Lung Cancer Exercise Training Study: A Randomized Trial of Aerobic Training, Resistance Training, or Both in Lung Cancer Patients

PROTOCOL FACE PAGE FOR MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Lee Jones, PhD	Medicine/Exercise Oncology
Co-Principal Investigator(s)/Department:	Valerie Rusch, MD	Surgery/Thoracic
	James Huang, MD	Surgery/Thoracic
	Jamie E. Chatt, MD	Medicine/Thoracic Oncology
Investigator(s)/Department:	Charles M. Rudin, MD, PhD	Medicine/Thoracic Oncology
	Alexander Drilon, MD	Medicine/Thoracic Oncology
	Mark G. Kris, MD	Medicine/Thoracic Oncology
	Piro Lito, MD, PhD	Medicine/Thoracic Oncology
	Paul K. Paik, MD	Medicine/Thoracic Oncology
	Gregory J. Riely, MD, PhD	Medicine/Thoracic Oncology
	Stephen R. Veach, MD	Medicine/Thoracic Oncology
	Helena A. Yu, MD	Medicine/Thoracic Oncology
	Matthew Hellmann, MD	Medicine/Thoracic Oncology
	Bob Li, MD	Medicine/Thoracic Oncology
	Marjorie G. Zauderer, MD	Medicine/Thoracic Oncology
	Prasad S. Adusumilli, MD	Surgery/Thoracic
	Manjit S. Bains, MD	Surgery/Thoracic
	Robert J. Downey, MD	Surgery/Thoracic
	David R. Jones, MD	Surgery/Thoracic
	Bernard J. Park, MD	Surgery/Thoracic
	Nabil Pierre Rizk, MD	Surgery/Thoracic
	Matthew Bott, MD	Surgery/Thoracic
	James Isbell, MD	Surgery/Thoracic
	Daniela Molena, MD	Surgery/Thoracic
	Smita Sihag, MD	Surgery/Thoracic
	Alison Berkowitz-Hergianto, NP	Nursing
	Dyana Katherine Sumner, NP	Nursing
	Stacie Corcoran, NP	Nursing
	Elizabeth Panora, NP	Nursing
	Leslie Tyson, NP	Nursing
	Amy Devigne, NP	Nursing
	Nicholas VanderEls, MD	Medicine/Pulmonary
	Mohit Chawla, MD	Medicine/Pulmonary
	Annemarie Shepherd, MD	Radiation Oncology
	Andreas Rimner, MD	Radiation Oncology
	Abraham Wu, MD	Radiation Oncology
	John Cuaron, MD	Radiation Oncology

	Richard M. Steingart, MD	Medicine/Cardiology
	Carol L. Chen, MD	Medicine/Cardiology
	Michael S. Baum, MD	Medicine/Cardiology
	Dipti Gupta, MD, MPH	Medicine/Cardiology
	Michelle N. Johnson, MD, MPH	Medicine/Cardiology
	Jennifer Liu, MD	Medicine/Cardiology
	Eileen P. McAleer, MD	Medicine/Cardiology
	Nancy Roistacher, MD	Medicine/Cardiology
	Wendy Schaffer, MD, PhD	Medicine/Cardiology
	Howard Weinstein, MD	Medicine/Cardiology
	Anthony Yu, MD	Medicine/Cardiology
	Jessica Scott, PhD	Medicine/Exercise Oncology
	Meghan Michalski	Medicine/Exercise Oncology
	Daniel Townend, BS	Medicine/Exercise Oncology
	Catherine Capaci, MS	Medicine/Exercise Oncology
	Kereshmeh Collins, BS	Medicine/Exercise Oncology
	Richard Happel, MS	Medicine/Exercise Oncology
	Kylie Rowed, MKin	Medicine/Exercise Oncology
	Jonathan Landa, DO	Radiology
Consenting Professional(s)/Department:	Lee Jones, PhD	Medicine/Exercise Oncology
	Jessica Scott, PhD	Medicine/Exercise Oncology
	Jamie E. Chaft, MD	Medicine/Thoracic Oncology
	Charles M. Rudin, MD, PhD	Medicine/Thoracic Oncology
	Alexander Drilon, MD	Medicine/Thoracic Oncology
	Mark G. Kris, MD	Medicine/Thoracic Oncology
	Piro Lita, MD, PhD	Medicine/Thoracic Oncology
	Paul K. Paik, MD	Medicine/Thoracic Oncology
	Gregory J. Riely, MD, PhD	Medicine/Thoracic Oncology
	Stephen R. Veach, MD	Medicine/Thoracic Oncology
	Helena A. Yu, MD	Medicine/Thoracic Oncology
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	Matthew Hellmann, MD	Medicine/Thoracic Oncology
	Bob Li, MD	Medicine/Thoracic Oncology
	Annemarie Shepherd, MD	Radiation Oncology
	Andreas Rimner, MD	Radiation Oncology
	Abraham Wu, MD	Radiation Oncology
	John Cuaron, MD	Radiation Oncology
	Meghan Michalski, MS	Medicine/Exercise Oncology
	Daniel Townend, BS	Medicine/Exercise Oncology
	Catherine Capaci, MS	Medicine/Exercise Oncology
	Kereshmeh Collins, BS	Medicine/Exercise Oncology
	Richard Happel, MS	Medicine/Exercise Oncology

	Kylie Rowed, MKin	Medicine/Exercise Oncology

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

Participating Institutions - If multicenter study coordinated by MSK:	PI's Name	Site's Role
Duke University	Pamela S. Douglas, MD	Data Analysis

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, New York 10065

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Primary Objective: To compare the efficacy of different types of exercise training modalities, relative to progressive stretching (attention control group), on exercise capacity ($V02peak$) in patients with lung cancer.

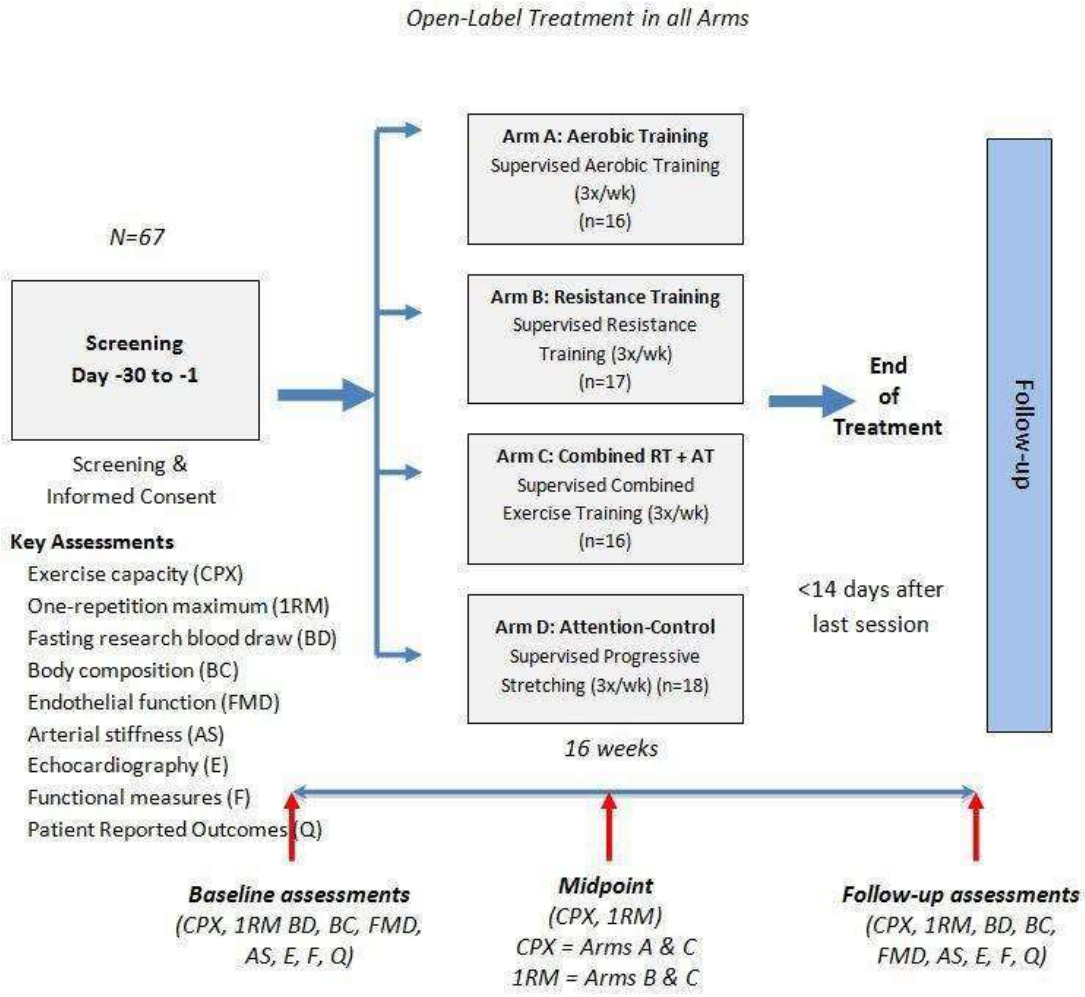
Design: Patients with Memorial Sloan Kettering Cancer Center (MSK) histologically-confirmed lung cancer will be randomized to one of the following four arms: **Arm A:** supervised aerobic training; **Arm B:** supervised resistance training; **Arm C:** supervised combined aerobic and resistance training; and **Arm D:** stretching (attention control group).

The goal of this RCT is to recruit a total of 160 patients with histologically-confirmed lung cancer at any stage or receiving any type of therapy. A total of 40 per arm patients will be randomized in a 1:1:1:1 ratio to the four study arms.

This RCT was initially initiated and conducted at Duke University Medical Center (DUMC) by the principal investigator (Lee Jones, PhD). The trial was suspended at DUMC (protocol-independent) due to change of the PI's institution (Dr. Jones is now at MSK). At the time of trial suspension, a total of 93 participants had been randomly allocated to the four study arms: **Arm A** supervised aerobic training (n=24), **Arm B:** supervised resistance training (n=23), **Arm C:** supervised combined aerobic and resistance training (n=24), and **Arm D:** progressive stretching (attention control group) (n=22)

At MSK, patients will be enrolled and randomized until target enrollment is met (67 patients in total at MSK): **Arm A:** supervised aerobic training (n=16), **Arm B:** supervised resistance training (n=17), **Arm C:** supervised combined aerobic and resistance training (n=16), and **Arm D:** progressive stretching (attention control group) (n=18); At the end of the trial, data will be analyzed for the pre-planned sample size (n=160).

Figure 1. Study Schematic for MSK Recruitment



2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective

To compare the efficacy of different types of exercise training modalities, relative to progressive stretching (attention control group), on VO_{2peak} in patients with advanced lung cancer or a history of operable lung cancer.

2.2 Secondary Objectives

- To compare the effects on one-repetition maximum
- To compare the effects on resting and exercise cardiac function
- To compare the effects on pulmonary function
- To compare the effects on arterial stiffness

- To compare the effects on endothelial function (Flow Mediated Dilation)
- To compare the effects on body compasition
- To compare the effects on functional measures of performance
- To compare the effects on patient-reported outcomes (e.g., quality of life, fatigue), and
- To collect and bank blood samples for future correlative studies.

3.0 BACKGROUND AND RATIONALE

3.1 Indication

The intended indication for supervised exercise training is the treatment of impaired exercise capacity (i.e., global cardiovascular function) in patients with lung cancer.

3.2 Background and Rationale

Improvements in surgical techniques, together with more effective cytotoxic therapies have led to improvements in overall survival (in patients with early-stage disease) and progression-free survival (in patients with advanced disease) . With improving prognosis, acute and longer-term disease- and treatment-related morbidity (symptom control) are now recognized as issues of major clinical importance in the multidisciplinary management of lung cancer.[1 6] A parameter of central importance that may mediate acute and late-occurring disease and treatment-related toxicity in lung cancer is exercise capacity. Exercise capacity, as measured by an objective cardiopulmonary exercise test (CPET), reflects the integrative capacity of components in the oxygen (02) cascade to supply adequate 02 for adenosine triphosphate (ATP) resynthesis. Peak oxygen consumption ($V0_2peak$) provides the gold standard (direct) assessment of exercise capacity. Direct or estimated measurement of $V02peak$ is a well-established independent predictor of mortality in a broad range of non-cancer, adult populations.[7,8]

Not surprisingly, lung cancer patients have significant and marked reductions in $V02peak$. Lung cancer patients are subject to the effects of normal aging, age-related and/or disease-related comorbid conditions and deconditioning that adversely impact components of the 0_2 cascade. However, these 'normal' consequences are profoundly accelerated by disease pathophysiology and the use of conventional adjuvant therapy to create a 'perfect deconditioning storm', reducing either the body's ability to deliver and/or utilize o_2 and substrate leading to poor $V02peak$.[9] Such effects have important implications across the entire lung cancer continuum.[10]

First, preoperative $V02peak$ is a well-established risk stratification tool to determine perioperative and postoperative complication risk.[11-14] Second, following resection, $V02peak$ - as well as self-reported exercise behavior (a major determinant of $V02peak$) - are strong predictors of patient-reported outcomes (PR0s), such as overall Q0L, fatigue, and other Q0L domains.[15] Finally, our group found that pre-operative $V02peak$ is a strong independent predictor of overall survival in lung cancer surgical candidates, even when controlling for performance status, gender, and age.[16] In totality, these data provide strong evidence that $V02peak$ is an attractive modifiable therapeutic

target to improve surgical risk and/or recovery, symptom control and, possibly, disease outcome in lung cancer.

Chronic, repeated aerobic training (i.e., continuous activity involving large muscle groups) is widely established as the most effective method to improve V_{O2peak} in healthy humans, although a paucity of studies have investigated the role of exercise in lung cancer.[10] Given the preliminary nature of this field, we recently completed two uncontrolled pilot studies investigating the feasibility and preliminary efficacy of supervised aerobic training in the pre-operative and post-operative setting in lung cancer. Results of these pilot studies provided 'proof of principle' that aerobic training is a safe and feasible intervention for lung cancer patients; however, the improvements in V_{O2peak} were modest (<15%), particularly in the post-operative setting (~10%), despite good exercise attendance rates (70% of planned sessions).[17 18]

The reasons for the relatively modest improvement in V_{O2peak} in lung cancer relative to other clinical populations (i.e., ~15%-20% improvement in V_{O2peak} following traditional aerobic training recommendations) remain to be elucidated. An obvious potential explanation is a ventilatory limitation or inadequate gas exchange following removal of a substantial portion of lung parenchyma. However, several elegant studies have demonstrated that V_{O2peak} is not limited by ventilation or diffusion capacity[19-22], suggesting that exercise-induced adaptations (or lack thereof) in the other organ components of the O_2 cascade are responsible. V_{O2peak} in lung cancer patients is likely principally governed by poor cardiovascular O_2 delivery and oxidative capacity *as* 'vt€// *as* unfavorable fiber type distribution and muscle atrophy/weakness similar to the limitations to exercise described in patients with chronic obstructive pulmonary disease (COPD). Major contributors to skeletal muscle dysfunction in lung cancer likely include direct skeletal myopathy (from the use of oral corticosteroids), deconditioning (from physical inactivity), and high levels of systemic inflammation (from underlying disease and therapy).[23]

Importantly, aerobic training will cause favorable adaptations in most O_2 transport components but will not reverse skeletal muscle atrophy/weakness, and will only partially reverse a more glycolytic fiber type distribution. Thus, aerobic training alone may be insufficient to ameliorate skeletal muscle dysfunction likely to manifest in lung cancer. Standard resistance training (i.e., activity involving the acute exertion of force) performed according to standard guidelines (i.e., 2-5 times/week, 50%-80% of one repetition maximum for 12-24 weeks) is unequivocally acknowledged as the most effective method to improve skeletal muscle function in human subjects.[24-28] tvbreover, in severely deconditioned adults, resistance training causes improvements in V_{O2peak}[29-34], although the mechanisms underlying this effect are not clearly understood. In theory, while aerobic and resistance training might independently improve V_{O2peak} in lung cancer, such improvements are likely to be modest (~10%). Instead, the combination of aerobic and resistance training may be the most effective form of exercise training to optimally augment V_{O2peak}. The complementary physiologic adaptations from the combination approach will result in higher cardiovascular O_2 delivery, skeletal muscle oxidative phosphoryation, muscle strength, and optimal fiber type composition, leading to higher muscle endurance, reduced fatigability, a higher threshold to the metabolic waste products of exercise, and reduced ventilatory requirements during exercise. This approach is hypothesized to maximize physiologic

adaptations in the principal factors underlying poor VO2peak in lung cancer patients more effectively than either exercise modality alone.

Against this background, we designed the Lung Cancer gxerclse Iraining Study (LUNGEVITY), a randomized trial to investigate the efficacy of different types of exercise training in post-operative NSCLC patients. The protocol was amended in July 2017 to include patients with advanced (inoperable) lung cancer. The fundamental rationale for this multi-center trial is to identify the optimal type of exercise training to improve VO2peak in lung cancer patients and understand the physiologimechanisms underlying this effect.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is an open-label, multi-center, four-arm randomized controlled trial (RCT) to compare the effects of different exercise training modalities, relative to progressive stretching (attention control group), in patients with lung cancer. The primary endpoint is VO2peak, as measured by a symptom-limited CPET assessed at baseline and follow up (Week 17). Secondary outcome assessments include muscle strength, cardiac function, pulmonary function, arterial/ vascular function, body composition, functional capacity, and patient-reported outcomes. All study outcomes will be assessed at baseline and follow up.

4.2 Intervention

As part of clinical trial participation, participants will undergo one of three training interventions - supervised aerobic training, supervised resistance training, or the combination. Exercise performed outside of the structured sessions (i.e., contamination) will be assessed via self-report of exercise behavior. We will encourage participants to maintain their level of exercise behavior prior to the initiation of the trial.

Following the successful completion of baseline assessments, eligible participants will be randomly assigned to one of four study arms - patients will be enrolled until 40 patients have been assigned to each study arm. The exercise training conditions (Arms A, B, and C) will include three supervised exercise sessions per week at an intensity between 50% to 100% of the individually determined VO2peakfor aerobic training, and an intensity between 30% to 100% of one-repetition maximum for resistance training.

At midpoint, some participants will perform a CPET as well as a 1RM test, in order to re-assess exercise capacity to re-prescribe aerobic training to ensure progressive cardiovascular adaptation across the entire intervention period.

Participants assigned to the attention-control group will be provided with a progressive stretching program matched to the exercise interventions in terms of program length (16 weeks), social interaction (all sessions will be one-on-one), sessions per week (3x/wk) and session duration (30-60 mins/session).

4.3 Future Use of Samples

Following the completion of the trial, banked samples will be used for future correlative studies to evaluate the effects of different aerobic training prescriptions, relative to attention-control, on blood-based biomarkers. Specific biomarkers of interest include metabolites and cytokine and angiogenic factors. Fasting plasma will be processed and banked at -80°C and stored at MSK. On a periodic basis, samples will be shipped to a biorepository facility, Kryosphere (dba KryoCal), for long-term banking. A material transfer agreement (MTA) will be instituted before any samples are transferred.

Any projects outside of the scope of this protocol will need to be approved by the IRB/PB. A biospecimen correlative protocol detailing the proposed project will need to be approved by the IRB/PB prior to the start of the project.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

There are no therapeutic agents in this trial.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Signed informed consent prior to initiation of study-related procedures
- Age 21-80
- Weight <205 kgs
- ECOG 1
- Diagnosed with histologically confirmed lung cancer, regardless of disease stage and receiving any prior line of any therapy in the context of metastatic disease
- An interval of at least three months following the completion of primary resection, if appropriate
- An interval of no longer than ten years following completion of primary therapy, if appropriate
- Life expectancy 4 months
- Performing less than 150 minutes of structured moderate-intensity or strenuous-intensity exercise per week.
- Exercise intolerance (i.e., patients must have a VO2reak below that predicted for active age and sex-matched individuals)
- Willing to be randomized to one of the study arms
- Willing to commit to the study program and comply with all related protocol procedures
- Able to achieve an acceptable peak baseline CPET, as defined by any of the following criteria:
    - achieving a plateau in oxygen consumption, concurrent with an increase in power output;
    - a respiratory exchange ratio 1.1O;
    - attainment of maximal predicted heart rate (HRmax) (i.e., within 10 bpm of age-predicted HRmax [HRmax = 220-Age[years]);

- volitional exhaustion, as measured by a rating of perceived exertion (RPE) 18 on the BORG scale.

- Able to complete an acceptable baseline CPET in the absence of high risk ECG findings or other inappropriate response to exercise as determined by the PI.
- Ability to achieve and complete an acceptable baseline one-repetition maximum muscular strength test as defined by the effective execution of protocol-specific joint and muscle ranges of motion without remarkable signs or symptoms of pain, discomfort or distress.

6.2 Subject Exclusion Criteria

- Presence of a concurrent, actively treated other malignancy, or history of other malignancy treated within the past 3 years (other than non-melanoma skin cancer);
- Room air desaturation at rest :5 85%;
- Mental impairment leading to inability to cooperate.
- Any of the following absolute contraindications to cardiopulmonary exercise testing:

  - Acute myocardial infarction (within 3-5 days of any planned study procedures);
  - Unstable angina;
  - Uncontrolled arrhythmia causing symptoms or hemodynamic compromise;
  - Recurrent syncope;
  - Active endocarditis;
  - Acute myocarditis or pericarditis;
  - Symptomatic severe aortic stenosis;
  - Uncontrolled heart failure;
  - Acute (within 3 months) pulmonary embolus or pulmonary infarction;
  - Thrombosis of lower extremities;
  - Suspected dissecting aneurysm;
  - Uncontrolled asthma;
  - Pulmonary edema;Respiratory failure;
  - Acute non-cardiopulmonary disorders that may affect exercise performance or be aggravated by exercise (i.e., infection, renal failure, thyrotoxicosis)

7.0 RECRUITMENT PLAN

Potential participants will be identified by a member of the patient's treatment team, the protocol investigator, or Exercise Oncology (ExOnc) personnel at MSK. If the investigator is a member of the treatment team, s/he will screen their patients' medical records for suitable research study participants and discuss the study and the potential for enrolling in the research study with eligible patients. Potential participants contacted by their treating physician will be referred to the investigator/research staff of the study.

Investigators and ExOnc staff may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach

these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSK in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient is found to be ineligible for the study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted by the treatment team, investigator or the ExOnc staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of: (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable)..

Three strategies will be employed for participant recruitment:

Mail-Based Recruitment: ExOnc research staff will obtain a list of potential eligible patients from dataline that meet basic eligibility criteria. ExOnc research staff will contact the potentially eligible patient's primary attending physician to confirm the patient's current status, if they are an appropriate candidate, and seek approval to send the patient a mail-based introductory letter **(see Appendix** I and a copy of the consent form. The letter of introduction will be signed by both the protocol PI and the patient's primary attending. Patients interested in trial participation will be directed to call or email the ExOnc office to ask any questions they may have, receive further instructions, and discuss next steps. Patients meeting all study requirements will be scheduled for a baseline protocol appointment where a consenting professional will obtain written informed consent.

Patients not responding to the mailed letter of introduction will be sent a second mailing. Patients still not responding a few weeks after the second mailing will be contacted by telephone by ExOnc personnel **(see Appendix G)** to gauge patient interest in trial participation. One additional phone call may be made to the patient, if needed. The study team will not make more than four total attempts (mailings and phone calls) to contact a patient.

Clinic-Based Recruitment: Potentially eligible patients attending a scheduled clinical visit will be approached following the clinical visit with their primary attending. ExOnc research personnel will obtain primary attending approval prior to approaching any patient about

trial participation. This initial encounter will include a discussion of the proposed trial, proposed treatments and the rationale for its use. Patients may also be given a brochure at this visit with their oncologist as an introduction to the program. Interested participants will answer questions from the exercise behavior questionnaire to assess eligibility. Eligible patients interested in trial participation will have the opportunity to review and sign an informed consent during their clinic visit.

Web-Based Recruitment: Potentially eligible patients attending a scheduled clinic visit with their primary attending oncologist may be approached via email following their visit. Ex One research staff will obtain primary attending oncologist approval prior or in conjunction with approaching any patient about trial participation. Potentially eligible patients will receive a recruitment email asking if they would be interested in participation **(see Appendix F)**. Patients are able to contact Ex One staff via phone or email. Ex One research staff will be able to follow up from an initial email with a phone call to see if a patient would like to participate

Following the initial consultation, interested participants will be contacted by telephone by members of the ExOnc team to schedule the baseline assessment visit. Patients will also receive a welcome packet **(see Appendices C-E).**

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSK in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective participant will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential participants; and (4) maintaining information in a screening log of patients approached (if applicable).

Minorities and women are well-represented in the Thoracic DMT clinics, and we expect that they will be well represented in the trial accrual.

Enrollment and study procedures are summarized in the following subsections. The timing of all study procedures is provided in the schedule of activities.

7.1 Screening Period

The screening period will take place within 4 weeks of Day 1, except where otherwise noted. Assessments not completed within the specified interval must be repeated.

7.2 Screening Identification Numbers

Study site personnel will maintain a screening log for all potential study participants, and will assign a screening identification (ID) number in consecutive order as listed on the screening log. The screening ID number will be used on all study forms and laboratory specimens throughout the study.

A new screening ID number will be assigned to a patient who is rescreened after originally failing to meet study eligibility.

For patients who provide informed consent and subsequently do not meet eligibility criteria, or withdraw consent, study site personnel will ensure that the source record includes appropriate documentation, such as eligibility criteria reviewed, protocol procedures performed, and reason for screen failure.

7.3 Study Procedures

Table 1. Schedule of Activities

			Treatment Period (16 weeks\			Follow-up
Study Period or Visit	**Screening**	**Baseline**	**Pre-Treatment**	**tweekly Traning**	**Midpoint Assessment**	**Study FU**
Study Week	**NA**	**-4 to -1**	**-2 to -1**		**8**	17
Window (Weeks)	**NA**	**NA**	**±1**		**±1**	**±2**
General Activities[1]						
Informed Consent		X				
Medical History	X					
Height, Weight	X	X			X	X
Vital Signs	X				X	X
Performance Status (ECOG)[1]	X					
Concomitant Medications	X					
Randomization[11]			X			
Study-Related End Points						
Cardiopulmonary exercise test (CPET)[4,5]		X			Arms A and Conly	X
One repetition maximum **(1RM)[6]**		X			Arms Band Conly	X
Functional performance measures		X				X
Resting left ventricular ejection fraction		X				X
Pulmonary Function Test		X				X
Post-exercise left ventricular ejection fraction		X				X
DEXA (body composition)		X				X
Regional arterial stiffness		X				X
Flow Mediated Dilation		X				X
Patient-reported outcomes (lifestyle questionnaire)		X				X
Training				X		
Complete Blood Count (CBC)		X				X
Research Blood draw		X				X

[1] Testing slo1s/procedures availability must be taken into consideration when scheduling study follow-up visi1s. Visi1s may be split across the window to permit for

completion of all study-related assessmen1s.

[2] Performance status by Eastern Cooperative Oncology Group (ECOG) scoring.

[3] Randomization should be performed on or up to 2 weeks prior to Day 1, but only after eligibility is confirmed.

[4] Must be assessed within 4 weeks of randomization to confirm eligibility. All potential participan1s will perform a second CPET at baseline to account for potential learning effec1s and variability to account for the presence of significant, and potentially clinically important, variability in CPET procedures (VO_2peakmeasurement),

[5] CPET at midpoint is for patients randomized to Arms A and Conly.

[6] One repetition maximum at midpoint is for patients randomized to Arms Band Conly.

7.4 Blinding

This study is open label. All patients and study exercise physiologists monitoring exercise training sessions will be unblinded to treatment allocation (due to the nature of aerobic training interventions, neither patients nor study personnel can be blinded to treatment allocation). Nevertheless, all study investigators will be blinded to intervention allocation. Only the trial statistician and the data monitoring committee will have access to unblinded data.

7.5 Study Duration

The study should be accruing patients for around 24 months from the start of accrual. Patients will be followed for up to one year following the last patients last follow up appointment.

8.0 PRETREATMENT EVALUATION

After obtaining written consent and GLTEQ, all participants will be scheduled for a baseline study assessment visit by a member of the ExOnc research team. Following appropriate scheduling procedures, at the study visit, the participant will complete the following assessments prior to randomization:

1. Fasting blood draw
2. Fasting, non-invasive measurement of regional arterial stiffness and flow mediated dilation
3. Resting assessment of left ventricular function using echocardiography
4. Symptom-limited cardiopulmonary exercise test with 12-lead electrocardiography (including pulmonary function testing) and post-exercise echocardiography
5. Functional measures
6. Body composition
7. Patient-reported outcomes
8. One repetition maximum

The completion of these assessments will take approximately 3 to 4 hours and will be conducted in the ExOnc Integrative Physiology Laboratories at either: I\t1ain Campus (in Cardiology), the Rockefeller Outpatient Pavilion at 53rd Street, or the Sidney Kimmel Center for Prostate and Urologic Cancers.

The DEXA scan will be performed at either the Breast and Imaging Center (BAIC) or the Rockefeller Outpatient Pavilion.

In order to maximize internal validity of study endpoint accessments efforts will be made to ensure assessments at baseline, midpoint and follow-up are in the same order.

All baseline study assessments are described in Table 2.

Table 2. Pretreatment Evaluations (including Baseline Study Measures)

Activity/ Assessment/ Timing	Comment

Symptom-limited cardiopulmonary exercise test (CPET) to assess peak oxygen consumption (V02peak)	VO_2peak will be evaluated using a magnetically-braked cycle ergometer test with 12-lead ECG monitoring (Mac® 5000, GE Healthcare) performed by certified exercise physiologists. Cardiopulmonary exercise testing is considered the gold standard assessment of exercise capacity and provides assessment of peak oxygen consumption (VO_2peak)- Expired gases will be analyzed continuously by a metabolic measurement system (Parvo Medics TrueOne 2400). After stable resting metabolic values have been achieved (including blood pressure and heart rate), participants will begin cycling at a participant-specific designated power output for 1 minute and the power output will be increased every 1 minute until exhaustion or a symptom-limited peak is achieved measured by peak oxygen consumption (VO_2peak) ($mL \cdot kg \cdot^{-1} min^{-1}$) This protocol has been previously demonstrated to be appropriate for measuring VO_2peak in our prior studies among cancer patients.[36,37] Acceptable test criteria for this assessment include any of the following: (1) a plateau or decrease in oxygen consumption concurrent with increased workload, 2) heartrate 220-age (±10 beats) (3) a respiratory exchange ratio =1.1, (4) volitional exhaustion, a rating of perceived exertion 18. This protocol has been previously demonstrated to be appropriate for measuring VO_2peak in our prior studies of early-stage and advanced cancer patients. [36,37] The test will be terminated if any ECG abnormalities are observed. Due to the presence of significant, and potentially clinically important, variability in CPET procedures (VO2peak measurement), all potential participants will perform a second CPET at baseline to account for potential learning effects and variability.[38] If both the first and second CPET achieve acceptable test criteria, the best test will be used.
One repetition maximum (1RM)	Participants will perform a cardiovascular warm-up on a treadmill or bicycle ergometer prior to testing for 5 minutes. After an appropriate rest period, participants will be familiarized with each of the resistance machines by performing 8-10 repetitions of a light load (~30-40% of predicted 1RM). After ~3 min of rest, participants will complete a priming load at 60-80% of estimated 1RM for 3-8 repetitions. Following 5 min of rest the participant will attempt a lift of ~90-100% of estimated 1RM through the full range of motion. After each successful performance, the weight will be increased until a failed attempt occurs. The highest weight moved once through the particular range of motion with maximal exertion will be defined as the 1RM. In order to allow for appropriate recovery and reduce the influence of fatigue, exercises will be alternated between the upper and lower body. Three to five minute rests will be given between each attempt and the 1RM will ideally be attained within 5 attempts.
Resting left ventricular function by 3-	Three-dimensional transthoracic echocardiograms will be

dimensional echocardiography (3DE)	performed by experienced sonographers and acquired with commercially available equipment (Vivid 7 or E9, GE Healthcare, Milwaukee, WI). Following completion of the 2DE, a full volume dataset will be acquired using a matrix array transducer with gated 4 beat acquisitions for assessments of left ventricular (LV) volumes by 3DE. A 3DE acquisition of the entire LV will be generally performed in <10 seconds. All assessments will be stored digitally for offline analyses performed using EchoPAC PC workstation (version BT11, GE Medical, Milwaukee, WI). Conventional 2D measurements of LV dimensions, Doppler, and diastolic function parameters will be performed and averaged over 3 cardiac cycles accordin to American Society of Echocardiography guidelines. [9 1 -4] Left l.€ntricular volumes and left 1.€ntricular ejection fraction (LVEF) by 3DE will be determined by manipulating the full volume dataset to derive conventional apical 4-, 3-, and 2-chamber views using TomTec offline analysis software (4D LV-Function, Unterschleisheim, Germany). After selection of reference points, a 3D endocardial contour will be automatically generated and manual adjustment will be performed as necessary. The resultant end-diastolic (EDV) and end-systolic volumes (ESV) will be used to calculate LVEF.[42]
Post $VO_{2peEJ<}$left ventricular function by 2-dimensional echocardiography (2DE)	Upon completion of the cardiopulmonary exercise test, subjects will be placed in the supine position and 2DE grayscale images will be obtained in the apical 4-, 3-, and 2-chamber views. Wall motion scoring index (WMSI) will be calculated at rest and post-exercise using the 17 segment model by adding the individual segment scores (1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia) and dividing by number of segments scored.[39] 2D LV v0lumes and LVEF will be calculated offline using the modified Simpson's biplane method. Cardiac output will be calculated as the product of LV stroke volume and heart rate, indexed to body surface area (BSA).
Regional arterial stiffness	Conduit regional artery stiffness of the entire aorta will be assessed non-invasively by measuring carotid-femoral pulse wave velocity (PWV) using 2 hand-held tonometers (SPT-301 Millar Instruments, Houston, TX). Carotid and femoral artery waveforms will be recorded independently, as long as the heart rate and rhythm are consistent throughout, with the mechanotransducers directly applied to the skin over the greatest area of pulsation. Twenty consecutil.€ reproducible beats will be collected at both sites, with a concurrent electrocardiograph to obtain R-R intervals. Pulse transit time will be determined as the difference in time from R interval to systolic upstroke at each location. Systolic upstroke will be determined by identifying the foot or "notch" of the blood pressure waveform. This will be done by applying a band pass filter between 5-30 Hz, selecting the minimum value of the filtered signal.

	Pulse distance will be determined using anthropometric measuring tape subtracting the distance from carotid measurement to sternal notch from the distance from sternal notch to femoral pulse measurement. This method has been shown to be the optimal non-invasi\€ measurement compared to invasive measure. PWV will then be determined by taking the pulse transit time/distance.
Flow Mediated Dilation	Peripheral artery flow-mediated dilatation (FMD) will be performed on one arm with the subject in a supine position with the forearm extended and slightly supinated. A rapid inflator blood pressure cuff will be placed on the forearm just distal to the antecubital crease and the brachia! artery will be imaged using high-resolution B-mode ultrasound and a 7.5MHz linear array transducer (Terason, t3200). Ten-second r-wave triggered digital clips (artery diastole) will be captured at baseline (following 10min of supine rest), during five minutes of forearm occlusion, and a 120 sec r-wave triggered digital clip will be captured beginnin at cuff deflation (hyperemia) as previously described. [7] Offline analysis using specialized software (Brachia! Tools, Medical Imaging Applications, Illinois) will permit for identification of peak dilation and dilation at specific pre-specified time points (60, 120 sec).[37]
Dual ebergy x-ray absorptiometry (DEXA) to assess body composition	Body fat percentage, and lean and fat body mass will be assessed by dual energy x-ray absorptiometry using a Lunar Prodigy multiple detector fan-beam densitometer (GE Medical Systems, Madison, WI). After calibration with an anthropomorphic phantom, single-beam, whole-body scanning will be employed on supine-positioned subjects. Data will be obtained from each scan for fat and lean body mass expressed to the nearest tenth of a gram (and percent) for the total body region, as well as in defined body zones (e.g., legs, trunk and arms). Each participant's Baseline and Follow Up DEXA assessments will be performed on the same machine as best possible.
Patient-reported outcomes (via questionnaire)	Patient-reported outcomes will be assessed using a patient-administered questionnaire to assess quality of life, fatigue, pain, and sleep quality. *Quality of Life (QOL)* will be assessed by the Functional Assessment of Cancer Therapy (FACT) scale developed for the assessment of patient symptoms and QOL in breast cancer patients.[38] *Fatigue* will be assessed using the 13-item FACIT-Fatigue scale for the assessment of fatigue in cancer patients.[39] *Pain* will be assessed using the 10-item Brief Pain Inventory (BPI) which was designed to measure multiple clinically relevant aspects of pain such as pain intensity

	and interference from pain in cancer populations.[4]u *Sleep Quality* will be assessed by the Pittsburgh Sleep Quality Index (PSQI).[41] *Medical Outcomes Trust Short Form Health Survey (SF-36):* The SF-36 is a psychometrically robust self-report questionnaire that measures general health-related quality of life in 8 domains of health: physical functioning (SF-36 PF), role limitations caused by physical health (role-physical), bodily pain, general health perceptions, vitality, social functioning, role limitation due to emotional problems (role-emotional) and mental health.[42]
Fasting research blood draw	Blood collection should take place prior to the initiation of any study related interventions, whenever possible.
Pulmonary function testing	Pulmonary function will be determined using standard spirometry. All measures will be performed in a sitting position according to the American Thoracic Society guidelines.[53]
Functional performance measures	Assessment of functional measures will include the performance of the following tests: • *Short Physical Performance Battery (SPPB):* The SPPB is a brief performance-based functional mobility measure that includes measures of standing balance, usual pace walking speed, and ability and time to rise from a chair 5 times. • *Six-Minute Walk Test (6MWT):* The 6MWT is a valid responsive, interpretable self-paced test that quantifies functional exercise capacity in terms of the distance walked in six minutes. • *Chair-stand test:* Chair-stand test (number of sit to stands a subject can complete in 30 seconds) will be used as a measure of functional lower body strength. • *Timed Up and* Go *(TUG):* TUG is a timed measure of balance and functional mobility. The test requires the patient to rise from a standard armchair, walk 3 meters at a comfortable pace, walk back to the chair, and sit down.

Following the completion of all baseline assessments, patients will be randomly assigned to one of the four study arms.

9.0 TREATMENT/INTERVENTION PLAN

9. 1 Evaluation Prior to Initiation of Intervention

Prior to the initiation of each intervention session participant resting vital signs will be assessed as per **Appendix H** to ensure the participant can safely proceed with the session. The planned session will not be initiated if the exercise physiologist observes any concerns that may compromise participant safety and/or the integrity of the planned session.

9.2 Study Interventions

The study interventions are supervised linear aerobic training (Arm A), supervised nonlinear aerobic training (Arm B), or progressive stretching (attention control) (Arm C). All sessions will be performed in a supervised setting by an exercise physiologist. Sessions will take place at the Sidney Kimmel Center for Prostate and Urologic Cancers or Sillerman Center for Rehabilitation.

All aerobic training sessions will be prescribed by an exercise physiologist under the direction of the Program Director. All exercise physiologists are trained in either Basic or Advanced Cardiovascular Life Support (BLS/ACLS).

Participants will be instructed to adhere to fasting guidelines for food, caffeine, tobacco, alcohol and exercise as outlined in Appendix H.

All sessions, regardless of randomization arm, will include a warm-up. The aerobic arms, A and B, will also include a cool-down. Heart rate, oxygen saturation and blood pressure will be assessed prior to and following each intervention session. All adjustments to the intervention sessions will be implemented according to the standard care procedures of the exercise physiologists and will be source documented.

Aerobic Training Interventions (Arms A-C) (General Considerations)

The overall goal for all the exercise training groups will be 3 supervised exercise sessions per week an intensity between 50 to 100% of the individually determined $V02peak$ for aerobic training and an intensity between 50% to 85% of 1-RM for resistance training. All the exercise interventions are designed such that participants begin exercising at a low intensity (~50%-60% $V02peak$ / 1RM) that is subsequently increased to more moderate to vigorous intensity(~70%-100% $V02peak$ / ~70-85% 1RM) when appropriate. All interventions will be individually tailored to each patient following the principles of aerobic or resistance training prescription guidelines for adults.

9.2.1 Arm A -Aerobic Training

All aerobic training sessions will be performed on a cycle ergometers, targeting delivery of three cycling sessions/week at 55%-100% of $V02peak$. In the introductory phase of the program (Weeks 1-4), the frequency, duration, and intensity of aerobic training will be progressively increased from an initial prescription of 3 session/wk for ~30-60 mins/session at ~60-70% of $V02peak$ to the overall goal of this prescription 60%-100% $V02peak$) at the end of Week 4. In Weeks 5 to 8 (intermediate phase), the goal will be to introduce higher intensity aerobic training. Specifically, exercise intensity will range between ~60%-70% $V02peak$ for two sessions per week; in the remaining session, exercise intensity will be set at ventilatory

threshold (~75% V_{02peak}). In Weeks 9 to 16 (optimization phase), similar to the intermediate phase, participants will be asked to perform 3 aerobic sessions per week; 2 sessions will be performed at ~60%-80% V_{02peak}, and one interval workout. Interval workouts will consist of 1-2 min at the workload associated with V_{02peak} (100% of V_{02peak}) followed by 2-4 min of active recovery for 8-12 or 4-6 intervals, depending on the length of the interval. At midpoint participants will undergo a CPET to re-assess V_{02peak}. On the basis of these results, the exercise prescription will be adjusted to ensure progressive improvements in V_{02peak} across the entire intervention.

9.2.2 Arm B - Resistance Training

Resistance training will be prescribed with the aim of increasing V_{02peak}. The ultimate goal for resistance training alone is 3 resistance training sessions/week at an intensity above 50% to 85% of 1-RM for 30-60 minutes/session. Resistance training will be performed on stationary weight machines, modification in equipment may be made by Exercise Physiologist. Patients will be progressively trained to perform two to three sets of 75-85% of maximal strength.

9.2.3 Arm C - Combined Aerobic and Resistance Training

Combined aerobic and resistance training will be prescribed with the and aim of increasing V_{02peak}. The ultimate goal will be three combined exercise sessions per week at an intensity above 50% V_{02peak} and above 50% 1-RM for aerobic and resistance training, respectively for 30-90 minutes/session. In this arm, the duration of aerobic training and resistance training will not be added together but rather the exercise prescription is designed to exploit the complementary properties of aerobic and resistance training to optimally improve V_{02peak}. The prescription will be balanced to ensure that on days when aerobic training is prescribed at a high-intensity, resistance training (on the same day) will be conducted at a lower (easy) intensity and vice versa. This approach will optimize the desired adaptations without causing excessive fatigue and will help avoid potential interference effects between aerobic and resistance training.

9.2.4 Arm D - Progressive Stretching Group (Attention-Control)

The ultimate goal for the progressive stretching program is 3 individual stretching sessions **(see Appendix H).** All sessions are required to be supervised. Duration of the stretching sessions is prescribed and implemented in accordance with standard stretching and flexibility training principles. This approach will be applied to guide each participant's prescribed stretching plan, with dose and scheduling modifications made by exercise physiologists, as required.

9.3 Intervention Attendance and Adherence

Attendance is calculated as the number of intervention sessions attended divided by the total number of planned sessions (i.e., 3 times/wk x 16 weeks= 48). *Adherence* is defined as the number of scheduled training sessions attended, as well as whether the training session dose was

successfully completed (i.e., participant completed the intervention session at the planned duration and intensity) divided by the total number of planned sessions (i.e., 48).

9.4 Aerobic and Resistance Training Dose Modification

Vital signs will be monitored during intervention sessions to ensure participant safety. Vital sign changes that are outside the expected range of the intervention will be monitored by the exercise physiologist. The exercise physiologist will use clinical discretion to determine if a modification to the prescription or termination of the session is required.

All modifications will be source documented and recorded in the study database, including the modification reason, how the session was modified, and clearance obtained, as appropriate.

Participants requiring consistent modification of the planned prescription will be reviewed by the study PI and exercise physiologists to determine appropriate action (e.g., early study withdrawal, physiological re-evaluation).

Final determination of the intensity and duration of the session against the planned session goals will be conducted by the supervising exercise physiologist following the session and will be source documented.

9.5 Aerobic Training /Resistance Training/ Progressive Stretching Discontinuation

Permanent treatment discontinuation is defined as cessation of aerobic training, resistance training or progressive stretching administration. When appropriate, follow up assessments will still be performed.

Temporary treatment interruption due to an adverse event is not considered permanent discontinuation. Patients whose treatment is interrupted due to an adverse event and then restarted will continue to have regularly scheduled study visits. In both experimental groups, the intensity and duration of the next scheduled session will be reviewed and discussed by ExOnc exercise personnel. However, if a participant misses more than 6 weeks of continuous sessions, the participant will begin the intervention from the starting prescription, due to the anticipated impact of deconditioning during the 6 weeks of intervention interruption.

9.6 Concomitant Medications

All concomitant medications at the time of study entry will be identified through a medical chart review and recorded in REDCap. Participation in the study intervention must not impact use of concomitant medications at any stage of the study period.

9.7 Effects of Aerobic Training or Resistance Training on Exposure to Other Conventional/ Novel Anticancer Therapies

There is no clinical data on the effect of aerobic training and/or resistance training (or progressive stretching) on the therapeutic index of anticancer agents used in the management of lung cancer.. All clinical studies to date have focused on the effects of exercise training interventions to prevent and/or mitigate the psychosocial and/or physiological side-effects of cancer therapy; whether exercise training influences the pharmacodynamics (PD) or pharmacokinetics (PK) of anticancer therapy has not been investigated.

9.8 Effects of Conventional/Novel Anticancer Therapies on Aerobic Training or Resistance Training

Our group, as well as others, have demonstrated that different forms of anticancer therapy causes unique and varying degrees of damage to various components of the cardiopulmonary system (heart-lung-blood-muscle axis). Collectively, these effects lead to significant and marked declines in global cardiopulmonary function, manifest as poor exercise tolerance (decreased $V02peak$)- A major rationale for this trial is to determine the optimal exercise training modality to mitigate and/or reverse this phenotype in patients with lung cancer.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

All evaluations being conducted during the treatment intervention, including the window of time in which conduct of these tests is required, are described in the schedule of activities (Table 1). Further details are provided herein. Assessments which are initially completed at baseline, midpoint and follow up may be repeated at the investigators discretion.

10.1 CPET

At the end of week 8, participants in the aerobic training arm (Arm A) and the combined aerobic and resistance training arm (Arm C) will repeat the cardiopulmonary exercise test. This test is repeated at this period to re-assess $V02peak$ under the expectation that $V02peak$ is likely to have improved in the first 8 weeks of the program. Thus, information from the second test is used to re-prescribe exercise training prescription to ensure continual cardiovascular adaptations across the entire study period. This test will not be repeated in the resistance training group (Arm B) or the progressive stretching group (Arm D).

10.2 1-RM Testing

At the end of Week 8, participants in the resistance training arm (Arm B) and the combined aerobic and resistance training arm (Arm C) will repeat the one repetition maximum strength test. This test is repeated at this period to re-assess lower and upper body strength under the expectation that these parameters would have improved in the first 8 weeks of the program. Thus, information from the second test is used to re-prescribe exercise training prescription to ensure continual strength adaptations across the entire study period. This test will not be repeated in the aerobic training group (Arm A) or the progressive stretching group (Arm D).

10.2 Fasting Blood Draws

At baseline and study follow-up, participants will undergo a fasting blood draw to obtain peripheral blood for complete blood count (CBC), and secondary endpoints. The CBC will be resulted by MSK clinical labs. In addition, data will be collected on any CBC tests that are performed as part of standard of care while the patient is on study.

Research blood samples will be collected, processed and stored per the Lab Manual.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity grading will be performed in accordance with NCI CTCAE, v 4.03. Adverse clinical symptoms that occur during or immediately following intervention sessions -with the exception of the expected heart rate, blood pressure, and SpO_2changes that are related to exercise - will be reported as adverse events. Adverse events will be reviewed by the exercise physiologist, and graded and attributed accordingly at the end of each session. Adverse events that are not resolved at the end of a session will be reviewed with the patient during the next scheduled session to assess whether or not the event is still ongoing. During the intervention phase, adverse events requiring adjustments to the two study aerobic training prescription approaches will be made according to the ExOnc Exercise Physiology standards of care and/or at the discretion of the Program Director.

11.1 Side Effects

Anticipated (expected) side-effects associated with a symptom-limited CPET, the two aerobic training doses, or progressive stretching include:

- Fatigue
- Myalgia
- Arthralgia
- Back pain
- Shortness of breath (dyspnea)

Unanticipated but possible side-effects that are *rare, but serious* include:

- Cardiovascular: angina, hypotension, palpitations, rebound hypertension, syncope
- Arrhythmias
- Heart attack
- Stroke

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Primary Study End Point

Exercise Capacity (VO_{2peak}): VO_2peak will be evaluated using an magnetically breaked cycle ergometer test with 12-lead ECG monitoring (Mac® 5000, GE Healthcare) performed by trained exercise physiologists.

Cardiopulmonary exercise testing is considered the gold standard assessment of exercise capacity and provides assessment of peak oxygen consumption (VO_2peak)- Expired gases will be analyzed continuously by a metabolic measurement system (Parvo Medics TrueOne 2400). After stable resting metabolic values have been achieved (including blood pressure and heart rate), participants will begin cycling at a participant-specific designated power output for 1 minute and the power output

will be increased every minute until exhaustion or a symptom-limited peak is achieved measured by peak oxygen consumption (VO_{2peak}) (mL·kg·-^{1}min-^{1}).

Acceptable test criteria for this assessment include any of the following: (1) a plateau or decrease in oxygen consumption concurrent with increased workload, 2) heartrate 220-age (±10 beats) (3) a respiratory exchange ratio =1.1, (4) volitional exhaustion, a rating of perceived exertion 18. This protocol has been previously demonstrated to be appropriate for measuring VO_{2peak} in our prior studies of early-stage and advanced cancer patients. [36,37]

All participants will be monitored continuously with 12-lead ECG during exercise and five minutes of recovery. During exercise, oxyhemoglobin saturation will be monitored continuously using finger pulse oximetery while blood pressure will be measured manually by auscultatory sphygmomanometer every two minutes.

Exercise testing-related events were operationalized as any event occurring during this procedure. SAEs will be defined as the occurrence of any of the following: (1) significant angina, (2) sustained ventricular tachycardia, (3) myocardial infarction, (4) external defibrillation or implantable cardioverter-defibrillator discharge, (5) syncope, (6) provision of cardiac life support medications, (7) direct admission to emergency room, or (8) death. A positive test was defined as identification of any of the following ECG changes: (1) significant ischemic changes in ECG during exercise or recovery or (2) development of exercise induced bundle branch block. Criteria for ischemic changes in ECG included 0·1 mV deviation of the ST segment horizontal to or away from the baseline isoelectric line at *O·OB* seconds after the J-point in the absence of significant resting ST-T abnormalities or left bundle branch block. ST segment changes toward the isoelectric line will not be considered positive, regardless of the magnitude of change. If the baseline ECG reveals a J-ST segment depression >0-05 mV, a "double criteria" (an additional 0·2 mV) of ST depression will be required with the appropriate horizontal or downsloping morphology to qualify as a positive test.

Clinical exercise physiologists within the ExOnc at MSK will perform all cardiopulmonary exercise tests. All personnel are trained to read (but not interpret) exercise ECG's and are trained in Advanced Cardiovascular Life Support (ACLS). All tests will only be conducted when physician coverage on the clinical floor is available.

All cardiopulmonary exercise testing will be conducted in Cardiology Service space either at Main Campus or in the Outpatient Facility on 53rd Street, or at the Sidney Kimmel Center for Prostate and Urologic Cancers, on designated ExOnc equipment specifically designated for research purposes.

If any ECG abnormalities are observed either prior to, during, or after the exercise test, all procedures will be immediately stopped. At this point, a cardiologist will be asked to review the ECG to determine the appropriate course of action. The participant will not be allowed to leave the facility until such an examination has been performed by the physician. All events will be recorded in the participants REDCAP. The participants attending oncologist will be informed of this event (by email) within 12 hours of the event.

Due to the presence of significant, and potentially clinically important, variability in CPET procedures (VO_{2peak} measurement), all potential participants will perform a second CPET at baseline to account for potential learning effects and variability.[30] If both the first and second CPET achieve acceptable test criteria, results of the second test will be used in all protocol procedures and statistical analyses.

12.2 Secondary Study End Points

- *Lol/1.er and Upper Body Maximal Muscular Strength* will be assessed as a voluntary one-repetition maximum (1-RM) using the following exercises: (1) leg press, (2) chest press, and (3) seated row. These tests will be repeated twice and the heaviest weight lifted while adhering to strict technique and form will be used as the score.

- *Resting left ventricular function by 3-dimensional echocardiography (3DE):* Three-dimensional transthoracic echocardiograms will be performed by experienced sonographers and acquired with commercially available equipment (Vivid 7 or E9, GE Healthcare, Milwaukee, WI).

  Following completion of the 2DE, a full volume dataset will be acquired using a matrix array transducer with gated 4 beat acquisitions for assessments of left ventricular (LV) volumes by 3DE. A 3DE acquisition of the entire LV will be generally performed in <10 seconds. All assessments will be stored digitally for offline analyses performed using EchoPAC PC workstation (version BT11, GE 1Vledical, Milwaukee, WI).

  Conventional 20 measurements of LV dimensions, Doppler, and diastolic function parameters will be performed and averaged over 3 cardiac cycles according to American Society of Echocardiography guidelines. [39-41]

  Left ventricular volumes and left ventricular ejection fraction (LVEF) by 3DE will be determined by manipulating the full volume dataset to derive conventional apical 4-, 3-, and 2-chamber views using TomTec offline analysis software (4D LV-Function, Unterschleisheim, Germany). After selection of reference points, a 3D endocardial contour will be automatically generated and manual adjustment will be performed as necessary. The resultant end-diastolic (EDV) and end-systolic volumes (ESV) will be used to calculate LVEF.[42]

  All resting echocardiography assessments will be conducted in Cardiology either at the Sidney Kimmel Center for Prostate and Urologic Centers or at the Main Campus or at the Rockefeller Outpatient Pavilion on 53rd Street, by a select group of sonographers in the Cardiology Service, using commercially-available GE Medical systems.

  If any cardiac abnormalities are observed either prior to, during, or after the exercise test, all procedures will be immediately stopped. At this point, the physician on the floor will be asked to review the echocardiographic images to determine the appropriate course of action. The participant will not be allowed to leave the facility until such an examination has been

performed by the physician. All events will be recorded in the participant's REDCAP. The participant's attending oncologist will be informed of this event by email within 12 hours of occurrence.

- *Post VO_{2peak} Left Ventricular Function by 3-Dimensional Echocardiography (3DE):Within* 30 seconds of completion of the cardiopulmonary exercise test, subjects will be placed in the supine position and 2DE grayscale images will be obtained in the apical 4-, 3-, and 2-chamber views. Wall motion scoring index (WMSI) will be calculated at rest and post-exercise using the 17 segment model by adding the individual segment scores (1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia) and dividing by number of segments scored.[39]

  30 LV volumes and LVEF will be calculated offline using the modified Simpson's biplane method. Cardiac output will be calculated as the product of LV stroke volume and heart rate, indexed to body surface area (BSA).

  All post-exercise echocardiography assessments will be conducted in Cardiology either at the Sidney Kimmel Center for Prostate and Urologic Centers or at the rv1ain Campus or at the Rockefeller Outpatient Pavilion on 53rd Street, by a select group of sonographers in the Cardiology Service, using commercially-available GE Medical systems.

  If any cardiac abnormalities are observed after the exercise test, all procedures will be immediately stopped. At this point, the physician on the floor will be asked to review the echocardiographic images to determine the appropriate course of action. The participant will not be allowed to leave the facility until such an examination has been performed by the physician. This event will be recorded in the participant's REDCAP. The participant's attending oncologist will be informed of this event by email within 12 hours of occurrence.

- *Regional Arterial Stiffness:* Conduit regional artery stiffness of the entire aorta will be assessed non-invasively by measuring carotid-femoral pulse wave velocity (PWV) using 2 hand-held tonometers (SPT-301 Millar Instruments, Houston, TX).

  Carotid and femoral artery waveforms will be recorded simultaneously with the mechanotransducers directly applied to the skin over the greatest area of pulsation. Twenty consecutive reproducible beats will be collected simultaneously at both sites, with a concurrent electrocardiograph to obtain R-R intervals.

  Pulse transit time will be determined as the difference in time from R interval to systolic upstroke at each location. Systolic upstroke will be determined by identifying the foot or "notch" of the blood pressure waveform. This will be done by applying a band pass filter between 5-30 Hz, selecting the minimum value of the filtered signal.

  Pulse distance will be determined using anthropometric measuring tape subtracting the distance from carotid measurement to sternal notch from the distance fr001 sternal notch to femoral pulse measurement. This method has been shown to be the optimal non-invasive

measurement compared to invasive measure. PWV will then be determined by taking the pulse transit time/distance.

All arterial stiffness measurements will be conducted in Cardiology Service space either at the Sidney Kimmel Center for Prostate and Urologic Centers or at the rvlain Campus or at the Rockefeller Outpatient Pavilion on 53rd Street, or at the Sidney Kimmel Center for Prostate and Urologic Cancers, on ExOnc equipment specifically designated for research purposes. All tests will be conducted by ExOnc exercise physiologists .

- *Flow Mediated Dilation:* Peripheral artery flow-mediated dilatation will be performed on the left arm with the subject in a supine position with the forearm extended and slightly supinated. A rapid inflater blood pressure cuff will be placed on the forearm just distal to the antecubital crease and the brachial artery will be imaged using high-resolution B-mode ultrasound and a 7.5MHz linear array transducer (Terason, t3200). Ten-second r-wave triggered digital clips (artery diastole) will be captured at baseline (following 10min of supine rest), during five minutes of forearm occlusion, and a 120 sec r-wave triggered digital clip will be captured beginning at cuff deflation (hyperemia) as previously described.[43] Offline analysis using specialized software (Brachia! Tools, Medical Imaging Applications, Illinois) will permit for identification of peak dilation and dilation at specific pre-specified time points (60, 120 sec).[44] Due to the potential confounding effects, patients will be asked to withhold vasodilatory substances (e.g., caffeine, exercise) 24 hours prior to assessment.

- *Body Composition:* Body composition will include percent body fat, fat mass (FM), and lean body mass (LBM) evaluated by dual-energy x-ray absorptiometry (DEXA) using a GE Lunar Prodigy multiple detector fan-beam densitometer.

- *Pulmonary Function* will be determined using standard spirometry. All measures will be performed in a sitting position according to the American Thoracic Society guidelines.[53]

- *Functional Performance Measures:* Assessment of functional measures will include the performance on the following tests:

    - *Short Physical Performance Battery (SPPB):* The SPPB is a brief performance-based functional mobility measure that includes measures of standing balance, usual pace walking speed, and ability and time to rise from a chair 5 times.

    - *Six-Minute Walk Test (6MWT):* The 6MWT is a valid responsive, interpretable self-paced test that quantifies functional exercise capacity in terms of the distance walked in six minutes.

    - *Chair-stand test:* Chair-stand test (number of sit to stands a subject can complete in 30 seconds) will be used as a measure of functional lower body strength.

- *Timed Up and* Go *(TUG):* TUG is a timed measure of balance and functional mobility. The test requires the patient to rise from a standard armchair, walk 3 meters at a comfortable pace, walk back to the chair, and sit down.

All functional performance measurements will be conducted by ExOnc exercise physiologist at the Sidney Kimmel Center for Prostate and Urologic Cancers or Sillerman Center for Rehabilitation.

- *Patient-Reported Outcomes:* Patient-reported outcomes will be assessed using a patient-administered questionnaire to assess quality of life, fatigue, pain, and sleep quality.
  - *Quality of Life* (QOL) will be assessed by the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale. The FACT-L contains subscales for physical (7 items), functional (7 items), emotional (6 items), and social or family well-being (7 items) that comprise the FACT-General (FACT-G) scale, plus a lung cancer subscale (7 items). The five subscales will be summed to obtain the FACT-L score (all 34 items; total score of 136). We will also compute the FACT-G score (27 items, excluding the breast cancer subscale; total score of 108).[45] All items are rated on a 0 to 4 Likert scale, using the following response format: 0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much. We will also calculate the Trial Outcome Index (TOI). The TOI is the sum of the Physical Well-Being (PWB), Functional Well-Being (FWB), and Lung Cancer subscales. Respondents are asked to respond to each question as it applies to the past 7 days. Higher scores on the FACT-L indicate higher QOL. Internal consistency for the FACT-G and FACT-Lis established.

  - *Fatigue* will be assessed using the 13-item FACT-fatigue scale for the assessment of fatigue in cancer patients.[46] the 13 items will be summed to obtain the total fatigue score (total score of 52). All items are rated on a Oto 4 Likert scale, using the following response format: 0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much. Respondents are asked to respond to each question as it applies to the past 7 days. Higher scores on the FACT-fatigue indicate higher fatigue. Internal consistency for the FACT-fatigue is well established.[46]

  - *Pain* will be assessed using the 10-item Brief Pain Inventory (BPI) which was designed to measure multiple clinically relevant aspects of pain such as pain intensity and interference from pain in cancer populations.[47] The BPI assesses for the presence of pain, pain intensity (i.e., worse, least, average, current) and functional interference from pain (i.e., activity, mood, walking ability, normal work, relations with others, sleep, and life enjoyment). It also catalogues the types of pain medications being used, and the percentage of pain relief obtained from medications.

    The BPI uses a mixture of item types. Items 1-3 querying about the presence of pain is a dichotomous "yes", "no". Items 4-7 (intensity items) utilize a 0 (no pain) to 10 (pain as bad as you can imagine) 11-point rating scale. Item 8 (percentage of pain

relief) ranges from 0% (no relief) to 100% (complete relief). Item 9 inquires about the effectiveness of pain medication (as appropriate). Item 10 (a-g) inquires about interference using an 11-point numeric rating scale. Each item ranges between 0 (does not interfere) to 10 (completely interferes). Respondents are asked to respond to each question as it applies to the past 7 days.

While some of the items represent single item values, pain intensity, indexed by the "Pain Severity Score" is calculated by obtaining the mean of the 4 pain intensity items. The Pain Interference Score is obtained by calculating the mean of the 7 interference items.

The "Pain Severity Score" has a maximum value of 10 (i.e., "pain as bad as you can imagine" and a minimum value of 0 (i.e., "No pain"). The Pain Interference Scale similarly has a maximum value of 10 (i.e., "Completely Interferes") to 0 (i.e., "Does not Interfere").

Internal consistency for the Pain Severity Score and for the Interference scale has been reported as being 0.85 and 0.88 respectively[47]

- *Sleep Quality* will be assessed by the Pittsburgh Sleep Quality Index (PSQI).[48] The PSQI assesses sleep disturbance over the past month. The PSQI is an 9-item self-report questionnaire. The PSQI uses a mixture of item types. Items 1-4 are open-ended questions that query about sleep habits. All remaining items are scored on a 4-point Likert scale which range from 0 (not during the past month) to 3 (3 or more times a week). The items produce seven component scores: sleep duration, sleep disturbance, sleep latency, daytime disturbance, habitual sleep efficiency, sleep quality, and use of sleep medications. The sum of these component scores yields a measure of global sleep quality which ranges from Oto 21. Reliability measures indicate that the PSQI generally has acceptable internal consistency (a = .80 to .85) and test-retest reliability (r = .85 to .87).[48]

- *Exercise behavior* will be assessed by the leisure score index (LSI) of the Godin Leisure-Time Exercise Questionnaire (GLTEQ) which is used to measure the minutes and type of exercise per week.[49,50] The LSI contains three questions that assess the average frequency of mild, moderate, and strenuous intensity exercise during free time in a typical week over the past month. In this protocol, participants will be asked to report their average weekly exercise over the past month. We will also ask for average duration within each exercise intensity. An independent evaluation of this measure found its reliability and validity to compare favorably to nine other self-report measures of exercise based on various criteria including test-retest scores, objective activity monitors, and fitness indices (Jacobs et al. 1993). The LSI demonstrated a one-month test-retest reliability of .62 and concurrent validity coefficients of .32 with an objective activity indicator (CALTRAC accelerometer), .56 with VO_{2max} (as measured by expired gases), and -.43 with% body fat (as measured by hydrostatic weighing).

- *Physical Functioning* will be assessed using the physical functioning subscale (PF) of the Short-Form (SF) 36.[51] The physical functioning subscale is a 6-item self-report questionnaire. The PF uses a mixture of item types. Item 1 queries about overall health, scored on a 5-point scale ranging from excellent to poor. Item 2 queries about limitations to normal activities of daily living including participation in vigorous and moderate activities. All items are rated on a 3-point Likert scale from yes, limited a lot to no, not limited at all. Item 3 queries about limitations relating to work over the past 4 weeks using a dichotomized response (yes vs. no). Item 4 queries about bodily pain over the past 4 weeks ranging from none to extremely. Item 5 queries about pain during the normal work week ranging from not at all to extremely. Finally, item 6 asks 4 statements asking about general health perceptions scored on 5-point Likert scale ranging from definitely true to definitely false. The sum of item 2 yields a measure of physical functioning ranging from Oto 20. Other items will be considered and summed as single items. Higher scores indicate higher physical functioning. The SF-36 has well established internal consistency and test-retest reliability.[51]

- *Safety* will be evaluated by the type and prevalence of adverse events during study-related assessments as well as exercise training sessions. The type and nature of SAEs considered in this trial include those DLTs listed in Section 9.3 as well as those events listed in Section 11.1 (the unanticipated but possible adverse events associated with CPET, 1RM, aerobic training or resistance training).

  Tracking and monitoring of exercise-related adverse events will be assessed using the following methods:

1. Stringent monitoring and recording (in the patient REDCAP) of physiologic outcomes and vital signs (e.g., heart rate, blood pressure, etc.) prior to, during, and following every intervention session.
2. At the beginning of each week, the exercise specialist will spend the first 10 minutes of every session discussing any potential negative side-effects of the intervention assignment and any injuries that may have occurred. All events will be recorded in the patient REDCAP.
3. Early stopping rules in response to a differential higher frequency of adverse events in a particular study group as identified in planned interim analyses (see **Section 14.0).**

13.0 CRITERIA FOR REMOVAL FROM STUDY

The primary reasons for permanent treatment discontinuation are listed in **Table 4**.

Table 4. Primary Reasons for Permanent Treatment Discontinuation

~~Reason~~	~~Comment~~
Self-withdrawal (withdrawal of consent)	Patients may permanently discontinue study treatment and

	withdraw from the study at any time for any reason. Following study intervention discontinuation, patients should have protocol-required safety follow-up and long-term follow-up assessments unless the patient specifically declines further follow-up.
Ad\terse event or intercurrent illness or disease recurrence	Any intolerable adverse event (associated or not associated with the study intervention) that cannot be ameliorated by the use of adequate medical intervention or that, in the opinion of the principal investigator would lead to undue risk if study treatment were continued.
Gross noncompliance with protocol (violation)	The investigator may request permanent discontinuation of study treatment in the event of a major protocol deviation, lack of cooperation, or complete noncompliance.
Lost-to-follow-up	Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete study-related assessments and record outstanding data.
Death	N/A

14.0 BIOSTATISTICS

14.1 Sample Size Calculation and Justification

This randomized phase trial will accrue 67 subjects with lung cancer over an accrual period of ~36 months. The primary analysis will compare the efficacy of different types of exercise training modalities, relative to progressive stretching (attention control group), on $V02peak$. Three separate t-tests will be used to compare each exercise training arm to the attention-control arm in mean change across time for $V02peak$. The overall alpha level will be controlled at a two-sided 0.05 by using Holm's procedure.[56] That is, Holm's procedure first ranks the three p-values from lowest to highest. The first (lowest) p-value has to be less than 0.05/3 (0.0167) to be significant and permit continuation to the other t-tests. The Holm's procedure continues sequentially in this fashion using alpha levels of 0.05/2 (0.025) and 0.05/1 (0.05) for the remaining two t-tests, respectively. Power for this study is defined as the probability that at least one of the three t-tests of the arm effect on $V02peak$ is significant; in other words, power is the probability that the first of the 3 ordered t-tests are significant. We assume that change in $V02peak$ will have a standard deviation of 3.0 $mL \cdot kg\text{-}\cdot^{1}min\text{-}^{1}$. Statistical power depends upon the configuration of mean change in $V02peak$ across the 4 arms. Thus, for example, 80% power is obtained when the mean change in $V02peak$ across Arms A, B, C, and Dis 0.60, 0.60, 2.10, and 0.0 ($mL \cdot kg\text{-}\cdot^{1}min\text{-}^{1}$), respectively.

A final important consideration when conducting exercise RCTs, is extent of exercise 'drop-in' or contamination in Arm D. In other words, the concern is that patients assigned to attention control independently initiate an exercise training program which, in turn, potentially dilutes the efficacy of aerobic training on the outcomes of interest. However, we feel this is less of a concern in the present study because patients (in the exercise training arms) will be provided with supervised, individualized training prescriptions (which will be difficult to replicate without sophisticated prescription algorithms and expertise) and attention-control participants are also provided with a supervised attention intervention.

Nevertheless, we will carefully monitor the amount of exercise performed outside of the study in all study arms using subjective (i.e., self-report exercise logs) methods.

14.2 Primary and Secondary End Point Analyses

14.2.1 Primary End Point Analysis: The primary analysis will compare the efficacy of different types of exercise training modalities, relative to progressive stretching (attention control group), on $V02peak$ in lung cancer.

An intent-to-treat statistical analysis will be conducted. Baseline characteristics will be compared using the Fisher exact test for categorical variables or a Wilcoxon rank sum test for continuous variables. The primary end point comparison will be analyzed using a multiple linear regression model to test for differences among and between the study arms in $V02peak$ from baseline to follow up. The multiple linear regression model will include the baseline value of $V02peak$, the stratification variables (i.e., chemotherapy treatment and sex), and study site.

In the absence of evidence to the contrary, multiple imputation strategies for missing Week 17 $V02_{peak}$ data will be performed assuming data were missing at random using linear regression. Results will be aggregated over 20 imputed sets using the variance formula by Rubin. In addition, a per-protocol analysis will be performed using a multiple linear regression model to test for differences among and between the study arms in $V02_{peak}$ from baseline to the post-intervention assessment (Week 17) on the basis of exercise attendance and adherence to the supervised exercise training in Arms A to C (<80% versus 80%).

14.2.2 Secondary End Point Analyses: As for the primary end point, the intention-to-treat principle will be employed for analysis of all secondary end points. Multiple linear regression models will be used to test for differences among and between the study arms in secondary end points from baseline to the postintervention assessment (Week 17). The multiple linear regression model will include the baseline value of $V02_{peak}$, the stratification variables (i.e., chemotherapy treatment and sex), and study site.

In the absence of evidence to the contrary, multiple imputation strategies for missing Week 17 end point data will be performed assuming data were missing at random using linear regression, as described above. Again, a per-protocol analysis will be performed using a multiple linear regression model to test for differences among and between the study arms in secondary end points from baseline to the post-intervention assessment (Week 17) on the basis of exercise attendance and adherence to the supervised exercise training sessions in Arms A to C (<80% versus 80%).

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Participants will be randomly allocated, on an individual basis, to one of the four study arms. Randomly allocated participants will remain in the same group for the entire duration of the intervention (i.e., no cross-over). To ensure randomized groups are similar at baseline, patient randomization will be stratified based on whether their lung cancer was operable or inoperable, prior treatment with chemotherapy (yes vs. no) and sex (male vs. female). Chemotherapy causes significant reductions in $V02_{peak}$, thus it is important for groups to be balanced on this factor. Similarly, male participants have higher $V02_{peak}$ than female

participants and therefore is also expected to influence the effect of exercise training on VO_{2peak} and other endpoints, thus it is important to ensure that groups are also balanced on this variable.

A permuted block design with allocation weight of 1:1: 1:1 is used to generate the treatment assignments. Following the successful completion of all baseline assessments, ExOnc research team personnel will enter randomization criteria into REDCap. Upon confirmation of stratification factors (chemotherapy treatment and/or sex) REDCap will electronically randomized the patient. Written confirmation of group allocation will be provided by email, a copy of which will be placed in the patient's case report form. The primary study RSA will then inform the participant of their group allocation.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Supervisor (CRS) and Research Study Assistant (RSA) will be assigned to the study, and will be under the close supervision of the Clinical Research Manager in the ExOnc. The responsibilities of the CRS and/or RSA include project compliance; data collection, abstraction and entry; data reporting; regulatory monitoring; problem resolution and prioritization; and coordinating the activities of the protocol study team.

The data collected for this study will be entered into the Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record. The principal investigator (Dr. Jones) will maintain ultimate responsibility for the clinical trial.

16.01 Role of Duke University Medical Center

This trial is a multi-site, randomized controlled trial comparing the effects of different exercise training interventions, relative to attention control, in patients with lung cancer following the completion of definitive adjuvant therapy. However, this trial represents a continuing effort that was first initiated at DUMC approximately 4 years ago by the principal investigator, Dr. Jones. Prior to his appointment at MSK in February 2014, Dr. Jones was a principal investigator at DUMC. During his tenure there, Dr. Jones secured a 5-year R01 grant from the National Cancer Institute to conduct the present study. During trial conduct, Dr. Jones accepted a position at MSK and hence all trial recruitment and study-related procedures were closed (all participants 'on trial' completed all study-related procedures but the study was closed to new patient enrollment).

IRB correspondence
All local IRB correspondence for DUMC that is initiated after the MSK protocol is open to accrual should be submitted to MSK. This includes but is not limited to approvals for amendments and continuing reviews as noted below. All other correspondence should be submitted to the local IRB according to local guidelines.

Amendments
Each change to the protocol document must be organized and documented by MSK and first approved by the MSK IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating

site(s). All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.

Duke must obtain IRB approval for all amendments within 90 calendar days of MSK IRB/PB approval.

Continuing Review Approval
The Continuing Review Approval letter from the DUMC IRB and the most current approved version of the informed consent form should be submitted to MSK within 7 days of expiration.

Document maintenance
The MSK PI and the DUMC PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

16.02 Current Status

As of September, 2013, the trial status is as follows: A total of 78 operable participants had been randomly allocated to four study arms: **Arm A** supervised aerobic training (n=20), **Arm B:** supervised resistance training (n=20), **Arm C:** supervised combined aerobic and resistance training (n=19), and **Arm D:** progressive stretching (attention control group) (n=19). Of these, 70 (88%) participants successfully completed all study procedures, with 8 (12%) participants lost-to-follow-up. The mean adherence rate was 77% across Arms A to C, with minimal adverse events, suggesting that all intervention sessions are well-tolerated.

A total of 15 inoperable patients had been randomly allocated to four study arms: **Arm A:** supervised aerobic training (n=4), **Arm B:** supervised resistance training (n=4), **Arm C:** supervised combined aerobic and resistance training (n=4), and **Arm D:** progressive stretching (attention control group) (n=3).

Additional details are available. Overall, we were pleased with the study progress at the time of trial suspension and patient self-reports of the benefits of the trial.

16.03 Proposed Plan at MSK

Following successful transition of the PI to MSK (and establishment of a close collaborative relationship with the Thoracic DMT under the leadership of Ors. Jones and Rudin), the goal of this continuation trial is to complete study accrual as planned (i.e., accrual of the remaining 67 patients). Based on the potential subject availability at MSK, we anticipate that subject accrual will take 24 months from the first accrual at MSK.

16.04 Data Management

All prior data collected on this protocol is securely stored and managed in a REDCap database system at DUMC under the stewardship of Pamela Douglas, MD and James E. Herndon, II, PhD. Although the trial has been closed to enrollment at DUMC, it remains open in the DUMC IRB to permit future medical chart data abstraction; Dr. Pamela Douglas is the acting PI at DUMC.

Given that this trial was developed and initiated at DUMC, we propose that DUMC remains the data management and statistical center for this trial under the direction of James E. Herndon, 11, PhD (trial biostatistician). Specifically, all study-related procedures and data collected here at MSK will be entered into two systems: (1) the CRDB here at MSK, and (2) REDCap software at DUMC.

In terms of the latter, REDCap software is a tool that does not require client local software and can be accessed from anywhere on the Internet. The program is secured on a Duke Health Technology Services (DHTS) server. This database will be developed, and maintenance performed, with support of the School of Medicine (SOM) Duke Office of Clinical Research (DOCR). SOM's DOCR has partnered with the School of Medicine (SOM) to implement REDCap (developed by Vanderbilt's CTSA and currently used and supported by more than 1000 consortium partners). REDCap provides: 1) a stream-lined process for rapidly building a database; 2) an intuitive interface for collecting data (with data validation and audit trail); 3) automated export procedures for seamless data downloads to common statistical packages (SAS, SPSS, etc.); 4) branching logic, file uploading, and calculated fields; and 5) a quick and easy protocol set-up.

REDCap accounts are stored within the DTMI LDAP server hosted by the Duke Office of Information Technology (OIT). Authentication occurs via the OIT implementation of Kerberos. All connections to the system, both external and internal, occur over encrypted channels. Access to components of the system is role-based and can only be granted by administrators of the system. All collected information is stored on a standalone database server hosted by Duke Health Technology Services (DHTS). The database server resides behind the DHTS internal firewall and access to the server is controlled via firewall rules.

All collected data is backed up daily, both on the local server and by the DHTS enterprise backup system. Cory Ennis (919-668-8284) is responsible for managing the server for REDCap. Ceci Chamorro, in the Duke Office of Clinical Research (919-668-9262), is responsible for managing the database platform for REDCap. At the time of this submission, REDCap is on version 5.0.20.

Server location: Fitz-East Data Center (Fitzpatrick); the directory is: /var/lib/mysql_backup/

Server support: Cory Ennis, DOCR - DHTS hosts servers (919-668-8284; cory.ennis@duke.edu)

Operational support: Ceci Chamorro, DOCR (919-668-9262; ceci.chamorro@duke.edu)

Of importance, staff entering MSK participant-related data from the ExOnc at MSK will not be able to view or manipulate data pertaining to DUMC participants already entered into the REDCap database. Similarly, only James E. Herndon, 11, PhD and Samantha Thomas, MS (trial statisticians) will have access to MSK PHI-related information.

The consent form contains language explaining that basic MSK participant information can only be accessed by specific individuals at DUMC.

16.1 Quality Assurance

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

16.2 Data and Safety Monitoring

This protocol describes a trial which is currently registered on ClinicalTrials.gov (it is currently registered to DUMC but will be switched to MSK upon IRB approval).

The Data and Safety Monitoring (DSM) Plans at MSK were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/patientsafety/dsm-guidelines/page1

The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

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

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

Trial Type/Level of Review: Phase II Behavioral Trial - This study does not involve the testing of pharmacologic agents or any therapeutic treatments. It is a randomized behavioral trial designed to compare the efficacy of different exercise training modalities relative to progressive stretching (attention control group), on VO_{2peak} in patients with lung cancer following the completion of definitive adjuvant therapy. Thus, it is classified as a Type 2 Study (Non-Therapeutic Intervention Study), a minimal risk level study.

17.0 PROTECTION OF HUMAN SUBJECTS

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

This protocol establishes operational guidance based on current ethical and legal standards for the procurement and storage of human biologic specimens for use in future biomedical research. The protocol includes an informed consent document and research authorization that meets statutory guidelines. They inform patients of the purpose of the bank, their rights in relation to it, and the safeguards in place to protect the confidentiality of their health information.

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

Potential Risks: Our eligibility criteria and screening procedures are established to exclude individuals for whom graded exercise testing, blood collection, and supervised moderate-intensity aerobic training are not appropriate. Our screening procedures begin with medical chart review to identify any individuals with any condition or reasons that may prohibit study entry, followed by oncologist approval to screen/identify patients who may not be eligible for any additional reasons. Finally, in-person assessments will be performed to screen/identify patients for cardiovascular or ECG contraindications on a symptom-limited graded exercise test. This multi-gated comprehensive approach should systematically identify and screen out any individual for whom this pilot study is contraindicated. The risks associated with trial participation are described in detail in **Section 11.**

Cardiopulmonary Exercise Testing (CPET) - Graded exercise testing carries a finite risk of adverse cardiovascular event with <1/100,000 in well individuals and 1/10,000 in clinical populations.

Blood Collection - There are some minor risks associated with a blood draw, i.e., bruising and/or discomfort; however this procedure is considered to be of minimal risk and will be performed by trained nurses/PA's either at the Sidney Kimmel Center for Prostate and Urologic Centers or at the Main Campus or the Rockefeller Outpatient Pavilion on 53rd Street.

Supervised Exercise Training - Similar to graded exercise testing, exercise training carries a finite risk of an adverse cardiovascular event. Under our laboratory conditions, we have not experienced any serious adverse events in five years of exercise training across literally hundreds of cancer patients and 1,000+ hours of exercise training. Further, all participants would have undergone a full ECG, graded exercise test prior to exercise training, and all sessions will be supervised by a exercise specialist.

Dual Energy X-ray Absorptiometry (DEXA) - a DEXA carries the risk of radiation exposure; the average full-body dose of radiation is 1 to 3 mrad per DEXA scan. In this study, three DEXA scans

will be completed for each patient enrolled, and the total average full-body dose of radiation per patient is 3 to 9 mrad over the course of the study.

There are no known risks to undergoing the other study-related assessments in this trial.

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

Benefits: A behavioral treatment strategy such as exercise training among patients with lung cancer who have exercise intolerance due to the direct and effects secondary effects of adjuvant therapy may improve these outcomes.

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

Costs/compensation: Patients will be charged for physician visits, routine laboratory tests and radiologic studies required for monitoring their condition. The patients will not be billed for any study-related procedures. The participant is informed that there are no plans to provide financial compensation for use of their human biologic specimens, nor are there plans for the participant to receive money for any new products, tests, and discoveries that might come from this research. Nevertheless, all participants will be reimbursed (in the form of two $50 gift certificates) for completion of study procedures. The total amount participants may receive is $50 for the completion of the baseline assessment and $50 for completion of the second assessment at the end of the study (Week 17).

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

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

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

Monitoring of data to ensure safety: This study is to be monitored by the institutional IRB. This incorporates an independent data and safety monitoring board established by arrangement with the

National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

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

Withdrawal: Participants may also decide at a later date that they do not want identified blood and/or tissue samples to be stored for future research. If participants decide to withdraw from the study, specimens will not be used in new studies and any remaining portions of samples that have not been used for research will be used only for clinical purposes or, if requested by the patient, destroyed. When a patient withdraws from protocol, OCR-PPR should be notified immediately. The withdrawal request will be documented in CRDBi and the system updated accordingly. In addition, a note-to-file documenting the patient's withdraw must be filed in his/her EMR.

17.1 Privacy

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

17.2 Serious Adverse Event (SAE) Reporting

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

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

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

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

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

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

The report should contain the following information:

Fields populated from CRDB:

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

Data needing to be entered:

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

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

18.0 INFORMED CONSENT PROCEDURES

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

1. The nature and objectives, potential risks and benefits of the intended study.

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

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

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

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20.0 APPENDICES

1. **Appendix A** Lifestyle Questionnaire
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