A PILOT STUDY OF RISK-GUIDED CARDIOPROTECTION WITH CARVEDILOL IN BREAST CANCER PATIENTS TREATED WITH DOXORUBICIN AND/OR TRASTUZUMAB	
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ClinicalTrials.gov Number	NCT04023110

University of Pennsylvania Research Study Summary for Potential Subjects

Protocol Title: CCT-Guide Pilot
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You are being invited to participate in a research study. Your participation is voluntary and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

Some cancer treatments can cause damage to your heart. We have developed a risk calculator to predict the likelihood that you will experience this damage (called cardiotoxicity). The research study is being conducted to test whether we can use this calculator to identify patients who may benefit from medicines to protect the heart and to test whether a medicine, called carvedilol, can be used to protect the heart during chemotherapy for patients who are identified as being at elevated risk.

If you agree to join the study, you will be asked to complete the following research procedures:

- We will calculate your risk score and determine whether you are in the *elevated risk group* or *low risk group*.
    - If you are in the *elevated risk group*, you will be randomly assigned to either usual care or the intervention with carvedilol.
    - If you are in the *low risk group*, you will be in the usual care arm.
- Usual care arm – you will be asked to come in regularly for visits to monitor your heart function during the study
- Intervention arm – you will be asked to take carvedilol twice a day for 1 year. You will have all of the same visits as patients on the usual care arm to monitor your heart function during the study. You will also have some extra visits when we will adjust the dose of the carvedilol and monitor for any side effects of the medicine

Your participation will last for 2 years. If you agree, we will also keep data and unused blood that we have collected as part of this study for use in future research; however, if you don't agree to this, you may still participate in the study.

There may be no direct benefit to being in this study. If you are in the elevated risk group and assigned to take carvedilol, the most common risks are tiredness and dizziness. If you have diabetes, carvedilol may mask the symptoms of low blood sugar and may worsen high blood sugar. You should not become pregnant while taking carvedilol.

Participating or choosing not to participate in this study will not change the treatment you receive for your cancer. Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

UNIVERSITY OF PENNSYLVANIA RESEARCH SUBJECT INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Protocol Title:	A Pilot Study of Risk-Guided Cardioprotection with Carvedilol in Breast Cancer Patients Treated with Doxorubicin and/or Trastuzumab
Principal Investigator:	Bonnie Ky, MD, MSCE 3400 Civic Center Blvd, 11-105 SCTR Philadelphia, PA 19104 215-573-6606
Emergency Contact:	Bonnie Ky, MD, MSCE 267-977-3126

Why am I being asked to volunteer?

You are being invited to participate in a research study because you have been diagnosed with breast cancer and will be receiving treatment with doxorubicin (Adriamycin) and/or trastuzumab (Herceptin) or trastuzumab-anns (Kanjinti). Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the investigator and/or the research team about this form. If you decide to participate, you will be asked to sign this form. Your doctor may be an investigator in this research study. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may want to ask for a second opinion about your care from another doctor who is not an investigator in this study. You do not have to participate in any research study offered by your doctor.

What is the purpose of this research study?

Some cancer treatments can cause damage to your heart. Our research group has developed a strategy (risk calculator) to predict the likelihood of your experiencing this damage (called cardiotoxicity). We believe that we can use this risk calculator as to identify patients before they start chemotherapy who may benefit from medicines to protect the heart.

If you agree to participate in this study, we will use information about your medical history, cancer treatment plan, and current heart function to calculate your risk of experiencing cardiotoxicity in the first year following start of treatment. We will group you as Elevated or Low Risk. We will tell you which risk group you are in. No matter which risk group you are in, we will follow your heart health using echocardiograms (ultrasounds of the heart), blood draws, and surveys while you are receiving chemotherapy and Herceptin or Kanjinti, and for a total of 2 years, and we will tell you and your doctors if we find any clinically significant changes in how your heart is functioning.

If you are in the Elevated Risk group, we will randomly (like with a coin flip) assign you to either a risk-guided intervention or to usual care. We will tell you to which arm you are assigned. If you are in the risk-guided intervention arm, we will ask you to take a medicine, carvedilol (also called Coreg), twice a day for the first year. If you are in the elevated risk group and assigned to usual care, or if you are in the low risk group, you will get all of the treatment and care you would get if you were not on the study, as well as the monitoring of your heart that we are doing in the study.

Carvedilol has been approved by the US Food and Drug Administration (FDA) to treat high blood pressure and heart failure, but it has not been approved to reduce the risk of cardiotoxicity related to chemotherapy. Some clinical trials have suggested that carvedilol may do this, but further research is needed. We believe that patients with low risk of cardiotoxicity prior to chemotherapy may get little to no benefit from treatment with carvedilol, but that treatment with carvedilol may offer some protection to patients who are at elevated risk of cardiotoxicity related to chemotherapy.

The purpose of this pilot study is to learn more about the strategy of treating elevated risk patients with carvedilol to protect the heart during chemotherapy. Specifically, we want to understand:

- Is the study of a risk-guided treatment strategy <u>feasible?</u> Will people agree to take part in the study? If they agree, will they be able to do what we ask them to do as part of the study?
- Is a risk-guided treatment strategy with carvedilol <u>safe and tolerable</u>? How does it affect symptoms and quality of life during cancer therapy?
- Are we able to use our risk calculator and accurately identify subjects at relatively greater risk of cardiotoxicity and who might benefit from an intervention?
- How a risk-guided treatment strategy affects heart function during the first year of cancer treatment.

How long will I be in the study? How many other people will be in the study? How long will the study last?

You will be in the study for about 2 years. If you are in the elevated risk group and randomized to the risk-guided intervention, you will take carvedilol for the first year.

We plan to enroll approximately 110 people in this study. We expect that it will take approximately 3.5 years for all subjects to complete the study.

What am I being asked to do?

If you agree to take part in this study, you will be asked take part in study visits before you start chemotherapy, while you are on chemotherapy and Herceptin or Kanjinti, and for up to 2 years. You may be asked to take the study medication for 1 year, starting on your first day of chemotherapy. Whenever possible, we will schedule visits to coordinate with times you will be coming to the Perelman Center to see your doctor or for other tests.

No matter which risk group you are in, or which arm you are assigned to, you will have several types of study visits while on this study:

- Screening: Before you start chemotherapy you will be asked to sign this consent form, and may be asked to complete other study activities (depending on what information is available in your medical record). After screening is completed, we will calculate your risk score and tell you whether you are in the low or elevated risk group. If you are in the elevated risk group, you will be randomized to either the risk-guided or usual care arm.
- Baseline Visit: The baseline visit will take place during your first chemotherapy treatment. If you are in the elevated risk group and randomized to the intervention arm, you will be given your carvedilol and asked to start taking it that evening.
- On Treatment Visits: You will have a number of visits in the first 12-15 months during which we will collect data to help us learn more about your heart function and your symptoms and quality of life; the exact number and timing of these visits will depend on the treatment you and your oncologist have decided to use.
- You will have a final visit 2 years after you start chemotherapy.

If you are in the elevated risk group and are randomized to the intervention arm, you will also have some additional visits:

- Dose Adjustment Visits: You will have 3 visits during the first 6 weeks (1-2 weeks; 3-4 weeks; and 6 weeks after starting chemotherapy) to allow us to check your vitals and adjust (or titrate) your dose of carvedilol. If you have symptoms that may be related to the study medication, you

may be asked to come in for additional Dose Adjustment Visits during the year.

- End of Intervention Check-In: Approximately 30 days after your last dose of study medication we will check to see if you have had any symptoms which may be related to the study medication. This may be done on the phone or in person.

Table 1 gives an overview of the types of visits you will have, and what activities will be done at each type of visit. Table 2 will tell you more about what you can expect from these visits depending on your cancer treatment. The study team will let you know which column applies to you.

STUDY ACTIVITIES

Risk Calculation and Randomization:

If you agree to sign consent and complete the screening activities, we will calculate your risk of cardiotoxicity. If your cardiotoxicity risk score is greater than 4.6 (more than 46 out of 1000 women with your characteristics are expected to experience cardiotoxicity in the first year after start of cancer therapy), you will be in the elevated risk group. Otherwise, you will be in the low risk group. The study doctor will tell you which group you are in and talk to you about what it means.

If you are in the elevated risk group, you will be randomized to either the Intervention Arm or the Usual Care Arm. There is a 50% chance (like a coin flip) that you will be randomized to the Intervention arm and a 50% chance that you will be assigned to the Usual Care Arm. If you are in the low risk group, you will be assigned to the Usual Care Arm. The study doctor will tell you which arm you are in.

Table 1: General Schedule of Events

	Screening (pre-chemo)*	Baseline (First Chemo)	Dose Adjustment Visits[C]	On Treatment Visits	End of Intervention Check-In[C]	2 Year Follow-up
Sign Consent Form	X					
Collect Medical History	X					
Vitals	X		X			
Pregnancy Test	X					
Risk Calculation	X					
Randomization[E]	X					
Clinical Data	X	X	X	X	X	X
Electrocardiogram	X					
Taking Study Medication[C]		X---------- X *(1 year total)*				
Symptoms Questionnaires		X		X		X
Social Determinants of Health Survey		X				
Family/Social History		X				
Research Blood Draw		X		X		X
Echocardiogram (standard of care or research)	X			X		X
Adverse Event Check			X	X	X	
Study Diary, & Pill Count[C]			X	X	X	

* Screening activities do not all have to occur on the same day. Some or all screening activities may take place on the same day as the baseline visit; [E] Elevated risk group only; [C] Elevated risk subjects randomized to take carvedilol only

Table 2: Timing of Visits by Type of Cancer Treatment Regimen

	Adriamycin	Herceptin or Kanjinti	Adriamycin and Herceptin or Kanjinti
Common Treatment Regimen(s) in this Group	*AC+T* *T+AC*	*TCH, TCHP*	*AC+TH+H* *THP+AC+H*
# of "On Treatment Visits"	*4*	*4*	*5*
Approximate Timing of "On Treatment Visits"	• *Between adriamycin and taxol* • *5 months* • *8 months* • *11 months*	• *3 months* • *6 months* • *9 months* • *12 months*	• *Between adriamcyin and taxol/Herceptin or Kanjinti* • *5 months* • *8 months* • *11 months* • *14 months*

AC = Adriamycin and Cytoxan ; T = Taxol; TCH = Taxol, Cytoxan, and Herceptin;
TCHP = Taxol, Cytoxan, Herceptin, and Perjeta; TH = Taxol and Herceptin; H = Herceptin

STUDY ACTIVITIES (continued)

Taking The Study Medication and Study Medication Dose Adjustment:

If you decide to take part in this study, are in the elevated risk group, and are randomized to the Intervention Arm, you will be asked to take carvedilol, starting the day that you start chemo. The carvedilol will be individually dosed, which means that we will adjust the dose until we find the level that you can tolerate. We will ask you to start by taking 3.125mg twice a day.

During the first 6 weeks you are on carvedilol, we will check in with you for 3 Dose Adjustment Visits during which we will check your blood pressure and heart rate, check if you are having any trouble taking the medication as directed, and ask you if you are having any symptoms. We will do our best to schedule these visits to coordinate with days you will be at the Perelman Center.

At the first Dose Adjustment Visit (week 1 to week 2), if your systolic blood pressure (top blood pressure number) is greater than 110mmHg and your heart rate is greater than 50 beats per minute (bpm), we will ask you to increase the dose to 6.25mg twice a day. Otherwise, you will continue at 3.25mg twice a day for the duration of the study.

At the second Dose Adjustment Visit (week 3 to week 4), if your systolic blood pressure is still greater than 110mmHg and your heart rate is greater than 50bpm, we will ask you to increase the dose again, to 12.5mg twice a day. Otherwise, you will continue at 6.5mg twice a day for the duration of the study.

At the third Dose Adjustment Visit (week 6), if your systolic blood pressure is still greater than 110mmHg and your heart rate is greater than 50bpm, we will ask you to increase the dose one last time to 25mg twice a day. Otherwise, you will continue at 12.5mg twice a day for the duration of the study.

We will ask you to continue taking carvedilol for 1 year. If your systolic blood pressure (top number) decreases to less than 90mmHg or your heart rate decreases to less than 45 beats per minute during the year *and* you have symptoms such as dizziness or lightheadedness you should tell the study team immediately. We may ask you to come in for an additional Dose Adjustment Visit to decrease your dose of study medication.

The study team will add “Investigational Carvedilol” to the medication list in your medical record. We will give you a “wallet card” to carry with you and show to your doctors with information about carvedilol and which drugs may interact with carvedilol, as well as contact information for the study team.

Vitals:

When we say we will check your vitals as part of this study, we mean that we will take your blood pressure and heart rate. This will typically be done while you are sitting down in an exam or infusion room. We will tell you what your blood pressure and heart rate are when we check them, and will document them in your medical record.

If you have your vitals checked during a visit with another doctor at the time-point when we would check them and the results are documented in your medical record, we may use those results instead of checking them ourselves.

Pregnancy Test:
Women who are pregnant are not eligible to participate in this study. If you are able to become pregnant and there is not a negative pregnancy test in your medical record within 10 days before you start on the study, we will arrange for a pregnancy test. This may be a blood or urine test. We will tell you the results of this test, and it will be documented in your medical record.

Clinical Data Collection, Medical History, and Family/Social History:
At many visits during the study, we will collect data from your medical record, and may also ask you questions to verify what is in your record or to get more detailed information. The information we collect will include date of birth, your height and weight, your blood pressure and heart rate, your current medications, your history of disease, results of lab tests ordered by your doctors, results of cardiovascular testing immediately prior to and while you are on the study, details about your cancer and cancer treatment, details about any hospitalizations or procedures you have while you are on the study, your family history of cancer and cardiac disease, and whether or not you use (or have used) tobacco. Some information will only be collected once during the study (during screening, at baseline, or at the final visit); there is other information that we will update each time we see you.

Symptoms Questionnaires:
At the baseline visit, visits on treatment, and at the 2 year follow-up visit, we will ask you questions about your symptoms and activity. You should notify your oncologist of any symptoms you may experience, especially during cancer therapy.

Social Determinants of Health (SDOH) Questionnaires
At the baseline and 5-year follow-up visits, we will ask you questions about individual social determinants of health (SDOH). We will ask you questions about your race and ethnicity, your level of education, your employment status, and occupation, your gender identity and sexual orientation, your annual income and health insurance coverage, your access to food and health services, as well as other questions that will help us to better understand social factors that could impact your health and health care. We understand that some of these questions are about very sensitive topics. You can skip any questions you prefer not to answer. Your answers to these questions will not be put in your medical record or shared with your doctor without your specific permission.

We will also use your address in your medical record to learn more about how factors relating to where you live (like air quality or community resources) can affect your health. We will not store your address in the study database.

Research Blood Draw:

You will be asked to provide a blood sample at the baseline visit, visits on treatment, and at the 2 year follow-up visit. We will try our best to ensure that blood samples for this research study are taken during routine blood draws that your doctor has ordered, to avoid an extra needle sticks for this research study. At baseline, we will collect approximately 1 tablespoon of blood (16mL). At the remaining visits, we will collect approximately 2 teaspoons of blood (12mL).

The results of these blood draws will not be used to make clinical decisions. Some of the blood taken from each sample will be used to measure levels of molecules or proteins. Some of the molecules may change when the heart functions less well. Some of the blood drawn may be analyzed for variations in certain genes believed to be associated with cardiovascular disease. The blood samples will be anonymously coded so that no one handling the samples will be able to identify you.

Because these samples are being drawn for research purposes only and the tests being done are exploratory, the results of these blood tests will not be given to you or the doctors taking care of you. They will not be entered into your medical record, and they will not affect your care in any way.

Echocardiogram (Echo):

Echocardiography, or cardiac ultrasound, is the most common way of monitoring heart function and is a non-invasive technique that uses sound waves to generate an accurate picture of the heart and to see how it is functioning. In this research study, we are going to take some additional pictures of the heart during these echocardiograms and analyze these pictures in new ways. We hope to learn whether new ultrasound measures of heart function can detect heart disease sooner than our usual measures of heart function, and how heart function may change over long-term follow-up.

Pre-chemotherapy Echo: Before starting chemotherapy or trastuzumab, your oncologist will check your heart, usually using an echocardiogram. This is considered standard of care (which means you would have it done even if you don't participate in this study).

If you decide to participate in this study, the study team will collect information from the report of your pre-chemotherapy echocardiogram as part of screening, to get some of the information needed to calculate your risk of cardiotoxicity. If you are eligible, we will also collect a copy of the images.

In some cases, your oncologist will use a test called a MUGA to check your heart instead of an echo. While this is a way to check your heart and gives your oncologist all of the information he or she needs, we cannot use a MUGA to calculate your risk.

If the information we need is not available in the pre-chemotherapy echo report, or if you have a pre-chemo MUGA, the study team will arrange for you to have an echo in our research lab as part of screening. We may also arrange for you to have an echo in our research lab if the pre-chemo echo is not done at the

Perelman Center, or if the pre-chemo echo does not include specific images. It is important for the study that we have all baseline echo images available for analysis. The study team can tell you whether or not you would need a research echo at screening/baseline.

Standard of Care Echoes During Chemotherapy and Herceptin or Kanjinti:
Patients being treated with Herceptin or Kanjinti get an echo approximately every 3 months. Patients who are treated with doxorubicin and Herceptin or Kanjinti will get an echo between the doxorubicin and Herceptin or Kanjinti and approximately every 3 months while on Herceptin or Kanjinti. Your oncologist will order these to monitor the heart during treatment and it is considered standard of care (meaning you would have it done even if you don't participate in this study). While you are on the study, your doctor may also order an echo for other reasons (if you have certain symptoms, because you will be starting a certain therapy, or to follow-up on an earlier result). Since your doctor is ordering it and you would get this echo even if you don't participate in this study, this would also be considered standard of care.

If you decide to participate in this study, we would obtain a copy of all standard of care echocardiograms and arrange (if possible) for several additional pictures of your heart to be taken during these standard of care echoes. There will be no extra cost to you for these extra pictures, but it may add about 10 minutes to the length of the test.

Research Echocardiograms: If you decide to participate in this study, you may have echos done solely for the purposes of this study. For patients treated with doxorubicin, this will be usually be done for all of the echoes except for the pre-chemotherapy echo. For patients treated with Herceptin or Kanjinti (with or without doxorubicin), this will be done at the 2 year follow-up and may be done at the final On Treatment Visit. However, if you are having a standard of care echo at, or close to, a time when we would do a research echo, the study may use the standard of care echo instead, so that you don't have to make an extra visit.

Each research echocardiogram will take 45 minutes to an hour and must be done in our research lab at the Hospital of the University of Pennsylvania. The results of these echos, based on current clinical standards, will be given to you. Any important findings based on current clinical standards will also be communicated to your doctor.

<u>Electrocardiogram:</u>
An electrocardiogram (EKG or ECG) is a test that uses sticky pads placed on your chest and connected to an EKG machine to measure the electrical activity of the heartbeat. If you don't have a recent EKG in your medical record, we may do one as part of screening. Any important findings from the EKG, based on current clinical standards, will be given to you and will also be communicated to your doctor.

<u>Study Diary, Pill Counts, and Survey:</u>

If you agree to participate in this study, are in the elevated risk group, and are randomized to the Intervention Arm, we will give you a form, called a study diary, to use to record each dose of study medication that you take and any symptoms you experience during the intervention.

At each visit during the study, we will ask you to bring your study diaries and study medication with you to the visit. The study team will review the diaries and count the number of pills that you have remaining. At these visits we will also ask you some questions about compliance with treatment.

After your final dose of study medication, the study team will collect any remaining pills and ensure that they are properly destroyed.

What are the possible risks or discomforts?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff.

The Cardiotoxicity Risk Score: If you decide to participate in this study, we will calculate your pre-chemotherapy risk of cardiotoxicity and tell you whether your risk is elevated or low. There are some things you should know about the cardiotoxicity risk score:

- We have developed and tested the cardiotoxicity risk score calculator using research performed here at Penn. However, there are still things we don't know about the risk calculator. In particular, we don't know if it can be used to identify patients who would benefit from cardioprotection during cancer therapy.
- All patients in this study will get the same level of monitoring, regardless of calculated risk or assigned arm. If the study finds anything to suggest that you may have damage to your heart from chemotherapy, we will tell you and your oncologist immediately so that you can be treated.

Risks from Carvedilol:

If you are in the elevated risk group and randomized to the intervention arm, there is a chance you could have side effects from the study drug. There are a few important points to keep in mind about side effects:

- The study doctors do not know who will or will not have side effects
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may be serious.

There are some things you and the study doctor can do to make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects
- The study doctor may adjust your study medication dose to try to reduce side effects

Table 3 lists the most common and the most serious side effects that researchers know about. There might be other serious side effects that researchers do not yet know about or are uncommon. If important new side effects are found, the study doctor will discuss these with you.

Table 3: Possible Side Effects of Carvedilol

COMMON, SOME MAY BE SERIOUS In 100 people receiving carvedilol, more than 20 and up to 100 may have	
• Tiredness • Dizziness	
RARE, AND SERIOUS In 100 people receiving carvedilol, 3 or fewer may have:	OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving carvedilol, 4 to 20 may have
• Fainting • Rash • Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body if allergic to medication • Worsening cataract eye disease • Blurred Vision • Severe asthma attack • Chest pain	• Hyperglycemia • Swelling of the body • Abnormal heartbeat • Low or high blood pressure • Heart Failure (which may cause shortness of breath, swelling of ankles, and tiredness) • Headache • Diarrhea • Nausea • Vomiting • Weight gain • Pain in joints • Cough • Fatigue • Swelling of the feet or ankles

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

The study medication may interact with some other medications. You should let all of your doctors know that you are on a clinical trial and are taking carvedilol. If your doctors start you on one of the below medications while you are taking carvedilol, please let the study team know immediately. We may talk to your doctors to see if there is another medication that could be used instead. If not, you may have to stop taking the study medication.

Tell the study team immediately if your doctor prescribes one of these medications:

- buproprion (Wellbutrin)
- fluozetine (Prozac)
- paroxetine (Paxil)
- quinidine (Quinidex)
- duloxetine (Cymbalta)
- sertraline (Zoloft)
- terabinafine (Lamisil)
- amiodarone (Cordarone)
- cimetidine (Tagamet)
- thioridazine (Mellaril)

If you have diabetes, carvedilol may mask the symptoms of hypoglycemia (low blood sugar) and may worsen hyperglycemia (high blood sugar), so it is important that you continue to see your primary doctor and/or endocrinologist regularly, and that you let them know that you are taking carvedilol.

Reproductive risks: Because of the effects of the study drug, there could be serious harm to unborn children or children who are breast-feeding. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child. If you are currently pregnant, it is important that you inform the investigator because you will not be able participate in the study. If you are able to become pregnant and there is not a recent negative pregnancy test in your medical record, you will be given a serum pregnancy test before entry into the study. You will be asked to use a medically adequate method of birth control while you are on carvedilol. If you have questions about adequate methods of birth control, you can discuss them with the study doctor. **You should not become pregnant while you are taking the study medication.** If you do become pregnant, you must tell the investigator and consult an obstetrician or maternal-fetal specialist.

Risks of Study Procedures

Echocardiography is a safe and noninvasive test that is widely used in medicine. There are no known risks associated with echocardiograms. There are no known risks associated with the extra pictures that will be obtained in this research study. It is possible that you may experience mild, temporary discomfort from the probe being pressed against your chest.

Blood sampling from the arm or hand may cause a small amount of bleeding or a bruise. Occasionally, a person feels faint or lightheaded when his/her blood is drawn. Rarely, an infection can develop that can be treated. To reduce discomfort and inconvenience, blood sampling will be combined with routine clinical blood draws whenever possible. If you have a port-a-cath, the study team may arrange to have your blood drawn from your port while it is being access for treatment or other blood draws.

Surveys and Questionnaires: There are no medical risks associated with answering survey questions. However, you may be uncomfortable answering personal questions. If a question makes you uncomfortable, you can skip it.

Electrocardiogram: There is no pain or risk associated with having an electrocardiogram.

Genetic Information: We will store the blood samples that we collect from you for later analysis. One possible use of your blood may be exploratory testing to see if there are genetic variations that are associated with an increased risk of cardiotoxicity, or with an increased likelihood that a patient benefits from treatment with carvedilol during chemotherapy.

This research includes genetic testing. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, it could make it harder for you to get or keep a job or insurance, or life insurance companies may charge a higher rate based on this information. We believe the chance these things will happen is very small, but we cannot make guarantees.

A federal law (Genetic Information Non-Discrimination Act, GINA) helps reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about GINA, you can find information about it on the internet or ask the study staff.

Time: If you take part in this study, you may lose time at work or home, and spend more time in the doctor's office than usual. As much as possible, we will schedule study visits on days when you will already be at the Perelman Center and will do our best to minimize the time you are asked to spend here.

Other: In addition, there may be other unforeseeable risks and inconveniences associated with participation in this study.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

There may be no direct benefit to being in this study.

This study may benefit future breast cancer patients by furthering efforts to better predict who is at risk for cardiotoxicity, and is an important first step in developing risk-guided strategies to protect the heart during cancer therapy.

What other choices do I have if I do not participate?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have.

Currently, there is not a standard treatment for possible heart problems that may occur from common cancer treatments. Your alternative is to not participate in this study.

Will I be paid for being in this study?

You will receive $6 for each visit for this study. If you have a study visit on a day that you are not here for an infusion visit, we will reimburse you for parking. We will use a reloadable debit card (called the Greenphire Clincard) to pay and reimburse you.

Will I have to pay for anything?

There are no costs to you for taking part in this study. All study costs, including carvedilol and procedures, echocardiogram, and blood draws that are related directly to the study will be paid for by the study.
However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's website at:
http://cancer.gov/clinicaltrials/understanding/insurance-coverage. Another way to get this information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at anytime. Withdrawal will not interfere with your future care.

What happens to my collected samples and data?

When you agree to participate in this study, you will be assigned a unique subject ID that will be used to label all of the data, images, and samples that we collect as part of this research. The list linking the code to information that could identify you (such as your name, date of birth, or medical record number) will be kept in a separate, secure location. Access to this list will be controlled by the study team, and limited to people who need it for the purposes of conducting or overseeing the study.

The echocardiographic images collected for this study will be linked to your medical record and stored on a secure server located at the Hospital of the University of Pennsylvania; they will be available for use in your clinical care now and in the future. We will also make a de-identified copy of the images (labeled with your unique subject ID) which will be stored on a DVD in a secure location at the Hospital of the University of Pennsylvania; we will use this copy to make our measurements on your heart function.

The data collected for this study (including information about your medical history and cancer treatment, results of echocardiograms and blood tests, and your answers to surveys) will be labeled with your subject ID, and will be stored in our electronic database, held on secure servers at the University of Pennsylvania. Access to the database will be controlled by the investigators and limited to people who need it for the purposes of conducting or overseeing the study. At the end of this form, we will ask you want you want us to do with this data at the end of the study.

The blood samples that we collect for this study will be labeled with your subject ID, so that no one handling the samples will be able to identify you. They will be stored at the Perelman School of Medicine of the University of Pennsylvania. They

will be kept until the samples are used completely, or until the testing planned for this study is complete. At the end of this form, we will ask you what you want us do if there is any blood remaining after the testing is complete. We may use the collected samples to perform genetic testing.

Your samples may be used to create products, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family

Whole genome sequencing (WGS) may be conducted on your samples. Whole genome sequencing involves analyzing your entire personal genetic code. WGS can be conducted to determine changes and mutations in DNA. The significance of these results may not be well defined. Not all genetic variations affect one's health.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Access to this information will be controlled by the Principal Investigator.

Protected Health Information collected from you for the purposes of this study may be placed in your medical record and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations. By signing this form, you give us permission to use your Protected Health Information for this study.

Electronic Medical Records and Research Results

What is an Electronic Medical Record and/or a Clinical Trial Management System?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.
Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

What information about me may be collected, used, or shared with others?

- Name, address, telephone number, date of birth, medical record number, email address
- Personal and family medical history
- Current and past medical history
- Current and past medications collected from existing records
- Information from a physical exam that generally also includes blood pressure reading, heart rate, breathing rate, and temperature
- Results from tests or procedures you will undergo during this research study, as described in this form

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- Conduct and oversee the research described in this form;
- Ensure the research meets legal, institutional, and accreditation requirements;

- Conduct public health activities (including reporting of adverse events or other events related to the safety or toxicity of the drug for the purpose of this or other research relating to the study drug and its use in cancer); and
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because this information may be necessary for your medical care.

Who may use and share information about me?
The following individuals may use or share your information for this research study:

- The Principal Investigator and the Investigator's study team including academic collaborators at the UPHS and the School of Medicine.
- Authorized members of the workforce of the UPHS and the School of Medicine, and University of Pennsylvania support offices, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring, to provide treatment, to manage accounting or billing matters, etc.). This may include personnel from the Institutional Review Board and the Abramson Cancer Center Clinical Trials Scientific Review and Monitoring Committee and Department of Operations, Compliance, and Monitoring;
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB.

Who, outside of the School of Medicine, might receive my information?

- Other people or laboratories providing services for this research project on behalf of the University of Pennsylvania and the School of Medicine;
- The sponsor(s) of the study, its subcontractors, and its agent(s):
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?
Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

This section is about an optional study in which you can choose to take part

This part of the consent form is about an optional study that you can choose to take part in. There may be no direct benefit to being this study. We hope the results of this study will help other people with breast cancer in the future.

You can still take part in the main study even if you say 'no' to this study.

Cardiotoxicity of Cancer Therapy 2: Mechanisms, Predictors, and Social Determinants of Health in Breast Cancer Patients Treated with Doxorubicin and/or Trastuzumab (CCT2)

This study will help us learn more about how two breast cancer therapies, Adriamycin (doxorubicin) and Herceptin (trastuzumab), affect the heart and how those effects relate to your medical history, other cancer therapies you may receive, and social determinants of health (such as race, gender identity, education, occupation, access to health services, and economic resources).

This optional study will involve echocardiograms, blood draws, and questionnaires about your symptoms, physical activity, and social history. The blood samples we collect for the optional study may be used to perform genetic testing. Whole genome sequencing may be performed on your sample. Whole genome sequencing involves analyzing your entire personal genetic code.

What is involved?

If you choose to participate in the optional study:

1. You will be in the optional study for up to 15 years.
2. For the next 2 years, you will not have any extra visits. You will allow us to use the data, blood, and echocardiograms we collect over the next 24 months for both the main study and the optional study. We will ask you some extra questions about your symptoms at each of the main study visits.
3. You will have a study visit 3 years after you start chemotherapy. After 3 years, we will see you once every other year for up to 15 years. Each study visit will include: an echocardiogram, a blood draw, and questionnaires about your symptoms and physical activity. We will also ask you the SDOH questionnaire at the 5-year visit.

What are the possible risks?

The risks relating to echocardiograms, blood draws, answering survey questions, and genetic testing are described on pages 12 and 13 of this form.

Will I receive the results of research testing?

Results of the research blood tests done for the optional study will not be returned to you because they would not be relevant to your health care.

The results of the research echocardiograms will be given to you and placed in your medical record. Any important findings based on current clinical standards of care will also be communicated to your doctor.

How will my personal information be protected?
Your privacy is very important. If you choose to participate in the optional study, we will take the same steps that we take for the main study to protect your personal health information.

What are the possible benefits?
There may be no benefits to you from taking part in this study. We hope that what we learn from this study will help cancer patients in the future.

Are there any costs or payments?
You will not be charged for any research echocardiograms or blood draws done only for this study. You will receive a payment of $15 for each visit you complete for the optional study. We will use the Greephire Clincard to pay you. We will also use the Clincard to reimburse you for parking for study visits for the optional study.

What if I have more questions?
If you have questions or concerns about the optional study, you can contact your study team or the study doctor, Dr. Bonnie Ky, at 215-573-6606.

Please indicate your choice by initialing the option below:

_____ I AGREE to participate in the optional study (CCT2)

_____ I DO NOT AGREE to participate in the optional study (CCT2)

Future Research

Because we are trying to learn more about the effects of cancer and cancer therapy on the heart, as well as learn more about strategies to protect the heart during cancer therapy, we would like to have your permission to contact you in the future and collect future information from your medical records available within UPHS. We would also like your permission to use data and samples collected as part of this study for future research. You may still participate in the study even if you do not give us this permission.

If you give us permission to update your records, contact you in the future, or use your data or samples for future research, information that can identify you will be kept in a secure research database as described above.

If you agree to allow us to use data and/or samples collected as part of this study for future research, your coded information and/or samples will be stored for future research purposes. Future researchers may receive information that could identify you. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information and samples only applies to the information and samples collected on this study.

The following identifiers will be retained with your information and samples: unique subject ID. In addition, we will keep a list linking your unique subject ID with your name and medical record number. The list linking subject ID with your name and medical record number will be kept separate from your samples and data and will not be shared with future researchers. Your information and samples, labeled with unique subject ID, may be stored, and used for future research purposes for an indefinite amount of time.

There are no plans to tell you about any of the specific research that will be done. Possible future research may include studying the effects of cancer and cancer therapy on the heart.

Your coded information and samples may be shared with other researchers within Penn, or other research institutions, as well as pharmaceutical, device, or biotechnology companies. We will not follow up with you to tell you about the specific research that will be done. It is possible that you may have chosen not to participate in these future research studies, had you been approached for participation. You will not be given the results from testing that may be performed on your identifiable specimens as a part of future research.

There is a risk of breach of confidentiality (unintentional release of your information). We will do our best to make sure that this doesn't happen. However, we cannot guarantee total privacy. We will protect your confidentiality during storage and sharing by storing records as described above. Access to this information will be controlled by the Principal Investigator.

You will likely not directly benefit from future research with your information and samples. Research with your coded information and samples may help others by

improving our understanding of health and disease, improving healthcare, and making safer or more effective medical therapies, and developing new scientific knowledge.

If you have questions about the storage of your information and samples, or have changed your mind, you can contact Dr. Bonnie Ky at 215-573-6606.

Please read the following two statements listed below and initial one of the lines indicating if research staff may collect future information from your medical records within UPHS.

_____ I give you permission to collect future information from my medical records available within UPHS.

_____ I do not give you permission to collect future information from my medical records available within UPHS.

Information from this study may lead to new questions that may result in new research studies. Please indicate below if we may contact you about studies for which you may qualify. Any new information will be kept in a secure database as described above. Choose one of the following options by initialing on the line:

_____I give you permission to contact me in the future about studies for which I may qualify.

_____I do not give you permission to contact me in the future about studies for which I may qualify.

We are collecting the amount of blood required for this study. However, it is possible that some may be left over after our planned testing is completed. Choose one of the following options by initialing on the line:

_____ I give you permission to use any of my remaining blood for purposes not discussed in this consent. Blood (labeled with your unique subject ID only) will be stored indefinitely at the University of Pennsylvania in the lab of Dr. Bonnie Ky, and will be used by the study investigators to learn more about the effects of cancer and cancer therapy on the heart, including the effects of risk-guided cardioprotection. Blood may also be shared with other researchers for the purpose of learning more about the effects of cancer and cancer therapy on the heart. These other researchers would not be given access to the list linking your study ID to your identifiable information, and will not be given any information which could potentially identify you.

_____ I do not give you permission to use any of my remaining blood for purposes not discussed in this consent. In this case, the investigator will ensure that remaining blood is destroyed after planned testing is completed.

The data collected for this study (including information about your medical history and cancer treatment, images and results of echocardiograms, results of blood tests, and your answers to the surveys) may also help us answer other questions about how cancer and cancer therapies affect the heart. Please choose one of the following options by initialing on the line.

_____ I give you permission to retain the data collected about me after the study is completed and to use it for purposes not specifically discussed in the consent. Any data that may identify you will be kept securely as described above. Data (labeled with your unique subject ID) may be used by the investigators for future research relating to the effects of cancer and cancer therapy on the heart. In addition, parts of the data may be shared with other investigators in the future, with the permission of the study investigators, for the purpose of researching the effects of cancer and cancer therapy on the heart. If the data are shared with other researchers, they will not be given access to the list linking your study ID to your identifiable information, and will not be given any information which could potentially identify you.

_____ I do not give you permission to use any of my data for purposes not discussed in this consent. In this case, the investigator will ensure that your data is destroyed once it is no longer needed for the purposes of conducting and overseeing this study.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns, or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____	
Name of Subject (Please Print)	Signature of Subject	Date

_____	_____	
Name of Person Obtaining Consent (Please Print)	Signature	Date