MET001 - A Phase II Pilot Study Using Metformin to Reduce Cardiac Toxicity in Breast Cancer Patients

NCT#: 02472353

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PROTOCOL SUMMARY

TITLE OF THE STUDY	A Phase II Pilot Study Using Metformin to Reduce Cardiac Toxicity in Breast Cancer Patients
STUDY OBJECTIVES	**Primary** • To determine if co-administration of metformin and doxorubicin in breast cancer patients receiving neoadjuvant or adjuvant therapy will reduce the number of patients who develop a significant change in left ventricular ejection fraction (LVEF) (≥ 5% Decrease) **Secondary** • To assess and compare the number of patients in each group who develop a decrease in LVEF of ≥10% from baseline • To assess the potential changes in diastolic function and compare the changes between the treatment arms • To explore whether the following biomarkers correlate with a change in cardiac function and activity of metformin: Troponin I, BNP, glutathione, circulating adiponectin, AMPK phosphorylation, and lipid peroxidation,) • To explore whether symptoms expressed on the TRSC correlate with known SNPs
STUDY DESIGN	Randomized, open-label

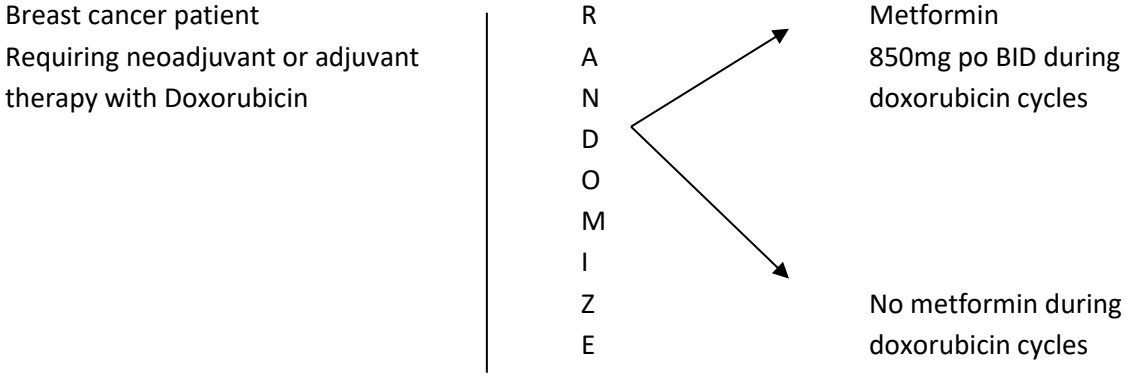
STUDY POPULATION	**Inclusion criteria:**
	• Histologically confirmed breast cancer requiring neoadjuvant or adjuvant chemotherapy with doxorubicin
	• Baseline lab work should be completed within 28 days prior to randomization. Biochemistry investigations should reflect values within the following parameters:
	  ○ AST < 2.5 X ULN
	  ○ ALT < 2.5 X ULN
	  ○ Alkaline Phosphatase < 2.5 X ULN
	  ○ Serum Creatinine < 1.5mg/dL
	  ○ Serum bilirubin < ULN
	• ECOG Performance Status of 0 or 1 (at baseline evaluation visit within 28 days prior to randomization)
	• Age ≥21 years of age
	• Protocol treatment should begin within 28 working days of patient randomization
	• Patient must sign consent form prior to

	randomization or registration **Exclusion criteria:** • Known diabetes (Type I or Type 2) • History of cardiac arrhythmias or symptomatic cardiac disease • Currently taking antiarrhythmic medications, beta-blockers or other rate controlling cardiac medications • Subjects who are already taking metformin and/or sulfonylureas • Known hypersensitivity or intolerance to metformin • Baseline ejection fraction of <50% measured by echocardiogram • Risk factors associated with increased risk of metformin-associated lactic acidosis (e.g. congestive heart failure, history of acidosis, habitual intake of 3 or more alcoholic beverages per day) • Currently pregnant
TOTAL NUMBER OF PATIENTS	The planned sample size is 44 patients with breast cancer requiring neoadjuvant or adjuvant therapy (80% power to detect significant change in LVEF with alpha=0.05)
STUDY TREATMENT	Patients will be equally randomized to either receive metformin concomitantly with standard of care therapy, or to receive standard therapy alone. Treatment with metformin on the experimental arm will commence approximately 7-10 days prior to the start of doxorubicin-containing cycles, and will stop once doxorubicin-containing cycles are complete (approximately 3-4 months)
STUDY EVALUATIONS	The following assessments will be performed: • Echocardiogram (assessment of LVEF) performed at baseline, post doxorubicin containing cycles, 1 year follow up, and 7 year follow-up • Biomarkers: Troponin I, BNP, glutathione, circulating adiponectin, AMPK phosphorylation, and lipid peroxidation. Biomarkers EXCEPT for Troponin I will be obtained prior to each doxorubicin infusion and within 28 days of last dose with other standard of care labs for a total of 5 times. Troponin I will be drawn at baseline and 2-3 days after each doxorubicin dose. Biomarkers will be assessed for a correlation with cardiac

	function as well as metformin activity • Whole blood banking: one tube whole blood will be obtained and banked for potential future, exploratory genomic analysis • Treatment Related Symptom Checklist (TRSC): obtained prior to each cycle of doxorubicin to assess symptoms experienced by patient. Symptoms reported on the TRSC will be correlated with known SNPs during genomic analysis (exploratory)
DURATION OF STUDY PERIOD	Treatment will continue until doxorubicin-containing cycles have been completed (within 28 days of completion), unless unacceptable toxicity occurs or the patient decides to withdraw from participation for any reason
STUDY PERIOD	Planned start date: 7/1/2014 Planned accrual start date: 7/15/2014 Planned accrual closure: 7/15/2015 Planned study closure: 7/15/2025

Treatment Schema

The study population will include adult women (≥21 years of age) who have received a diagnosis of breast cancer that requires neoadjuvant or adjuvant therapy with doxorubicin. After obtaining informed consent, subjects will be equally randomized to the experimental or control arm:



Patients will be excluded if they are already taking metformin, have a known hypersensitivity or intolerance to metformin, have abnormal renal or liver function, history of cardiac arrhythmias and/or symptomatic cardiac disease, are currently taking antiarrhythmic medications, beta-blockers, or other rate controlling cardiac medications, are already taking metformin and/or sulfonylureas, or have conditions associated with an increased risk for metformin-associated lactic acidosis.

Treatment with metformin on the experimental arm will commence approximately 7-10 days prior to the start of doxorubicin-containing cycles, and will stop once doxorubicin-containing cycles are complete

(within 28 days of completion). The patient will have an approximate total of 3-4 months of treatment with metformin.

1.0 BACKGROUND INFORMATION AND RATIONALE

About 2.6 million living women in the US have been previously diagnosed with breast cancer (http:// seer.cancer.gov/statfacts/html/breast.html). A large portion of these women will have been treated with adjuvant therapies that include four cycles of doxorubicin. Half of them will be under age 61 and many are expected to have long-term survival and thus increased risk for late effects. Since the goal of adjuvant therapy is cure, the benefits should outweigh the risk of short and long-term toxicities [1].

The anthracycline doxorubicin is a potent chemotherapeutic agent used to treat a broad spectrum of cancers. A serious side effect of doxorubicin is cardiotoxicity. Acute toxicity is predicted to occur in less than 1% of patients immediately after treatment and is generally considered to be transient in nature [2]. Chronic cardiotoxicity is much more serious and often culminates in irreversible congestive heart failure (CHF) [3-5]. Onset is generally within 1 year after treatment but it can also present 10-20 years later [2]. Patients that develop doxorubicin-related cardiomyopathy have a very poor prognosis [6, 7]. Paradoxically, longer survival is a significant risk factor for doxorubicin-related heart problems in breast cancer patients [8].

The incidence of cardiotoxicity is well documented in the literature. In a trial of more than 3,000 patients receiving adjuvant breast therapy with doxorubicin, a 1%-2% incidence of CHF after treatment was seen [9]. A pivotal trial by Perez et al evaluated changes in left ventricular ejection fraction (LVEF) before and after treatment with doxorubicin [1]. Results demonstrated out of 1538 patients evaluated, over 50% of patients had a change in LVEF from baseline and over 23% of patients had either grade 1 or grade 2 LVEF toxicity as graded by NCI criteria. Using the SEER database, a cumulative 38% rate of CHF in women aged 66 years and older that had received anthracyclines during adjuvant therapy was found [10]. Furthermore, a systematic review by Smith et al reported that anthracyclines increased the risk of clinical cardiotoxicity by 5.43 fold, subclinical cardiotoxicity by 6.25 fold, risk for cardiac death by 4.94 fold, and any cardiotoxicity by 2.27 fold [8].

Cardiotoxicity limits the dose of doxorubicin that can be used in cancer therapy and thus the total cumulative dose of the drug must be watched very carefully. Cumulative doses exceeding 300mg/m2 have been linked with increased cardiac damage [1]. Studies have shown that doxorubicin-induced CHF can occur in 3%-5% of patients with maximum doses at 400mg/m2; at 550mg/m2 the incidence increased to 26% [2]. For this reason, the maximum lifetime cumulative dose of doxorubicin is 400mg/m2 to 550mg/m2 [2]. This value can be even lower depending on age, pre-existing conditions, and combinations with other drugs. Beyond reducing the total cumulative dose of doxorubicin, other strategies for limiting its cardiotoxicity have been pursued. Attempts to develop chemical analogs that retain anti-tumor properties but have reduced cardiotoxicity have had minimal success [11]. Among numerous compounds tested,

only dexrazoxane, an iron chelator, has been approved for clinical use due to its ability to decrease doxorubicin-dependent free radical generation and reduce cardiac damage [12, 13]. However, dexrazoxane may lead to myelosuppression and potential interference with chemotherapeutic efficacy [14]. Thus a major impact would be realized by identifying new compounds that protect against doxorubicin-induced heart damage while at the same time maintaining or enhancing the antitumor activity of the drug.

1.1 Pre-Clinical Data

Metabolism-targeted drugs that promote mitochondrial function have potential as protective agents against doxorubicin-induced heart damage. While the major mechanism by which doxorubicin kills cancer cells is to induce DNA damage [5], doxorubicin cardiotoxicity is related to cellular metabolism. Mitochondrial damage plays a central role in this process [15-21]. Doxorubicin has been shown to enter the mitochondria where it can accept an electron from Complex I, forming a free radical. Subsequent donation of an electron to O_2 produces superoxide, leading to mitochondrial damage and cellular oxidative stress [17, 18]. Doxorubicin treatment is associated with loss of mitochondrial membrane potential and inhibition of oxidative phosphorylation [22, 23]. Mitochondrial dysfunction following doxorubicin treatment causes a shift from preferentially using β-oxidation of fatty acids for energy metabolism to anaerobic glycolysis [24]. Maintaining mitochondrial integrity and sustaining mitochondrial oxidative metabolism is protective against doxorubicin cardiotoxicity [25]. Thus metabolism-targeted drugs that enhance mitochondrial quality control and promote efficient oxidative phosphorylation are expected to be effective against doxorubicin induced heart damage.

Laboratory data from Asensio-Lopez et al demonstrated that in adult mouse cardiomyocytes, metformin reduced oxidative stress and cardiomyocyte apoptosis in the presence of doxorubicin [26]. Metformin was also found to modulate the adiponectin system, which plays a pivotal role in the mechanism of protection against doxorubicin induced cardiac damage [26]. Futhermore, data from the same laboratory has recently identified the ability of metformin to upregulate gene and protein expression of the ferritin heavy chain (FHC), a crucial role in the protection of cardiomyocytes from doxorubicin damage [27].

We propose that drugs which inhibit glycolysis and/or promote mitochondrial function and integrity, like metformin, will protect against doxorubicin cardiotoxicity. Metformin has been associated with decreased risk of heart failure in diabetic patients [28]. Long-term use of metformin is linked to reduced cardiovascular mortality [29]. Population studies indicate that diabetics taking metformin have significantly reduced risk of cancer and lower cancer-related mortality than diabetics not taking metformin [30-32]. For diabetic patients with breast cancer, patients on metformin had a significantly better response to neoadjuvant chemotherapy than patients not on metformin [32] Numerous

studies have revealed a cardioprotective role for metformin under various pathological conditions [33-37].

The proposed study, if successful, is likely to have a major impact on breast cancer patients receiving therapy for a curative intent. Additionally, doxorubicin is used in many types of cancer, thereby creating the potential to study metformin and doxorubicin in other populations. Specifically, the proof-of-concept from this project could be rapidly translated into use for cancer patients because metformin has already been used in clinical settings for different purposes. Data from this study will also be used to leverage access to large data sets from ECOG, IBCSG, and others to retrospectively substantiate our findings.

1.2 Background Therapeutic Information

Metformin is a well-known oral agent used to treat Type 2 diabetes as well as insulin resistance. It is readily available and generally well tolerated. Its most potentially dangerous toxicity is lactic acidosis, with an estimated incidence of 3 cases per 100,000 patient years. Due to results from a meta-analysis, debate exists on whether the lactic acidosis that occurs in diabetics receiving metformin is due to metformin, or to the presence of diabetes. The meta-analysis showed comparable rates of lactic acidosis among diabetics who did, and who did not receive metformin, as well as a failure to correlate metformin levels in diabetics with lactic acidosis. Additionally, an increase in lactic acidosis rates was not seen after the introduction of metformin in the United States. Nevertheless, when lactic acidosis occurs it can be fatal. Therefore, individuals with increased risk factors for developing lactic acidosis should avoid the use of metformin. Risk factors include: greater than 80 years of age, individuals with current or past congestive heart failure, renal or hepatic insufficiency, excessive alcohol intake, and individuals with a prior history of metabolic acidosis. It is believed that the risk for lactic acidosis increases after surgery and with the use of radiologic contrast material, therefore metformin should be temporarily discontinued for approximately 48 hours in these circumstances. Common side effects of metformin (occurring in >1/10) are generally gastrointestinal in nature and include diarrhea, nausea, vomiting, abdominal bloating, flatulence, anorexia, and metallic taste. These side effects are usually transient and resolve spontaneously with continued treatment. Other toxicities are as follows: rash (<1/10,000), subnormal vitamin B12 (9% after 6 months, therefore a Vitamin B level and hemoglobin levels are monitored at 6-12 months), hepatic dysfunction (<1/10,000), elevations in TSH (<1/10,000), modest weight loss (up to 5 pounds) is common. Metformin does not normally cause hypoglycemia. Rarely, extreme caloric restriction or excessive physical activity without adequate caloric intake may lead to hypoglycemia. Metformin has been used for many years without cumulative adverse effects.

Name and Chemical Information

N,N – dimethyl biguanide hydrochloride

1.3 Mechanism of Action

Metformin HCl is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or a diabetic animal and only when insulin is secreted. Metformin has no effect on pancreatic beta cells. The mode of action of metformin is not fully understood, but it has been postulated that metformin may potentiate the effect of insulin or reduce hepatic gluconeogenesis.

Absorption of metformin may extend over approximately six hours. The drug is excreted in urine at high renal clearance rates, about 450mL/min. Initial elimination is fairly rapid with a half-life varying between 1.7 and 3 hours. Terminal elimination is slow with a half-life between 9-17 hours, and accounts for about 4-5% of the absorbed dose. Metformin is not metabolized. Main sites of concentration are the intestinal mucosa and the salivary glands.

Some drugs can potentiate the effect of metformin, specifically the sulfonylurea types of drugs in the treatment of type 2 diabetes. Simultaneous administration of metformin and sulfonylurea can produce a hypoglycemic reaction, particularly if patients are receiving other drugs that can potentiate the effect of sulfonylureas such as long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid, and propanolol. Metformin is less likely to interact with highly protein-bound drugs (i.e. salicylates, sulfonamides, chloramphenicol, and probenecid) given its negligible binding to plasma proteins; sulfonylureas are extensively bound to serum proteins.

1.3.1 Pregnancy Category B

Animal studies show no risk or adverse fetal effects but controlled human 1st trimester studies are not available. No evidence of 2nd or 3rd trimester risk.

Lactation is probably safe. Limited information in animals and/or humans demonstrates no risk/minimal risk of adverse effects to infant/breast milk production; caution advised.

1.3.2 Pharmaceutical Data

Metformin: 850mg tablet

Storage: Store at room temperature in well-closed containers

Route of administration: Orally, with food

1.4 Chemotherapy and Concomitant Metformin

Metformin is routinely taken in patients with type 2 diabetes that are also receiving chemotherapy for cancer. The chemotherapies used in standard of care neoadjuvant or adjuvant therapy for breast cancer are not contraindicated or listed as interacting drugs with metformin in standard drug information guides like Micromedex. The most likely concern warranting close monitoring is the patient's renal function, which is standard of care and built into this protocol.

Unlike other drugs used for cardioprotection such as dexrazoxane, which potentially interfere with the efficacy of the chemotherapy, metformin has been shown to inhibit the growth of cancer cells [34-37]. Furthermore, a recent retrospective trial was completed on breast cancer patients receiving neoadjuvant chemotherapy, comparing diabetic patients taking metformin, diabetic patients not taking metformin, and nondiabetic patients [32]. The large database (N=2,529) found that diabetic patients receiving metformin and neoadjuvant chemotherapy had a significantly higher rate of pathologic complete responses (pCR) [32]. Other observational studies have associated diabetics receiving metformin with reduced cancer incidence and or mortality [29-31].

1.5 Echocardiogram

Echocardiograms will be performed to assess LVEF as an indication of left ventricular systolic function. Additionally, since diastolic dysfunction is detected earlier on echocardiograms in patients that are exposed to anthracyclines, diastolic function will also be assessed with each echocardiogram as a secondary endpoint. Cardiotoxicity due to anthracyclines can be acute and/or manifest years after treatment; therefore echocardiograms will be obtained at baseline, upon completion of the doxorubicin containing cycles (within 28 days of completion), and at the one year and seven year follow-up time points.

Echocardiography creates an image of the heart using high-frequency sound waves. It is a non-invasive, safe procedure that does not require special preparation. An echocardiogram procedure usually lasts between 30-60 minutes. The use of contrast echocardiography (Definity contrast) will be preferred for each patient given the reduced variability and increased accuracy in LVEF measurements. If patients have already had an echocardiogram at baseline before consenting to this study, then a non-contrast echocardiogram will be accepted. If patients have a known hypersensitivity to contrast used with echocardiograms, then a non-contrast echocardiogram will be accepted. All attempts will be made to maintain the same echocardiogram type (contrast or no contrast) that the patient has at baseline for the remainder of the study.

All attempts will be made to have the same cardiologist read the echocardiograms for each patient enrolled in the study. Additionally, all attempts will be made to have the

echocardiogram procedure for each patient completed by one of two experienced technicians chosen for this study in order to reduce potential variation in technique.

1.6 Correlative Studies

Correlative studies will be incorporated into this pilot study. The following biomarkers will be correlated with cardiac function measured on echocardiogram: Troponin I, glutathione, and BNP. Troponin I is released when cardiomyocyte destruction occurs, thereby indicating cardiomyocyte damage. Glutathione levels reflect oxidative stress, which is part of the mechanism for cardiomyocyte damage. BNP is secreted by the ventricles of the heart in response to excessive stretching of the cardiomyocytes, which occurs with left ventricular dysfunction.

The following biomarkers will be obtained to correlate the effects of metformin: AMPK phosphorylation, adiponectin, and lipid peroxidation.

1.7 Study Checklists and Questionnaires

1.7.1 Treatment-Related Symptom Checklist

The Therapy-Related Symptom Checklist (TRSC) is a patient self-report tool that allows for the subjective measure of therapy-related symptom severity [38] (Appendix 1). Patients rate 25 symptoms on severity using a five-point scale; other symptoms may be added and rated as well. A higher total score on the TRSC indicates greater frequency and severity of symptoms. Prior studies have indicated that TRSC scores correlate inversely with the Karnofsky scales, showing the TRSC's construct validity. Additionally, use of the TRSC has led to improved symptom documentation and management, thereby affecting patients' quality of life [38,39]. The TRSC has demonstrated good psychometric properties in previous studies.

1.7.2 Symptom Alleviation: Self-Care Methods (SASCM)

Based on the TRSC symptoms, the Symptom Alleviation: Self-Care Methods (SASCM) tool will record self-care strategies used by patients to alleviate the symptoms reported and whether the method helped or did not help [40-45] with reported Cronbach's alpha of .89.[40] (Appendix 2). This will be a one-time measure at the end of treatment that is completed by the patients.

1.7.3 Health-Related Quality of Life Linear Analogue Self-Assessment (HRQOL-LASA)

Patient quality of life (QOL) will be assessed using the Health-Related Quality of Life Linear Analogue Self-Assessment (HRQOL-LASA), which is completed by the patient. The HRQOL-LASAS measures six items on a 10-point scale from 0 (as bad as can be) to 10 (as good as can be). These items have been validated as measures of global QOL constructs in numerous settings [46-49] (Appendix 3).

1.8 Whole Blood Banking

If willing, all enrolled patients will provide a sample of whole blood. DNA and RNA will be extracted from the whole blood sample and banked for further exploratory analysis.

2.0 STUDY DESIGN

This is a randomized, open-label, phase II design pilot study in patients with breast cancer requiring neoadjuvant or adjuvant chemotherapy. Eligible patients will be equally randomized to either receive metformin plus standard of care therapy or to standard of care therapy alone. Approximately 7-10 days prior to the first doxorubicin dose patients randomized to the experimental arm will begin taking metformin per the ramp up period schedule (see section 5.4). Patients receiving metformin will continue the drug until the doxorubicin-containing cycles are complete, unless unacceptable toxicity occurs or the patient decides to withdraw from the study. Both arms of the study will undergo echocardiograms at baseline, upon completion of doxorubicin containing cycles (within 28 days of completion), and at the one year and seven year follow up time points. Additionally, biomarker labs will be obtained prior to each doxorubicin infusion for all enrolled patients with the exception of Troponin I, which will be drawn two to three days post each doxorubicin infusion. Prior to each doxorubicin containing cycle, the TRSC will be used for symptom assessment for all enrolled patients. If willing, all enrolled patients will provide a sample of whole blood for further exploratory analysis. Symptoms reported on the TRSC will be correlated with known SNPs found during an exploratory genomic analysis. The study will be conducted at the Avera Cancer Institute in Sioux Falls, SD, as well as Avera St. Luke's Cancer Center in Aberdeen, SD.

3.0 OBJECTIVES

3.1 Primary Objective

To determine if co-administration of metformin and doxorubicin in breast cancer patients receiving neoadjuvant or adjuvant therapy will reduce the number of patients who develop a significant change in left ventricular ejection fraction (LVEF) indicated by a decrease in LVEF of ≥5% from baseline.

3.2 Secondary Objectives

- To assess and compare the number of patients in each group who develop a decrease in LVEF of ≥10% from baseline
- To assess the potential changes in diastolic function and compare the changes between the treatment arms
- To explore whether the following biomarkers correlate with changes in cardiac function and with the activity of metformin: Troponin I, BNP, glutathione, circulating adiponectin, AMPK phosphorylation, and lipid peroxidation
- To explore whether symptoms expressed on the TRSC correlate with known SNPs found during exploratory genomic analysis
- Whole blood banking for future, exploratory genomic analysis

4.0 PATIENT SELECTION

To be eligible for this study, the following inclusion and exclusion criteria must be met:

4.1 Inclusion Criteria

- Histologically confirmed breast cancer requiring neoadjuvant or adjuvant chemotherapy with doxorubicin
- Baseline lab work should be completed within 28 days prior to randomization. Biochemistry investigations should reflect values within the following parameters:
  - AST < 2.5 X ULN
  - ALT < 2.5 X ULN
  - Alkaline Phosphatase < 2.5 X ULN
  - Serum Creatinine < 1.5mg/dL
  - Serum bilirubin < ULN
- ECOG Performance Status of 0 or 1 (at baseline evaluation visit within 28 days prior to randomization)
- Age ≥21 years of age
- Protocol treatment should begin within 28 working days of patient randomization
- Patient must sign consent form prior to randomization or registration

4.2 Exclusion Criteria

- Known diabetes (Type I or Type 2)
- Subjects who are already taking metformin and/or sulfonylureas
- Known hypersensitivity or intolerance to metformin
- History of cardiac arrhythmias or symptomatic cardiac disease
- Currently taking antiarrhythmics, beta-blockers or other rate controlling cardiac medications
- Baseline ejection fraction of <50% as measured by echocardiogram
- Risk factors associated with increased risk of metformin-associated lactic acidosis (e.g. congestive heart failure, history of acidosis, habitual intake of 3 or more alcoholic beverages per day)
- Currently pregnant

5.0 TREATMENT PLAN

5.1 Identification of Potential Subjects

Potential subjects will be identified by the breast surgeons and medical oncologists, as well as during multidisciplinary breast tumor conferences. Subjects will be adult (≥21 years of age) who have received a diagnosis of breast cancer that requires neoadjuvant or adjuvant therapy.

5.2 Randomization

After obtaining informed consent, subjects will be randomized using a permuted block randomization.

Patients will be equally randomized to one of the following arms:

ARM	AGENT	DOSE	ROUTE	DURATION
1	Metformin	850mg	P.O. (with food)	Twice daily during doxorubicin-containing cycles (approximately 3 months)
2	Standard of care – no metformin	N/A	N/A	N/A

5.3 Metformin Dispensing and Administration

There will be a ramp-up period for the metformin dosing and will occur as follows:

- One, 850mg tablet daily for ideally 7-10 days prior to starting therapy. However if the patient needs to start chemotherapy sooner than the ramp up period allows, the treating physician can choose to increase the metformin to twice daily sooner than 7 days
- Approximately 2-3 days prior to treatment with doxorubicin, increase to one, 850mg tablet twice daily until 28 days post last infusion of doxorubicin . Goal is to have subject on 850mg of metformin twice daily prior to commencement of doxorubicin

The usual recommended starting dose of metformin is 500mg or 850mg daily. Metformin is then titrated by adding 500mg/week or 850mg/2 weeks to a maximum dose of 2550mg/day. The dose of 850mg twice daily was chosen based on standard dosing and acceptable tolerability; the same dose is being used in breast cancer patients in larger scale studies where overall survival is the primary endpoint [50].

Metformin will be ordered by the cancer center's pharmacy which will maintain a careful record of the drug's receipt and disposition. Metformin pills will be dispensed to the patient by the research coordinator. Patients should bring their labeled pill bottles to the research coordinator at every protocol-mandated visit and at the end of the treatment period. A calendar schedule containing a place to mark when a dose of metformin is taken will be provided to each patient (see Appendix 4). The calendar will be used as a way to monitor treatment adherence, in addition to pill counts.

5.4 Pre-Treatment Evaluation

	Investigations	Timing
History and Physical Exam including:	Performance Status, alcohol intake, cardiac history, demographic information	Within 28 days prior to randomization
Pathology	Confirmation of breast cancer	Any time prior to randomization
Hematology	CBC with differential	Within 28 days prior to randomization
Biochemistry	Comprehensive metabolic panel	Within 28 days prior to

		randomization
Pregnancy Testing (for women of child-bearing potential)	Serum Pregnancy Test	As close to randomization as possible
Medication Reconciliation	Current medications and indications	Within 28 days prior to randomization
Adverse Events	Evaluation of baseline adverse events	Within 28 days prior to randomization
Whole blood banking	Exploratory analysis	Whole blood is one time draw (during regularly scheduled labs any time during study)
Therapy-Related Symptom Checklist	Baseline evaluation of symptoms	Prior to first cycle of chemotherapy (can occur anytime between consent and initiation of C1D1 of chemotherapy)
HRQOL-LASA	Baseline health-related quality of life measure	Prior to first cycle of chemotherapy (can occur anytime between consent and initiation of C1D1 of chemotherapy)
Echocardiogram	Baseline LVEF, diastolic function assessment	Within 28 days prior to randomization (± 2 weeks)

5.5 Evaluation During and After Protocol Treatment

All subjects on study should be evaluated according to the schedule below:

	Investigations	**Timing**
History and Physical Exam including:	Compliance with metformin	At minimum Day 1 of doxorubicin-containing chemo cycles
Labs	Biochemistry (Complete Metabolic Panel) in addition to other standard of care labs	At minimum Day 1 of doxorubicin-containing cycles
Echocardiogram	LVEF, diastolic function assessment	Within 28 days of last doxorubicin infusion (± 2 weeks)
Biomarkers*	BNP, glutathione, AMPK phosphorylation, lipid peroxidation, adiponectin	Prior to each cycle of doxorubicin containing cycles and within 28 days of last dose
Biomarker	Troponin I	Prior to C1D1 of doxorubicin (baseline) and 2-3 days after each doxorubicin infusion
Adverse Events	Graded using CTC 4.0	Day 1 of doxorubicin-containing cycles
Symptoms	Therapy-Related Symptom Checklist (TRSC)	Day 1 of doxorubicin-containing cycles
Self-care methods	SA:SCM	End of treatment visit

Health-related quality of life	HRQOL-LASA	End of treatment visit

*Will attempt to draw all biomarkers (except Troponin I) at the same time as other standard of care labs are drawn

5.6 Follow-Up Period

	Investigation	**Timing**
History and physical exam	Clinical assessment	Each clinic visit (per discretion of treating physician)
Echocardiogram	LVEF, diastolic function assessment	12 months post last doxorubicin infusion (± 60 days); 7 years post last doxorubicin infusion (±3 months)

Other follow up exams are per the investigator's discretion.

5.7 Patient Monitoring

Patients will be assessed prior to each cycle of doxorubicin-containing therapy for medication compliance and toxicity. Since the major toxicity of metformin is gastrointestinal in nature, the dose may need to be adjusted during the ramp up period. If subjects are experiencing gastrointestinal symptoms they should be encouraged to take metformin with food. If there is no improvement, subjects can try taking metformin every other day for one week, every day for one week, then twice per day thereafter. If subjects are still not tolerating metformin, they may go off study. Pills should not be split or crushed.

Toxicity	**Grade**	**Action**
Bilirubin >ULN (except for Gilbert's disease)	Grade 1 (or higher)	Hold metformin for up to 2 weeks. If bilirubin returns to normal during the 2 week period, restart metformin per the ramp up dosing
AST or ALT=2.5 -3.0 X ULN	Use CTC 4.0 for grading	Repeat AST and ALT in 2 weeks. If either >2.5 X ULN then continue at investigator's discretion, monitoring labs at least every 2 weeks
AST or ALT = 3.0 X ULN	Use CTC 4.0 for grading	Hold metformin and repeat labs in 2 weeks. If AST or ALT <2.5 X ULN then restart metformin based on the ramp up dosing. If AST or ALT 2.5 – 3.0 X ULN then continuation of metformin is per the investigator's discretion with frequent lab monitoring If still 3.0 X ULN or higher come off study
Creatinine ≥ 1.5	Use CTC 4.0 for grading	Hold metformin for up to 2 weeks. When/if resuming, use the ramp up dosing schedule
Acidosis (Lactate ≥5.0mM;	Use CTC 4.0 for	Stop metformin and do not restart. Report as

pH <7.3)	grading	serious adverse event
GI toxicity of any type	Grade 1	Encourage patient to stay on schedule as side effects are usually transient
GI toxicity (nausea, diarrhea, etc.)	Grade 2 or higher	Reduce metformin to 1 tablet daily x 1 week. If tolerates, resume full dose. If grade 2 or higher toxicity reoccurs, reduce to 1 tablet for the remainder of the study. If unable to tolerate dose reduction to 1 tablet, stop metformin completely
Hospitalization (any reason)	Use CTC 4.0 for grading	Hold metformin. Investigator should determine if safe to restart and should be restarted based on ramp up dosing
Other	Use CTC 4.0 for grading	Contact PI with questions

5.8 Other circumstances

5.8.1 Surgery

If surgery necessitating anesthesia is required for any reason, metformin should not be taken on the morning of surgery and for 48 hours after surgery. Metformin can be restarted at full dose provided there is evidence of normal renal function.

5.8.2 Diagnostic Imaging

If the subject needs any CT scan requiring IV contrast material, metformin should be stopped 24 hours before the procedure and held for 48 hours after the procedure. Metformin can then be resumed at full dose as long as there is no evidence of renal dysfunction. Creatinine should be checked prior to restarting the metformin.

If contrast is used for the echocardiogram then the contrast used is Definity contrast, which is filtered through the lungs and therefore does not affect the kidneys. Metformin does not need to be held for the Definity contrast.

5.8.3 Medically Necessary

The investigator can hold metformin for any situation deemed medically necessary. The investigator can determine if resumption of metformin is appropriate. The ramp up dosing schedule should be followed when restarting if off of metformin for greater than 1 week.

5.8.4 Adverse Events

Adverse events will be graded using the NCI Common Terminology Criteria version 4.0.

5.8.5 Concomitant Medications

Concomitant medications need to be documented in the medical record. Certain medications are not permitted and include: sulfonylureas, thiazolidenediones, insulin, antiarrhythmics, beta-blockers, or other rate controlling cardiac medications. If these drugs are necessary to treat a new diagnosis or for any other reason, the patient will have to come off study. If there is a question regarding the appropriateness of a medication, please contact the principle investigator (PI).

5.8.6 Duration of Therapy

Subjects will take metformin twice daily with food, 850mg in the am and 850mg in the pm. Treatment will continue until doxorubicin-containing cycles have been completed (approximately 28 days after last doxorubicin infusion), unless unacceptable toxicity occurs or the subject decides to withdraw from participation for any reason.

6.0 SERIOUS ADVERSE EVENT (SAE) REPORTING

All SAEs must be reported to the PI within 24 hours and be documented on the case report forms. An update on the SAE should be reported to the PI within 7 days.

All SAEs that are unexpected and related to the study drug, in this case metformin, need to be reported within 24 hours to the PI, including events occurring during the study period and within 30 days after the last dose of metformin is taken.

A SAE is any adverse event that at any dose:

- Results in death
- Is life threatening
- Results in permanent or significant disability
- Requires inpatient hospitalization
- Results in congenital anomaly or birth defect

7.0 PATIENT DISCONTINUATION

The treating physician will make every reasonable effort to keep each patient on study. If, however, a patient is removed from the study or the patient declines further participation, a final assessment of the patient's LVEF and diastolic function and biomarkers should be obtained. These results, along with the reason for study discontinuation, must be recorded in the CRF.

Patients will discontinue treatment if any of the following occur:

- Unacceptable toxicity

- Patient withdrawal of consent of HIPAA Authorization
- Investigator/treating physician decision
- New diagnosis of diabetes requiring other medications such as sulfonylureas

8.0 DATA ANALYSIS

The primary outcome of interest is a decrease in systolic function defined as a drop in LVEF of ≥5%. To assess differences between groups we will use a Fischer's exact test to compare proportions. In addition, the logistic regression model will be done as a secondary analysis. This will allow us to include patient and treatment characteristics that may be unbalanced at baseline due to the relatively small number of subjects included in the trial. Secondary analysis will be performed to assess the relationship between the change in biomarker levels and the change in LVEF using logistic or linear regression as appropriate and will include a term for treatment group as well as an interaction with treatment group since the patterns of change may be different based on treatment with metformin. Model assumptions will be assessed and transformations and/or nonparametric methods will be used where necessary.

8.1 Sample Size Determination

With standard treatment, we expect that 50% of patients will have a significant decrease in LVEF while in those taking concomitant metformin only 10% of patients will have a significant decrease in LVEF. Assuming a significance level of 0.05, we will have 80% power to detect such a difference between the two groups with 19 subjects in each group. To account for potential drop-out, estimated to be 15%, we will enroll 22 subjects in each group.

9.0 STUDY ADMINISTRATION

This study will be conducted in compliance with the protocol, the principles of Code of Federal Regulations (CFR), ICH GCP and the Declaration of Helsinki as amended in Edinburgh (2000) (Appendix 5).

9.1 Informed Consent

The principles of informed consent and GCP guidelines in FDA-Regulated Clinical Trials are described in the 21 CFR 50, Protection of Human Subjects.

These regulations must be followed in conducting and monitoring clinical investigations. Consent for participation in the study will be obtained and documented.

The investigator/physician will thoroughly explain to the patient the purpose and methods of the study, as well as any expected effects and adverse reactions, before any study-specific screening procedures are conducted. The patient will be provided with a copy of the consent and will be given sufficient time and opportunity to inquire about the details of the trial and to decide whether or not to participate. The patient and the

person with whom the informed consent is discussed will sign and date the consent form.

The investigator/treating physician will explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time and for any reason. Similarly, the investigator/treating physician and/or Sponsor will be free to withdraw the patient at any time for safety or administrative reasons. Any other requirements necessary for the protection of the human rights of the patient will also be explained, according to current CFR (21, parts 312D, 50 and 56), ICH (ICH E6 1997) and GCP guidelines and the Declaration of Helsinki, 1964 [as amended in Edinburgh (2000)]. A copy of the Declaration of Helsinki is provided in Appendix 5.

9.2 Institutional Review Board Approval

This study must be approved by an appropriate institutional review board/committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1891, Part 56) and the Office of Human Research Protection (45 CFR 46). Prior to screening any patients for participation into this study, the investigator/treating physician must obtain and provide written documentation of IRB review and approval of the protocol and the informed consent document to study sponsor.

The IRB must also be informed of any protocol amendments prior to implementation. The investigator/treating physician must provide reports of any change in research activity (e.g. the completion, termination or discontinuation of the study) to the IRB.

9.3 Modification of the Protocol

Protocol amendments to the ongoing study that could potentially adversely affect the safety of participating patients, or that alter the scope of the investigation, the scientific quality of the study, the experimental design, duration of therapy, assessment variables, the number of patients treated or patient selection criteria must be made only after consultation with the Lead Principal Investigator.

Protocol amendments will be prepared, reviewed and signed by the Lead Principal Investigator.

Any amendments to the protocol that are made after receipt of initial IRB approval must be submitted by the investigator to the IRB and Regulatory Authorities (where required) in accordance with local procedures and regulatory requirements, before the changes can be implemented. Amendments to the protocol that eliminate an apparent immediate hazard to patients do not require pre-approval by the IRB.

Administrative amendments that do not affect the conduct of the study or patient safety, and do not significantly reduce the scientific value of the protocol; will not be

resubmitted for formal ethics review or lead to a change in the patient information sheet. Such amendments will be sent to the IRB for information only.

9.4 Protocol Compliance

Deviations from the approved study protocol will be noted during the monitoring process and will be required to be reported to the IRB by the investigator/treating physician per their governing IRB policy for reporting protocol deviations/violations.

9.5 Case Report Forms (CRFs)

CRFs will be used to collect the data, and all data management activities will be carried out by Avera Research. The investigator/treating physician is responsible for maintaining accurate, complete and up-to-date records for each patient. The investigator/treating physician is also responsible for maintaining all source documentation related to the study. All CRFs should be completed in a neat, legible manner to ensure accurate interpretation of the data.

9.6 Study Records

The investigator/treating physician must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Documents include the protocol and protocol amendments (if applicable), CRFs, CRF query forms, IRB and regulatory authority approval with correspondence, informed consent, screening and enrollment logs, staff résumé and authorization forms and other appropriate documents and correspondence. Patient clinical source documents will include patient and/or hospital clinical records, physician's and nurse's notes, appointment book, original laboratory reports, ECG and imaging reports, pathology and special assessment reports, consultant letters, and other relevant documents and correspondence.

The patient's involvement in the study should be clearly documented in the clinical records. Details should include the study protocol number, the hospital/ clinic unit code, the patient's identification number, the patient's consent to take part in the study (including the date of consent), the dates of eligibility confirmation by investigator/treating physician, dates of all study visits, date of procedure to obtain tissue specimen for study, and date and reason for study discontinuation.

The original reports, tracings and films must be retained by the investigators/treating physician for future reference. Copies of the CRFs must be retained by the investigators/ treating physicians, for as long as is legally required after completion of the study, to comply with CFR/ICH GCP guidelines. All data relating to the study, including study master file contents, CRFs and source data will be stored by the investigator/treating physician for at least 15 years.

If the investigator/treating physician cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements must be made between the investigator/treating physician and the Sponsor, to store these in a secure archive facility outside the site; they can therefore be returned to the investigator/ treating physician in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside the site.

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Appendix 1

THERAPY-RELATED SYMPTOMS CHECKLIST (TRSC)

Name: _____ Hospital #_____ Date:

PLEASE **CHECK** THE PROBLEMS YOU HAVE HAD IMMEDIATELY AFTER AND SINCE YOUR LAST TREATMENT. PLEASE CIRCLE HOW SEVERE THE PROBLEM WAS ACCORDING TO THE FOLLOWING SCALE:

0 = NONE 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE

CHECK	EXAMPLE	Degree of Severity **(CIRCLE)**				
☒☒	Pain	0	1	2	③③	4
☐☐	Taste Change	0	1	2	3	4
☐☐	Loss of appetite	0	1	2	3	4
☐☐	Nausea	0	1	2	3	4
☐☐	Vomiting	0	1	2	3	4
☐☐	Weight loss	0	1	2	3	4
☐☐	Sore mouth	0	1	2	3	4
☐☐	Cough	0	1	2	3	4
☐☐	Sore throat	0	1	2	3	4
☐☐	Difficulty swallowing	0	1	2	3	4
☐☐	Jaw pain	0	1	2	3	4
☐☐	Shortness of breath	0	1	2	3	4
☐☐	Numbness in fingers and/or toes	0	1	2	3	4
☐☐	Feeling sluggish	0	1	2	3	4
☐☐	Depression	0	1	2	3	4
☐☐	Difficulty concentrating	0	1	2	3	4
☐☐	Fever	0	1	2	3	4
☐☐	Bruising	0	1	2	3	4
☐☐	Bleeding	0	1	2	3	4
☐☐	Hair loss	0	1	2	3	4
☐☐	Skin changes	0	1	2	3	4
☐☐	Soreness in vein where chemotherapy was given	0	1	2	3	4
☐☐	Difficulty sleeping	0	1	2	3	4
☐☐	Pain	0	1	2	3	4
☐☐	Decreased interest in sexual activity	0	1	2	3	4
☐☐	Constipation	0	1	2	3	4
	Other problems (please list below)					
☐☐		0	1	2	3	4
☐☐		0	1	2	3	4

Appendix 2

TRSC Symptom Alleviation: Self-Care Methods (SA:SCM)
ID# _____Date: _____
Data Collector: _____

	ALLEVIATION METHODS DONE OR USED	*How often Done? 4, Very Often Done; 3, Often Done; 2, Done Occasionally; 1, Seldom Done; 0, Not Done	Did it Help? (Yes/No)
Taste Change			
Loss of appetite			
Nausea			
Vomiting			
Weight loss			
Sore mouth			
Cough			
Sore throat			
Difficulty swallowing			
Jaw pain			
Shortness of breath			
Numbness in fingers and/or toes			
Feeling sluggish			
Depression			
Difficulty concentrating			
Fever			
Bruising			
Bleeding			
Hair loss			
Skin changes			
Soreness in vein where chemotherapy given			
Difficulty sleeping			
Pain			
Decreased interest in sexual activity			

	ALLEVIATION METHODS DONE OR USED	*How often Done? 4, Very Often Done; 3, Often Done; 2, Done Occasionally; 1, Seldom Done; 0, Not Done	Did it Help? (Yes/No)
Constipation			
Other problems (please list below)			

***Rate *each alleviation method* used-- each reported symptom would have a *mean* rating**

Appendix 3

Health-Related Quality of Life (HRQOL), Linear Analogue Self Assessment (LASA)

Patient Name: _____Date: _____
Patient Number: _____

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

How would you describe:

1. your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

2. your overall mental (intellectual) well-being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

3. your overall physical well-being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

4. your overall emotional well-being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

5. your level of social activity?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

6. your overall spiritual well-being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

Appendix 4

Example of Study Calendar

◄ Dec 2013			~ January 2014 ~			Feb 2014 ►
Sun	**Mon**	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**
			1 AM Metformin ___ PM Metformin ____	**2** AM Metformin ___ PM Metformin ____	**3** AM Metformin ___ PM Metformin ____	**4** AM Metformin ___ PM Metformin ____
5 AM Metformin ___ PM Metformin ____	**6** AM Metformin ___ PM Metformin ____	**7** AM Metformin ___ PM Metformin ____	**8** AM Metformin ___ PM Metformin ____	**9** AM Metformin ___ PM Metformin ____	**10** AM Metformin ___ PM Metformin ____	**11** AM Metformin ___ PM Metformin ____
12 AM Metformin ___ PM Metformin ____	**13** AM Metformin ___ PM Metformin ____	**14** AM Metformin ___ PM Metformin ____	**15** AM Metformin ___ PM Metformin ____	**16** AM Metformin ___ PM Metformin ____	**17** AM Metformin ___ PM Metformin ____	**18** AM Metformin ___ PM Metformin ____
19 AM Metformin ___ PM Metformin ____	**20** AM Metformin ___ PM Metformin ____	**21** AM Metformin ___ PM Metformin ____	**22** AM Metformin ___ PM Metformin ____	**23** AM Metformin ___ PM Metformin ____	**24** AM Metformin ___ PM Metformin ____	**25** AM Metformin ___ PM Metformin ____
26 AM Metformin ___ PM Metformin ____	**27** AM Metformin ___ PM Metformin ____	**28** AM Metformin ___ PM Metformin ____	**29** AM Metformin ___ PM Metformin ____	**30** AM Metformin ___ PM Metformin ____	**31** AM Metformin ___ PM Metformin ____	**Notes:**

EXAMPLE ONLY

APPENDIX 5. DECLARATION OF HELSINKI

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research investigators/treating physician should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator/treating physician, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well- informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator/treating physician must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator/treating physician must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators/treating physicians are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in

the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 6

Schedule of Events

Procedure	Screening/ Enrollment	Start of Treatment[l]	On Study	End of treatment	Follow Up 12 months	Follow Up 7 years
Window	Within 28days prior to randomization	-14 to 0	Day 1 of each doxorubicin containing cycle	Within 28 days of last doxorubicin infusion	± 2 months	± 3 months
Informed Consent/HIPPA	X					
Inclusion/Exclusion	X	X[g]				
Patient Registration	X					
Demographics	X					
Medical History	X	X[i]	X	X (+/-) 2 weeks	X	
Physical Exam	X	X[i]	X	X (+/-) 2 weeks	X	
Performance Status – ECOG	X	X[i]	X	X(+/-) 2 weeks	X	
Medication Reconciliation	X	X[i]	X	X(+/-) 2 weeks	X	
Hematology[a]	X					
Chemistry Panel[b]	X	X[i]	X	X(+/-) 2 weeks		
Biomarkers[c] (except Troponin I)		X[i]	X	X		
Troponin I		X[i]	X[d]	X		
Echocardiogram	X (± 2 weeks)			X (± 2 weeks)	X	X
Adverse Effects	X	X[i]	X	X(+/-) 2 weeks	X	
TRSC		X[j]	X	X(+/-) 2 weeks	X	
HRQOL-LASA[e]		X		X(+/-) 2 weeks		
Whole blood banking		X				
Pregnancy Test[g]	X					
SA:SCM [k]				X(+/-) 2 weeks		
Compliance with metformin		X	X	X		
Dispense Metformin	X	X				
Survival Status					X	X

[a] CBC, differential, platelet count, hemoglobin

[b] ALT/SGPT, AST/SGOT, Alk Phos, total bilirubin, creatinine, electrolytes

[c] Biomarkers (EXCEPT TROPONIN I) will be drawn at the same time as other standard of care labs, and will include BNP, glutathione, lipid peroxidation, AMPK phosphorylation, and adiponectin. With the exception of BNP and Troponin I, other blood samples for other biomarkers will be frozen, stored, and processed in batches

[d] Troponin I will be drawn 2-3 days after each doxorubicin infusion

[e] Health-related quality of life to be completed prior to starting treatment (can occur anytime between consent and initiation of C1D1 of chemotherapy) and at end of treatment visit

[f] The whole blood sample can be drawn anytime during the active study phase, and should be collected in EDTA tubes

[g] Mandatory for women of child-bearing potential (serum test)

[h] Investigator/treating physician will need to ensure that patient's baseline evaluations still meet eligibility criteria or will report any exclusionary criteria to the PI for review prior to starting patient on treatment

[i] Screening clinical evaluations and laboratory assessments may be used as the baseline evaluations if they are done within 14 days prior to starting the recommended treatment

[j] Baseline TRSC can occur anytime between consent and initiation of C1D1 of chemotherapy

[k] Symptom Alleviation: Self-Care Methods to be completed at end of treatment visit

[l] Start of doxorubicin