PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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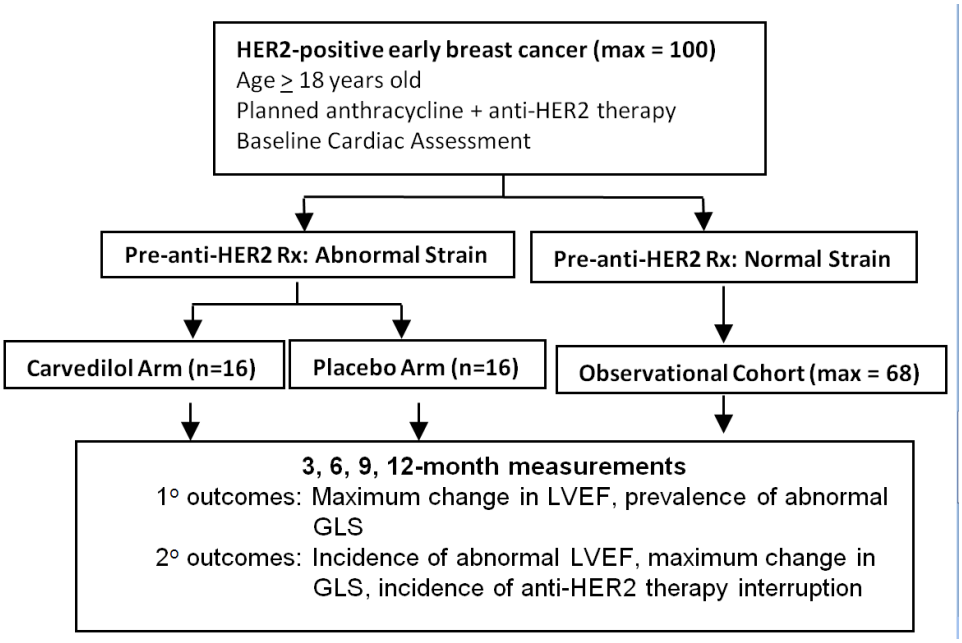
Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This phase II placebo-controlled study will evaluate the effect of carvedilol, compared to placebo, on anthracycline/anti-HER2 therapy induced left ventricular dysfunction in patients with HER2-positive breast cancer who are receiving adjuvant or neoadjuvant therapy. Upon enrollment and after providing informed consent, a saliva sample will be obtained by use of protocol 06-107, and banked for future correlative gene analysis. All patients (minimum 80 patients to maximum 100 patients) will undergo routine cardiac surveillance with 2D echocardiograms per standard of care at multiple time points, which will align as closely as possible to the following: pre-anthracycline (baseline), pre-anti-HER2 therapy, and 3, 6, 9, and 12 months (+/- 4 weeks) after initiation of anti-HER2 therapy. In the case that standard of care echocardiograms are not done at these time points, either due to a delay in anti-cancer therapy or due to the patient's medical condition, the principal investigator will determine if the standard of care echocardiogram may be used in lieu of one of the time points listed. Additional speckle tracking strain analysis will be performed on these echocardiograms, and blood specimens will be drawn at several time points for biomarker analysis.

After completion of anthracycline treatment and prior to initiation of anti-HER2 therapy, 32 patients with abnormal myocardial strain, defined as global longitudinal strain < 19% or % change from baseline by ≥ 11%, will be randomized in a 1:1 ratio to carvedilol versus placebo. Carvedilol will be administered twice daily for approximately 1 year OR until the end of anti-HER2 therapy, if it is discontinued prior to 1 year. Treatment in both carvedilol and placebo groups will be systematically up-titrated at weeks 3, 6, and 9 (+/- 1 week) after randomization to a goal dose of 25mg twice daily. The primary and secondary outcome measures will be evaluated at months 3, 6, 9, and 12 (+/- 4 weeks). In addition, the prevalence of subclinical LV dysfunction after completion of anthracycline and anti-HER2 therapy will be estimated.



2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Aims:

Aim 1: To estimate the prevalence of subclinical LV dysfunction by completion of anthracycline and anti-HER2 therapy among consecutive women scheduled to receive anthracycline chemotherapy and anti-HER2 therapy for HER2-positive early breast cancer, as defined by abnormal global longitudinal strain (< 19% or % change from baseline ≥ 11%). Study participants will be followed with serial echocardiograms, ordered as per standard of care, with speckle tracking imaging as close as possible to the following time points: pre-anthracycline, pre-anti-HER2 therapy, and 3, 6, 9, and 12 months (+/- 4 weeks) after the start of anti-HER2 therapy.

Aim 2: To generate preliminary evidence of the effect of prophylactic treatment with carvedilol on anthracycline-anti-HER2 induced changes in LV systolic function. Patients with abnormal myocardial strain at pre-anti-HER2 therapy imaging will be randomized to carvedilol vs placebo starting at a dose of 3.125mg twice a day and up titrated to a maximal dose of 25mg twice a day.

Hypothesis: Prophylactic treatment with carvedilol can prevent the development of anthracycline-anti-HER2 associated LV systolic dysfunction.

Secondary Aims:

Aim 3: To explore the effect of prophylactic carvedilol on indices of LV function and the incidence of anti-HER2 therapy interruption.

Exploratory Aims:

1. To collect and bank specimens for future use in evaluating the association between echocardiographic markers of systolic function, specifically myocardial strain imaging, with cardiac biomarkers of cardiac injury and remodeling (troponin-I) and inflammation and candidate single nucleotide polymorphisms.
2. To explore the effect of prophylactic carvedilol treatment on local or distant breast cancer recurrence, development of second primary cancers, and all-cause death.

3.0 BACKGROUND AND RATIONALE

3.1. Overview of HER2-positive Breast Cancer:

Breast cancer is the most commonly diagnosed cancer in women, and the 2nd leading cause of cancer death in women—an estimated 232,340 new cases of invasive breast cancer will be diagnosed this year.[1] However, earlier detection and improved treatment have resulted in steadily decreasing rates of breast cancer related death. Women surviving breast cancer represent 22% of all cancer survivors U.S.,[2, 3] with more than 2.9 million breast cancer survivors estimated in the U.S. today.[4] The human epidermal growth factor receptor 2 (HER2) oncogene encodes a transmembrane tyrosine kinase receptor that is critical for cell growth and survival. HER2 is over-expressed or amplified in 20-30% of invasive breast cancers and is associated with poor prognosis.[5, 6] Trastuzumab (Herceptin) is a humanized monoclonal antibody against the

extracellular domain of HER2 and was shown to reduce the risk of breast cancer recurrence by 40-50% in several landmark clinical trials.[7-9] Since that time, trastuzumab therapy has become the standard of care among patients with HER2-positive breast cancer and is used mostly in combination with adjuvant chemotherapy.

3.2. Treatment Associated Cardiotoxicity:

The benefit of trastuzumab therapy is substantial although there is a small risk of trastuzumab associated cardiotoxicity. The concern over cardiac safety of trastuzumab was first raised during early clinical trials of patients with metastatic disease, in which increased rates of cardiac dysfunction were unexpectedly observed in 27% of patients receiving anthracycline based chemotherapy plus trastuzumab compared to 3-8% among patients receiving trastuzumab or anthracyclines alone.[10] Subsequent trials of trastuzumab therapy in the adjuvant setting have shown fewer cardiac events. In the joint analysis of the National Surgical Adjuvant Breast and Bowel (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials, the cardiac event rate (defined by cardiac related death or symptomatic CHF) was < 4% among the trastuzumab treated group.[11]

Although the risk of symptomatic CHF is low in the adjuvant setting, milder forms of cardiac dysfunction are more common. In the HERA trial 9.8% of patients treated with trastuzumab compared to 2.9% in the control group had at least one significant decline in LVEF (defined as a decrease of >10% from baseline to below 50%).[12] Asymptomatic declines in LVEF led to discontinuation of trastuzumab in 14% of patients in NSABP B-31.[13] However, in clinical practice, the incidence of significant asymptomatic LVEF decline is higher (17%-23%).[14-16] As a result of these studies, an intensive cardiac surveillance program was mandated in order to detect signs of treatment associated cardiotoxicity. LVEF assessment is performed most commonly by echocardiogram at baseline and every 3 months during trastuzumab therapy. However, abnormalities of LV systolic function as determined by LVEF are a late manifestation of cardiotoxicity and may indicate the presence of irreversible myocardial damage.

3.3. Mechanism of Treatment Associated Cardiotoxicity-

Trastuzumab associated cardiotoxicity, in contrast to anthracycline mediated cardiotoxicity, is generally considered to be reversible after discontinuation of trastuzumab. It occurs in a minority of patients, is not dose related, and shows no identifiable abnormalities on endomyocardial biopsy.[17] An early study by Ewer et al demonstrated that, among 38 patients with trastuzumab-associated cardiotoxicity, LVEF improved in 37 patients with no evidence of ultrastructural changes on myocardial biopsy in 9 of these patients.[18] However, this concept of reversibility has recently been challenged in the 7 year follow-up from the NSABP B-31 study, in which 36 of 147 patients who discontinued trastuzumab for cardiac-related reasons had a LVEF < 50%.[11] The irreversibility in these patients is likely due to the anthracycline chemotherapy, but it is unclear on the contribution from trastuzumab. The exact mechanism of trastuzumab-induced cardiotoxicity has yet to be elucidated; however several hypotheses have been proposed. HER2/neu (also known as ERBB2) is known to be required for cardiac development and is a critical component of the stress response of the heart. In mice, inactivation of ERBB2 was shown to result in failure of ventricular trabeculation during midgestation.[19] A study by Grazette et al demonstrated that inhibition of ERBB2 leads to mitochondrial dysfunction and activates the mitochondrial apoptosis pathway.[20] Ventricle restricted ERBB2 knockout mice displayed features of dilated cardiomyopathy and were more

sensitive to biomechanical stress of volume overload and anthracycline therapy.[21] In clinical practice, the risk of trastuzumab cardiotoxicity is most relevant among patients with prior treatment with anthracycline based chemotherapy. This may suggest a two-hit model in which anthracycline exposure first induces cellular injury through free radical production. When faced with the loss of HER2/neu signaling during trastuzumab therapy, cardiomyocytes are more susceptible to the adverse effects of cardiac stressors and at increased risk for further cardiac injury.

3.4. Oncologic and Cardiac Implications of Trastuzumab Cardiotoxicity:

Although trastuzumab therapy is commonly interrupted or discontinued in 15-25% of patients when there is evidence of changes in cardiac function, the impact of this practice on breast cancer outcomes is unknown. Asymptomatic LV dysfunction is a significantly more common adverse event than symptomatic heart failure, and LV dysfunction can persist in some patients despite withdrawal of trastuzumab exposure. Currently, no data is available on the association between treatment-induced asymptomatic LVEF decline and subsequent development of cardiac events (i.e. CHF or cardiac death), and longer prospective follow-up is needed to further investigate this. Based on long term follow-up from the Framingham Heart Study, it has been shown that patients with asymptomatic LV dysfunction (ALVD) are at high risk of CHF and death, even when only mild impairment of EF is present.[22] Rates of CHF among subjects with normal LV function and ALVD were 0.7 and 5.8 per 100 person years, respectively. Mild ALVD (EF 40% to 50%) was associated with a hazards ratio for CHF of 3.3 compared to individuals with normal LV function.

3.5. Interruption of anti-HER2 therapy and Breast Cancer Outcome

Trastuzumab therapy can be interrupted or permanently discontinued for a significant decrease in left ventricular function; however the impact of this practice on breast cancer outcomes has never been studied prospectively. To investigate this question further, we conducted a retrospective cohort study to assess the incidence of trastuzumab interruption in clinical practice and evaluate the effect of trastuzumab cardiotoxicity and subsequent trastuzumab interruption on breast cancer outcomes. Among 585 patients with early HER2-positive breast cancer, 85 patients (14.9%) had trastuzumab treatment interrupted, and treatment associated cardiotoxicity was the most common reason for interruption. Patients in the interrupted group had a higher BMI (28.5 vs 26.8, p =0.027) and more had estrogen receptor-negative (49.4% vs 31.7%, p=0.001) and progesterone receptor-negative (59.8% vs 45.8%, p=0.016) disease. In terms of disease-free survival, the hazard ratio for a first event in the interrupted group, compared to the continuous group, was 2.58 (95 percent confidence interval, 1.848 to 7.059; p<0.001). Among patients with trastuzumab interruption due to trastuzumab cardiotoxicity, the hazard ratio for a disease free survival event was 2.37 (95 percent confidence interval, 1.45-7.56, p=0.004).[23] Patients in the interrupted group had poorer prognostic features and this could have accounted for more DFS events. However, as this was a retrospective study, no definitive conclusion can be made on the association between trastuzumab interruption and breast cancer outcomes. Additional prospective data are needed.

3.6. ACE-inhibitors and Beta Blockers May Reduce Trastuzumab Associated Cardiotoxicity:
Cardinale et al performed a prospective randomized trial to study the effect of enalapril treatment on the prevention of cardiotoxicity among high risk patients receiving high dose chemotherapy, and showed that 43% of control and 0% in the enalapril group had >10% drop in LVEF.[24] In a study of patients receiving anthracycline based chemotherapy, patients randomized to carvedilol 12.5mg

daily showed no change in LVEF after chemotherapy compared to the placebo group, in which there was an absolute reduction in LVEF by 17%.[25] Seicean et al retrospectively analyzed data of patients receiving anthracycline and/or trastuzumab for breast cancer and observed that use of BBs was associated with a lower incidence of heart failure.[26] These studies suggest that ACE-I and BBs may effectively reduce the risk of trastuzumab-associated cardiotoxicity.

3.7. Speckle Tracking Strain Echocardiography for Early Detection of Cardiotoxicity

Speckle tracking strain imaging is a new echocardiographic modality that measures myocardial deformation and provides a more sensitive and quantitative assessment of cardiac contractile function than conventional 2D echocardiographic indices.[27, 28] Strain is a highly reproducible and objective measurement that is superior to EF or fractional shortening in the detection of early subclinical myocardial dysfunction and has been shown to be useful in the early diagnosis of trastuzumab associated cardiotoxicity.[29, 30] In a prospective multicenter study by Sawaya et al, global longitudinal strain < 19% was predictive of subsequent development of cardiotoxicity and present in all patients who later developed symptoms of heart failure.[30] A study by Negishi et al also showed that an 11% reduction in global longitudinal strain was predictive of subsequent trastuzumab associated cardiotoxicity.[31]

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

A prospective observational cohort study design will be used to determine the prevalence of subclinical LV dysfunction by 1 year from the start of anti-HER2 therapy, as defined by global longitudinal strain < 19% or % reduction in global longitudinal strain by ≥ 11% from baseline. All patients with HER2-positive early breast cancer and treated with anthracycline plus anti-HER2 therapy will be eligible for this study, and serial echocardiograms will be performed with additional speckle tracking strain analysis throughout the duration of therapy. The minimum planned accrual for this study is 80 patients, and enrollment will continue to a maximum of 100 patients to allow for randomization of 32 patients in the treatment arm.

After completion of anthracycline based chemotherapy and prior to initiation of anti-HER2 therapy, study participants will undergo a repeat routine transthoracic echocardiogram. Thirty-two patients with abnormal global longitudinal strain (< 19% or a relative decrease in global longitudinal strain by ≥ 11% from baseline) and who do not meet any exclusion criteria (outlined in section 9.0) will be randomized in a 1:1 ratio to receive carvedilol versus placebo prior to initiation of anti-HER2 therapy. Study drug will be started on the first day of anti-HER2 therapy (+/- 1 week), and administered twice daily for the duration of the study period (approximately 1 year, or sooner if anti-HER2 therapy is discontinued prematurely). Routine serial echocardiograms with speckle tracking strain analysis will be performed for the duration of therapy. Patients with normal global longitudinal strain at the end of anthracycline chemotherapy will be followed observationally and undergo routine serial echocardiograms with speckle tracking strain analysis until 1 year after anti-HER2 therapy is initiated.

All patients will undergo biomarker testing as outlined in the study calendar in section 10.0, and all patients not previously registered to protocol 06-107 will be approached with the consent and option for banking of an Oragene sputum specimen for future DNA analysis at the time of enrollment.

4.3 Intervention

The minimum planned accrual for this study is 80 patients. These patients will undergo routine serial LVEF assessments by 2D echocardiography at standard of care time points, as previously described. We will perform additional speckle tracking strain analysis on all echocardiograms using these clinically indicated echocardiograms. A sputum specimen will be collected and banked from all study participants for future correlative studies. In addition, blood specimens will be collected for biomarker testing in tandem with anti-HER2 therapy administration and as close as possible to the following time points: baseline, pre-anti-HER2 therapy, and at 3 and 6 months (+/- 4 weeks). If anti-HER2 therapy is interrupted or delayed for any reason, blood specimens for biomarker testing will be collected once treatment resumes. Should anti-HER2 therapy be interrupted for a significant length of time, it will be at the principal investigator's discretion whether to "skip" any given time point (for example, if there is a shorter window of time between the 3 month and 6 month time points due to a treatment delay.) All echocardiograms will be read by a core lab with readers blinded to treatment allocation. For strain analysis, a non-sequential test ID will be assigned for each examination, identifiers and clinical information removed, and all will be interpreted by a single echocardiographer masked to treatment allocation, 2D echocardiogram results, and prior strain analyses. The clinical treatment team will have access to results of routine 2D-echocardiogram measurements only (per standard of care).

A total of 32 patients eligible for Aim 2 will be randomized in a 1:1 fashion to carvedilol versus placebo as follows. After completion of anthracycline based chemotherapy and prior to initiation of anti-HER2 therapy, study participants will undergo a repeat routine transthoracic echocardiogram. Patients with abnormal global longitudinal strain (< 19% or a relative decrease in global longitudinal strain by $\geq$ 11% from baseline) who do not meet any exclusion criteria (outlined in section 9.0) will be randomized in a 1:1 ratio to receive carvedilol versus placebo prior to initiation of anti-HER2 therapy. Study drug will be started on the first day (+/- 1 week) of anti-HER2 therapy, and administered twice daily for the duration of the study period (approximately 1 year, or sooner if anti-HER2 therapy is discontinued prematurely).

The following parameters for carvedilol dosing will serve as a guide for the protocol. The investigator may opt for different carvedilol management at his or her discretion. Carvedilol will be started at an initial dose of 3.125mg twice a day to a target dose of 25mg twice a day, and treatment in both the carvedilol and control groups will be systematically up-titrated at weeks 3, 6, and 9 (+/- 1 week) after clinical assessment by a cardiology investigator. Criteria for up-titration are described in section 9.0. All dosages will be labeled by dose level (1, 2, 3, or 4) and will be otherwise identical in appearance.

Dose level 1	3.125mg oral twice daily
Dose level 2	6.25mg oral twice daily
Dose level 3	12.5mg oral twice daily
Dose level 4	25mg oral twice daily

Treatment will be continued until the completion of the 1 year course of anti-HER2 therapy or earlier if anti-HER2 therapy is prematurely discontinued. 2D echocardiograms with strain analysis will be performed as described in Aim 1. In addition, follow-up visits will be scheduled with the Cardiology PI at 0, 3, 6, and 12 months (+/- 4 weeks) for patients who are randomized to study drug or placebo,

to assess for adverse medication effects and symptoms of congestive heart failure. Patients will continue with all preplanned cardiac evaluations irrespective of anti-HER2 interruption.

4.4 Future Use of Samples

Sputum samples (Oragene-DNA kit, DNA Genotek, Kanata, Ontario, Canada) will be collected and banked at room temperature and stored at the Breast and Imaging Center for future correlative studies to evaluate the association between anthracycline-anti-HER2 associated changes in myocardial function and candidate single nucleotide polymorphisms (i.e. HER2 polymorphisms *Ile655Val* and *Ala1170Pro* and polymorphisms of carbonyl reductase *CBPR1* and *CBPR3*). This biospecimen collection will be performed under protocol #06-107. Any projects outside of the scope of this protocol will need to be approved by the IRB/PB. An Biospecimen Research Protocoldetailing the proposed project will need to be approved by the IRB/PB prior to the start of the project.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Commercially available carvedilol/placebo is provided by the study and will be administered by the MSKCC pharmacy. The medication will be dispensed at the beginning of each treatment cycle and a pill diary will be used to track adherence. Carvedilol and placebo will be supplied in bottles containing a 4 week (for titration) or 12 week (maintenance) supply. Carvedilol and placebo should be stored at room temperature, not above 25°C (77°F). Both carvedilol and placebo will be dispensed in capsules of uniform shape and color, and the packaging will be identical.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

All patients must meet the following criteria:

1. Female
2. Age ≥ 18 years
3. Non-metastatic histologically confirmed primary invasive breast carcinoma
4. Pathologically confirmed HER2-positive breast cancer
5. Scheduled to receive anthracycline chemotherapy followed by anti-HER2 therapy at MSKCC
6. Able and willing to provide informed consent
7. Willing and able to comply with the requirements of the protocol
8. Able to swallow capsules

For Aim 2, all patients must meet the following criteria:

1. Meet all inclusion criteria above
2. LVEF $\geq$ 50%
3. Abnormal global longitudinal strain (<19%, or a % decrease of $\geq$ 11% from baseline) prior to initiation of planned anti-HER2 therapy
4. Heart rate $\geq$ 50 beats per minute
5. Sitting systolic blood pressure > 90 mmHg

6.3 Subject Exclusion Criteria

Patients are to be excluded from randomization for Aim 2 of this study if they meet any of the following criteria:

1. Current treatment with ACE-inhibitors or beta blockers

2. Allergies or inability to tolerate beta blockers previously due to bradycardia, hypotension, or AV block.
3. Known history of NCI CTCAE (Version 4.0) Grade $\geq$ 2 symptomatic CHF, myocardial infarction within 12 months prior to randomization, significant symptoms (Grade $\geq$ 3) relating to left ventricular dysfunction, significant (moderate or severe) valvular disease, or significant cardiac arrhythmia (Grade $\geq$ 3)
4. Pre-menopausal women without a negative serum or urine pregnancy test within 4 weeks of starting treatment
5. Enrollment in a therapeutic intervention trial in the Breast Medicine service

7.0 RECRUITMENT PLAN

A member of the Breast Cancer Medicine Service will identify a patient before starting her on adjuvant/neoadjuvant therapy. The patient will be seen by Dr. Yu or Dr. Liu (or other members of the Cardiology Service) timely for eligibility and will discuss the study and the possibility of enrollment in the research study with the patient. Minorities and women are well represented in the breast cancer medicine clinics, and we expect that they will be well represented in the trial accrual. The principal investigator, Dr. Yu, will be available to all patients for further questions and information through a contact number which is provided on the consent form. Given the annual estimate of ~125 patients seen at MSKCC with newly diagnosed HER2 positive early breast cancer, and a high historical participation rate in clinical protocols, this recruitment goal will be feasible within the prespecified study period. We expect study accrual will be completed in 18 months.

The research investigators may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study. Such patients are already contained in institutional databases and are part of the sampling frame. During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary for the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

8.1 PRETREATMENT EVALUATION

All aspects of the screening evaluation should be completed within four weeks of starting treatment unless otherwise noted.

- Documentation of HER2-positive status
- Full medical history (to be performed by primary oncologist)
- Physical examination, complete vital signs, height, and weight (by breast cancer medicine service) at baseline
- 12-lead electrocardiogram within 3 months
- Serum or urine pregnancy test

- Baseline 2D echocardiogram with strain imaging

9.0 TREATMENT/INTERVENTION PLAN

There are two components of this study. For Aim 1, a prospective cohort study design will be used to determine the prevalence of subclinical LV dysfunction, as defined by global longitudinal strain <19% or % reduction by ≥11% from baseline, among all patients diagnosed with HER2-positive early breast cancer and treated with anthracycline based chemotherapy plus anti-HER2 therapy. These patients will undergo routine serial LVEF assessments by 2D echocardiography, per standard of care, as previously described..

Conventional 2-dimensional and Doppler echocardiography will be performed using a commercially available standard ultrasound scanner (E9, GE Medical Systems, Horten, Norway). All echocardiograms will be performed by a registered diagnostic cardiac sonographer according to a standardized protocol. Chamber quantification and other standard hemodynamic variables will be obtained according to the American Society of Echocardiography (ASE) guidelines.[32] Diastolic function will be assessed using pulsed wave Doppler and tissue Doppler imaging.

During the standard 2D echocardiogram, three apical views will be acquired at an increased frame rate (at least 80 frames per second) to allow for offline speckle tracking strain analysis (Echopac, GE Medical Systems). This analysis will be performed independent of the clinical interpretation of the 2D echocardiogram. The methods of image acquisition and strain measurements with speckle tracking have been previously described.[33] Briefly, after initial automated tracking of the endocardial border and software processing, manual correction will be performed to ensure adequate tissue tracking as needed. Each view will be divided into 6 segments, and the entire myocardium will be represented by a 17 segment model. In the case of unsatisfactory tracking due to inadequate image quality, that segment will be eliminated from analysis. After longitudinal strain and strain rate curves are generated for each segment, peak global longitudinal strain will be calculated as the average value of the peak systolic strain values for all the segments within the 3 standard apical views.

All echocardiograms will be read by a core lab blinded to treatment allocation. For strain analysis, a non-sequential test ID will be assigned for each examination, identifiers and clinical information removed, and all will be interpreted by a single echocardiographer masked to treatment allocation, 2D echocardiogram results, and prior strain analyses. The clinical treatment team will have access to results of routine 2D-echocardiogram measurements only (per standard of care).

If the patient had an echocardiogram or multi-gated acquisition scan done locally before enrolling onto the study, the patient will be asked to have another baseline echocardiogram with strain imaging, which will not be charged to the patient. This will be covered by with internal funding.

A double blind randomized placebo controlled study design will be used to accomplish the goals of Aim 2 (Fig 1). After completion of anthracycline based chemotherapy and prior to initiation of anti-HER2 therapy, study participants from Aim 1 with abnormal global longitudinal strain (< 19% or a relative decrease in global longitudinal strain by ≥ 11% from baseline) will be eligible for this study. Patients in the observational group who develop abnormal strain after initiation of anti-HER2 therapy will not be eligibile for randomization.

Treatment Arms:

Prior to initiation of anti-HER2 therapy, patients will be randomized in a 1:1 ratio to receive carvedilol versus placebo through the MSKCC Protocol Participant Registration (PPR) system (see section 15.2). Study drug will be started on the first day of anti-HER2 therapy (+/- 1 week), and administered twice daily for the duration of the study period (approximately 1 year, or sooner if anti-HER2 therapy is discontinued prematurely).

Commercially available carvedilol and placebo will be provided by the study at no cost to the study participants. Study drug will be prepared by the research pharmacy staff at SKI (Core Manager: Mark G. Klang, MS, RPh, BCNSP, PhD).

Dosing:

Carvedilol will be started at an initial dose of 3.125mg twice a day to a target dose of 25mg twice a day, and treatment in both the carvedilol and control groups will be systematically up-titrated at weeks 3, 6, and 9 (+/- 1 week) by the PI or other member of the research team. Criteria for up-titration will include the following: heart rate $\geq$ 50 beats per minute, systolic blood pressure > 90 mmHg, and absence of dose-limiting symptoms suggestive of medication intolerance including dizziness, fatigue, or weakness. Toxicity will be graded according to NCI CTCAE, version 4.0. All capsules will be labeled by dose level (1, 2, 3, or 4) and will be otherwise identical in appearance. If a DLT is observed at dose level 1, patients will come off study.

Dose level 1	3.125mg oral twice daily
Dose level 2	6.25mg oral twice daily
Dose level 3	12.5mg oral twice daily
Dose level 4	25mg oral twice daily

Treatment will be continued until the completion of the 1 year course of anti-HER2 therapy or earlier if anti-HER2 therapy is prematurely discontinued. 2D echocardiograms with strain analysis will be performed in all enrolled patients for the duration of the study period as described in Aim 1, irrespective of treatment interruption.

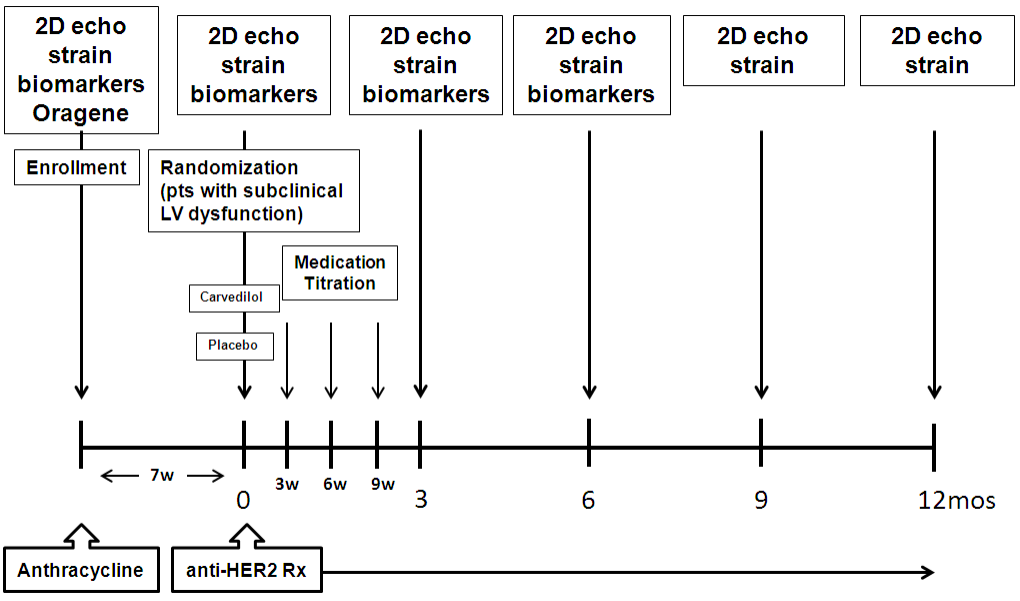


Figure 1 – Study Design

For the exploratory aim, blood specimens will be collected for biomarker analysis at baseline prior to anthracycline treatment as well as pre- and post- anti-HER2 infusion at approximately month 0, 3, and 6, per the study design outlined in Fig. 1.). If anti-HER2 therapy is interrupted or delayed for any reason, blood specimens for biomarker testing will be collected once treatment resumes. Leftover blood samples will be stored for additional biomarker analysis (to be determined), including but not limited to ultrasensitive troponin-I which we anticipate will be FDA approved and available for clinical use in the next year and circulating markers of cardiac inflammation. Study participants will also be asked to provide an optional saliva sample for DNA extraction and future study under protocol #06-107. Specimens will be assigned a unique identification code that is independent of the patient's medical record number to protect the confidentiality of the patient, while still facilitating subsequent correlation with clinical data. DNA extraction kits ((Oragene-DNA kit, DNA Genotek, Kanata, Ontario, Canada) will be stored at room temperature for future correlative studies to evaluate the association between anthracycline-anti-HER2 associated changes in myocardial function and candidate single nucleotide polymorphisms (i.e. HER2 polymorphisms *Ile655Val* and *Ala1170Pro* and polymorphisms of carbonyl reductase *CBPR1* and *CBPR3*).

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Study drug administration:

Investigators and patients will be blinded and study agents will be indistinguishable from each other. Patients who cannot swallow pills should not be enrolled, as capsules may not be opened. Study agent will begin on the same day as anti-HER2 therapy (+/- 1 week). Each study participant will self-administer 1 capsule by mouth twice daily. Participants will document the number of capsules taken and any side effects on the study medicine daily log (**Appendix A)**

Carvedilol and placebo will be started at an initial dose of 3.125mg twice a day. Treatment in both the carvedilol and control group will be systematically up-titrated at weeks 3, 6, and 9 (+/- 1 week). All capsules will be labeled by dose level (1, 2, 3, 4) and will otherwise be identical in appearance. The plan outlined in Section 11.0 "Toxicities/Side Effects" will be utilized to inform the patient about adverse events. Study drug will be made by the research pharmacy staff at SKI (Core Manager: Mark G. Klang, MS, RPh, BCNSP, PhD). Upon completion of the study period, the principal investigator, treating cardiologist, and study staff will be unblinded to the patient's randomization arm, so as to appropriately plan ongoing cardiology care for the patient. The decision to continue carvedilol therapy as standard cardiac treatment can be made at the discretion of the treating cardiologist after the patient is removed from the study.

Cardiac Assessment:

Routine evaluations will occur at each breast cancer medicine visit per standard of care. In addition, among patients in the randomized arm, follow-up visits will be scheduled with the Cardiology PI prior to initiation of anti-HER2 therapy and at 3, 6, and 12 months (+/- 4 weeks) after randomization to assess for adverse medication effects and symptoms of congestive heart failure. Additional cardiology visits will be scheduled on an as needed basis if further dose adjustments are deemed necessary by the breast medicine oncologists or investigators. The PI will be available throughout

the study period to address any clinical concerns or evaluate patients as needed. The evaluations are further defined in the study calendar.

At any point during this study, study participants and their oncologists will be notified of a significant decline in LVEF (defined as an absolute decrease from baseline LVEF of 10-15% to below 50%, or decrease of $\geq$ 16%), and referral to cardiology will be recommended.

Biomarker evaluation:

From each patient at 7 prespecified timepoints, and in tandem with anti-HER2 therapy as per standard of care, approximately ten mL of peripheral blood will be collected (1 green top tube, 1 lavender top tube) for the measurement of TnI and high sensitivity TnI. For the troponin assays, plasma will be separated from peripheral blood and samples will be frozen for analysis and will not be known to the investigator until the completion of the study. The TnI samples will be evaluated by the Clinical Laboratory at MSKCC. At all MSKCC sites, blood samples should be clearly labeled before transfer to Main campus. This labeling should include the study identifier (IRB-assigned protocol number), MSKCC-assigned patient identifier (once available), test ("troponin") and the time point of sample measurement. TnI concentrations will be determined by a fluorometric enzyme immunoassay analyzer (Tosoh Bioscience, Inc., San Francisco, CA) with a low end sensitivity of 1.6 ng/ml. Results will be blinded to the investigators until study is complete. Any leftover plasma will be stored at -80^{o}C by Dr. Ramanathan in Laboratory Medicine to allow for additional biomarker analysis (to be determined), including but not limited to ultrasensitive troponin-I which we anticipate will be FDA approved within the next 12 months or circulating markers of cardiac inflammation. Additional biomarker testing will be performed either by the Clinical Laboratory at MSKCC, the Schmitt Lab at MSKCC, or Singulex (Alameda, CA).

Study Calendar (for observational cohort):

Study Assessments	**Baseline**	**Pre-Anti-HER2 therapy**	**Follow up month 3 (+/- 4 weeks)**	**Follow-up month 6 (+/- 4 weeks)**	**Follow-up month 9 (+/- 4 weeks)**	**Study week 52, or time of anti-HER2 therapy discontinuation (if before study week 52) (+/- 4 weeks)**
Informed consent	X					
Medical history	X					
Physical exam	X					
Vital Signs	X					
12-lead EKG (within 3 months of study entry)	X					
2D echocardiogram with strain	X	X	X	X	X	X
Laboratory Assessments	X	X[1]	X[1]	X[1]		

Study Calendar (for randomized subjects):

Study Assessments	**Baseline**	**Pre-Anti-HER2 therapy**	**Follow up weeks 3, 6, 9**	**Follow up month 3 (+/- 4 weeks)**	**Follow-up month 6 (+/- 4 weeks)**	**Follow-up month 9 (+/- 4 weeks)**	**Study week 52, or time of anti-HER2 therapy discontinuation (if before study week 52) (+/- 4 weeks)**
Informed consent	X						
Medical history	X						
Physical exam	X						
Vital Signs	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
12-lead EKG (within 3 months of study entry)	X						
Pregnancy Test*	X						
2D-echocardiogram with strain	X	X		X	X	X	X
Laboratory Assessments	X	X[1]		X[1]	X[1]		
Informed Consent for randomization		X					
Randomization		X					
Dispense study agent		X	X	X	X	X	
Cardiology Visit		X	X[2]	X	X		X
Adverse Events Form		As needed	As needed	As needed	As needed	As needed	As needed

Whenever possible, all imaging studies and lab assessments will be completed within the protocol window of +/- 28 days. However, investigator discretion may determine the alignment of protocol time points with standard of care imaging studies and lab assessments, if needed.
Initiation of study agent and titration assessments have a window of +/- 7 days.
[1]Biomarkers will be drawn pre- and post- anti-HER2 infusion, and in tandem with the patient's anti-HER2 treatment schedule
[2]Focused visits for study drug titration.
[3]Heart rate and blood pressure only.
*Pregnancy test in pre-menopausal women only.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity grading will be performed in accordance with NCI CTCAE, version 4.0. If toxicities are encountered, adjustments will be made to the study drug dose, based on the treated physician's discretion. Only severe or life-threatening events (Grade 3 or 4) will be recorded. For safety and adverse event reporting, see section 17.0

Toxicities with carvedilol that are likely (>20%) include:

- Dizziness
- Fatigue

Toxicities with carvedilol that are *less likely* (<20%) include:

- Bradycardia
- Hypotension
- Headache
- Syncope
- Weakness
- Cough
- Diarrhea
- Nausea and vomiting
- Weight Gain
- Hyperglycemia
- Chest pain
- Edema
- Arthralgias
- Abnormal vision
- High cholesterol
- Abnormal LFTs

Side effects that are *rare, but serious* include:

- Stevens-Johnson syndrome
- Bronchospasm

- Hypersensitivity reaction
- Pneumonitis
- Angioedema

11.1 Management of carvedilol related toxicities
Carvedilol dose modifications will be made according to the criteria outlined in Table 11.1.

Table 11.1: Carvedilol dose modification criteria

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hypotension	Continue at same dose level	Reduce by 1 dose level	Withhold therapy dose until toxicity is grade ≤ 1, then resume treatment at dose level -1	Withhold therapy dose until toxicity is grade ≤ 1. Retreatment at dose level -1 at the discretion of the investigator
Bradycardia	Continue at same dose level	Reduce by 1 dose level	Withhold therapy dose until toxicity is grade ≤ 1, then resume treatment at dose level -1	Withhold therapy dose until toxicity is grade ≤ 1. Retreatment at dose level -1 at the discretion of the investigator
Non-cardiovascular, general	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is grade ≤ 1, then resume treatment at same dose level, or dose level -1, at the discretion of the investigator	Withhold dose until toxicity is grade ≤ 1, then resume treatment at same dose level, or dose level -1, at the discretion of the investigator

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1. 2D Echocardiography and Speckle Strain

For Aim 1, the primary outcome variable will be the prevalence of subclinical left ventricular dysfunction during anthracycline and anti-HER2 therapy as defined by an abnormal global longitudinal strain of < 19% or a change from baseline of ≥ 11%. For Aim 2, the maximum change in global LVEF (continuous variable) from beginning to end of anti-HER2 therapy (approximately 1 year or time of anti-HER2 therapy discontinuation) will serve as the primary outcome variable. Markers of LV systolic function by myocardial strain imaging will be followed throughout the study, and secondary outcome variables will include 1) incidence of abnormal LVEF (< 50%) and 2)maximum % change from baseline in global longitudinal strain.

12.2. Breast Cancer Specific Outcomes

Patients will be followed for incidence of anti-HER2 therapy interruption (secondary outcome), defined as > 1 cycle of therapy missed (equal to or greater than 6 week gap between consecutive

anti-HER2 therapy treatments). As per the exploratory aim, patients will be followed for breast cancer recurrence, development of second primary cancer, or all-cause death.

12.3. Cardiac Bioimarkers, DNA analysis

Blood samples will be drawn at prespecified timepoints as outlined in previous sections of this protocol. From each patient at 7 prespecified timepoints approximately ten mL of peripheral blood will be collected (1 green top tube, 1 lavender top tube) for the measurement of TnI (exploratory outcome). For the troponin assay, plasma will be separated from peripheral blood and samples will be frozen for analysis and will not be known to the investigator until the patient has completed the study. The TnI samples will be evaluated by Clinical Laboratory at MSKCC. At all MSKCC sites, blood samples should be clearly labeled before transfer to Main campus. This labeling should include the study identifier (IRB-assigned protocol number), MSKCC-assigned patient identifier (once available), test ("troponin") and the time point of sample measurement. TnI concentrations will be determined by a fluorometric enzyme immunoassay analyzer (Tosoh Bioscience, Inc., San Francisco, CA) with a low end sensitivity of 0.06 ng/ml. Leftover plasma will be stored at -80°C by Dr. Ramanathan in Laboratory Medicine to allow for additional biomarker analysis (to be determined), including but not limited to ultrasensitive troponin-I which we anticipate will be FDA approved within the next 12 months or circulating markers of cardiac inflammation. Additional biomarker testing will be performed either by the Clinical Laboratory at MSKCC, the Schmitt Lab at MSKCC, or by Singulex (Alameda, CA)

Saliva samples will be collected under protocol #06-107, using the Oragene-Discover kit (DNA GEnotek, Ontario, Canada) at the time of enrollment, and banked at the Breast and Imaging Center for future analysis to assess the association between candidate polymorphisms (i.e. HER2 polymorphisms *Ile655Val* and *Ala1170Pro* and polymorphisms of carbonyl reductase *CBPR1* and *CBPR3*) (exploratory outcome) and changes in myocardial strain .

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time.

13.1. Criteria for discontinuation of study agent

Patients randomized to carvedilol versus placebo will be discontinued from study agent should they experience any of the following:

- Severe, unexpected toxicities or side effects, i.e. symptomatic bradycardia or hypotension, that is not responsive to dose modification per section 11.1.
- If their treatment with anti-HER2 therapy is discontinued.
- A significant decline in LVEF, defined by an absolute decrease in LVEF from baseline of 10-15% to below 50%, or absolute decrease in LVEF of $\geq$ 16%.

After discontinuation, every effort will be made to continue with routine cardiac surveillance and cardiology follow-up per protocol. Participants will be followed clinically until adverse events resolve, if applicable.

Other reasons for study discontinuation at the discretion of the investigator include, but are not limited to:

- Change in patient eligibility

- Non-compliance with the defined treatment plan
- Protocol violation
- Investigator's decision based on patient's best interest
- Withdrawal of consent
- Lost to follow-up
- Death

14.0 BIOSTATISTICS

14.1. Statistical Analysis:

Aim 1: The proportion of patients with abnormal global longitudinal strain values by the planned end of anthracycline + antiHER2 therapy (approximately 14 months after initiating treatment with anthracycline chemotherapy and 1 year after initiating anti-HER2 therapy) will be estimated together with the corresponding 95% confidence interval using all women enrolled to this study. All women eligible for the randomized study will be counted as having abnormal global longitudinal strain for this analysis. This number will be added to the remaining women who do not have abnormal global longitudinal strain by the end of anthracycline therapy but develop abnormal strain at a later timepoint to form the numerator of the estimated proportion. The denominator will consist of all women enrolled to the study.

Aim 2: The primary endpoint of the randomized study is the maximum change in global LVEF from the start of anti-HER2 therapy until 1 year later. The difference in the maximum global LVEF therapy will be compared between the two arms using a two-sided 0.05 level Wilcoxon rank-sum test. Although every effort will be made to continue imaging patients who discontinue treatment, it is possible that dropout will occur. To make use of the longitudinal nature of these data taking into account potential dropout, in a secondary analysis we will also explore analyzing the data using a linear mixed effects model with robust standard errors and an exchangeable covariance structure using global LVEF at each time point as the outcome modeled as a function of time, randomization arm, age, presence of hypertension, and the interaction between time and randomization arm. The mixed effects model produces valid estimates of the treatment effect as long as data are missing at random (missingness is independent of unobserved measurements conditional on the observed data), allows participants with incomplete data to contribute information to the estimated treatment effect, and is consistent with the intent-to-treat principle.[34, 35]

Secondary aims: Secondary endpoints for the randomized study that will be described in an exploratory manner include changes in global longitudinal strain and the proportion of patients who discontinue anti-HER2 therapy. Proportions will be estimated with 95% confidence intervals separately in the two arms. Although formal testing for differences between the arms for these secondary endpoints is not a primary goal of this study, depending upon the data we may further explore differences between the arms using a Wilcoxon rank-sum test or linear mixed models with an indicator for treatment arm in the model to explore differences in changes in global longitudinal strain

Exploratory aims: The proportion of patients with local or distant breast cancer recurrence, second primary cancer, and death will be described in an exploratory manner. We expect the number of women who develop a recurrence, a second primary cancer or die within the time frame

of this study to be too small to do any type of analysis. However, if the data permit we may estimate the cumulative incidence of these events using methods for competing risks as appropriate.

General analysis: In the observational cohort, we will descriptively estimate the proportion of patients with abnormal LVEF (< 55%) at each time point and the proportion who discontinue anti-HER2 therapy.

14.2. Sample Size:

Aim 1: With a minimum of 80 patients, we will be able to estimate the proportion of patients with abnormal global longitudinal strain to within $\pm$ 0.11.

Aim 2: The study is designed to detect an intergroup difference of absolute difference of 10 percentage points (simple difference) in the change in LVEF between the experimental and control group. Ten percent is the change in LVEF that is associated with differing degrees of left ventricular dysfunction, and long-term studies among non-cancer patients have shown that outcomes differ among groups of patients who have LVEF differing by 10%.[22] Assuming a standard deviation of 8 (based on our preliminary data), at least 28 patients (14 patients per arm) will be needed to demonstrate this aim with 90% statistical power if the data were normally distributed and we were to use a t-test a two-sided Type I error probability of 0.05. To account for the possibility that the maximum change in LVEF measurements may not be normally distributed, we have planned to use a Wilcoxon rank-sum test for the analysis. The relative efficiency of the rank-sum test compared with the t-test is approximately 95%if the data are normally distributed and is greater if the data are skewed indicating that we should maintain greater than 80% power for this analysis. [36] To allow for approximately 10% of the patients to drop out, we plan to enroll a total of 32 patients to the randomized study. Based on preliminary data,[30] we estimate that 41% of patients with early HER2-positive breast cancer treated with anthracyclines followed by taxanes and trastuzumab (or other anti-HER2 regimens) will develop abnormal global longitudinal strain (<19%) at the completion of anthracycline treatment. To achieve our target sample size of 32 patients in Aim 2, a minimum of 80 patients will be enrolled for Aim 1. To account for the possibility that some patients enrolled in Aim 1 may already be taking ACE-inhibitors or beta blockers (expected to be no more than 10-15%) and not be eligible for Aim 2 we may enroll an additional 20 patients as needed in order to reach our randomization target. The maximum accrual for this study is 100 patients. Given the annual estimate of ~115-125 patients seen at MSKCC with newly diagnosed HER2 positive early breast cancer, and a high historical participation rate in clinical protocols, this recruitment goal will be feasible within the prespecified study period. We expect study accrual will be completed in 18 months. With 14 months of follow-up on all patients, the total duration of this study is expected to be approximately 32 months.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

Of note, patients who are eligible for Aim 2 will be re-registered through PPR, using a separate (Part 2) Eligibility Checklist, before beginning this arm, in order to minimize risks for protocol violations regarding eligibility.

15.3 Randomization

After completion of anthracycline based chemotherapy and prior to initiation of anti-HER2 therapy, study participants from Aim 1 will undergo a repeat routine transthoracic echocardiogram. Patients with abnormal global longitudinal strain (< 19% or a relative decrease in global longitudinal strain by ≥ 11% from baseline) and who do not meet any exclusion criteria (outlined in section 9.0) will be randomized in a 1:1 ratio to receive carvedilol vs placebo prior to initiation of anti-HER2 therapy. After eligibility is established and immediately after consent is obtained, patients will be registered with PPR. Randomization will be accomplished by the method of random permuted block.

16.1 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database (Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and

Safety Monitoring of Clinical Trials" which can be found at:
http://www.cancer.gov/clinicaltrials/patientsafety/dsm -guidelines /page1

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:
http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

There are several different mechanisms by which clinical trials are monitored for data safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level or risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industry sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits and serial cardiac monitoring. Specific guidelines for symptom management are in place to protect the study participant.

Consent process: All patients at MSKCC who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 18.0.

Possible Toxicities/Side-Effects: There are risks associated with treatment as described in Section 11.0; however, patients screened for enrollment will be deemed appropriate for treatment independent of this study.

Risks of research participation: The greatest risk is release of information from health or research records in a way that violates privacy rights. MSKCC will protect records so that name, address, phone number, and any other information that identifies the participant will be kept private. It will be stated to the participant that the chance that this information will be given to an unauthorized individual without the participant's permission is very small.

Benefits: A preventive treatment strategy with beta blockers among patients who are at increased risk for cardiotoxicity due to abnormal myocardial strain may lower the risk for developing treatment

associated cardiotoxicity. Treatment with beta blockers may also increase the likelihood of receiving anti-HER2 therapy without interruption, which has the potential to decrease breast cancer events.

It is unlikely that the research using collected biospecimens will be of any medical benefit to participants. Neither the patient nor the treating physician will be told of the specific results of any research tests on the samples; except in the case of an uncovered incidental finding which may be critical to the preventive care of the participant or their family. Research using blood or tissues in this study could lead to medical and scientific products that could improve prevention, diagnosis and treatment of disease.

Costs/compensation: Patients will be charged for physician visits, routine laboratory tests and radiologic studies required for monitoring their condition. The patients will not be billed for the study drug, carvedilol/placebo. The participant is informed that there are no plans to provide financial compensation for use of their human biologic specimens, nor are there plans for the participant to receive money for any new products, tests, and discoveries that might come from this research.

Alternatives: The alternative to this trial would be not to participate in the study and receive routine standard of care.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g. qualified monitors from MSKCC) and external personnel, its authorized agents, the FDA, and/or other governmental agencies) may review patient records as required.

Patient safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: This study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring board established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

Voluntariness of research participation: It is stated that taking part in this study is voluntary and patients have the right to withdraw at any time. Participation in the study will not impact on the clinical care patients receive.

17.2 Privacy

Medical information is confidential. The participant's personal identity will not be used in reports that are written about the research. The MSKCC IRB/PB will review all requests for research performed involving biospecimens ascertained through this protocol. Blood and tissue samples will be stored with a code linked to the patient's medical record. With the permission of the IRB/PB, research studies on cellular, genetic, immunologic, or other features of tumor or normal samples may be performed with no names attached to the samples but linked by codes to personal identifiers. The results of any research using blood or tissues will not be placed in the medical record.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that samples and genetic information collected may be shared with other qualified researchers. Such information will not include identifying information such as name. It is also stated in the consent and Research Authorization that research data (e.g. genomic sequence) may be placed into databases monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

17.2.1

Not applicable.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to

signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A: Maintenance Period Pill Diary

Appedix B: Dose Titration Period Pill Diary