Resiliency among Older Adults Receiving Lung Cancer Treatment (ROAR-LCT)

Principle Investigator:	Carolyn Presley, MD, MHS
Co-Investigators:	Ashley Rosko, MD Erin Bertino, MD Dwight Owen, MD Greg Otterson, MD David Carbone, MD PhD Kai He, MD PhD Peter Shields, MD Barbara Anderson, PhD
Key Personnel:	Karen Hock, PT, MS, CLT-LANA Amy Compston, PT, DPT, CLT-LANA Madison Grogan Nicole Arrato Stephen Lo Brittany Knauss Elyse Redder Nyelia Williams
External Collaborators:	Sarah Janse, PhD
Scientific Leads:	Christin Burd, PhD & Dan Spakowicz, PhD
Statisticians:	Jason Benedict, MS
Protocol/Version/Date:	Original/ V7 Mar 2021
NCT #:	NCT04229381

Table of Contents

HYPOTHESIS AND OBJECTIVES

1.1 Primary Objective

To assess the feasibility of a novel, weekly supervised virtual health-assisted physical therapy plus relaxation intervention delivered to older adults with advanced thoracic malignancy (N=20). The overall goal is to be able to pilot this intervention targeting modifiable risk factors for worsening functional status: physical performance and negative mood.

1.2 Hypothesis

We hypothesize that we will be able to accrue 20 older adults (≥ 60 years) with a thoracic malignancy and implement a 12-week virtual health-assisted physical activity + relaxation intervention program with biospecimen collection. We hope to achieve 70% adherence to all sessions and a total patient retention rate of 60% at the end of the 12 – week intervention program.

2.0 BACKGROUND AND RATIONALE

2.1 Lung Cancer in Older Adults

Lung cancer is a disease that disproportionally affects older adults as the median age of diagnosis is 70 years.[1] This is important because older adults are the fastest growing demographic in not only the United States but worldwide.[2] However, this population is significantly under-represented in clinical trials that examine outcomes of new lung cancer drugs.[3] This is particularly relevant due to the approval of novel cancer drugs called immune checkpoint inhibitors (Immunotherapy: IO; e.g. pembrolizumab, atezolizumab). The new standard of care for first-line treatment for either advanced non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) includes combination of chemotherapy plus IOs, [4,5] affecting 2/3rds of patients with advanced disease. The effect on older adult's functional status and their ability to complete basic activities of daily living (ADLs) while on these new treatment plans is still widely unknown. This lack of information on how these new treatments may affect older adult's functional status maintains feelings of uncertainty regarding treatment plans.

2.2 Functional Decline + Resiliency

Functional status and resiliency are patient-centered outcomes that should be prioritized in research among older adults with cancer.[6] Functional status refers to the behaviors needed for an individual to maintain an independent lifestyle. It is defined as an individual's ability to perform basic activities of daily living,[7] instrumental activities of daily living[8], and mobility[9]. The majority of older adults with a chronic disease, including cancer, prioritize remaining functionally independent over survival.[10] Even so, functional status is not a primary endpoint in oncology research.[11] Resiliency among patients with cancer can be defined as the ability to recover one's functional status after an intervening health care event, e.g. treatment, toxicity, disease progression.[12] Resiliency is important because it demonstrates one's ability to "bounce

back" from a stressor or intervening event. Resiliency is incompletely understood among patients with lung cancer.

2.3 Targeted Interventions

Poor physical performance and negative mood are two risk factors for a decline in functional status.[9] Targeted interventions to address these two risk factors with the goal of improving functional status and resiliency are urgently needed. Physical therapy[13,14] and relaxation interventions[15] (i.e. progressive muscle relaxation) are two such interventions that can improve symptoms and quality of life for patients with cancer.

3.0 METHODS

3.1 Study Overview

This is a prospective, longitudinal study of 20 adults ≥ 60 years of age with advanced thoracic malignancy (NSCLC or SCLC) who plan to receive either immunotherapy and or chemotherapy treatment from the OSUCCC Thoracic Oncology clinic. This cohort is a 12-week pilot intervention consisting of a physical therapy and progressive muscle relaxation program delivered to older adults with advanced lung cancer. Functional trajectories and resiliency will be characterized in this cohort. Enrolled patients will participate in in-person physical therapy and progressive muscle relaxation sessions that are incorporated into routine treatment visits as well as performed via virtual health on the non-treatment weeks. Patients' functional status will be assessed every 3 weeks and clinical outcomes will be evaluated every 6 weeks. Correlative biomarkers will also be assessed through blood and stool sample collection. Patient follow up will continue through 24 months post enrollment for 1 year and 2 year overall survival.

3.2 Patient Selection

Patients diagnosed with a thoracic malignancy age ≥ 60 will be recruited from the OSUCCC Thoracic Oncology Clinic. Patients who plan to receive either immunotherapy and/or chemotherapy treatment at the James OSUCCC Thoracic Oncology Clinic will receive information regarding the study via physician's referral. Those individuals agreeing to participate will sign the study consent which includes the HIPAA authorization. Patients who sign the informed consent will be assigned a unique study ID.

Failed screening will be captured as a part of feasibility analysis. Reasons for patient decline will be noted and tracked without the use of patient identifiers.

3.3 Inclusion Criteria

- Age ≥ 60
- Diagnosed with advanced lung cancer: unresectable stage IIIA, IIIB, or stage IV NSCLC or extensive stage SCLC
- Intent to receive treatment from the OSUCCC Thoracic Oncology Clinic
- Patients are eligible at any time point during their treatment here at OSU. Rationale for this timeframe is due to the overwhelming nature of the first few visits and uncertainty

around an eventual treatment plan. Patients at any stage of their treatment can participate and benefit from a physical therapy and psychosocial intervention. Patients will be approached at their initial visit but we can also offer enrollment at any one of the patients regularly scheduled clinic visits. .

- Ability to understand and willingness to sign an informed consent document (or indicate approval or disapproval by another means).

3.4 Patient Exclusion Criteria

- Prisoners are excluded from participation
- There is **NO** exclusion criteria pertaining to ECOG performance status, laboratory values, prior cancer diagnoses, presence of comorbidities or brain metastases.

3.5 Informed Consent

Discussions between the study coordinators and/or treating physician and study participants will occur in the regular Thoracic Oncology Clinic setting. The study coordinators will address all questions regarding the study outline and that participation is voluntary and the participant can withdraw from the study at any time. If eligible patients are interested, study compensation including the virtual health equipment will then be explained to ensure no unethical coercion led to the patient enrollment. If eligible patients decide to participate in the study they will sign the consent form, be assessed for eligibility and, when applicable, register as detailed below.

In the case of natural disasters or pandemic reasons there will be the option for the informed consent to be performed through the telephone. The research coordinators will follow a script [APPENDIX T]. If the patient is interested in the study the ICF will be sent through REDCap to the patients email. REDCap allows for electronic signature. The research coordinator will walk through the consent form with the patient at this time.

3.6 Inclusion of Women and Minorities

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

4.0 STUDY DESIGN

4.1 Overview of Study Design

This is a prospective longitudinal study of 20 adults older than 60 years who have been diagnosed with a thoracic malignancy who intend to receive treatment at the Ohio State University. Eligible participants will undergo the informed consent process. With IRB and participant permission, demographic information will be collected on potential participants who decline enrollment in the study by use of a non-enrollment survey [Appendix A].

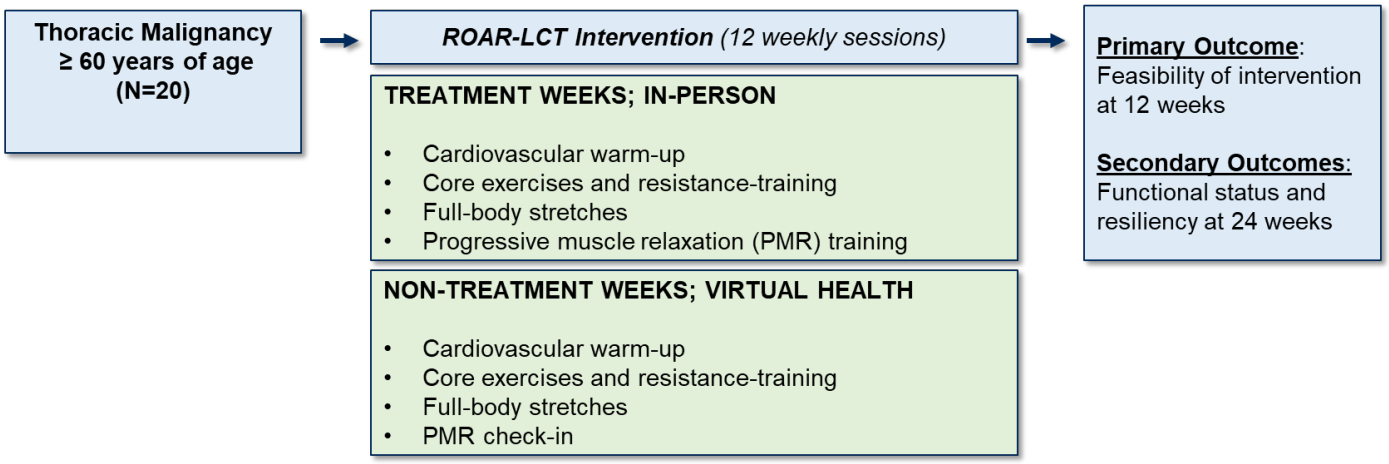
Participants will undergo treatment prescribed by the treating physician as per standard of care. In addition, patients will undergo an in-person and virtual health physical therapy program. The

in-person program will include a 10-minute cardiovascular warm up on a portable exercise peddler, using either their upper or lower extremities depending on patient abilities. The warm up will be followed by a resistance training module using exercise resistance bands. This is designed to strengthen the core and upper/lower extremities. The workout will end with full body stretches that are held for 30 seconds each. The virtual health visits will include the exact same regimen and equipment as the in-person visits. The portable peddler and resistance bands will be given to the patients either in clinic or mailed to their home based on patient preference.

In addition to the physical therapy program, participants will undergo progressive muscle relaxation (PMR) performed by research graduate students (MA and PhD level) in clinical psychology. The patient is taught to systematically tense and release 16 different muscle groups. Patients will be seen during their regularly scheduled clinic visits and with virtual health "check-ins" in the off-treatment weeks.

Patients enrolled in this study will complete baseline assessments consisting of demographic information, disease assessment, functional status assessments, depression/anxiety screenings, a quality of life measure, toxicity assessment, as well as a physical performance and an endurance test. A study coordinator will assess functional status every 3 weeks either in person, by phone, or virtual health monitoring. Participants' clinical outcomes will be collected every 6 weeks during their regularly scheduled clinic visits (baseline, 6 weeks, 12 weeks, and 24 week time points). Triggered assessments will be collected on patients with any presence of disease progression, a new toxicity grade, fall, or healthcare utilization such as emergency department visit, inpatient admission, or worsening functional status on either survey. The study intervention will last approximately 12 weeks (3 months). If a patient cancels due to scheduling conflicts or treatment fatigue they will be given the option to reschedule their visit. At the end of the 12 weeks if a patient is still benefiting from PT then those missed visits can be scheduled out. Study assessments will still take place at 12 weeks in an effort to control for time-varying confounders. In the case a patient does make up any visits beyond the study 12 week time period there will be an additional study visit that takes place. This will be an "end of treatment" visit rather than a 12 week visit. The same study assessments performed at baseline will be completed at this time. The patients will be followed until 24 months post-enrollment for 1-year and 2-year overall survival. An additional qualitative assessment will be conducted on those patients that are agreeable and consent to being either video or voice recorded. Patients will participate in a semi-structured interview to assess overall study acceptability. This assessment will help capture the "joy" our novel supportive care intervention brings to the patient, patient's family, and clinic team.

Figure 1. Study Schema



4.2 Physical Therapy Intervention

The Physical Therapy Intervention will include a total of 12 weeks with one PT visit per week virtually or in-person depending on in-person clinic limitations due to pandemic or natural disasters. Week1 assessment will be during an in-person visit with physician team within the OSU Brain and Spine Hospital The other weekly visits will occur through virtual health monitoring at the best availability of the patient and Physical Therapist. There will be a final visit during week 13 where participants undergo the same assessments as the baseline visit as a routine usual care physical therapy discharge visit. The VH visits will be billed as research or as standard-of-care depending on insurance reimbursement changes for VH visits.

The exercise intervention will begin with a 10 minute warm-up using a portable exercise peddlers either using the patient's feet or arms, depending on their mobility and pain status. For example, if the patient is non-ambulatory and does not have the use of their legs, they will be instructed in peddler use with their arms. The Core exercises will include; seated posterior pelvic tilts and seated without back support seated marches. The resistance training exercises will include shoulder press, tricep extension, bicep curls, upper extremity side raises, chest press, calf raises, marches, standing side leg lifts, leg extension in standing, seated knee extension and clamshells. These will be done in 2 sets of 10 reps using resistance bands appropriate for patient's level of fitness. The cool-down portion will include stretches targeting upper extremities (chest, shoulders, and triceps), lower extremities (calves, quadriceps, and hamstrings) and trunk. Each stretch will be held for 30 seconds each. At week 1 visit patient will receive exercise packet including handouts for above therapeutic exercises three resistance bands (yellow, red and green) in order to progress resistance at home based on patient feedback. The physical therapist will educate and demonstrate appropriate use of the equipment during virtual visits or in-clinic visits depending on encounter type. In order to evaluate how hard the participant is working during the virtual health visits; the relative perceived effort (RPE)[16] will

be used with a target goal of 12-14 on the Borg Rating Scale.[17] This indicates a moderate level of intensity.

An exercise log in the patient's electronic medical record will be filled out after each workout to keep track of patient progress. The patient will first be prescribed weekly sessions, then it will increase to twice weekly, then three times weekly based on patient behavior and activity tolerance. One session per week will be supervised virtually or in-person by the physical therapist. Additional sessions will be done by the patient on their own per standard-of care physical therapy practice. During the virtual health sessions, the physical therapist will assess barriers to doing their physical therapy and will problem solve with the patients on how to improve adherence. Please see [Appendix B] for a detailed description of the study exercise log.

Physical Therapy Safety Procedures

Upon the initial in-person visit the physician team or physical therapist will perform a standard-of-care safety screening of pulse oximetry assessment, heart rate and blood pressure monitoring, asking if patient has cardiac or pulmonary history. This screening will take into account if the patient is on oxygen, wears glasses or hearing aids. The in-person visit will also determine the location of the VH physical therapy, their emergency contact, and will verify their home address. It will be recommended that the patient perform their physical therapy in the same location each time. The physical therapist will perform a VH safety checklist at the beginning of each session. This checklist may include but not limited to the following questions:

-Where are you currently located?

-Is anyone else home with you?

-Is your cell phone charged and located near you?

-Have you had any new or different chest pain in the last week?

-Have you had any new or different shortness of breath in the last week?

During the VH visits, similar to an in-person visit, if the patient experiences any sudden chest pain or shortness of breath, they will be instructed to stop the activity, sit-down, and call their emergency contact within the home. If they are unable to call for help or are home alone, the physical therapist will call 911 and will notify the treating physician.

4.3 Progressive Muscle Relaxation

In addition to the exercise intervention, patients will participate in progressive muscle relaxation training at week 1 visit and will undergo "check-ins" each week following either during their regularly scheduled clinic visits (whether in-person or virtually) or through virtual-health study visits. During the training, one of the study psychology graduate students will meet with the patient for approximately 20 minutes. Following the training, the trainer will provide a brief summary of PMR and its efficacy for cancer symptoms. Using the standardized procedures of Bernstein and Borkovec,[18] tension/release procedures for 16 muscle groups are described and demonstrated: right hand and forearm; right bicep; left hand and forearm; left bicep; forehead; upper cheeks and nose; lower cheeks and jaw; neck and throat; chest, shoulders, and upper back; stomach; right thigh; right calf; right foot; left thigh; left calf; and left foot. The trainer will solicit feedback from the patient and all questions will be answered.

ROAR-LCT Study Assessments (Baseline, Weeks 7, 13, and 24)	
Assessment/Test	**What it measures**
Short Physical Performance Battery (SPPB)	Physical performance
2-6 minute walk test	Endurance
EQ-5D-5L & 16 item Functional activity scale	Functional status surveys
GAD-7	Anxiety Screening
PHQ-9	Depression Screening
PROMIS-10	Quality of Life
Blood & stool sample	Microbiome
Common Toxicity Criteria for Adverse Event (CTCAE v5)	Toxicity
RECIST 1.1 criteria	Disease response
EORTC QLQ C-30 + LC-13	Symptom monitoring
POMS	Symptom monitoring

EQ-5D-5L performed every 3 weeks Not assessed at baseline

PMR is most effective when practiced regularly. To facilitate at-home practice and standardization, patients will also be provided with a PMR CD with standardized shortened versions of PMR and instructions [APPENDIX C] for shortening the 16-muscle-group program to 8 and 4 muscle groups. Additionally, patients will be given a written description of PMR with directions for tensing and releasing each muscle group, following the same sequence of the CD. Individuals are encouraged to practice at home at least 3-5 times per week, and to record the frequency and duration of home practice in a log sheet provided [APPENDIX D].

4.4 Short Physical Performance Battery (SPPB)

Every six weeks (regularly scheduled clinic visits) patients will undergo the short physical performance battery [APPENDIX E]. This will result in a total of four SPPB measurements. This test will be administered by the Clinical Research Coordinator (CRC) in-person or the physical therapist virtually and scores will be captured. The SPPB [19] is a validated tool used to assess lower extremity functioning. It is comprised of three objective measures testing for standing balance, normal gait speed, and strength performance by use of a timed sit-to-stand. The participants are asked to stand with their feet side by side, semi tandem, and tandem for 10 seconds each to assess balance. Normal gait speed is tested by asking participants to walk 8 feet at his or her normal speed. Strength performance is tested by asking participants to complete five timed chair sit to stands without the use of hands. These three measures are scored individually from 0 to 4 with an aggregate score ranging from 0 to 12, with higher scores correlating with a

greater functional status. The scores are then classified into 4 categories; very low physical function (0-3); low physical function (4-6); moderate physical function (7-9); and high physical function (10-12). This tool can be administered in under 10 minutes and has been found to accurately predict falls, disability, and nursing home admissions among older adults.[19] It also has been found to be a prognostic biomarker among older adult cancer survivors[20] as well as serve as Quality of Life predictors.[21] In order to support safety at home for patient while performing test, physical therapist will instruct patient to perform test near stable surface that patient can support themselves on in order to reduce fall risk. If at any point during test patient demonstrates fall risk physical therapist will hold from advancing on to the next phase of the test.

4.5 6 Minute Walk Test

If patients are able to see PT in-person the 2 or 6 minute walk [APPENDIX F] test will be done as an additional physical function measure. This will be performed every 6 weeks. [APPENDIX F]. The 6MWT (6 Minute Walk test) is a validated tool used to assess endurance and overall functional exercise capacity.[22] Patients are instructed to walk on a treadmill at their own pace for as long as they are able. At the end of the allotted 6 minutes patients are told to stop and the total distance covered is recorded. Participants walking less than 300 meters are considered to have low endurance while those walking over 300 meters are considered to have normal endurance.[23] The distance covered has been found to be strongly related to important clinical outcomes and is positively associated with peak exercise capacity and quality of life, and negatively associated with risk of disease exacerbation, number of hospitalizations, and mortality.[24] If the patient is unable to perform the 6-minute walk test, they will be transitioned to the 2-minute walk test.

4.6 Functional Status Assessments

The Functional Status Assessment survey [APPENDIX G] will be assessed every 3 weeks by the CRC either in person, by phone, by email, or through virtual health monitoring. These surveys will be comprised of 16 activities including seven Activities of Daily Living (ADL) meausres[7], 5 Instrumental Activities of Daily Living (IADL) measures[25], and 3 mobility activities.[9] For each activity, disability is defined as the need for personal assistance or inability to perform the activity. Activities are scored as 0 being no help, 1 being with help, and 2 meaning unable to perform the activity. Higher scores indicate greater disability or a lower functional status. The ADL trajectories will include; eating, grooming, bathing, dressing, walking, toileting, and transferring, the IADL trajectories include; shopping, housework, meal preparation, taking medications, and managing finances, and the mobility measures will include; walking a quarter mile, climbing a flight of stairs, or lifting/carrying a 10lbs. The final mobility activity included is if the participant drove a car in the past month, where disability is defined as having not driven. In addition to these 16 measures, the patients will undergo the EQ-5D-5L [APPENDIX H]. The EQ-5D-5L[26] is a brief 5 question assessment that captures disability in self-care, mobility, and usual activities. It uses a scoring scale from 3, meaning no disability to 15 points, indicating severe disability. This tool has been mapped to the EORTC-QLQ-C30,[27]specifially in patients with advanced NSCLC[28]. However, the EQ-5D-5L has been shown to be the preferred assessment due to its shortened length and its improved sensitivity and face validity.[26]

4.7 PROMIS-10

The Patient-Reported Outcome Measurement Information System (PROMIS) Global Health Scale Short Form v1.1 HRQL [APPENDIX I] is the most widely used self-rated health item. It has been shown to be a useful tool in screening for disability and improving communication between patients and clinicians.[29] This assessment consists of each domain of health with items representing physical health, pain, fatigue, mental health, social health, and overall health. Each of the 10 measures consist of five responses; Excellent, Very good, Good, Fair, and Poor. The CRC will administer the PROMIS by use of IPads during the patient's regularly scheduled visits or by phone approximately every 6 weeks.

4.8 GAD-7

The GAD-7[30] **[**APPENDIX J] is a reliable tool used to assess the prevalence and severity of Generalized Anxiety Disorder (GAD) in clinical settings. This assessment is a 7 item questionnaire that asks patients how often in the past 2 weeks, have they been bothered by each symptom. The responses are scored as 0 being "not at all," 1 being "several days," 2 being "more than half the days", and 3 being "nearly every day," for an aggregate score of 21. Higher scores indicate a higher prevalence of anxiety and are strongly associated with multiple domains of functional impairment and disability days.[30]

4.9 PHQ-9

The Patient Health Questionnaire is a self-administered assessment used for diagnostic purposes of common mental disorders.[31] The PHQ-9 [APPENDIX K] is the 9-item depression segment which assesses the severity of depressive symptoms within the last two weeks. Patients will complete the PHQ-9 approximately every 6 weeks administered by the CRC. Items are scored from 0-3 with higher scores indicating greater levels of depression. If 5 or more of the 9 symptoms have been present for "more than half the days," then major depression is indicated. Other depression is indicated if 2, 3, or 4 of the symptoms have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia.

4.10 EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 [APPENDIX P] is a widely used quality of life assessment for cancer patients.[32] It is comprised of five functional scales, three symptom scales, a global health scale and one quality of life scale. This measure takes an average of 11 minutes to complete and is a reliable and valid measure to assess quality of life in cancer patients. The EORTC QLQ-LC13 [APPENDIX Q] is a modular supplement to the EORTC QLQ C30. This is a 13 item lung cancer-specific questionnaire that assesses for symptoms such as coughing and dyspnea.[33] It has been shown to be a valid assessment for monitoring symptoms in patients with a thoracic malignancy. Patients will complete both the EORTC QLQ C30 and the LC13 along with the other assessments during their regularly scheduled visits.

4.11 POMS-Revised

The original POMS is 65 items. The POMS Short Form (POMS-SF) is 37 items and there are many studies that have shown its reliability and validity. The "POMS-12" {APPENDIX R] was created in the following way. [34] Factor analysis of the 37-item version identified 6 factors, which are identified as the subscales. For each subscale, the two items with the largest factor loading were selected and included in this abbreviated version. This method has been validated in previous research.

4.12 Biomarkers

Peripheral blood and stool samples will be collected at baseline prior to treatment and pre and post PT + PMR session. Thereafter, blood will be collected every 6 weeks pre and post PT + PMR session and at additional triggered time points for correlative biomarker studies. Each patient will have a minimum of 6 research blood draws performed (2 pre-treatment) and 4 total post-treatment. The post-PT +PMR blood sample will be drawn from the peripheral IV so an additional needle stick is not required. The blood will be processed into peripheral blood T lymphocytes (PBTLs), plasma, and serum for cellular senescence correlative analyses. The analysis consists of routine laboratory values including hematologic functions, renal function, hepatic function and calculated creatinine clearance, and markers of inflammation and coagulation, and potential molecular markers of aging ($P16^{INK4a}$ Expression, DNAge). The details of this biological assessment are below:

Table 2: Biomarker Assessment

Laboratory Values captured in Routine Practice		Biologic Correlates*	
Hematologic functions:	WBC HGB Platelets Absolute Neutrophil count Absolute Lymphocyte count Absolute Lymphocyte count	Molecular markers of aging:	OSU_Senescence DNAge Inflammatory Cytokines Peripheral blood T Lymphocyte subtyping
Renal Function:	BUN Creatinine		
Hepatic function:	AST ALT Total Bilirubin Alkaline Phosphatase Albumin		

*patients who have already begun treatment prior to visit 1 will not partake in research blood samples in order to preserve the integrity of the data.

Stool samples will be used for microbiome correlative analyses. At their clinic visit patients will be given a home microbiome collection kit that includes instructions for collecting a sample within 24 hours of their next clinic visit. (Please see **APPENDIX L** for the instructions included in this box.) Briefly, a rigid plastic scaffold is placed over the toilet seat to collect stool in a plastic tub. Patients return the sample at their next clinic. Staff transfer the samples to the Spakowicz lab (IBC 2018R00000115) where stool is transferred to cryo-vials and stored at -80C until processing in batch.

DNA is purified using the QIAGEN PowerSoil kit and the 16S rDNA amplified using barcoded universal primers (V3-V4). Sequencing is performed on an Illumina MiSeq 2x300 for 16S to a depth of > 105k reads per sample. Demultiplexed fastq files are cleaned and paired using Spakowicz Lab resources in the Ohio Supercomputing Center and analyzed following the DADA2[3532] pipeline in R[33].

Sequences are processed to identify amplicon sequence variants (ASVs) and then to closest taxonomic identification using the SILVA[34] and GreenGenes[35] databases. Metabolic pathway composition is inferred using the PICrUST pipeline. Samples are clustered by ASV abundances using Non-Metric Multidimensional Scaling[36], with the significance of clusters defined by the multi-response permutation procedure[37], calculated in the vegan package in R[38]. The alpha diversity metric Simpson's Index calculated to quantify the number of species and evenness of the stool microbiome samples. Taxon abundances, at each taxonomic rank, and pathway abundances are modeled using formulae appropriate for each hypothesis, most commonly using the DESEQ2 package in R to accommodate the negative binomial distribution of microbial abundances[39].

4.13 Toxicities

The toxicity assessment and chemo drug & dose information will be collected by the CRC or a member of the clinical team at the beginning of every treatment cycle. Therapeutic toxicity will be collected using NIA Common Toxicity Criteria for Adverse Event v5 (CTCAE v5)[40]. During each scheduled doctor's appointment or telephone encounter a research staff member or nurse will collect the therapy toxicities including grade and attribution to therapy. Additional toxicities may be collected from clinical encounters (scheduled or emergency visits) within the medical record. The clinical encounters include clinic notes, emergency room visits, and hospitalization. Furthermore, dose reductions, dose delays or discontinuation of the therapy course and the cause of each aforementioned event will be recorded.

Serious Adverse Event (SAE) per the NIA Common Toxicity Criteria for Adverse Event v5 (CTCAE v5)[40] is defined as any adverse event that results in one of the following: 1.) death; 2.) a life-threatening event; 3.) inpatient hospitalization or prolongation of an existing hospitalization >24 hours; 4.) persistent or significant incapacitation or substantial disruption to the participants ability to conduct normal life functions; 5.) congenital anomaly/birth defect; 6.) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization but may be considered serious when, based upon medical judgement, the event may jeopardize the patient

and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. The occurrence and incidence of SAE will be documented as part of toxicity assessment per CTCAE guidelines at each treatment visit.

4.14 Disease Response

Disease response will be routinely evaluated and will be classified using RECIST 1.1 criteria.[41] The current version of RECIST is the most widely used tumor response criteria used in clinical trials. RECIST categorizes disease as either measurable or non-measurable. The disease response is then classified into the following categories; complete response (CR), partial response (PR), non-CR/non-PR, and Progressive disease (PD).[42] The study clinician will evaluate individual disease response for all 20 study participants. The CRC will be notified of any PD as this will require triggered study assessments.

4.15 Virtual Telehealth

Epic is a secure, electronic medical record platform that can utilize embedded technology from Vidyo to allow video encounters between patients and providers. Patients log in through the My Chart app and the physician logs in through Epic to kick off the video. Alternative virtual health options include doximitry, UpDox, or another OSU-approved virtual interface such as facetime, facebook messenger, zoom or a new preferred virtual health interface as dictated by OSU.

Steps for virtual health visit: example using mychart. Instructions will be similar if using other interface.

1. Eligible patients are identified by OSU staff.
2. Device criteria is reviewed and if needed, a mobile or tablet device is provided to the patient.
3. OSU staff provides patient with “MyChart Video Visit Instructions for Patients” document. Instructions are also provided within the appointment. [APPENDIX M]
4. Video visit appointment is scheduled for patient.
5. The patient signs up for MyChart if they have not done so already.
6. Patient installs the MyChart app on a mobile or tablet device (preinstalled if OSU provides the device)
7. Once the patient appointment is scheduled, it is accessible in MyChart.
8. Before the appointment, patient can enter the appointment via the MyChart app, complete e-checkin and test their video. Video testing is unavailable within 20 minutes of the appointment time
9. At the time of the visit, patient can enter the appointment, complete e-check-in if not already completed, and then click “begin visit.”
10. Provider enters the scheduled encounter in Epic and has option to pre-chart and then begin video visit at the appropriate time.
11. They perform the video session
12. Either side can click ‘disconnect’ to end the session as appropriate.

Video visits are encrypted and are not recorded. The patient and provider can only access the video visit by clicking on the appointment in MyChart and Epic respectively. They can only access the appointment if they are logged into these systems using their individual credentials.

4.16 Actigraph/ActivPal

In addition to the physical therapy peddler, the participants will receive either an actigraph or an activpal. They will be instructed to wear the actigraph or activepal 24 hours a day for three weeks at the beginning of the intervention and three weeks post intervention, An actigraph is a small watch-like band worn on the non-dominant wrist and the active pal is a small adhesive monitor placed on the outer thigh.

The actigraph will be used to measure gross motor activity and monitor sleep patterns. The activpal will be used to monitor physical activity habits such as time sedentary, standing, steps, and intensity of activities. This allows patients to go about their regular routines while simultaneously collecting important data regarding calories burned, wake-time activity, circadian rhythm sleep disorders, insomnia, energy expenditure, steps taken, and sleep efficiency.

At the end of the PT intervention the participants will be asked to bring their actigraph or activpal back in to the research team. All of the data is saved on the watch or monitor until it is brought back in and then downloaded. Programs such as SAS or R have the capabilities to download and analyze the circadian rhythmicity. This data will be looked at in regards to clinical outcomes among our patient population.

4.17 Study Compensation

Participants who do not currently have one of our study compatible devices (iPhone, IPad, or Samsung phone or tablet) with internet access will be given one of our internet-compatible donated devices. We will confirm device functioning prior to the start of each patient program start. Patients that do require the use of a loner tablet will be asked to return the device at the completion of all 12 sessions or when coming off study. Meaning that if a patient schedules any missed visits beyond the 12 weeks they may hold on to the device in order to complete these visits. The CRC will follow up with the patient to serve as a reminder of when they should return their study materials.The enrolled participants will also be compensated with a $50 Visa gift card for study participation. Study compensation will be monitored and completed by the CRC. If a patient does schedule any missed or canceled visits beyond the 12-week study time period they will still be paid their visa giftcard at the 12 week time point.

4.18 Potential Risks

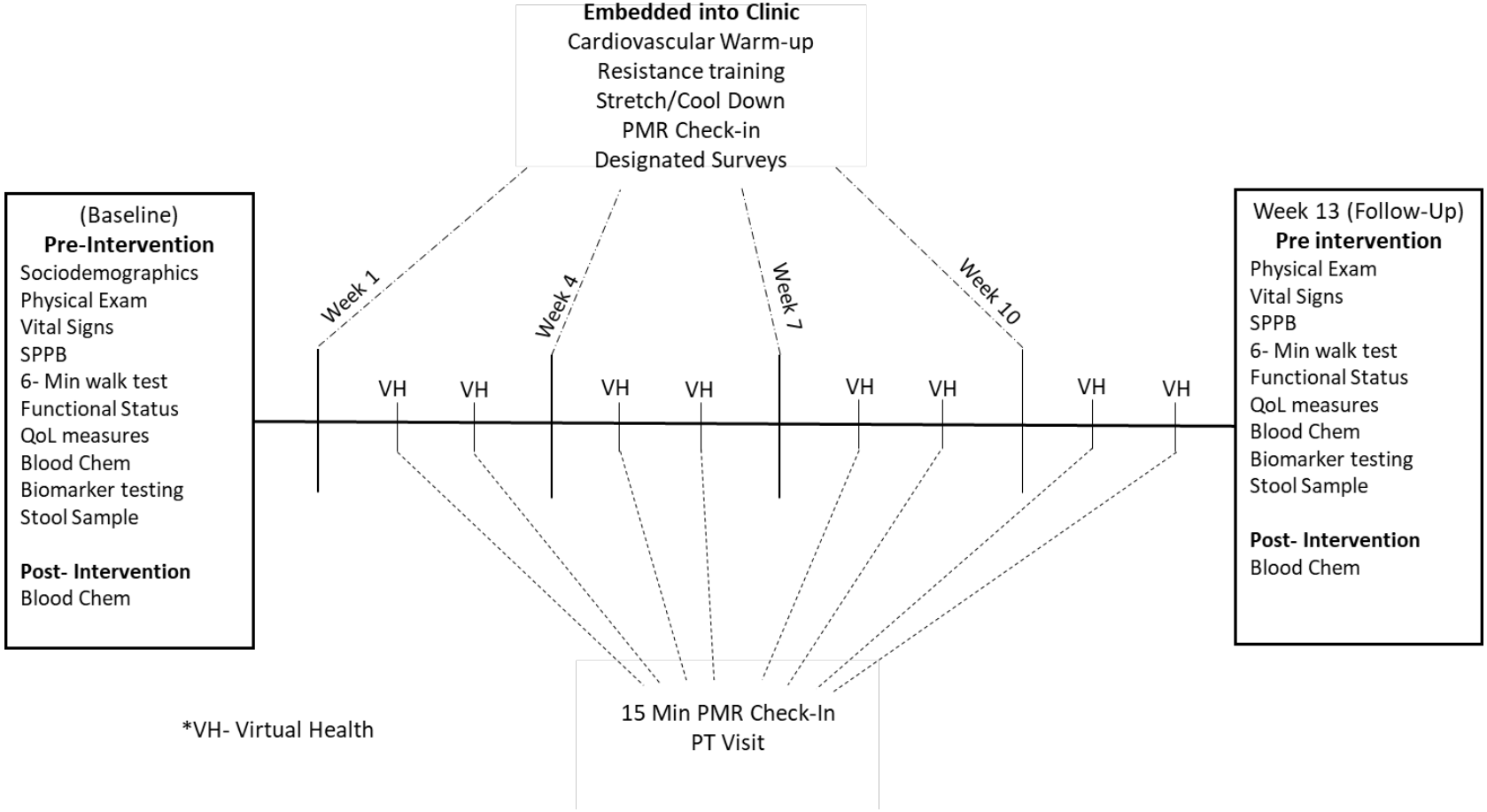
Our study team anticipates that there will be minimal physical and psychological risks or discomforts for the study participants. Informed consent will be obtained from all participants prior to study enrollment to ensure all potential risks are understood by participant. There is a small risk that patients have some distress associated with the completion of the study questionnaires. However, if this occurs, questions are easily skipped and the study staff will speak to the participant about the distress that the surveys have caused and will offer referral to a mental health professional if necessary. There is also a small risk of injury due to the prescribed exercise intervention. Patients will be taught by a licensed Physical Therapist how to safely

perform these exercises and instructed to only perform each task to the level of his or her physical ability. A safety checklist will be performed as detailed above before every physical therapy session. In the case of an injury, the on-study Physical Therapists will assess the patient and his or her exercise intervention may be modified accordingly.

4.19 Semi-Structured Interview

Study participants will be asked to participate in a semi-structured interview conducted by the study CRC or another study team member. These questions will serve as proof of concept for our study emphasizing the importance of supportive care and targeted interventions among older adults with lung cancer [APPENDIX V]. Interviews will be conducted through either updox, teams, or zoom platforms. Patients are not required to turn on video capabilities but must consent to voice recording. The interviews will then be transcribed and coded by a study team member for analysis. Our primary rationale for this qualitative assessment is to be able to capture the joy this study has brought to our patients and clinic team. Our quantitative acceptability questions fail to do this in the same way qualitative interviews can. The interview recordings will be stored in a password-protected folder within our secure study folder in the shared T-drive. Only study personnel will have access to this folder. Upon analysis of interview transcripts, the recordings will be deleted and transcripts will be de-identified in order to protect patient private health information. Patients are not excluded from participation if they decline participation in this additional qualitative assessment.

Figure 2. Study timeline



5.0 DATA COLLECTION AND MANAGEMENT

5.1 Registration Process

- Potential patient identified
- Patient signs informed consent and HIPAA form
- Eligibility Screening
- Register the patient on the study (Oncore)
- Assign a patient study number
- Pend blood work orders
- Documentation of Consent in EPIC

5.2 Electronic Data Capture

5.2.1 IPad Survey Administration

All of our study assessments are either self-administered or done by the CRC during regularly scheduled clinic visits whether in-person or virtual. In the case a patient does not have a monthly visit scheduled, the surveys will be administered over the phone or by use of a survey email link [APPENDIX N]. All assessments in survey form are completed via IPad and compatible pen with the exception that the CRC will administer the SPPB. Patients unable or unwilling to use the IPad will be offered a paper copy as an alternative to the electronic version.

5.2.2 Survey Software and Data Management

All data obtained via the IPad survey platform is supported by REDCap. The Ohio State University (OSU) Research Informatics Services (RIS) core utilizes REDCap as its primary Electronic Data Capture (EDC) support. The REDCap platform is a secure, web-based application flexible enough to be used for a variety of types of research, provides an intuitive interface for users to enter data, and enforces real time validation rules (with automated data type and range checks) at the time of entry.

REDCap data collection projects rely on a study-specific data dictionary defined in an iterative self-documenting process. The project specific data dictionary is defined by the research team with assistance from RIS staff. As part of the data dictionary development process, individual fields can be denoted as identifiers. When exporting a de-identified dataset, these variables are omitted. Additionally, the data export tool allows for the shifting/removal of dates. REDCap supports electronic signatures by positively identifying the user through a unique username and password combination. The provisioning of authorization (e.g. access to specific projects, user rights within the project, etc.) for all projects is managed by RIS staff in conjunction with the project Primary Investigator (PI).

5.2.3 DATA AND SAFETY MONITORING PLAN

Though this is not a clinical trial per the NIH definition, we have developed a Data and Safety Monitoring Plan for this project. The purpose of the data and safety monitoring plan is to ensure the safety of participants, the validity and integrity of data, and the appropriate termination of projects for which significant benefits or risks have been uncovered or when it appears that the project cannot be concluded

successfully. Risks associated with participation in research must be minimized to the extent practical, and the method and degree of monitoring should be commensurate with risk. The essential elements of the Data and Safety Monitoring Plan include:

- Monitoring the progress of the project and the safety of participants;
- Plans for assuring compliance with requirements regarding the reporting of adverse events (AE);
- Plans for assuring that any action resulting in a temporary or permanent suspension of the project is reported to the appropriate agencies; and
- Plans for assuring data accuracy and protocol compliance. Prior to the initiation of the project, staff will receive standardized training to ensure that the activities of the project are conducted in a uniform, safe, confidential and secure manner. A tracking system will be implemented to document data collection activities, and reports will be generated on a weekly and monthly basis to monitor the project activities. Research project meetings will take place on a monthly basis to monitor the activities of the project and to continually reassess the progress of the project, including assessments of data quality, timeliness, participant recruitment, accrual, retention and monitoring of the risks versus benefits throughout the project period. In addition, face-to-face meetings with project staff will take place once per week to discuss the project activities.

We will use REDCap (Research Electronic Data Capture) electronic data capture tools hosted by the Center for Clinical and Translational Science (CCTS) at OSU for data collection. REDCap provides a secure, web-based, HIPAA compliant application that is housed behind the OSU Medical Center firewall. This platform provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, and real-time data monitoring/querying of participant records. REDCap has multiple data export options to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

To monitor data quality, the clinical research coordinator will conduct a 10% project eligibility verification. If a violation is noted, the clinical research coordinator will document the violation and inform the research project and the PI the matter. The appropriate action will be taken to rectify the violation and to determine what, or if any, corrective actions need to take place. All protocol violations will be documented and reported to the appropriate IRBs. Also, any privacy violations will be reported to the IRBs and the institutional privacy offices. All privacy violations, AEs, and protocol violations will be reported to and reviewed by the PI and the research team, who will be responsible for reporting to the OSU Office of Responsible Research Practices/IRB.

The clinical research coordinator will be responsible for submitting reports; annual reports will be sent to the OSU IRB, External Advisory Board, and, as required, to the OSUCCC Data and Safety Monitoring Board and the NIA project office. Information included in the reports will include the number of individuals enrolled in the project, dropout rates and any protocol deviations.

Any unexpected SAE will be reported to the NIA, DSMC, and IRB within 48 hours of occurrence, while any other SAEs, protocol deviations, and anticipated problems will be made note to file and reported to the NIA, DSMC, and IRB within 72 hours. Any expected AE such as chemotherapy toxicity will not be reported but made note to file and documented within our REDCap database. The DSMC reviews safety reports every 6 months while all SAE reports are reviewed monthly. All submissions are made via OnCore. The PI will also submit a progress report (biannually for Phase II and quarterly for Phase I) that will be reviewed by the committee per the IRB of record as per the policies of the IRB.

5.3 Baseline Demographic Questionnaire

Patient demographic information will be collected via a standard form [APPENDIX O] administered at baseline. The information with be pulled from the patient demographics section in IHIS.

5.4 Clinical Data

Clinical data regarding the specifics of the patients thoracic malignancy will be collected from IHIS including but not limited to, diagnosis, diagnosis date, stage, genetic mutation information, prognostic measures, treatment history, medications, hospitalizations, readmissions, hematologic and chemistry parameters (e.g. creatinine, BUN, albumin).

6.0 STATISTICAL ANAYLYSIS

6.1 Primary Endpoint

In order to evaluate the feasibility of the pilot intervention we will determine, recruitment, adherence, and retention rates at 12-weeks of follow-up. Follow-up will continue through 24 weeks post-enrollment. Recruitment rates will be defined as the proportion of screened older adults accrued relative to those approached in the OSUCCC Thoracic Oncology Clinic. Successful recruitment rates will be defined as ≥ 50% of older adults (≥ 60 years) approached agree to participate. Study adherence will be defined as the completion of ≥ 70% of the program sessions, repeated assessments, and collection of bio specimens either at the end of the study period or death, whichever occurs first. Retention rates will be defined as the percentage of participants not lost to follow-up at 6, 12, and 24 weeks post-enrollment. Death during active follow-up will not be considered as lost to follow-up. We are excluding those people who die because our population of interest is those who live long enough to benefit from this intervention. We will enroll 30 participants to account for a conservative drop out of 30% for a projected sample size of 20 participants who survive a 6 – month period. Reasons for missing any scheduled collection dates will be documented, and the proportions of missing information at each time point will be calculated.

6.2 Secondary Endpoints

Functional trajectories and resiliency will be evaluated using generalized linear mixed models (GLMMS). This model allows for the estimation of intercept and slopes at both the individual and sample level. GLMMs can determine whether factors affect all patient trajectories in similar ways or whether they affect individual trajectories differently. To allow for possible changes in functional status over time (e.g., a change-point analysis) the 'segmented' package in R will be used.[43,44] Participants' functional status scores will be modeled using a segmented mixed model with random change points. Estimating the change point identifies the point in time that patients' functional status scores change during the 12-months post-diagnosis. We anticipate that the start of treatment will be a change point depending on treatment tolerability vs. toxicity. This model allows for random and fixed effects, permitting analysis of between-subject and within-subject variance in longitudinal observations.

Resiliency will be defined as the ability to maintain or regain at least 50% of baseline functional status at any point during the 12 months after diagnosis with specific emphasis at 3 and 6-months post- the start of treatment. The association between resiliency and clinical factors will be evaluated with appropriate statistical techniques for the specific measure (e.g. Chi-square tests will compare categorical variables between participants demonstrating resiliency vs. worsening functional status; a two-sample t-test or Wilcoxon Rank Sum test will compare continuous variables). We will characterize differences in resiliency within each of these pre-defined groups. GLMMs will test for differences in resiliency between these groups. Models will be adjusted for important clinical and demographic variables. The data obtained from the primary endpoint will be used to refine the timing and duration of the pilot intervention as described in our secondary endpoint. Using GLMMS we will compare functional status in the 24-week follow-up period using both functional status measurement strategies to inform the survey design of a larger intervention trial.

6.2.1 Power Calculations

A follow-up rate of study participation at 12 weeks of at least 60% (p_1) would be desirable; a continuation rate below 40% (p_0) would be unacceptable. With 20 eligible and recruited participants alive during a 24 week follow-up period, this study is powered to reject acceptability of these measures if the follow-up rate is less than 40% (10% one-sided type one error) and deemed feasible if the follow-up rate is 64% or more (80% power). If 13 of the 20 patients continue at 12 weeks, we will consider this method to have acceptable adherence for further study (follow-up rate >40%). We will also determine adherence and follow-up rates for both PT and PMR at 24 weeks of follow-up.

7.0 CORRELATIVE ANALYSIS

7.1 Overview

Peripheral blood will be obtained for mRNA, DNA, and flow cytometry analyses. While specific details of the processing, extraction, and analysis are included in this protocol, these details may change with innovations in laboratory techniques and hence are considered general guidelines only.

7.2 Correlative Analysis Procedures

Patients enrolled will have peripheral blood collected for analysis before therapy initiation. Patients who have started on chemotherapy (within 30 days) will not have correlative analysis performed. Peripheral blood will be obtained and separated for serum and PBMC analysis. Peripheral blood will be obtained in EDTA coated tubes and CD3+ T-cells isolated using RosetteSep Reagents. We developed a custom Nanostring Codeset, OSU_Senescence, to comprehensively assess the phenotypes of human PBTLs. The OSU_Senescence platform measures *p16* and 70+ additional transcripts indicative of immunosenescence, cell cycle/cellular senescence, T-cell subtype, exhaustion and cytokine production. Examples of OSU_Senescence detectors include T-cell subtypes (e.g.*TBX21*/TH1, *GATA3*/TH2, *FOXP3*/Treg), immunosenescence (e.g. *CD27, CD28*); exhaustion markers (e.g. *PRDM1*/Blimp-1, *PDCD1*/PD-

1, *CD274*/PDL-1) and standard housekeeping genes. The ability of OSU_Senescence to report dynamic changes in T-cell subtype is a major advantage over traditional real-time PCR-based methods to detect *p16*. Moreover, OSU_Senescence is more cost effective, focused and analytically straightforward than RNA-seq. To increase the power of our Codeset, we developed and tested a companion flow cytometry-based immunophenotyping assay, which can be used to isolate specific T-cell subtypes for downstream functional assays. In addition, we have consulted with Zymo Research Corp. to concurrently analyze changes in the Horvarth[45] epigenetic clock/DNAge of these cells and PBMCs providing further insight into the global, molecular changes that accompany *p16* expression in PBTLs. All of these studies can be completed from a single, 20 mL sample of human peripheral blood. DNAge and OSU_Senescence mRNA expression will be compared to an age-matched control database developed at OSU.

Patients enrolled have peripheral blood collected for OSU_Senescence analysis serially at Visit 1 (Baseline) and Visit 4 (End of Treatment). Peripheral blood will be obtained in EDTA coated tubes and 10 mL used to isolate CD3+ T-cells using RosetteSep Reagents. At the same time, PBMCs will be isolated from 10 mL of peripheral blood using standard density gradient centrifugation procedures. PBMCs will be cryopreserved in media containing 10% DMSO for future flow cytometric and/or senescence evaluation. RNA and DNA will be extracted from purified PBTL or PBMCs using a column-based commercial nucleic acid kit. Measurement of OSU_Senescence transcripts will then be performed in accordance with standard Nanostring protocols and may be validated by RNA reverse-transcription followed by quantitative real-time PCR. DNA from T-cells and/or PBMCs will be sent to Zymo for DNAge analysis. Levels of OSU_Senescence mRNA expression or DNAge values will be compared to an age-matched control dataset.
PBMCS will also be analyzed by flow cytometry to allow for simultaneous multiparametric analysis of cellular markers. Markers of cellular senescence, exhaustion and T-cell regulation will be analyzed.

7.3 Statistical Considerations

Pearson correlations and Spearman correlations will be used to explore the strength of the relationship between p16, senescence transcripts, and quantitative prognostic factors (e.g., age). Two-sided hypothesis tests of the correlations will be used to determine if there is evidence of an association between variables. With such a small sample size, this is an exploratory aim. One-way ANOVA and the Tukey-Kramer multiple comparison procedure [46] will be used to compare levels OSU_Senescence transcripts across the levels of categorical prognostic variables (e.g. stage of disease).

7.4 Obtaining Samples

Peripheral blood will be obtained by clinic staff for mRNA, DNA, and flow cytometric studies. Samples will be obtained in clinical space (currently on HTC and 5th floor James, or inpatient settings as examples). Specifically, approximately 40ml of peripheral blood will be collected into phlebotomy tubes: up to 20ml in purple top EDTA tubes and 20ml in serum separator tubes.

7.5 Sample processing

Sample pick up and processing will be performed in the Leukemia Tissue Bank using the following general procedure for cryopreservation of samples.

Plasma: To obtain the plasma the blood collected in EDTA coated tubes will be transferred to 50 ml sterile tube and centrifuged at 1800 rpm for 10min at room temperature. The supernatant (plasma) will be collected and stored at -80°C for further studies. The cellular pellet will be gently re-suspended in PBS to reach 2X the original volume (for 10ml of plasma 20ml PBS) and then stratified in 1X of Ficoll-Paque. This will be centrifuged at room temperature for 20 min at 2000 rpm. The white ring containing monocytes, T- and B- lymphocytes will be removed and washed with FBS enriched culture media. The tube will be centrifuged at 1200 rpm at room temperature for 6 min. The cellular pellet will be resuspended in 90% FBS and 10% DMSO and placed in cryo-tubes at -80°C and after 3 days will be placed in liquid nitrogen for long-term storage.

Serum/PBMCs: For the serum collection the tubes will be centrifuged at 2,200-2,500 rpm for 15 min and the serum will be stored at -80°C. PBMC: Blood samples will be diluted in an equal volume of phosphate buffered saline containing 2% fetal bovine serum (PBS/2%FBS). Diluted samples will be gently mixed and then carefully layered on top of Histopaque 1077 density medium (Sigma-Aldrich #10771) in a conical tube. The amount of density medium used will equal the original blood aliquot volume. Tubes will then be centrifuged at 1200xg for 20 minutes at room temperature with the centrifuge brake set to 'off'. Following separation, PBMCs will be removed from the gradient interface, placed into a fresh conical tube, washed in PBS/2%FBS solution, pelleted and then stored in cryopreservation medium.

T-cells: Whole blood collected in a purple top EDTA tube will be divided into two equal volume portions, approximately 5mL each. RosetteSep Human T Cell Enrichment Cocktail (Stem Cell Technologies # 15061) will be added to each tube at a ratio of 50uL per mL of whole blood. Tubes will be mixed by inversion and incubated for 20 minutes at room temperature. Next, samples will be diluted in an equal volume of phosphate buffered saline containing 2% fetal bovine serum (PBS/2%FBS). Diluted samples will be gently mixed and then carefully layered on top of Histopaque 1077 density medium (Sigma-Aldrich #10771) in a 50mL conical tube. The amount of density medium used will equal the original blood aliquot volume (~5mL). Tubes will then be centrifuged at 1200xg for 20 minutes at room temperature with the centrifuge brake set to 'off'. Following separation, enriched T-cells will be removed from the plasma interface using a pipette and placed into a fresh 15mL conical tube. The cells will be washed by adding PBS/2%FBS to the tubes until they are filled to the top fill line. Tubes will then be centrifuged at 400 x g for 4 minutes at room temperature with maximum brake. The resulting supernatant will be removed with a pipette and transferred to a 1.5 mL microcentrifuge tube. This sample will be centrifuged at 400 x g for 4 minutes at room temperature with maximum brake. The resulting supernatant will be carefully and completely removed using a pipette. The remaining T-cell pellet will be stored in a -80 ° freezer until processing.

DNA/RNA recovery and basic analyses: Under the supervision of Dr. Burd, harvested cell mRNA will be converted to cDNA using the Promega ImProm-II Reverse Transcription System (Promega

#A3802) and random hexamer primers (Invitrogen #588875) as directed by the manufacturers. p16 levels will be measured using a Taqman-based quantitative RT-PCR methods essentially as described by Liu et al. (20). Validated Taqman-based controls for T-cell purity (CD3G, Applied Biosystems #4331182 Hs00962186), sample viability (p14ARF, Applied Biosystems #4351370 HUMP14-ARF3) and RNA quantity (YWHAZ, Applied Biosystems #4331182 Hs03044281) are included in this analysis. Data clean up: Data will be filtered to exclude relatively invariant features (IQR = 0.5) and features below the detection threshold (defined for each sample by a cutoff corresponding to approximately twice standard deviation of negative control probes plus the mean of them) in at least half of the samples. Basic analysis Using R/Bioconductor and the filtered dataset, linear models for microarray data analysis[47] will be employed with a contrast matrix for the comparisons. P values will be used to rank miRNAs and mRNA of interest, and correction for multiple comparisons will be done by the Benjamini-Hocheberg method.[48]

Assessment*:	Screen	Visit 1 (Baseline)	Every Treatment Visit	Visit 2 (4 weeks)	Visit 3 (7 weeks)	Visit 4 (10 weeks)	Visit 5 (13 Weeks) End of intervention	Visit 6 (24 weeks)	Follow up to 24 months (2 years)
Signed Informed Consent	x								
Inclusion/Exclusion	x								
Medical & Cancer History	x								
Sociodemographic		x							
Disease Assessments		x						x	
Physical Exam		x			x		x	x	
Vital Signs		x			x		x	x	
SPPB		x			x		x	x	
2-6 MWT		x			x		x	x	
PROMIS-10		x			x		x	x	
Blood Chemistry		x			x		x	x	
Biomarker Testing (blood and stool)		x			x		x	x	
Functional Status Assessments		x	x	x	x	x	x	x	
PROMIS-10		x		x	x	x	x	x	
GAD-7		x		x	x	x	x	x	
PHQ-9		x		x	x	x	x	x	
EORTCQLQ-30		x		x	x	x	x	x	
EORTC LC-13		x		x	x	x	x	x	
POMS-12		x	x	x	x	x	x	x	

Toxicities/ Disease Response		x		x	x	x	x	x	
Survival Status									x
Semi-structured interview							x		

8.0 STUDY CALENDAR

*** all screening and study visits have the option of being virtual depending on clinic requirements due to pandemic status or natural disasters**

9.0 References

1. Gajra A, Jatoi A. Non-small-cell lung cancer in elderly patients: a discussion of treatment options. *J Clin Oncol.* 2014;32(24):2562-2569.
2. Mitka M. IOM report: Aging US population, rising costs, and complexity of cases add up to crisis in cancer care. *JAMA.* 2013;310(15):1549-1550.
3. !!! INVALID CITATION !!! 3.
4. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med.* 2018;378(22):2078-2092.
5. Horn L, Mansfield AS, Szczesna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med.* 2018;379(23):2220-2229.
6. Kuchel GA. Frailty and Resilience as Outcome Measures in Clinical Trials and Geriatric Care: Are We Getting Any Closer? *J Am Geriatr Soc.* 2018;66(8):1451-1454.
7. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist.* 1970;10(1):20-30.
8. Lawton MP. Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living1. 1969.
9. Presley CJ, Han L, Leo-Summers L, et al. Functional trajectories before and after a new cancer diagnosis among community-dwelling older adults. *J Geriatr Oncol.* 2018.
10. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. *N Engl J Med.* 2002;346(14):1061-1066.
11. !!! INVALID CITATION !!! 11.
12. Hurria A, Soto-Perez-de-Celis E, Allred JB, et al. Functional Decline and Resilience in Older Women Receiving Adjuvant Chemotherapy for Breast Cancer. *J Am Geriatr Soc.* 2018.
13. Morten Quist SWL, Mikael Rørth et al. "EXHALE": exercise as a strategy for rehabilitation in advanced stage lung cancer patients: a randomized clinical trial comparing the effects of 12 weeks supervised exercise intervention versus usual care for advanced stage lung cancer patients. *BMC Cancer.* 2013(13):477.
14. Quist M, Adamsen L, Rorth M, Laursen JH, Christensen KB, Langer SW. The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. *Integr Cancer Ther.* 2015;14(4):341-349.
15. Pelekasis P, Matsouka I, Koumarianou A. Progressive muscle relaxation as a supportive intervention for cancer patients undergoing chemotherapy: A systematic review. *Palliat Support Care.* 2017;15(4):465-473.
16. Rajarajeswaran P, Vishnupriya R. Exercise in cancer. *Indian J Med Paediatr Oncol.* 2009;30(2):61-70.
17. Borg GA. Psychophysical bases of perceived exertion. *Medicine and science in sports and exercise.* 1982;14(5):377-381.
18. Bernstein DAB, T.D. *Progressive relaxation training: A manual for the helping professions.* 5 ed: University of Michigan: Research Press; 1973.
19. Guralnik JM, Simonsick EM, Ferrucci L, et al. A Short Physical Performance Battery Assessing Lower-Extremity Function - Association with Self-Reported Disability and Prediction of Mortality and Nursing-Home Admission. *Journals of Gerontology.* 1994;49(2):M85-M94.
20. Brown JC, Harhay MO, Harhay MN. Physical function as a prognostic biomarker among cancer survivors. *Br J Cancer.* 2015;112(1):194-198.

21. Oh B, Cho B, Choi HC, et al. The influence of lower-extremity function in elderly individuals' quality of life (QOL): an analysis of the correlation between SPPB and EQ-5D. *Arch Gerontol Geriatr.* 2014;58(2):278-282.
22. Gloeckl R, Teschler S, Jarosch I, Christle JW, Hitzl W, Kenn K. Comparison of two- and six-minute walk tests in detecting oxygen desaturation in patients with severe chronic obstructive pulmonary disease - A randomized crossover trial. *Chron Respir Dis.* 2016.
23. Boxer R, Kleppinger A, Ahmad A, Annis K, Hager D, Kenny A. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. *Congest Heart Fail.* 2010;16(5):208-213.
24. Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J.* 2014;44(6):1447-1478.
25. M. Powell Lawton P, 2 and Elaine M. Brody, ACSW3. Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living1. *Gerontologist.* 1969(9):179-186.
26. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20(10):1727-1736.
27. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *JNCI Journal of the National Cancer Institute.* 1993;85(5):365-376.
28. Khan I, Morris S, Pashayan N, Matata B, Bashir Z, Maguirre J. Comparing the mapping between EQ-5D-5L, EQ-5D-3L and the EORTC-QLQ-C30 in non-small cell lung cancer patients. *Health Qual Life Outcomes.* 2016;14:60.
29. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res.* 2009;18(7):873-880.
30. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006;166(10):1092-1097.
31. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9 - Validity of a brief depression severity measure. *Journal of General Internal Medicine.* 2001;16(9):606-613.
32. !!! INVALID CITATION !!! .
33. Team RC. *R: A Language and Environment for Statistical Computing.* Vienna, Austria: R Foundation for Statistical Computing; 2017.
34. Quast C, Pruesse E, Yilmaz P, et al. The SILVA ribosomal RNA gene database project: improved data processing and web-based tools. *Nucleic Acids Research.* 2013;41(Database issue):D590-D596.
35. DeSantis TZ, Hugenholtz P, Larsen N, et al. Greengenes, a chimera-checked 16S rRNA gene database and workbench compatible with ARB. *Applied and Environmental Microbiology.* 2006;72(7):5069-5072.
36. Kruskal JB. Multidimensional scaling by optimizing goodness of fit to a nonmetric hypothesis. *Psychometrika.* 1964;29(1):1-27.
37. Mielke Jr PW, Berry KJ, Johnson ES. Multi-response permutation procedures for a priori classifications. *Communications in Statistics-Theory and Methods.* 1976;5(14):1409-1424.
38. Oksanen J, Blanchet FG, Friendly M, et al. *vegan: Community Ecology Package.* 2018.
39. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biology.* 2014;15(12):550.
40. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). 2010;4.

41. Mizuki Nishino M, MPH. Tumor Response Assessment for Precision Cancer Therapy: Response Evaluation on Criteria in Solid Tumors and Beyond. *American Society of Clinical Oncology Educational Book.* 2018;38:1019-1029.
42. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
43. Muggeo VM. Estimating regression models with unknown break-points. *Stat Med.* 2003;22(19):3055-3071.
44. Muggeo VM. Segmented: An R Package to Fit Regression Models With Broken-Line Relationships. *R News.* 2008;8(1):20-25.
45. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol.* 2013;14(10).
46. Hochberg YaT, A.C. (1987). Multiple Comparison Procedures. Wiley, New York.
47. Smyth G, ed *Limma: linear models for microarray data.* New York: Springer; 2005. Gentleman RVC DS, Irizarry R, Huber W, ed. Bioinformatics and Computational Biology Solutions using R and Bioconductor.
48. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B (Methodological).* 1995;57(1):289-300.