoring and Blood draws

After the study candidates consent to participating in the study, they will be evaluated with baseline CBC, chemistry, and liver function tests. They will also undergo CT scan of the chest abdomen pelvis for initial staging and assessment of disease and bone scan (PET/CT scans are acceptable) for RECIST [version 1.1] measurements and in the case of patients with LABC, for baseline eligibility assessment (i.e., to exclude evidence for distant metastasis)..

The patients will undergo every three months cardiac monitoring by echocardiogram or MUGA scan while on treatment. If there is a decrease in ejection fraction, patient will undergo more frequent cardiac monitoring as described above in the trastuzumab dose modification section.

The patient will be monitored clinically by their primary oncologist every three weeks along with CBC, chemistry, and liver function tests. Those with MBC will also undergo repeat imaging studies with CT scan of the chest, abdomen, and pelvis and bone scan (or, in case of PET/CT assessment as baseline, repeat testing with the same as appropriate) every 9 weeks. They will continue to be treated with the combination therapy and monitored until progression. Patients enrolled with LABC will have their imaging studies repeated only as clinically indicated.

11.0 Data Safety and Monitoring Plan

A) Definition of Risk Level

This is a Risk Level 3 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx because it is a Phase II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

B) Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Table 1: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement

RL 1, RL2, and Compassionate Use Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

Data and safety will be reported to the COH DSMC using the PMT report and submitted accoring to the timelines in Table 1 above. Protocol specific data collection will include the following items: a summary of accrual, adverse events and treatement related mortality.

C) Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

Serious Adverse Event (SAE) [21 CFR 312.32] is defined as *any expected or unexpected adverse event that results in any of the following outcomes:*

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization

- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary Malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

12.0 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the protocol continuation reports and PMT report (see Table 2 below).

Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

Externally Sponsored Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED[1]**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 1 and 2	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the study will be suspended, terminated, amended, or allowed to continue without amendment.

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

12.1 Methods and Timing for Assessing AND Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

12.1.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

12.1.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the pertuzumab, trastuzumab, and nab-paclitaxel combination, and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the pertuzumab, trastuzumab, and nab-paclitaxel combination, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the pertuzumab, trastuzumab, and nab-paclitaxel combination; and/or the AE abates or resolves upon discontinuation of the pertuzumab, trastuzumab and nab-paclitaxel combination or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the AE has an etiology other than the pertuzumab, trastuzumab and nab-paclitaxel (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to pertuzumab, trastuzumab and nab-paclitaxel administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

12.2 Procedures for Eliciting, Recording, and Reporting Adverse Events

12.2.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

12.2.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When

recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the {study drug} should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior pertuzumab, trastuzumab and nab-paclitaxel exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are

identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

h. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product

12.3 SAE Reporting to Celgene

The Investigator will utilize the FDA MedWatch program for the reporting of adverse events and follow up information to those events. Full information regarding these procedures is described on the FDA website. (http://www.fda.gov/medwatch/).
The Sponsor-Investigator will also utilize the Celgene SAE Completion Form for the reporting of adverse events and follow up information to those events.
All serious adverse events regardless of severity or relationship must be reported to Celgene Corporation within 24 hours of the investigational staff's knowledge.

Celgene Corporation
Drug Safety Department
86 Morris Avenue
Summit, NJ 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

and
Industry Contact:
Norma Powers
Director, Medical Operations
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Mobile: 267-337-2720
Fax: 908-673-2779
Email: npowers@celgene.com

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (SAE's will be reported from the time the patient starts

treatment to at least 28 days after the last dose of investigational product.) , and those made known to the Investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (e.g., missing causality assessment) may be handled by phone.

Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to the IP based on the Investigator Brochure.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (i.e., SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- In Japan, measures taken in foreign countries to ensure patient safety, study reports that indicates potential risk of cancer, etc., or biannual SAE report according to the local regulations.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC.

Celgene Drug Safety Contact Information:

Celgene Corporation

Drug Safety

86 Morris Avenue

Summit, N.J. 07901
Toll Free: (800)-640-7854
Phone: (908) 673-9667
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

12.4 SAE Reporting to Genentech

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682
OR
(650) 225-5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to the combination of pertuzumab, trastuzumab, and nab-paclitaxel and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the pertuzumab, trastuzumab, and nab-paclitaxel will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- Additional Reporting Requirements to Genentech include the following:
- Any reports of pregnancy following the start of administration with the pertuzumab, trastuzumab, and nab-paclitaxel will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

Note: Investigators should also report events to their IRB as required.

MedWatch 3500A Reporting Guidelines
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

Additional Reporting Requirements for IND Holders
For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:
The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of pertuzumab. An unexpected adverse event is one that is not already described in the pertuzumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report
The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of pertuzumab. An unexpected adverse event is one that is not already described in the pertuzumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the

event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

Randomization Codes for blinded clinical trials

The blind will be broken for ADR reports that are Serious and Unexpected, unless otherwise agreed with applicable regulatory authorities.

FDA fax number for IND Safety Reports:
Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:
Fax: (650) 225-4682 or (650) 225-5288

And to the Site IRB:
City of Hope IRB
email: **IRBeSubmit@coh.org**
Tel: 626-256-4673 ext.63374

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 OR (650) 225-5288

IND Annual Reports

Copies to Genentech:
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

Study Close-Out
Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Pertuzumab and trastuzumab Protocols
Email : herceptin-gsur@gene.com OR pertuzumab-gsur@gene.com
Fax : 650-360-6908

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET
Genentech Supported Research

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]
Follow-up Report Date	[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]

Subject Initials (Enter a dash if patient has no middle name)	[INSERT investigational product name] - [INSERT investigational product name] - [INSERT investigational product name]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

13.0 Agent Information

13.1 Drug Information on Pertuzumab

Effects in Humans

13.1.1 Pharmacokinetics

Similar pharmacokinetics (PK) was observed across studies with no change in clearance at doses from 2.0 to 15.0 mg/kg (140 mg to 1050 mg for a 70 kg patient). A two compartment model adequately described the concentration-time data with a systemic serum clearance of approximately 0.24 L/day and a terminal half-life of approximately 17 days for a typical patient. Based on these data, a dosing interval of three weeks (q3w) is recommended in clinical studies. In Phase II studies, a loading dose of 840 mg (followed by 420 mg q3w), was capable of attaining steady-state trough and peak concentrations by the second cycle. Population PK modeling of data from Phase Ia and Phase II studies supports the continued use of fixed, non-weight-based dosing in female patients (insufficient data for male patients). There was no evidence of an impact of pertuzumab on the PK of co-administered gemcitabine, docetaxel, capecitabine or erlotinib in Phase Ib studies.

13.1.2 Efficacy

Clinical activity has been observed in patients with HER2 low-expressing tumors who have received pertuzumab either as a single agent or in combination with cytotoxic chemotherapy. Complete responses have not been observed in any of these trials.
In single agent pertuzumab studies partial responses or stable disease lasting ≥ 6 months have been observed in 15% of patients with ovarian cancer (study TOC2689g) and in 8% of patients with HER2 low-expressing breast cancer (BO16934). No responses were observed in clinical studies of single-agent pertuzumab in patients with hormone refractory prostate cancer (Studies BO17004 and TOC2682g) or NSCLC (Study TOC2752g).

Partial responses were observed in 3 out of 15 patients (20%) with NSCLC who received pertuzumab in combination with erlotinib (Study WO20024). In Study TOC3258g pertuzumab with gemcitabine given to patients with platinum-resistant ovarian cancer showed prolongation of PFS over gemcitabine alone (Hazard ration [HR] 0.66; 95% CI: 0.43, 1.03). However, in platinum-sensitive ovarian cancer patients, addition of pertuzumab to a carboplatin-based doublet of chemotherapy did not improve PFS (Study BO17931). In Study BO17929 four complete responses and 12 partial responses (24% objective response rate) were observed in patients with previously treated HER2-positive MBC following combined treatment with pertuzumab and trastuzumab. In Study WO20697 patients with EBC receiving triple combination neoadjuvant therapy of pertuzumab, trastuzumab and docetaxel had a pathological complete response (pCR) rate of 46%, compared with 29% in patients receiving trastuzumab plus docetaxel (P=0.0141, 95% CI 21- 39).

13.1.3 Safety

CONTRAINDICATIONS
Known hypersensitivity to pertuzumab or to any other compound of the product

WARNINGS AND PRECAUTIONS
Risk of Allergic Reactions, Including Anaphylaxis and Infusion-Associated Symptoms and Respiratory Events
Like other monoclonal antibodies, pertuzumab may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and/or vomiting. Such reactions typically occur during or very shortly after an infusion but may also show a delayed onset. Infusion-associated symptoms tend to be more frequent and severe with the first infusion than subsequent infusions. Serious events compatible with infusion-associated reactions/hypersensitivity reactions (hypersensitivity, urticaria, pulmonary edema, fatal ARDS, anaphylaxis, hypertension & dyspnea) have been reported with pertuzumab.

Intravenous administration of pertuzumab should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. Patients will be monitored during each pertuzumab infusion and following the completion of the infusion for any adverse effects as specified in the study protocol. If infusion-associated symptoms occur, patients must be monitored until complete resolution of signs and symptoms. Patients who experience infusion-associated symptoms may be pre-medicated with antihistamines, paracetamol (acetaminophen) or corticosteroids for subsequent infusions.

Patients should be monitored during and following completion of each pertuzumab infusion for any adverse effects. Since there is the potential for a delayed onset of infusion-associated reactions patients should be instructed to contact the treating physician with any concerns.

Infusion of pertuzumab should be stopped in patients who develop dyspnea or clinically significant hypotension (defined per investigator discretion). Patients who experience an NCI-CTC Grade 4 allergic reaction or acute respiratory distress syndrome should not receive any further doses of pertuzumab.

A low rate of respiratory events compatible with an infusion-associated reaction or hypersensitivity reaction/anaphylaxis has been reported. Although pertuzumab targets the HER2 receptor it inhibits heterodimerization with other members of the HER family (eg, EGFR [HER1]). Accordingly, it may cause toxicities associated with the use of EGFR inhibitors, such as interstitial lung disease. The few reports of interstitial lung disease occurring in pertuzumab-treated patients received so far also had evidence of alternative causes, eg, concomitant medication, preceding/concurrent neutropenia with potential infection or relevant medical history.

13.1.4 Risk of Cardiac Dysfunction

HER2-targeted therapy, notably treatment with trastuzumab, is associated with cardiac dysfunction. In patients treated with trastuzumab, the incidence of left ventricular dysfunction was greatest among those who received concurrent treatment with anthracyclines. Because pertuzumab is also directed against HER2, there is a risk of cardiac dysfunction with pertuzumab treatment.

All patients enrolled in pertuzumab studies undergo regular LVEF monitoring by echocardiography or MUGA scan. Monitoring of LVEF is advised while patients are receiving pertuzumab. If symptomatic left ventricular dysfunction develops (NCI-CTC Grade 3 or 4), the patient must discontinue pertuzumab. Left ventricular dysfunction, whether symptomatic or not, should be treated and followed according to standard medical practice. For further guidance, please see individual study protocols.
Patients with significant cardiac disease or baseline LVEF below the institution's lower limit of normal should not receive pertuzumab. Specific risk factors for pertuzumab associated cardiac dysfunction are not known at this time but are likely to be similar to the risk factors for trastuzumab-associated cardiac dysfunction and cardiac disease in general (low LVEF, prior or concurrent anthracyclines, hypertensive and/or ischemic heart disease etc). The risks of cardiac dysfunction with pertuzumab treatment should be carefully weighed against the potential benefit of pertuzumab in patients who have received prior anthracyclines.

13.1.5 Serious Adverse Reactions

List of preliminary adverse drug reactions:

- Infusion-associated reactions (including pyrexia, chills, nausea, vomiting,
- dyspnea, rash, urticaria, vision blurred, dizziness, headache, hypertension)
- Hypersensitivity reactions including anaphylaxis
- Rash
- Abdominal pain
- Diarrhea
- Nausea
- Vomiting
- Cardiac dysfunction (asymptomatic decrease in left ventricular systolic
- dysfunction or symptomatic as heart failure):
- Neutropenia (exacerbation of chemotherapy-associated myelosuppression
- including febrile neutropenia, neutropenic infection or neutropenic sepsis)
- Asthenic conditions

13.1.6 Non-Serious Adverse Reactions

No additional non-serious adverse reactions.

13.1.7 Interactions With Other Medicinal Products and Other Forms of interaction

None known

13.1.8 Use in Special Populations

No studies have been performed in pediatric patients. Patients aged > 18 years have been included in studies to date ie, there is no exclusion based on advanced age. No studies

have been performed in patients with renal or hepatic impairment.

13.1.9 Pregnancy

Impairment of fertility: Long-term studies in animals have not been performed to evaluate the effect of pertuzumab on fertility. No fetal studies in humans have been performed but in the preclinical reproductive toxicity study in cynomolgus monkeys, there were findings of delayed renal development, oligohydramnios, and intrauterine death. Moreover, in the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab. Therefore, pertuzumab should not be used in pregnant women. Because of the long half-life of pertuzumab women are to be warned not to become pregnant for at least 6 months after completion of treatment. For further guidance, please see individual study protocols.

Nursing Mothers

It is not known whether pertuzumab is excreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, pertuzumab should not be administered to nursing women.

13.1.10 Overdose

Safety in Phase I Studies / Information on MTD

Five dose levels of pertuzumab ranging between 0.5 mg/kg and 15 mg/kg were evaluated in Study TOC2297g. Using body weight-based dosing, individual single doses ranged from 29 mg up to 1635 mg. Twenty-one patients received at least one dose of pertuzumab and all 21 experienced at least one AE. The maximum tolerated dose (MTD) was not reached at any dose level. The most commonly reported events were fatigue (52%), vomiting (52%), nausea (48%), diarrhea (29%), and rash (29%). The majority of AEs were NCI CTC Grade 1 or 2 in severity. Twelve patients in this study experienced at least one Grade 3 or 4 AE. Grade 3 or 4 AEs that were observed in two or more patients included dyspnea, pleural effusions, and abdominal pain. No relationship to dose level was observed for any of these common AEs.

In a Japanese Phase I dose escalation study in 18 patients, pertuzumab was well tolerated up to maximum dose of 25mg/kg and the MTD was not reached. Individual single doses ranged from 215 mg up to 1728 mg. The safety profile was consistent with that observed in other phase I studies. The most common toxicities were diarrhea, rash, nausea, vomiting, and lymphopenia. No clear dose-relationship was observed.

Drug Biochemistry

Pertuzumab is a fully humanized monoclonal antibody based on the human IgG1 (κ) framework sequences and consists of two heavy chains (449 residues) and two light chains (214 residues). Like trastuzumab, pertuzumab is directed against the extracellular domain of HER2. However, it differs from trastuzumab in the epitope-binding regions of the light chain (12 amino acid differences) and heavy chain (29 amino acid differences). As a result, pertuzumab binds to an epitope within what is known as subdomain 2 of HER2 while the epitope for trastuzumab is localized to subdomain 4 [3.1, 3.2].

Manufacturing Procedures
Pertuzumab is produced in Chinese hamster ovary (CHO) cell cultures and purified by protein A column affinity chromatography, followed by ion-exchange column chromatography. Because of the high degree of homology between pertuzumab and trastuzumab, procedures similar to those developed for trastuzumab are used for the manufacturing process, the in-process controls, and the characterization of pertuzumab.

No bovine-derived raw materials are used in the manufacture of pertuzumab.
Each lot of the recombinant antibody produced for clinical purposes meets USP requirements for sterility and safety. In addition, each lot is extensively characterized and meets the required specifications for identity, purity, and potency.

Clinical Formulation and Storage Requirements
Pertuzumab drug product is provided as a single use formulation containing 30 mg/mL pertuzumab in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20. Each 20 mL vial contains 420 mg of pertuzumab (14.0 mL/vial). Upon receipt of pertuzumab vials are to be refrigerated at 2°C–8°C (36°F–46°F) until use. Pertuzumab vials should not be used beyond the expiration date provided by the manufacturer. Because the formulation does not contain a preservative, the vial seal may only be punctured once. Any remaining solution should be discarded. Vial contents should be protected from light, and should not be frozen.

The solution of pertuzumab for infusion, diluted in PVC or non-PVC polyolefin bags containing 0.9% Sodium Chloride Injection, USP, may be stored for up to 24 hours prior to use. Diluted pertuzumab has been shown to be stable for up to 24 hours at a temperature range of 2°C–25°C. However, since diluted pertuzumab contains no preservative, the diluted solution should be stored refrigerated (2°C–8°C).

Support for Dose Regimen
A dosing regimen of pertuzumab administered every 3 weeks to patients in Phase II studies (TOC2689g, BO16934) using a fixed 840 mg loading dose (equivalent to 12 mg/kg for a 70 kg patient) for treatment cycle 1 followed by a fixed 420 mg "maintenance" dose (equivalent to 6 mg/kg) for subsequent treatment cycles resulted in steady-state serum trough concentrations of approximately 60 µg/mL by the second treatment cycle. In nonclinical dose-response xenograft studies using nude mice implanted with NSCLC and breast cancer tumors (low and high HER2 expression levels), > 80% suppression of tumor growth was achieved when steady-state trough concentrations of pertuzumab were 5-25 µg/mL. Thus the steady-state serum trough concentrations obtained in patients are in excess of concentrations shown to be efficacious in animal tumor models, and therefore expected to result in a biologic effect.

A preliminary population PK analysis of the Phase Ia (TOC2297g) and Phase IIa (TOC2689g, BO16934) studies, comprising 153 patients (weight range: 45.0-150.6 kg) and 1458 concentration-time points, showed that the population variability of steady-state trough concentration and exposure were similar with fixed-, body surface area-, and weight-based dosing. A dose based on body-surface area or weight was not superior to a

fixed dose, supporting the continued use of a fixed dose of pertuzumab in female patients with MBC and ovarian cancer [5.12].

The dependence of pertuzumab serum clearance on body weight for both female and male patients will be evaluated further using all available clinical pharmacokinetic data from the Phase II studies.

13.1.11 Risk of Cardiac Dysfunction

HER2-targeted therapy, notably treatment with trastuzumab, is associated with cardiac dysfunction. In patients treated with trastuzumab, the incidence of left ventricular dysfunction was greatest among those who received concurrent treatment with anthracyclines. Because pertuzumab is also directed against HER2, there is a risk of cardiac dysfunction with pertuzumab treatment.

All patients enrolled in pertuzumab studies undergo regular LVEF monitoring by echocardiography or MUGA scan. In pertuzumab single-agent Phase II studies, the incidence of LVEF decrease was similar to that reported with trastuzumab. A fall in LVEF of ≥ 10 percentage points to a LVEF value < 50% was observed in 21/302 patients (7%) who had a post-baseline LVEF assessment. Nine of these patients had received prior anthracycline treatment. In studies where the primary safety analysis has been completed, the incidence of cardiac dysfunction associated with pertuzumab in combination with chemotherapy, does not appear to be any greater than that associated with trastuzumab plus chemotherapy. In patients selected for good cardiac function at baseline and with minimal cardiac risks, the combination of trastuzumab and pertuzumab also appears to be well tolerated, with no increase in the rate of cardiac events reported to date, compared with rates in patients receiving trastuzumab alone. Furthermore, pertuzumab, trastuzumab and non-anthracycline based neoadjuvant chemotherapy did not result in any significantly greater incidence of LVEF decline in EBC patients than the incidence seen in patients receiving trastuzumab and chemotherapy.

Overall, five symptomatic cardiac failure events have been reported in patients treated with pertuzumab from studies where the primary safety analysis has been completed. Two of these events occurred in patients with MBC who had received prior anthracyclines: one of these patients was treated with single agent pertuzumab (Study BO16934) and the second patient was receiving concomitant trastuzumab (Study TOC3487s). Two events occurred in patients with ovarian cancer, who were receiving concomitant chemotherapy (gemcitabine for one patient in Study TOC3258g and paclitaxel plus carboplatin for one patient in Study BO17931). The fifth event occurred in a patient with EBC receiving concomitant trastuzumab (Study WO20697). Three further events of CHF have been reported in ongoing studies. One event occurred in a patient with EBC (Study BO22280) who had just completed FEC treatment and was receiving concurrent docetaxel and trastuzumab. The second occurred in a patient with MBC (Study MO22324) who was treated with concomitant trastuzumab and capecitabine. This patient had a history of hypertensive heart disease, prior anthracycline (epirubicin) treatment and radiotherapy to the left chest. The third event occurred in a patient with

NSCLC (Study TOC4603g) who was receiving pertuzumab in combination with erlotinib.

Patients with significant cardiac disease or baseline LVEF below the institution's lower limit of normal should not receive pertuzumab. Specific risk factors for pertuzumab associated cardiac dysfunction are not known at this time but are likely to be similar to the risk factors for trastuzumab-associated cardiac dysfunction and cardiac disease in general (low LVEF, prior or concurrent anthracyclines, hypertensive and/or ischemic heart disease etc). The risks of cardiac dysfunction with pertuzumab treatment should be carefully weighed against the potential benefit of pertuzumab in patients who have received prior anthracyclines.

Monitoring of LVEF is advised while patients are receiving pertuzumab. If symptomatic left ventricular dysfunction develops (NCI-CTC grade 3 or 4), the patient must discontinue pertuzumab. Left ventricular dysfunction, whether symptomatic or not, should be treated and followed according to standard medical practice until resolution or a final outcome.

13.1.12 Risk of EGFR-Related Toxicities

Although pertuzumab targets the HER2 receptor it inhibits heterodimerization with other members of the HER family (eg, EGFR [HER1]). Accordingly, it may cause toxicities associated with the use of EGFR inhibitors such as diarrhea, rash and other dermatologic toxicities (eg, dry skin, pruritus, nail disorders, mucositis).

Diarrhea

In the 7-week IV and 26-week toxicity studies in cynomolgus monkeys, there was a treatment-related increase in the incidence of diarrhea. Diarrhea has been observed in approximately 60% of patients (treatment-related diarrhea in 50% of patients) being treated with pertuzumab in Phase II single-agent studies, and up to approximately 70% of patients in combination therapy studies. Diarrhea was NCI-CTC grade 1 or 2 in the majority of cases. To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication should be considered and patients treated with fluids and electrolyte replacement, as clinically indicated.

Rash

Rash has also been observed with EGFR inhibitors, mostly of mild to moderate intensity. Rash has been observed in approximately 17% of patients receiving pertuzumab in Phase II single-agent studies and up to 73% of patients in combination studies. The rash was generally of NCI-CTC grade 1 or 2 severity. Treatment recommendations for EGFR associated rash include topical or oral antibiotics, topical pimecrolimus, topical or (for severe reactions) systemic steroids [6.1]. These agents may be used in patients experiencing pertuzumab-related rash, as clinically indicated, although they have not been studied in this context.

Risk of Neutropenia

Trastuzumab has been shown to increase NCI-CTC grades 3 and 4 neutropenia/febrile neutropenia when used in combination with higher dose (100 mg/m2) docetaxel in patients with MBC [6.2]. Pertuzumab, at a dose of 420 mg, was well tolerated in combination with docetaxel up to 75 mg/m2 in the Phase Ib study, BO17021. However, pertuzumab in combination with 100 mg/m2 docetaxel was not well-tolerated. Dose limiting toxicity was observed, including febrile neutropenia. In light of these data, patients receiving pertuzumab in combination with docetaxel in ongoing studies are treated initially with 75 mg/m2 docetaxel, and only patients who tolerate 75 mg/m2 are eligible for dose escalation to 100 mg/m2 (as described in the protocol dose escalation rules). This strategy is intended to ensure both tolerability and optimal individual patient exposure to docetaxel. Using this approach in the Phase II WO20697 study in patients receiving docetaxel with pertuzumab and/or trastuzumab as neoadjuvant therapy for EBC, between 56% and 71% of patients experienced a neutropenic AE, and 8% to 20% of patients required study drug dose modification. However, only 1 patient withdrew due to neutropenia. Patients receiving pertuzumab in combination with docetaxel or other cytotoxic agents should undergo careful hematological monitoring for neutropenia during treatment, and should be treated promptly with antibiotics and other supportive measures as clinically indicated.

13.1.13 Precautions

Special Care

Laboratory and Diagnostic Tests

Pertuzumab may contribute to a risk of cardiac dysfunction. Noninvasive cardiac monitoring, such as echocardiography, should be performed at scheduled time points, as specified in the study protocols, to ensure that pertuzumab treatment can be promptly withheld and medical treatment initiated if indicated.

Drug–Drug Interactions/Drug–Laboratory Test Interactions

Three Phase Ib and II studies have evaluated the pharmacokinetics of co-administered cytotoxic agents, gemcitabine, capecitabine, and docetaxel when administered with pertuzumab. These studies show that concomitant administration of pertuzumab does not affect the pharmacokinetics of these agents. The pharmacokinetics of erlotinib also appears to be unaltered by concomitant administration of pertuzumab, when compared to historical data from erlotinib NSCLC studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of pertuzumab or its effect on fertility.

Pregnancy

No fetal studies in humans have been performed but pertuzumab caused oligohydramnios, delayed renal development and embryo-fetal deaths in pregnant cynomolgus monkeys. Moreover, in the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab (for further details, see

Herceptin Prescribing Information). Therefore, pertuzumab should not be used in pregnant women. Protocols for ongoing pertuzumab studies indicate that highly effective contraceptive measures must be used; continuous pregnancy monitoring must be performed during the trials and for 6 months after the last dose of study drug is administered. Because of the long half-life of pertuzumab women should be warned not to become pregnant for at least 6 months after completion of treatment

Nursing Mothers
It is not known whether pertuzumab is excreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, pertuzumab should not be administered to nursing women.

Pediatric Use
No studies have been performed in pediatric patients.

13.1.14 Supplier
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990 U.S.A.
F. Hoffmann-La Roche Ltd.
Grenzacherstrasse 124
Basel, Switzerland

13.2 Drug Information on Nab-Paclitaxel (ABI-007; tradename: Abraxane®)

ABRAXANE for Injectable Suspension (also known as ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents. The active agent in ABRAXANE is paclitaxel.

In the United States, ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

13.2.1 Risks and Contraindications

Preclinical Studies with ABRAXANE

Preclinical studies comparing ABRAXANE to Taxol® (paclitaxel ® EL solvent-based, BMS) demonstrated lower toxicities, with an MTD approximately 50% higher for ABRAXANE compared to Taxol. At equal doses there was less myelosuppression and

improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, ABRAXANE treated groups showed more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival. At equal dose, tumor paclitaxel area under the curve was 33% higher for ABRAXANE versus solvent based paclitaxel, indicating more effective intratumoral accumulation of ABRAXANE[35]

13.2.2 Clinical Studies with Abraxane®

Weekly for 3 Weeks, Every 4 Weeks Schedule

Thirty-nine patients were enrolled into a Phase I study of ABRAXANE administered QW for 3 weeks followed by a 1 week rest in patients with advanced solid tumors[36] The MTDs for heavily and lightly pre-treated patients were 100 and 150 mg/m^2 respectively. Dose limiting toxicities included grade 4 neutropenia and grade 3 sensory neuropathy. Premedication was not required, and unexpected, non-taxane associated toxicities were not observed.

In a Phase II trial in heavily pretreated patients with taxane-refractory metastatic breast cancer, objective antitumor responses occurred in 14% of women treated with ABRAXANE 100 mg/m^2 QW schedule. ABRAXANE weekly regimen was well tolerated; 91% of 106 patients were treated at the full dose of 100 mg/m^2 of ABRAXANE without dose reductions. Based on the activity and low toxicity documented with this schedule, the study was expanded to evaluate the efficacy and safety/tolerability of a higher dose of ABRAXANE 100 mg/m^2 weekly regimen in 75 additional patients. Results of this dose-finding study confirm the dose of ABRAXANE 100 mg/m^2 as the appropriate dose for further study in this patient population[35]

In an open-label, randomized, multicenter phase II study comparing the antitumor response and toxicity of in two QW dosing regimens, ABRAXANE dosed Q3W, and Taxotere® (polysorbate solvent-based docetaxel Sanofi-Aventis] Q3W for the first-line treatment of metastatic breast cancer[24], a total of 300 patients were randomized to one of four treatment arms: (A) ABRAXANE 300 mg/m^2 IV Q3W, (n=76); (B) ABRAXANE 100 mg/m^2 (n=76); (C) ABRAXANE 150 mg/m^2 QW (n=74) QW every 28 days; or (D) Taxotere 100 mg/m^2 Q3W (n=74). The primary objective of the trial was to evaluate the antitumor activity and safety of three different ABRAXANE regimens to determine the optimal dose and frequency to be used. Secondary objectives included the comparisons of each treatment group with respect to efficacy and safety, specifically: ABRAXANE to Taxotere; ABRAXANE QW regimens to ABRAXANE Q3W regimen; and the two dose levels of QW ABRAXANE. Patients received ABRAXANE as a 30-minute IV infusion without premedication; Taxotere was administered as a 60-minute infusion with corticosteroid premedication. Total of 75% of all patients were post-menopausal with a mean age of 53.9 years at randomization.

Both ORRs and total response rates were higher in all ABRAXANE arms compared to the Taxotere arm. The investigator-reported ORRs were 46%, 63%, 74%, and 39%, for arms A, B, C, and D, respectively. This difference was statistically significant for both QW dosing arms of ABRAXANE compared with Taxotere, (P = 0.002 for arm B *v* D, and P <0.001 for arm *v* D). The corresponding investigator-reported total response rates were

72%, 83%, 91% and 69% for the four arms, respectively. This difference reached statistical significance for arms B and C compared to Taxotere (P = 0.009 for arm B *v* D, and p=0.005 for arm C *v*. D). No significant difference in ORR was noted between the two weekly dosing arms (arm B vs. C, P = 0.24). A significant increase in PFS was observed in the 150 mg/m^2 QW arm compared to the Taxotere arm (14.6 *v* 7.8 months, respectively, P = 0.012, hazard ratio 0.57). No significant difference in PFS was found between the ABRAXANE 300 mg/m^2 Q3W arm and Taxotere arm (A and D). Similarly, PFS was not significantly different between arms A and C, or arms B and D.

All three ABRAXANE arms demonstrated a favorable safety profile when compared with the Taxotere arm. The most frequent hematologic adverse event was neutropenia, with significantly lower rates of Grade 3/4 neutropenia in all ABRAXANE arms (Grade 4, 5%, 5%, 9%, 75% for arms A, B, C, D, respectively). ABRAXANE also had lower rates of febrile neutropenia (1%, 1%, 1%, 8% for arms A, B, C, D, respectively) and fatigue (Grade 3, 5%, 0%, 3%, 19% for arms A, B, C, D, respectively) compared to Taxotere. While the incidence of sensory neuropathy was similar in the ABRAXANE and Taxotere arms, the median time to improvement in patients with Grade 3 neuropathy was shorter in all three ABRAXANE arms (22, 22, 19 and 37 days in arms A, B, C and D, respectively).The ABRAXANE arms demonstrated improved safety and increased efficacy compared with Taxotere. All three ABRAXANE regimens produced lower rates of neutropenia, febrile neutropenia, and fatigue than Taxotere.[24]

Continuous Weekly (QW) Schedule in Neoadjuvant Breast Cancer

The NSABP studied the administration of ABRAXANE in a neoadjuvant setting to patients with locally advanced breast cancer at a dose of 100 mg/m^2 QW for 12 weeks, with no break[52]. Four cycles of FEC were administered sequentially based on patients' HER2 status: HER2 negative patients received FEC-100 (F: 500 mg/m^2, E: 100 mg/m^2, C: 500 mg/m^2 Q3 weeks) and HER2 positive patients received weekly trastuzumab in addition to FEC-75 (F: 500 mg/m^2, E: 75 mg/m^2, C: 500 mg/m^2 Q3 weeks). Weekly trastuzumab was permitted during ABRAXANE and FEC-75 treatment at the discretion of the investigator. The primary objective of the trial was to determine the pathologic complete response rate (pCR) in the breast. At the time of initial report at SABCS 2006, 65 patients had been entered on study and were evaluable for cCR and safety. Following 12 weeks of ABRAXANE, a clinical complete response rate (cCR) of 32% was noted. The therapy was well tolerated, with 48/65 patients receiving 12 doses in 12 weeks and 13/65 receiving 12 doses in 13-14 weeks. The incidence of peripheral (sensory) neuropathy was low (11% grade 2, 5% grade 3) as was neutropenia (3% grade 3 and no grade 4). The authors concluded that the administration of ABRAXANE 100 mg/m^2 QW x 12 was both effective and tolerable.

At the time of this update, more than 20 abstracts and publications have been presented at major oncology conferences or published in medical journals related to ABRAXANE QW schedule in breast cancer, including completed and ongoing studies.

13.2.3 Human Toxicity:

Please refer to the Clinical Investigator's Brochure for details of the Adverse Reactions in the overall Safety Database for Abraxane®. The following have been observed:

myelosuppression, nausea and vomiting, diarrhea, mucositis, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, sensory neuropathy, bilirubin/liver enzyme elevations, allergic reactions, alopecia, asthenia, arthralgia, and myalgia. During post marketing surveillance, rare cases of severe hypersensitivity reactions have occurred.

Pregnancy
Abraxane® may cause fetal harm when administered to a pregnant woman. A developmental toxicity study in rats showed that no gross external, soft tissue or skeletal fetal alterations were caused by Abraxane® at doses of 0.5 mg/kg/day. Higher doses of Abraxane® resulted in significant maternal toxicity. This was evidenced by increased mortality, reduction in body weight gain, reduced terminal body weight, reduced food intake, and embryo-fetal lethality. Dose-related increases in malformations, variations, fetal deaths and/or resorptions occurred in pregnant rats that were administered intravenous doses of 1 or 2 mg/kg/day of Abraxane®.

There are no adequate and well-controlled studies of Abraxane® in pregnant women. If Abraxane® is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Nursing Mothers
It is not known whether paclitaxel (and therefore Abraxane®) is excreted in human milk. It has been reported that following IV administration of 14C- paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving Abraxane® therapy.

13.2.4 Concomitant Medications/Precautions
Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Concurrent treatment with bisphosphonates is allowed. Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.

13.2.5 Storage and Stability
Storage: Store the vials in original cartons at 20º C to 25º C (68º F to 77ºF). Retain in the original package to protect from bright light.
Stability: Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial
Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25º C) and lighting conditions for up to 8 hours.

13.2.6 Formulation/Agent Preparation

Nab-paclitaxel, Abraxane®, is a -free formulation of paclitaxel albumin for injectable suspension. Each 50 mL vial contains 100 mg of paclitaxel, and human albumin, as a white to off-white sterile lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection USP.

13.2.7 Supplier

Abraxane® will be supplied by Celgene Corporation. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel.

Celgene Corporation
86 Morris Avenue
Summit, N.J. 07901
Toll Free: (800)-640-7854
Phone: (908) 673-9667
FAX: (908) 673-9115

Drug Distribution and Destruction

a. Drug Distribution

ABRAXANE® will be distributed by Abraxis BioScience, LLC. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject.

Upon identification of a potential subject, sites must fax a completed Drug Request Form to Abraxis BioScience, LLC. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays.

b. Drug Return and Destruction

If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Abraxis using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Abraxis Clinical Supplies Dept. using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Abraxis Medical Operations.

If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Abraxis Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Abraxis Medical Operations.

13.3 Drug Information for trastuzumab (Herceptin®)

The below information is largely duplicated from the Herceptin package insert.[53]
Relevant points are summarized as follows.

Other names: none

13.3.1 Mode of Action: recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2.

Availability: Trastuzumab is commercially available

13.3.2 Risks and Contraindications

13.3.2.A Cardiotoxicity:

Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S_3 gallop, or reduced ejection fraction, have been observed in patients treated with trastuzumab. Congestive heart failure associated with trastuzumab therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke. The clinical status of patients in the trials who developed congestive heart failure was classified for severity using the New York Heart Association classification system (I-IV, where IV is the most severe level of cardiac failure). (See Table 6.0)

Table 6.0: Incidence and Severity of Cardiac Dysfunction

	Trastuzumab alone[31] n = 213	Trastuzumab + Paclitaxel[32] n = 91	Paclitaxel[32] n = 95	Trastuzumab + Anthracycline+ cyclophosphamide[32] n = 143	Anthracycline+ cyclophosphamide[32] n = 135
Any Cardiac Dysfunction	7%	11%	1%	28%	7%
Class III-IV	5%	4%	1%	19%	3%

31 (see reference): Open-label, single-agent Phase II study (94% received prior anthracyclines).
32 (see reference): Randomized Phase III study comparing chemotherapy plus trastuzumab to chemotherapy alone, where chemotherapy is either anthracycline/cyclophosphamide or paclitaxel.

Candidates for treatment with trastuzumab should undergo thorough baseline cardiac assessment including history and physical exam and one or more of the following: echocardiogram, and MUGA scan. There are no data regarding the most appropriate method of evaluation for the identification of patients at risk for developing cardiotoxicity. Monitoring may not identify all patients who will develop cardiac dysfunction.

Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction.

Patients receiving trastuzumab should undergo frequent monitoring for deteriorating cardiac function.

The probability of cardiac dysfunction was highest in patients who received trastuzumab concurrently with anthracyclines. The data suggest that advanced age may increase the probability of cardiac dysfunction.

Pre-existing cardiac disease or prior cardiotoxic therapy (e.g., anthracycline or radiation therapy to the chest) may decrease the ability to tolerate trastuzumab therapy; however, the data are not adequate to evaluate the correlation between trastuzumab-induced cardiotoxicity and these factors.

Discontinuation of trastuzumab therapy should be strongly considered in patients who develop clinically significant congestive heart failure. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy often including discontinuation of trastuzumab. The safety of continuation or resumption of trastuzumab in patients who have previously experienced cardiac toxicity has not been studied. There are insufficient data regarding discontinuation of trastuzumab therapy in patients with asymptomatic decreases in ejection fraction; such patients should be closely monitored for evidence of clinical deterioration.

13.3.2.B Precautions

General: Trastuzumab therapy should be used with caution in patients with known hypersensitivity to trastuzumab, Chinese Hamster Ovary cell proteins, or any component of this product.

Drug Interactions: There have been no formal drug interaction studies performed with trastuzumab in humans. Administration of paclitaxel in combination with trastuzumab resulted in a two-fold decrease in trastuzumab clearance in a non-human primate study and in a 1.5-fold increase in trastuzumab serum levels in clinical studies.

Benzyl Alcohol: For patients with a known hypersensitivity to benzyl alcohol (the preservative in Bacteriostatic Water for Injection) reconstitute trastuzumab with Sterile Water for Injection (SWFI), USP. DISCARD THE SWFI-RECONSTITUTED TRASTUZUMAB VIAL FOLLOWING A SINGLE USE.

Immunogenicity: Of 903 patients who have been evaluated, human anti-human antibody (HAHA) to trastuzumab was detected in one patient, who had no allergic manifestations.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Trastuzumab has not been tested for its carcinogenic potential.

Mutagenesis: No evidence of mutagenic activity was observed in Ames tests using six different test strains of bacteria, with and without metabolic activation, at concentrations of up to 5000 µg/mL trastuzumab. Human peripheral blood lymphocytes treated *in vitro* at concentrations of up to 5000 µg/plate trastuzumab, with and without metabolic activation, revealed no evidence of mutagenic potential. In an *in vivo* mutagenic assay (the micronucleus assay), no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg trastuzumab.

Geriatric Use: Trastuzumab has specifically evaluated in 133 patients who were 65 years of age or over. The risk of cardiac dysfunction may be increased in geriatric patients. The reported clinical experience is not adequate to determine whether older patients respond differently from younger patients.

13.3.2.C Adverse Reactions

Cardiac Failure/Dysfunction: For a description of cardiac toxicities, see above.

Anemia and Leukopenia: An increased incidence of anemia and leukopenia was observed in treatment groups receiving trastuzumab and chemotherapy, especially in those receiving trastuzumab with AC The majority of these cytopenic events were mild or moderate in intensity and reversible

Hematologic toxicity is infrequent following the administration of trastuzumab as a single agent, with an incidence of Grade III toxicities for WBC, platelets, hemoglobin all <1%.

Diarrhea: Of patients treated with trastuzumab as a single agent in various studies, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving trastuzumab in combination with chemotherapy.

Infection: An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed in patients receiving trastuzumab in combination with chemotherapy.

Infusion Reactions: During the first infusion with trastuzumab, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients in clinical trials. The symptoms were usually mild to moderate in severity and were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of trastuzumab infusion). Trastuzumab discontinuation is rarely necessary. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, rash and asthenia. The symptoms occur infrequently with subsequent trastuzumab infusions.

Table 7.0: Adverse Events Occurring in ≥ 5% of Patients or at Increased Incidence in the Trastuzumab Arms of Various Randomized Studies (Percent of Patients)[30]

	Single Agent n = 352	Trastuzumab + Paclitaxel n = 91	Paclitaxel Alone n = 95	Trastuzumab + AC n = 143	AC Alone n = 135
Body as a Whole					
Pain	47	61	62	57	42
Asthenia	42	62	57	54	55
Fever	36	49	23	56	34
Chills	32	41	4	35	11
Headache	26	36	28	44	31
Abdominal pain	22	34	22	23	18
Back pain	22	34	30	27	15

Infection	20	47	27	47	31
Flu syndrome	10	12	5	12	6
Accidental injury	6	13	3	9	4
Allergic Reaction	3	8	2	4	2
Cardiovascular					
Tachycardia	5	12	4	10	5
Congestive heart failure	7	11	1	28	7
Digestive					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Nausea and vomiting	8	14	11	18	9
Anorexia	14	24	16	31	26
Heme & Lymphatic					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34
Metabolic					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
Nervous					
Insomnia	14	25	13	29	15
Dizziness	13	22	24	24	18
Paresthesia	9	48	39	17	11
Depression	6	12	13	20	12
Peripheral neuritis	2	23	16	2	2
Neuropathy	1	13	5	4	4
Respiratory					

Cough increased	26	41	22	43	29
Dyspnea	22	27	26	42	25
Rhinitis	14	22	5	22	16
Pharyngitis	12	22	14	30	18
Sinusitis	9	21	7	13	6
Skin					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	<1
Urogenital					
Urinary tract infection	5	18	14	13	7

Other serious adverse events

The following other serious adverse events occurred in at least one patient on trastuzumab being treated in clinical trials:

Body as a Whole: cellulitis, anaphylactoid reaction, ascites, hydrocephalus, radiation injury, deafness, amblyopia

Cardiovascular: vascular thrombosis, pericardial effusion, heart arrest, hypotension, syncope, hemorrhage, shock, arrhythmia

Digestive: hepatic failure, gastroenteritis, hematemesis, ileus, intestinal obstruction, colitis, esophageal ulcer, stomatitis, pancreatitis, hepatitis

Endocrine: hypothyroidism

Hematological: pancytopenia, acute leukemia, coagulation disorder, lymphangitis

Metabolic: hypercalcemia, hypomagnesemia, hyponatremia, hypoglycemia, growth retardation, weight loss

Musculoskeletal: pathological fractures, bone necrosis, myopathy

Nervous: convulsion, ataxia, confusion, manic reaction

Respiratory: apnea, pneumothorax, asthma, hypoxia, laryngitis

Skin: herpes zoster, skin ulceration

Urogenital: hydronephrosis, kidney failure, cervical cancer, hematuria, hemorrhagic cystitis, pyelonephritis

13.3.3 Supplier

Trastuzumab will be ordered from the City of Hope pharmacy.

13.3.4 Dose and Administration

13.3.4. A Usual Dose

The recommended initial loading dose is either 4 mg/kg trastuzumab administered as a 90-minute infusion (if planning weekly dosing) or 8 mg/kg trastuzumab administered as a 90-minute infusion (if planning every three week dosing). The recommended weekly maintenance dose is 2 mg/kg trastuzumab and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. The recommended every three week maintenance dose is 6mg/kg trastuzumab and can be administered as a 30 minute infusion if the loading dose was well tolerated. Trastuzumab may be administered in an outpatient setting. Trastuzumab is to be diluted in saline for IV infusion. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS** (see **Administration**). There is no change in dosage for obese patients.

13.3.4. B Administration

Treatment may be administered in an outpatient setting by administration of either a 4 mg/kg trastuzumab loading dose by intravenous (IV) infusion over 90 minutes or 8mg/kg trastuzumab loading dose by intravenous infusion. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** Patients should be observed for fever and chills or other infusion-associated symptoms (see ADVERSE REACTIONS). If prior infusions are well tolerated, subsequent weekly doses of 2 mg/kg trastuzumab may be administered over 30 minutes, or subsequent doses of 6mg/kg trastuzumab may be administered every three weeks.

Trastuzumab should not be mixed or diluted with other drugs. Trastuzumab infusions should not be administered or mixed with Dextrose solutions.

13.3.5 Storage

Vials of trastuzumab are stable at 2-8°C (36-46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted trastuzumab solution should be used immediately and any unused portion must be discarded. DO NOT FREEZE TRASTUZUMAB THAT HAS BEEN RECONSTITUTED.

The solution of trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, may be stored at 2-8°C (36-46°F)

for up to 24 hours prior to use. Diluted trastuzumab has been shown to be stable for up to 24 hours at room temperature (2-25°C). However, since diluted trastuzumab contains no effective preservative, the reconstituted and diluted solution should be stored refrigerated (2-8°C).

13.3.6 Structure and Molecular Weight

Formula: $C_{6470}H_{10012}N_{1726}O_{2013}S_{42}$

Molecular Mass: 14531.5 g/mol

Herceptin (Trastuzumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. The antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

13.3.7 Formulation/Agent Preparation

Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. The nominal content of each Herceptin vial is 440 mg trastuzumab, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, 400 mg trehalose dihydrate, and 1.8 mg polysorbate 20, USP. Reconstitution with **only 20 mL of the supplied Bacteriostatic Water for Injection (BWFI), USP,** containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.

13.3.8 Preparation

The diluent provided has been formulated to maintain the stability and sterility of HERCEPTIN for up to 28 days. Other diluents have not been shown to contain effective preservatives for HERCEPTIN. Each vial of Herceptin should be reconstituted with **ONLY 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied,** to yield a multi-dose solution containing 21 mg/mL trastuzumab. Use of all 30 mL of diluent results in a lower-than-intended dose of HERCEPTIN. THE REMAINDER (approximately 10 mL) OF THE DILUENT SHOULD BE DISCARDED. Immediately upon reconstitution with BWFI, the vial of Herceptin must be labeled in the area marked "Do not use after:" with the future date that is 28 days from the date of reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, Herceptin must be reconstituted with Sterile Water for Injection (see PRECAUTIONS). HERCEPTIN WHICH HAS BEEN RECONSTITUTED WITH SWFI MUST BE USED

IMMEDIATELY AND ANY UNUSED PORTION DISCARDED. USE OF OTHER RECONSTITUTION DILUENTS SHOULD BE AVOIDED.

Shaking the reconstituted Herceptin or causing excessive foaming during the addition of diluent may result in problems with dissolution and the amount of Herceptin that can be withdrawn from the vial.

Use appropriate aseptic technique when performing the following reconstitution steps:

a. Using a sterile syringe, slowly inject **20 mL** of the diluent into the vial containing the lyophilized cake of trastuzumab. The stream of diluent should be directed into the lyophilized cake.

b. Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., agitation or rapid expulsion from a syringe. **DO NOT SHAKE.**

c. Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The solution should be essentially free of visible particulates, clear to slightly opalescent, and colorless to pale yellow.

Determine the number in mg of trastuzumab needed, based on a loading dose of 4 mg trastuzumab/kg body weight or a maintenance dose of 2 mg trastuzumab/kg body weight. Calculate the volume of 21 mg/mL trastuzumab solution and withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DEXTROSE (5%) SOLUTION SHOULD NOT BE USED.** Gently invert the bag to mix the solution. The reconstituted preparation results in a colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

No incompatibilities between Herceptin and polyvinylchloride or polyethylene bags have been observed.

13.3.9 Stability

A vial of Herceptin reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2-8°C (36-46°F), and the solution is preserved for multiple use.

14.0 Endpoints/Statistical Analysis

To evaluate the combination of pertuzumab, trastuzumab and nab-paclitaxel in HER2+ breast cancer, we can combine the ability of this regimen to shrink/control the tumor in untreated breast cancer cases whether it is in a metastatic patient or in the neoadjuvant setting, as both are untreated HER2+ breast cancers. The assumption is that a promising result in one setting would translate into a promising result in the other. To combine these two, we note the

CLEOPATRA trial[20,21] observed a median PFS of 18.5 months in metastatic breast cancer with pertuzumab, trastuzumab and docetaxel. As a result, a success for an individual patient can be defined as PFS>=18.5 months, with an observed success rate of 50% in CLEOPATRA. In the neoadjuvant setting, a pCR rate (success rate) of 39.3% was observed with the pertuzumab, trastuzumab and docetaxel.[26] As a result, this study will be designed to declare the study successful if it at least matches CLEOPATRA for MBC patients and NEOSPHERE for LABC patients, respectively, due to the presumed lower toxicity of using nab-paclitaxel on the proposed dose and schedule rather than docetaxel. 65 patients will be accrued, with 25 metastatic breast cancer (MBC) patients and 40 LABC neoadjuvant cases.

At the final analysis, the matching target success rate would be (0.393*40+0.5*25)/65=43.4% or 28 successes. If the true success rate is 10% above the matching success rate this design has 94% power to declare a success. If the true success rate is 10% below the matching success rate, this design has a type I error less than 5% (one sided). This design is equivalent to testing the null hypothesis H0: success rate is 33.4% against an alternative H1: success rate is 53.4%, with a type I error (one-sided) of 5% and a type II error of 6% (94% power). These error estimates are conservative due to the slight underdispersion resulting from the combination of two binomials.

In addition to the combined endpoint, each strata will be evaluated independently. With 25 metastatic cancer patients, the median PFS will be estimated. If accrual is within 24 months, and follow-up is approximately 24 months after accrual completes, the probability of a true median survival of 24 months being less than 18.5 months is less than 20% (80% power), and the probability of a true median survival of 13 months exceeding 18.5 months is approximately 13.4% (type I error, one sided). This is assuming a non-parametric estimate of the median survival and uses the Brookmeyer-Crowley method. This design is equivalent to testing the null hypothesis H0: median survival is 13 months against an alternative H1: median survival of 24 months, with a type I error (one-sided) of 13.5% and a type II error less than 20% (80% power). If accrual is longer, with follow-up after the last accrual unchanged, the type I and type II error are reduced.

With 40 neoadjuvant cases, the probability of a true discouraging neoadjuvant pCR rate of 29.3% exceeding the benchmark of 39.3% (16 or more) is 10% (type I error), and the probability of a true neoadjuvant pCR rate of 49.3% resulting in a observation below 39.3% (15 or less) is less than 10% (>90% power). This design is equivalent to testing the null hypothesis H0: pCR rate is 29.3% against an alternative H1: pCR rate is 49.3%, with a type I error (one-sided) of 10% and a type II error less than 10% (at least 90% power).

The study is likely to accrue 2 patients per months in the locally advanced cohort , the 40 patient LABC accrual should be met by the end of 2016.

For interim analysis, no formal analysis is planned due to the time required to assess the PFS endpoint and the expected rapidity of accrual. However, a report will be generated after 29 patients have been accrued to review with the Sponsor and PI, with a report to the COH

DSMB. At the final analysis, the PFS (for stage IV cases), the pathological complete response rate (for neoadjuvant cases) and toxicity/tolerability may refine the decision to pursue the combination, or may suggest restricting this combination to more fragile patients less able to receive more aggressive chemotherapy combinations.

The National Cancer Institute Common Toxicity Criteria Version 4.0 will be used to assess toxicities.

There will be interim analysis for toxicity. Specifically, if dose limiting toxicity (grade 3 or higher treatment-related non-hematologic toxicity other than readily reversible electrolyte abnormalities or diarrhea/ nausea/vomiting that lasts less than 24 hrs after treatment or any treatment related grade 4 toxicity) is observed in 2 of the first 6 patients treated during the first cycle of treatment (28 days), or in more than 30% of the patients thereafter, the study will hold accrual pending review by the COH DSMC, PI and Sponsor.

15. 0 Feasibility

City of Hope (COH) Comprehensive Cancer Center is a private, non-sectarian, multi-specialty hospital and research. COH has been at the forefront of medical and basic science research since it was established in 1918. A formal research program structure was initiated in 1951 and expanded rapidly in terms of staff, facilities, and institutional support. Major groups of investigators were recruited and merged into the Research Institute. City of Hope has been continuously funded as an NCI-designated Cancer Center since 1975, with Comprehensive Cancer Center status as of 1998. The scientific goals of the Cancer Center are the provision of personalized, interdisciplinary care of the highest quality for every cancer patient seen at COH, the creation of a climate fostering collaboration among basic scientists, clinical researchers, and physicians; and the provision of cancer education and outreach programs into both the medical and lay communities in our region. Currently, COH is comprised of 178 basic science and clinical researchers from every major Department and Division of the Medical Center and the Beckman Research Institute of City of Hope.

All research projects will be carried out in the outpatient facilities at City of Hope. Outpatient care is rendered in the Brawerman Ambulatory Care Center. The outpatient clinics service almost 5,000 patients per month. In addition, the investigational drug pharmacy, with a long track record of appropriate handling of CTEP-supplied and other investigational agents, has facilities for secure storage of agents at room temperature, -20 ºC and -70 ºC. Other facilities included in this new outpatient area are satellite laboratories, procedure suites, and biostatistical and data management offices.

In 2005, COH opened the 340,000 sq ft state-of-the-art Helford Clinical Research Hospital incorporating the latest in medical, surgical, radiological, and communications technologies, combining modern diagnostic, radiology, and imaging tools in a digital environment. Surgical “super suites” include laparoscopic and robotic instrumentation and advanced information and audio/video systems, allowing multidisciplinary teams to effectively collaborate during procedures. COH has developed a substantial base of patients who have been entered on investigational cancer research trials. Accruals favor investigator-initiated interventional trials over externally-sponsored or cooperative group trials by 85% to 15%.

This bias is even more pronounced for non-interventional trials, where 89% of patients are entered onto investigator-initiated trials. In 2009, there were 1,694 patients accrued to intervention studies and 5,621 patients accrued to non-intervention studies at City of Hope.

16. 0 Correlative Studies

Tissue and blood samples may be collected under the current trial, and, under other institutionally IRB approved protocols (if signed independently) and in accordance with an IRB-approved HIPPA compliant and signed consent form. (IRB 05091 Tissue and blood library establishment for molecular, biochemoical, and histologic study of breast disease; IRB 08128 Characterization of circulating tumor cells to direct pre-operative and systemic therapy in patients with locally advanced or metastatic stage IV breast cancer). Please refer to study calendar for timing of tissue and blood collections.

Biopsy cores will go to the Pathology Core Lab under Dr. Peiguo Chu. Optional biopsies of up to 65 samples will be conducted. 45 of those samples will be baseline biopsies, and 20 additional biopsies may be collected at the end of study treatment. The samples that are collected may be frozen and or parffin embedded. They may be processed for further genetic and molecular profiling including but not exclusive to PTEN, p53, HER2, ER/PR based on specific IRB protocols approved by the institution. Molecular profiling will be carried out at COH (Dr. P. Lee, Shiuan Chen and core labs), and as feasible, in collaboration with scientists at TGEN (under the leadership of Dr. Trent), the Jackson Laboratory (under the leadership of Dr. Ed Liu and Francesca Mengi, Dr. Emily Wang (UC San Diego, R01 supported), and in collaboration with Agendia – all under already approved MTAs in place.

More over, 10 mL of blood will be drawn into CellSave tubes (Immunicon) for Circulating Tumor Cells enumeration and 10 mL of blood will be drawn into a CPT tube for assessment of glycan profile and two red top tubes with 7.5 mL each will be drawn, totaling 25 mL of blood drawn for research purposes. One of the red top tubes will be assessed for a glycan and protein profile (Hickey laboratory), and the second tube will be used for micro RNA analysis (E. Wang laboratory). Time points include pre-teratment, during treatment (see study calendar (optional draw), at the time of the subject's end of study.

17. 0 Study Calendar

Baseline evaluations are to be conducted within 1 week prior to administration of protocol therapy. Scans must be done within 4 weeks prior to the start of therapy. Tests/procedures indicated for the following weeks maybe performed within ± three days of the indicated dates. Brief interruptions and delays in the 21 day cycle may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, government holidays, etc. This can also extend to complications of disease or unrelated medical illness not related to disease progression. These delays will not be considered protocol violations. Therapy can be delayed (after cycle 1) up to 3 days due to holidays/personal reasons.

	Pre-Study	Pre Cycle 1 Day 1	Cycle 1 Wk 1	Wk 2	Wk 3	Cycle 2 Wk 1	Wk 2	Wk 3	Cycle 3 Wk 1	Wk 2	Wk 3	Cycle 4 thru progression = same as Cycles 1 & 2	Follow-up[e]
Trastuzumab			Day (D) 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15		
Pertuzumab			D 1			D1			D 1				
nab-paclitaxel			D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15		
Informed consent	X												
Medical history	X												
Concurrent meds	X----------X												
Physical exam, Height, weight	X		X			X			X				X
Vital signs	X		X			X			X				X
ECOG	X		X			X			X				X
CBC w/diff, plts	X		X	X	X	X	X	X	X	X	X		X
Serum chemistry[a]	X		X	X	X	X	X	X	X	X	X		X
EKG (as indicated)	X												
Adverse event evaluation			X----------X										
Tumor measurements as applicable (clinical)	X		For patients with MBC, tumor assessments (clinical) are repeated every 9 weeks. Documentation (radiologic or clinical) must be provided for patients removed from study for progressive disease.										
Radiologic evaluation	X		Radiological assessment will be carried out at the conclusion of 9 weeks of therapy, as applicable (Mammogram, US, MRI, as deemed appropriate by the treatment team). Patietns will be assessed by clinical means every three weeks while receiving treatment for LABC.										X[h]
MUGA/ECHO[b]	X												
B-HCG[c]	X												
Biopsy (Optional)* -IHC profiling -Gene profiling	X								X			X#	
Correlative Blood Draw (Optional) -Glycan profiling -CTC -Micro RNA profiling	X								X			X# At progression	
Survival													X

aAlbumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT}, sodium

bEcho/MUGA: Baseline within 42 days of Day 1 of treatment (see section 3.1.4); Subsequent every 12 weeks (See section 10.0)

c Pregnancy test at baseline

d Tissue and blood may be procured for patients who consent to blood draws and biopsy with possible tissue and blood storage for correlative studies. Correlative studies may include gene analysis, glycan profiling, and IHC panel profiling.

e Follow up to be done every 3 months x 4 years; then every 6 months x 1 year. After 5 years, follow up should be as per standard of clinical practices.

h Requested as per standard of care.

#for LABC, at the time of definitive breast surgery

*As available, specimens will be analysed at COH with collaborators (Dr. Lee, Chen, core labs), as well as collaborators at TGEN – Dr. Trent-, MTA in place, Agendia-MTA in place, Jackson Laboratory-Drs. Mengi and Liu-MTA in place, UC San Diego-Dr. Emily Wang, R-01 supported). In addition, as feasible, PDX models would be generated in collaborations at COH/through Jun Wu (core at COH) and with the Jackson Laboratory.

18. 0 Evaluation Criteria/Measurement of Effect

18.1 Response Criteria

For the purposes of this study, patients with MBC should be reevaluated for response every 9 weeks. Patients with LABC will be evaluated at the beginning of each cycle via physical exam, and at the time of planned definitive breast surgery by pathology. Imaging (prior to surgery) will be left to the treating physician's discretion.

Response and progression for MBC will be evaluated in this study using the new updated international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee version 1.1. Per the new RECIST criteria, as disease response is not the primary endpoint of this trial, confirmatory scans following documentation of progression or response will not be required. Rather, progression/response will be determined based on results of the single scan.

18.2 Definitions

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

18.3 Disease Parameters

Measurable disease. In patients with MBC, measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10mm with conventional techniques (CT, MRI, or caliper measurement) and as ≥20mm by chest X-ray (if clearly defined and surrounded by aerated lung.) Lymph nodes greater than 10mm on short axis are considered measureable as well. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm by chest X-ray or <10 mm using CT, MRI or caliper measurement), are considered non-measurable disease. Organomegaly, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Lymph nodes less than 15mm in the short axis can not be used as target lesions. 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 reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

18.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

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

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

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

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US): Ultasound is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

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

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

18.5 Response Criteria

18.5.1 Evaluation of Target Lesions in patients with MBC

Complete Response (CR): Disappearance of all target lesions. Lymph node CR is when the lymph node has decreased to less than 10mm in the short axis.

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

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (including the baseline scan if that is the smallest), and at least a 5mm increase or the appearance of new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

18.5.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

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

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. However, unequivocal progression should not normally trump target

disease status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

18.5.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of measurement criteria, but confirmation is not necessary.

Table 10: Assessment of Best Overall Response Using Target and Non-Target Lesions

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

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

18.5.4 Duration of Response

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

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

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

18.6 Progression-Free Survival

Progression-free survival is defined as the length of time between study enrollment and when objective evidence of disease progression is documented.

18.7 Analysis of Secondary Endpoints

The outcome status in terms of toxicity, reason off study, overall survival and laboratory correlates of all eligible patients will be reported.

18.7.1 Overall Survival

Overall survival is defined as the length of time between study enrollment and death.

Patients' survival times will be measured from the initial date of treatment to the recorded date of death. Survival (both overall and progression-free) will be estimated by the Kaplan-Meier method. The corresponding median survival times (with 90% confidence limits) will be determined.

18.7.2 Safety Profile

Using NCI CTCAE (v4.0), the number of patients experiencing SAEs (serious adverse events) in each cycle of treatment, and for 30 days beyond the last protocol treatment administered, will be characterized by type of adverse event and grade, and by the time of onset in relation to the first day of therapy for each cycle. Attribution of SAEs to treatment (unrelated, unlikely, possible, probable, or definite) will also be reported. We will also report the cumulative percentage (%) of patients experiencing treatment-related SAEs and its relationship to treatment duration.

18.8. In patients with locally advanced breast cancer response will be assessed as pathologic complete response (pCR) in breast and lymph nodes at the time of definitive surgery vs. less than pCR; response will also be analyzed using residual cancer burden score (RCB).

19.0 Data Reporting/Protocol Deviations

19.1 Data Reporting

19.1.1 Confidentiality of Records

The original data collection forms will be stored in the Department Clinical Trials Office, in a secure location. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, Genentech and Celgene Corporation under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects.

19.1.2 Subject Consent Form

At the time of registration, the original signed and dated Informed Consent form, HIPAA research authorization form, and the California Experimental Subject's Bill of Rights (for

the medical record) and three copies (for the subject, the research record, and the Coordinating Center) must be available. All Institutional, NCI, Federal, and State of California requirements and requirements by Genentech and Celgene Corporation, will be fulfilled.

19.1.3 Data Collection Forms and Submission Schedule

All data will be collected as per standard institutional timeline using data collection forms and electronic data entry as per COH standard. Data will be stored in a secure location/and in secure format.

19.1.3.1 Eligibility Checklist

The Eligibility Checklist must be completed by a protocol nurse or clinical research associate and signed by an authorized investigator prior to registering the subject. See Section 4.3 for the registration procedure.

19.1.3.2 Prior Therapy and On-Study Data

Within a week of registration, the clinical research associate will submit on-study checklist form.

19.1.3.3 Treatment Data

Within four (4) weeks of completion of each course the following data should be recorded in the EDC:

19.1.4.3.1 Treatment and Adverse Events
19.1.4.3.2 Supplemental Data
19.1.4.3.2 Flow Sheets

19.1.3.4 Response/Off-Study/Follow-up

Each time a patient is evaluated for response and/or new follow-up information is obtained, the CRA should record this in the appropriate section of the EDC.

19.1.3.5 Results Reporting

Preliminary and full results of this clinical and translational research trial may be reported in abstract form(s) at national meeting(s) and in full manuscript form(s) in appropriately selected journal(s). The manuscripts/abstracts will be sent to Genetech for review before presentation or publication.

19.2 Protocol Deviations

19.2.1 Deviation Policy

Planned deviations may be permitted in accordance with the COH policy on "Clinical Research Protocol Planned Deviations and Single Subject Exception." These planned deviations, considered Single Subject Exceptions, are considered an Amendment to the Protocol. In addition, if contractually obligated, the sponsor must also approve any planned deviations.

19.2.2 Reporting of Unplanned Deviations

All unplanned deviations will be reported to the COH DSMC who will forward to the IRB following review.

19.2.3 Resolving Disputes

If there is a dispute among the persons involved in the provision of research treatment, in regard to whether a treatment deviates from the protocol, resolution will be resolved in accordance with the Clinical Research Protocol Planned Deviations and Single Subject Exceptions policy.

19.3 Reporting and Exclusions

19.3.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with trastuzumab+pertuzumab + nab-paclitaxel.

19.3.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. In addition, patient response could be categorized in one of the following categories which would be considered a non-response: stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death because of other cause, or unknown (not assessable, withdrew consent, insufficient data).

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) should be included in the main analysis of the response rates. An incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients who receive any of the study drug. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

20.0 Human Subject Issues

20.1 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

20.2 Recruitment of Subjects

Participants for this study will be recruited from among patients undergoing treatment at City of Hope Cancer Center for stage IV breast adenocarcinoma or locally advanced stage II-III breast cancer (including inflammatory breast cancer). Patients will be recruited through encounters by the Breast Oncologists in the Department of Medical Oncology and/or Breast Surgical Oncologists of the Department of General Oncological Surgery. They will be indentified, screened, consented, eligibility criteria established by members of a designated research team within the Breast Cancer Program, under the guidance and together with the PI and co-investigators and participating clinical investigators listed on the protocol. Once all pretreatment evaluations have been performed, patients will be entered on study after review of patient eligibility by a member of the Department of Clinical Trials Office. Patients may be screened for registration by calling the City of Hope Department of Clinical Trials Office, ext. 62468.

This study will be performed at COH, and will be listed at www.clinicaltrials.gov.

20.3 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). The study will record clinical characteristics, response to treatment by clinical, imaging, and pathological means, in addition to toxicities, and other outcomes, as appropriate (recurrence-free/overall survival). These findings, as well as data generated from the translational research investigations of procured biological specimens, will be linked to the subject's identity using a coded study number designated by the statistician/Department of Bioinformatics and in conjunction with the Translational Research Core of COHCC. The principal investigator and the statistician, and laboratory technicians will have access to this information, but all information will be treated confidentially. No identifiers will be used in any subsequent publication of these results.

Financial Obligations and Compensation

The study drug, Abraxane (nab-paclitaxel), will be provided by the manufacturer (Celgene Corporation) free of charge to patients on this study research. The study drug pertuzumab will be provided by the manufacturer (Genentech Inc.) free of charge to patients on this study research The Research lab draws, processing, and results will be free of charge as a part of research. Routine standard of care clinic visits, laboratory tests, and tumor imaging will be billed to the patient and/or the patient's insurance. Trastuzumab, the infusion center time, and routine nursing care involved in administering of these drugs and supportive medications during infusion will be billed to the patient and/or the patient's insurance. Medication and/or treatment needed for side effects of either study drug will be billed to the patient and/or the patient's insurance.

If there is a serious medical complication of the research, treatment will be available at City of Hope, but there will be no compensation to the subject for this injury.

20.4 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any

reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope.

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