DF/HCC Protocol #: 17-022

TITLE: Ivabradine in the management of cardiac autonomic dysfunction associated with thoracic radiation therapy.

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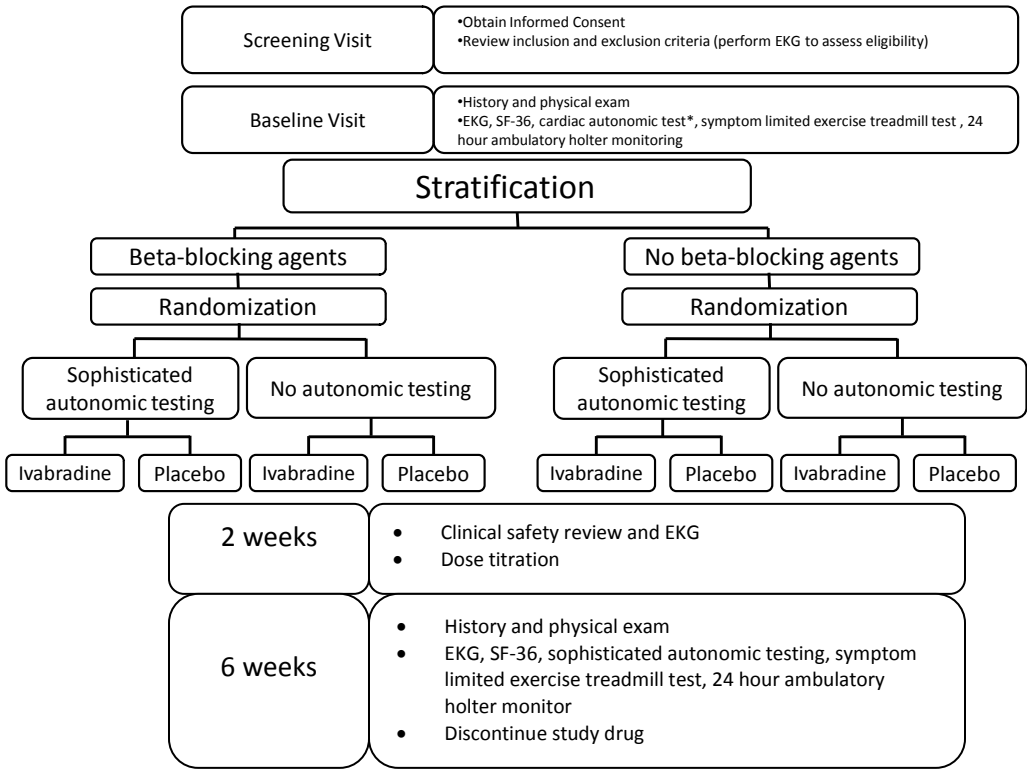
Other Agent(s): Ivabradine, Amgen

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

Protocol Type / Version # / Version Date: Original/Version #1/December 16, 2016

SCHEMA



***Cardiac autonomic testing will be carried out in the 30 patients who are randomized to receive this component of the protocol.**

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1. OBJECTIVES

To evaluate whether ivabradine lowers resting heart rate and improves exercise duration in survivors of lymphoma with mediastinal involvement (including both Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma) with evidence of radiation-induced autonomic dysfunction, manifested as a resting heart rate ≥ 80 bpm.

1.1 Study Design

This is a single center Phase II/pilot study to evaluate the safety and efficacy of ivabradine in survivors of lymphoma with mediastinal involvement (including both Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma) with post-radiation cardiac autonomic dysfunction, manifested as a resting heart rate ≥ 80 bpm. This study is a randomized, double-blind, placebo-controlled, parallel design trial.

1.2 Primary Objectives

To evaluate whether ivabradine reduces resting heart rate compared to placebo in survivors of lymphoma with mediastinal involvement (including both Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma) who were treated with mediastinal/mantle radiation and have a resting heart rate ≥ 80 bpm.

1.3 Secondary Objectives

To evaluate whether ivabradine improves exercise duration compared to placebo in survivors of lymphoma with mediastinal involvement (including both Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma) who were treated with mediastinal/mantle radiation and have a resting heart rate ≥ 80 bpm.

1.4 Exploratory Objectives

(i) To evaluate whether ivabradine improves additional markers of cardiac sympatho-vagal balance compared to placebo in survivors of lymphoma with mediastinal involvement (including both Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma) who were treated with mediastinal/mantle radiation and have a resting heart rate ≥ 80 bpm.

(ii) To evaluate whether ivabradine improves health related quality of life compared to placebo in survivors of lymphoma with mediastinal involvement (including both Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma) who were treated with mediastinal/mantle radiation and have a resting heart rate ≥ 80 bpm.

2. BACKGROUND

2.1 Study Disease(s)

Thoracic radiation therapy (RT) is associated with an increased risk of cardiovascular morbidity and mortality.[1, 2] In particular significant delayed cardiotoxicity has been observed among long-term survivors of Hodgkin lymphoma (HL) treated with mantle/mediastinal radiation.[3, 4] These patients also frequently report exercise intolerance. Elevated resting heart rate and abnormal heart rate recovery following exercise are established markers of cardiac autonomic dysfunction[5] and are strongly associated with cardiovascular morbidity and mortality in the general population

[6-11] as well as in survivors of Hodgkin lymphoma treated with mediastinal RT.[12]

Heart rate and rhythm are largely regulated by the autonomic nervous system. Parasympathetic influence is mediated via acetylcholine release by the vagus nerve and sympathetic influences are mediated via the secretion of epinephrine and norepinephrine. Acetylcholine reduces heart rate by increasing the potassium conductance of pacemaker cells in the sino-atrial node[13] and inhibiting the hyperpolarization activated I_f channel to delay slow diastolic depolarization.[14] Conversely, sympathetic activation increases intracellular calcium[15] and activates the I_f channel[16] to accelerate slow diastolic depolarization and increase heart rate. We have previously shown that thoracic RT is associated with autonomic dysfunction, as measured by elevated resting heart rate and abnormal heart rate recovery.[12] Furthermore, we were the first to report that these abnormalities are associated with impaired exercise tolerance among 263 Hodgkin lymphoma survivors treated with RT. Exercise duration was significantly reduced among RT patients with an elevated resting heart rate (9.2±2.9 versus 10.7±3.1 minutes, $p<0.0001$) and those with abnormal heart rate recovery (8.3±3.1 versus 10.6±2.9 minutes, $p<0.0001$).[12] We hypothesize that this is related to depressed parasympathetic stimulation secondary to RT-induced injury to the vagus nerve.

RT may also affect cardiovascular sympathetic function in Hodgkin lymphoma survivors. We have previously shown that thoracic RT is associated with a blunted systolic blood pressure (BP) response to exercise (OR 1.88, 95% CI 1.25-2.81). [12] In unpublished data, we compared supine and standing systolic BPs of 200 RT patients and 517 age, sex and cardiovascular risk-score matched control patients. The mean ± SD postural decrease in SBP was significantly greater in the RT cohort compared to controls: -4.7 ± 9.9 versus -2.7 ± 10.8 mmHg, p= 0.02. The prevalence of orthostatic hypotension (defined as a postural decrease in SBP of ≥ 20 mmHg **or** a postural decrease in DBP of ≥ 10 mmHg) was 7.5% in the RT cohort. Such BP abnormalities predispose to intolerance of traditional atrioventricular node blocking drugs such as beta-blockers or calcium channel blockers that might be considered for this patient cohort with elevated resting heart rates who describe exercise intolerance.

2.2 IND Agent(s): N/A

The FDA has deemed this study exempt from an IND (see attached FDA correspondence).

2.3 Other Agents

Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I_f current, resulting in heart rate reduction with no effect on ventricular repolarization and myocardial contractility. Ivabradine causes a dose-dependent reduction in heart rate. The size of the effect is dependent on the baseline heart rate (i.e., greater reduction occurs in subjects with higher baseline heart rate). At recommended doses (2.5-7.5 mg twice daily), HR reduction is approximately 10 bpm at rest and during exercise. Analysis of HR reduction vs. dose indicates a plateau effect at doses > 20 mg twice daily. Ivabradine increases the uncorrected QT interval with HR slowing but does not cause rate-corrected prolongation of QT.

Following oral administration, peak levels of ivabradine are reached in approximately 1 hour under fasting conditions. The oral bioavailability is about 40% due to first pass metabolism in

the gut and liver. Food delays absorption by 1 hour and increases plasma exposure by 20-40%. Therefore, it is recommended that ivabradine be taken with food. It is about 70% plasma-protein bound with a volume of distribution of approximately 100 L at steady state.

Ivabradine is metabolized by the liver and intestines via CYP3A4 mediated oxidation. The major metabolite is the N-desmethylated derivative (S 18982), which is equipotent to ivabradine and circulates at concentrations approximately 40% that of ivabradine. The N-desmethylated derivative is also metabolized by CYP3A4. Ivabradine plasma levels decline with a distribution half-life of 2 hours and an effective half-life of approximately 6 hours. The total clearance of ivabradine is 24 L/h, and renal clearance is approximately 4.2 L/h, with ~ 4% of an oral dose excreted unchanged in urine. The excretion of metabolites occurs to a similar extent via feces and urine. No adjustment in dose is required for hepatic or renal dysfunction. Due to the fact that it is metabolized by CYP3A4, concomitant administration of others drugs that are metabolized by CYP3A4, such as ketoconazole, diltiazem, verapamil, grapefruit juice and St. John's wart is not recommended.

Ivabradine is well tolerated with a similar incidence of adverse effects when compared to placebo in a large (n=6,505) clinical trial involving patients with chronic systolic heart failure (SHIFT: Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial).[17] It is approved by the FDA to decrease heart failure related deaths and hospitalizations in patients with systolic heart failure (LVEF $\leq$ 35%) who have a resting HR $\geq$ 70 beats per minute despite maximal tolerated doses of beta-blockers. We wish to investigate whether ivabradine can achieve HR reduction in patients with a resting heart rate $\geq$ 80 bpm as a consequence of thoracic RT irrespective of baseline LVEF, and if so whether observed reductions in HR translate into improvements in exercise capacity. In addition, we wish to investigate whether ivabradine improves cardiac sympatho-vagal balance and patient-reported quality of life in this cohort. To date, this will be the first randomized trial of any therapeutic agent in the management of these patients. We will use a dose scheme similar to that used in the SHIFT trial.[17]

Matching placebo tablets will be manufactured and supplied by the Investigational Drug Pharmacy at Brigham and Women's Hospital.

2.4 Rationale

Survivors of mediastinal RT have increased cardiovascular morbidity and mortality. We have previously shown that thoracic RT is associated with cardiac autonomic dysfunction, as manifested by elevated resting HR and abnormal HRR after exercise.[12] Furthermore, we were the first to report that these abnormalities are associated with impaired exercise tolerance and increased mortality (for HRR only) among 263 HL survivors treated with RT.[12] Furthermore, HL survivors treated with RT had a blunted BP response to exercise.[12] Ivabradine is a drug that lowers HR without significantly impacting BP. We hypothesize that ivabradine will lower HR in HL survivors treated with RT. We further hypothesize that this reduction in HR will lead to increased exercise capacity, improved sympatho-vagal balance, and improved health related quality of life in these patients.

2.5 Correlative Studies Background: N/A

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Survivors of mediastinal lymphoma (either Non-Hodgkin's Lymphoma or Hodgkin's Lymphoma) with no active malignancy

3.1.2 Prior mediastinal or mantle radiation ≥ 5 years prior to enrollment in the study

3.1.3 Age 18-80 years. Patients < 18 years will be excluded since ivabradine has not previously been studied in children. Patients > 80 years will be excluded since patients have to be able to perform a treadmill exercise stress test as part of this study.

3.1.4 ECOG performance status: N/A

3.1.5 Life expectancy: N/A

3.1.6 Participants must have normal organ function as defined below:

- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal

- creatinine clearance ≥ 15 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.

3.1.7 Normal sinus rhythm with resting heart rate ≥ 80 bpm on screening EKG

3.1.8 Based on findings in animals, ivabradine may cause fetal harm when administered to a pregnant woman. For this reason, women of child-bearing potential must agree to use highly effective contraception (as described in Appendix A) prior to study entry and for at least 2 weeks after the last dose of ivabradine. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Participants who are receiving any other investigational agents.

3.2.2 History of allergic reaction to *ivabradine.* Ivabradine is the first selective I_f channel sinus node inhibitor and therefore there are no other available drugs in this class.

3.2.3 Participants receiving any medications or substances that are inhibitors or inducers of cytochrome P450 3A4 are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, acute coronary syndrome, symptomatic known coronary artery disease, severe valvular heart disease, active malignancy, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.5 Pregnant women are excluded from this study because ivabradine is an agent with the potential for teratogenic effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ivabradine, breastfeeding should be discontinued if the mother is treated with ivabradine.

3.2.6 HIV-positive participants on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with ivabradine.

3.2.7 Patients with systolic blood pressure < 90 mm Hg.

3.2.8 Patients with sick-sinus syndrome, sino-atrial block, third degree heart block, atrial fibrillation, and those with permanent pacemakers.

3.2.9 Patients with other established indications for ivabradine: stable, symptomatic chronic HF with a left ventricular ejection fraction ≤ 35% and in sinus rhythm with a resting HR ≥ 70 bpm, who are taking maximally tolerated doses of beta-blockers or have contraindications to beta-blocker use.

3.2.10 Patients with severe hepatic dysfunction (Child Pugh Class C)

3.2.11 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier will be excluded.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. 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 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. Registration cancellations must be made in OnCore as soon as possible.

Following randomization by ODQ to ivabradine or placebo, ODQ will send subject registration information to the unblinded investigational pharmacy staff at bwhrxids@partners.org.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites: N/A

4.4 Registration Process for Other Investigative Sites: N/A

5. TREATMENT PLAN

5.1 Treatment Regimen

A total of 60 eligible patients will be randomized to ivabradine or placebo. Ivabradine or placebo will be administered for a total of 6 weeks. Treatment will be administered on an outpatient basis. On assessment days, no dose holds will occur. Reported adverse events and potential risks are described in Section 7.

Ivabradine will be started at a dose of 5 mg p.o. twice daily with meals. The patient will then be assessed after 2 weeks and the dose will be adjusted as shown in the Table below:

Heart Rate	**Dose Adjustment**
> 60 bpm	Increase dose to 7.5 mg p.o. twice daily
50-60 bpm	Maintain dose at 5 mg p.o. twice daily
< 50 bpm or signs and symptoms of bradycardia	Decrease dose to 2.5 mg p.o. twice daily

If the patient continues to have symptomatic bradycardia or HR < 50 on 2.5 mg twice daily, ivabradine will be discontinued.

If symptomatic bradycardia occurs on ivabradine 7.5 mg or 5 mg twice a day at any point in the study, without objective hemodynamic compromise (SBP > 80 mm Hg), the medication can be resumed at a lower dose (2.5 mg reduction) after a 24 hour drug-free interval (i.e. 1 missed dose). If symptomatic bradycardia persists despite dose reduction, then the study drug will be further reduced by 2.5 mg or discontinued as per the discretion of the investigator. A maximum of 2 dose reductions would be allowed for patients on 7.5 mg twice daily and 1 dose reduction for those on 5 mg twice daily. Patients requiring dose reduction will not have a subsequent dose escalation at any point during the study.

Placebo will be used in a similar manner. Patients will be maintained on the best tolerated dose for a total of 4 weeks.

Patients randomized to either ivabradine or placebo will be asked to maintain a drug diary as detailed in Appendix B to assess compliance.

5.2 Pre-Treatment Criteria

5.2.1 Screening Visit: After written informed consent is obtained, we will:

a) Obtain a detailed history and physical examination

b) Obtain an EKG to make sure that patients meet eligibility criteria i.e. are in sinus rhythm, have a resting HR ≥ 80 bpm, and do not have evidence of high grade AV block.

c) Review laboratory values obtained within the last 12 months for liver and renal function as described in the inclusion/exclusion criteria.

5.2.2 Baseline Visit: In addition to a detailed history and physical examination, we will:

a) Obtain an EKG to make sure that patients are in sinus rhythm, have a resting HR ≥ 80 bpm, and do not have evidence of high grade AV block prior to study drug randomization.

b) Obtain a urine pregnancy test to ensure that women of child-bearing age are not pregnant prior to study drug randomization.

5.2.3 2 week visit: In addition to a detailed history to review side effects from study drug treatment, we will:

a) Obtain an EKG to assess heart rate to determine dose adjustment as stated in section 5.1.

5.2.4 6 week visit: In addition to study procedures outlined below, we will:

a) Obtain a pregnancy test to ensure that women of child bearing age are not pregnant.

5.3 Agent Administration

Patients will take ivabradine or placebo for a total of 6 weeks. Ivabradine will be started at a dose of 5 mg p.o. twice daily with food. Ivabradine or placebo must not be crushed, chewed, or dissolved in water. The dose will be adjusted as per the Table in section 5.1 at the 2 week visit. Patients will continue the maximal tolerated dose for an additional 4 weeks. Placebo will be administered in a similar manner.

Ivabradine is FDA approved to reduce heart failure hospitalizations in patients with systolic heart failure (left ventricular ejection fraction ≤ 35%) who have resting HR > 70 bpm, despite maximal tolerated doses of beta-blockers. This study is evaluating ivabradine for a non-FDA approved indication and the drug titration protocol is per the Table in section 5.1.

Ivabradine is metabolized by the liver and intestines via CYP3A4 mediated oxidation. Therefore, patients will be instructed to avoid other drugs metabolized by the CYP3A4 system and grapefruit, star fruit, and pomegranate, in any form, for the duration of the study.

Patients will be asked to maintain a drug diary to assess compliance during the study. Patients will be instructed to note a missed or vomited dose and take the next dose as scheduled.

5.3.1 CTEP and/or CIP IND Agent(s), or other IND agent: N/A

5.3.2 Other Agent(s): N/A

5.3.3 Other Modality(ies) or Procedures

All patients will have a standard 12 lead EKG performed at the screening, baseline, 2 week and 6 week visits.

All patients will undergo exercise treadmill testing at the baseline and 6 week visits.

All patients will have a 24 hour ambulatory Holter monitor placed at the baseline and 6 week visits.

All patients will complete the SF-36 quality of life questionnaire at the baseline and 6 week visits.

Due to cost constraints, a subset of patients (n=30) will undergo further sophisticated autonomic function testing at the baseline and 6 week visits. Depending on scheduling limitations, they may have to return for a second day at each of these visits to complete the additional autonomic function tests.

a) Exercise treadmill testing

All exercise stress tests will be performed in the cardiovascular stress testing laboratory at Brigham and Women's Hospital by trained exercise physiologists under the supervision of a staff

cardiologist. Patients will avoid consumption of all caffeine containing products for 24 hours prior to exercise treadmill testing. All patients will undergo exercise treadmill testing using a symptom-limited Bruce protocol according to established guidelines.[18] Exercise will be continued until one or more of the following endpoints: exhaustion, symptom limitation, ≥ 85% of age-predicted maximal HR, ≥ 10 mmHg drop in systolic blood pressure (SBP) from baseline, sustained ventricular tachycardia, ST-segment depression ≥ 3 mm measured 80 msec after the J junction, or ST-segment elevation of ≥ 1 mm.

b) 24 Hour Ambulatory Holter Monitor

All patients will have a 24 hour ambulatory Holter monitor placed at baseline prior to study drug initiation and at the 6 week time point, prior to study drug termination. Holter monitors will be placed by the cardiology department at Brigham and Women's Hospital. Patients will be asked to return the Holter monitor in person or via mail to Brigham and Women's Hospital.

c) SF-36 Quality of Life Questionnaire

All patients will be asked to complete short form 36 (SF-36) quality of life healthcare questionnaires at the baseline and 6 week visits.

d) Sophisticated autonomic function testing

All of the additional autonomic function tests will be performed by Dr. Peter Novak in the autonomic function testing laboratory at Faulkner Hospital. Cardiac autonomic function will be assessed using:

1. Deep breathing:

   Deep breathing tests cardiac parasympathetic functions. All subjects will be asked to avoid smoking, intake of caffeinated beverages, and strenuous exercise for 12 hours prior to the test. Subjects will be asked to empty their bladder before the test to prevent sympathetic over-activity. They will then be asked to lie quietly in a temperature-controlled room for 20 minutes. A baseline EKG recording will be obtained for one minute to ensure a stable resting heart rate. Subjects will then be asked to inhale and exhale slowly at a rate of 6 breaths/minute and a continuous EKG will be recorded during deep breathing. Respiratory sinus arrhythmia (RSA) amplitude, defined as the difference in heart rate between end expiration and end inspiration, will be recorded for each respiratory cycle and the average RSA will be reported.[19]

2. Valsalva manuever:

   Valsalva maneuver evaluates sympathetic adrenergic function using the blood pressure responses and parasympathetic function using the heart rate responses. The Valsalva maneuver consists of forced expiration against resistance with an expiratory pressure during strain of 40 mm Hg for 15 seconds. The maneuver will be performed in the supine position. Patients will be asked to breath into a 10 ml plastic syringe that is connected to a

pressure gauge. They will be asked to take a deep breath and blow into the syringe and keep the pressure at 40 mm Hg for 15 seconds. Subjects will be asked to practice the maneuver to ensure that they can do it correctly prior to the actual measurements. Once they have mastered the manuever, they will be asked to rest for 3-5 minutes before repeating the maneuver. Heart rate and blood pressure will be recorded non-invasively using the Finapres NOVA system (Finapres Medical Systems, Netherlands). The Valsalva ratio, defined as the maximum heart rate during the maneuver divided by the lowest heart rate obtained within 30 seconds of the peak heart rate, will be measured.[19]

3. Tilt Testing:

   Tilt tests predominantly evaluate adrenergic function by applying orthostatic stress. Patients will be placed in the supine position and baseline heart rate and blood pressure will be acquired over 5-10 minutes. The patient will then be tilted up to an angle of 70 degrees over 5-10 seconds. Patients will be closely observed for chest pain, shortness of breath, dizziness, lightheadedness or syncope. If they have no adverse reaction, the heart rate and blood pressure will be assessed every minute for 10 minutes. The patient will then be placed back in the supine position. The increase in heart rate and drop in blood pressure in response to the tilt will be recorded.[19]

4. Heart rate variability:

   Heart rate variability with low frequency and high frequency oscillations in RR intervals assesses the balance of sympathetic and parasympathetic influences in the heart. Measures of overall heart rate variability and spectral analysis of heart rate variability will be performed with a Matlab based computer system.[20]

5. Sudomotor testing

   Electrochemical skin conductance (ESC) is a new noninvasive test for measurement of sudomotor functions.[21] ESC correlates with loss of small fiber skin nerves, and it is useful for evaluation of small fiber neuropathy. Measurements using ESC will be performed as described previously.[22]

The RSA and Valsalva ratio will be compared to age and gender based normative values (Tables 1 and 2). The cardiovagal composite autonomic severity score (CASS) will be calculated (Table 3). The adrenergic CASS will be calculated (Table 4).[19]

Table 1: Normal Values for Deep Breathing Test

Age range (years)	Minimum Normal RSA (beats/min)
10-29	≥ 14
30-39	≥ 12
40-49	≥ 10
50-59	≥ 9
60-69	≥ 7

Table 2: Normal Values for Valsalva Ratio

Age range (years)	Minimum Normal Valsalva Ratio	
	Women	Men
10-29	1.46	1.59
30-39	1.5	1.52
40-49	1.51	1.44
50-59	1.47	1.36
60-69	1.39	1.29

Table 3: Calculation of Cardiovagal Score

Result	Degree of Abnormality	Cardiovagal Score	Definition
Normal		0	
Abnormal	Mild	1	RSA or Valsalva ratio reduced but ≥ 50% of minimal normal values
	Moderate	2	RSA or Valsalva ratio < 50% of minimal normal values
	Severe	3	Both RSA and Valsalva ratio < 50% minimal normal values

Table 4: Calculation of Adrenergic Score:

Result	Degree of Abnormality	Adrenergic Score	Definition
Normal	0		
Abnormal	Mild	1	Valsalva maneuver: Early phase 2 drop in BP: 20-40 mmHg *OR* Late phase 2 BP does not return to baseline *OR* Pulse pressure reduction ≤ 50% of baseline *OR* Systolic pressure recovery time 4-5 seconds
	Moderate	2	Valsalva maneuver: Early phase 2 drop in BP: 20-40 mmHg *AND* Absent late phase 2 *OR* Absent phase 4 *OR* Systolic pressure recovery time 6-9 seconds
	Severe	3	Tilt: SBP reduction ≥ 30 mmHg; MAP reduction ≥ 20 mmHg *OR* Valsalva maneuver:

			Early phase 2 drop in BP ≥ 40 mmHg *AND* Absent phase 2 *AND* Absent phase 4 *OR* Absent phases 2 and 4 systolic pressure recovery time = 10 seconds
	Severe	4	Tilt *AND* Valsalva maneuver responses in #3

5.3.4 Investigational Imaging Agent Administration: N/A

5.4 For Phase 1 Protocols Only: Definition of Dose-Limiting Toxicity (DLT): N/A

5.5 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of ivabradine with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

5.6 Criteria for Taking a Participant Off Protocol Therapy

Patients will receive ivabradine or placebo for a total of 6 weeks. Treatment may continue for 6 weeks 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 procedure/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.

An 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 DF/HCC website at http://www.dfhcc.harvard.edu/research/clinical-research-support/document-library-forms-sops-etc/.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, *Anju Nohria, MD* at *617-732-5700 beeper 30350*.

5.7 Duration of Follow Up

Participants will be followed till the end of the study protocol. 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).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

All patients will be started on ivabradine 5 mg po twice daily or placebo. Dose modifications will be made at the 2 week visit as indicated in the following table(s).

Heart Rate	**Dose Adjustment**
> 60 bpm	Increase dose to 7.5 mg p.o. twice daily
50-60 bpm	Maintain dose at 5 mg p.o. twice daily
< 50 bpm or signs and symptoms of bradycardia	Decrease dose to 2.5 mg p.o. twice daily

If the patient continues to have symptomatic bradycardia or HR < 50 on 2.5 mg twice daily,

ivabradine will be discontinued. Placebo will be used in a similar manner. Patients will be maintained on the best tolerated dose for a total of 4 weeks.

If symptomatic bradycardia occurs on ivabradine 7.5 mg or 5 mg twice a day at any point in the study, without objective hemodynamic compromise (SBP > 80 mm Hg), the medication can be resumed at a lower dose (2.5 mg reduction) after a 24 hour drug-free interval (i.e. 1 missed dose). If symptomatic bradycardia persists despite dose reduction, then the study drug will be further reduced by 2.5 mg or discontinued as per the discretion of the investigator. A maximum of 2 dose reductions would be allowed for patients on 7.5 mg twice daily and 1 dose reduction for those on 5 mg twice daily. Patients requiring dose reduction will not have a subsequent dose escalation at any point during the study.

Any patients with symptoms of bradycardia after drug titration will be brought in for an additional clinical evaluation and EKG.

Overdosage of ivabradine may lead to severe and prolonged bradycardia. In the event of bradycardia with poor hemodynamic tolerance, the drug should be withdrawn. Supportive treatment, including intravenous fluids, atropine, intravenous beta-stimulating agents (isoproterenol) or temporary pacing may be considered.

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 For CTEP protocols only: Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs): N/A

7.2 For CTEP protocols only: Adverse Event Characteristics: N/A

7.3 For CTEP protocols only: Expedited Adverse Event Reporting: N/A

7.4 For CTEP protocols only: Routine Adverse Event Reporting: N/A

7.5 For CTEP protocols only: Secondary Malignancy: N/A

7.6 For CTEP protocols only: Second Malignancy: N/A

7.7 Expected Toxicities

7.7.1 Adverse Events List(s)

7.7.1.1 Adverse Event List(s) for Ivabradine

a) Fetal toxicity
b) Atrial fibrillation
c) Bradycardia
d) Conduction disturbances including heart block and sinus arrest
e) Ventricular arrhythmias including torsades de pointes, ventricular fibrillation, and ventricular tachycardia
f) Hypotension
g) Syncope
h) Hypertension
i) Phosphenes (luminous phenomenon)
j) Angioedema
k) Erythema
l) Rash
m) Pruritis
n) Urticaria
o) Vertigo
p) Diplopia
q) Visual distrubance

7.7.1.2 Adverse Event List(s) for Other Agent(s): N/A

7.8 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 agent(s) 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 protocol 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.

7.9 Expedited Adverse Event Reporting

7.9.1 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. Serious criteria includes: death, hospitalization, event that results in disability, life-threatening event, congenital anomaly, or any event determined to be medically significant by the investigator.

7.9.2 N/A

7.9.3 DF/HCC Expedited Reporting Guidlines

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

7.9.4 N/A

7.10 Expedited Reporting to the Food and Drug Administration (FDA): N/A

7.11 Expedited Reporting to the NIH Office of Biotechnology Activities (OBA): N/A

7.12 Expedited Reporting to the Institutional Biosafety Committee (IBC): N/A

7.13 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.

7.14 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 also be reported in routine study data submissions.**
The Overall PI must report all pregnancies and pregnancies occurring in the partner of a patient participating in the study or potential infant exposure through lactation within 10 calendar days of PI's awareness to Amgen. Amgen will contact the investigator/study site and request the site attempt to obtain authorization from the pregnant or breast feeding woman to provide Amgen with pertinent information regarding the pregnancy and birth outcome or health of the breastfed infant.

8. PHARMACEUTICAL 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 7.7.

8.1 Ivabradine

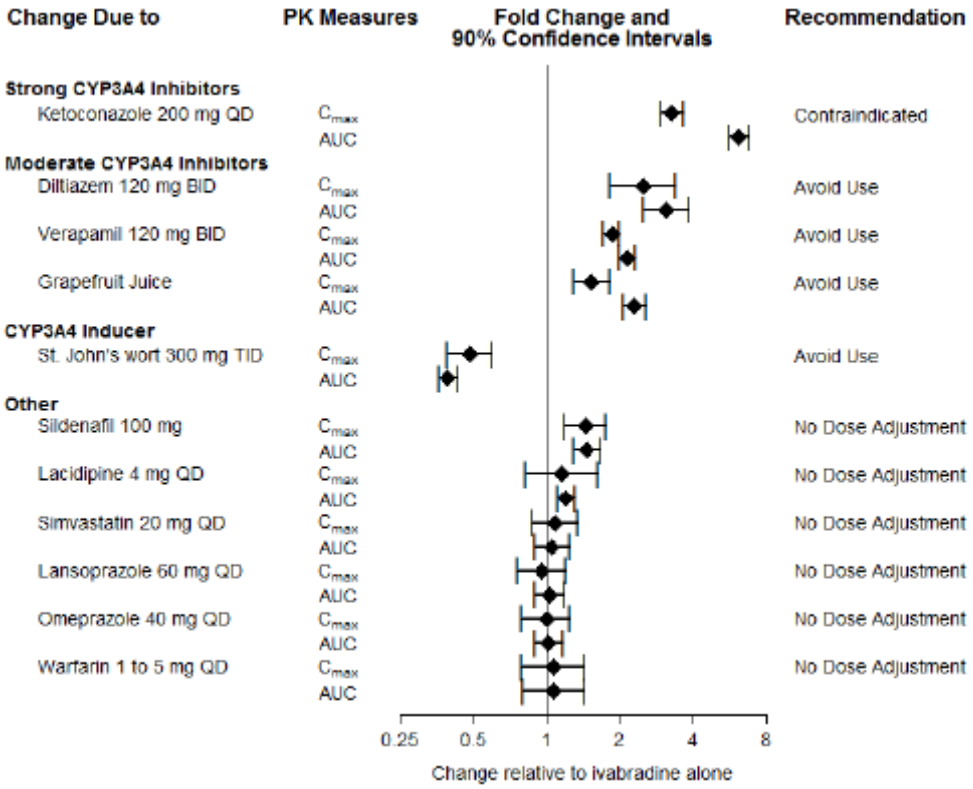
8.1.1 **Description**

Ivabradine is a hyperpolarization-activated cyclic nucleotide gated channel blocker that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I_f current, resulting in heart rate reduction with no effect on ventricular repolarization and no effects on myocardial contractility.

The chemical name for ivabradine is 3-(3-{[((7S)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7 yl)methyl] methyl amino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride. The molecular formula is C27H36N2O5, HCl, and the molecular weight (free base + HCl) is 505.1 (468.6 + 36.5).

Ivabradine is extensively metabolized in the liver and intestines by CYP3A4-mediated oxidation. The major metabolite is the N-desmethylated derivative (S 18982), which is equipotent to ivabradine and circulates at concentrations approximately 40% that of ivabradine. The N-desmethylated derivative is also metabolized by CYP3A4. Ivabradine plasma levels decline with a distribution half-life of 2 hours and an effective half-life of approximately 6 hours. The total clearance of ivabradine is 24 L/h, and renal clearance is approximately 4.2 L/h, with ~ 4% of an oral dose excreted unchanged in urine. The excretion of metabolites occurs to a similar extent via feces and urine.

The effects of coadministered drugs (CYP3A4 inhibitors, substrates, inducers, and other concomitantly administered drugs) on the pharmacokinetics of Corlanor were studied in several single- and multiple dose studies. Pharmacokinetic measures indicating the magnitude of these interactions are presented in the Figure below:



8.1.2 Form

Ivabradine is manufactured by Amgen under the trade Corlanor. It is supplied as:
Corlanor 5 mg: salmon-colored, oval-shaped, film-coated tablet, scored on both edges, debossed with "5" on one face and bisected on the other face. The tablet is scored and can be divided into equal halves to provide a 2.5 mg dose.
Corlanor 7.5 mg: salmon-colored, triangular-shaped, film-coated tablet debossed with "7.5" on one face and plain on the other face.

8.1.3 Storage and Stability

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F).

8.1.4 Compatibility

N/A

8.1.5 Handling

There are no special considerations for the handling of ivabradine.

8.1.6 Availability

Ivabradine, which is commercially available, will be provided free of charge for this

study by Amgen. The study drug will be sent by Amgen to the principal investigator, Dr. Anju Nohria, and will be stored and dispensed by the Investigational Pharmacy at Brigham and Women's Hospital. Matching placebo tablets will also be manufactured and stored by the Investigational Drug Pharmacy at Brigham and Women's Hospital.

8.1.7 **Preparation**

After randomization, ivabradine or matching placebo tablets will be supplied by the Investigational Drug Pharmacy at Brigham and Women's Hospital.

Active medication will be blinded using over-encapsulation in an empty gelatin capsule by the Investigational Drug Pharmacy at Brigham and Women's Hospital. The matching placebo will be a capsule filled with microcrystalline cellulose also prepared by the Investigational Drug Pharmacy at Brigham and Women's Hospital.

Both the patient and investigators will remain blinded to study drug assignment throughout the duration of the study.

8.1.8 **Administration:**

Medication will be taken P.O. twice daily with food. Medication will be taken outpatient. Pills should be swallowed whole.

8.1.9 **Ordering**

Ivabradine will be provided by Amgen prior to study initation. Placebo will be manufactured by the Investigational Drug Pharmacy. Both ivabradine and placebo will be stored and dispensed by the Investigational Drug Pharmacy at Brigham and Women's Hospital.

8.1.10 **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.)

8.1.11 **Destruction and Return**

Unused and expired supplies of ivabradine will be returned to Amgen at the end of the study**.**

8.2 IND Agent #2: N/A

8.3 Other Agent #1: N/A

8.4 Other Agent #2: N/A

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies: N/A

9.2 For IDE Protocols Only: Investigational Device Information: N/A

9.3 Laboratory Correlative Studies: N/A

9.4 Other Agent #2: N/A

10. STUDY CALENDAR

Baseline evaluations/tests are to be conducted within 1 week prior to start of protocol therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of therapy.

2 week study evaluations and drug up-titration should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

Week 6 study evaluations/tests should be conducted within ± 7 days of the protocol-specified date and should be completed prior to termination of study drug.

	Screening visit	Baseline	Week 2	Week 6
Agents:		Ivabradine vs. placebo	Ivabradine or placebo dose titration	Study End
Informed consent	X			
Demographics	X			
Medical history	X		X	X
Physical exam		X	X	X
Concurrent Meds	X	X	X	X
Vital signs	X	X	X	X
Height		X		X
Weight		X		X
Serum chemistry[a]	X			
EKG (as indicated)	X	X	X	X
B-HCG		X[b]		X[b]
Exercise stress test		X		X
24-hr ambulatory Holter monitor		X		X
SF-36 QOL questionnaire		X		X
Sophisticated autonomic function testing[c]		X		X
Adverse event evaluation		X----------X		

a: Review of SGOT [AST], SGPT [ALT], creatinine obtained within the last 12 months.
b: Urine pregnancy test (women of childbearing potential).
c: For subset of patients randomized to receive autonomic function testing

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect- Solid Tumors: N/A

11.2 Antitumor Effect- Hematologic Tumors: N/A

11.3 Other Response Parameters

Primary end point:

1. Change in HR from baseline to 6 weeks with ivabradine vs. placebo.[17]

Secondary end point:

1. Change in exercise duration from baseline to 6 weeks with ivabradine vs. placebo.[23]

Exploratory end points:

1. Change in markers of additional cardiac autonomic function: respiratory sinus arrhythmia amplitude, Valsalva ratio, heart rate variability, cardiovagal CASS and adrenergic CASS from baseline to 6 weeks.[19]

2. Change in patient reported quality of life (as assessed using then SF 36 questionnaire) from baseline to 6 weeks with ivabradine compared to placebo.[24]

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 Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality according to the schedule set by the DF/HCC SOPs.

12.1.3 Confidentiality Protections

Data will be obtained from a complete history, physical examination, symptom limited exercise stress test, 24 hour ambulatory Holter monitor, cardiac autonomic testing, and a self-reported health related quality of life questionnaire (SF-36) before and after the 6

week treatment period. Data will also be collected from the 14-day safety visit. The data will be shared with investigators/personnel involved in the study and will be retained for at least 5 years after completion of the study. The data source files will be kept in a locked room in the cardiovascular offices at Brigham and Women's Hospital. The data will be stored in a de-identified manner in an encrypted Partners computer.

The identifiable information will not be reused or disclosed except as consistent with this protocol and signed HIPAA Authorization for Research.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines: N/A

12.4 Collaborative Agreements Language: N/A

13. STATISTICAL CONSIDERATIONS

This is a randomized double-blind, placebo-controlled study evaluating the effect of ivabradine on resting heart rate and exercise capacity in survivors of lymphoma with mediastinal involvement who were treated with mediastinal/mantle RT.

Survivors of mediastinal RT have increased cardiovascular morbidity and mortality. We have previously shown that thoracic RT is associated with cardiac autonomic dysfunction, as measured by elevated resting HR and abnormal HRR after exercise.[12] Furthermore, we were the first to report that these abnormalities are associated with impaired exercise tolerance and increased mortality (for HRR only) among 263 HL survivors treated with RT.[12] Furthermore, HL survivors treated with RT had a blunted BP response to exercise.[12] Ivabradine is a drug that lowers HR without significantly impacting BP. We hypothesize that ivabradine will lower HR in HL survivors treated with RT. We further hypothesize that this reduction in HR will lead to increased exercise capacity, improved sympatho-vagal balance, and improved health related quality of life in these patients.

The study will enroll adult survivors of lymphoma with mediastinal involvement (including both

Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma) who have been treated with mediastinal/mantle radiation at least 5 years prior to enrollment and have a resting heart rate ≥ 80 bpm. The detailed eligibility criteria are outlined in sections 3.1 and 3.2 above.

13.1 Study Design/Endpoints

Primary End point:

The primary objective of this study is to investigate whether ivabradine lowers resting HR, compared to placebo, in survivors of lymphoma with mediastinal involvement who were treated with mediastinal/mantle radiation and have a resting HR ≥ 80 bpm.

Secondary End-point:

The secondary objective of this study is to evaluate whether ivabradine improves exercise duration, compared to placebo, in survivors of lymphoma with mediastinal involvement who were treated with mediastinal/mantle radiation and have a resting HR ≥ 80 bpm.

Exploratory End-points:

1) To evaluate whether ivabradine improves additional markers of cardiac sympatho-vagal balance, compared to placebo, in survivors of lymphoma with mediastinal involvement who were treated with mediastinal/mantle radiation and have a resting HR ≥ 80 bpm.
2) To evaluate whether ivabradine improves health related quality of life, compared to placebo, in survivors of lymphoma with mediastinal involvement who were treated with mediastinal/mantle radiation and have a resting HR ≥ 80 bpm.

- The patients will be accrued on a continuous basis from the out-patient survivorship, cardio-oncology, and radiation oncology clinics at DFCI, Massachusetts General Hospital, Brigham and Women's Hospital, and Boston Children's Hospital till target accrual is completed. Eligible patients from sites other than the Brigham will be referred to the Brigham for all study procedures.

- There are no explicit early stopping rules for this study. However, the data will be reviewed periodically by the DFCI DSMB and the study will be terminated if the DSMB deems it necessary to do so.

- The target sample size for this study is 54 patients. We plan to enroll a total of 60 patients to account for screen failure, resting HR < 80 at baseline visit, withdrawals, or loss to follow up. Based on our clinical volume, we plan to recruit 2-3 patients per month over a cumulative accrual period of 24-36 months. Each patient will be followed for the 6 week duration of the study. There is no long-term follow-up planned in this study.

- We hypothesize that ivabradine will lower resting HR, compared to placebo, in survivors of lymphoma with mediastinal involvement who were treated with mediastinal/mantle radiation

and have a resting HR ≥ 80 bpm. We further hypothesize that this reduction in HR will be associated with increased exercise duration in these patients.

- In the Ivabradine and chronic outcomes in heart failure (SHIFT) trial, the net reduction in heart rate with ivabradine was 10.9 (95% CI 10.4-11.4) bpm, with a standard deviation of 10.5 bpm. Thus, with a sample size of 27 patients in each group, we will have 95% power to detect this net reduction in heart rate assuming a probability of making a type I error of 0.05.[12] To allow for incomplete primary end point data due to withdrawals or loss to follow up, we will aim to recruit 30 patients in each group.

- With a sample size of 27 subjects in each group, we will have 90% power to detect a clinically meaningful improvement of 34% in exercise duration on treadmill testing assuming a probability of making a type I error of 0.05, an improvement in the placebo group of 12%, and a standard deviation of 24%.

- All patients will first be stratified into two groups according to pre-randomization treatment with beta-blocking agents. Patients within each beta-blocker group will then undergo four way randomization using permuted blocks, dividing the two strata into four groups each: ivabradine with sophisticated autonomic testing, placebo with sophisticated autonomic testing, ivabradine with no sophisticated autonomic testing, placebo with no sophisticated autonomic testing. These four groups will be created in a 1:1:1:1 ratio. Randomization will be performed by the ODQ at Dana Farber Cancer Institute.

- If patients are randomized into the sophisticated autonomic testing group and are not able to complete sophisticated autonomic function testing for any reason, but are willing to continue taking the study medication (ivabradine or placebo), they will be encouraged to continue taking part in all other study protocols for the duration of the study: twice daily ivabradine or placebo, history and physical exam, EKG, SF-36 questionnaire, exercise treadmill test, and 24 hour ambulatory holter monitoring.

13.2 Sample Size, Accrual Rate and Study Duration

The target sample size for this study is 54 patients. We plan to enroll a total of 60 patients to account for screen failure, resting HR < 80 at baseline visit, withdrawals, or loss to follow up. Based on our clinical volume, we plan to recruit 2-3 patients per month over a cumulative accrual period of 24-36 months. Each patient will be followed for the 6 week duration of the study. There is no long-term follow-up planned in this study.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	3	+	4	=	7
Not Hispanic or Latino	24	+	29	=	53

Ethnic Category: Total of all subjects	27	(A1)	+	33	(B1)	=	60 (C1)
Racial Category							
American Indian or Alaskan Native	1		+	1		=	2
Asian	1		+	1		=	2
Black or African American	3		+	4		=	7
Native Hawaiian or other Pacific Islander	1		+	1		=	2
White	21		+	26		=	47
Racial Category: Total of all subjects	27	(A2)	+	33	(B2)	=	60 (C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)

13.3 Stratification Factors

All patients will first be stratified into two groups according to pre-randomization treatment with beta-blocking agents. Patients within each beta-blocker group will then undergo four way randomization using permuted blocks, dividing the two strata into four groups each: ivabradine with sophisticated autonomic testing, placebo with sophisticated autonomic testing, ivabradine with no sophisticated autonomic testing, placebo with no sophisticated autonomic testing. These four groups will be created in a 1:1:1:1 ratio. Randomization will be performed by the ODQ at Dana Farber Cancer Institute.

Monitoring and efficacy determination will not be done separately for the different strata. An ANCOVA model (for normally distributed data) adjusting for the stratification factors (beta blocking agents [Yes, No], autonomic function testing [Yes, No]) or Quade test adjusting for the stratification factors (beta blocking agents [Yes, No], autonomic function testing [Yes, No]) (for non-normally distributed data) will be implemented to compare the change in various endpoint with ivabradine versus placebo.

13.4 Interim Monitoring Plan

Patients will be enrolled continuously in this trial over the course of the trial. Each patient will be followed for the 6 week duration of thestudy. There are no formal interim monitoring plans in this trial. However, data will be submitted to the DFCI DSMB every 6 months and the recommendations of the DSMB regarding trial continuation will be followed accordingly.

13.5 Analysis of Primary Endpoint

The primary end-point of this study is the change in resting HR with ivabradine, compared to placebo, in survivors of lymphoma with mediastinal involvement who were treated with mediastinal/mantle radiation and have a resting HR ≥ 80 bpm.

We will calculate the change in resting HR (from EKGs) from baseline to 6 weeks for each patient in the study (n=60). An ANCOVA model (for normally distributed data) adjusting for the stratification factors (beta blocking agents [Yes, No], autonomic function testing [Yes, No]) or Quade test adjusting for the stratification factors (beta blocking agents [Yes, No], autonomic function testing [Yes, No]) (for non-normally distributed data) will be implemented to compare the change in resting HR with ivabradine versus placebo. A p value < 0.05 using a two-sided test will be considered statistically significant.

13.6 Analysis of Secondary Endpoints

The secondary end-point of this study is the change in exercise duration with ivabradine, compared to placebo, in survivors of lymphoma with mediastinal involvement who were treated with mediastinal/mantle radiation and have a resting HR ≥ 80 bpm.

We will calculate the change in exercise duration (from exercise treadmill stress tests) from baseline to 6 weeks for each patient in the study (n=60). An ANCOVA model (for normally distributed data) adjusting for the stratification factors (beta blocking agents [Yes, No], autonomic function testing [Yes, No]) or Quade test adjusting for the stratification factors (beta blocking agents [Yes, No], autonomic function testing [Yes, No]) (for non-normally distributed data) will be implemented to compare the change in exercise duration with ivabradine versus placebo.

We will then repeat the analysis with change in resting HR as an additional independent variable to assess whether change in resting HR affects exercise duration. A p value < 0.05 using a two-sided test will be considered statistically significant.

<u>Exploratory end-points of this study are:</u>

1) Change in additional markers of cardiac sympatho-vagal balance with ivabradine, compared to placebo, in survivors of lymphoma with mediastinal involvement who were treated with mediastinal/mantle radiation and have a resting HR ≥ 80 bpm.

   Since this is an exploratory end-point and due to cost constraints, it will only be conducted in half the patients enrolled in the trial (n=30) and no power calculation has been made. The cardiovagal composite autonomic severity score (CASS) and adrenergic CASS will be calculated at baseline and at 6 weeks (as decribed in Section 5.3.3) for each patient in this substudy. The change in CASS and adrenergic CASS will then be assessed for each patient. Quade test adjusting for the stratification factors (beta blocking agents [Yes, No], autonomic function testing [Yes, No]) (for ordinal data) will be implemented to compare the change in CASS and adrenergic CASS in patients treated with ivabradine versus placebo. A p value < 0.05 using a two-sided test will be considered statistically significant.

2) Change in health related quality of life with with ivabradine, compared to placebo, in survivors of lymphoma with mediastinal involvement who were treated with

mediastinal/mantle radiation and have a resting HR ≥ 80 bpm.

All patients (n=60) will complete the SF-36 health survey at baseline and at 6 weeks. The SF-36 questionnaire consists of eight subsections; physical functioning, social role functioning, physical role functioning, emotional role functioning, mental health, vitality, bodily pain, and general health perceptions. For each section, item scores are coded from 0 (worst health status) to 100 (best health status). Total scores are also obtained for two main domains: a physical component -consisting of physical function, role physical, bodily pain, and general health subscales- and a mental component -consisting of role emotional, social functioning, mental health, and vitality. SF-36 has been used to assess quality of life in several cancer populations. Change in SF-36 scores from baseline to 6 weeks will be calculated for each patient. An ANCOVA model (for normally distributed data) adjusting for the stratification factors (beta blocking agents [Yes, No], autonomic function testing [Yes, No]) or Quade test adjusting for the stratification factor (beta blocking agents [Yes, No], autonomic function testing [Yes, No]) (for non-normally distributed data) will be implemented to compare the change in quality of life with ivabradine versus placebo. A p value < 0.05 using a two-sided test will be considered statistically significant.

13.7 Reporting and Exclusions

All patients who complete the baseline and 6 week assessments will be included in the analyses.

13.7.1 Evaluation of Toxicity

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

13.7.2 Evaluation of the Primary Efficacy Endpoint

Since the primary end-point is assessing change in HR from baseline to 6 weeks, we will only include those patients who complete both the baseline and 6 week visit for evaluation of the primary efficacy end-point. However, we will have HR data at the 2 week titration visit and will report this if there is a significant rate of study withdrawal or loss to follow up in the ivabradine group.

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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APPENDIX A Birth Control Measures

A woman is considered to be of childbearing potential unless she meets at least one of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy, or hysterectomy
- Premature ovarian failure confirmed by a specialist
- Pre-pubescence, XY genotype, Turner Syndrome, uterine agenesis
- Post-menopausal, defined as 12 consecutive months with no menses without an alternative medical cause

Women of Childbearing potential must use a reliable method of contraception during treatment with ivabradine and for an additional 2 weeks after the last dose of ivabradine. The use of the following options is regarded as highly effective contraception:

Option #1

One method from this list:
Combined (estrogen and progesterone containing) hormonal contraception: - Oral - Intravaginal - Transdermal - **OR** Progesterone-only hormonal contraception: - Oral - Injectable - Transdermal

Option #2

One method from this list:
Intrauterine device (IUD) Intrauterine hormone-releasing system (IUS)

Option #3

One method from this list:
Partner's vasectomy with medical confirmation of surgical success Bilateral tubal occlusion Sexual abstinence

APPENDIX B Drug Diary

Study Participant
Self-Administration
Study Drug Diary
Dana-Farber/Harvard Cancer Center

Participant Identifier: _____
Protocol #
Study MD _____ Phone _____

STUDY DRUG INSTRUCTIONS:

Study Drug: Ivabradine
How Much: a) 2.5 milligrams,
b) 5 milligrams, OR
c) 7.5 milligrams
How Often: Twice daily
When: With breakfast and with dinner

SPECIAL INSTRUCTIONS:
i) do not consume grapefruit, grapefruit juice, or any other form of grapefruit
ii) do not consume starfruit
iii) do not consume pomegranate, pomegranate juice or any other form of pomegranate
iv) Store drug at room temperature and keep drug in provided pill bottle
v) a dose should be considered missed if it has not been taken within 6 hours prior to the next scheduled dose. If you miss a dose or vomit after taking the medication, please make a note of this in your drug diary. Take your next dose at your regularly schedule time
vi) if you experience any side effects, please note this in your drug diary. If these side effects interfere with your ability to carry out your daily activities, please contact the study staff.
vii) please keep drug in provided pill bottle
viii) bring any unused drug, your pill bottle, and this diary to your next clinic visit
ix) do not crush, chew, or dissolve drug in water
x) do not skip drug on days where you come to see your doctor
xi) please update this diary daily

OTHER MEDICATIONS TAKEN

If you take a daily medication or supplement (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

Drug Name	Dose	Dates Taken	Reason Taken

Study Participant Initials _____ Date _____

FOR STUDY TEAM USE ONLY Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

DOSING LOG

Ivabradine
For each AM dose take: 1 pill
For each PM dose take: 1 pill

Please indicate the date, time, amount taken and any comments.

	Date	Amount Taken		Comments
		AM dose	PM dose	
Ex:	6/1/2009	8 am - 1	7:30 pm - 1	forgot PM pill
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
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Day 42				
Day 43				
Day 44				
Day 45				
Day 46				
Day 47				
Day 48				
Day 49				
Day 50				

SYMPTOMS/SIDE EFFECTS

Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended. Please evaluate the severity of the symptom according to the following scale:

Mild: Awareness of sign or symptom; easily tolerated and did not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention.

Moderate: Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention.

Severe: Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve.

Please Note: The severity should reflect the most severe level experienced during the time period.

Symptom	Start Date	End Date	Severity

APPENDIX C Information On Possible Drug Interactions

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

Ivabradine interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Ivabradine interacts with a specific enzyme in your liver. The enzyme in question is known as **Cytochrome P450 3A4**, also known as **CYP 3A4.** Ivabradine is broken down and metabolized by **CYP 3A4**.

Ivabradine must be used very carefully with other medicines that need **CYP3A4** to be effective or to be cleared from your system.

Substances that increase **CYP3A4** activity (known as "inducers") could reduce the effectiveness of ivabradine, while substances that decrease the **CYP3A4** activity (known as "inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.

You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.

Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4.**

Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.

Please also avoid any grapefruit products, star fruit, or pomegranate products for the duration of the study since these foods are inhibitors of **CYP3A4** activity.

Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

Be careful to avoid the following drugs, foods, and supplements while taking ivabradine:

- **CYP3A4 inhibitors**: ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, saquinavir, boceprevir, telaprevir, iopinavir, fosamprenavir, darunavir, tipranavir, atazanavir, nelfinavir, amprenavir, idinavir, verapamil, diltiazem, erythromycin, grapefruit, pomegranate, and star fruit,
- **CYP3A4 inducers:** carbamazepine, rifampicin, rifabutin, phenytoin, St. John's Wort,

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is Dr. Anju Nohria and she can be contacted at (617) 525-7052.