PROTOCOL

STUDY TITLE:	A phase II study of NEOADjuvant Aromatase inhibitor and Pertuzumab/Trastuzumab (NEOADAPT)
STUDY DRUG:	HERCEPTIN (trastuzumab) PERJETA (pertuzumab)
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1. INTRODUCTION

1.1 DISEASE BACKGROUND

Breast cancer is the most common cancer in women with a global prevalence of more than 1 million patients and a mortality rate of approximately 400,000 deaths per year (International Agency for Research on Cancer; http://www-dep.iarc.fr; Globocan 2002). While improved early detection and advances in systemic therapy for early stage disease have resulted in a small decline in breast cancer mortality since 1989, patient advocacy groups have cited an unmet patient need for clinical research to validate more treatment options with less long-term toxicity. Major untested opportunities exist in the area of HER2-targeted therapy of early stage breast cancer, specifically in the area of a chemotherapy-free approach to early stage hormone receptor (HR) positive and HER2 positive breast cancer.

1.2 HER2 AND BREAST CANCER

Growth factors and their receptors play critical roles in development, cell growth, differentiation, and apoptosis (Cross and Dexter 1991). Such receptors span the cell membrane, with the extracellular domain binding specific growth factors and the intracellular domain transmitting growth signals. Interaction of the extracellular domain with its cognate ligand often results in intracellular activation of tyrosine kinase activity. Overexpression of human epidermal growth factor receptor 2 (HER2, also known as *erb*B2, neu, and p185HER2) is observed in approximately 25-30% of human breast cancers (Slamon et al. 1987). HER2 overexpression has been reported to only rarely occur in the absence of gene amplification (Kallioniemie et al. 1992; Pauletti et al. 1996). High level of HER2 expression has been correlated with poor clinical outcome (Slamon et al. 1987).

Several lines of evidence support a direct role for HER2 overexpression in the pathogenesis and poor clinical course of human tumors (Hynes 1994). When the mutated gene is transfected into murine fibroblast (NIH 3T3) cells, it causes transformation, and the resulting cells are tumorigenic in the nude mice (Di Fiore et al. 1987; Hudziak et al. 1987). Additionally, transgenic mice that overexpress the rodent homolog of the human HER2 gene develop breast cancer (Guy et al. 1992). Finally, specific antibodies to the extracellular domain of HER2 inhibit the experimental growth of tumors that overexpress the gene (Drebin et al. 1985, 1988; Fendly et al. 1990). These data suggest a direct role for HER2 in both malignant transformation and enhanced tumorigenicity. Therefore, a strategy to antagonize the abnormal function of overexpressed HER2 was developed to improve the course of patients with HER2-overexpressing tumors. Monoclonal antibodies directed against the HER2 protein were developed and humanized to minimize the likelihood of immunogenicity. One of these antibodies (trastuzumab) was very effective in inhibiting both in vitro and in vivo

proliferation of human breast cancer tumor cells overexpressing the HER2 protein and in mediating antibody-dependent cellular cytotoxicity in the presence of human effector cells (Jurianz et al. 1999).

There is substantial preclinical evidence that inhibition of signal transduction pathways can potentiate the cytotoxic activity of chemotherapeutic drugs. Indeed, trastuzumab has been shown to have synergy, in vitro and in vivo, with several chemotherapeutic drugs including cisplatin, doxorubicin, thiotepa, etoposide, vinorelbine, and taxanes (Pegram et al. 2000; Pietras et al. 1994; Arteaga et al. 1994; Hancock et al. 1991; Baselga et al. 1998; Pegram et al. 1997). Given this promising preclinical data, trastuzumab was tested in the clinic both as a single agent and in combination with chemotherapy.

1.3 TRASTUZUMAB AND PERTUZUMAB CLINICAL EXPERIENCE

Trastuzumab Clinical Experience in Metastatic Breast Cancer

The clinical benefit of trastuzumab in women with metastatic breast cancer has been demonstrated in two pivotal studies.

A large Phase II trial (H0649g) assessed the activity of trastuzumab as a single agent in 222 women with HER2 overexpressing metastatic breast cancer with progressive disease after one or more chemotherapy regimens (Cobleigh et al. 1999). A blinded, independent response evaluation committee identified 8 complete and 26 partial responses, for an objective response rate of 15% in the intent-to-treat population (95% confidence interval, 11% to 21%). The median duration of response was 9.1 months, and the median duration of survival was 13 months. The most common adverse events, which occurred in approximately 40% of patients, were mild to moderate infusion-associated fever and/or chills. These symptoms usually occurred only during the first infusion. The most clinically significant event was cardiac dysfunction, which occurred in 4.7% of patients.

A large, open-label, randomized Phase III study (H0648g) in 469 patients with HER2-positive metastatic breast cancer was conducted to evaluate the efficacy of trastuzumab in combination with chemotherapy as first-line treatment. Patients who were anthracycline-naïve were randomized to receive either anthracycline plus cyclophosphamide (AC) or trastuzumab plus AC. Patients who had received prior anthracyclines in the adjuvant setting were randomized to receive paclitaxel or paclitaxel plus trastuzumab. Patients randomized to trastuzumab and paclitaxel measurably benefited in comparison to patients treated with chemotherapy alone in terms of time to disease progression, overall response rate, median duration of response, and survival. As determined by an independent Response Evaluation Committee (REC), trastuzumab prolonged median time to disease progression from 4.6 months to 7.4 months ($p<0.001$), improved the overall response rate (complete and partial responses) from 32%

to 50% (p<0.001), and increased median duration of response from 6.1 to 9.1 months (p<0.001). Compared to chemotherapy alone, the addition of trastuzumab significantly lowered the incidence of death at one year from 33% to 22% (p=0.008) and increased median overall survival 24% from 20.3 months to 25.1 months (p=0.046)(Slamon et al. 2001). The observed survival advantage remained despite crossover of 66% of patients initially randomized to chemotherapy alone who elected to receive trastuzumab upon disease progression (Tripathy et al. 2000). Fever/chills were observed with the initial trastuzumab infusion in approximately 25% of patients. Class III or IV cardiac dysfunction was observed in 16% of the trastuzumab + AC subgroup; increasing age was an associated risk factor for the development of cardiotoxicity in this treatment cohort.

Based on these data, trastuzumab was approved by the U.S. Food and Drug Administration (FDA) for use in HER2-overexpressing metastatic breast cancer in combination with paclitaxel for first-line treatment and as a single agent for patients failing prior chemotherapy for metastatic disease. However, current usage patterns of trastuzumab indicate that the drug is now being used in a broader array of circumstances that in the pivotal clinical trials. Since initiation of the pivotal clinical trials, docetaxel has become a commonly used taxane in the treatment of metastatic breast cancer (Chevallier et al. 1995) and new data have emerged on the weekly use of paclitaxel (Akerley et al. 1997). Trastuzumab has been studied in combination with paclitaxel and docetaxel using a variety of doses and schedules with promising results (Seidman et al. 1999; Nicholson et al. 2000; Kuzur et al. 2000). In addition, the combination of trastuzumab with vinorelbine has recently been studied (Burstein et al. 2001). In this study, 30 of 40 women treated with trastuzumab (4 mg/kg x 1, 2 mg/kg weekly thereafter) and vinorelbine (25 mg/m^2 weekly, with dose adjusted each week for neutrophil count) responded to therapy, for an overall response rate of 75% (95% confidence interval 57% to 89%). Neutropenia was the only grade IV toxicity. No patients had symptomatic heart failure. Grade 2 cardiotoxicity was observed in 3 patients; prior cumulative doxorubicin dose in excess of 240 mg/m^2 and borderline pre-existing cardiac function were associated with this toxicity.

Trastuzumab Clinical Experience in Adjuvant Breast Cancer

Four large, randomized, phase III trials showed significant reduction in risk of disease recurrence with the addition of 1 year of trastuzumab to adjuvant therapy in patients with HER2-positive, early breast cancer. The 3-year planned joint interim analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP B-31) and the North Central Cancer Treatment Group (NCCTG N-9831) trials demonstrated significant improvements in disease-free survival (DFS) (hazard ratio [HR] 0.48, p<0.0001) and overall survival (OS) (HR 0.67, p=0.015) when 1-year of trastuzumab is added to adjuvant chemotherapy in patients with HER2-positive breast cancer (Romond et al 2005). At the 4-year follow-up, DFS and OS results were consistent (Perez et al 2011). At 8.4 years of median follow-up, the magnitude of DFS benefit and OS were maintained

over time, with HRs of 0.60 (p<0.0001) and 0.63 (p<0.0001), respectively (Perez et al. 2012). In HERA (trastuzumab adjuvant), single agent trastuzumab after adjuvant chemotherapy demonstrated significant improvements in DFS (HR 0.64, p<0.0001) and OS (HR 0.66, p=0.0115) compared with observation alone at a median follow-up of 23.5 months (Smith et al 2007). At a median follow-up of 48.4 months, a DFS benefit was observed (HR 0.66, p=0.0115) with 1 year of trastuzumab, however, the OS benefit was not statistically significant at 4 years (HR 0.85, p=0.11). At the time of analysis, over 50% of patients in the observation arm had crossed-over to receive trastuzumab (Gianni et al. 2011). The third protocol-specified analysis of the Breast Cancer International Research Group (BCIRG) 006 study continued to show that the addition of 52 weeks of trastuzumab to docetaxel-based adjuvant regimens significantly improved DFS. At a median follow-up of 65 months, 5-year DFS rates were 84% (HR 0.64, p<0.001) and 81% (HR 0.75, p=0.04) in the doxorubicin-containing trastuzumab and non-anthracycline-containing trastuzumab arms, respectively (Slamon et al. 2011).

Trastuzumab Clinical Experience in Neoadjuvant-Adjuvant Treatment of Early Breast Cancer

Study MO16432/NOAH investigated the effect of adding trastuzumab to neoadjuvant chemotherapy using doxorubicin plus paclitaxel, then paclitaxel, then cyclophosphamide plus methotrexate plus fluorouracil (CMF) in patients with HER2-positive locally advanced breast cancer. Patients who were randomized to trastuzumab, received it for a total of one year before and after surgery. The primary endpoint was event-free survival; secondary endpoints included pathological complete response (pCR) rate, and safety. At the time of the primary analysis, 118 HER2-positive patients were enrolled in the chemotherapy-alone arm with 116 HER2-positive patients enrolled in the chemotherapy plus trastuzumab arm. Baseline characteristics were well-balanced across treatment arms. Thirty-six percent of HER2-positive tumors were hormone-receptor positive. In the HER2-positive population, the 3-year EFS was 71% (95% CI, 61%-78%) in the Herceptin-containing combination arm compared with 56% (95% CI, 46%-65%) in the chemotherapy-alone arm. The unadjusted HR were 0.59 (p=0.0123) for EFS and 0.62 (p=0.114) for overall survival (OS) in the HER2-positive population. In the HER2-positive population, both ORR and pCR in breast tissue were significantly higher in the trastuzumab with chemotherapy arm compared with chemotherapy alone: 87% vs 74% for ORR (p=0.009); 43% vs 22% for pCR in breast tissue (p=0.0007), respectively. Overall, treatment was well-tolerated with acceptable cardiac safety (Gianni et al. 2010).

Pertuzumab Clinical Experience

Pertuzumab, a humanized monoclonal antibody to the HER2 receptor, represents a promising new anti-HER2 agent with a novel mechanism of action targeting inhibition of HER2 dimerization. Nonclinical and clinical data to date

indicate that pertuzumab provides a broader HER2 blockade through inhibition of HER2 heterodimerization. Pertuzumab has been shown in preclinical experiments to have superior anti-tumor effects when combined with other anti-HER2 treatments such as trastuzumab than when used as monotherapy.

Trastuzumab and pertuzumab monoclonal antibodies bind to distinct epitopes on the HER2 receptor without competing with each other, resulting in distinctive mechanisms for disrupting HER2 signaling. These mechanisms are complementary and result in augmented therapeutic efficacy when pertuzumab and trastuzumab are given in combination.

Preclinical data indicate at least additive efficacy when the two agents are administered together, resulting in significantly reduced tumor volume compared with either agent alone. Clinically, pertuzumab may have optimal therapeutic effects when given in combination with trastuzumab to patients with HER2-positive cancers, evidenced by data generated in a Phase II study of patients with previously treated HER2-positive MBC (Baselga et al. 2010). A recently published meta-analysis of pertuzumab phase II trials concluded that pertuzumab has a low cardiac risk and there is no notable increase in cardiac events when pertuzumab is used in combination with other anticancer agents (Lenihan et al. 2011).

Trastuzumab and Pertuzumab Combination Therapy in Patients with HER2-positive Tumors

Metastatic Breast Cancer: In the Phase III, pivotal study WO20698/TOC4129g (CLEOPATRA; N=808) in patients with previously untreated HER2-positive MBC, a statistically significant and clinically meaningful improvement in PFS, based on tumor assessments by an independent review facility (IRF), was observed in patients treated with pertuzumab, trastuzumab and docetaxel (N=406) compared with those receiving placebo, trastuzumab and docetaxel (N=402). PFS was prolonged at the median by 6.1 months and the risk of disease progression or death was reduced by 38% (Hazard ratio [HR] = 0.62; 95% CI = 0.51, 0.75; $p < 0.0001$) with an improvement in median PFS from 12.4 months to 18.5 months. Results of the investigator-assessed PFS analysis (HR = 0.65 [0.54, 0.78], $p < 0.0001$; median 12.4 vs 18.5 months, respectively) were consistent with those observed for IRF-assessed PFS. A second interim analysis of OS (performed one year after the primary analysis of efficacy) crossed the predefined stopping boundary for statistical significance ($p \leq 0.0138$), demonstrating that treatment with pertuzumab, trastuzumab and docetaxel significantly improved OS when compared with the placebo arm (HR = 0.66; 95% CI: 0.52, 0.84; $p = 0.0008$). The updated analysis of investigator-assessed PFS demonstrated that the PFS benefit observed at the primary analysis was maintained after an additional year of follow-up. The HR of 0.69 and the increase in median PFS of 6.3 months (from 12.4 months in the placebo arm to 18.7 months in the treatment arm) were highly consistent with those from the

first analysis of investigator-assessed PFS and consequently also with the primary IRF analysis (Swain et al. 2013).

In a Phase II, single-arm study (BO17929; N= 66) in patients with previously-treated HER2-positive MBC, four complete responses and 12 partial responses (24% objective response rate) were observed following combined treatment with pertuzumab and trastuzumab (Baselga et al. 2010).

Early Breast Cancer: In the Phase II study WO20697 (NEOSPHERE; N=417) patients with HER2-positive early breast cancer (EBC) receiving combination neoadjuvant therapy with pertuzumab, trastuzumab and docetaxel (N=107) had a pathological complete response (pCR) rate of 46%, compared with 29% in patients receiving trastuzumab plus docetaxel (N=107) (P=0.0141, 95% CI 21-39) (Gianni et al. 2012). The primary endpoint pCR in the breast was defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumor at surgery. Remaining in-situ lesions were allowed. The Phase II study BO22280 (TRYPHAENA; N=223) investigated neoadjuvant pertuzumab and trastuzumab a) concomitantly with anthracycline-based treatment (N=72); b) following anthracycline-based treatment (N=75) or c) concomitantly with a carboplatin-based regimen in patients with HER2-positive EBC (N=76). High pCR rates (57-66%) were achieved with all three treatment regimens (Schneeweiss et al. 2013).

1.4 TRASTUZUMAB AND PERTUZUMAB SAFETY

Trastuzumab Safety

Experience with trastuzumab administration has shown that the drug is relatively safe. The most significant safety signal observed during clinical trials was cardiac dysfunction (principally clinically significant heart failure [CHF]), particularly when trastuzumab was given in combination with an anthracycline-containing regimen. Much of the cardiac dysfunction was reversible on discontinuation of trastuzumab.

In addition, during the first infusion with trastuzumab, a symptom complex most commonly consisting of fever and/or chills was observed in approximately 40% of patients. The symptoms were usually mild to moderate in severity and controlled with acetaminophen, diphenhydramine, or meperidine. These symptoms were uncommon with subsequent infusions. However, in the post-approval setting, more severe adverse reactions to trastuzumab have been reported. These have been categorized as hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary events. Rarely, these severe reactions culminated in a fatal outcome.

There are no adequate or well-controlled studies in pregnant women, and animal reproduction studies are not always predictive of human response.

Therefore, trastuzumab should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus. In the post-marketing setting, oligohydramnios (decreased amniotic fluid) has been reported in women who received trastuzumab during pregnancy, either in combination with chemotherapy or as a single agent. Advise pregnant women and women of childbearing potential that trastuzumab exposure can result in fetal harm. Advise women of childbearing potential to use effective contraceptive methods during treatment and for seven months after last dose of trastuzumab (TWIMC letter 2014). Advise nursing mothers treated with trastuzumab to discontinue nursing or discontinue trastuzumab, taking into account the importance of the drug to the mother. Encourage women who are exposed to trastuzumab during pregnancy to enroll in the MotHER Pregnancy Registry (phone: 1-800-690-6720).

Trastuzumab appears to be relatively non-immunogenic. Only 1 of 903 patients evaluated developed neutralizing antibodies to trastuzumab. The development of anti-trastuzumab antibodies in this patient was not associated with clinical signs or symptoms.

Pertuzumab Safety

As of February 2014, safety data are available from 2949 patients with cancer treated with pertuzumab in company-sponsored pertuzumab trials, and from an additional 167 patients treated with pertuzumab in combination with investigational compounds.

Overall, data indicate that pertuzumab is well-tolerated as monotherapy and that it can be given in combination with trastuzumab and a range of other therapeutic agents with manageable additional toxicity. No new or unexpected toxicities were encountered other than those that are known for agents that target the HER family of receptors. Serious or severe infusion-associated symptoms have been rarely observed in patients receiving pertuzumab. A low level of cardiac toxicities, predominantly asymptomatic declines in left ventricular ejection fraction (LVEF), has been reported. In the pivotal Phase III trial WO20698/TOC4129g the rates of symptomatic and asymptomatic left ventricular systolic dysfunction (LVSD) were not higher in patients receiving pertuzumab, trastuzumab and docetaxel than in those receiving placebo, trastuzumab and docetaxel.

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 trastuzumab 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 six 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 six months after completion of treatment.

1.5 TRASTUZUMAB AND PERTUZUMAB CLINICAL PHARMACOKINETICS

Clinical Pharmacokinetics of Trastuzumab

A Phase I single dose study (H0407g) of intravenous trastuzumab infusions ranging from 10-500 mg resulted in dose-dependent pharmacokinetics (PK) with serum clearance of trastuzumab decreasing with an increasing dose at doses <250 mg. PK modeling of trastuzumab concentration-time data from 7 patients that were administered doses of 250 mg and 500 mg had in a mean half-life of 5.8 days (range 1-32 days). Additionally, PK modeling showed that weekly trastuzumab doses ≥250 mg resulted in serum trough levels of >20 □g/mL that was above the minimum effective concentration observed in preclinical xenograft studies in tumor-bearing mice. The Phase I data supported the weekly dosing schedule that was implemented in all subsequent Phase II and Phase III clinical trials. A weight-based dose schedule was adopted after two Phase II trials (H0551g and H0552g) suggested that inter-subject variability in trastuzumab PK was related to body weight. These findings resulted in a trastuzumab dose schedule of a 4 mg/kg loading dose followed by a weekly 2 mg/kg maintenance dose utilized in the two pivotal Phase III trials (H0648g and H0649g) that were the basis of the BLA filing and subsequent FDA approval of trastuzumab for HER2+ metastatic breast cancer.

The trastuzumab PK data from studies H0407g (Phase I), H0551g (Phase II), and H0649 (pivotal) have been subsequently reanalyzed by a population PK approach using nonlinear mixed effect modeling (NONMEM)(Bruno et al. 2005). A linear two-compartment model best described the concentration-time data, and accounted for the accumulation of trastuzumab serum concentrations seen in the Phase II and Phase III clinical studies. A covariate analysis was conducted using the subjects from these single agent studies to evaluate the effect of pathophysiologic covariates (e.g. age, weight, shed antigen) on the PK parameter estimates. The covariates, that significantly influenced clearance, were the level of shed antigen and the number of metastatic sites. Volume of distribution was significantly influenced by weight and shed antigen level. Additionally, data from the Phase III study, H0648g, were added to assess the influence of concomitant chemotherapy on trastuzumab PK. Importantly, chemotherapy (AC or paclitaxel) did not significantly alter trastuzumab PK. The estimated half-life of trastuzumab based on the final model was 28.5 days.

Analysis of data obtained from two Phase II studies which utilized a loading dose of 8 mg/kg trastuzumab followed by a 6 mg/kg maintenance dose administered every 3 weeks (q3 week) as a single-agent, and in combination

with paclitaxel (175 mg/m^2)(Leyland-Jones et al. 2000), confirmed that a two-compartment model best describes the PK of trastuzumab. Model-independent analysis of the of the data obtained in these studies gives comparable PK parameter estimates to those obtained by the population PK model, thus confirming the validity of the population PK model. In addition, the population PK model adequately predicted trastuzumab serum concentrations obtained independently in these studies. After two treatment cycles, trastuzumab exposure were similar to those measured in the once weekly dosing regimen used in the pivotal trials. Trough levels were in excess of the targeted serum concentrations established from preclinical xenograft models, and as expected, peak levels were greater than those observed upon weekly administration. The apparent half-life of trastuzumab in these studies was determined to be approximately 21 days, and the PK was supportive of a q3 week dosing schedule.

The efficacy and safety results from these Phase II studies with q3 week dosing do not appear to be different from those with weekly dose-schedules. In the trastuzumab q3 weekly monotherapy study, 105 patients with HER2+ metastatic breast cancer were treated, with an objective response rate of 19% (23% in patients with measurable centrally confirmed HER2+ disease). The median baseline LVEF was 63%, which did not significantly change during the course of the study. One patient experienced symptomatic CHF, which resolved with medical treatment for CHF and discontinuation of trastuzumab. In the study of q3 weekly trastuzumab and paclitaxel, 32 patients were treated with an investigator-assessed response rate of 59%. Ten patients had a decrease in LVEF of 15% or greater. One patient experienced symptomatic CHF, which improved symptomatically after medical therapy for CHF and discontinuation of trastuzumab.

Clinical Pharmacokinetics of Pertuzumab

A comprehensive population pharmacokinetics (popPK) analysis was conducted by using concentration data obtained from 481 cancer patients across twelve Phase I/II/III studies in patients with solid tumors, ovarian cancer, prostate cancer, NSCLC, and breast cancer. In the popPK analysis, a two-compartment linear model with first-order elimination from the central compartment described serum pertuzumab PK in the dose range 2.0 to 25.0 mg/kg (equivalent to 140-1750 mg for a 70-kg patient). In the final model, clearance (CL), central volume of distribution (Vc), and terminal elimination half-life were 0.235 L/day, 3.11 L, and 18 days, respectively. Lean body weight and serum albumin were identified as statistically significant covariates for pertuzumab PK. CL decreased in patients with higher baseline albumin concentrations and increased in patients with greater lean body weight. However, sensitivity analyses indicated that dose-adjustment based on these covariates would not lead to a meaningful reduction in exposure variability since the covariate effect on pertuzumab exposure was relatively small compared to the overall inter-individual variability of the population. No statistically significant effects of other covariates on PK

parameters were detected, including demographic variables (age, gender, race [Japanese versus non-Japanese]), laboratory variables related to hepatic and renal function (ALT, AST, TBIL, ALK, CrCL), and disease variables (ECOG/KPS, MBC versus other tumor types, number of metastatic sites, liver metastases and concomitant chemotherapy).

The fixed (non-weight based) pertuzumab dosing regimen of an 840 mg loading dose followed by a 420 mg maintenance dose, administered q3w, in patients with MBC and other solid tumors included in the model, is well supported by these popPK results (Ng et al. 2006).

Pertuzumab PK in Study WO20697 (NEOSPHERE) were consistent with the previous popPK model predictions, suggesting similarity in pertuzumab PK between the patient population included in the NEOSPHERE study (patients with LABC, IBC and EBC) and patients with advanced malignancies, including the first-line MBC population.

Results from studies where pertuzumab was administered in combination with various small molecule chemotherapeutic agents (gemcitabine, capecitabine, erlotinib or docetaxel), indicate that pertuzumab does not alter the PK of these agents and the PK of pertuzumab is similar to that observed in single-agent pertuzumab studies. In addition, data from the Phase III trial WO20698/TOC4129g demonstrate that pertuzumab administration did not change the PK of trastuzumab, and there was no evidence of drug-drug interactions (DDI) when docetaxel was combined with pertuzumab plus trastuzumab.

1.6 DATA SUPPORTING TRASTUZUMAB AND PERTUZUMAB WITHOUT CHEMOTHERAPY

HER2 is overexpressed in 20% of early stage breast cancer diagnoses, and half of those will be hormone receptor positive (ER or PR positive). Although HER2 overexpression has been shown to be an adverse prognostic factor for disease recurrence after curative intent treatment – the development of HER2 targeted antibodies, i.e. trastuzumab and now pertuzumab, has helped to neutralize this negative prognostic factor. As NEOSPHERE showed surprising bioactivity (pCR of 29.1%) of 12 weeks of neoadjuvant trastuzumab and pertuzumab without chemotherapy in HR- HER2+ disease, and TBCRC 006 (Rimawi et al) showed 12 weeks of hormone therapy with trastuzumab and lapatinib yielded a pCR rate of 21% with another 22% having low residual disease (or <1 cm), it is reasonable to expect an even higher pCR rate with hormone therapy and trastuzumab and pertuzumab, for a treatment duration longer than 12 weeks. NSABP-52 is a currently active clinical trial which proposes neoadjuvant treatment of HER2+ breast cancer with TCHP (taxotere, carboplatin, trastuzumab and pertuzumab) with or without hormone treatment, with pCR rate as the primary endpoint. It is expected that the pCR rate observed in NSABP-52 will be nominally higher in the HR+ HER2+ subset compared to the pCR rate

identified in NEOADAPT (this protocol) but *it will not answer questions about a neoadjuvant chemotherapy free approach*, again not addressing patient advocacy groups' demands for more treatment options with less toxicity. The closest study to NEOADAPT in terms of a chemotherapy free approach for HR+ HER2+ breast cancer is PERTAIN another active phase II clinical trial in the metastatic breast cancer space. PERTAIN proposes randomized controlled first line treatment of metastatic HR+ HER2+ breast cancer with an aromatase inhibitor and trastuzumab with or without pertuzumab where concurrent chemotherapy is allowed if deemed necessary. The median duration of treatment seen in the subset of patients who randomize to trastuzumab and pertuzumab and do not get concurrent chemotherapy will be of interest to compare notes with the median duration of treatment with NEOADAPT.

For a more detailed discussion, refer to 3.2 Rationale for Study Design.

1.7 OTHER STUDY DRUG(S) BACKGROUND

N/A

2. OBJECTIVES

This is a prospective single arm phase II study of 32 evaluable patients treated with NEOADjuvant Aromatase inhibitor and Pertuzumab/Trastuzumab (NEOADAPT) without chemotherapy for HR+ (Hormone receptor positive, i.e. ER and/or PR+) HER2+ localized, non-metastatic stage I-II breast cancer

2.1 PRIMARY OBJECTIVE

To document the pCR (pathological complete response) rate of an aromatase inhibitor, trastuzumab and pertuzumab (henceforth referred to as "biological therapy") without chemotherapy for HR+ HER2+ localized, non-metastatic breast cancer.

2.2 SECONDARY OBJECTIVES

To describe the median duration of neoadjuvant treatment with biological therapy for HR+ HER2+ localized, non-metastatic breast cancer

To conduct an exploratory analysis of whether Agendia's Mammaprint and Blueprint test could prospectively identify patients who are more likely to have a pCR or not with biological therapy alone.

To describe the sensitivity and specificity of radiographic complete response (rCR) by dynamic contrast-enhanced breast MRI in predicting pathological

complete response (pCR) with neoadjuvant biological therapy for HR+ HER2+ localized, non-metastatic breast cancer

3. STUDY DESIGN

See Figure 1. Study Schema for an overview (page 51).

3.1 DESCRIPTION OF THE STUDY

This is an open-label non-randomized single arm phase II descriptive study of 32 evaluable patients with localized, non-metastatic HR+ HER2+ breast cancer who will be given neoadjuvant "biological therapy" i.e. an aromatase inhibitor (anastrazole, letrozole or exemestane allowed), and trastuzumab and pertuzumab. If the patient is pre-menopausal then either a GnRH agonist (goserelin or leuprolide) or a bilateral oophorectomy would be required.

Patients who have HR+ HER2+ localized, non-metastatic breast cancer (i.e. radiological stage I-IIb) and have not received any systemic breast cancer treatment nor have completed definitive surgical resection of the primary are eligible for study.

A total of 32 evaluable patients will be enrolled into a single arm of neoadjuvant "biological therapy". The intent of neoadjuvant treatment is to continue treatment as long as there is no evidence of radiographic progression to a maximum of one year or until 12 weeks after a "radiographic complete response" (rCR) is observed. The 12 weeks of additional treatment after rCR accounts for a known weakness of breast MRI in monitoring neoadjuvant treatment: underestimation of minimal residual disease.

Neoadjuvant "biological therapy" includes the following drugs:

Pertuzumab: per FDA approved schedule, to be given every 3 weeks starting with an 840mg loading dose for 60 minutes for cycle 1 (henceforth referred to as Day 0), and then 420mg maintenance dose every 3 weeks over 30-60min until progressive disease, 3 months after suspected pCR by imaging and exam, one year of treatment delivered, or patient withdrawal from study.

Trastuzumab: per FDA approved schedule, to be given every 3 weeks starting with an 8mg/kg loading dose over 60-90 minutes on Day 0, and then 6mg/kg maintenance dose every 3 weeks over 30-60min until progressive disease, 3 months after suspected pCR by imaging and exam, or patient withdrawal from study.

Aromatase inhibitor: to be started +/- 7 days before or after Day 0 and can include any one of several FDA approved aromatase inhibitors such as anastrazole 1mg/d, letrozole 2.5mg/d, or exemestane 25mg/d. For pre-menopausal women, a GnRH agonist such as goserelin 3.6mg monthly or

10.8mg every 3 months or leuprolide 3.75mg every month or 11.25mg every 3 months or bilateral oophorectomy is required to be enrolled on study as is standard of care for pre-menopausal women receiving an aromatase inhibitor. As the aromatase inhibition aspect of the intervention is current standard of care for (neo)adjuvant treatment of hormone receptor positive breast cancer, we will focus more on the study aspect of the intervention, i.e. the use of trastuzumab and pertuzumab. Side effects are defined in the informed consent.

Adaptive duration of treatment. Patients should remain in the treatment phase of the study until investigator-assessed radiographic or clinical progressive disease, unmanageable toxicity, study termination, or a maximum of 12 months of treatment. Patients will be followed every 3 weeks with a requisite breast exam, CBC, BMP and review of new symptoms and/or side effects of treatment. An MRI of the breast will be required every 12 weeks or more frequently if clinical suspicion or abnormal exam warrants. Additional imaging including but not limited to diffusion-weighted MRI, mammogram, tomosynthesis, PET and breast/axillary ultrasound are allowed, if felt clinically warranted by the investigator although MRI has been shown to be the most effective imaging modality for monitoring (Esserman et al 1999, Balu-Maestro et al 2002) response during neoadjuvant treatment for breast cancer. It is preferred that an MRI is done to document progression rather than relying on clinical exam alone, before taking a patient off treatment protocol.

Response evaluation criteria for breast MRI. The algorithm for treatment decisions based on MRI results will rely on modified RECIST 1.1 criteria where the target lesion (i.e. the primary tumor) and a second target lesion if applicable (i.e. a smaller satellite lesion or largest pathological lymph node) are assessed. Of note, the target lesion can be less than 1.0 cm as the intent of the study is to include patients with T1a-c tumors. To qualify as a second target lesion, the mass or lymph node should be biopsied and proven to be of the same phenotype (i.e. HR+ HER2+). *Radiographic complete response (rCR) is defined as the disappearance of all target lesions in the breast with no residual enhancement in the breast that can be reasonably attributed to tumor*. Of note this does not require complete disappearance of target lesions if they involve lymph nodes. Specifically, enhancement thought to be more likely due to marker placement is a possible scenario where an MRI film with residual enhancement might still be called a rCR. Another example is subtle enhancement only observed in delayed phase images and not in the early phase images can be considered rCR. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm. If a lymph node is called too small to measure, a default short axis measurement of 5mm will be recorded.

Radiographic partial response will be defined as 30% decrease in the sum of the longest diameter of the target lesions. Progressive disease will be defined as a 20% increase in the sum of the longest diameter of the target lesions or a 33% increase in the longest diameter of a non-target axillary lymph node. Stable disease is defined as small changes that do not meet the above criteria.

If an MRI documents at any time rCR, protocol treatment will be continued for another 12 weeks to provide consistency to the neoadjuvant strategy for duration of treatment and to accommodate for a known shortcoming of breast MRI – underestimation of minimal residual disease.

If MRI shows stable disease, it is recommended to continue biological therapy until there is documented progressive disease. MRI can be increased in frequency to more than every 12 weeks if in the judgement of the clinician it is appropriate for the clinical situation. If MRI shows progressive disease, the patient is classified as a non-pCR and taken off treatment protocol. The investigator is allowed to either switch to a different neoadjuvant strategy or proceed to immediate surgical resection. Study follow-up will continue until definitive surgery. Should the patient proceed immediately to definitive surgery after being taken off protocol treatment with no interim tamoxifen, chemotherapy or radiation or alternative treatment given with the intent of anti-tumor response, and the surgical pathology shows no residual invasive disease in the breast or lymph nodes (i.e. the MRI turns out to be a false negative), only then can the patient be reclassified from a non-pCR to a pCR for the purposes of this study.

See Appendix B for more on breast MRI response evaluation criteria.

Once a patient has either definitive surgical resection of the breast cancer, metastatic disease, death or elects to be withdrawn from study whichever comes first, the patient is officially no longer in follow-up or on study. It is not the intent of this clinical trial to specify what should be done after definitive surgery with curative intent. It is recommended that standard of care be followed.

Definition of pCR rate. The primary endpoint of the study, pCR rate, will be calculated based on the following definition of pathological complete response (pCR) per FDA guidance documents (www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm305501.pdf): "absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected *breast specimen* and all *sampled regional lymph nodes* following completion of neoadjuvant systemic therapy (i.e. ypT0Tis ypN0 in the current AJCC staging system).

As implied by the above definition, choice of breast conserving surgery vs mastectomy and axillary LN management is up to the clinicians and not defined by the study protocol. The only requirement is that at minimum as per standard of care at Cancer Treatment Centers of America, a sentinel LN biopsy is done with the usual dual blue dye and radioisotope tracers, particularly when the radiographic axillary staging is negative. Resection of at least two nodes is encouraged whenever possible.

The primary site for this clinical study, Midwestern Regional Medical Center of Cancer Treatment Centers of America, receives around 270 patients/year with a new diagnosis of stage I-III breast cancer. 10% or 27 are anticipated to have

ER+ HER2+ breast cancer. When accounting for physician preferences and logistical challenges for patients we anticipate accruing 1 patient/month and to assure completion of accrual within 1 year, the study will also be open at two sister CTCA sites, Western Regional Medical Center (Goodyear, AZ) and Southeastern Regional Medical Center (Atlanta, GA).

It is anticipated that due to logistics, patient preferences and uncontrollable factors that about 10% of patients will withdraw from study for reasons not related to toxicity of treatment. If a patient on study withdraws by choice due to primarily logistical issues such as travel time, costs or personal non-health related issues including death deemed not directly related to cancer or cancer treatment, then the patient will still count as part of the intention to treat analysis but not the final reported pCR rate. Since the primary intent of this study is to establish efficacy of a neoadjuvant biological therapy strategy, it is anticipated that 36 patients will need to be recruited to achieve the goal of having 32 evaluable patients.

The trial will officially close when 32 evaluable patients have surgical pathology results.

3.2 RATIONALE FOR STUDY DESIGN

The precedent for this clinical study was established with Neosphere (Gianni et al, 2012), which showed surprising bioactivity of a 12 week course of neoadjuvant pertuzumab and trastuzumab without chemotherapy for HER2+ localized breast cancer. The pCR rate overall in this subgroup was 16.8%, and 5.9% and 29.1% for HR+ (hormone receptor positive) and HR- subsets respectively. Importantly, none of the patients in the HR+ subsets received concurrent hormone therapy.

TBCRC 006 showed that if hormone therapy was added to dual-HER2 blockade therapy with lapatinib and trastuzumab for 12 weeks as neoadjuvant therapy for HER2+ breast cancer (a similar duration of treatment used in Neosphere), the pCR rate was 21% with another 22% having low residual disease or < 1 cm (Rimawi et al 2013). While TBCRC 006 established that a 21% pCR rate is the current floor for hormone treatment combined with dual-targeted HER2 therapy, there are 2 pivotal reasons to expect significantly higher pCR rates with this clinical trial.

In the final analysis of CLEOPATRA, the addition of pertuzumab to docetaxel and trastuzumab led to an unprecedented improvement in PFS and OS (6.3 months PFS difference and 15.7 month OS difference) (Gianni et al 2012) making trastuzumab and pertuzumab the HER2 targeted strategy of choice in the first line treatment of metastatic HER2+ breast cancer, not lapatinib or Kadcyla (TDM-1).

Meanwhile, our understanding of neoadjuvant hormone treatment for HR+ (HER2-) breast cancer is that extending aromatase inhibitor (letrozole) treatment beyond 3 months leads to additional reduction in clinical tumor volume, and the majority of patients utilizing this strategy continue to have reduction of tumor volume 6-12 months after start of therapy (Dixon et al 2009).

Therefore, the primary purpose of this study is to describe the pCR rate associated with a non-fixed adaptive-duration of neoadjuvant aromatase inhibitor, trastuzumab and pertuzumab in the treatment of HR+ HER2+ breast cancer. We expect the secondary objective of median duration of treatment in this study as well as that seen in PERTAIN (phase II study looking at first line treatment of metastatic HR+HER2+ breast cancer with an aromatase inhibitor, trastuzumab and/or pertuzumab) will help provide relevant data to guide a possible future, larger and more definitive clinical trial of a more fixed duration of neoadjuvant treatment with an aromatase inhibitor with trastuzumab and pertuzumab.

A randomized controlled study utilizing a fixed duration of biological therapy was not deemed to be a practical study mainly because the number of patients required to have a statistically meaningful study would be prohibitive. Also, the study arm would be plagued by lack of any frame of reference as to what an optimal duration of neoadjuvant biological therapy would be.

The potential significance of this study is that it answers directly to patient advocate groups' plea for clinical research to yield more treatment options for women with breast cancer, particularly those with less toxicity, even if it might sacrifice some degree of efficacy. It could lay down the foundation for a new era of chemotherapy free neoadjuvant treatment of early stage ER+HER2+ breast cancer.

3.3 OUTCOME MEASURES

Patients will be screened and consented for study in between the time of diagnosis of localized HR+HER2+ breast cancer and the start of any definitive treatment including hormone therapy, surgery and/or radiation. Once enrolled, patients will be followed until the time of definitive surgery, with surgical pathology results (i.e. designation of achievement of pCR or not) being the end point of follow-up. Other unlikely potential end points of follow-up include death, metastatic disease, patient or physician decision to opt out of surgery.

The primary and secondary outcome measures are clinically meaningful as it will provide clinical investigators, physicians and patients with more prospective data to make informed decisions regarding a chemotherapy-free approach to localized HR+ HER2+ breast cancer. Several studies cover similar terrain as this study but will not provide the information this trial, NEOADAPT, will provide. For example, PERTAIN a phase II randomized clinical trial, has completed

enrollment (as of 2015) with results not yet reported, and it too studies treatment with an aromatase inhibitor with trastuzumab and pertuzumab, but instead of neoadjuvant, as first line treatment for metastatic HR+ HER2+ breast cancer (with trastuzumab alone as a control). While its primary endpoint is to validate the results seen with pertuzumab in CLEOPATRA (marked PFS and OS benefit in HER2+ breast cancer of the addition of pertuzumab to docetaxel and trastuzumab) for patients with exclusively HR+ HER2+ metastatic breast cancer, it will not address the neoadjuvant or curative intent space of NEOADAPT. However, the median duration of treatment with the trastuzumab and pertuzumab arm in PERTAIN would provide synergistic information with the results of median duration of neoadjuvant treatment in NEOADAPT to help guide a future definitive neoadjuvant clinical trial.

Also NSABP-52 will offer neoadjuvant treatment of HER2+ breast cancer with TCHP (taxotere, carboplatin, trastuzumab and pertuzumab) with or without hormone treatment) with pCR as the primary endpoint. It is expected that the pCR rate will be nominally higher in the HR+ HER2+ subset compared to the pCR rate identified in NEOADAPT but it will not answer questions about a neoadjuvant *chemotherapy free* approach, again not addressing patient advocacy groups' demands for more treatment options with less toxicity.

3.3.1 Primary Outcome Measure

The primary endpoint of the study, pCR rate, will be calculated based on the following definition of pathological complete response (pCR) per FDA guidance documents (www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm305501.pdf): "absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected *breast specimen* and all *sampled regional lymph nodes* following completion of neoadjuvant systemic therapy (i.e. ypT0Tis ypN0 in the current AJCC staging system).

3.3.2 Secondary Outcome Measures

The first secondary objective is median duration of treatment. Median duration of treatment is defined as the number of days between Day 0 (first treatment of trastuzumab and pertuzumab) and three weeks after the last dose of neoadjuvant trastuzumab and pertuzumab on treatment protocol.

The intent of neoadjuvant treatment is to continue treatment as long as there is no evidence of radiographic progression to a maximum of one year or until 12 weeks after a "radiographic complete response" (rCR) is observed. The 12 weeks of additional treatment after rCR accounts for a known weakness of breast MRI in monitoring neoadjuvant treatment: underestimation of minimal residual disease.

"Radiographic complete response" will be defined by modified RECIST 1.1 criteria where the target lesion (i.e. the primary tumor) and a second target

lesion if applicable (i.e. a smaller satellite lesion or pathological lymph node) are assessed. To qualify as a second target lesion, the mass or lymph node should be biopsied and proven to be of the same phenotype (i.e. HR+ HER2+). Radiographic complete response (rCR) is defined as the disappearance of all target lesions in the breast with no residual enhancement in the breast that can be reasonably attributed to tumor. Of note this does not require complete disappearance of target lesions if they involve lymph nodes. Specifically, enhancement thought to be more likely due to marker placement is a possible scenario where an MRI film with residual enhancement might still be called a rCR. Another possible scenario of rCR would be subtle enhancement only observed in delayed phase images and not in the early phase images. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm. If a lymph node is called too small to measure, a default short axis measurement of 5mm will be recorded.

In some cases, rCR might be difficult to classify and another protocol-valid way to clarify which breast MRI is the first to document rCR is that the follow-up MRI required by protocol does not show any further reduction in breast enhancement or mass (for example, dense breasts might make it difficult to measure residual mass dimensions). If further reduction in enhancement or mass is seen, the protocol allows for reclassification of the prior film as partial response and identification of the latest MRI as the first film that shows complete response (and hence, by protocol treatment will continue and another MRI will be done in 12 weeks).

Cessation of protocol treatment is mandatory if progressive disease is observed, i.e. a 20% increase in the sum of the longest diameter of the target lesions, or a 33% increase in the longest diameter of a non-target axillary or intramammary lymph node. Stable disease is defined as small changes that do not meet the criteria of radiographic complete response, partial response or progressive disease. If stable disease is observed on the 12-week breast MRI, clinical judgment is allowed as to whether the patient or clinician/investigator wishes to call the RECIST 1.1-defined stable disease as progressive enough to justify taking the patient off protocol treatment although at least over a 10% increase in the sum of the longest diameter of the target lesions is recommended.

Stable and progressive disease is defined by the delta between the peak response breast MRI measurements (i.e. the baseline MRI or the follow-up MRI which showed the most significant reduction) and the current breast MRI being read.

An echocardiogram or MUGA is required every 12 weeks or every 4 cycles of trastuzumab and pertuzumab or as needed based on clinical suspicion. If trastuzumab and pertuzumab are held due to a drop in ejection fraction (EF) > 10% and absolute value of < 50%, (see Appendix E) a repeat echocardiogram or MUGA is advised no later than 3 weeks. If the EF returns either to normal range or within an absolute 10% of the baseline EF, trastuzumab and

pertuzumab may be restarted. The patient will be counted as being still on treatment protocol and the days of holding trastuzumab and pertuzumab will still be counted as part of the “duration of treatment” calculation if treatment is resumed. If the EF is still > 10% decreased from the baseline or < absolute 50%, then continue to hold the treatment and repeat echo in another 3 weeks. Any treatment delay greater than 6 weeks will result in mandatory cessation of treatment protocol and duration of treatment will be calculated up to 3 weeks after the last dose of trastuzumab and pertuzumab. Of note, the aromatase inhibitor should not be held during a hold of trastuzumab and/or pertuzumab for cardiac reasons. If the patient develops symptomatic CHF it is mandatory to take patient off treatment protocol in which case a cardiology consult is highly recommended.

If the patient or physician chooses to switch to another aromatase inhibitor for whatever reason (arimidex, letrozole or exemestane) but continues concurrent trastuzumab and pertuzumab then the patient is still considered on protocol treatment.

If the patient or physician chooses to no longer treat with any component of treatment protocol (aromatase inhibitor, trastuzumab or pertuzumab) for reasons related to the cardiac criteria above or completely unrelated reasons, or chemotherapy is added to the protocol regimen, then the patient is no longer on protocol treatment and off study.

Another secondary outcome measure involves Agendia’s Mammaprint and Blueprint testing. Mammaprint is an FDA-cleared 70-gene signature assay that classifies breast cancer into low or high risk. Currently, we do not have a validated biomarker to predict which patients with HR+ HER2+ breast cancer would be most likely to achieve a pCR with neoadjuvant aromatase inhibitor and trastuzumab and pertuzumab. A secondary objective of NEOADAPT is to do an exploratory analysis of whether patients who test as “low risk” by Mammaprint are more likely to obtain a pCR.

Knauer et al (2010) tested Mammaprint in 168 patients with T1-3 N0-1 HER2+ breast cancer, 89 of which did not receive chemotherapy. 20/89 (22%) tested as good prognosis with a 10-year distant disease-free survival (DDFS) of 84% and 69/89 (78%) tested as poor prognosis with a 10-year DDFS of 55%. The hazard ratio was 4.5 (95% confidence interval 1.1-18.7 p=0.04). Most relevant to this clinical study, a subset analysis of 40 patients with HER2+ and highly endocrine responsive tumors according to the St. Gallen criteria (both >50% ER and PR positive) showed that all 11 patients who tested as low risk by Mammaprint had 10-year DDFS.

Blueprint is an 80 gene molecular subtyping assay that rather than traditional and approved subtyping based on IHC and FISH focuses more on the functional level of gene expression to classify patients into the luminal, HER2 and basal subtypes of breast cancer. The Neoadjuavant Breast Registry Symphony Trial

(NBSRT) study generated provocative results that suggested that patients with HER2+ breast cancer who classify as luminal type, particularly benefited from the addition of pertuzumab to trastuzumab-based chemotherapy and pCR rate increased from 6% to 39% (SABCS 2015). It is hypothesized that Blueprint might help identify patients with HER2+ breast cancer (those identified as luminal by Blueprint) that particularly benefit from “biological” therapy with aromatase inhibitors and trastuzumab and pertuzumab.

Therefore, Mammaprint and Blueprint testing will be attempted on the initial diagnostic biopsy, but the results need not be final prior to starting protocol treatment. If insufficient tissue is available for Mammaprint testing, Mammaprint and Blueprint testing will be requested on the definitive surgical pathology specimen, assuming the patient has not achieved a pCR.

Estrogen receptor, progesterone receptor and HER2 status as determined by Blueprint testing is not to be used in lieu of standard of care immunohistochemistry and FISH when applicable (per relevant ASCO guidelines). Of note, neither Mammaprint nor Blueprint is currently validated nor FDA approved for triaging treatment decisions related to HER2+ breast cancer.

The third and last secondary objective is self-explanatory, to identify the sensitivity and specificity of radiographic complete response (rCR) by dynamic contrast-enhanced breast MRI in predicting pathological complete response (pCR) under NEOADAPT protocol-defined treatment.

3.4 SAFETY PLAN

Patients will be evaluated at each study visit for the duration of their participation in the study (see Section 4.5 and Appendix A, Study Flowchart), i.e. every 3 weeks. Specific potential safety issues for this trial are outlined below.

RISK OF LEFT VENTRICULAR DYSFUNCTION

LVEF declines have been reported with drugs that block HER2 activity, including pertuzumab and trastuzumab.

Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab can also cause asymptomatic decline in left ventricular ejection fraction (LVEF). (Please refer to Herceptin investigator’s brochure and prescribing information for details)

In the pivotal trial WO20698/TOC4129g (CLEOPATRA), pertuzumab in combination with trastuzumab and docetaxel was not associated with increases in the incidence of symptomatic LVSD or LVEF declines compared with placebo in combination with trastuzumab and docetaxel. In this study, patients who had received prior anthracyclines or prior radiotherapy to the chest area were at higher risk of decreased LVEF (regardless of treatment arm).

Pertuzumab combined with trastuzumab and chemotherapy also did not result in a significantly greater incidence of symptomatic LVSD or LVEF declines than trastuzumab plus chemotherapy, in patients with EBC treated in the neoadjuvant setting (Study WO20697 [NEOSPHERE]).

Pertuzumab has not been studied in patients with the following: a pretreatment LVEF ≤ 50%; a prior history of CHF; LVEF declines to <50% during prior trastuzumab adjuvant therapy; conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360mg/m2 of doxorubicin or its equivalent.

Cardiac exclusion criteria are specified in the protocol and will be closely followed.

Management of Cardiac Safety

All patients must have a baseline evaluation of cardiac function including a measurement of LVEF by either MUGA or ECHO prior to entry into the study. Only patients with an LVEF ≥ 50% should be entered into this study.

LVEF should be assessed (by ECHO or MUGA scan) at regular intervals of every 12 weeks or 4 treatments with pertuzumab and trastuzumab to ensure that LVEF does not decrease > 10% and below the institution's normal cutoff. ECHO or MUGA scans should be scheduled at the same radiology facility where the patient's baseline ECHO or MUGA was conducted whenever possible. LVEF measurements should be required at protocol-specified time-points and after a patient has any of the following: discontinuation of protocol therapy, congestive heart failure (CHF), breast cancer recurrence, or a second primary cancer.

During the course of trastuzumab and pertuzumab therapy, patients should be monitored for signs and symptoms of CHF (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). The confirmation of the CHF diagnosis should include the same method used to measure LVEF at baseline (either ECHO or MUGA).

Pertuzumab and trastuzumab should be discontinued in any patient who develops clinical signs and symptoms suggesting CHF. 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 in LVEF.

Neoadjuvant Breast Cancer Protocols (refer to Appendix E)

Refer to Appendix E for Algorithm for Continuation and Discontinuation of HER2 Targeted Study Medication for Early Breast Cancer Trials

If the criteria to hold pertuzumab treatment are met (based on Appendix G) repeat LVEF assessment within approximately 3 weeks.

If after a repeat assessment in 3 weeks, the LVEF has not improved, or has declined further, discontinuation of pertuzumab and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. If LVEF is ≥50% or <10 points decline from baseline, pertuzumab and trastuzumab treatment may be resumed.

For delayed or missed doses, if the time between 2 sequential infusions is less than 6 weeks, the 420 mg IV dose of pertuzumab should be administered. Do not wait until the next planned dose. If the time between 2 sequential infusions is 6 weeks or more, the initial dose of 840 mg pertuzumab should be re-administered as a 60 minute IV infusion followed every 3 weeks thereafter by a dose of 420 mg IV administered over 30-60minutes.

Pertuzumab should be withheld or discontinued if trastuzumab treatment is withheld or discontinued.

Pregnancy and Contraception Use

There are no clinical studies of pertuzumab or trastuzumab in pregnant women. IgGs are known to cross the placental barrier. Nonclinical reprotoxicity data in cynomolgus monkeys treated with pertuzumab showed embryofetal losses, oligohydramnios, and renal hypoplasia (please refer to the pertuzumab investigator's brochure for details). Neither pertuzumab nor trastuzumab should be used during pregnancy.

It is not known whether trastuzumab or pertuzumab is excreted in human milk. Because maternal IgG is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least seven months following the last dose of either monoclonal antibody.

For women of childbearing potential (who have not undergone surgical sterilization), and the female partners of male participants; agreement must be obtained to use highly effective contraception.

On the basis of pharmacokinetic considerations, contraception methods should start a minimum of 14 days prior to the first administration of study drug and continue for the duration of study treatment and for at least 7 months after the last dose of study treatment (please refer to trastuzumab investigator's brochure for details).

Encourage pregnant women with breast cancer who are exposed to trastuzumab or pertuzumab to enroll in the MotHER Pregnancy Registry (phone 1-800-690-6720).

Infusion-Related Reactions (IRRs)

Like other monoclonal antibodies, pertuzumab has been associated with IRRs (such as chills, diarrhea, fatigue, headache, nausea, and pyrexia), and with hypersensitivity reactions. In the pivotal Phase III trial (WO20698/TOC4129g [CLEOPATRA]), on the first day when only peruzumab was administered, the overall frequency of IRRs was 13.0% in the pertuzumab-treated group and 9.8% in the placebo-treated group, with the majority of reactions being mild or moderate. Close observation of the patient during and for 60 minutes after the first infusion and during and for 30 minutes following subsequent infusions is recommended following the administration of pertuzumab. If an IRR occurs, the infusion rate should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction.

Anaphylaxis and Hypersensitivity

Anaphylaxis or hypersensitivity reactions are known risks following infusion with monoclonal antibodies. Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis, has been observed in clinical trials with treatment of pertuzumab. The infusion should be discontinued immediately if a serious hypersensitivity reaction occurs. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Risk of Respiratory Events

In the pivotal study CLEOPATRA, respiratory events (i.e., dyspnea, cough) were reported in >10% in pertuzumab-treated patients, which are unspecific symptoms of various conditions, including infusion associated reaction or hypersensitivity/anaphylaxis, cardiac dysfunction, and respiratory disease. Because of pertuzumab's role in inhibiting heterodimerization with other members of the HER family, including EGFR, there is a potential risk of interstitial lung disease (ILD). However, few reports of ILD have been received for patients receiving pertuzumab and these indicated possible alternative causes for the events (eg, concomitant medication, preceding/concurrent neutropenia with potential infection) or relevant medical history.

3.5 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).

3.5.1 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 in up to 90% of patients in combination therapy studies. Diarrhea was NCI-CTCAE 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.

3.5.2 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 CTC Grade 1 or 2 in severity. Treatment recommendations for EGFR associated rash include topical or oral antibiotics, topical pimecrolimus, topical or (for severe reactions) systemic steroids. These agents may be used in patients experiencing pertuzumab-related rash, as clinically indicated, although they have not been studied in this context.

3.6 RISK OF NEUTROPENIA

Neutropenic events are virtually absent with chemotherapy-free pertuzumab regimens and with single-agent pertuzumab. In the pivotal study WO20698/TOC4129g incidence of neutropenic events was increased in patients receiving pertuzumab, trastuzumab and docetaxel, compared to patients in the placebo-controlled arm. This was largely driven by an increase in Grades 3 and 4 febrile neutropenia. No febrile neutropenia events occurred after docetaxel discontinuation. In the Phase Ib study, BO17021, 420 mg pertuzumab in combination with 75 mg/m2 docetaxel was well tolerated; however, dose-limiting toxicity, including febrile neutropenia, was observed with 420 mg pertuzumab in combination with 100 mg/m2 docetaxel. To reduce the risk of Grade ≥ 3 neutropenic events, patients receiving pertuzumab in combination with docetaxel in ongoing studies are treated initially with 75 mg/m2 docetaxel. The dose of docetaxel may be escalated to 100 mg/m2 after the first cycle, provided that the patient does not experience significant toxicities at the starting dose. This strategy is intended to ensure optimum individual exposure for patients receiving docetaxel in combination with pertuzumab.
Patients receiving pertuzumab without docetaxel, or other cytotoxic agents, would be highly unlikely to develop clinically significant neutropenic fever.

3.6.1 Management of Hematologic Toxicities

Protocol: NEOADAPT: Neoadjuvant aromatase inhibitor with pertuzumab and trastuzumab

Care should be taken to carefully monitor the patient's hematologic status throughout the course of the trial. Use of hematopoietic growth factors to ameliorate hematologic toxicity is at the discretion of the physician investigator and should be in accordance with the American Society of Clinical Oncologists (ASCO) guidelines.

Please refer to the trastuzumab and pertuzumab Investigator Brochure for a detailed description of the safety profile of trastuzumab.

See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

3.7 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

4.0 MATERIALS AND METHODS

4.1 SUBJECTS

The study population for this clinical trial includes patients with HR+ HER2+ early stage breast cancer who have not been previously treated with definitive surgery, radiation or systemic therapy.

4.1.1 Subject Selection

The clinical trial will be registered on clinicaltrials.gov and it is anticipated that some patients will self-refer to the study. Potential eligible patients will be screened by the study coordinator assigned to the clinical trial at each site and in cooperation with the breast site group coordinator. Patients may also be identified during discussions at breast tumor board.

4.1.2 Inclusion Criteria

Disease specific inclusion criteria:

- Histologically or cytologically confirmed adenocarcinoma of the breast with localized non-metastatic disease (stage I-II) and a candidate for curative-intent treatment.
- Breast cancer that is both hormone receptor positive i.e. ER and/or PR positive and HER2-positive (FISH-positive or IHC 3+) by latest ASCO guidelines
- Multifocal breast cancer is allowed on the provision that satellite lesions are biopsied and confirmed to also be ER and/or PR positive and HER2-positive and felt by the pathologist to be the same tumor

General inclusion criteria:

- Age $\geq$ 18 years

- Life expectancy greater than 5 years
- Left Ventricular Ejection Fraction (LVEF) $\geq$ 50% at baseline (within 30 days of day 0) as determined by either ECHO or MUGA (ECHO is the preferred method). If the patient is enrolled, the same method of LVEF assessment, ECHO or MUGA, should be used throughout the study, and to the extent possible, be obtained at the same institution.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2.
- Signed, written informed consent (approved by the IRB) obtained prior to any study procedure
- Adequate bone marrow function as indicated by the following:
  ANC >1000/μL

  Platelets $\geq$50,000/μL

  Hemoglobin >8.0 g/dL, lower allowed only if it is due to readily reversible conditions such as iron deficiency without active blood loss.
- Adequate renal function, as indicated by creatinine $\leq 3.0\times$ upper limit of normal (ULN)
- Adequate liver function, as indicated by bilirubin $\leq 3.0\times$ ULN
- AST or ALT $<5.0 \times$ ULN
- A negative serum pregnancy test must be available for premenopausal women and for women <12 months after the onset of menopause, unless they have undergone surgical sterilization.
- Women of childbearing potential and male participants with partners of childbearing potential must agree to use a “highly effective”, non-hormonal form of contraception or two “effective” forms of non-hormonal contraception by the patient and/or partner. Contraception must continue for the duration of study treatment.
- Male patients are allowed, and will not be excluded.

4.1.3 Exclusion Criteria

Patients will be excluded from the study based on the following criteria:

- Active infection
- Presence of known metastases (i.e. stage IV disease)
- Pregnant or lactating women
- Prior chemotherapy or radiation therapy for the breast cancer primary

- Concomitant malignancies or previous malignancies within the last 5 years, with the exception of adequately treated basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix.
- History of significant cardiac disease or uncontrolled arrhythmias. Specifically patients will be screened with an echocardiogram or MUGA to make sure they do not have baseline EF of ≤50%, and the intent of this exclusion criteria is to make sure the patient is not at significantly greater risk of trastuzumab/pertuzumab cardiotoxicity. Lipid profiles will not be considered a reason for exclusion. History of coronary artery disease also is not a reason for exclusion if current EF satisfies, and there is no clinical history of unstable angina.
- Current severe, uncontrolled systemic disease (i.e. clinically significant cardiovascular, pulmonary or metabolic disease including diabetes, wound healing disorders, ulcers or bone fractures)
- Major surgical procedure or significant traumatic injury within 28 days prior to study treatment start or anticipation of the need for major surgery during the course of study treatment
- Current known infection with HIV, HBV or HCV
- Receipt of intravenous antibiotics for infection within 14 days of study treatment
- Current chronic daily treatment with corticosteroids (dose >10mg/d methylprednisolone equivalent) excluding inhaled steroids
- Known hypersensitivity to any of the study drugs
- Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

4.2 METHOD OF TREATMENT ASSIGNMENT

As this is a single arm prospective study, there will not be any randomization process. Intent of inclusion and exclusion criteria is to include a more heterogeneous patient population with more medical comorbidities and challenges where a chemotherapy-free treatment option would be even more in demand.

4.3. STUDY TREATMENT

Currently, trastuzumab and pertuzumab are not FDA approved for neoadjuvant use without chemotherapy; however, trastuzumab and pertuzumab is generally approved for coverage by insurance for optimal treatment of HER2+ breast cancer. Aromatase inhibitors are FDA approved and part of standard of care for curative intent treatment of HR+ breast cancer, and will be covered by patient

insurance. If insurance does not approve coverage for trastuzumab and pertuzumab and/or the cost of insurance copayment is too prohibitive, the study physician has the option to help the patient apply for Genentech/Roche's patient assist and free access program.

4.3.1 Trastuzumab Formulation

Trastuzumab is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administration. Each multi-dose vial of trastuzumab contains 400 mg of trastuzumab, 9.9 mg of L-histidine HCl, 6.4 mg of L-histadine, 400 mg of α,α-trehalose dihydrate, and 1.8 mg of polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection (BWFI) USP, containing 1.1% benzyl alcohol as a preservative, yields 21 mL of a multidose solution containing 21 mg/mL trastuzumab, at a pH of ~6.

Each single-dose vial of trastuzumab contains 150 mg of trastuzumab, 3.4 mg of L histidine HCl, 2.2 mg of L histadine, 136.2 mg of □,□ trehalose dihydrate, and 0.6 mg of polysorbate 20, USP. Reconstitution with 7.4 mL of sterile Water for Injection (SWFI) USP yields 21 mL of a single dose solution that delivers 7.15 ml trastuzumab, at a pH of ~6.

Pertuzumab Formulation

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).

4.3.2 Trastuzumab Dosage, Preparation, Administration and Storage

a. Dosage and Administration

When administered with pertuzumab, the recommended initial loading dose is 8 mg/kg trastuzumab administered as a 60-90-minute infusion. The recommended maintenance trastuzumab dose is 6 mg/kg q3wk and can be administered as a 30-minute infusion if the initial loading dose was well tolerated. Trastuzumab may be administered in an outpatient setting. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

b. Preparation

Use appropriate aseptic technique. Each multi-dose vial of trastuzumab should be reconstituted with 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied, to yield a multidose solution containing 21 mg/mL trastuzumab. Immediately upon reconstitution with BWFI, the vial of trastuzumab must be labeled in the area marked "Do not use after" with the future date that is 28 days from the date of reconstitution.

Each single-dose 150 mg vial should be reconstituted with 7.4 ml of SWFI, USP, to yield a solution containing 21 mg/ml trastuzumab.

If the patient has known hypersensitivity to benzyl alcohol, trastuzumab must be reconstituted with sterile water for injection (see PRECAUTIONS). Trastuzumab that has been reconstituted with SWFI must be used immediately and any unused portion discarded. Use of other reconstitution diluents should be avoided.

Determine the dose of trastuzumab needed, based on a loading dose of 8 mg trastuzumab/kg body weight for q3wk dosing schedules or a maintenance dose of 6 mg/kg trastuzumab/kg body weight for q3w dosing schedules. Calculate the correct dose using 21 mg/mL trastuzumab solution. Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% sodium chloride, 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 trastuzumab and polyvinylchloride or polyethylene bags have been observed.

Trastuzumab should not be mixed or diluted with other drugs. An amendment will be made if the VELVET study proves that trastuzumab and pertuzumab can be safely given in one mixed preparation.

c. Storage

Vials of trastuzumab are stable at 2°C–8°C (36°F–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A multi-dose vial of trastuzumab reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2°C–8°C (36°F–46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved SWFI (not supplied) is used, for the multi-dose vial or a 150 mg single-dose vial is utilized 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 for injection, USP, may be stored at 2°C–8°C (36°F–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 15°C–25°C; however, since diluted trastuzumab contains no effective preservative the reconstituted and diluted solution should be stored refrigerated (2°C–8°C).

Pertuzumab Dosage, Preparation, Administration, and Storage

a. Dosage

The initial dose of pertuzumab is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 - 60 minutes

When administered with pertuzumab the recommended initial dose of trastuzumab is 8 mg/kg followed every 3 weeks thereafter by a dose of 6 mg/kg.

b. Preparation

Special Instructions for Use Handling and Disposal of pertuzumab instructions for Dilution:

Pertuzumab is for single use only and is administered intravenously by infusion. Pertuzumab does not contain any antimicrobial preservative. Therefore, care must be taken to ensure the sterility of the prepared solution for infusion and should be prepared by a healthcare professional.

Pertuzumab should be prepared by a healthcare professional using aseptic technique.

- 14 ml pertuzumab liquid concentrate should be withdrawn from the vial and diluted into a 250-mL PVC or non-PVC polyolefin 0.9% sodium chloride infusion bag. After dilution, 1 mL of solution should contain approximately 3.36mg of pertuzumab (840mg/250mL) for the initial dose, where two vials are required, and approximately 1.68 mg of pertuzumab (420mg/250mL) for the subsequent dose where one vial is required.
- Dextrose (5%) solution should not be used.
- The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discolouration prior to administration. Once the infusion is prepared it should be administered immediately.

c. Administration

Treatment may be administered in an outpatient setting by administration of a 840 mg pertuzumab loading dose by intravenous (IV) infusion over 60 minutes,

followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 - 60 minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.**

When administered with pertuzumab, the recommended initial dose of trastuzumab is 8 mg/kg followed every 3 weeks thereafter by a dose of 6 mg/kg.

Patients should be observed for fever and chills or other infusion-associated symptoms.

Table 1

Trastuzumab and Pertuzumab Infusion Time and Post-Infusion Observation Period

		Infusion Time (minutes)	Post-Infusion Observation Period (minutes)
TP Loading Doses (8 mg/kg and 840mg)	First Infusion	60-90	60
TP (6mg/kg and 420mg) q3w	Subsequent Infusions	30 [a]	30 [a]

[a] Only if previous dose was well tolerated, otherwise 60

A rate-regulating device may be used for all study-drug infusions. When the study drug IV bag is empty, 50 mL of 0.9% sodium chloride injection may be added to the IV bag or an additional bag will be hung, and the infusion may be continued for a volume equal to that of the tubing to ensure complete delivery of the study drug.

Should extravasation of the study drug infusion occur, the following steps should be taken:
- Discontinue the infusion,
- Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent,
- If a significant volume of the study drug infusion remains, restart the infusion at a more proximal site in the same limb or on the other side.

d. Storage

Upon receipt, 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).

e. Incompatibilities

No incompatibilities between pertuzumab and polyvinylchloride, polyethylene or non-PVC polyolefin bags have been observed [3.3, 3.4]. Dextrose (5%) in water (D5W) solution should not be used to dilute pertuzumab since it was chemically and physically unstable in such solutions [3.4] (dilute formulations of pertuzumab liquid formulations in D5W IV bags did not maintain stable pH after storage at room temperature (27-33°C) for 24 hours followed by 24 hours at refrigerator temperature [2-8°C]).

Pertuzumab should not be mixed or diluted with other drugs. An amendment will be made if the VELVET study proves that trastuzumab and pertuzumab can be safely given in one mixed preparation.

4.3.3. Trastuzumab and Pertuzumab Dosage Modification

Dose modification of trastuzumab and pertuzumab is not permitted.

4.3.4 Trastuzumab and Pertuzumab Overdosage

There is no experience with overdosage in human clinical trials.

4.4 CONCOMITANT AND EXCLUDED THERAPY

Concomitant therapy

It is recommended but not required that all patients receive famotidine 20mg IV and diphenhydramine 25mg IV or oral as premedication for trastuzumab and pertuzumab treatment, or pharmacy equivalent. Prior adverse reactions or patient preference are allowed exceptions. It is not recommended to use routine dexamethasone or steroid equivalent as a premedication but physician discretion is allowed, particularly if the patient has experienced a previous allergic reaction with trastuzumab and/or pertuzumab.

An assessment of serum Vitamin D 25 levels as is standard of care at Cancer Treatment Centers of America, and replacement with vitamin D to correct vitamin D deficiency is not only allowed but also encouraged.

Treatments focused on reducing morbidity and toxicity of protocol treatment are allowed, including interventions for aromatase inhibitor side effects such as hot flashes, arthralgias as long as it is not estrogen replacement. Discussion with the Principle Investigator is encouraged.

Trials or interventions designed to improve lifestyle habits are allowed.

Excluded therapy

Any concomitant treatment that could be reasonably expected to interfere with the efficacy of trastuzumab and pertuzumab or aromatase inhibitor therapy should be avoided, but clinical judgment with consultation of the Principal Investigator is encouraged.

Treatment with other systemic anti-cancer agents such as chemotherapy, non-protocol specified hormonal therapy, immunotherapy (i.e. PD1 or PDL1 inhibitors, TNF-alpha inhibitors, anti-T cell antibodies) not specified by protocol

Concurrent investigational agents of any type with the primary intent of being provided as cancer treatment. Herbal remedies initiated prior to study entry by the patient is allowed unless in the judgment of the clinician/naturopath that sufficient evidence exists that harm outweighs any putative benefits.

4.5 STUDY ASSESSMENTS

Signed, IRB-approved informed consent must be obtained from patients prior to the pretreatment assessments.

The following are required evaluations: (See Appendix A: Study Flowchart)

- Evaluation of subject's cardiac function by either echocardiogram or MUGA
- Immunology: evaluation of ER, PR, HER2/*neu* status of the primary breast cancer by ASCO approved methodologies.
- Pregnancy test for pre-menopausal patients or patients who have not had active periods for less than a year. Exception is allowed for study patients who have had surgical procedures normally done to reliably induce infertility, but not for those whose partner has had surgical procedures for infertility.
- Mammaprint and Blueprint testing on the diagnostic biopsy. Agendia agrees to cover the cost of the test if insurance does not cover the costs. If there is insufficient tissue, Mammaprint and Blueprint testing should be pursued on the final surgical pathology specimen after neoadjuvant treatment is completed.
- CBC, BMP and liver function tests
- Breast exam

- Baseline MRI of the breast

4.5.1 Assessments during Treatment

The following are recommended evaluations: (See Appendix A: Study flowchart)

- Monitor CBC, chemistries, etc. per institutional guidelines. A CBC and BMP is required at a minimum for each infusion/clinic visit (i.e. every 3 weeks +/- 3 days including the day 0 visit, i.e. screening labs can be used for the day 0 visit if still within that date range). Routine CBC and BMP checks without clinical reason in between scheduled visits are discouraged.

- Regular assessment of cardiac function by either echo or MUGA (depending on the baseline study chosen) is required at a minimum of every 12 weeks or every 4 cycles of treatment (+/- 28 days) as per standard of care.

- If trastuzumab and pertuzumab is put on hold due to a significant decline in LVEF, a repeat echo or MUGA (depending on the baseline study chosen) is required every 3 weeks until LVEF is normalized. If LVEF is not normalized within 6 weeks +/- 1 week then the patient is to be taken off protocol treatment.

- An MRI of the breast is required every 12 weeks (+/- 28 days) to monitor response to treatment. Additional imaging, including diffusion-weighted MRI, mammogram, ultrasound, tomosynthesis, PET is allowed if clinically indicated or recommended by the treating physician or radiologist. An MRI of the breast is considered standard of care for neoadjuvant treatment of breast cancer both prior to initiation of neoadjuvant treatment and prior to surgery for surgical planning, and will be covered by insurance. Any additional costs associated with the required MRI assessment during neoadjuvant treatment will be absorbed by the study site and patients may not be charged for these expenses including if for whatever reason insurance does not cover the first and pre-surgical MRI.

- A physical exam of the breasts must be documented with each visit for intravenous trastuzumab and pertuzumab (every 3 weeks +/- 3 days, but need not be on the same exact day as infusion of trastuzumab and pertuzumab). If progression is suspected, a repeat MRI and radiologist-recommended imaging modality is required to confirm progression.

4.5.2 Follow-Up Assessments

The only assessments required by the study protocol after neoadjuvant protocol treatment is completed are as follows:

Date of definitive surgery and/or additional surgery to obtain clear margins including surgical pathology reports that ideally will include the following details (repeat confirmation of ER, PR and HER2 status) of the primary tumor assuming it is still present: size of primary tumor in 3 dimensions, size of lymph node involvement if applicable, number of lymph nodes removed and number of lymph nodes with residual disease and whether it is by IHC only, microscopic

disease or gross residual disease, presence or absence of lymphovascular invasion, margin involvement and degree of margin freedom if <1cm.

Mammaprint testing on the surgical specimen if unable to acquire with the diagnostic biopsy

If patient is taken prematurely off study – identification of the reason such as patient logistics, treatment toxicity, progressive disease.

It is not an endpoint of the study to identify treatments given after surgery but if the patient receives further neoadjuvant treatment after protocol treatment, drugs used, doses and number of cycles will be documented.

4.6 DISCONTINUATION OF PROTOCOL-SPECIFIED THERAPY

Protocol-specified therapy may be discontinued for any of the following reasons:

- Progressive disease
- Unacceptable toxicity
- Patient election to discontinue therapy (for any reason)
- Physician's judgment

4.7 SUBJECT DISCONTINUATION

If for whatever reason a subject is taken prematurely off study protocol, the patient will continue to be followed until the point of either curative intent surgery, documented refusal of surgery by the patient, or development of metastases.

If a subject is withdrawn specifically due to the event of a pregnancy patient will be withdrawn from study protocol.

The reason for premature discontinuation of a subject must be recorded on the Case Report Form.

4.8 STUDY DISCONTINUATION

The Principal Investigator has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory

- Data recording are inaccurate or incomplete
- Study protocol not followed
- Cancer Treatment Centers of America Affiliated Hospitals are no longer able to continue the clinical trial

4.9 STATISTICAL METHODS

4.9.1 Analysis of the Conduct of the Study

This study protocol will be approved through the Western IRB. The Human Research Protection Program, a division of Cancer Treatment Centers of America's Medicine and Science will act as the monitor for this investigator-initiated study and actively track for enrollment status, protocol violations, and other data that reflect the general conduct of the study. The study coordinators assigned to the study will be delegated authority to screen potential patients for clinical trial, and will inform the primary oncologist if the patient is a candidate. A screening log is to be used at each study site.

4.9.2 Analysis of Treatment Group

Variables will be analyzed to assess the characteristics of the treatment cohort such as demographics, baseline characteristics, compliance and concurrent treatments.

The primary endpoint of the study is the rate of pathological complete response (pCR) of patients receiving treatment protocol. This will be assessed with both an intention-to-treat analysis and a planned subset analysis of evaluable patients, with pCR defined as the absence of invasive cancer in the breast and lymph nodes where ductal carcinoma in situ is allowed. The subset of "evaluable patients" will be favored for final analysis of efficacy since the intent of this clinical study is to establish whether an aromatase inhibitor combined with trastuzumab and pertuzumab is efficacious and bioactive. Since patients treated at Midwestern Regional Medical Center (MRMC), Cancer Treatment Centers of America travel on average 400 miles from their home town to MRMC, we do not want to introduce a negative bias to this study towards the null hypothesis due to the unique logistical issues CTCA patients face. Therefore, evaluable patients will include those who are enrolled into study and successfully complete study treatment protocol until either progression or suspected pCR based on MRI imaging.

The Fleming two stage design will be implemented with stopping rules (Fleming 1982). The null hypothesis is that the pCR rate is $\leq$ 0.2 (treatment warrants no further investigation) versus the alternative hypothesis where the pCR rate is $\geq$ 0.4 (treatment shows promising therapeutic efficacy that warrants further investigation). The null hypothesis will be treated against the one sided

alternative hypothesis. In the first stage, 15 evaluable patients will have surgical results and if there are two or fewer responses in these first 15 patients, the study will be stopped and the alternative hypothesis will be rejected. If there are 7 or more complete responses in 15 patients, the study will be stopped and the null hypothesis rejected. Otherwise, the study will continue into the second stage and 17 additional patients will be allowed to accrue for a total of 32 patients. The null hypothesis will be rejected if 10 or more responses are observed in 32 patients in the final analysis. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 0.4.

Alternative pCR rate	Null pCR rate	Stage 1 stopping rule	Stage 1 continuing rule	Stage 2 not encouraging	Stage 2 favorable	Power
40%	20%	<=2/15	>=3/15	<=9/32	>=10/32	80%

Reference: Fleming (1982) *Biometrics* 38: 143-151

4.9.3 Efficacy Analysis

a. Primary Endpoint

Pathological Complete Response (pCR) Rate

Pathological complete response (pCR) will be defined as the absence of invasive disease in both breast and lymph nodes and allow for residual ductal carcinoma in situ. Both an intention-to-treat analysis and a subset analysis of evaluable patients will be performed. Evaluable patients will include those who are enrolled into study and successfully complete study treatment protocol until either progression or suspected pCR based on MRI imaging. Patients can be omitted from the intention-to-treat analysis if it is discovered that they were enrolled when they did not pass all eligibility and exclusion criteria (see Section 4.1).

The pCR rate will be described with a range for 95% confidence interval.

b. Secondary Endpoints

Median duration of treatment will represent time from Day 0 i.e. first dose of trastuzumab and pertuzumab to 3 weeks after the last dose of trastuzumab and pertuzumab.

An exploratory analysis will be performed to assess whether Mammaprint and Blueprint results (i.e. low risk and luminal subtype) predicts whether patients are more likely to obtain a pCR after neoadjuvant treatment of HR+ HER2+ localized breast cancer with an aromatase inhibitor and trastuzumab and

pertuzumab. Descriptive tables will show distribution of Mammaprint low and high risk results amongst those who obtain pCR and those who do not.

Sensitivity and specificity of radiographic complete response (rCR) as detected by breast MRI in predicting pathological complete response (pCR) will also be calculated.

4.9.4 Safety Analysis

Since safety is not either a primary or secondary endpoint of this study and already established by large randomized clinical trials such as CLEOPATRA, and ongoing studies such as APHINITY and PERTAIN, descriptive procedures will be used to represent frequency of adverse events such as a significant decline in EF, infusion reactions, rash and diarrhea with the treatment protocol.

4.9.5 Missing Data

Any missing data that cannot be corrected with chart review or directed inquiry will be registered as not available, and if appropriate, protocol violation will be reported to IRB.

4.9.6 Determination of Sample Size

A sample size of 32 evaluable patients was selected for reasons described in more detail in Section 4.9.2 where 32 patients would yield a type I error rate of 0.05 and power of 80% if the true pCR rate is 0.4.

The sample size will be adjusted to accommodate dropouts or exclusions. The number of subjects that should be enrolled into clinical trial is therefore (32 evaluable patients)/(90%, i.e. expected proportion of enrolled subjects who will be evaluable) = 36 patients.

4.10 DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

5. REPORTING OF ADVERSE EVENTS

5.1 ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to trastuzumab and pertuzumab, all events of death, and any study specific issue of concern. Because the study is already declared IND exempt by the FDA, and

the study is not specifically sponsored by Genentech/Roche, direct reporting of AE/SAE will be primarily reported to the WIRB. SAE's will also be reported directly to the principal investigator, Dr. Eugene Ahn. See section 5.3i for contact info.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with trastuzumab and pertuzumab, that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (i.e. aromatase inhibitor, premedication use of famotidine and benadryl, etc)

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drugs.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

5.2 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 appropriate IRB (Western IRB or WIRB) and all SAEs are reported to the principal investigator Dr. Eugene Ahn in accordance with CFR 312.32 (IND Safety Reports).

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 21 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.

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 {study drug} (see following guidance), 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 trastuzumab and pertuzumab, 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 trastuzumab and pertuzumab; and/or the AE abates or resolves upon discontinuation of the trastuzumab and pertuzumab or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the trastuzumab and pertuzumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to trastuzumab and pertuzumab 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.

5.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

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?"

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 21 days after the last dose of study drug, a report should be completed and expeditiously submitted to the WIRB and principal investigator. 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 trastuzumab and pertuzumab 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 trastuzumab and pertuzumab 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. 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 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

The Trastuzumab and Pertuzumab Events of Special Interest are:

- Left Ventricular Dysfunction
- Infusion-associated Reactions, Hypersensitivity Reactions/Anaphylaxis
- Embryo-fetal Toxicity or Birth Defects

i. SAE Reporting

Investigators must report all SAEs to Western IRB (WIRB) and the principal investigator Dr. Eugene Ahn (PI) within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to the WIRB and e-mailed or faxed to the PI.

Western IRB
WIRB U.S. Office
1019 39th Avenue SE Suite 120
Puyallup, WA 98374-2115
Office: (360) 252-2500 or (800) 562-4789
Fax: (360) 252-2498

Principal Investigator
If e-mailing, please send to both the PI and study coordinator
Eugene.ahn@ctca-hope.com (principal investigator)
Anjanette.sorensen@ctca-hope.com (study coordinator)
If faxing, please add “Attention to: Anjanette Sorensen”)
Office: (847) 731-1777
Fax: (847) 731-1215

- Relevant follow-up information should be submitted to WIRB and the PI as soon as it becomes available.
- Serious AE reports that are related to the trastuzumab and pertuzumab and AEs of Special Interest (regardless of causality) will be transmitted to WIRB and PI within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the trastuzumab and pertuzumab will be transmitted to WIRB and PI within thirty (30) calendar days of the Awareness Date.
- Additional Reporting Requirements to WIRB and PI include the following:
- Any reports of pregnancy following the start of administration with the trastuzumab and pertuzumab will be transmitted to WIRB and PI within thirty (30) calendar days of the Awareness Date.
- All Non-Serious Adverse Events originating from the Study will be forwarded in a bi-annual (every 6 months) report to WIRB

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with the Cancer Treatment Centers affiliate site's research office.

- Original U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the local Principal Investigator.

  The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.

- Current *curriculum vitae* of the local Principal Investigator

- Written documentation of IRB approval of protocol and informed consent document

- A copy of the IRB-approved informed consent document

6.2 STUDY COMPLETION

All investigators will be notified when the study has one remaining patient slot available for enrollment, and afterwards when the last patient has officially enrolled. The Enterprise Review committee (ERC) will also monitor accrual pace and may request process improvements if pace falls behind schedule.

6.3 INFORMED CONSENT

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

6.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the WIRB for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify the WIRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. The WIRB may have other specific adverse event requirements that investigators are expected to adhere.

6.5 STUDY MONITORING REQUIREMENTS

N/A

6.6 DATA COLLECTION

Accurate and reliable data collection will be assured by verification and cross-check of paper CRFs against the source records by the CTCA Human Research and Protection Program (HRPP).

Throughout the study the study management team including the Principal Investigator's office and HRPP will monitor the data periodically as a process of self-audit and quality control.

6.7 STUDY MEDICATION ACCOUNTABILITY (IF APPLICABLE)

N/A

6.8 DISCLOSURE AND PUBLICATION OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the WIRB, HRPP and PI office, if appropriate.

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for the publication of study results.

Additionally, Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) (PDF) requires Responsible Parties to register and submit summary results of clinical trials with ClinicalTrials.gov. The law applies to certain clinical trials of drugs (including biological products) and medical devices. (refer to FDAAA 801 Requirements to learn about Responsible Party, Applicable Clinical Trials, and deadlines for registration and results submission)

6.9 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified. Genentech will notify the Principal Investigator of these events.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with U.S. FDA IND regulations and with the record retention policies of the relevant national and local health authorities.

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Figure 1. STUDY SCHEMA

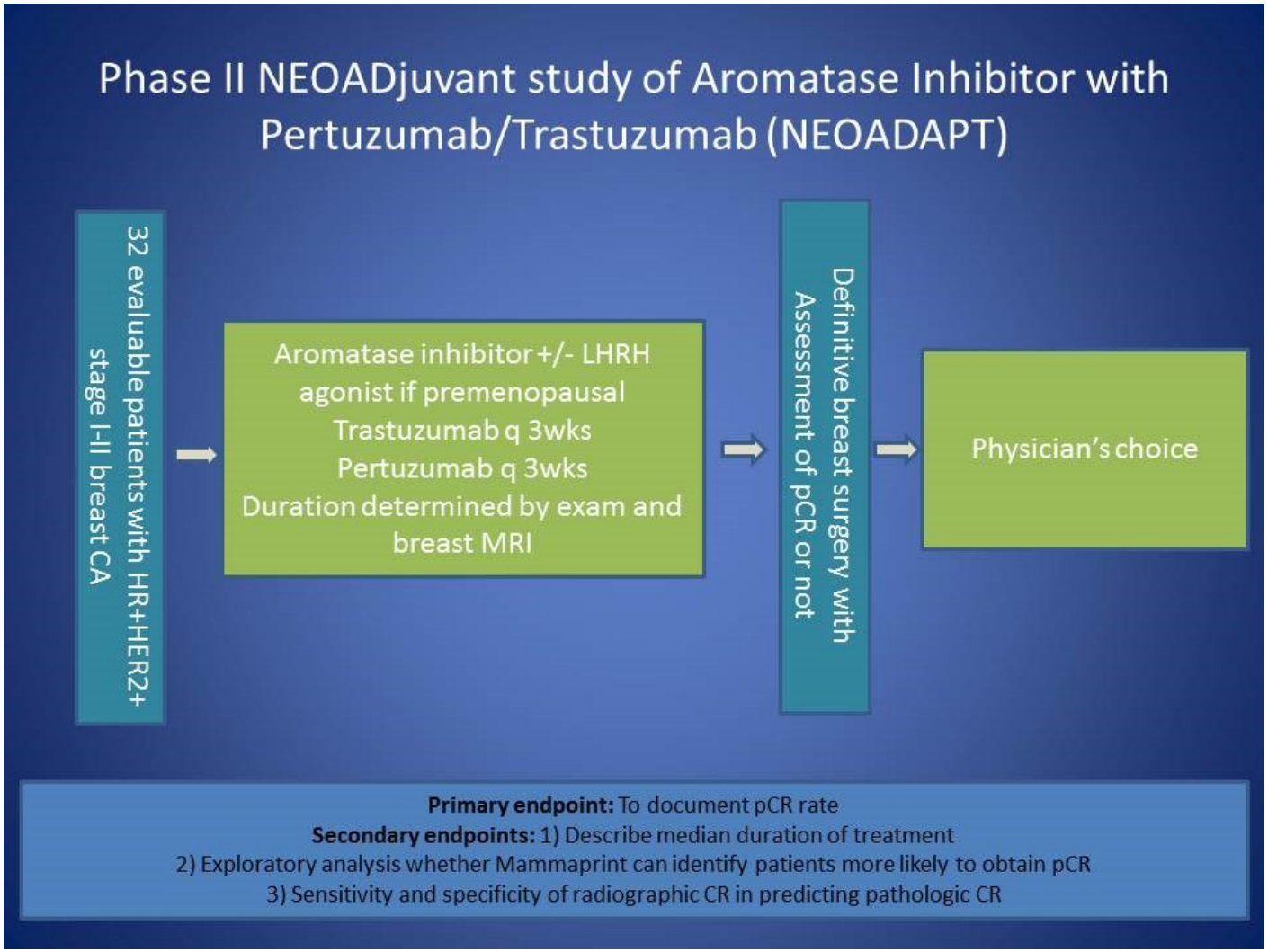
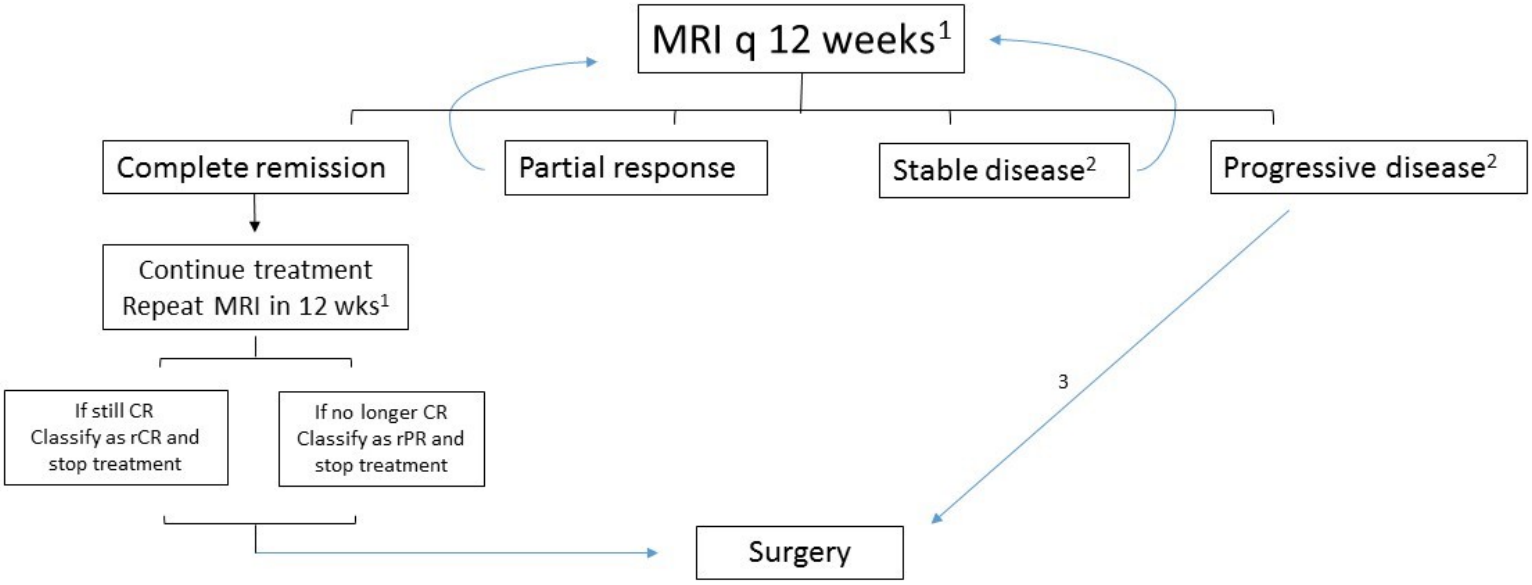


Figure 2. Overview of how breast MRI will guide protocol treatment



[1]MRI can be done earlier if clinical judgement warrants but after a 1st radiographic CR report, 12 weeks is encouraged

[2]Stable or progressive disease as determined from the smallest RECIST measurement whether that is the baseline or a follow up MRI

[3]If patient stops protocol treatment due to progressive disease, physician/investigator has discretion of whether to proceed directly to surgery or to offer more neoadjuvant treatment off protocol

APPENDIX A

Study Flowchart

	Days –30 to –1	Cycle #1 (Day 0)	Every 3 weeks beginning with Cycle #2 (+/- 7days)	Every 12 weeks (+/- 4 weeks)	End of study
Trastuzumab and pertuzumab administration		X	X		
Review of AI compliance			X[2]		
Complete medical history	X				
Complete physical exam	X				
Clinical assessment	X	X[2]	X[2]		
Vital signs, weight, height	X	X[2]	X[2]		
ECOG performance status	X				
Toxicity evaluation			X[2]		
Mammaprint and Blueprint		X[1]			X[1]
Serum or urine pregnancy test	X				
Echo/MUGA	X			X	
CBC, BMP	X	X[2]	X[2]		
LFT	X				
MRI	X			X	
Physical exam of breast	X	X[2]	X[2]		
Surgical pathology of breast					X

[1] Blueprint/Mammaprint (not required to be successful prior to day 0 as the information should not be used to determine whether or not patient should start treatment, but another attempt should be done on the surgical pathology specimen if patient does not achieve pCR)
[2] Can be done +/- 3 days around actual infusion day

APPENDIX B

Response Evaluation Criteria in Breast Cancer via RECIST Criteria Modified for Neoadjuvant Treatment

Modified RECIST criteria as detailed below should be used to assess response to treatment. Only subjects with measurable disease either based on mass or enhancement should be entered in the study. Measurable disease is defined as the presence of one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) via MRI imaging. If for whatever reason another imaging study such as mammogram or ultrasound is helpful at following response to neoadjuvant treatment, the mammogram or ultrasound may be used as a complement to MRI. Evaluable lesions will be followed for the assessment of response.

All measurable lesions, up to a maximum of 2 lesions since for the purposes of this protocol focus is confined to one organ, the breast/axilla, should be identified as target lesions and recorded and measured at baseline. A sum of the longest diameter for the target lesions will be calculated and reported as the baseline sum longest diameter. The index lesion can be less than 1.0 cm. The baseline sum longest diameter will initially be used as the reference by which to characterize the objective tumor response, but if any reduction in diameter is seen on a subsequent MRI, the shortest sum longest diameter will always be used as the reference point to calculate the following:

- Radiographic complete response (rCR)

  Disappearance of all evidence of tumor including any residual enhancement interpreted by the radiologist to be due to residual tumor <u>in the breast</u> on two MRI scans separated by 12 weeks (only one MRI required if the first complete response MRI occurs at the end of one year of treatment). If a lymph node is identified as a target lesion, obviously disappearance of the lymph node is not a reasonable requirement. As long as the lymph node (target or non-target) is shrunk to <1 cm, the MRI still qualifies as a complete response.

- Radiographic partial response (rPR)

  At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the <u>baseline</u> sum longest diameter.

- Stable disease (SD)

  Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the <u>smallest</u> sum longest diameter since the treatment started.

- Progressive disease (PD)

At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the beginning of treatment or the appearance of one or more new lesions. If a non-target lesion in the breast/axilla increases by >33% the patient can also be classified as progressive disease.

APPENDIX C

National Cancer Institute Common Toxicity Criteria v4.03
obtained from http://evs.nci.nih.gov/ftp1/CTCAE/About.html

APPENDIX D

SAFETY REPORTING FAX COVER SHEET

WIRB FAX# (360) 252-2498 PI FAX# (847) 731-1215

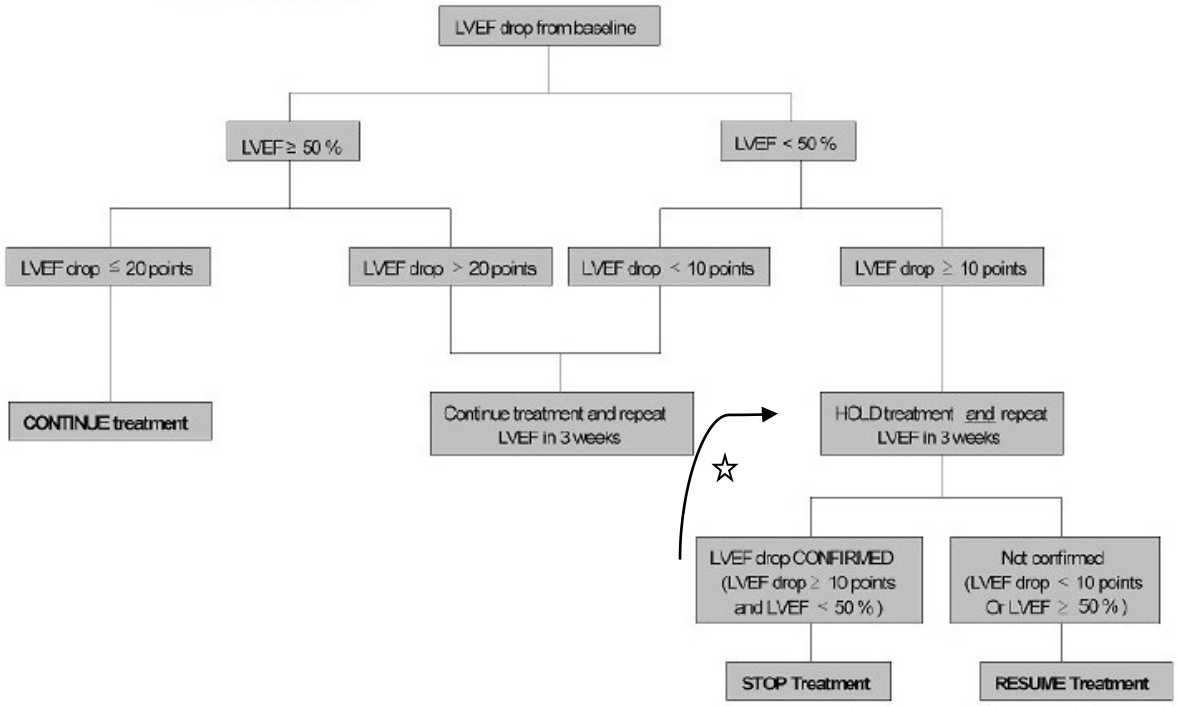
Study Number	ML30001
Principal Investigator	Eugene Ahn MD
Site Name	Cancer Treatment Centers of America Midwestern Regional Medical Center
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY] (leave blank if N/A)

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

PLEASE PLACE SAFETY REPORT BEHIND THIS COVER SHEET

APPENDIX E: Algorithm for Continuation and Discontinuation of Pertuzumab and Trastuzumab Based on LVEF Assessments



☆ *Protocol allows for 6 weeks of q 3 week echo/MUGA follow up testing prior to being required to stop protocol treatment*

APPENDIX F

Data Collection Form (to be kept for each enrolled patient)

Preferred data entry will be through the CTMS Merge software when available at each site.

An excel spreadsheet will be provided to each site upon request.

Name

Date of Birth

Date(s) of diagnostic biopsy(ies)

Diagnostic pathology result including ER%, PR%, HER2 result by IHC and/or FISH, nuclear grade 1-3, presence of lymphovascular invasion, presence of perineural invasion

MRI measurement of primary lesion

MRI measurement of pathological lymph nodes

Mammaprint result

Day 0 date:

Aromatase inhibitor(s) used and date of use

Serious adverse events

End of protocol treatment date

Reason for end of protocol treatment among following reasons

- rCR
- unacceptable toxicity
- progressive disease (describe best result including radiographic partial response, one radiographic complete response followed by progressive disease, stable disease then progression, etc)
- patient election to discontinue therapy (provide descriptive reason)
- physician judgment (provide descriptive reason)

Additional neoadjuvant treatment given off protocol

Date of surgery

Surgical pathology results with both details and determination of pCR or not and quantification of residual disease