SUMMARY OF CHANGES

For Protocol Amendment # to: 16-440

NCI Protocol #:
DF/HCC Protocol #: 16-440

NCI Version Date:
Protocol Date: 2/2/17

#	Section	Page(s)	Change
1.	10	21	Added Perceived Stress Scale questionnaire
2.	1	1	Added PI name
3.	Schema	2	Changed "NHL" to "lymphoma" in Schema diagram
4.	1.0	5	Changed "NHL" to "lymphoma"
5.	1.2	5	Changed "NHL" to "lymphoma"
6.	2.1 A.2.1	6	Changed "non- Hodgkin lymphoma" to "lymphoma"
7.	2.1 A.2.1	7	Added "over"
8.	2.1 A.2.2	7	Changed "NHL" to "lymphoma"
9.	2.1 A.2.2	7	Removed "and the overall survival of patients"
10.	2.1 A.2.2	7	Changed "of patients" to "rate"
11.	2.1 A.2.2	7	Added "over"
12.	2.1 A.2.3	7	Changed "NHL" to "lymphoma"
13.	2.1 A.2.4	7	Changed "NHL" to "lymphoma"
14.	2.1 A.2	7	Changed "Non- Hodgkin lymphoma (NHL)" to "lymphoma"
15.	2.1 A.4	8	Changed "NHL" to "lymphoma"
16.	2.1 A.5	8	Changed "NHL" to "lymphoma"
17.	2.1 A.5	9	Changed "NHL" to "lymphoma"
18.	2.1 A.8	10	Changed "NHL" to "lymphoma"
19.	2.1 b	11	Remove "the majority of whom had NHL"
20.	2.1 b	11	Add "cancer"
21.	3.1	12	Changed "NHL" to "lymphoma"
22.	3.3	12	Changed "Non- Hodgkin lymphoma" to "lymphoma"
23.	13.1	24	Changed "NHL" to "lymphoma"
24.	13.2	27	Changed "NHL" to "lymphoma"

#	Section	Page(s)	Change
25.	13.2	27	Changed "NHL" to "lymphoma"

NCI Protocol #: N/A

DF/HCC Protocol #: 16-440

TITLE: STOP-CA (Statins TO Prevent the Cardiotoxicity from Anthracyclines)

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Responsible Research Nurse: NA

Responsible Data Manager: NA

NCI-Supplied Agent: NA
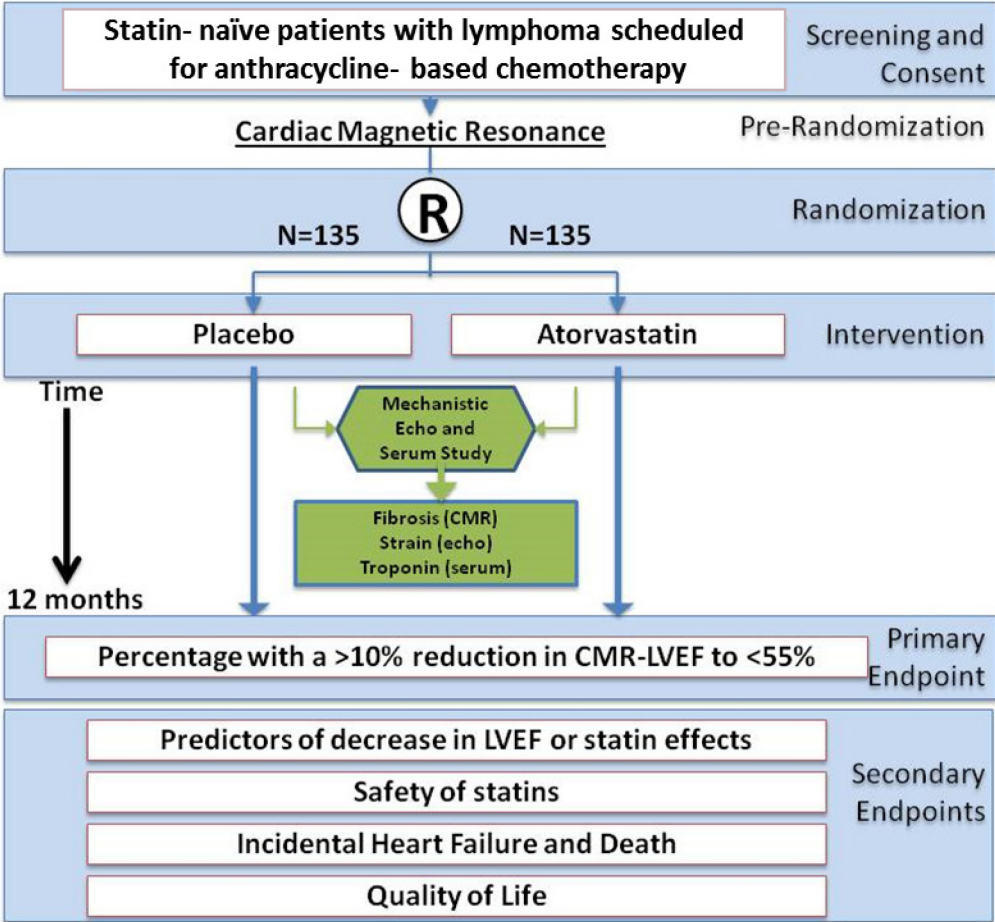
IND: NA

IND Sponsor: NA

Study Exempt from IND Requirements per 21 CFR 312.2(b).

Protocol Type / Version # / Version Date: Original/version#1/8/18/2016

SCHEMA

A flowchart diagram describing the study schema:

Screening and Consent: Statin-naïve patients with lymphoma scheduled for anthracycline-based chemotherapy

Pre-Randomization: Cardiac Magnetic Resonance

Randomization: R — N=135 / N=135

Intervention: Placebo | Atorvastatin

Mechanistic Echo and Serum Study → Fibrosis (CMR), Strain (echo), Troponin (serum)

Time → 12 months

Primary Endpoint: Percentage with a >10% reduction in CMR-LVEF to <55%

Secondary Endpoints:
- Predictors of decrease in LVEF or statin effects
- Safety of statins
- Incidental Heart Failure and Death
- Quality of Life

TABLE OF CONTENTS

1.0 OBJECTIVES

The purpose of this protocol is to test the effect of statin therapy, as compared to placebo, on the cardiac dysfunction after administration of anthracyclines among patients with lymphoma.

Anthracyclines are a mainstay of cancer treatment with more than 100,000 patients treated per year with anthracyclines in the United States; however, their use is associated with increased rates of heart failure and left ventricular (LV) dysfunction. Once anthracycline-induced cardiotoxicity (AIC) is symptomatic, survival is dramatically decreased. There is significant scientific plausibility and supportive observational data that statins may protect the heart during the administration of anthracyclines. STOP-CA (Statins TO Prevent the Cardiotoxicity from Anthracyclines) is a multi-center randomized double-blind placebo controlled trial, in 270 statin-naive patients who will be randomized 1:1 to atorvastatin 40mg/daily or placebo to determine whether atorvastatin started prior to anthracyclines reduces anthracycline-induced cardiotoxicity (AIC) among patients with newly diagnosed lymphoma. The endpoint AIC is defined based on expert consensus as a ≥10% reduction in LVEF to <55% within the first 12 months after therapy.[1-3] LVEF will be measured using the gold-standard, cardiac magnetic resonance (CMR), performed in an established core clinical trials laboratory by expert readers. Participants will be recruited over 3 years from large volume academic oncology networks. Myocardial fibrosis is a key intermediary that occurs prior to the development of LV dysfunction. CMR is the gold-standard imaging technique for fibrosis;[4, 5] therefore, to test whether the sub-acute development of myocardial fibrosis can predict the late occurrence of AIC and whether statins reduce myocardial fibrosis, we also propose measuring the extent of fibrosis at baseline and 6 months. We hypothesize that statins will attenuate myocardial fibrosis and that the extent of early fibrosis will predict the decrease in LVEF at 12 months. Both echocardiography and serum troponin are more widely available than CMR; therefore, in a third aim, we will test whether strain by echocardiography and troponin levels measured early during chemotherapy (after 4 of 8 standard cycles, ≈ 3 months), can identify patients at high risk of AIC.

If successful, this study will show that statins started prior to anthracyclines preserve LVEF, that statins prevent anthracycline-induced myocardial fibrosis and that the early measurement of myocardial strain or troponin during anthracyclines can identify patients at high risk of a subsequent LVEF decrease.

1.1 Study Design
This is randomized double blind placebo controlled clinical trial.
They will be treated with atorvastatin or placebo for 12 months.
The endpoint will be left ventricular ejection fraction (LVEF) by cardiac MRI measured at 12 months

1.2 Primary Objectives
To determine whether atorvastatin results in a significant reduction in the incidence of AIC among patients with lymphoma over 12 months; AIC is defined as a reduction of ≥10 percentage points in LVEF to <55%.

1.3 Secondary Objectives

Number 1: To compare the effect of statins, vs. placebo, on the development of myocardial fibrosis after anthracyclines. In a sub-study of 80 patients from Aim 1 (n=40 in each arm), we will measure myocardial fibrosis by calculation of the myocardial extracellular volume (ECV) using CMR, as previously described,[6-8] at baseline and 6 months to determine:
a.   Whether statins prevent the anthracycline-induced increase in myocardial fibrosis at 6 months.
b.   Whether a change in fibrosis or LVEF at 6 months predicts the occurrence of AIC at 12 months.

Number 2: We will determine whether an early decrease in myocardial strain or an increase in high-sensitivity troponin *during* anthracyclines (after 4 of 8 standard cycles ($\approx$ 3 months)) can predict subsequent development of AIC at 12 months. We will test:
a.   Whether statins, as compared to placebo, prevent the reduction in strain or the increase in troponin throughout the study period (12 months).
b.   Whether a change in troponin, strain, or both at 3 months predicts AIC at 12 months.
c.   Whether a change in troponin, strain or both at 3 months predicts fibrosis detected by ECV at 6 months.

2.0 BACKGROUND

2.1 Study Disease

There are 13.7 million cancer survivors in the United States, and it is estimated that over 2 million are at risk for cancer treatment-induced cardiotoxicity (National Cancer Institute NIOH et al., n.d.). The number of patients at risk may further increase with the lengthening of survival, aging of patients, and multiplication of novel additional treatments. Of these patients, a large proportion is at risk of developing anthracycline-induced cardiotoxicity (AIC).

The primary aim of STOP-CA (Statins TO Prevent the Cardiotoxicity from Anthracyclines) is to test in a multi-center randomized double-blind placebo controlled trial whether statins attenuate the anthracycline-induced reduction in left ventricular ejection fraction (LVEF) in patients with lymphoma. If successful, this study will show that statins started prior to anthracyclines preserve LVEF, that statins prevent anthracycline-induced myocardial fibrosis and that the early measurement of myocardial strain or high-sensitivity troponin during anthracyclines can identify patients at high risk of a subsequent LVEF decrease.

A.1. Anthracycline-induced cardiotoxicity is a major adverse factor in the long-term outcomes of cancer survivors: Survival after a cancer diagnosis has dramatically improved.[9] Anthracyclines are a key component of standard chemotherapy regimens among patients with breast cancer, leukemia, lymphoma and sarcoma. Congestive heart failure (CHF), driven primarily by the use of anthracyclines, is now a leading cause of death and disability among cancer survivors [10, 11] and the National Cancer Institute's estimates that over 2 million cancer

Figure 1: Risk of developing clinical CHF after the administration of anthracyclines at conventional doses.[33]

survivors are at risk of CHF from anthracyclines.[9, 12] The rates of cardiotoxicity and CHF described among patients treated with anthracyclines vary depending on the definition used, length of follow-up and the population at risk. However, data suggest that between 15% and 45% of patients will have a significant decline in LVEF of ≥10% [13-15] and that at 5 years up to 20% develop symptomatic heart failure (Figure 1).[16] Once established, anthracycline-induced symptomatic heart failure has a predicted two-year survival of 40%.[17] **Therefore, survival is improving among cancer patients; however, CHF after anthracyclines is a major cause of long-term morbidity and mortality among cancer survivors.**
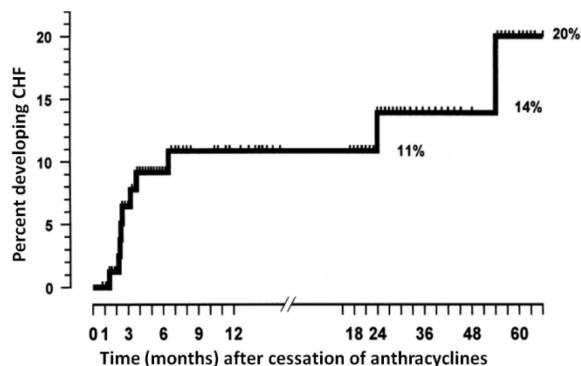
A.2. Why Lymphoma? We propose to study patients with lymphoma for the following reasons:
1. Lymphoma is a frequent malignancy with over 80,000 patients diagnosed each year in the USA.[9]
2. Survival is improving among patients with lymphoma and the overall survival of patients is high (over 70% at 5 years),[9] emphasizing the importance of preventing co-morbidities associated with cancer treatment.
3. The use of anthracyclines among patients with breast cancer has declined over the last decade from 80% to 30%;[18] In contrast, anthracyclines remain a standard therapy in >80% of lymphoma patients.[9]
4. Studies have consistently shown that over 20% of patients with lymphoma treated with anthracyclines will have a significant decrease in LVEF of ≥10% to less than 55% within 12 months.[13-15]
5. In preliminary data (see preliminary data section), the rate of heart failure and death among 1644 patients with lymphoma treated with anthracyclines was almost 6 times that of breast cancer patients and 2 times that of patients with other cancers similarly treated with anthracyclines.

Anthracycline-based chemotherapy is the standard treatment for lymphoma, the most frequent hematological malignancy in the United States. Patients with lymphoma are at higher risk of heart failure as compared to other patients treated with anthracyclines.

A.3. Potential approaches to prevent anthracycline-induced cardiotoxicity: Current approaches to preventing the progression from AIC to symptomatic heart failure include instituting a cardioprotective regimen once a decrease in LVEF is detected. However, Cardinale *et al.* demonstrated that such an approach is ineffective as almost 40% of patients did not recover their LVEF despite immediate intervention.[19] An alternative approach is to start

Table 1: Randomized Studies Testing the Effect of ACE Inhibitors , ARB, Beta-blockers on LVEF in Patients Receiving Chemotherapy				
Author	Number of Patients	Therapy	Difference in LVEF	P value
Bosch[20]	90	ACE and BB	3%	0.045
Georgakopoulos[35]	58	ACE or BB	3.7%	0.24
Kalay[37]	50	BB	18%	<0.01
Nakamae[36]	40	ARB	5%	0.09

ACE = Angiotensin converting enzyme inhibitor; BB = Beta-blocker; ARB = Angiotensin receptor blocker.

medications prior to administration of anthracyclines to prevent or limit the occurrence of AIC; this has been the focus of several clinical studies that have reported either a small or no effect on LVEF and low tolerated treatment doses (Table 1).[14, 19-22] Dexrazoxane, an iron chelator, has also been shown in studies to reduce cardiotoxicity.[23] However, small studies reported an increase in the incidence of second primary malignancies in dexrazoxane-treated patients; therefore the FDA has advised that its use be limited.[24-26] **Thus, current therapies that have been tested to prevent progression of AIC or to prevent or reduce AIC, using medications such as ACE inhibitors, beta-blockers, or dexrazoxane have either a small or no effect or have toxicity concerns.**

A.4. There is significant plausibility supporting the potential role of statins, specifically atorvastatin 40 mg, to prevent or reduce anthracycline-induced cardiotoxicity: The only available prospective data stem from a randomized trial of 40 patients testing whether statins prevent the anthracycline-induced reduction in LVEF;[27] the authors randomized 20 patients to pre-treatment with atorvastatin 40 mg and 20 patients to placebo and found a significant difference of 9% in LVEF between experimental groups over 6 months. Larger populations have been studied retrospectively, with the results suggesting that statins reduce heart failure admissions and the rate of clinical heart failure (6 vs. 18%) among patients treated with anthracyclines.[28, 29] Furthermore, experimental data support a protective role for statins for prevention of AIC and preservation of LVEF.[30-32] In mice treated with anthracyclines, statins reduced oxidative stress, myocardial cell death and preserved cardiac function.[30-32] A key advantage of statin therapy is an acceptable risk-to-benefit ratio, their use is not limited by the adverse hemodynamic changes associated with ACE inhibition or beta-blockade and there is no concern for an increased risk of secondary malignancies.[33] **There is significant biological plausibility and supportive preliminary clinical data to hypothesize a positive effect of statins on the anthracycline-induced reduction in LVEF. The only randomized study on the effects of statins on the cardiac function of patients treated with anthracyclines included 11 patients with lymphoma. Therefore, additional work is required to provide support for a large multi-center RCT powered to clinical end-points.**

A.5. LVEF is a robust surrogate for adverse cardiac events and the primary end-point chosen for STOP-CA, an reduction in LVEF of ≥10% to <55%, occurs frequently among lymphoma patients and predicts the subsequent development of clinical heart failure in patients receiving anthracyclines: Left ventricular ejection fraction is a robust surrogate for adverse cardiovascular outcomes including heart failure and cardiovascular death among broad groups of patients.[34-36]

The American College of Cardiology/American Heart Association heart failure guidelines identify 4 stages of heart failure. Stage B CHF is defined as an asymptomatic reduction of cardiac function below the normal range (e.g., LVEF <55% by CMR) and is associated with an increased risk of progression to heart failure.[37, 38] We will use the definition for a significant change in LVEF after anthracyclines as recommended by both Oncology and Cardiology statements, a reduction in LVEF of ≥10% to <55%.[1-3] Among patients treated with anthracyclines, consistent data have shown that at least 20% of patients with lymphoma will develop a ≥10% reduction in LVEF to <55% at 1 year.[13-15] Additionally, data have shown that a reduction in LVEF of ≥10% to <55% has marked clinical prognostic significance. Specifically, in a study of 1487 subjects who received anthracyclines, there was a 16% rate for the subsequent development of clinical heart failure among those who had a ≥10% fall in LVEF as compared to a 0% rate among those who did not.[39] **Therefore, LVEF is a robust surrogate for the risk for clinical heart failure and cardiovascular death and a decrease in LVEF of ≥10% to <55% is frequent, is a recognized definition of anthracycline-induced cardiotoxicity and predicts the development of heart failure.**

A.6. LVEF by CMR is the gold-standard: Measurement of the LVEF using cardiac magnetic resonance (CMR) is the gold standard technique to reliably and reproducibly quantify the LVEF with less than a 3% temporal variability.[40, 41] The variability of LVEF, a combination of the biological and technical variability, is a major factor in the ability of a technique to perform serial monitoring during chemotherapy or to act as a robust end-point in clinical trials. **Therefore, we will measure LVEF using CMR as the primary modality as it is the gold-standard method.**

A.7. Anthracyclines induce myocardial fibrosis that is detectable using novel CMR sequences and statins may prevent AIC by a reduction in myocardial fibrosis: Pathological studies in animal and humans have consistently shown that anthracyclines induce myocardial fibrosis [42-44] and myocardial fibrosis is a key intermediate step between injury and the development of heart failure.[45] Magnetic resonance imaging is the gold-standard non-invasive technique for the detection of myocardial fibrosis.[5] However, we found that late gadolinium enhancement (LGE), the current clinical standard CMR sequence for

FIGURE 2: A) The ECV is increased in patients with prior anthracyclines (AC) compared to healthy controls (CTRL) * P< 0.05 vs. CTRL B) Late Gadolinium enhancement is not detected in patients with prior AC. C) Bull's Eyes depicting diffuse fibrosis by CMR-derived ECV in a patient with prior AC.

detection of fibrosis, was present in only 6% of patients treated with anthracyclines (Figure 2);[46] LGE-based methods need a normal reference myocardium to identify abnormal; with anthracyclines, the fibrosis is diffuse and thus, is underestimated.[8] Therefore, we, and others, have developed a CMR technique using the relative distribution of gadolinium to obtain a quantitative measure of the extracellular volume (ECV).[6-8, 47, 48] The ECV has been validated as a robust measure of myocardial fibrosis in both mice and humans.[7, 49] In a retrospective clinical study, we found that the ECV was markedly elevated in patients with prior anthracycline treatment (Figure 2) and found that the greater the increase in the ECV, the more extensive the degree of cardiac dysfunction.[8] Additionally, in preliminary findings in mice, we show using

CMR that anthracyclines induce myocardial fibrosis and that the extent of myocardial fibrosis is associated with survival (see preliminary data). Therefore, we propose in a sub-study to test whether anthracyclines induce myocardial fibrosis in humans and whether myocardial fibrosis predicts later AIC. In mice, statins prevent the anthracycline-induced cardiac dysfunction possibly via prevention of myocardial fibrosis.[31] Therefore, we hypothesize that statins may reduce myocardial fibrosis in humans. **Therefore, we will test whether ECV by CMR identifies patients at high risk of AIC and whether statins reduce myocardial fibrosis in humans.**

A.8. Improving on current clinical and widely applicable methods for detection of AIC: The serial measurement of LVEF is the current gold-standard technique for detection of AIC.
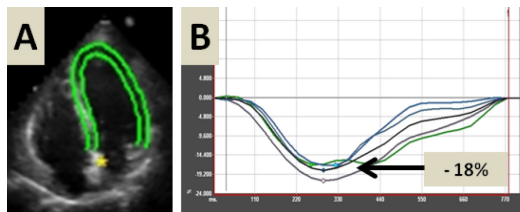

FIGURE 3: A) Apical 4-chamber view of the LV with strain region of interest. B) 6 longitudinal strain curves representing each of the 6 myocardial segments in that view. The X-axis is time and the Y-axis is the strain value. The average strain value in this example was -18%.

However, even in expert hands, data show that LVEF may underestimate the presence and extent of cardiomyocyte damage.[50] Furthermore, intervention once the LVEF is decreased fails to reverse the LV dysfunction in over 40% of patients.[19] Therefore, research has focused on more sensitive and earlier detection of AIC.[51, 52] Troponin is a marker of myocardial injury that is increased after anthracyclines.[23, 51, 53] Similarly, among patients receiving anthracyclines, peak myocardial systolic strain, a sensitive echocardiographic marker of systolic function (Figure 3) decreases prior to a change in LVEF and predicts the late reduction in LVEF. In prior work we found that, in patients with breast cancer treated with anthracyclines, taxanes, and trastuzumab, an increase in high-sensitivity troponin to >99th percentile upper normal reference limit and a ≥10% reduction in myocardial strain, both measured after the cessation of anthracyclines, were predictive of a subsequent decrease in LVEF.[53, 54] Indeed the combination of troponin and strain after the cessation of anthracyclines had a sensitivity of 87% and a negative predictive value of 91% for the detection of subsequent AIC.[53] However, no such serial data exists among patients with lymphoma and there are no data testing the predictive value of strain and troponin measured during anthracyclines. The standardization and widespread application of strain are major goals of the American Society of Echocardiography (ASE) and have led to the development of novel algorithms and measurements methods that we will test.[55, 56] These new techniques are easy to implement and common to all echocardiography machines and softwares.[56] **Therefore, strain and high-sensitivity troponin detect AIC early. Both measures are available and widely scalable. We found that a reduction in myocardial strain and an increase in troponin *after cessation of anthracyclines* predicted the late reduction in LVEF. Therefore, we propose to test whether measurement of troponin and strain *earlier during anthracyclines* can predict AIC.**

b. Previous studies supporting the proposed research

Evidence to support the primary hypothesis that statins will prevent the anthracycline-induced reduction in LVEF: We prospectively recruited 72 patients with breast cancer undergoing anthracycline-based chemotherapy and measured LVEF prior to and after 12 months.[53] In total, 8 patients (11%) were treated with statins prior to the initiation of chemotherapy. There was no

difference in the baseline LVEF between patients who were or were not on statins prior to chemotherapy (64±5% in both groups). After anthracyclines, there was no decrease in LVEF in the statin group (64±9%); in comparison there was a decrease of 5% in the LVEF in the placebo groups (59±6%, p=0.06). This trend persisted even after adjustment for traditional cardiovascular risk factors and for treatment by ACE inhibitors and beta-blockers (p=0.08). Similarly, in a retrospective study, , Chotenimitkhun *et al.* tested the effect of incidental statin therapy on the reduction in LVEF after anthracyclines among 52 patients.[29] They found that the LVEF after anthracyclines was unchanged in the statin group but the LVEF was 7% lower in the placebo-treated group.[29] In the only randomized clinical trial testing the effect of statins on LVEF, Acar *et al.* found that the LVEF was unchanged among the 20 patients in the statin-treated group and was decreased by 9% among the 20 patients on placebo.[27] **Therefore, preliminary data support the hypothesis that there is no decrease in LVEF after anthracyclines among patients on statins.**

The rate of death or heart failure admission after treatment with anthracyclines is higher among patients with lymphoma than in other patients treated with anthracyclines: Overall, 1644 consecutive MGH patients with lymphoma treated with anthracyclines were followed for a median of 3 years. In that period, 67 (4%) developed symptomatic heart failure or cardiac death. In comparison, the other major population that is treated with anthacyclines are patients with breast cancer. In a similar follow-up period of 3 years, 5 (0.7%) of 711 patients with breast cancer developed symptomatic heart failure or cardiac death (P<0.0001 vs. lymphomas).

Therefore, patients with lymphomas have a higher rate of cardiac death or heart failure from anthracyclines than other similarly-treated cancer populations.

Summary of the preliminary results: The preliminary data suggests the following;
1. In two retrospective series and one small randomized study, statins prevented any anthracycline-associated reduction in LVEF.
2. Patients with lymphoma treated with anthracyclines develop more major cardiac events than similarly-treated patients with other cancers.

2.2. Other Agent(s)

The overall rate of statin-related side effects is anticipated to be low. In statin clinical trials, the reported rate of myopathy and hepatotoxicity is ≈ 0.5%. Statin therapy has not been shown to adversely affect cancer-related outcomes, and indeed in large epidemiological studies statins have been reported to decrease recurrence rates of cancers.

2.3 Rationale

The background has been provided in 2.1

3.0 PARTICIPANT SELECTION

3.1 Inclusion Criteria:
- ≥18 years of age

- All patients with newly diagnosed lymphoma
- Scheduled to receive anthracycline-based chemotherapy therapy

3.2 Exclusion Criteria:
- Statin use or Statin use is indicated based on guidelines
- Pregnancy or breastfeeding
- Unable to provide informed consent
- Unexplained persistent elevation of transaminases (>3 times upper limits of normal)
- Concomitant use of oral cyclosporine
- Contraindication to a CMR (metallic object, severe claustrophobia, pacemaker, vascular clip

3.3 Inclusion of Women and Minorities

Approximately 45% of new cases of lymphoma are women. Therefore, we anticipate that the final study population will be relatively evenly divided between men and women. Women with child-bearing potential may potentially also be recruited, however, it is unlikely that a pregnant woman will be undergoing anthracycline-based chemotherapy but for completeness a urine pregnancy test will be administered and in the unlikely case of a pregnancy, the patient will be excluded. Gadolinium chelates, while widely used and generally safe as intravenous cardiac magnetic resonance contrast agents, may dissociate in amniotic fluid and are considered "Class 3" drugs; they should only be used when the anticipated benefit outweighs the potential risk and are generally avoided in pregnancy. Statins are Category D drugs which includes those" which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage" and may also have adverse pharmacological effects. We will therefore exclude pregnant women.

Subjects will be recruited without regard for racial, social, economic, or other status. There is no evidence that race or ethnicity influences the prevalence of anthracycline-induced cardiac dysfunction. The population of the greater Boston area is 80% Caucasian, 6% Black, 8% Hispanic, 4% Asian and 2% other. In general, subject recruitment should occur in proportion to the ethnic balance of the referral community. However, because we recognize that minorities are relatively under-represented in clinical studies, we will make an active effort to include minorities. We will support this effort by making all IRB-approved advertisements and study materials available in Spanish, Portuguese, French/Creole and Mandarin.

4. REGISTRATION PROCEDURES

4.1   General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Office of Data Quality (ODQ) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the ODQ protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the ODQ Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The ODQ registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.
- Complete the ODQ protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.** Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for a treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.
- Fax the eligibility checklist(s) and all pages of the consent form(s) to the ODQ at 617-632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.
- The ODQ Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.
- An email confirmation of the registration and/or randomization will be sent to the site's oncology clinical trials pharmacy.

4.3 External Site Registration process

- The external site obtains informed consent and screens the participant for eligibility.
- An appropriately delegated and qualified individual at the external site signs off as screening staff on the eligibility checklist.
- The external site sends the completed eligibility checklist and signed informed consent document to the DF/HCC coordinating center.
- When required per REGIST-104, an enrollment monitor at the coordinating center must verify participant eligibility and sign the eligibility checklist.

- The DF/HCC coordinating center is responsible for registering the subject in OnCore (de-centralized), or sending the registration packet to ODQ (centralized).
- The DF/HCC coordinating center will forward registration confirmation to the external site.
- The external site must notify the coordinating center of subject status changes (off treatment, off study).
- The DF/HCC coordinating center is responsible for updating the subject status in OnCore (de-centralized), or notifying ODQ (centralized).

5. TREATMENT AND/OR IMAGING PLAN

5.1 Treatment Regimen

Atorvastatin (or placebo) will be at a dose of 40 mg once a day. If the participant develops muscle pain, myalgia, then the study drug dose can be reduced to 20 mg once a day or placebo.

Atorvastatin (or placebo) will be taken nightly. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7.

5.2 Pre-Treatment Criteria

If required (no recent measurement of < 1 month), measurement of CBC, potassium, renal function and liver function will be obtained. Lab values will be used from oncology providers if needed.

5.3 Lab Values

Lab values for follow up visits will be taken from subjects oncology team throughout study calendar until patient is off study.

5.4 Agent Administration

The drug is taken by mouth, once a day (evening) for the entire study. The study medication should be swallowed. The drugs can be taken with food and with any other medications. Any unused study drug will be brought back for the next study visit. The medications can be stored at room temperature for the duration of the study. If the medication is vomited, it can be taken again within the same day.

5.5 General Concomitant Medication and Supportive Care Guidelines

Atorvastatin is widely used in clinical care and is not an investigational agent.

Patients will be followed throughout the study by a nurse practitioner under the supervision of a cardiologist.

5.6   Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will be of 12 months. In the absence of treatment delays due to adverse event(s), treatment may continue for 12 months or until one of the following criteria applies:
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

Emergency unblinding will occur in case of unacceptable adverse event that may be caused by atorvastatin, i.e. severe allergic reaction or rhabdomyolyis.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Tomas G Neilan at 617 7269292 (page) or 617 6864322 (cell phone).

5.7   Duration of Follow Up

This study lasts for 12 months after start of the treatment. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.8   Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

6. DOSING DELAYS/DOSE MODIFICATIONS

Treatment will be temporarily suspended if the liver function tests elevate by more than 3 times normal. If it is determined that the elevation in liver function tests are due to another cause, the treatment will be reinstated provided the liver function tests return to normal. The patients with side effects will not be excluded from the protocol. If the participant develops muscle pain, myalgia, then the study drug dose can be reduced to 20 mg once a day or placebo. If the symptoms do not respond to this within 1 week then the study drug is stopped. This is what happens in clinical practice.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1.1 Adverse Event List(s) for Commercial Agent(s)

Atorvastatin: Subjects will be randomized to either placebo or atorvastatin as part of the proposed protocol.

Risk of statin therapy: Subjects will be randomized to either placebo or atorvastatin as part of the proposed protocol. The reported risks of atorvastatin therapy include statin myopathy, rhabdomyolyis, renal failure as a result of rhabdomyolysis, and hepatotoxicity.
Muscle toxicity: In statin clinical trials, the reported incidence of myopathy is low (0.1%) and data from a large meta-analysis (with 246,955 patients) of patients taking statins has been reported the incidence of myopathy to be similar to control. In another compilation of randomized controlled statin trials revealed that among 83,858 patients randomly assigned to receive either statin treatment or placebo, there were 49 cases of myositis and 7 cases of rhabdomyolyis in the statin groups, compared with 44 cases of myositis and 5 cases of rhabdomyolyis in the placebo groups. The risk of skeletal muscle effects such as myopathy and rhabdomyolyis increase in a dose-dependent manner with advanced age (≥65) and renal impairment. However, patients with renal failure will be excluded due to the administration of CMR contrast.

Hepatotoxicity: Based on guidelines, a modest elevation in transaminases to less than 3 times the upper limits of normal will not be considered a contra-indication to inclusion in the study. The incidence of elevated liver biochemical tests is increased to 1% of patients on statins. The majority of liver abnormalities occur within the first 3 months of therapy. Fulminant hepatic failure from statin therapy, without the presence of rhabdomyolyis and renal failure, is rare.

7.2   For non-CTEP protocols only: **Expected Toxicities**

7.2.1   Adverse Events List(s)

Reported in 7.1.1

7.3   For non-CTEP protocols only: **Adverse Event Characteristics**

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the <u>agent(s)</u> that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the <u>protocol</u> that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
  - Possible – The AE may be related to the study treatment.
  - Unlikely – The AE is doubtfully related to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

7.4   For non-CTEP protocols only: **Expedited Adverse Event Reporting**

7.4.1   Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.4.2   The following text is required for DF/HCC-led multi-institutional studies only and must be deleted for studies performed solely at DF/HCC and/or DF/PCC institutions. For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.4.3   <u>DF/HCC Expedited Reporting Guidelines</u>

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

The following text and table apply to DF/HCC-led multi-institutional studies only and must be deleted for studies performed solely at DF/HCC and/or DF/PCC institutions.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

	DF/HCC Reportable AEs				
Attribution	**Gr. 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days$^{\#}$	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days$^{\#}$	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study **or** for AEs occurring within 30 days of the last intervention, the AE should be reported within <u>24 business hours</u> of learning of the event.					

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

<u>For this protocol only</u>, the AEs/grades listed below <u>do not require expedited reporting to the Overall PI or the DFCI IRB</u>. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments

7.5   Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6   For non-CTEP protocols only: **Routine Adverse Event Reporting**

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8.   PHARMACEUTICAL AND/OR IMAGING AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1   IND Agent #1: Atorvastatin

8.1.1   Description

Atorvastatin is a member of the drug class known as statins, which are used primarily as a lipid-lowering agent and for prevention of events associated with cardiovascular disease. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue that plays a key role in production of cholesterol in the body.

Atorvastatin undergoes rapid absorption when taken orally, with an approximate time to maximum plasma concentration (Tmax) of 1–2 h. The absolute bioavailability of the drug is about 14%, but the systemic availability for HMG-CoA reductase activity is approximately 30%. Atorvastatin undergoes high intestinal clearance and first-pass metabolism, which is the main cause for the low systemic availability. Administration of atorvastatin with food produces a 25% reduction in Cmax (rate of absorption) and a 9% reduction in AUC (extent of absorption), although food does not affect the plasma LDL-C-lowering efficacy of atorvastatin. Evening dose administration is known to reduce the Cmax and AUC by 30% each. However, time of administration does not affect the plasma LDL-C-lowering efficacy of atorvastatin.

It is highly protein bound (≥98%), and studies have shown it is likely secreted into human breast milk.

Atorvastatin metabolism is primarily through cytochrome P450 3A4 hydroxylation to form active ortho- and parahydroxylated metabolites, as well as various beta-oxidation metabolites. As a substrate for the CYP3A4 isozyme, it has shown susceptibility to inhibitors and inducers of CYP3A4 to produce increased or decreased plasma concentrations, respectively. This interaction was tested in vitro with concurrent administration of erythromycin, a known CYP3A4 isozyme

inhibitor, which resulted in increased plasma concentrations of atorvastatin. It is also an inhibitor of cytochrome 3A4.

Atorvastatin is primarily eliminated via hepatic biliary excretion, with less than 2% recovered in the urine. Bile elimination follows hepatic and/or extrahepatic metabolism. There does not appear to be any entero-hepatic recirculation. Atorvastatin has an approximate elimination half-life of 14 h. Noteworthy, the HMG-CoA reductase inhibitory activity appears to have a half-life of 20–30 h, which is thought to be due to the active metabolites. Atorvastatin is also a substrate of the intestinal P-glycoprotein efflux transporter, which pumps the drug back into the intestinal lumen during drug absorption.

Specific populations:

Geriatric: Plasma concentrations of atorvastatin in healthy elderly subjects are higher than those in young adults, and clinical data suggests a greater degree of LDL-lowering at any dose for patients in the population as compared to young adults.

Gender: Plasma concentrations are generally higher in women than in men, but there is no dose adjustment suggested.

Renal impairment: Renal disease has no influence on plasma concentrations of atorvastatin and dosing need not be adjusted in these patients.

Hemodialysis: Hemodialysis will not significantly alter drug levels or change clinical effect of atorvastatin.

Hepatic impairment: In patients with chronic alcoholic liver disease, levels of atorvastatin may be significantly increased depending upon the extent of liver disease.

8.1.2 Form

Atorvastatin will be given as 40 mg capsules (or 20 mg capsules if myalgias) supplied by the MGH and BWH pharmacy or the external sites pharmacy.

8.1.3 Storage and Stability

The capsules can be kept at room temperature throughout the study.

8.1.4 Availability

Study staff will provide pharmacy with a fund number to purchase and blind study drug. The compounding pharmacy will blind active drug and provide a matching placebo and the clinical trials pharmacy will dispense the blinded study drug to subjects free of charge.

8.1.5 Preparation

The dose will be a capsules prepared by the pharmacy.

8.1.6 Administration

Atorvastatin will be taken each evening. The capsules can be swallowed. If a dose is missed (not taken by midnight of the scheduled day) then the participant will not take an extra dose the following day but will just take the regular dose.

8.1.7 Ordering

The agent is commercially available and will be ordered through the MGH and BWH pharmacy or the external sites pharmacy.

8.1.8 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.9 Destruction and Return

Unused supplies of atorvastatin will be returned by the patients at each visit and destroyed immediately. Expired capsules can be destroyed per DFCI/HCC SOP since expiration dates will not be extended.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1   Biomarker Studies

We will draw blood before chemotherapy, at 3 cycles and at the end of the study (12 months treatment). We will measure biomarkers of cardiac injury, in particular troponin, which we have shown to be a predictor of later cardiac dysfunction in women with breast cancer treated with anthracyclines, taxanes and trastuzumab and correlate them with measures of cardiac function. We have already measured these biomarkers in another population.

9.2   Laboratory Correlative Studies

Include the following collection/processing details when developing this section: (a) amount and type of specimen collected; (b) number, size, and type of tubes or cryovials used for collection; and (c) processing instructions.

9.2.1   Troponin – Laboratory Correlative Study #1

9.2.1.1   Collection of Specimen(s)
30 ml of blood will be sampled.

9.2.1.2   Handling of Specimens(s)
Blood will be processed within 30 minutes, frozen and stored at -80°C.

9.2.1.3   Shipping of Specimen(s)
At regular intervals, the specimens will be shipped to the MGH where they will be stored.

9.2.1.4   Site(s) Performing Correlative Study
MGH/DFCI

10. STUDY CALENDAR

After consent is obtained, patients will undergo a baseline visit including a questionnaire, vital sign measurements, an MRI, echocardiogram and blood sampling. A pregnancy test (urine beta-HCG) will be performed as appropriate. A second visit similar to the first one will be scheduled after 3 cycles of chemotherapy (approx 3 months). The final study visit will be at 12 months where subjects will undergo an echo, MRI and blood sampling.

An additional visit for the sub-group in the MRI mechanistic sub-study will occur at 6 months where this sub-group will undergo an additional cardiac MRI.

We will do a balanced randomization with blocks of 2 patients for each cancer site.

Baseline evaluations are to be conducted within 1 week prior to start of anthracyclines therapy. Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 7 days of the protocol-specified date, unless otherwise noted.

	Pre-Study	Study Drug	1 month	2 months	3 months	6 months	12 months	24 months
Atorvastatin/placebo		X--X						
Informed consent	X							
Demographics	X							
Medical history	X							
Perceived Stress Scale	X				x	x	x	
Physical exam	X				x		x	
Vital signs	X		x		x		x	

Height	X						
Weight	X				x	x	
Phone call: Adverse and clinical events	X	x	x	x	x	x	x
LFTS	X	x		x			
Lipids/Blood biomarkers	X			X		X	
B-HCG	X				x	x	
Echocardiogram	X			x		x	
MRI	X				x	x	
Pill count (Monthly)							

11. MEASUREMENT OF EFFECT

11.1   Other Response Parameters

The primary outcome measure is LVEF compared between groups. Specifically, we will measure the LVEF between baseline and the endpoint of the study (12 months after randomization).

The secondary outcome measures include adverse cardiac events (heart failure requiring diuretics, admission for heart failure, or death), strain and biomarkers.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1   Data Reporting

12.1.1 Method

The research staff will collect, manage, and perform quality checks on the data for this study via REDCAP. Outside site research staff will be given access to REDCAP after approval from OncPro and will have privileges to ensure data capture.

12.1.2 Responsibility for Data Submission

The responsibility will lie on the site staff from DF/HCC, DF/PCC, and external sites to submit data and/or data forms as needed into REDCAP

12.2   Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1   Study Design/Endpoints

Randomization process: Within the DF/HCC, randomized comparative studies are conducted in a manner such that for a blinded randomization, the individual assigning study treatment is not a member of the study team but from the office for the Office of Data Quality (ODQ). Central randomization is performed according to an algorithm provided by the statistician. This will be a permuted blocks algorithm, with block size of 4. Randomized treatment assignment will be delivered to research pharmacy at the site in an unblinded fashion, and pharmacy will dispense blinded study drug. ODQ has extensive experience working with both local and distant research pharmacies on blinded randomized placebo-controlled studies, and the system is already in place.

Primary End-Point

Our primary endpoint will be the proportion of patients in each group that have a decrease of 10% or more in LVEF to <55% from baseline to 12 months after initiation of anthracyclines.

Assumptions: We anticipate that 20% of the patients in the placebo group will reach the primary end-point. This assumption is based on significant prior literature; specifically, Limat *et al.* performed a prospective study where they enrolled patients similar to those proposed in this study (lymphoma receiving anthracycline-based chemotherapy) and performed a baseline measurement of LVEF and a measurement at 1 year. Their primary end-point was a more stringent cut-off than recommended by guidelines or being used in this study, a decrease of >15% in LVEF. They found that 20% of their population had a reduction of >15% in LVEF. Using CMR, two studies have tested the percentage of patients with a significant reduction in LVEF after anthracyclines. In a prospective observational study, Drafts and colleagues found

that 26% of patients decreased their LVEF to <50% and in a prospective randomized study, Bosch and colleagues found that up to 33% of patients decreased their LVEF to <55%. In the single small randomized study which also used 40 mg of atorvastatin with 20 subjects in each arm, there was no decrease in LVEF after anthracyclines among patients on statins. Our base case assumptions are as follows: 20% of the placebo group and 5% of the statin treatment group will meet the primary endpoint and we will be able to enroll 300 patients meeting all inclusion and exclusion criteria. From these, we anticipate a drop-out rate of approximately 10% due to a one year mortality of ≈5% and atorvastatin related side-effects in 4% of patients. The remaining 270 patients will provide us with a 98% power to detect a 15% difference in the proportions of those achieving the primary end-point at a one-sided significance level of 0.05. Moreover, we will have a 70% power if the difference in the percentage reaching the primary end-point between groups falls as low as 10%.

Analysis Plan: The study is designed as a prospective double-blind randomized study. All statistical analyses will be performed based on intent-to-treat and repeat imaging will be performed at 1 year in all patients. In particular, we will include subjects who could not complete the study protocol due to statin toxicity and patients who started anthracyclines but did not complete the entire scheduled protocol. Chi-square analysis will be used to determine whether statins decrease the primary end-point.

Secondary End-Points Aim 1:
Aim 1a. We will test whether cardiac risks factors (blood pressure, age, sex, glucose or cholesterol levels, prior history of cardiac disease, LVEF at baseline) or cancer specific risk factors (anthracycline dose, radiotherapy) are predictive of the effect of statins on LVEF.

*Analysis Plan***:** In patients treated with statins, we will use a logistic regression model to evaluate whether cardiac risks factors or cancer specific risk factors are predictive of the effect of statins on LVEF. Patients on statins and eligible for statins will be excluded. Therefore, cholesterol levels will be relatively homogenous and we will not pre-stratify our cohort based on cholesterol. Radiotherapy is not routinely used in the cohort and is used in <5% of cases, there we will also not pre-stratify based on the use of radiotherapy. However, we will use cholesterol values (as a continuous variable) and the use of radiotherapy (as a binary variable) to perform a post-hoc analysis. Additionally, all patients are intended to have the same dose of anthracyclines and dose adjustments are made during therapy in response primarily to toxicities. Therefore, we will additionally test the interaction between the dose of anthracyclines and the effect of statins as a post-hoc analysis.

Aim 1b. We will test whether statins reduce cardiac events.

Adjudication plan: The occurrence of clinical adverse cardiac events will be adjudicated based on consensus opinion of a clinical adjudication committee containing three board-certified cardiologists blinded to experimental group (Drs. Francis, Scherrer-Crosbie and Neilan).

Analysis Plan: All statistical analyses will be performed based on intent-to-treat. Fisher exact tests will be used to determine whether statins decrease the combined end-point of death or heart failure.

Aim 1c. We will test whether statins are safe.

Analysis Plan: Chi-square will be used to test for differences between the two treatment groups for categorical secondary endpoints.

Specific Aim 2:
Determine the effect of statins on myocardial fibrosis. In a sub-study of 80 patients from Aim 1 (n=40 in each arm), we will measure myocardial fibrosis by calculation of the myocardial extracellular volume (ECV) using CMR, as previously described, at baseline and 6 months to determine:
c. Whether statins prevent the anthracycline-induced increase in myocardial fibrosis at 6 months as compared to placebo.
d. Whether a change in fibrosis or LVEF at 6 months predicts the occurrence of AIC at 12 months.

Statistical Analysis
Aim 2a. *Assumptions:* In our retrospective clinical study the ECV in healthy age-matched volunteers was 0.28 and was 0.04 lower than in patients treated previously with anthracyclines (0.32, mean difference and SD: 0.04±0.05). Based on these data, with 80 patients (40 from each treatment group) we will have 94% power to detect a treatment difference with a two-sided 0.05 significance level. If the actual difference in the ECV between groups is only 0.03 with a SD of 0.05, then we will still have a 75% power to detect a difference between the groups. We are assuming a 10% drop-out for participants in Aim 1. If we assume the same dropout rate for Aim 2, then our final sample size will be 36 per group. A final sample size of 72 will have a 92% power to detect a treatment difference between the means. *Analysis Plan:* The ECV is a unit-less continuous variable. The change in ECV levels from baseline to 6 months will be compared between the statin- and placebo treated groups using a Student t test.

Aim 2b. *Analysis plan:* The predictive value of the change in ECV between 0 and 6 months for the occurrence of the primary end-point of Aim 1 (a reduction in LVEF of ≥10% to less than 55% at 12 months) will be determined using a logistic regression model.

Specific Aim 3:
Early clinical identification of patients at high risk of AIC. We will determine whether an early decrease in myocardial strain or an increase in high-sensitivity troponin *during* anthracyclines (after 4 of 8 standard cycles (≈ 3 months)) can predict subsequent development of AIC at 12 months. We will test:
  d. Whether statins, as compared to placebo, prevent the reduction in strain or the increase in troponin throughout the study period (12 months).
  e. Whether a change in troponin, strain, or both at 3 months predicts AIC at 12 months.
  f. Whether a change in troponin, strain, or both at 3 months predicts fibrosis detected by ECV at 6 months.

Statistical Analysis:

Aim 3a. *Assumptions:* Based on existing literature and our prior data, our assumption is that the decrease in strain after 4 cycles of chemotherapy ($\approx$200mg/m2 dose) in the placebo group will be 9±10%.

Sample Size and Power: with a type I error of 0.05, a sample of 270 patients will have a power of 0.99 to detect a statin effect if there is no change in strain in the statin group and a power of 0.96 if the decrease in strain in the statin group is 50% less than that of the placebo group (9% in the placebo group and 4.5% in the statin group). ***Analysis Plan:*** We will first characterize the distribution and time course of strain and troponin in patients who do or do not reach the primary outcome (significant change in LVEF at 12 months on CMR as defined in Aim 1) using descriptive statistics. As troponin levels at baseline, 4 cycles and their changes do not follow normal distributions, they will be log transformed. To study the effect of statins on the time rends of strain and troponin, we will use a mixed-design ANOVA model to test for differences between the groups while incorporating repeated strain and troponin measurements at 0, 4 cycles and 12 months.

Aim 3b. *Analysis Plan:* The predictive value of the change in strain and/or troponin after 4 cycles for a significant change in LVEF on CMR at 12 months (primary endpoint of Aim 1) will be explored using a mixed design ANOVA model. A multivariable logistic regression model will then be applied, entering strain and troponin as variables. The model may be adjusted for additional key variables such as clinical univariate predictors and change in echocardiographic LVEF.

Aim 3c. *Analysis Plan:* The predictive value of the change in strain and/or troponin after 4 cycles for the change of fibrosis (assessed by ECV) at 6 months will be explored using a mixed-design ANOVA model. The model may be adjusted for additional key variables such as clinical univariate predictors and change in LVEF.

13.2   Sample Size, Accrual Rate and Study Duration

Feasibility: In 2012, there were 412 patients with lymphoma treated with anthracyclines at MGH, DFCI and BWH (110 at MGH and 312 at DFCI and BWH). In the large cohort of lymphoma patients that we reported in our preliminary data, only 8% of patients (n=33) were on statins at the time of chemotherapy and would be excluded. Even using the new more expansive cholesterol guidelines [57] and assuming that all the patients who were eligible to receive statins were treated with statins, more than 80% of patients (n=330) would be eligible for enrollment annually. In aggregate, less than 30 of the remaining 330 patients would be excluded based on these criteria and this would leave <u>a final total of 300 patients with lymphoma per year that would meet entry criteria and not meet exclusion criteria.</u> Based on prior trials recruited by this group,[51, 53, 54, 58, 59] we anticipate enrollment of 33% of eligible patients ($\approx$100 per year, 8 per month); 5-6 patients per month will be enrolled from DFCI/BWH and 2-3 patients per month from the MGH. We expect a total of about 3 years to complete enrollment.

In total 300 patients need to be enrolled.

Accrual Targets

Ethnic Category	Sex/Gender					
	Females		**Males**		**Total**	
Hispanic or Latino	25	+	26	=	51	
Not Hispanic or Latino	125	+	124	=	249	
Ethnic Category: Total of all subjects	150 (A1)	+	150	=	300	
Racial Category						
American Indian or Alaskan Native	0	+	0	=	0	
Asian	16	+	15	=	31	
Black or African American	14	+	13	=	27	
Native Hawaiian or other Pacific Islander	0	+	0	=	0	
White	115	+	117	=	232	
Racial Category: Total of all subjects	150(A2)	+	150 (B2)	=	300 (C2)	

(A1 = A2)   (B1 = B2)   (C1 = C2)

13.3   Interim Monitoring Plan

See section 6

13.4   Analysis of Primary Endpoints

See section 13.1

13.5   Analysis of Secondary Endpoints

See section 13.1

13.6   Reporting and Exclusions

Participants who never start protocol therapy will be excluded ("inevaluable") from the analysis.

13.6.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.6.2 Evaluation of the Primary Efficacy Endpoint

Analyses are intent-to-treat. Specifically, all eligible participants included in the study must be assessed for response/outcome to therapy, even if there are major protocol

therapy deviations.

Sub-analyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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