SAFE-HEaRt: A pilot study assessing the cardiac **SAFE**ty of **HE**R2 targeted therapy in p**a**tients with HE**R**2 posi**t**ive breast cancer and reduced left ventricular function

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and International Conference on Harmonization (ICH) guidelines.

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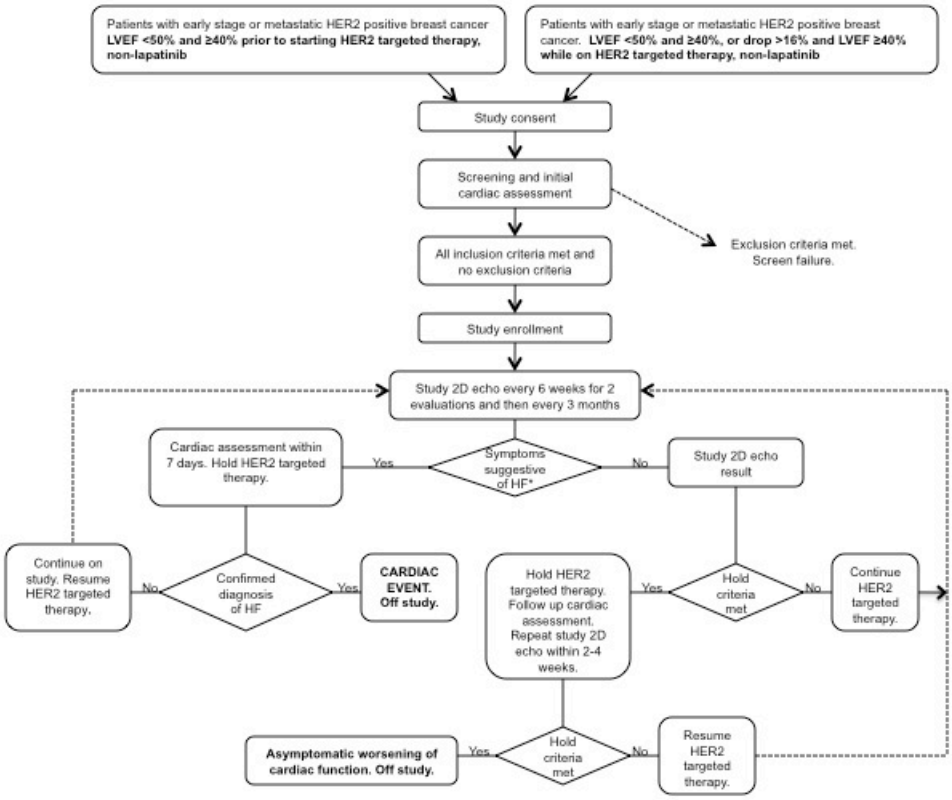
STUDY SCHEMA

Figure 1: Flowchart of patient enrollment and management



*Increasing shortness of breath, orthopnea, paroxysmal nocturnal dyspnea (PND), bilateral ankle swelling

Hold criteria:

LVEF decrease ≥ 10% points from baseline or to ≤ 35%

Cardiac event criteria:

1. Presence of symptoms attributable to Heart Failure (increasing shortness of breath, orthopnea, Paroxysmal Nocturnal Dyspnea, bilateral ankle swelling) as confirmed by a cardiologist
2. Cardiac arrhythmia requiring pharmacological or electrical treatment
3. Hospitalization due to a cardiovascular cause, e.g. myocardial infarction
4. Sudden cardiac death or death due to myocardial infarction, arrhythmia or HF

Asymptomatic worsening of cardiac function defined as:

- Asymptomatic decline in LVEF ≥ 10% points from baseline and/or EF ≤ 35% corroborated by a confirmatory echocardiogram in 2-4 weeks

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LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
ALT	Alanine Aminotransferase
ARB	Angiotensin II Receptor Blocker
AST	Aspartate Aminotransferase
ASCO	American Society of Clinical Oncology
B-Blockers	Beta-blockers
BP	Blood pressure
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CE	Cardiac Event
CI	Confidence Intervals
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRC	Clinical Research Committee
CRF	Case Report Form
cTns	Cardiac Troponins
cTnI	Cardiac Troponin I
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease Free Survival
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
EF	Ejection Fraction
EGFR	Epidermal Growth Factor Receptor
ERNA	Equilibrium Radionuclide Angiocardiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HER2	Human Epidermal Growth Factor Receptor 2
HF	Heart failure
HR	Heart Rate; Hazard Ratio
HRPP	Human Research Protections Program
hs-cTnT	Highly sensitive cardiac troponin T
IAR	Infusion Associated Reaction
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
MGUH	MedStar Georgetown University Hospital
MI	Myocardial Infarction

MSKCC	Memorial Sloan Kettering Cancer Center
MUGA	Multi Gated Acquisition Scan
MWHC	MedStar Washington Hospital Center
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NRH	Nodular Regenerative Hyperplasia
NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	Overall Survival
PD	Progressive Disease
PE	Physical Exam
PFS	Progression Free Survival
PND	Paroxysmal Nocturnal Dyspnea
PR	Partial Response
ROS	Revision of Organs and Symptoms
RR	Response Rate
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Stable Disease
SNPs	Single Nucleotide Polymorphisms
T-DM1	Ado-trastuzumab emtansine
TTP	Time to Progression
WBC	White Blood Cells

1.0 STUDY SUMMARY

Table 1: Synopsis

Title	A pilot study evaluating the cardiac safety of HER2 targeted therapy (non-lapatinib) in patients with HER2 positive breast cancer and reduced left ventricular function
Protocol Number	2013-0278
Phase	Pilot study
Study Duration	4 years with up to 5 additional years of follow up
Study Center(s)	3 centers will be participating initially: MedStar Washington Hospital Center (MWHC), MedStar Georgetown University Hospital (MGUH) and Memorial Sloan Kettering Cancer Center (MSKCC)
Primary Objective	To evaluate the cardiac safety of HER2 targeted therapy (non-lapatinib) in patients with HER2 positive breast cancer and reduced left ventricular ejection fraction (LVEF) when given concomitantly with cardiac treatment.
Secondary Objectives	• To evaluate time to development of cardiac event or asymptomatic worsening of cardiac function; • Absolute changes in LVEF; • Delays in HER2 therapy attributed to cardiac causes; • Correlations between echocardiographic myocardial strain, cTnI and hs-cTnT at baseline and over time with cardiac events and asymptomatic worsening of cardiac function
Sample size	30 patients
Diagnosis and Main Inclusion Criteria	HER2 positive breast cancer, stage I-IV. Mildly decreased cardiac function (LVEF <50% and ≥40%) prior to or while receiving non-lapatinib HER2 targeted therapy
Cardiac Intervention	Beta-blockers and ACE-inhibitors titrated to the maximum tolerated doses
Oncology study Products, Doses, Routes, Regimens	• Trastuzumab: loading dose of 8 mg/kg IV, followed by a maintenance dose of 6 mg/kg every 3 weeks, or a loading dose of 4 mg/kg followed by a maintenance dose of 2 mg/kg every week. • Pertuzumab: loading dose of 840 mg IV, followed by 420 mg IV every 3 weeks, administered concomitantly with trastuzumab. • Ado-trastuzumab emtansine: 3.6mg/kg IV every three weeks. Note: both trastuzumab and pertuzumab may be administered alone or in combination with other systemic or radiation therapy.
Duration of drug administration	Maximum of 12 months.

Statistical Methodology	Cardiac events are defined as any of the following: - Presence of symptoms and signs attributable to HF (increasing shortness of breath, orthopnea, PND, bilateral ankle swelling) as confirmed by a cardiologist - Cardiac arrhythmia requiring pharmacological or electrical treatment - Myocardial infarction - Sudden cardiac death or death due to myocardial infarct, arrhythmia or HF Asymptomatic worsening of cardiac function defined as: - Asymptomatic decline in LVEF $\geq$ 10% points from baseline and/or EF $\leq$ 35% corroborated by a confirmatory echocardiogram in 2-4 weeks Planned oncologic therapy is defined as: - In the adjuvant setting: completion of 1 year total of HER2 targeted therapy. If a patient already received part of the planned HER2 targeted therapy prior to enrollment in this trial, planned oncologic therapy will be achieved when a total of 1 year is completed. - In the metastatic setting: cessation of treating regimen due to progressive disease or non-cardiac toxicity or non-cardiac death. The study is designed to assess the rate of completion of planned oncology therapy in the absence of a cardiac event or asymptomatic worsening of cardiac function. A completion rate of 30% is considered of clinical relevance as to benefit breast cancer patients who would otherwise not be given HER2 targed therapy, where as a completion rate is of 10% is considered similar to the current practice. A two stage design with a total of 30 patients is used to test if the completion rate is at least 30% versus if it is below 10% with 80% power at a significance level of 5%. An exact confidence interval of the completion rate will be calculated. We estimate there will be no more than a 10% cardiac event rate. Due to the low expected cardiac event rate and small sample size, the analysis of secondary endpoints will be descriptive and will not include specific hypothesis testing. We will summarize the strain, troponins at each time point and graphically assess these measures over time in patients that do and not experience cardiac events.

1.0 BACKGROUND AND RATIONALE

Trastuzumab for HER2 Positive Breast Cancer

Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 25% of breast cancers[1]. In the era preceding the development of HER2 targeted therapies, HER2 positive breast cancer was associated with a poor prognosis[2]. However, the development of trastuzumab, a monoclonal antibody against the HER2 receptor, resulted in improvements in survival in both adjuvant and metastatic HER2 positive breast cancer[3-7].

- Efficacy

The pivotal phase-III trial of trastuzumab plus chemotherapy in the first-line management of HER2-positive metastatic breast cancer (MBC) demonstrated robust improvements in response rates (RRs; 50% *vs.* 32%), median time to progression (TTP; 7.4 *vs.* 4.6 months) and median overall survival (OS; 25 *vs.* 20 months) with the addition of trastuzumab[3]. In the adjuvant setting, trastuzumab was also found to be associated with improved survival outcomes. In a review of eight trials that involved 11,991 women with HER2 positive operable breast cancer, trastuzumab significantly reduced recurrence and mortality: hazard ratio (HR) 0.66, 95% CI 0.57 to 0.77, $p < 0.00001$ for OS, and HR 0.60, 95% CI 0.50 to 0.71, $p<0.00001$ for disease free survival (DFS) favoring the trastuzumab-containing regimens)[8].

- Cardiac toxicity

HER2 targeted therapy has been associated with cardiac dysfunction. Although not expected in the initial trials of trastuzumab for metastatic breast cancer, retrospective analysis revealed rates of left ventricular (LV) dysfunction ranging from 3 to 27%. The incidence was greatest in patients receiving concomitant anthracyclines[9], particularly if the cumulative dose of doxorubicin given concurrently with trastuzumab exceeded 300mg/m^2. As a result, when the evaluation of trastuzumab moved into the adjuvant setting, most trials avoided co-administration of trastuzumab with anthracyclines and cumulative anthracyclines doses were limited. In addition, trials employed stringent cardiovascular eligibility criteria, cardiac monitoring schema, algorithms for holding trastuzumab in the setting of cardiac toxicity and early stopping rules [4-7].

Although difficult to generalize due to differing definitions of cardiac endpoints across the trials, observed rates of severe trastuzumab-associated cardiac toxicity, (including various classes of symptomatic heart failure and cardiac death) in the adjuvant trastuzumab trials were low (0-4.1%) and early stopping rules were not reached. For example, in the combined analysis of the NSABP B-31 and NCCTG N9831 trials of adjuvant trastuzumab, 14.2% of patients temporarily discontinued trastuzumab due to confirmed asymptomatic declines in left ventricular ejection fraction (LVEF) and 4.7% due to symptomatic heart failure (HF) or other adverse cardiac events[4]. Similarly, in the BCIRG006 adjuvant trastuzumab trial, 9-18% of the trastuzumab treated patients experienced a sustained drop in LVEF[7].

Trastuzumab-associated cardiac toxicity often occurs early during the course of treatment (median time to presentation 7.8 months) and is most commonly manifested by an asymptomatic decrease in LVEF[10]. In contrast to anthracyclines-associated cardiac toxicity[9,11-13], trastuzumab-associated cardiac toxicity is not dose-dependent and is reversible within six months of discontinuing trastuzumab therapy for the majority of patients[14]. Recent data on long-term follow up of cardiac function in NSABP B-31 reveals that the 7-year cumulative incidence of protocol defined cardiac events (CEs) was 4.0% in patients who received trastuzumab and 1.3% in patients who did not resulting in an absolute difference in events of 2.7%. CEs were

defined as a definite or probable cardiac death or congestive heart failure (CHF) manifested by dyspnea with normal activity or at rest and associated with an absolute decrease in LVEF of greater than 10 percentage points from baseline to a value less than 55% or a decrease of more than 5% to a value below the lower limit of normal. Only two CEs occurred more than 2 years after initiation of trastuzumab[15]. Reported predictors of trastuzumab-associated cardiac toxicity have not been consistent across trials, although older age, hypertension, anthracycline exposure and lower baseline LVEF have been reported in several trials[14,16].

Cardiotoxicity induced by trastuzumab is though to occur at least in part due to the inhibition of cellular repair mechanisms that result from downstream HER2 inhibition. If trastuzumab inhibits this repair during a vulnerable period after anthracycline injury, the anthracycline damage could be augmented, resulting in increased myocyte death. This hypothesis could explain why some patients do not fully recover from the damage that, at least temporally, seems related to the administration of trastuzumab. Furthermore, such a mechanism would predict that the sooner trastuzumab is given following doxorubicin administration, the greater the extent of cardiotoxicity[17]. Indeed, in the combined analysis of NSABP B31 and NCCTG N9831, of 3497 patients who had an evaluation of LVEF after doxorubicin and cyclophosphamide therapy, 233 (6.7 percent) had an LVEF that declined at least 16 percentage points from baseline or that declined below the lower limit of normal or had cardiac symptoms during such treatment that would preclude the initiation of trastuzumab therapy[4].

- Current clinical recommendations

According to the current Food and Drug Administration (FDA) approved package insert, patients should have LVEF evaluation prior to initiation of trastuzumab and at regular intervals during treatment. Patients should not receive it if there is evidence of cardiomyopathy. During treatment, if patients are found to have an absolute decrease in LVEF $\geq$16% from pre-treatment values or LVEF $\leq$50% and $\geq$10% absolute decrease from baseline, trastuzumab should be held until repeated echocardiogram confirms LVEF recovery.

Newer HER2 targeted therapies

More recently, the development of newer HER2 targeted therapies, such as lapatinib, pertuzumab and ado-trastuzumab emtansine (also known as T-DM1), have led to continued improvements in outcomes for HER2 positive breast cancer [18-20].

- Efficacy

Lapatinib with capecitabine has been shown to be superior to capecitabine alone in women with HER2 positive advanced breast cancer that had progressive disease after exposure to trastuzumab[18]. Lapatinib received approval by the FDA in 2007 for use in combination with capecitabine, and in 2010 for use in combination with letrozole for women with advanced or metastatic HER2 positive breast cancer.

Like trastuzumab, pertuzumab targets the HER2 extracellular domain but at a different epitope, resulting in inhibited dimerization of HER2 with other HER family receptors (EGFR/HER1, HER3 and HER4). Recently published results of the Cleopatra trial showed an increase in progression free survival (PFS) of 6.1 months ($p<0.001$) with the addition of pertuzumab to trastuzumab with docetaxel in first line treatment of metastatic HER2 positive breast cancer, as well as a strong trend towards improved OS in the pertuzumab group[19]. The FDA recently approved pertuzumab

in combination with trastuzumab and docetaxel for first line treatment of patients with HER2 positive metastatic breast cancer and LVEF of 50% or more.

Ado-trastuzumab emtansine is a novel anti-HER2 antibody-drug conjugate that comprises trastuzumab and the cytotoxic agent mertansine (DM1), a highly potent derivate of the antimicrotubule agent maytansine. Results from the EMILIA study, a phase III trial of ado-trastuzumab emtansine compared with capecitabine plus lapatinib in metastatic HER2 positive patients who had progressed after taxane/trastuzumab therapy, revealed a significant improvement in PFS favoring ado-trastuzumab emtansine (9.6 vs. 6.4 months)[20]. Median OS at the second interim analysis crossed the stopping boundary for efficacy (30.9 months vs. 25.1 months; HR for death from any cause, 0.68; 95% CI, 0.55 to 0.85; P<0.001). The FDA recently approved ado-trastuzumab emtansine for use in patients with metastatic breast cancer.

- Cardiac toxicity

In the cardiac safety evaluation, lapatinib infrequently affected the LVEF, with only 1.6% of patients experiencing a decrease in LVEF and most of them asymptomatic (1.4%). In a pooled analysis of 3689 patients enrolled in 44 clinical studies, of the total of 7 patients with symptomatic LVEF decrease, cardiotoxicity resolved in all but one, which suggests that cardiac effects of lapatinib are mild and mostly reversible[21].

Since trastuzumab and pertuzumab both target the HER2 receptor and are structurally similar, additive cardiac toxicity could be anticipated when the two drugs are administered concurrently. However the addition of pertuzumab did not increase rates of symptomatic or asymptomatic cardiac dysfunction in the Cleopatra trial. The rate of LV systolic dysfunction of any grade was 8.3% in the placebo group and 4.4% in the pertuzumab group. Similarly, the rate of grade 3 or higher cardiac toxicity was 2.8% in the placebo group and 1.2% in the pertuzumab group. Notably, only patients with LVEF of 50% or more were enrolled in this trial[19].

Regarding ado-trastuzumab emtansine, cardiac toxicity was not increased in the cohort of patients treated with the experimental drug, compared to the lapatinib arm (1.7% vs.1.6%)[20]. However, the data on cardiac safety with novel anti-HER2 agents need to be interpreted with caution because the trials are conducted in carefully selected populations.

- Current clinical recommendations

Current FDA prescribing information recommends the confirmation of a normal LVEF prior to starting lapatinib. While on treatment, patients who develop an asymptomatic drop in LVEF below 50%, defined as grade 2 or greater by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, or drop in LVEF below the institution's lower limit of normal, should have lapatinib discontinued. It may be restarted at a reduced dose (1,000 mg/day) after a minimum of 2 weeks if the LVEF recovers to normal and the patient is asymptomatic.

Regarding pertuzumab and ado-trastuzumab emtansine, the package insert recommends to acess LVEF prior to initiation of these agents and at regular intervals (e.g., every three months). In addition it should only be administered to patients with LVEF within normal limits and held if there is a drop in LVEF to less than 40% or LVEF of 40% - 45% with ≥10% absolute decrease below pretreatment values.

Detection of cardiac toxicity

- Echocardiogram with Strain analysis

Traditionally, trastuzumab-associated cardiac toxicity has been identified through assessment of LVEF by equilibrium radionuclide angiocardiography (ERNA), more commonly known as multi-gated acquisition (MUGA), or by 2D echocardiography. Clinical trials used different LVEF criteria for enrollment (most commonly LVEF >50% or institution's lower limit of normal) as well as holding and stopping criteria based on LVEF results. However, both standard echocardiography and MUGA scanning have limitations and neither is able to detect cardiac dysfunction prior to the reduction in LVEF, which represents a late stage of drug-related cardiac toxicity.

Myocardial strain is a new echocardiographic measure of cardiac contractility that offers the potential to detect subtle, early signs of cardiac dysfunction[22]. Among trastuzumab-treated patients, early decline in myocardial strain has been shown to predict subsequent decline in LVEF[23-25]. Sawaya et al prospectively evaluated 43 breast cancer patients receiving adjuvant trastuzumab and found that a decrease in global longitudinal strain after 3 months of therapy was an independent predictor of cardiac toxicity after 6 months of therapy[23]. This was confirmed in the follow-up multicenter study by the same group that included 81 women treated with anthracyclines followed by taxanes and trastuzumab and followed throughout the course of the treatment[24].

- Troponins

Cardiac troponins (cTns) are structural proteins unique to the heart and their detection in peripheral blood indicates cardiac damage. cTnI is an established clinical marker for the diagnosis of acute myocardial infarction. cTnI has also been used in patients with cancer undergoing high-dose chemotherapy where it predicted subsequent development of cardiac dysfunction[26]. Recently developed, "highly-sensitive cTn assays" (hs-cTnT) differ from "standard" clinically-used cTn assays in their ability to detect positive levels in the majority of healthy patients and in their acceptable imprecision (coefficient of variation <10%) at the 99th percentile of a normal reference population[27]. The Roche Diagnostics hs-cTnT has been tested in several large cardiovascular cohorts where it predicted future cardiovascular events including heart failure events as well as overall mortality[28,29]. The results of these studies suggest that hs-cTnT assays may have a role in detecting subclinical cardiac dysfunction and assessing the cardiovascular risk in the general population.

- Stages of development of HF and recommended therapy by stage

HF is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema. Clinical guidelines recommend using classified stages of development of HF that can guide appropriate therapy for each stage[30]. Patients at high risk for HF but without structural heart disease or symptoms of HF are classified as stage A. Patients receiving chemotherapy agents that are known to affect the heart function, such as anthracyclines or trastuzumab, fall into this category. Stage B includes patients with structural heart disease but without signs or symptoms of HF, such as patients with asymptomatic LV dysfunction or patients with valvular heart disease. Stage C includes patients with current or past symptoms of HF and stage D designates patients with refractory HF who might be eligible for advanced treatment strategies[31].

The goal of therapy for patients in stage A is to treat hypertension, encourage smoking cessation, treat lipid disorders, encourage regular exercise, discourage alcohol intake or illicit drug use, as well as control of metabolic syndrome if present. Patients in stage B, in addition to all the above measures, are recommended to receive ACE inhibitors or angiotensin-receptor blockers (ARB), and beta-blockers (B-Blockers), if no contraindications[31]. Treatment with ACE inhibitors is supported by large randomized studies in which ACE inhibitors have been shown to delay the onset of HF symptoms and decrease the risk of death and hospitalization for HF in asymptomatic patients with reduced LVEF, whether due to a remote ischemic injury or to a nonischemic cardiomyopathy[32,33]. Importantly, in a randomized trial that included patients at high-risk for HF but without LV dysfunction, defined as LVEF<40%, ramipril reduced the risk of HF hospitalization and HF death[34]. There are no studies that specifically address the use of ARBs in asymptomatic patients with reduced LVEF but the results of studies in symptomatic patients with low EF suggest that ARBs may be an appropriate alternative, particularly in patients who cannot tolerate ACE inhibitors [35,36].

The use of different B-Blockers in patients with low EF has been supported by large randomized trials in symptomatic HF patients, as well as in asymptomatic patients with LV dysfunction following myocardial infarction[37-40]. Studies that compared different BB strategies suggest that carvedilol may be superior to metoprolol in patients in producing greater beneficial effects on left ventricular ejection fraction when given in similar doses that were used in clinical trials[40,41].

- Cardiac therapy in prevention and treatment of cardiotoxicity associated with trastuzumab

Both ACE inhibitors and B-Blockers have been successfully used in the treatment and prevention of anthracycline-induced cardiotoxicity[42-44]. Two retrospective studies provide insight on LV dysfunction and response to cardiac treatment in the setting of trastuzumab therapy. A single institution report from MD Anderson Cancer Center describes experience with 38 patients referred for evaluation of trastuzumab-related cardiotoxicity because of either symptomatic or asymptomatic LV dysfunction. Trastuzumab was stopped in all but one patient, and the majority of patients received standard HF treatment with an ACE inhibitor and B-Blocker that were given at the discretion of the treating physician. Important findings of this study included an increase in LVEF in the majority of patients following the discontinuation of trastuzumab, as well as the feasibility of trastuzumab-rechallenge in a significant number of patients (66%) who had had prior favorable oncological response to trastuzumab and who experienced a period of stability of LV function and absence of symptoms[45]. The second study from the same institution retrospectively looked at 173 patients who received trastuzumab over a period of 5 years and reported cardiac events (including symptoms of HF and asymptomatic decreases in LVEF) in 44 (28%) patients, HF symptoms in 15 (8%) and one cardiac death. That investigation also reported recovery of LVEF and resolution of symptoms with discontinuation of trastuzumab and start of cardiac treatment in the majority of patients[46].
There are no prospective trials that address the role of specific HF treatment choice, B-Blockers or ACE inhibitors, in trastuzumab-induced LV dysfunction. In addition, the majority of the patients in the trastuzumab trials had also received prior anthracycline treatment thus making it challenging to separate the effects of anthracyclines and trastuzumab and the cardiac treatment effects[47,48].

Rationale

Given the substantial oncologic benefit of these newer HER2 targeted therapies and their favorable cardiac toxicity profiles and the retrospective data demonstrating resolution of most trastuzumab induced cardiotoxicity with appropriate cardiac management, we seek to further evaluate the cardiac safety of non-lapatinib HER2 targeted therapy while on optimized cardiac therapy. We will not include lapatinib in our study given the low incidence of cardiac events associated with its use.

Cardiotoxicity induced by trastuzumab is thought to occur at least in part due to the inhibition of cellular repair mechanisms that result from downstream HER2 inhibition. If trastuzumab inhibits this repair during a vulnerable period after anthracycline injury, the anthracycline damage could be augmented, resulting in increased myocyte death. This hypothesis could explain why some patients do not fully recover from the damage that, at least temporally, seems related to the administration of trastuzumab. Furthermore, such a mechanism would predict that the sooner trastuzumab is given following doxorubicin administration, the greater the extent of cardiotoxicity[17]. Based on this hypothesis, we will hold trastuzumab for at least 60 days after the last dose of anthracyclines. In this situation if a patient is planned to receive taxanes and trastuzumab after antracycline containing regimen as part of adjuvant treatment, we will proceed with the taxanes and postpone trastuzumab for 60 days.

In this study we will also evaluate specific markers that may help predict earlier patients more likely to develop cardiac events or asymptomatic further worsening of cardiac function induced by HER2 targeted therapy: 1) myocardial strain analysis 2) cTnI and hs-cTnT. Earlier detection of these patients may allow consideration of alternative oncological treatments and/or different cardiac prevention strategies in these patients to prevent progressive LV dysfunction.

With the results of this pilot study, we plan to proceed to a phase II trial that would support a change in the current recommendations regarding the initial recommendations regarding cardiac function and stopping rules for HER2 targeted therapies.

2.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

2.1.1 Primary Objective

To evaluate the cardiac safety of HER2 targeted therapy (non-lapatinib) in patients with HER2 positive breast cancer and reduced LVEF when given concomitantly with cardiac treatment.

2.1.2 Secondary Objectives

1) To evaluate time to development of cardiac events or asymptomatic worsening of cardiac function (secondary endpoint #1)
2) To evaluate absolute changes in LVEF (endpoint #2)
3) To evaluate delays in HER2 therapy attributed to cardiac causes (endpoint #3)
4) To evaluate correlations between echocardiographic myocardial strain, cTnI and hs-cTnT at baseline and over time with cardiac events and asymptomatic worsening of cardiac function (endpoints #4,5)

3.2 Endpoints

3.2.1 Primary Endpoint

Proportion of patients who complete planned oncologic therapy without the development of a cardiac event or asymptomatic worsening of cardiac function.

CEs are defined as any of the following:
- Presence of symptoms and signs attributable to HF (increasing shortness of breath, orthopnea, PND, bilateral ankle swelling) as confirmed by a cardiologist
- Cardiac arrhythmia requiring pharmacological or electrical treatment
- Myocardial infarction
- Sudden cardiac death or death due to myocardial infarct, arrhythmia or HF

Asymptomatic worsening of cardiac function defined as:
- Asymptomatic decline in LVEF $\geq$ 10% points from baseline and/or EF $\leq$ 35% corroborated by a confirmatory echocardiogram in 2-4 weeks

Planned oncologic therapy is defined as:
- In the adjuvant setting: completion of 1 year total of HER2 targeted therapy. If a patient already received part of the planned HER2 targeted therapy prior to enrollment in this trial, planned oncologic therapy will be achieved when a total of 1 year is completed.

- In the metastatic setting: cessation of treating regimen due to progressive disease or non-cardiac toxicity or non-cardiac death.

3.2.2 Secondary Endpoints

1) Median time to development of an event defined as CE or asymptomatic worsening of LV dysfunction, among patients who developed one event.

2) Absolute changes in LVEF during HER2 targeted therapy

3) HER2 therapy holds attributed to proportion of patients with symptomatic or asymptomatic cardiotoxicity.
   - Hold is defined as any delay or discontinuation of HER2 targeted therapy due to cardiac toxicity. One cycle of HER2 targeted therapy will be considered 3 weeks. One therapy hold will be defined as any 3-week HER2 targeted therapy missed dose or 1/3 if one weekly trastuzumab dose. For patients who had a hold and resumed HER2 targeted therapy, duration of treatment hold will be described.

4) Correlation of global longitudinal myocardial strain with CEs and asymptomatic worsening of cardiac function

5) Correlation of standard cTnI and hs-cTnT with CEs and asymptomatic worsening of cardiac function

3.0 PATIENT ELIGIBILITY

4.1. Inclusion Criteria

1) Female or male patient diagnosed with stage I-IV breast cancer

2) HER2 positive breast cancer, defined by immunohistochemical staining for HER2 protein of 3+ intensity and/or amplification of the HER2 gene on fluorescence in situ hybridization (FISH) $\geq$ 2.0 on breast specimen or biopsy of a metastatic site

3) LVEF < 50% and $\geq$ 40% documented in echocardiogram done within the last 30 days

4) HER2 therapy naïve or currently receiving non-lapatinib HER2 targeted therapy

5) Patient receiving or planning to receive trastuzumab, trastuzumab with pertuzumab or ado-trastuzumab emtansine, for at least 3 months, alone or in combination with other systemic treatment or radiation

6) Age ≥ 18 years

7) Patient is willing and able to comply with protocol required assessments and procedures

4.2. Exclusion Criteria

1) Previous hospitalization due to documented heart failure in the last 12 months

2) Current signs or symptoms of HF or ischemia

3) History of arrhythmia requiring pharmacological or electrical treatment

4) Concomitant use of anthracyclines or use of anthracyclines in the last 50 days

5) History of significant neurologic or psychiatric disorders including psychotic disorders or dementia that would prohibit the understanding and giving of informed consent

6) Pregnant or lactating patients. Patients of childbearing potential must implement contraceptive measures during study treatment and for 7 months after the last dose of the study drug.

4.0 STUDY DESIGN

Pilot study

This will be a pilot study evaluating the cardiac safety of physician's choice HER2 targeted therapy (non-lapatinib) in 30 patients with HER2 positive invasive breast cancer and mildly decreased LV function (LVEF ≥40% and <50%) while on concomitant cardiac treatment with B-Blockers and ACE inhibitors.

Sample size

We will use a sample size of 30 patients determined based on the primary endpoint of therapy completion (see Section 9.0). In addition, we will estimate the rate of cardiac events and asymptomatic worsening of LV function with a 90% confidence interval. To achieve this goal we will add 10% of patients to our sample size to account for potential drop out before starting HER2 targeted therapy. Therefore we will plan to enroll 33 patients. In terms of patients screened, given the fact that patients will already have been "pre-screened" by the oncologists who will refer them to the study based on LVEF between 40 and 49%, we dont expect that we will have a very high screening failure. We anticipate that we may screen 4 to get 3 patients. So the anticipated number of patients to be screened would be around 44.

Summary of our intervention

The study will include patients in the adjuvant or metastatic setting, expected to receive at least 3 months of HER2 targeted therapy (non-lapatinib). Patients will be candidates for trastuzumab, pertuzumab/trastuzumab or ado-trastuzumab emtansine at the discretion of their treating oncologist, alone or in combination with other systemic treatment or radiation.

Patients included will either be found to have mildly decreased LVEF at the initial echocardiogram prior to HER2 targeted therapy or will have developed mildly reduced EF while receiving HER2 targeted therapy. This will classify the majority of the participants as stage B in the stages of development of HF[31] (appendix B). Patients who have a remote history of symptomatic HF, i.e. more than one year prior to study enrollment, will be considered for the study and based on the HF guidelines they would be classified as stage C HF. While this

staging system recognizes that HF has established risk factors and structural prerequisites, it also emphasizes that HF is not equivalent to cardiomyopathy or to LV dysfunction, but is rather a clinical syndrome characterized by specific signs and symptoms.

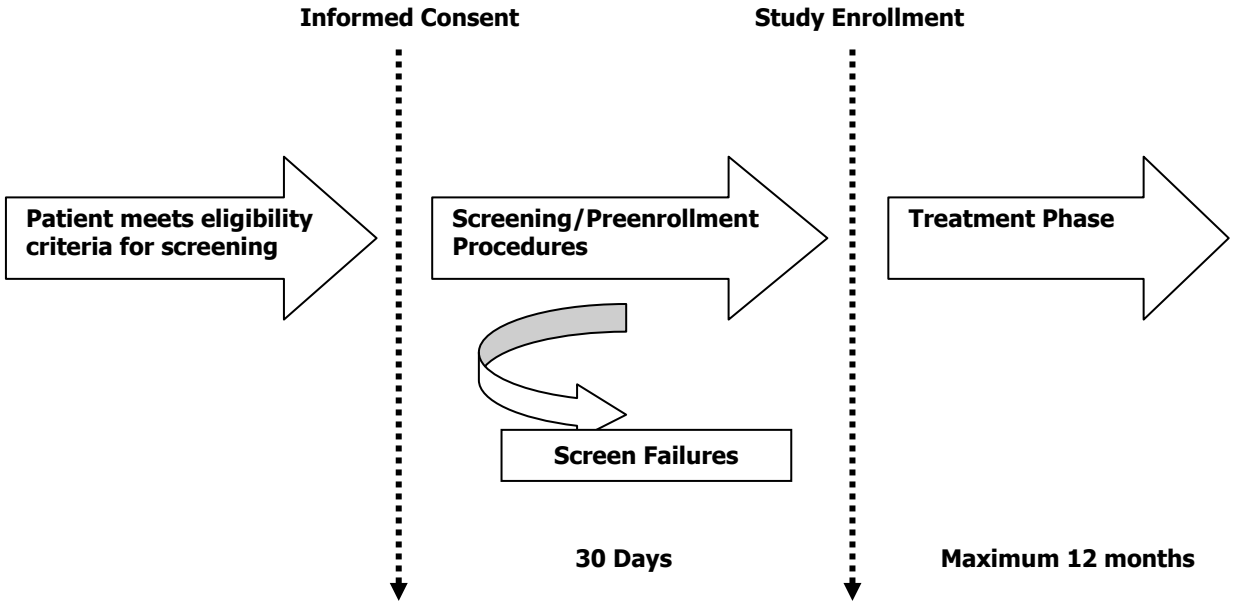
While on study, patients will be followed by an investigator cardiologist for evaluation of symptoms and signs of heart failure and for initiation and/or titration of cardiac medications (B-blockers and ACE inhibitors).

A schema will be followed to determine when HER2 targeted therapy should be held, when it may be rechallenged and when it must be stopped (figure 1). If at any time the patient develops symptomatic heart failure confirmed by the cardiologist, the patient will go off study.

A blood specimen will be collected at baseline and stored for potential analysis of targets identified in the future.

5.0 INTERVENTION

Figure 2. Study Phases



5.1 Subject Selection and Screening

Patients who meet eligibility criteria (page 14) and sign informed consent will be registered for screening and assigned an ID number. All protocol-specific screening procedures must be performed within 30 days after signing informed consent.–The decision about the need to

perform an exercise stress echocardiogram or other test to exclude myocardial ischemia will be made at the discretion of the treating study cardiologist.

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. **Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for screening or other study purposes so long as they are done within 30 days prior to signing the consent. Screening and enrollment case report forms (CRFs) should be filled at this point (appendices K-L)**.

5.1.1 Screening Procedures:

- Screening study echocardiogram confirmation by the Core lab (appendix I)
- Cardiac questionnaire (appendix E)
- EKG
- Six minute walk test
- Laboratory work:
    - Troponin I (Tn-I)
    - Pregnancy test
- Additional laboratory work if clinically indicated:
    - BNP or NT proBNP
    - Comprehensive metabolic panel (CMP) including albumin, alkaline phosphatase, ALT/sGPT, AST/sGOT, BUN, creatinine, sodium, potassium, calcium, chloride, bicarbonate, glucose, and total bilirubin;
    - Fasting lipid profile (total cholesterol, triglycerides, LDL and HDL cholesterol) for those who are on lipid-lowering agents
    - Hemoglobin A1c
    - Thyroid stimulating hormone (TSH) and free T4
    - Serum free ferritin
- Exercise stress echocardiogram (if considered appropriate by the treating study cardiologist)
- Summary of initial cardiac assessment (appendix G)
- Oncology Visit
- Cardiology Visit

After signing the consent patient will undergo additional protocol-specific screening procedures to exclude presence of coronary ischemia or other treatable causes of cardiomyopathy. If ischemia is suspected patients will not be enrolled in the study unless the results of further, more specific ischemia work-up, excludes presence of ischemia. The results of the tests and procedures, such as lab tests or cardiac imaging, performed for clinical indications prior to signing of the consent may be used at the discretion of study investigators.

Coronary artery disease is believed to be the underlying cause in approximately two thirds of patients with HF and low EF and also contributes to the progression of HF through mechanisms that include endothelial dysfunction, ischemia and infarction. The decision about the need to perform an exercise stress echocardiogram or other test to exclude myocardial ischemia will be made at the discretion of the treating study cardiologist. Patients who undergo a stress test and are found to have positive test, i.e. wall motion abnormality with stress consistent with ischemia, will be excluded from the study and will pursue further clinically-indicated work-up and treatment

that may include cardiac catheterization and revascularization. If findings of the further work-up are negative and no ischemia is found, or the patient is revascularized, she/he may be re-considered for the study if anti-HER2 treatment is still indicated in the opinion of treating oncologist. For patients who had a prior stress test or other ischemia evaluation the results of these tests will be reviewed by a study cardiologist who will make a decision about whether repeat stress echocardiogram or other cardiac ischemia evaluation is needed.

If a patient cannot complete exercise stress test, for example, because of the inability to walk on the treadmill, the need for further ischemia work-up will be decided by the study cardiologist taking into consideration cardiac risk factors, presence of symptoms, as well as the results of EKG, troponin, and presence of wall motion abnormalities on 2D echocardiogram. This work-up may include pharmacological stress testing (for example, dobutamine stress echocardiogram or regadenoson perfusion study by cardiac MR), cardiac CT or coronary angiogram. Patient may be enrolled in the study if: a) further stress testing is considered not necessary given low risk for ischemia or b) the results of the performed functional or anatomical test are negative for significant ischemia or significant coronary disease.
Thyroid function and serum free ferritin will be performed for clinical indications according to the American College of Cardiologists (ACC)/ American Heart Association (AHA) Practice Guideline recommendations to exclude possible treatable causes of LV dysfunction. Work-up for other systemic conditions such as hemochromatosis, rheumatologic disease, sleep-disturbed breathing or human-immunodeficiency virus infection will be assessed as clinically indicated.

Standard cTnI will be collected as a screening procedure for each patient. If the results of the standard cTnI assay are > 1ng/ml, the results of the stress test will be reviewed and the patient will be scheduled for a clinical visit and appropriate clinical work-up will be initiated. Until further work up is completed and troponin ≤ 1ng/ml, the patient will not participate in the study. If exercise stress echocardiogram result is normal, patients may be allowed to participate in the study. This decision will be made by the study cardiologist.

5.1.2 Screen Failure:

The following instances will be considered a screen failure:

- Study echocardiogram doesn't confirm LVEF reported in initial echocardiogram (LVEF<50% and ≥40%)
- Presence of treatable and reversible HF cause as assessed by study cardiologist (for example, hyperthyroidism)
- Presence of ischemia (as assessed by study cardiologist)
- Positive pregnancy test. Patients of childbearing potential must have negative urine or serum pregnancy test within 21 days after signing initial consent.

After completion of all screening procedures, patients unable to continue will be considered screen failures. Patients able to continue the study, i.e., did not meet any screen failure criteria, will enroll and move to the treatment phase.

5.2 Enrollment and Treatment Phase

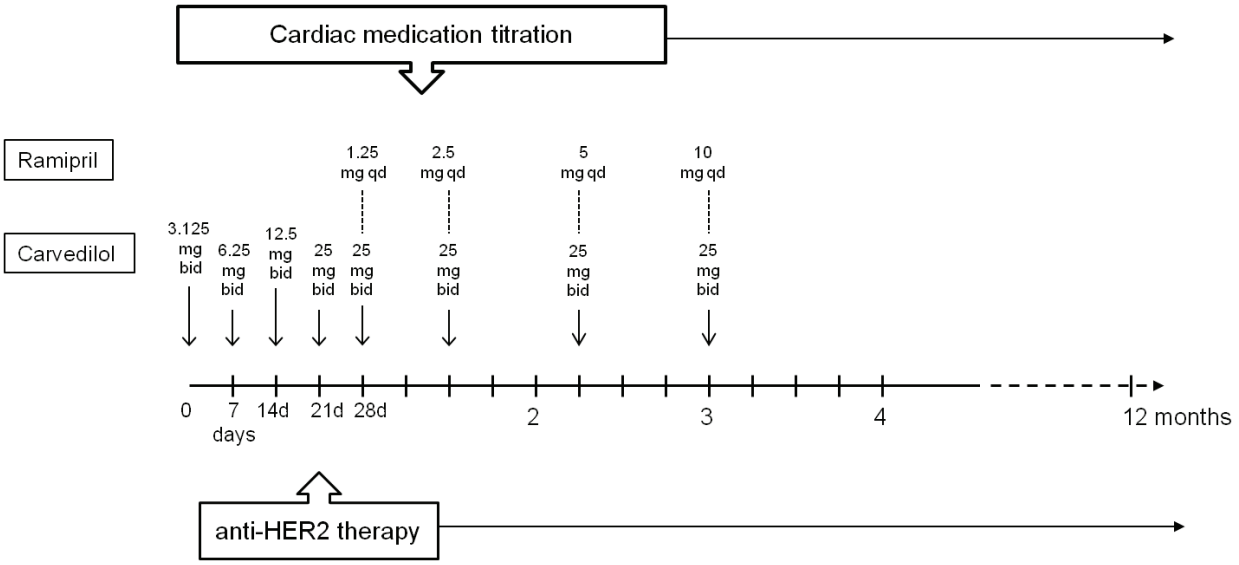
At the moment of the study enrollment, the date of initiation of study treatment will be determined on the basis of expected duration of cardiac therapy optimization. This period cannot be longer than 21 days.

5.2.1 Cardiac Assessments on Study (timeframe per schedule of events):

- NYHA class assessment
- Mandatory Laboratory work:
    - hs-cTnT (timeframe per schedule of events)
- Review of cardiac medications: initiation and/ or modifications and titration (can be initiated in the screening phase if deemed appropriate by study treating cardiologist)
- Patient will be given a Blood pressure (BP) monitor cuff and BP daily log (appendix T) at the first cardiac study visit. (can be given in the screening phase if deemed appropriate by study treating cardiologist)
- Lipid profile will be reviewed and optimization of statin therapy will be done at discrection of study cardiologist.
- Patient will be given education material about exercise and low-salt diet (appendices X-Y)
- Referral for smoking cessation counseling will be provided for smokers

Cardiac Medications Inititation and Titration

Figure 3. Flow diagram of cardiac medication titration (example of a patient not previously on cardiac medications and tolerating increases in medication doses)



✓ Typically, after the study enrollment, cardiac treatment with beta-blockers and ACE inhibitors will be started in all patients who do not have contraindications. Cardiac medications can be initiated in the screening phase if deemed appropriate by study treating cardiologist. Decision on the initiation of beta-blockers will be based on the initial screening ECG, blood

pressure and other clinical characteristics. For patients with bradycardia (heart rate ≤ 60) beta-blocker will not be started and ACE-inhibitor will be considered as the first choice. Carvedilol will be initiated with the starting dose of 3.125 mg twice a day with dose increases as tolerated. In patients who already take different beta-blockers for the treatment of blood pressure or other reasons their beta-blockers will be substituted for a corresponding dose of carvedilol. In the absence of hypotension (symptoms of lightheadedness or BP < 100/60 mmHg), or bradycardia (heart rate <60 bpm) the dose of carvedilol will be increased at weekly intervals up to 25 mg twice daily (Figure 3). If the titration is not possible due to hypotension or bradycardia the patient will be kept on the same dose and re-evaluated in two weeks for titration. Carvedilol will be our beta-blocker of choice because it has been showed to have beneficial effects in patients with chronic HF as well as benefit over metoprolol tartarate[49].

✓ Once a patient reaches the maximum tolerated dose of carvedilol twice daily, ramipril will be added at 1.25mg daily dose. Ramipril dose will be doubled approximately every 3 weeks to coincide with infusion center visits for HER2 targeted therapy, assuming a 3 week treatment schedule. It will be uptitrated to the maximum tolerated dose, up to a maximum dose of 10mg. Patients who are on different ACE inhibitors, including lisinopril and enalapril, for the treatment of blood pressure or other causes, will be continued. Figure 3 is representative of events in patients not on beta-blocker, ACE inhibitor or ARB at the time of study entry and who are able to tolerate increases in beta-blockers and addition ACE inhibitor without low blood pressure, bradycardia and/or other side effects.

✓ In patients who have a history of allergy or intolerance to ACE inhibitors, angiotensin receptor blockers (ARBs) will be started instead of ACE inhibitors. Candesartan will be considered as the first ARB of choice. Other approved ARBs can be used depending on clinical circumstances or insurance coverage at the discretion of study cardiologist. If the patients are already on valsartan or other approved ARBs, their dose will be continued and up titrated as tolerated.

✓ Patients will not receive ACE inhibitors, B-blockers or ARBs if they have known allergy to any of these classes of drugs, history of bronchial asthma or related bronchospastic conditions, hereditary or idiopathic angioedema or history of severe hypersensitivity reactions to drugs or other causes, i.e. bee stings. If a patient can't receive any of the cardiac medications due to any contraindication, patient can still participate in the study. If for any reason a patient is unable to receive the choice ACE-inhibitor or/and B-blocker, appropriate substitutions will be made according to study cardiologist.

✓ Patients with baseline creatinine of equal or more than 1.5 mg/dl will not initiate ACE inhibitors or ARBs but they will be allowed to participate in the study. Serum creatinine level will be assessed after the first dose of either ACE inhibitor or ARB and following after every dose increase, until creatinine levels is stable defined as less than 10% change from baseline creatinine. If there is an increase of serum creatinine of more than 0.5mg/dL from baseline, the medication will not be increased further and serum creatinine will be repeated.. If the creatinine continues to be elevated to more than 30% of baseline value the dose will be reduced or, if the patient is on the lowest dose, the medication will be stopped.

Other Medications

Patients' medications will be reviewed during initial cardiac assessment and the following drugs that can exacerbate or provoke the syndrome of HF will be discontinued and/or replaced with alternative agents as possible. These drugs include calcium channel blockers (all with the

exception of amlodipine and felodipine), antiarrhythmic agents and nonsteroidal anti-inflammatory drugs (all with the exception of aspirin).

If patient does not meet his/her LDL goal based on standard NCEP/ATP (National Cholesterol Education Program/ Adult Treatment Panel) guidelines and is not on statin therapy, atorvastatin will be initiated according to the standard clinical practice. In patient who require either new initiation of statin therapy or dose escalation, lipid profile will be repeated in 3 months and statin dose will be further increased as clinically indicated. In patients intolerant of statins other lipid-lowering medications can be used at the discretion of study cardiologist.

Blood pressure log

✓ Patients will be instructed to take their blood pressure (BP) every day during the first month or until maximum tolerated cardiac medication dose is achieved. Patients will be provided with a BP monitor cuff and taught how to use it. After that, patients will be instructed to take their BP weekly while participating in the study. BP results will be documented on a BP Daily Log (appendix T). In case the patient cannot adequately learn how to monitor his BP at home, she/he will come once a week to the hospital and he will have BP registered, for the first month or until maximum tolerated dose of cardiac medications has been achieved. After that blood pressure will be checked at routine study visits.

✓ The titration of the medications will be pursued based on the results of the BP daily log. As an example, if there are no values of systolic blood pressure of less than 100 mmHg and the median weekly systolic BP is >110mmHg the medication will be up titrated according to the schema in figure 3. Otherwise patients will be continued on the current dose of medication. In case of symptoms of lightheadedness or 2 or more values of systolic blood pressure of less than 100 mmHg, the dose of medication will be reduced or stopped if the patient is one the minimal dose. If a patient cannot check the blood pressure at home she/he will come for the BP appointment.

On Study Cardiac Visits

After receiving the first dose of HER2 targeted therapy while on study, patients will come for cardiology follow up assessments (appendix I) every six weeks (+/- 10 days) for a total of 2 visits and then every twelve weeks (+/- 10 days). Medical history and physical exam will be performed at each follow up cardiac assessment visit. Echocardiogram and laboratory testing including other serum chemistries and BNP may be performed at cardiologist‘s discretion if there is a concern for HF signs and symptoms based on the review of systems and physical exam during the follow-up assessment visit.

The treating physicians will have access to the LVEF assessed by the Core lab that will be used for clinical decision making. (see 6.1.3.2)

Criteria for withholding HER2 targeted therapy will be followed according to Figure 1. If a patient has an asymptomatic absolute decline in LVEF of ≥10% points from baseline or to equal or less than 35%, HER2 targeted therapy will be temporarily held. At any time that HER2 targeted therapy is withheld, the patient will undergo follow up cardiology assessment to evaluate for the presence of HF signs and symptoms. Further testing including chest X-ray, echocardiogram and laboratory testing will be done at the discretion of the cardiologist.

Confirmatory study echocardiogram will be performed within 2-4 weeks (Figure 1). If repeated study echocardiogram confirms the change in LVEF that meets holding criteria, patient will come off the study. This will be named asymptomatic worsening of cardiac function and considered a primary endpoint. However, if repeated echocardiogram shows improvement in LVEF and holding criteria are not further met, HER2 targeted therapy will be resumed and patient will undergo regular cardiac assessments and study echocardiograms every 6 weeks for two times and then every 12 weeks. Dose reduction will not be considered for any of the HER2 targeted therapies in the case of cardiac toxicity.

If a patient develops symptoms suggestive of HF, he/she will undergo follow-up cardiac assessment. If patient presents with symptoms mandating urgent medical evaluation (worsening dyspnea, hemodynamic compromise), he/she will be directed to the nearest emergency room or a tertiary acute care center. HER2 targeted therapy will be temporarily held in any patient who develops clinical signs and symptoms suggestive of HF until cardiology assessment. If symptoms are confirmed to be due to HF, the patient will be taken off the study. At the time of any cardiac event, any grade 3 or 4 adverse event will be collected (Appendix S).

Adverse events related to cardiac medications (B-Blockers, ACE inhibitors and/or ARBs) will be treated at the discretion of the treating cardiologist.

6.2.1.2 Study Echocardiograms

Screening Echocardiogram:

Patients will be initially identified based on LVEF (< 50% and ≥ 40%) detected in a routine clinical echocardiogram. If LVEF was assessed using different cardiac imaging modality (cardiac MR or radionuclide imaging (MUGA)) the same LVEF criteria will apply for determination of eligibility (< 50% and ≥ 40%). Patients will sign consent and will undergo screening procedures.

LVEF value will be confirmed through the MedStar Health Research Institute Cardiovascular Ultrasound Core Laboratory (Core Lab) LVEF assessment. Clinical echocardiogram that was used to obtain eligibility will be sent to the Core Lab labeled with the subject's Study ID, Date of Study and Time Interval. If the images of the clinical echocardiogram used to determine eligibility are not available, or LVEF was obtained using different cardiac imaging technique, the patient will undergo a new study echocardiogram in this period.

Baseline and Subsequent Study Echocardiogram:

"Screening" echocardiogram may be used as a baseline study echocardiogram if the study is available and fulfills the following: it was completed within 30 days prior to study enrollment, it includes raw frequency data (for strain assessment) and all the measurements listed in the Echocardiography protocol (Appendix H) are included and are evaluable as determined by the Core lab.

Study echocardiograms will be performed at clinical echocardiography laboratories following the Echocardiography protocol (Appendix H) and will include transthoracic echocardiograms with strain analysis, 2D and 3D measurements. The echocardiograms will be sent for interpretation, electronically or using a DVD copy, to the **MHRI's Cardiovascular Core lab**.

The echocardiograms will be performed at baseline and after starting HER2 therapy every 6 weeks for 2 assessments and then every 3 months while on study. Additional echocardiograms may be performed at the discretion of study investigators to evaluate changes in cardiac function while patients is on study. These echocardiograms will be paid by the study if indicated for study reasons, for example, suspected symptoms of HF.

All echocardiograms need to be scheduled with enough time prior to the next dose of HER2 targeted therapy to allow image transfer, processing and reporting from the Core Lab.

The echocardiograms will be labeled as:

- Study ID, Date of Study and Time interval:
  - -Screening
  - -Baseline (as above, screening echo may qualify for baseline)
  - -6 weeks
  - -12 weeks (3 months)
  - -24 weeks (6 months)
  - -36 weeks (9 months)
  - -48 weeks (12 months)
  - -Off Study
  - -6 months post Off Study
  - -Other: Clinical (for additional echocardiograms ordered at discretion of study investigators due to change in clinical status),
  - -Other: Safety Check 1 etc (additional echocardiograms ordered for subjects whose EF has dropped as per protocol parameters)

In the case of treatment delay, both weeks and cycles follow the infusion of HER2 therapy. Therefore, 3 weeks corresponds to cycle 1 etc.

6.2.1.3 Transfering and Core Lab Reporting of Study Echocardiograms

Echocardiographic images will be transferred digitally or recorded on a DVD and brought/shipped to the Core Lab. Core Lab personnel will be notified of image transfer and will be provided with the Study label including Study ID, Date of Study and Time Interval as above.

Case report form (CRF, Appendix I) will be sent back to the research coordinator within 72 business hours from the time the Core Lab receives the study images and the notification with Study label. Scheduling of echocardiograms will be done in accordance to this timing.

LVEF reported in the CRF will be used for decision making in the study in the following fashion:

- If 3D measurement LVEF is available it will be used as LVEF of record for that study,
- if 3D measurement is not available, 2D LVEF will be used,

- if neither 3D or 2D measurements are available, visual EF will be used.

Other measures, including measures of diastolic function and strain measures will be collected in the CRF but will not be provided to the treating physicians and will not influence management of the patients.
Screening echocardiograms will have only LVEF measured and reported, and Baseline echocardiograms will have all the fields reported..

5.2.2 Oncology Assessments on Study

Initial oncological assessment must include:

- TNM staging
- ER, PR, HER2 status
- Previous treatments received for breast cancer: radiation, surgery, chemotherapy, endocrine or targeted therapies
- Performance status (appendix C)

CRF on previous hormonal and chemotherapy agents received, radiation therapy and previous breast surgery will be filled by the investigator during initial oncological assessment (Appendices N-Q). In this initial oncological assessment, the planned oncologic therapy will be defined by the investigator and fill the appropriate form (appendix N).

Patients will receive one of the three following HER2 targeted therapies at the discretion of their oncologist: trastuzumab, trastuzumab/pertuzumab or ado-trastuzumab emtansine. These will be administered on an outpatient basis. The first dose of HER2 targeted therapy will be initiated after BB +/- ACE inhibitor doses have been optimized at the discretion of one of the study cardiologists. Supportive care medications such as anti-emetics, growth factors and medications to prevent infusion reactions may be given at the treating oncologist's discretion.

Table 2. Treatment dosage and administration

Agents	Indication, dosage, route of administration, cycle length
Trastuzumab	For intravenous (IV) infusion only. Do not administer as an IV push or bolus. Administer at either: Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 52 weeks, or initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30−90 minutes IV infusion every three weeks for 52 weeks. There is no need for a loading dose if the patient has been on trastuzumab and the last dose was given less than 6 weeks prior, or less than 2 weeks prior if on weekly infusions. If given in the metastatic setting, continue trastuzumab beyond 52 weeks if considered appropriate by the treating oncologist. No need for premedications.
Pertuzumab	For intravenous infusion only. Do not administer as an IV push or bolus. The initial dose is 840 mg administered as a 60-minute IV infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute IV infusion. There is no need for a loading dose if the patient has been on pertuzumab and the last dose was given less than 6 weeks prior.
Ado-trastuzumab emtansine	3.6mg/kg IV every three weeks. The first infusion will be administered over 90 minutes (± 10 minutes). Following the first dose, patients will be observed for at least 60 minutes for fever, chills, or other infusion-associated symptoms. If prior infusions were well tolerated, subsequent doses of ado-trastuzumab emtansine may be administered over 30 minutes (± 10 minutes), with a minimum 30-minute observation period after infusion.

Screening and Off Study evaluations are required. Other oncology visits will be at the discretion of the treating oncologist. Routine laboratory studies required to evaluate oncologic therapy-related, non-cardiac toxicity are at the discretion of the treating oncologist and, therefore, have not been specified in the protocol. Restaging scans will be performed as needed at the discretion of the treating oncologist. Appropriate form with information from each patient regarding ongoing HER2 targeted therapy, dose and days of treatment, concomitant chemotherapy, endocrine therapy and/or radiation therapy will be filled by the investigator (appendix AA).

Dose reductions for trastuzumab and pertuzumab will not be allowed. Ado-trastuzumab emtansine dose can be reduced to 3.0 mg/kg and 2.4 mg/kg, in case of thrombocytopenia, hepatotoxicity, neurotoxicity or other toxicities, and will be at discretion of the treating oncologist.

For delayed or missed doses, if the time between 2 sequential infusions is less than 6 weeks, the 420 mg IV dose of pertuzumab will be administered without waiting until the next planned dose. If the time between 2 sequential infusions is 6 weeks or more, the initial dose of 840 mg pertuzumab will 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.

HER2 targeted therapies have been associated with both cardiac (see section 6.3.1) and non-cardiac toxicities. Among non-cardiac toxicities, infusion-associated symptoms, hematologic toxicity, neutropenic infections, respiratory events, diarrhea, rash, liver toxicity and peripheral

neuropathy have been associated with HER2 targeted therapy. Assessment and treatment of non-cardiac toxicities will be done at the discretion of the treating oncologist.

For oncological treatment other than HER2 targeted therapies, management of adverse events will be at the discretion of the treating oncology. Delays of chemotherapy based on side effects from non-HER2 targeted therapy will be up to the treating oncologist. If HER2 targeted therapy is held for non-cardiac reasons for more than 9 weeks (more than 3 cycles of HER2 targeted therapy), patient will go off study.

6.4 Treatment delays

Cardiac assessments (echocardiogram, cardiology visit and blood samples) are done in accordance with administration of HER2 targeted therapy. Treatment delays will be documented. If HER2 therapy is on hold for more than 9 weeks for any reason patient will be removed from protocol.

5.5 Schedule of Events

The schedule of events table present in appendix Z will be followed for patients who do not have significant drops in the LVEF that mandate to hold treatment. If patient develops a significant drop in the LVEF and/or symptoms and signs suggestive of heart failure, follow up will be done according to Figure 1.

5.6 Removal of patients from protocol therapy

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

6.6.1 Patient voluntarily withdraws from treatment (follow-up permitted);

6.6.2 Patient withdraws consent (termination of treatment and follow-up);

6.6.3 Patient is unable to comply with protocol requirements;

6.6.4 Treating physician judges continuation on the study would not be in the patient's best interest;

6.6.5 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

6.6.6 Lost to follow-up;

6.6.7 Completion of planned course of HER2 targeted therapy;

6.6.8 Cardiac event or asymptomatic worsening of cardiac function as defined in protocol that preclude continuation of patient participation in the study;

6.6.9 HER2 therapy on hold for more than 9 weeks due to non-cardiac reasons.

6.6.10 Disease progression with change in treatment regimen.

5.7 Duration of study

Patients will be followed for up to 12 months on study. For patients with metastatic breast cancer who may be appropriate to continue on HER2 therapy beyond the 12 month study period, this will be allowed off-study at the discretion of the treating oncologist. Patients who complete their current HER2 targeted therapy regimen will be taken off the study prior to 12 months of follow-up. For the normal course of the study, completion of planned course of HER2 targeted therapy will mark the end of treatment. However, if patients experience a Cardiac event or asymptomatic worsening of cardiac function (as defined in protocol) that precludes continuation of patient participation in the study, then this event will mark the end of treatment.

5.8 Off Study Procedures

- Complete medical history and physical exam
- Troponin I, hs troponin
- Study echocardiogram

Off Study procedures will be performed within 30 days after the patients' end of treatment determination.

5.9 Duration of follow up after being off study

At the time of going off study, patients will have completed HER2 targeted therapy if they were being treated in the adjuvant setting. If they are being treated in the metastatic setting they may continue to receive HER2 targeted therapy after the study is finished. All patients will be followed for 6 months after being off study. Cardiac medications will be continued at the discretion of the treating physicians. Cardiac events occurring during this period of 6 months will be recorded and considered as possibly related to HER2 targeted therapy, independently of whether HER2 targeted therapy is continued off study. All the patients will be reevaluated in a single visit at 6 months (+/- 10 days) with:

- Complete history and physical exam
- Study echocardiogram (6 months post Off Study)
- Lipid profile for patients who were started on a lipid lowering agent while on the study
- Troponin I, hs troponin

5.9.1 Optional extended follow up after being off study

- Patients will be provided with an optional consent where they are asked to allow for extended follow up up to 5 years after being off study. For patients who continue to be followed in the participating institutions this would mean to agree to have records reviewed periodically up to 5 years. For patients no longer being followed in the clinic this would mean to be contacted periodically by a member of the research staff regarding any new symptoms or events since coming off study, as well as authorization to request records during this period of time.

5.10 Compliance with laws and regulations

This study will be conducted in accordance with FDA regulations, the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (October 1996), and applicable local, state, and federal laws.

6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording protocol-defined AEs and serious adverse events (SAEs); measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drugs.

The Sponsors or their designee are responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

All cardiac AE occurring on or after the date of the first study treatment administered will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE version 4.0 toxicity grades.

6.1 Adverse event

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 patient that emerge during the protocol-specified AE reporting period.
- Complications that occur as a result of protocol-mandated interventions.
- AEs that occur prior to assignment of study treatment that are related to a protocol mandated intervention.
- Preexisting medical conditions judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

AEs attributed to ACE inhibitors and B-blockers will be documented but not reported:

- Renal insufficiency
- Cough
- Anaphylaxis
- Hypotension
- Dizziness
- Weight gain

- Depression
- Weakness
- Impotence
- Nausea/vomiting/diarrhea

Very common non-cardiac AEs attributed to T-DM1 will be documented but not reported:

- fatigue, weight loss, decrease in appetite
- nose bleed
- upper respiratory tract infection, cough
- fever, chills
- urinary tract infection
- depression
- nausea, vomiting, constipation, diarrhea
- low numbers of white blood cells (cells that fight infection, all types) or red blood cells (may make you feel tired)
- rash
- dry mouth
- edema (swelling due to a buildup of fluid under skin) in arms and legs
- neuropathy in arms and legs (tingling, pain, numbness, itching, pins and needles)
- muscle spasms
- low potassium in blood (caused by the loss of fluids due to vomiting, diarrhea or sweating a lot)
- pain in joints, muscles, back, arms and legs, headaches

Very common non-cardiac AEs attributed to Trastuzumab and Pertuzumab:

- Weakness
- Diarrhea
- Skin rashes
- Chest pain, abdominal pain, joint pain, muscle pain
- Febrile neutropenia (infection due to low white blood cell count)
- Mucosal inflammation (inflammation of the mucosal surfaces throughout the body

6.2 Serious adverse event (Immediately reportable to the sponsor)

An SAE is any AE that result in the following outcomes or require medical intervention to prevent any of these outcomes:

- Fatal (i.e., the AE actually causes or leads to death, sudden cardiac death or death due to myocardial infarct, arrhythmia or heart failure). If death results from progression of the disease, it should be reported as a SAE.
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death at the time of the event)
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s).

- Considered a significant medical event by the investigator (e.g., may jeopardize the patient or require medical/surgical intervention to prevent one of the outcomes listed above)
- Pregnancies

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). “Serious” is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations. Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF. Grading will be based on CTCAE v. 4.0. The CTCAE v4.0 is available at: http://ctep.cancer.gov/reporting/ctc.html.

7.3 Non serious adverse events of special interest (Immediately reportable to the sponsor)

Non-serious AEs of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event); AEs of special interest for this study include the following:

- any cardiac event (CE) defined as any of the following:
- Presence of symptoms attributable to HF (increasing shortness of breath, orthopnea, PND, bilateral ankle swelling) as confirmed by a cardiologist
- Cardiac arrhythmia requiring pharmacological or electrical treatment
- Myocardial infarction

Heart failure should be graded according to NCI CTCAE v4.0 for “heart failure” (Grade 2, 3, 4, or 5) and in addition according to the NYHA classification.

Any CE should be reported to the Cardiac Review Panel within three weeks after learning of the CE.

Asymptomatic declines in LVEF will not be reported. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF $\geq$ 10 percentage-points from baseline to an LVEF $\leq$35% must be reported as an AE with the term of “ejection fraction decreased” as per NCI CTCAE v4.0, and, in addition, a comment in the AE comments field should confirm that this was asymptomatic.

7.4 Reporting Requirements for Pregnancies

7.4.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy).The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the

patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

7.4.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. Male patients whose partners are pregnant must use condoms for the duration of the pregnancy. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy). Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

6.5 Methods and timing for assessing and recording safety variables

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

6.5.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends when the patient comes off study. During the 6 month follow up period only SAEs and AE of special interest will be reported.

7.5.2. Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the HER2 targeted therapies 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 HER2 targeted therapies, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the HER2 targeted therapies; and/or the AE abates

or resolves upon discontinuation of the HER2 targeted therapies or dose reduction and, if applicable, reappears upon re-challenge.

- **No:** Evidence exists that the AE has an etiology other than the HER2 targeted therapies (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to HER2 targeted therapies 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.

6.6 Expedited Reporting Requirements for Adverse Events of Special Interest

The Sponsors or their designee will notify the, DSMC, Genentech and the FDA within 7 business days of learning of any unexpected adverse event of special interest that is thought to be related to the study intervention. These adverse events of special interest will be reported to the IRB at annual renewal along with all other adverse events. DSMC and IPRC reports of these events will be submitted to the IRB as an amendment.

6.7 Expedited Reporting Requirements for Serious Adverse Events

The Sponsors or their designee will notify the FDA within 7 business days of learning of any unexpected fatal or life-threatening adverse event with possible relationship to study drugIn addition, the cause of death will be summarized (e.g., disease related, treatment related, other, unknown). The Sponsor or their designee will notify the IRB, DSMC and Genentech of relevant SAEs (i.e., death, a life-threatening experience, inpatient hospitalization, prolonged hospitalization or significant disability/incapacity) by a written safety report within 24 hours of learning of the serious adverse event.

SAEs must be reported whether or not considered related to the treatment under investigation. An early report can then be followed up by a more detailed report. The clinical course of the serious adverse evenrt, regardless of its relationship to the study intervention, should be managed according to accepted standards of medical practice. Patients will be monitored until the SAE resolves or the symptoms or signs that constitute the event return to baseline; or a satisfactory explanation is found or the investigator considers it medically justified to terminate follow-up of the event; or death (a full pathology report shold be supplied if possible).

Reports should include the following information:

- ✓ Protocol number
- ✓ Disease information
- ✓ Date event occurred
- ✓ Event grade
- ✓ To what degree the event is related to the study intervention
- ✓ If the event was expected

- ✓ Severity of the event
- ✓ Intervention
- ✓ Event Detail - Detailed text that includes the following information:
  - Event description and how it was handled
  - Current condition of participant
  - Indication if participant remains on the study
- ✓ Indicate if an amendment to protocol and/or consent is necessary
- ✓ Indicate if the report is a follow-up to a previously submitted event report

6.8 MedWatch 3500A reporting guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

6.8.1 Follow-up Information

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

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

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

7.0 CORRELATIVES/SPECIAL STUDIES

7.1 Cardiac troponins

Cardiac troponin I will be performed in the clinical laboratories at MWHC, MGUH and MSKCC collected in accordance with institutional protocol and using standard cTnI assay. These results will be available to the treating physician but will not be used to make clinical decisions unless it is is more than 1ng/ml. Based on the published data[50], mild elevation of troponin in patients receiving chemotheray is common and its prognostic significance is being investigated in this study. However, higher elevations of troponin which we arbitrarily set as troponin higher than 1ng/ml are not expected in this patient population and may indicate presence of cardiac ischemia or an inflammatory process such as myocarditis. Therefore, if the results of the standard cTnI assay are higher than 1ng/ml patient will come for a clinical visit and appropriate clinical work-up will be initiated.

Hs-cTnT assay will be measured offsite by Roche Diagnostics. These results will not be available to the treating physician, will only be used for research purposes and no clinical decisions will be made based on Hs-cTnT measurements.
Standard cTnI and Hs-cTnT will be performed at enrollment, every 6 weeks after starting HER2 therapy for 2 assessments and thereafter every 12 weeks.

7.2 Optional Sample Collection Guidelines for future analysis

We will collect a specimen of blood at enrollment from each participant and then at 6 weeks, 12 weeks, 6 months, 9 months and 12 months after starting HER2 therapy. Blood specimens will be obtained at the same time with the samples for cardiac troponin and/or clinical laboratory. Whole blood will be collected and processed within 24h to separate the buffy coat from the plasma and RBCs. Buffy coat and plasma will be frozen at -80°C and processed for DNA or biomarkers at a later date. Serum samples will be processed, aliquoted and frozen at --80°C for analysis at a later day.

After enrollment, and if patient accepts to have collected blood for future analysis, approximately 16 ml of blood will be collected for research (storage for future analysis and troponins) and approximately 15ml for clinical labs. At week 6, 12, 24, 36 and 48 after initiating HER2 therapy, approximately 11 ml will be collected for research.

Patient samples collected for this study will be kept at Georgetown University, at Medstar Washington Center Campus or at MHRI headquarters in Hyattsville. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the blood samples.
The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information.

The collection of blood for future analysis is optional and patients that declined to have their blood collected and stored for future analysis can still participate in the study.

8.0 STATISTICAL CONSIDERATIONS

8.1 Two-stage design, Sample Size, Accrual and Study Duration

The study is designed to assess the rate of completion of planned oncology therapy in the absence of cardiac event and asymptomatic worsening of cardiac function. The primary endpoint is the proportion of patients who completed planned oncologic therapy without developing a cardiac event or asymptomatic worsening of cardiac function.

There is no data about the current proportion of patients with low LVEF who are being treated with HER2 targeted therapy but we estimate to be fewer than 10% based on current clinical recommendations. We consider that if 30% or more of patients will be able to safely receive HER2 targeted therapy despite low LVEF it will be clinically meaningful allowing additional patients to receive this beneficial treatment. Therefore we defined a completion rate of 30% as considered of clinical relevance, where as a completion rate is of 10% is considered similar to the current practice.

A two stage design with a total of 30 patients is used to test if the completion rate is at least 30% versus it is below 10% with 80% power at a significance level of 5%[51,52]. This multistage design has operating properties similar to that of the Simon's two-stage designs but this two stage design offers flexibility in monitoring and interim analysis should the planned schedule be variated. Morevoer it allows an early assessment of statistical evidence for both efficacy and futility, and provides a discordance probability that early trend could be reversed should the trial continue to to enroll all 30 patients. At the first stage, 15 patients will be entered. If one or more patient complete therapy in the absence of cardiac event, then an additional 15 patients will be enrolled in the second stage; If none of the 15 patients in the first stage complete the therapy, we will conclude that the therapy is not feasible in this patient population. The protocol will be amended. The chance for a reversal of the conclusion either for efficacy or for futility based on this decision rule is less than 2% (the discordance probability). At the completion of the second stage, if more than 6 among the 30 patients complete the therapy, we conclude that the therapy is feasible in this patient population, and otherwise it is not.

This statistical design would have 80% probability to consider the therapy as beneficial to this patient population with reduced LVEF if the true completion rate is indeed 30% and 5% probability to consider this therapy as beneficial if the completetion rate is indeed only 10% or below. Exact binomial calculations were used. The intention-to-treat (ITT) population of this trial will be composed of patients who are actually enrolled and received at least one dose of HER2 targeted therapy since they are on study.

CE is defined as any of the following:

- Presence of symptoms attributable to HF (increasing shortness of breath, orthopnea, PND, bilateral ankle swelling) as confirmed by a cardiologist
- Cardiac arrhythmia requiring pharmacological or electrical treatment
- Hospitalization due to a cardiovascular cause, e.g. myocardial infarction
- Sudden cardiac death or death due to myocardial infarct, arrhythmia or HF

We estimate there will be no more than 10% cardiac events by month 6 based on Tarantini et al[53]. With 30 patients we will be able to estimate the cardiac event rate within 13% accuracy at a confidence level of 95%, or estimate it within 11% accuracy at a confidence level of 90%. We will plan to enroll additional 10% of our sample size (N=3) to account for patients that will drop out after enrollment and before receiving any HER2 targeted therapy.

We anticipate to accrue 1 patient per month based on our historical data. If we do not have enough accrual among the two institutions (MWHC and MGUH), we plan to expand the study to other institutions that have the capability of performing echocardiograms with strain analysis. The accrual period is expected to be approximately 30 months. All patients will be followed for a maximum of 12 months. Study duration will be approximately 4 years with additional extended follow up up to 9years.

8.2 Statistical Analysis Plan

The two-stage analysis will follow the design described in 9.1. An exact confidence interval of the completion rate based on binomial calculation will be obtained. We estimate there will be no more than 10% cardiac events.

The outliers and data errors will be checked. Descriptive statistics will be used to characterize the demographic profile of the subjects. Frequency and percentages will be used to summarize categorical variables. Mean (SD) or median (interquartile range) based on the normalization of the data will be used to summarize continuous variables.

The incidence of CEs and asymptomatic worsening of cardiac function during study treatment will be calculated, as well as time to CEs and asymptomatic worsening of cardiac function. Due to the expected small number of subjects with incident CE, descriptive statistics and graphical analyses will be used to assess the difference between those with and without cardiac dysfunction. We will calculate the mean (SD) of the strain, cTn I and hs-cTn T at each time point and graphically assess these measures over time in patients that had an event and that did not have an event. Difference (95% CI) in mean of the strain, cTn I and hs-cTn T between those with and without incident CE event at each time point will be calculated. The mean change in strain, cTn I and hs-cTn T from baseline to each follow-up point will be calculated in those with and without incident CE. Generalized linear model will be utilized for the correlative analysis of completion rate and cardiac events. The longitudinal generalized linear model will be used to assess the serial strain, cTn I and hs-cTn T measures with the clinical outcomes (completion rate and cardiac events). These analyses will most likely be in a pairwise fashion given the moderate sample size.

8.2.1 Interim Analysis:

The study has a two-stage design. There will be an interim analysis after enrollment of 50% of the patients. The interim analysis plan is contained in 9.1 two stage design description.

8.2.2 Safety Analysis:

All subjects who have received treatment will be in the safety analysis. All adverse events will be summarized in terms of frequency, severity and relatedness to the study treatment. At the end of the study, the cumulative incidences of adverse events will be calculated.

8.3 Safety Stopping Rules

Early stopping rules will be incorporated for safety based on cardiac death and symptomatic HF separately. If one cardiac death related to treatment is observed the trial will be terminated. With 30 patients enrolled, if 0 cardiac deaths are observed, the exact binomial 90% CI would be 0 to 9.48%. Thus we feel confident that the true cardiac death rate in this population is less than 10%. The probability of observing at least one cardiac death, for a range of true underlying rates, is summarized in Table 4, indicating for example, that if the true cardiac death rate is as high as 10% then the study has a 0.96 probability of observing one or more when 30 patients are treated, and even if as high as 5% there is a 0.79 probability of having observed one or more.

If we don't observe any cardiac death, then the likelihood that the true rate is 10%, is extremely low.

Table 4. Probability of observing at least one cardiac death, for a range of true underlying event rates, with n=30 patients.

	True Probability of Cardiac Death						
	.01	.05	.1	.2	.3	.4	.5
Probability	0.26	0.79	0.96	1	1	1	1

If 3 patients experience symptoms of HF (increasing shortness of breath, orthopnea, PND, bilateral ankle swelling) and confirmed by the cardiologist, then the trial will be terminated. Adjuvant phase III clinical trials reported an incidence of HF that ranged from 2.1% (BCIRG006[7], only grade 3/4 reported) to 4% (NSABP at 7y[15]). In a retrospective study with patients at a higher cardiovascular risk, a rate of 9% of symptomatic HF was reported[54]. Based on these reports, we will accept a rate of less than 10% for events of symptomatic HF, which represents less than 3 events. With 30 patients enrolled, if 3 symptomatic HF events are observed, the exact binomial 90% CI would be (2.78% to 23.85%). The probability of observing 3 or more symptomatic HF events, for a range of true underlying rates, is summarized in Table 5, indicating for example, that if the true rate is as high as 10% then the study has a 0.59 probability of observing three or more when 30 patients are treated, and if as high as 15% there is a 0.85 probability of having observed three or more.

If the rate of symptomatic HF events in a sample of 30 patients is higher than what was expected from the adjuvant and metastatic setting observed in randomized trials, the likelihood of detecting it is high.

Table 5. Probability of observing at least three symptomatic HF events, for a range of true underlying event rats, with n=30 patients.

	True Probability of Symptomatic HF event						
	.03	.04	.05	.06	.07	.10	.15
Probability	.06	.12	.19	.27	.35	.59	.85

9.0 DATA SAFETY MONITORING COMMITTEE AND CARDIAC REVIEW PANEL

9.1 Data and Safety Monitoring Committee (DSMC)

As this study is an investigator initiated study utilizing FDA approved agents it is considered a moderate risk study which requires real-time monitoring by the PI and study team and semi-annual reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at weekly disease group meetings and on monthly network disease group teleconferences. The investigators shall meet regularly to review toxicities and follow up on results of patients enrolled on the study.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 6 months from the time the first patient is enrolled on the

study. Results of the DSMC meetings will be forwarded to the IRB. E-mail notification from the PI will be sent to the DSMC Chair any time there is a major event or issue with the trial affecting patient safety or conduct of the trial. The DSMC Chair has the discretion to have the study reviewed by the DSMC sooner more frequently than every 6 months based on information received.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. In addition, all SAEs will be submitted to the DSMC at time of submission to IRB and/or Sponsor. Based on SAEs, the IRB retains the authority to close the study to further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC, then the Lombardi Cancer Center Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the Lombardi Cancer Center ADCR will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision.

An external cardiologist expert will be added to the DSMC particularly for this study given its nature.

9.2 Cardiac Review Panel

A cardiac review panel will be formed and quarterly review data on clinical and echocardiographic data. Cardiac data will be reviewed by the cardiac review panel within three weeks in case of any CE.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by Medstar Health Research Institute. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

All oncology clinical research protocols must be submitted to the Clinical Research Committee (CRC) for scientific review before submission to and final approval by the IRB. The initial review includes an assessment of the specific plans for data and safety monitoring, which vary depending on the study type, phase, size, and sponsorship.
For Investigator Initiated studies, the PI will write the data and safety monitoring plan for approval by the CRC. The PI will also perform ongoing monitoring with oversight by the DSMC, which conducts a formal review at established increments. This type of study is considered to have moderate level of risk (investigator initiated study with commercially available agents investigated or use in an unapproved indication). As such, requirements include real-time monitoring by the PI and study team; quarterly reviews by the DSMC and reviews by an independent DSMC every 6 months.

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Research Office.

A copy of the official IRB approval letter for the protocol and informed consent

- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

Before the start of this study, the following documents must be on file with Genentech or a Genentech representative:

- Original U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the 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 Principal Investigator
- Written documentation of IRB approval of protocol and informed consent document
- A copy of the IRB-approved informed consent document
- A signed Clinical Research Agreement

10.4 Registration and Enrollment Procedures

All participants must be registered and enrolled through the Oncology Research office at the Washington Cancer Institute. Participating sites should fax or email (redacted if from entity outside MedStar Georgetown Cancer Network) completed enrollment case report forms (CRFs), together with all source documentation used to support eligibility, ordered per the CRF. Please send these during business hours Monday - Friday between 8am and 4:30pm (EST), the latest at the moment that patient is signing informed consent. In the event that there is a time constraint, please notify the research office at (202)877-8839 to discuss possibility of expediting the process.

10.5 Data Management and Monitoring

Data management and monitoring will be performed by MHRI.

10.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

10.6.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator and the IRB.

10.6.3 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Minor deviations should be summarized and reported to the IRB at the time of continuing review. Major deviations should be summarized and reported to the Regulatory Affairs Coordinator who will submit to the IRB as soon as possible, but not more than 10 calendar days after acquiring information reasonably suggesting that a reportable (major) deviation has occurred.

Protocol Violations: Violations should be reported by study personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

10.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all

case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.10 Study Medication Accountability

HER2 targeted therapies will be provided by Genentech. The recipient (MHWC, MGUH or MSKCC) will acknowledge receipt of the drug by returning the INDRR-1 form indicating shipment content and condition. Damaged supplies will be replaced. All study drug will be stored at 2-8°C (36-46°F) upon receipt. Vials should not be used beyond the expiration date provided by Genentech.

Accurate records of all study drug receipt, disposition and return should be maintained by using the institution's drug inventory log or the NCI drug accountability log.

- Separate logs will be maintained at each site for each of the three study drugs provided.
- Study drug supplies are not patient specific.
- Pertuzumab and ado-trastuzumab vials are for single use only with unused portions discarded immediately. Dose preparation is per institutional standard.
- Trastuzumab, when reconstituted according to package instructions with supplied diluent (bacteriostatic water for injection), will be used as a multi-dose vial and may be used to prepare doses for more than one patient. Upon reconstitution, the solution will be stored at 2-8°C (36-46°F) and used within 28 days. Any reconstituted solution remaining after 28 days will be discarded immediately. If trastuzumab must be reconstituted with sterile water for injection (no preservative), the vials will be considered single use only with unused portions discarded immediately. Dose preparation is per institutional standard. To maintain accurate drug accountability of partial vials, the study site will record trastuzumab inventory in milligrams.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

10.11 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study.

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13. LIST OF APPENDICES

A – New York Heart Association Classification

B - Stages of Development of HF and recommended therapy by stage

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D – Framingham criteria for the definition of Congestive Heart Failure (CHF)

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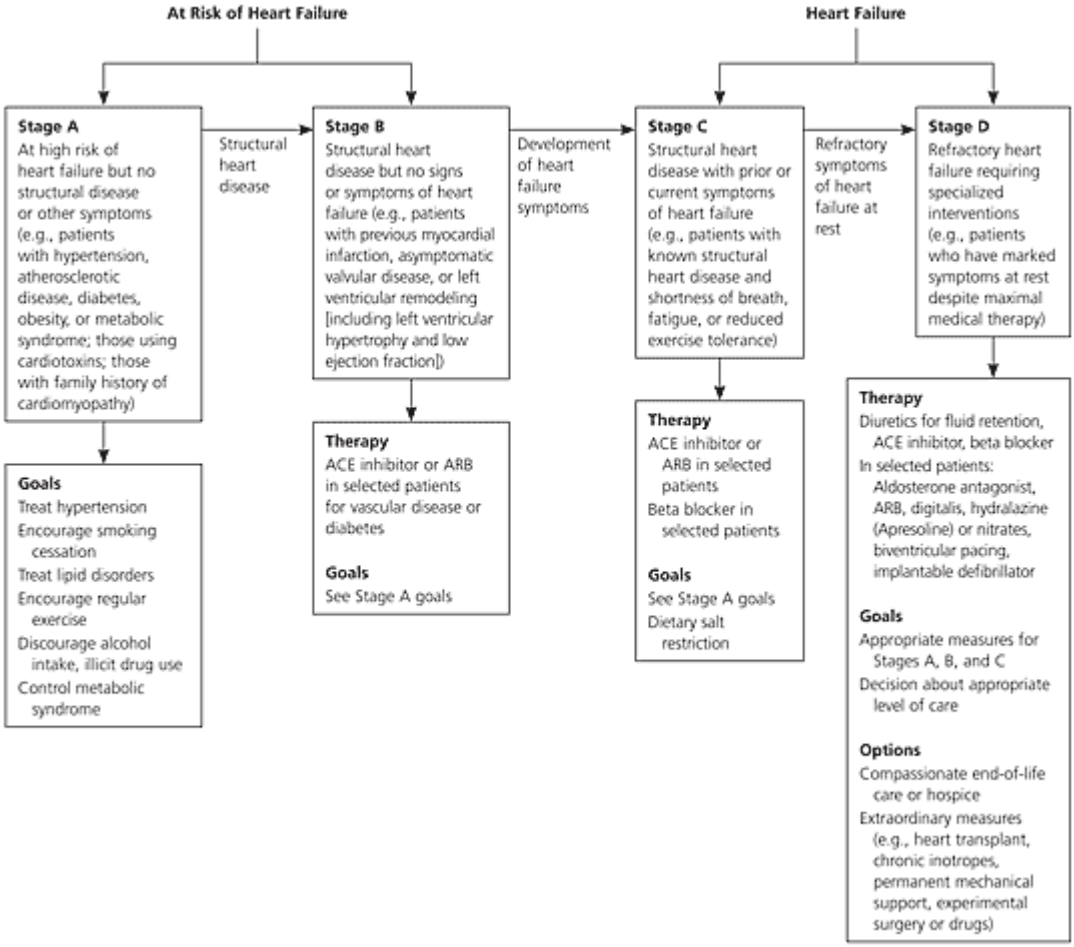
BB- Flow sheet for Patient Recruitment

Appendix A: New York Health Association Classification

Functional Capacity
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

<u>Appendix B:</u>Stages of Development of HF and recommended therapy by stage

Figure 4. Recommended therapy for patients with heart failure, by disease stage. (ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker)



Adapted from Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2005;112:1830

Appendix C.: ECOG (Eastern Cooperative Oncology Group) PERFORMANCE STATUS*

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

Appendix D.: Framingham criteria for the definition of Congestive Heart Failure (CHF)

Diagnosis of CHF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

Major criteria:

- Paroxysmal nocturnal dyspnea
- Neck vein distention
- Rales
- Radiographic cardiomegaly (increasing heart size on chest radiography)
- Acute pulmonary edema
- S3 gallop
- Increased central venous pressure (>16 cm H2O at right atrium)
- Hepatojugular reflux
- Weight loss >4.5 kg in 5 days in response to treatment

Minor criteria:

- Bilateral ankle edema
- Nocturnal cough
- Dyspnea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Decrease in vital capacity by one third from maximum recorded
- Tachycardia (heart rate>120 beats/min.)

Minor criteria are acceptable only if they can not be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome).

The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure.

McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971 Dec 23;285(26):1441-6.

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix E: Cardiac Questionnaire (Initial Visit)

Medical History:

1. Have you been diagnosed with diabetes? ☐No ☐Yes
   a. If yes, are you taking insulin? ☐No ☐Yes
2. Have you been diagnosed with high blood pressure? ☐No ☐Yes
3. Have you been diagnosed with high cholesterol or other lipid problem? ☐No ☐ Yes
4. Have you ever had any of the following:

a. Heart attack	☐No	☐Yes	Year _
b. Angioplasty (balloon angioplasty, stent procedure)	☐No	☐Yes	Year_____
c. Coronary artery bypass grafting (CABG)	☐No	☐Yes	Year_____
d. Heart surgery for another reason	☐No	☐Yes	Year_____
e. Angina (chest pain)	☐No	☐Yes	Year____
f. Heart Murmur	☐No	☐Yes	Year____
g. Heart failure	☐No	☐Yes	Year____
h. Needed a pacemaker or defibrillator (ICD)	☐No	☐Yes	Year____
i. Peripheral arterial disease	☐No	☐Yes	Year____
j. Surgery for circulation problem in the legs	☐No	☐Yes	Year____
k. Carotid artery disease	☐No	☐Yes	Year____
l. Transient ischemic attack (TIA)	☐No	☐Yes	Year____
m. Stroke	☐No	☐Yes	Year____
n. Rheumatic fever	☐No	☐Yes	Year____
o. Rheumatologic disease such as systemic lupus erythematosus, scleroderma or rheumatoid arthritis	☐No	☐Yes	Year____
p. Thyroid disease	☐No	☐Yes	Year____
q. Pheochromocytoma	☐No	☐Yes	Year____

5. Do you have congenital heart disease? ☐No ☐Yes
   a. If known, what congenital heart disease do you have?

Appendix E: Cardiac Questionnaire (pg2)

6. Do you have history of weak muscles *myopathy"? ☐No ☐Yes

7. Do you have history of sleep-disordered breathing (sleep apnea)? ☐No ☐Yes
   a. If yes, are you using CPAP (continuous positive pressure treatment) at night?
      ☐No ☐Yes
8. Other than your ongoing cancer treatment, do you have prior history of receiving chemotherapy? ☐No ☐Yes Year ___

9. Other than your ongoing cancer treatment, do you have prior history of receiving radiation therapy? ☐No ☐Yes Year___

10. Are you HIV positive? ☐No ☐Yes

Family History

1. Has anyone in your immediate family (your blood-related parent, brother, sister or child) been diagnosed with any of the following:

   a. Premature cardiovascular disease, either heart attack, coronary artery bypass surgery or stroke before age 55 (male relatives) or before age 65 (female relatives)?
      ☐No ☐Yes

   b. Heart failure? ☐No ☐Yes

   c. Unexplained heart muscle weakness? ☐No ☐Yes

   d. Sudden cardiac death? ☐No ☐Yes

   e. Need for pacemaker? ☐No ☐Yes

   Please write down who from your relatives had the event and his/her/their age at the time of the event, if known:

   _____
   _____
   _____
   _____
   _____
   _____

Habits

1. Are you a current smoker? ☐No ☐Yes
   (Answer "Yes" if you have smoked cigarettes within the past month)

2. Have you ever smoked? ☐No ☐Yes
   a. If Yes, how many years ago did you stop smoking? _____

Appendix E: Cardiac Questionnaire (pg3)

b. How many packs per day? _____
c. For how many years? _____

3. Have you ever used any of the following substances: cocaine, amphetamines or fen-phen (fenfluramine, phentermine, dexfenfluramine)? ☐ No ☐ Yes
   a. If Yes, which substances? _____
   b. How many years ago did you stop using them? _____
   c. For how many years did you use these substances? _____
4. Do you drink more than one drink a day? ☐ No ☐ Yes
   (One drink is equivalent of 5 fluid ounces of wine, 12 fluid ounces of beer, or 1.5 fluid ounces of 80-proof spirits such as whisky or vodka)
5. Have you ever drunk more than one drink a day over a period of week or longer? ☐ No ☐ Yes
   a. If Yes, how many years ago have you stopped drinking? _____
   b. For how many years were you drinking more than a drink per day? _____

Please list your medications:

_____
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Allergies:

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_____
_____
_____

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix F: Cardiac Visit CRF (to be filled by investigator)

Cardiology Visit #:_____ Date: _____

Medications:

Carvedilol Y☐ N☐ Dose_____ Side effects Y☐ N☐ Describe_____

Ramipril Y☐ N☐ Dose_____ Side effects Y☐N ☐ Describe_____

Statin Y☐ N☐ Dose _____Side effects Y☐N ☐ Describe_____

Other Medications:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Presence of HF symptoms

Paroxysmal nocturnal dyspnea YES ☐ NO ☐

Orthopnea YES ☐ NO ☐ If yes, how many pillows does the patient sleep on ___

Nocturnal cough YES ☐ NO ☐

Shortness of breath with exertion YES ☐ NO ☐

Shortness of breath when going up one flight of stairs without stopping? (ordinary exertion) YES ☐ NO ☐

Shortness of breath with walking around your home and activities of daily living? YES ☐ NO ☐

Shortness of breath at rest YES ☐ NO ☐

Appendix F: Cardiac Visit CRF (pg2)

Indicate NYHA class _____

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Physical Exam
Height:
Weight (measured):
Blood pressure (sitting):
Heart rate:
Oxygen saturation:
Jugular venous distention: YES ☐ NO ☐

If yes, estimated JVP (cm H2O) above the right atrium:_____

Crackles or rales on lung auscultation: YES ☐ NO ☐

Pleural effusion: YES ☐ NO ☐

Hepatojugular reflux: YES ☐ NO ☐

Pulmonary edema: YES ☐ NO ☐

Presence of S3 gallop: YES ☐ NO ☐

Hepatomegaly: YES ☐ NO ☐

Bilateral ankle edema: YES ☐ NO ☐

(If Yes, describe extent using the scale: 1+ minimal edema, 2+ mild edema, 3+ moderate edema, 4+ significant edema) _____

Additional tests ordered based on findings:

- Chest X Ray: Ordered ☐ Not-ordered ☐ Result:_____
- EKG: Ordered ☐ Not-ordered ☐ Result:_____
- BNP: Ordered ☐ Not-ordered ☐ Result:_____ (baseline BNP)_____
- CMP: Ordered ☐ Not ordered ☐ Result:_____ (baseline creatinine) ____

Appendix F: Cardiac Visit CRF (pg3)

Other tests ordered (please specify):

_____
_____
_____
_____
_____

Page: 3 of 3	Investigator's Signature:	Date

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix G: Summary of Initial Cardiac Assessment CRF (to be filled by investigator)

2D echocardiogram baseline LVEF result: _____
Presence of symptoms and signs of HF: YES ☐ NO ☐
ECG result:
- ☐ Normal ECG
- ☐ ECG suggestive of ischemia
- ☐ ECG with evidence of atrial fibrillation
- ☐ Other: _____

Stress Echocardiogram done: YES ☐ NO ☐
If Yes, Stress Echocardiogram Result:
ECG evidence of ischemia: Yes/ No/ Equivocal
Wall motion abnormalities suggestive of ischemia: Yes/No/ Equivocal

Laboratory test results:
- Troponin I _____
- BNP _____
- Creatinine _____

Based on the initial evaluation ischemia is suspected. Patient needs further testing.
YES ☐ NO ☐
- Test of choice ordered:
- Date of test:
- Result
- Ischemia and other reversible causes of cardiomyopathy still suspected: YES ☐ NO ☐

6 minute walk test:
Meters walked _____
BP, HR and O2 sats at the start and at the end _____
Presence of symptoms _____

Lipid profile result: TC _____ HDL _____ TG _____ LDL_____
LDL goal: _____
Patient meets LDL goal. YES ☐ NO ☐
Start or increase dose of statin is needed to meet goal YES ☐ NO ☐

Appendix G: Summary of Initial Cardiac Assessment CRF (pg2)

If, yes, indicate statin and the dose prescribed: _____

Patient has contraindications to start or increase the dose of beta-blocker: YES☐ NO☐

Patient has contraindications to start or increase the dose of ACE-inhibitor: YES☐NO☐

Page: 2 of 2	Investigator's Signature:	Date

Appendix H: Echocardiographic Acquisition Protocol

Echocardiography will be used to make assessments of left ventricular (LV) and left atrial dimensions and volumes, LV wall thickness and LV mass, LV ejection fraction (LVEF), as well as LV myocardial strain measured by speckle-tracking echocardiography. All study echocardiograms will be performed at clinical echocardiographic laboratories and sent to the MHRI Core lab for the study analysis and interpretation.

Equipment
Contemporary echocardiographic equipment (Philips, Andover MA, iE33 or newer) with strain assessment capacity will be used in this protocol. All images will be transferred (digitally or on a DVD) to the Core lab and securely stored.

The acquisition Transthoracic Echo (TTE) protocol listed below may be further modified to be compatible with different echocardiographic machines and operating systems.

Transthoracic Echo (TTE) Protocol:

- Long Axis
  - Parasternal Long Axis View
  - 2-D measurements
    - LVIDd
    - LVIDs
  - 'Zoom' in on the LVOT for diameter measurement
  - Color Flow of Mitral and Aortic Valves

- Right ventricular inflow view
  - 2D of RV inflow
  - Color and spectral Doppler of the tricuspid regurgitation

- Short Axis – Aortic Level
  - 2-D imaging of the aortic valve
    - 'Zoom' in on the aortic valve
    - Color Doppler of aortic valve
  - 2-D imaging of the tricuspid valve
    - Color Doppler of valve
    - Spectral Doppler of TR
  - 2-D imaging of the pulmonic valve
    - Color Doppler of pulmonic valve

- Short Axis – Mitral level
  - 2-D imaging of the Mitral Valve
  - Color Doppler of the Mitral Valve

- Short Axis – Papillary and LV apex level
  - 2-D imaging of the mid-papillary level, acquiring images at both the papillary level and the apical level

Appendix H.: Echocardiographic Acquisition Protocol (pg2)

- Apical 4 Chamber
  - 2-D image of the LV for LVEF measurements (assure that all LV walls remain within the field during all part of the cardiac cycle). Optimize picture to visualize the endocardial border.

  - Mitral Valve
    - 2D image of valve
    - Color imaging of valve
    - Pulsed Doppler at the leaflet tips

  - Tricuspid Valve
    - 2D image of tricuspid valve
    - Color Flow Imaging
    - CW of tricuspid regurgitation

- Apical 5 Chamber
  - 2-D image of aortic valve
    - Color Doppler of aortic valve
    - Pulsed Doppler of LVOT (just proximal to the aortic valve)
  - Continuous wave Doppler through the aortic valve

- Apical 2 Chamber
  - 2-D image of the entire LV for LVEF measurements
  - 2-D imaging of the mitral valve
  - Color Doppler of mitral valve

- Apical 3 Chamber (Apical Long Axis)
  - 2-D imaging of LV and valves
  - Color Doppler of mitral valve
  - Color Doppler of aortic valve

- Subcostal View
  - 2D image of LV and RV
  - 2D image of IVC

- **3D 4 beat Full Volume view of the LV**

Strain Protocol

- Obtain the Apical 4 Chamber (AP4) View
- Adjust Depth so that the LV fills the screen (with the MV annulus visible) and center the LV in the sector
- Obtain the Apical 4 chamber (AP4) with focus on the RV
- Center RV in the middle of the screen
- Obtain the Aortic Valve Closure Time (AVC time)
- Obtain the Apical 2 Chamber (AP2) View
- Obtain the Apical 3 Chamber (AP3) View
- Obtain the Parasternal Short Axis View at the mid papillary level (SAX M)

Appendix H.: Echocardiographic Acquisition Protocol (pg3)

Contrast Use Protocol (for technically difficult Echocardiograms)
Contrast use for enhancing endocardial borders in patients with technically difficult images will be indicated if endocardial border cannot be visualized in two consecutive segments. Contrast will be used only **after the strain protocol is completed** as speckle tracking cannot be reliably performed post administration of echocardiographic contrast. Intravenous access will be obtained and contrast (Definity, Bristol Myers Squibs or Optison, GE Healthcare) will be administered according to manufacturer's protocol. Two chamber and four-chamber apical views (AP2 and AP4) will be obtained following the administration of the contrast for the calculation of LV volumes and EF.

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix I. : Core Lab Case Report Form

Safe Heart

Echo Core Lab Case Report Form

Patient ID _____ Interval: _____

Procedure Date: _ _ _____
dd-mmm-yyyy

If Other _____

Baseline EF ___ %

2D LV and LA Measurements

☐ NE LVIDd ____ cm
☐ NE LVIDs ____ cm
☐ NE IVSd ____ cm
☐ NE LVPWd ____ cm
☐ NE LA Volume ____ ml

LV Ejection Fraction

2D Measurements

☐ NE LVEDV ___ ml
☐ NE LVESV ___ ml
☐ NE LVEF ___ %

3D Measurements

☐ NE LVEDV 3D ___ ml
☐ NE LVESV 3D ___ ml
☐ NE LVEF 3D ___ %

☐ NE Visual EF____ %

Diastolic Function Assessment

☐ NE MV E Wave ____ cm/sec
☐ NE MV A Wave ____ cm/sec
☐ NE MV E/A ____
☐ NE Septal E' ____ cm/sec
☐ NE Septal E/E' ____
☐ NE Diastolic Function _____

Longitudinal Strain (Q Lab)

☐ NE AP4 ___ %
☐ NE AP2 ___ %
☐ NE AP3 ___ %
☐ NE Global ___ %

Page: 1 of 1	Investigator's Signature:	Date

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix J: Eligibility Checklist - Inclusion Criteria (prior to screening procedures)

	Yes	No
Female or male patient diagnosed with stage I-IV breast cancer **Source Document + Date: _____**		
HER2 positive breast cancer, defined by IHC immunohistochemical staining for HER2 protein of 3+ intensity and/or amplification of the HER2 gene on fluorescence in situ hybridization (FISH) ≥ 2.0 on breast specimen or biopsy of a metastatic site **IHC and FISH report date: _____ Score IHC/FISH:_____**		
LVEF < 50% and ≥ 40% (initial clinical report) documented in cardiac imaging done within the last 30 days **Date of Last Echocardiogram:_____**		
HER2 therapy naïve or currently receiving non-lapatinib HER2 targeted therapy **Source Document + Date last treatment:** **_____**		
Patient receiving or planning to receive trastuzumab, trastuzumab with pertuzumab or T-DM1- ado-trastuzumab emtansine, for at least 3 months, alone or in combination with other systemic treatment or radiation **HER2 treatment plan (drug): _____**		
Age ≥ 18 years **DOB: _____**		
Patient is willing and able to comply with protocol required assessments and procedures		

Appendix J: Eligibility Checklist (pg2)
Eligibility Checklist: Exclusion Criteria (prior to screening procedures)

	Yes	No
Previous hospitalization due to documented heart failure in the last 12 months **Source document + Date: _____**		
Current signs or symptoms of HF or ischemia **Source Document + Date: _____**		
History of arrhythmia requiring pharmacological or electrical treatment **Source Document + Date: _____**		
Concomitant use of anthracyclines or use of anthracyclines in the last 50 days **Last date of anthracycline use: _____**		
History of significant neurologic or psychiatric disorders including psychotic disorders or dementia that would prohibit the understanding and giving of informed consent.		

ELIGIBILITY DETERMINATION:

Is patient eligible based on above inclusion and exclusion criteria to sign informed consent?

Yes □ No □

_____ _____

(Physician Verification) *(Date)*

_____ _____

(Enrolling Coordinator Signature) *(Date)*

Note: Final eligibility will be determined after screening procedures are performed. Participants who do not meet screening criteria will be screen failures and will not be enrolled

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix K: Eligibility Procedures for Enrollment

Inclusion Criteria

	Yes	No
Confirmed baseline LVEF < 50% and ≥ 40% (by Core Lab)		

Exclusion Criteria

	Yes	No
Presence of treatable and reversible HF cause as assessed by study cardiologist		
Presence of ischemia (as assessed by study cardiologist)		
Pregnant or lactating patients. (Patients of childbearing potential must implement contraceptive measures during study treatment and for 7 months after the last dose of the study drug and must have negative urine or serum pregnancy test within 21 days after signing initial consent). Urine/Serum pregnancy test date: _____ Result: Positive or negative		

FINAL ELIGIBILITY DETERMINATION:

Is patient eligible based on above screening criteria for study enrollment?
Yes □ No □

_____ _____
(Cardiologist Verification) *(Date)*

_____ _____
(Enrolling Coordinator Signature) (Date)

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix L: Study Requirements (to be filled by research coordinator):

Pre-enrollment Evaluation:

- ☐ Informed Consent
- ☐ Complete history and physical examination
- ☐ Cardiac questionnaire
- ☐ Study echocardiogram read by the Core lab
- ☐ Pregnancy test
- ☐ Exercise stress testing (if deemed appropriate by study cardiologist)
- ☐ EKG
- ☐ Troponin I, hs-tropo, research sample

Initial cardiac assessment: (Day 1 +/- 7 days)

- ☐ hs-cTnT, research blood sample
- ☐ 6 minute walk test
- ☐ Initiation of cardiac medications
- ☐ Provide Blood pressure cuff and BP diary
- ☐ Provide Education on exercise and low salt diet

Follow up cardiac assessment #1:

- ☐ Complete history and physical examination
- ☐ Cardiac questionnaire
- ☐ Troponin I, hs-cTnT, research blood sample
- ☐ Study echocardiogram read by the Core lab
- ☐ Review BP diary

Follow up cardiac assessment #2:

- ☐ Complete history and physical examination
- ☐ Cardiac questionnaire
- ☐ Troponin I, hs-cTnT, research blood sample
- ☐ Study echocardiogram read by the Core lab
- ☐ Review BP diary

Appendix L: Study Requirements (pg2)

Follow up cardiac assessment #3:

- ☐ Complete history and physical examination
- ☐ Cardiac questionnaire
- ☐ Troponin I, hs-cTnT, research blood sample
- ☐ Study echocardiogram read by the Core lab
- ☐ Review BP diary

Follow up cardiac assessment #4:

- ☐ Complete history and physical examination
- ☐ Cardiac questionnaire
- ☐ Troponin I, hs-cTnT, research blood sample
- ☐ Study echocardiogram read by the Core lab
- ☐ Review BP diary

Follow up cardiac assessment #5:

- ☐ Complete history and physical examination
- ☐ Cardiac questionnaire
- ☐ Troponin I, hs-cTnT, research blood sample
- ☐ Study echocardiogram read by the Core lab
- ☐ Review BP diary

Follow up cardiac assessment #6:

- ☐ Complete history and physical examination
- ☐ Cardiac questionnaire
- ☐ Troponin I, hs-cTnT, research blood sample
- ☐ Study echocardiogram read by the Core lab
- ☐ Review BP diary

Off-Study/Post-Study evaluation (within 30 days of the patient's end of treatment determination):

- ☐ Complete history and physical examination
- ☐ Troponin, hs-cTnT, research blood sample
- ☐ Study echocardiogram read by the Core lab

Follow up visit 6 months after being off study:

- ☐ Complete history and physical examination
- ☐ Study echocardiogram read by the Core lab
- ☐ Troponin I, hs-cTnT, research blood sample

MedStar Washington Hospital Center
Washington Cancer Institute

Case Report Form
Washington Cancer Institute
Clinical Research

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Demographics

Sex: ☐ Male ☐ Female

Date of Birth: ___/___/_____ (MM/DD/YYYY)

Age: _____

Enrollment date ___/___/_____ (MM/DD/YYYY)

Race: ☐ White ☐ Black or African American ☐ Asian ☐ Native Hawaiian/Pacific Islander ☐ American Indian or Alaskan Native ☐ Other ☐ More than one

Ethnicity: ☐ Hispanic or Latino ☐ Non-Hispanic ☐ Unknown

Registration Institution: _____

Zip Code: _____

Disease Information

Stage at diagnosis: ☐ Stage I ☐ Stage II ☐ Stage III ☐ Stage IV

Date of Original Diagnosis: ___/___/_____ (MM/DD/ YYYY)

Indication for treatment: ☐ Adjuvant ☐ Neoadjuvant ☐ Locally advanced unresectable disease ☐ Metastatic

Planned oncologic therapy: ☐ _____ months (adjuvant or neoadjuvant setting)

☐ until disease progression (locally advanced or metastatic disease)

ECOG Performance Status: ☐ 0 ☐ 1

Informed Conset

Date Informed Consent: ___/___/_____ (MM/DD/YYYY)

Page:	Investigator's Signature:	Date
1 of 1		

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix N: Prior Hormonal Therapy & Chemotherapy

Regimen Number	Date of First Dose	Date of Last Dose	Agents	Dose & Schedule	Cycle Length	Number of cycles
_____ ☐ Neoadj ☐ Adj ☐ Met	__/__/____ (MM/DD/YYYY)	__/__/____ (MM/DD/YYYY)	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	____

Reason for Discontinuation:

- ☐ Completed Treatment
- ☐ Progression
- ☐ Toxicity/Side Effects/Complications
- ☐ Change of Therapy (despite not meeting criteria for progressive disease nor experiencing unacceptable tox.)
- ☐ Complete Response
- ☐ Maximum Benefit (for Neoadjuvant or adjuvant therapy)
- ☐ Other: _____

Toxicities:

Regimen Number	Date of First Dose	Date of Last Dose	Agents	Dose & Schedule	Cycle Length	Number of cycles
_____ ☐ Neoadj ☐ Adj ☐ Met	__/__/____ (MM/DD/YYYY)	__/__/____ (MM/DD/YYYY)	_____ _____ _____ _____	_____ _____ _____ _____	_____ _____ _____ _____	____

Reason for Discontinuation:

- ☐ Completed Treatment
- ☐ Progression
- ☐ Toxicity/Side Effects/Complications
- ☐ Change of Therapy (despite not meeting criteria for progressive disease nor experiencing unacceptable tox.)
- ☐ Complete Response
- ☐ Maximum Benefit (for Neoadjuvant or adjuvant therapy)
- ☐ Other: _____

Toxicities:

Note: if patient received > 2 prior regimens, this form can be copied and filled out again.

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix O: Prior Radiation Treatment

Has patient received prior radiation treatment: ☐ Yes ☐ No

Prior Radiation				
No.	**Total dose**	**First Dose**	**Last Dose**	**Site (Laterality, areas involved)**
1	_____ Gy	__/__/____	__/__/____	
2	_____ Gy	__/__/____	__/__/____	
3	_____ Gy	__/__/____	__/__/____	
4	_____ Gy	__/__/____	__/__/____	
5	_____ Gy	__/__/____	__/__/____	

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix P: Prior Breast Surgical History:

Has patient received prior surgical treatment: ☐ Yes ☐ No

Surgical History		
Type of Surgery	Date (Year)	Comments:

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix Q: Laboratory data (to be filled by research coordinator)

	Unit	Initial Visit __/__/__	Cycle #1 __/__/__	Cycle #2 __/__/__	Cycle #3 __/__/_	Cycle #4 __/__/_	Cycle #5 __/__/_	Cycle #6 __/__/_	Off Study __/__/__	F/u at 6m __/__/__
CMP										
Glucose	mg/dL									
BUN	mg/dL									
Creatinine	mg/dL									
Sodium	Mmol/l									
Potassium	Mmol/l									
Chloride	Mmol/l									
Calcium	mg/dL									
Magnesium	mg/dL									
Phosphorus	mg/dL									
CO2	Mmol/l									
Alk. Phos	Lu/l									
AST	Lu/l									
ALT	Lu/l									
Protein Ttl	Gm/dL									
Albumin	Gm/dL									
Total Bili	Gm/dL									
Cardiac work-up										
Troponin I	Ng/mL									

Appendix Q: Laboratory data (pg 2)

BNP	ng/L									
TSH/fT4	mU/l/ng/dL									
Hemoglobin A1c	%									
Serum free ferritin	ng/mL									
Total Cholesterol	Mg/dL									
LDL/HDL Cholesterol	Mg/dL									
Triglycerides	Mg/dL									
CBC										
BWC	K/uL									
RBC	M/uL									
HGB	Gm/dL									
HCT	%									
Platelet count	K/mm^3									
Neutrophils Abs	K/uL									
Lymphocyte Abs	K/uL									
Monocyte Abs	K/uL									
Eosinophil	K/uL									
Basophil Abs	K/uL									

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix R: Adverse Events

SAFE-HEaRt: A pilot study assessing the cardiac **SAFE**ty of **HE**R2 targeted therapy in p**a**tients with HE**R**2 posi**t**ive breast cancer and reduced left ventricular function

Adverse Events:

Adverse Event Description	Onset Date mm/dd/yyyy	Resolution Date mm/dd/yyyy	AdEERs Filed (Y/N)	Grade*	Attribution	Dose Limiting Toxicity (Y/N)	Action	Therapy	Outcome	Comments**

*Refer to NCI Common Toxicity Grading Criteria.

** Please provide a comment about the likely attribution of the adverse event, if not definitely attributable to the study drug

Attribution:	**Action:**	**Outcome:**	**Therapy:**
1 = Unrelated	1 = None	1 = Recovered	1 = None
2 = Unlikely	2 = Dose Reduced	2 = Still under treatment/ observation	2 = Symptomatic
3 = Possible	3 = Regimen Interrupted	3 = Alive with sequelae	3 = Supportive
4 = Probable	4 = Therapy Discontinued	4 = Died	4 = Vigorously Supportive
5 = Definite			

MedStar Washington Hospital Center
Washington Cancer Institute

Case Report Form
Washington Cancer Institute
Clinical Research

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix S: Blood Pressure Daily Log

Date (MM/DD/YY)	Did you take your medicine	Blood pressure	Symptoms (List the number showing the severity of the symptoms) 0= None 1=Mild 2=Moderate 3=Severe				
			None today	Shortness of breath	Tiredness	Fainting Dizziness	Any others (please specify)
__/__/__	Y☐ N☐	___/___	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________
__/__/__	Y☐ N☐	___/___	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________
__/__/__	Y☐ N☐	___/___	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________
__/__/__	Y☐ N☐	___/___	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________
__/__/__	Y☐ N☐	___/__	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________
__/__/__	Y☐ N☐	___/__	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________
__/__/__	Y☐ N☐	___/__	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________
__/__/__	Y☐ N☐	___/__	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________
__/__/__	Y☐ N☐	___/__	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________
__/__/__	Y☐ N☐	___/__	Y☐ N☐	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	Y☐ N☐ ___ (0-3)	________ ________

Page: 1 of 1	Investigator's Signature:	Date

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix T: Off Study Summary

Date of Off Study: ___/___/_____
(MM/DD/YYYY)

Off Study Summary:

Reason for off Study: *(Choose appropriate box)*

- ☐ *Lost to Follow-up (Date last Known Alive: ___/___/_____ (MM/DD/YYYY)*
- ☐ *Completion of planned course of HER2 Targeted Therapy*
- ☐ *Cardiac events that preclude further HER2 directed treatment*
- ☐ *Patient voluntarily withdraws from treatment (follow-up permitted)*
- ☐ *Patient is unable to comply with protocol requirements*
- ☐ *Patient withdraws consent (termination of treatment and follow-up)*
- ☐ *HER2 therapy on hold for > 9 weeks due to non-cardiac causes*
- ☐ *Disease Progression with change in treatment regimen*
- ☐ *End of Study*
- ☐ *Treating physician decision*
- ☐ *Patient becomes preganant*
- ☐ *Protocol Violation*

During treatment, and documented:

	Dates *(MM/DD/YYYY)*
☐ *Cardiac event criteria*	___/___/____
☐ *Asymptomatic worsening of cardiac function*	___/___/____
☐ *Symptoms of HF*	___/___/____
☐ *Cardiac arrhythmia requiring pharmacological or electrical treatment*	___/___/____
☐ *Hospitalization due to a cardiac cause*	___/___/____
☐ *Sudden cardiac death or death due to MI, arrhythmia or HF*	___/___/____

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix U: Death Summary

Date of Last Follow up:
__/__/____
(MM/DD/YYYY)

Date of death:

List any further treatments:

_____ _____
_____ _____
_____ _____

Has subject developed a new primary cancer? ☐ Yes ☐ No
If Yes, Diagnosis: _____ Date: __/__/____
(MM/DD/YYYY)

Cause of Death: (Check appropriate box)

☐ Malignant Disease ☐ Toxicity from Protocol Treatment ☐ Infection

☐ Other: _____

Autopsy? ☐ Yes ☐ No

Cause of Death at Autopsy: (Check appropriate box)

☐ Malignant Disease ☐ Toxicity from Protocol Treatment ☐ Infection

☐ Other: _____

Site of Disease at Autopsy:

_____ _____
_____ _____

NOTE: If patient dies within 30 days of off-study, an SAE must be filed.
Assess for any unresolved toxicities at that time.

Page:	Investigator's Signature:	Date
1 of 1		

Appendix V: Exercise and chronic disease (info for patients)

CardioSmart
American College of Cardiology

www.CardioSmart.org

Exercise: Being Active When You Have a Chronic Disease

Exercise is good for everyone. But if you have a chronic disease, the benefits of exercise will be even greater for you than for most people. Whether your goal is to live a more active life, to be more independent, to take fewer medicines, or just to feel better, exercise should be a regular part of your life.

A safe level of exercise will depend on your health and the stage of your disease. But even a small amount of exercise is better than none.

What are the benefits of regular exercise?

- It reduces cholesterol.
- It lowers your blood pressure.
- It makes your heart stronger and healthier so it can send more blood and oxygen all through your body.
- It helps you control your weight.
- It builds muscle strength so you can be more active.
- It may reduce your need for medicines. This can lower the cost of caring for your disease.
- It reduces stress and lifts your mood.
- If you have diabetes, exercise can help you control your blood sugar.

People with chronic diseases often find that exercise reduces their symptoms. It may also help them avoid depression, which is common in those with long-term diseases.

Should you see your doctor before you start exercising?

Yes. Before you start any exercise program, see your doctor for a complete physical exam. He or she may want to run some tests. These can help your doctor know how often and how long you should exercise.

You may need to check your heart rate when you exercise. Your doctor can tell you how fast your heart rate should be during exercise.

There is an easy way to know if your heart rate is at the right level during exercise:

- If you cannot talk and exercise at the same time, you are working too hard.
- If you can talk while you exercise, you are doing fine.
- If you can sing while you exercise, you may not be working hard enough.

What types of exercise are best?

The three basic types of exercise are:

- Stretching. Stretching is good for everyone. It can help you be more flexible and prevent injuries.
- Strength training. Lifting light weights can help tone your muscles. Your doctor can advise you about which types of strength

training you can do and which types you should avoid.

- Activities that raise your heart rate. These are called aerobic exercise. Most people can do some form of aerobic exercise.

Of the three types, aerobic exercise has the most benefits. Your doctor can suggest a safe level of aerobic exercise for you. Moderate-intensity aerobic exercise is helpful and safe for most people. Some examples include:

- Brisk walking, hiking, and stair climbing.
- Jogging, bicycling, rowing, and swimming.
- Sports such as tennis, soccer, and basketball.

Low-intensity aerobic exercise has a lower risk of injury. This is recommended for people with many types of health problems. Some low-intensity activities are:

- Walking.
- Gardening and other yard work.
- Housework.
- Dancing.
- Water aerobics.

Any exercise program should include:

- A warm-up (such as a short walk) to get your muscles ready to work. And then do some stretches.
- Some aerobic activity.
- A cool-down period to let your body recover.

How can you exercise safely?

- Start out slowly. Over time, you will become able to do more.
- Watch for signs that you are doing too much. You are pushing yourself too hard if you cannot talk while you are exercising. If you become short of breath, nauseated, or dizzy, or if you have chest pain, stop, sit down, and rest. If these symptoms do not go away, call your doctor.
- If you feel "wiped out" the day after you exercise, exercise more slowly or for a shorter time until you can work up to a better pace.
- If your medicines change, ask your doctor whether you should continue your exercise program. New medicines can affect how you feel when you exercise.
- Adjust your exercise program if it is interrupted for more than a couple of days. Gradually increase to your regular activity level.
- Talk to your doctor or a certified fitness professional about your progress. He or she may be able to help if you have problems.

Take these safety measures:

- Do not exercise outdoors when it is very cold, very hot, or very humid. When the weather is bad, exercise indoors or walk at a mall.
- Learn about the risks of any new exercise you start. Use proper form. Take lessons if you need to.
- Avoid holding your breath when doing exercises such as push-ups and sit-ups. Also avoid heavy lifting.
- Do not take hot or cold showers or sauna baths right after you exercise. Very hot or very cold temperatures can be dangerous.
- Do not exercise during times when your disease is not under control unless your doctor has told you it is okay.

Appendix W: Exercise: Finding Activities That Work for You

CardioSmart
American College of Cardiology

www.CardioSmart.org

Exercise: Finding Activities That Work for You

What do you enjoy?

Some people like to run, take classes at the gym, or shoot hoops. But what others do to stay active may not work for you. Maybe you can't afford to join a gym, or you hate being indoors. Or maybe you have injuries that make some activities difficult.

The key to making fitness a lifelong habit that improves your health is to find an activity you like. If you enjoy it, you're more likely to keep doing it.

What fits your lifestyle?

An important part of choosing an activity is having your own reason for wanting to be active. It's not always easy to make activity a regular part of your life. Taking the time to think about what motivates or inspires you will help you stay with it.

Do you like to be with others?

Joining a group or a class can help keep you motivated. Or you may be more likely to stay with an activity or exercise if you do it alone.

Do you like to compete?

Some people do better if they have someone to compete with—even if that someone is themselves.

Others do better when there's no competition to worry about. For example, you might choose gardening or dancing instead of team sports or tennis if you don't like competition.

Do you need a mental challenge?

Team sports exercise your brain as well as your body. Bicycling requires you to pay close attention to your surroundings and where you're headed. If you'd rather shut off your brain and let your body do the work, try raking leaves.

Are you on a budget?

You can walk around your neighborhood without spending any money. Exercise DVDs involve a small one-time cost or a trip to the public library. You may be able to join a community yoga or tai chi class for a small fee. Wait until you know that you really enjoy the activity before you spend the money.

How much exercise do you need?

To feel your best, you need at least 2½ hours of moderate activity a week. Brisk walking is an example. But any activities—including daily chores—that raise your heart rate can be included. It's fine to be active in blocks of 10 minutes or more throughout your day and week.

Appendix W: Exercise: Finding Activities That Work for You (pg 2)

What are some of your choices?

Moderate activity can help improve your health. If improving fitness is your goal, include some vigorous activity. Talk to your doctor before starting an exercise program.

Activity ideas		
	Moderate intensity	**Vigorous intensity**
General exercise	• Brisk walking • Light to moderate calisthenics (for example, home exercises or back exercises) • Low-impact aerobic dancing • Weight lifting, body building	• Jogging or running • Walking uphill • Heavy calisthenics (push-ups, sit-ups, jumping jacks) • High-impact aerobic dancing
Water exercise	• Treading water with moderate effort • Water aerobics or water calisthenics • Kayaking, canoeing, paddle boating • Springboard or platform diving	• Swimming laps with fast, vigorous effort • Treading water with fast, vigorous effort • Water jogging • Skin diving and scuba diving
Outdoor activities	• Fishing and hunting • Children's games, like hopscotch, 4-square, and dodge ball • Downhill skiing • Shoveling snow	• Horseback riding (trotting or galloping) • Competitive sports like rugby, field hockey, and soccer • Mountain biking • Snowshoeing and cross-country skiing
House and yard work	• Sweeping, vacuuming, and mopping floors • Mowing or raking the lawn • Digging in the garden	• Carrying groceries upstairs • Carrying boxes or furniture • Baling hay or cleaning the barn with vigorous effort

Appendix X: Low salt diet (info for patients)

CardioSmart
American College of Cardiology

www.CardioSmart.org

Healthy Eating: How to Eat a Low-Salt Diet

Almost all foods contain sodium, or salt, naturally or as an ingredient.

Reducing salt in your diet can prevent high blood pressure. If you have high blood pressure, eating less salt can help you lower it. By reducing salt in your diet, you may be able to lower your dose of blood pressure medicine.

What is a low-salt diet?

If you have high blood pressure, diabetes, or chronic kidney disease, if you are African American, or if you are older than age 50, try to limit the amount of salt you eat to less than 1,500 milligrams (mg) a day. People who do not fall into one of those categories should limit salt to 2,300 mg a day. Most of us eat much more than that. Most of the sodium that people eat comes from processed foods, not from salt they add at the table.

You can limit sodium in your diet by counting the milligrams of sodium in everything you eat. Learn to choose lower-sodium foods by reading food labels for the sodium content. For example:

- ½ cup of canned tomatoes may contain 220 to 350 mg of sodium.
- ½ cup of low-sodium canned tomatoes may contain 15 to 30 mg of sodium.

If you choose foods that are canned without sodium, you will have room in your diet to include other foods you like that might have more sodium. In the example above, if you choose fresh tomatoes instead of canned, the sodium content will be even lower (one medium tomato has 11 mg of sodium).

If you need help changing your diet, talk to your doctor. He or she may refer you to a registered dietitian, an expert in healthy eating.

Will eating less sodium make me healthier?

If you have high blood pressure, eating less salt may lower it. That will lower your chances of getting heart disease, stroke, and kidney damage.

If you have heart disease, you may need to lower your blood pressure. Eating less salt can help you do that. Controlling your blood pressure lowers your chances of stroke and heart attack. Salt causes your body to hold extra water, making it harder for your heart to pump. That also can make your legs and hands swell.

If you have kidney disease, eating less salt may help you lower your blood pressure and prevent or delay kidney failure. Over time, high blood pressure gradually damages the tiny blood vessels in your kidneys.

Foods to avoid

Foods that are usually high in salt include:

- Smoked, cured, salted, and canned meat, fish, and poultry.
- Ham, bacon, hot dogs, and lunch meats.
- Regular hard and processed cheese, and regular peanut butter.
- Snack crackers.
- Frozen prepared meals.
- Regular canned and dried soups and broths.
- Regular canned vegetables.
- Salted snack foods such as chips and peanuts.
- French fries, pizza, tacos, and other fast foods.
- Pickles, olives, sauerkraut, and other pickled or cured vegetables.
- Ketchup and other condiments, especially soy sauce, Worcestershire sauce, steak sauce, and seasonings high in salt.
- Food from restaurants can be very high in salt, especially fast food and Chinese food.

What is hidden sodium?

Sodium can be found in many items that you might not suspect. Some over-the-counter medicines and many canned and other processed foods contain sodium.

Check your food labels. Sodium can have many different names.

Be careful about using products that include:

- Monosodium glutamate, also called MSG. (MSG is often added to Chinese food.)
- Sodium citrate.
- Sodium sulfite.
- Sodium caseinate.
- Sodium benzoate.
- Sodium hydroxide.
- Disodium phosphate.

Check your medicines. Sodium can be an ingredient in drugs.

- **Prescription medicines.** Talk with your doctor or pharmacist about whether the medicines you take contain sodium.
- **Over-the-counter medicines.** Many drugs that you can buy without a prescription contain sodium. Read the labels. If you are not sure, ask a pharmacist. Check with your doctor before you take any new over-the-counter drugs.

What can I use in place of salt?

Flavor your food with garlic, lemon juice, onion, vinegar, herbs, and spices instead of salt.

Use less salt (or none) when recipes call for it. You can often use half the salt a recipe calls for without losing flavor. Foods such as rice, pasta, and grains do not need added salt.

If you have heart failure and you want to use a salt substitute, check with your doctor first. Salt substitutes contain potassium, which may affect some heart failure medicines.

Appendix Y: Schedule of Events

Study Procedures	Screening[A]	Study Visits and Assessments (+/- 10 days)									
		Enroll[B]	Period of cardiac meds titration [E]	Treatment Period						EOT / Early Termination[H]	Study visit 6 months post EOT
Cycle[^]				1	3	5	9	13	17		
Beginning of Week[^]				1	6	12	24	36	48		
Informed Consent	X										
Medical History	X										
Physical Exam	X				X	X	X	X	X	X	X
Oncology visit[F]	X									X	
Cardiology visit	X[I]				X[I]	X[I]	X[I]	X[I]	X[I]	X[I]	X[I]
EKG	X										
Pregnancy Test	X										
Cardiac questionnaire	X										
Study Echocardiogram[J]	X[I]				X[I]	X	X	X	X[I]	X[I]	X[I]
6 min. walk test	x										
Exercise Stress Test	X[L]										
HS-Troponin[C]				X[I]	X[I]	X[I]	X[I]	X[I]	X[I]	X[I]	X[I]
Regular Troponin	X				X[I]	X[I]	X[I]	X[I]	X[I]	X[I]	X[I]
Blood sample for storage				X[I]	X[I]	X[I]	X[I]	X[I]	X[I]		
Blood Pressure Log (weekly during cardiac medications titration)[D]											
Initiation of HER2 Targeted Therapy[G]				X[I]							

A. Protocol specific procedures should be completed within 30 days after signing informed consent. Clinical assessments used for meeting screening eligibility can be used if done w/in 30 days prior to signing informed consent
B. Once enrollment has occurred, all visits/assessments should occur +/- 10 days of scheduled date.
C. Collection of hs Troponin for central laboratory. Refer to section 8.0 for shipping instructions.
D. Provide patient with blood pressure cuff and provide instructions for blood pressure monitoring and recording throughout study treatment. Please refer to section 6.2.1.
E. Patient will initiate appropriate cardiac therapy as assigned by cardiologist. If a patient is already on a BB or ACE inhibitor they will be uptitrated to the maximum tolerated dose. Please refer to section 6.2.1. Please refer to page 18 fig 3 for more detailed instructions regarding titration of cardiac medications.
F. Oncology visit is mandatory at screening and Off Study. All other visits should be scheduled according to standard of care. These will not be research visits.
G. HER2 targeted therapy should begin within 3 weeks of enrollment and continued on Q 1-3 weeks according to treating oncologist.
H. Off Study visit should occur within 30 days after last treatment or unacceptable toxicity, symptomatic cardiac disease, or ECHO has met hold criteria.
I. Research will arrange for the visit/test and will cover the costs. Research will cover Week 1 drug, but not drug administration.
J. All echocardiograms need to be completed at least 2 days prior to the next HER2 targeted therapy
K. Treatment will be assessed starting with weeks. In the event of treatment delays, time will be counted according to the administration of HER2 targeted therapy so that cardiac assessments (echocardiogram, cardiology visit and blood samples) are done in accordance with this administration. Echocardiograms sent to the Core lab need to be labeled according to the weeks on HER2 therapy.
L. The exercise stress test will be performed only if deemed appropriate by the treating study cardiologist

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix Z: Oncological therapy while on study

Cycle # Date (MM/DD/YY)	HER2 targeted therapy	Dose	Endocrine therapy	Chemotherapy	Radiation (local, dose)
Cycle #____ __/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				
Cycle #____ __/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				
Cycle #____ __/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				
Cycle #___ ___/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				
Cycle #____ __/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				
Cycle #____ __/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				
Cycle #___ ___/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				
Cycle #___ ___/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				
Cycle #____ __/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				
Cycle #____ __/__/__	Trastuzumab ☐ Tras/Pertuzumab ☐ Ado-trastuzumab emtansine ☐				

Date form completed:	Institution Code:	Patient ID:	Patient Initials/Name:

Appendix AA: Specimen Form

Treating Institution: _____ Date: ___ / ____ / ____

Shipping Institution to fill out (please copy for your records)

Patient Study ID# _____ Study Site ID: (circle) WCI / GT

Study Time point: _____

Date/Time drawn: ___ /___ / ___ Time: ___ : ___

1. STORAGE SAMPLES:

BL ONLY: (PRPL) PLASMA: Type of Tubes _____ # of Tubes _____

BL ONLY: (PRPL) BUFFY COAT Type of Tubes _____ # of Tubes _____

ALL VISITS:(RED) SERUM Type of Tubes _____ # of Tubes _____

2. HS-TROPONIN: Type of Tubes _____ # of Tubes _____

Form completed by: _____ Email/Phone Number: _____

Signature: _____

FEDEX Tracking Number_____

Date/Time Shipped: ___ /___ / ___ Time: ___ : ___

Appendix AA: Specimen Form (pg2)

Receiving Institution to fill out

Date Received in Lab: ___ /____ / ____ Type of Tubes _____ # of Tubes _____ Study ID # _____ Received in good condition ☐ Not received in good condition. Explain: _____ Received by: _____
PLEASE RETAIN A COPY OF THIS FORM IN THE PATIENT'S STUDY BINDER

Appendix BB: Flow Sheet for Patient Recruitment