Protocol #: LCI-LUN-NSC-SBRT-001

TITLE: PHASE II PROSPECTIVE TRIAL OF PRIMARY LUNG TUMOR STEREOTACTIC BODY RADIATION THERAPY FOLLOWED BY CONCURRENT MEDIASTINAL CHEMORADIATION AND ADJUVANT IMMUNOTHERAPY FOR LOCALLY-ADVANCED NON-SMALL CELL LUNG CANCER

LAY TITLE: USE OF HIGH DOSE RADIATION FOLLOWED BY CHEMOTHERAPY AND RADIATION AND ADJUVANT IMMUNOTHERAPY TO TREAT LOCALLY ADVANCED NON SMALL CELL LUNG CANCER

Coordinating Center:
Levine Cancer Institute
1021 Morehead Medical Drive
Charlotte, NC 28204

Sponsor-Investigator:
John H. Heinzerling, MD
Levine Cancer Institute
1021 Morehead Medical Drive
Charlotte, NC 28204
Phone: (704) 403-1577
Email: John.Heinzerling@atriumhealth.org

Statistician:
James Symanowski, Ph.D.
Levine Cancer Institute
Department of Cancer Biostatistics
1021 Morehead Medical Dr
Charlotte, NC 28204
Telephone: (980) 442-2371
Email: James.Symanowski@atriumhealth.org

Myra Robinson, MSPH
Levine Cancer Institute
Department of Cancer Biostatistics
1021 Morehead Medical Dr
Charlotte, NC 28204
Telephone: (980) 442-2390
Email: Myra.Robinson@atriumhealth.org

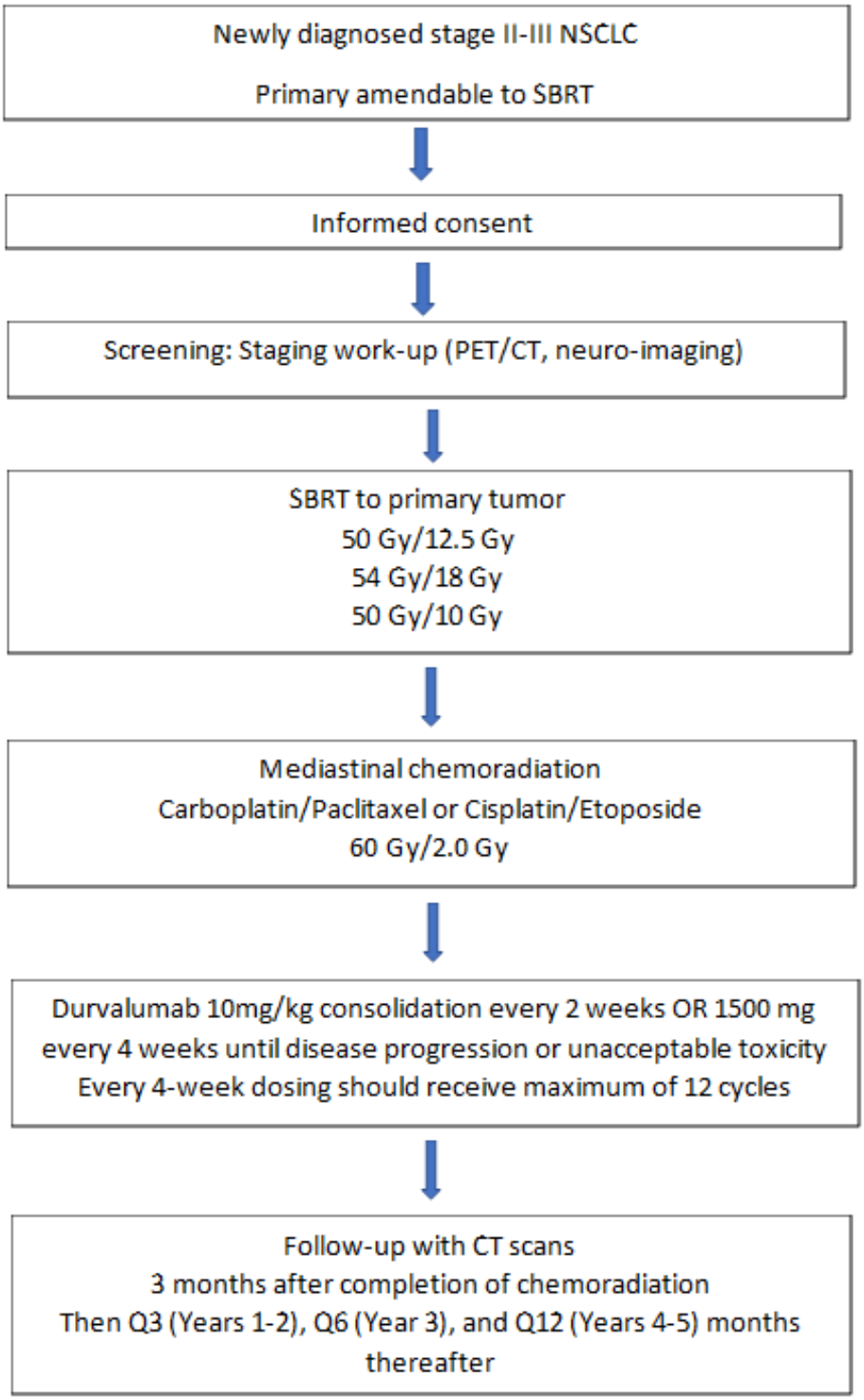
The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Original Phase II / Version 7 / Date 03/16/2023

PROTOCOL SUMMARY

A. Study Title	Phase II Prospective Trial of Primary Lung Stereotactic Body Radiation Therapy Followed by Concurrent Mediastinal Chemoradiation and Adjuvant Immunotherapy for Locally-advanced Non-small Cell Lung Cancer
B. Indication	Lung Cancer, first line treatment
C. Clinical Phase	II
D. Summary of Rationale	A challenge in the treatment of locally-advanced NSCLC is the synergistic toxicity of chemotherapy and radiation therapy when administered concurrently. This is particularly true when treating a non-centrally located primary tumor and associated nodal metastasis, which often exposes the lung to considerable incidental radiotherapy doses. Our hypothesis is that initial treatment of the primary tumor with SBRT followed by concurrent chemotherapy and mediastinal radiation therapy will improve progression-free survival in subjects with locally-advanced NSCLC by improving the primary tumor control, which can allow also for an improvement in overall survival. We also hypothesize that this treatment regimen will be well-tolerated and associated with lower rates of radiation pneumonitis compared with conventional primary tumor and mediastinal concurrent chemoradiation.
E. Study Objectives	To determine the one-year progression-free survival rate, progression-free survival, overall survival, and toxicity of subjects with locally-advanced non-small cell lung cancer treated with stereotactic body radiation therapy followed by concurrent mediastinal chemoradiation.
F. Sample Size	60 PFS1 evaluable subjects (section 12.3)
G. Inclusion/ Exclusion	• Newly diagnosed stage II or III non-small cell lung cancer • Primary tumor ≤ 7cm that is peripheral or at least 2 cm away from involved nodal disease and amenable to SBRT • Candidate for definitive chemoradiation based on clinical and laboratory evaluation
H. Dosage/ Dosage Form, Route, And Dose Regimen	SBRT 50-54 Gy in 3-5 fractions, Mediastinal Irradiation to 60 Gy in 2.0 Gy fractions with concurrent chemo radiation +adjuvant immunotherapy
I. Statistical Analysis	This study will enroll 60 PFS1 evaluable subjects and the frequency and proportion of subjects alive and progression free after 1-year will be calculated, along with a 95% Clopper-Pearson confidence interval. A one-sided test of proportions, with $\alpha = 0.10$, will be carried out testing the null hypothesis that the 1-year progression free survival probability is less than 60%.

SCHEMA


Newly diagnosed stage II-III NSCLC
Primary amendable to SBRT
Informed consent
Screening: Staging work-up (PET/CT, neuro-imaging)
SBRT to primary tumor
50 Gy/12.5 Gy
54 Gy/18 Gy
50 Gy/10 Gy
Mediastinal chemoradiation
Carboplatin/Paclitaxel or Cisplatin/Etoposide
60 Gy/2.0 Gy
Durvalumab 10mg/kg consolidation every 2 weeks OR 1500 mg every 4 weeks until disease progression or unacceptable toxicity
Every 4-week dosing should receive maximum of 12 cycles
Follow-up with CT scans
3 months after completion of chemoradiation
Then Q3 (Years 1-2), Q6 (Year 3), and Q12 (Years 4-5) months thereafter

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
CR	Complete Response
CRF	Case Report Form
CT	Computerized Tomography
CTV	Clinical Target Volume
DLCO	Diffusing Lung Capacity for Carbon Monoxide
DSMC	Data and Safety Monitoring Committee
EC	Ethics Committee
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life core questionnaire
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer quality of life Lung cancer module
FEV1	Forced Expiratory Volume in 1 second
Gy	Gray
GTV	Gross Tumor Volume
ICF	Informed Consent Form
IGTV	Internal Gross Tumor Volume
IRB	Institutional Review Board
MDASI-LC	M.D. Anderson Symptom Inventory-Lung Cancer
NSCLC	Non-Small Cell Lung Cancer
OAR	Organ-At-Risk
OS	Overall Survival
PD	Progressive Disease
PET/CT	Positron Emission Tomography/Computed Tomography
PFS	Progression-Free Survival
PHI	Protected Health Information
PI	Principal Investigator

PR	Partial Response
PTV	Planning Target Volume
QOL	Quality of Life
RBE	Relative Biological Effectiveness
RECIST	Revised Reponse Evaluation Criteria in Solid Tumors
SBRT	Stereotactic Body Radiation Therapy
SD	Stable Disease
S-I	Sponsor-Investigator

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1. OBJECTIVES

1.1. Primary Objective

To assess the efficacy of a treatment regimen which involves Stereotactic Body Radiation Therapy (SBRT) delivered to the primary tumor followed by concurrent mediastinal chemoradiation by evaluating the proportion of subjects with locally-advanced non-small cell lung cancer (NSCLC) stage II/III who are alive and progression free at 12 months, and to compare to relevant historical controls.

1.2. Secondary Objectives

Secondary objectives will be to evaluate the treatment regimen based on the following:

a. Progression free survival
b. Overall survival
c. Radiologic clinical complete response rate following completion of therapy
d. Objective response rate as defined by RECIST v 1.1
e. Local and locoregional control
f. Patterns of failure (primary, locoregional, or distant)
g. Quality of life

1.3. Safety Objectives

The safety objectives are to assess complications and adverse events that occur throughout the treatment regimen. Specific adverse events of interest will be the following:

a. Rate of grade 2+ radiation pneumonitis
b. Rate of grade 3+ pulmonary events

1.4. Exploratory Objectives

Exploratory objectives include:

- Differential expression of cytokines and chemokines associated with the radiation therapy will be determined and associations with radiation-induced lung toxicity will be evaluated.
- Quantify and categorize lung texture changes using lung density analysis (LDA) and lung texture analysis (LTA) algorithms and quantify changes over time up to 24 months after radiation treatment.
- Evaluate dosimetric causes of lung texture changes and small airway collapse utilizing post treatment CT scans
- Correlate selected outcomes (including toxicity and PFT changes) with lung changes as quantified by lung texture analysis software.

2. BACKGROUND AND RATIONALE

2.1. Study Disease

Outcomes for non-small cell lung cancer (NSCLC) patients who present with locally-advanced disease remain poor, with 5-year overall survival of 15%[1] and primary tumor local control of only 51%[2] following concurrent chemoradiation when radiotherapy is delivered in conventional fractionation in 1.8-2.0 Gy per fraction.

2.2. SBRT in the treatment of lung cancer

A newer approach that has been extremely effective in controlling lung primary tumors is stereotactic body radiation therapy (SBRT). SBRT delivers an ultra-high dose per fraction (typically >8-10 Gy per fraction) of radiation to a target. By delivering ablative radiotherapy doses, SBRT allows for maximizing cell-killing effect of tumor, likely due to delivery of higher biological equivalent doses of radiotherapy than achievable with conventionally fractionated irradiation. SBRT also minimizes dose received by surrounding organs due to a rapid dose falloff gradient encompassing the tumor.[3] In prospective phase II studies, SBRT has been associated with local control rates of over 90% for patients with medically inoperable stage I NSCLC.[6] SBRT has also improved survival for medically inoperable patients with stage I NSCLC compared with conventionally fractionated radiotherapy.[3] However, SBRT has not routinely been incorporated into the treatment paradigm for unresectable locally-advanced NSCLC due to concerns about the potential toxicity of high doses per radiotherapy fraction to central structures when treating mediastinal lymph node metastases.

2.3. Background

Studies have shown that the principle site of intrathoracic failure is at the primary tumor and isolated mediastinal nodal failures are extremely rare.[7,2] Another challenge in the treatment of locally-advanced NSCLC is the synergistic toxicity of chemotherapy and radiation therapy when administered concurrently. This is particularly true when treating a non-centrally located primary tumor and associated nodal metastasis, which often expose the lung to considerable incidental radiotherapy doses. The risk of radiation pneumonitis is highest when a large volume of lung is being irradiated and when concurrent chemotherapy is administered, and this subacute toxicity can be fatal.[8,7] In fact, the rates of radiation pneumonitis with conventionally fractionated concurrent chemoradiation for locally-advanced NSCLC are approximately 30%[8] , compared with approximately 3% with SBRT for stage I NSCLC. [20]

Acute radiation pneumonitis is thought to be largely inflammatory and exudative in nature, with cytokine and inflammatory marker changes evident during and at the time of radiation therapy completion. Additionally, acute radiation pneumonitis is highly correlated with the subsequent development of late pulmonary fibrosis[4], which limits patient lung function and is the primary factor accounting for up to 47% of NSCLC patients reporting a decline in overall quality of life by 12 months after radiation therapy.[5] Although cytokine changes are evident during treatment, radiation-induced pulmonary fibrosis clinically occurs months to years after radiation therapy, when the lung tissue enters a fibrotic state in which inflammatory cell concentrations decrease and a marked thickening of alveolar walls occurs due to collagen deposition.

Although it is well known that external beam radiation therapy induces both acute and late

pulmonary changes in normal tissues, little is known regarding which cytokines and chemokines are important regulators in the development of acute pneumonitis or chronic pulmonary fibrosis. Even less data is available regarding the effects that radiation therapy has on such cytokines and chemokines. In a review of current literature, the over- or under- expression of a number of chemokines, cytokines, and inflammatory markers have been implicated in the pathogenesis of radiation pneumonitis and radiation-induced pulmonary fibrosis for both conventionally fractionated radiation therapy and SBRT. These include IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, MCP-1α, IFN-γ, MIP-1α, TNF-α, TGF-β, Eotaxin, GM-CSF, and CXCL-1. Adjuvant immunotherapy with durvalumab recently showed benefit after chemoradiation in stage III NSCLC and has become standard treatment after chemoradiation for unresectable stage III NSCLC.[19] Immunotherapy has known synergistic effects with radiation and immune cell killing often indicated by cytokine release. Little data exists regarding which cytokines and chemokines may regulate this cell kill process in relation to timing with radiation and effects of high dose radiation on immune associated tumor response.

2.4. Study Rationale

Our hypothesis is that initial treatment of the primary tumor with SBRT followed by concurrent chemotherapy and mediastinal radiation therapy will improve progression-free survival in subjects with locally-advanced NSCLC by improving the primary tumor control, which can allow also for an improvement in overall survival.

We also hypothesize that this treatment regimen will be well-tolerated and associated with lower rates of radiation pneumonitis compared with conventional primary tumor and mediastinal concurrent chemoradiation.

2.4.1. Rationale for Correlatives

We hypothesize that IL-1α and IL-6 will be overexpressed during radiation therapy, whereas TGF-β and IL-13 will be overexpressed following radiation therapy completion, and that cytokine and chemokine change will be more pronounced during conventionally fractionated radiation therapy.

3. SUBJECT SELECTION

3.1. Accrual

A total of 60 PFS1 evaluable subjects (section 12.3) will be enrolled to this study over approximately 4 years.

Subjects will be recruited from the Levine Cancer Institute (LCI) and possibly other participating sites.

Both men and women of all races and ethnic groups are eligible for this trial. We would expect about 50% of the subject accrual to include women and 20% of the subject accrual to be minority subjects based on our current studied population and patient demographics.

3.2. Inclusion Criteria

Subjects must meet all the following criteria:

a. Histologic or cytologic documentation of NSCLC (all histologies allowed)
b. Stage II or III disease (AJCC 7th Edition) based on imaging as required during screening:
    i. Stage II disease includes only subjects with medically inoperable N1 disease otherwise meeting eligibility criteria
    ii. Primary tumor ≤ 7 cm
c. Subjects with non-malignant pleural effusion identified on CT scan are eligible provided the effusion is not known or demonstrated to be an exudative effusion.
    i. If a pleural effusion is present, the following criteria must be met to exclude malignant involvement:
        1. A pleuracentesis is required if pleural fluid is present and visible on both CT scan and chest x-ray. Pleural fluid cytology must be negative for malignancy.
        2. Effusions that are minimal and too small for pleuracentesis as determined by the investigator will be eligible for enrollment.
d. FEV1 ≥ 1.0 Liter or ≥ 40% predicted with or without bronchodilator within six months prior to initiation of study treatment.
    i. Subjects who meet the criterion above without O_2, but who need acute (started within 10 days prior to enrollment) supplemental oxygen due to tumor-caused obstruction/hypoxia are eligible, provided the amount of the O_2 needed has been stable.
e. Age ≥18 years.
f. ECOG performance status ≤ 2
g. Subjects must have normal organ and marrow function as defined below:
    i. Leukocytes ≥4,000/mcL
    ii. Absolute neutrophil count ≥1,500/mcL
    iii. Platelets ≥100,000/mcL
    iv. Total bilirubin ≤1.5 times the upper limit of normal
    v. Creatinine clearance > 25 mL/min/1.73 m2
h. Negative serum or urine pregnancy test prior to enrollment for women of childbearing age and potential
i. The effects of radiation on the developing human fetus are not well described and animal studies have shown that durvalumab can cause fetal harm when administered to a pregnant woman. For these reasons, women of child-bearing potential and non-sterilized men who are sexually active with a woman of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study treatment. Women of child-bearing potential must agree to use contraception for 3 months after the last dose of durvalumab. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
j. Must be considered a candidate for durvalumab, per the treating

investigator

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

3.3. Exclusion Criteria

Subjects must not meet any of the following criteria.

a. Subjects who have had prior systemic therapy for lung cancer
b. Subjects who have had prior radiation to the region of the chest that would result in overlap of radiation therapy fields and determined by the treating physician to impede the treatment of the study malignancy.
c. Subjects who are actively being treated on any other interventional research study.
d. Prior invasive malignancy unless disease free for a minimum of 3 years from enrollment. However, non-melanoma skin cancer, low risk prostate cancer, well differentiated thyroid cancers, in situ carcinomas of the breast, oral cavity, cervix, and other organs, and tumors (regardless of invasive or non-invasive) that are not thought to impact the life expectancy of the subject according to the treating investigator is permissible.
e. Centrally located primary tumor < 2 cm from involved nodal disease which would result in significant overlap of radiation dose. Centrally located is defined as within or touching the zone of the proximal bronchial tree, which is a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi).

4. INVESTIGATIONAL PLAN

4.1. Study Milestones

Enrollment date: the date of first SBRT dose

Treatment Discontinuation date: the date the investigator decides to discontinue subject from all study treatment (defined as SBRT, concurrent mediastinal chemoradiation, or durvalumab)

4.2. Overall Study Design

This is a single-arm, single-stage Phase II study designed to evaluate the 1-year PFS rate in subjects with locally-advanced NSCLC (stage II/III) (Study Schema). A total of 60 PFS1 evaluable subjects (section 12.3) will be enrolled.

Data from this study will be collected on electronic case report forms (eCRFs) and stored in the study database.

4.3. Registration and Enrollment

No protocol related assessments may be performed prior to obtaining informed consent.

Following informed consent, subjects will be registered and assigned a Sequence Number. The Sequence Number will be a four-digit number sequentially assigned to the subject.

A subject who, for any reason (i.e. failure to satisfy the eligibility criteria or withdraws consent), terminates their participation in the study before receiving first dose of SBRT is regarded as a "screen failure." Screen failures will not be included as enrolled subjects or count towards sample size requirements.

4.4. Pre-Treatment

Visit 1: Subject undergoes history and physical per standard of care and is identified for study by the treating physician. Pathologic and radiologic review of available studies are performed per standard of care and at the discretion of the treating physician. Informed consent is obtained and necessary tests ordered. Please see Study Calendar, Section 5, for details regarding baseline condition, pretreatment scans, labs, smoking history and blood collection.

Visit 2: Simulation/planning session for SBRT.

4.5. Study Treatment

Visit 3: Blood sample for research obtained prior to starting SBRT. If not already completed, Quality of Life (QOL) Evaluation should be obtained prior to SBRT. Subject begins SBRT. Treatment course is 3 to 5 total visits over 1-2 weeks. Blood sample for research obtained during the course of SBRT. For acceptable time frame refer to Section 4.6 Biospecimen Collection.

Visit 4: Subject undergoes simulation/planning session for mediastinal irradiation.

Visit 5: Subject begins concurrent chemoradiation. Treatment course is 30-37 visits over 6-8 weeks. QOL Evaluation after completion of SBRT but prior to initiation of concurrent chemoradiation. See Section 4.4 for details regarding the QOL time-point. CBC with differential and chemistries checked as per standard of care. Blood sample for research obtained during the course of concurrent chemoradiation. For acceptable time frame refer to Section 4.6 Biospecimen Collection. Toxicity assessment done weekly.

Visit 6: Subject begins durvalumab after completion of concurrent chemoradiation. Subjects will receive durvalumab per Section 6.3.7. Study procedures to be performed per Section 5.

4.6 Quality of Life (QOL) Assessments:

QOL assessments utilizing the M.D. Anderson Symptom Inventory-Lung Cancer (MDASI-LC), European Organization for Research and Treatment of Cancer quality of life core questionnaire Version 3 (EORTC QLQ-C30) and European Organization for Research and Treatment of Cancer quality of life Lung cancer module (EORTC QLQ-LC13) lung surveys will be obtained at six time points: prior to the initiation of SBRT, after the completion of SBRT but prior to the initiation of concurrent mediastinal chemoradiation, one month after the completion of concurrent

mediastinal chemoradiation, and at 3, 6, and 12 months after the last treatment of concurrent mediastinal chemoradiation. Note: The "prior to the initiation of concurrent mediastinal chemoradiation" QOL time-point should ideally be done prior to initiation of concurrent mediastinal chemoradiation. However, it is acceptable to administer the QOL within the first 3 days of initiation of concurrent mediastinal chemoradiation. In the event that radiation and chemotherapy are not started on the same day, the QOL should be administered ideally prior to the start of the first modality (i.e. radiation or chemotherapy) but it is acceptable to administer within 3 days of the start of the first modality initiated. QOL questionnaires may be administered in the clinic or over the phone.

4.7 Biospecimen Collection

Biospecimens will be collected as described below. The results of any analyses will not be included in subjects' clinical medical record. Samples will be labeled with a study specific Sequence Number without the use of personal health information (PHI). Blood samples will be obtained at the time of clinical blood collection for standard of care labs whenever possible to minimize additional discomfort to subjects.

4.7.1 Blood Samples for Correlatives

Blood samples will be obtained exclusively for research purposes at the time points specified below. Analyses will include inflammatory marker analysis to determine which cytokines and chemokines are differentially expressed with radiation therapy and may be associated with radiation-induced lung toxicity. Additional blood samples will be collected and stored for potential future analysis.

Inflammatory Marker Analysis: Blood samples (two 10-ml EDTA tubes) will be processed and stored at -80°C for analyses.

1. Prior to the initiation of SBRT
2. During the course of SBRT (preferentially on the final day of SBRT but within the range of the day of the fraction before the final fraction of SBRT and 5 days after completing SBRT):
3. During the course of concurrent mediastinal chemoradiation (preferentially in the final week of conventionally fractionated radiation therapy but within the range of two weeks before the final fraction of conventionally fractionated radiation therapy and one week after completing conventionally fractionated radiation therapy)
4. Two–five weeks after the first dose of durvalumab (just prior to the 2nd dose of durvalumab). Sample not required for subjects who have already received the second dose of durvalumab at the time of the amendment approval or for subjects who do not ultimately initiate durvalumab for whatever reason.

Additional blood for potential future analysis will be collected as follows:

- Two 10 ml EDTA tubes will be collected, processed and stored at -80°C
- Two 8.5 ml CPT tubes will be collected for blood cell separation and storage

1. Prior to the initiation of SBRT
2. During the course of concurrent mediastinal chemoradiation (in the final week of conventionally fractionated radiation therapy but within the range of two weeks before the final fraction of conventionally fractionated radiation therapy and one week after completing conventionally fractionated radiation therapy)
3. Two-five weeks after first dose of durvalumab (just prior to the 2nd dose of durvalumab). Sample not required for subjects who have already received the second dose of durvalumab at the time of the amendment approval or for subjects who do not ultimately initiate durvalumab for whatever reason.

Blood samples stored for future use will be stored with a study-specific Sequence Number without the use of personal health information (PHI).

4.7.2 Archived Tumor Tissue for Correlatives

Archived tumor tissue samples for potential future analysis will be collected (if available) for each enrolled subject.

The best available tissue block (preferably > 20% tumor content; equivalent of 4-6 14-gauge cores or ~ 5x5 mm of tissue) will be obtained and sent to the Atrium Health Biospecimen Repository. If a block is not able to be sent, the site may send 20 unstained slides (4 to 6 microns each).

4.8 End of Concurrent Mediastinal Chemoradiation

Subjects will have toxicity assessment and QOL evaluation approximately 30 days after the last treatment of concurrent mediastinal chemoradiation. Subjects will be followed for a minimum of 12 months after the last treatment of concurrent mediastinal chemoradiation to determine safety and acute toxicity. SAEs will be reportable for up to 90 days after the last dose of durvalumab (subjects who receive durvalumab) per Section 10.8.

4.9 Adjuvant Immunotherapy

Subjects will receive adjuvant durvalumab per Section 6.3.7 after completion of concurrent mediastinal chemoradiation.

4.10 Post-Concurrent Mediastinal Chemoradiation Assessments

All subjects will be evaluated approximately 3 months from the last treatment of concurrent mediastinal chemoradiation by the treating radiation oncologist, referring physician, or physician extender. Thereafter, subjects will be evaluated approximately every 3 months for the remainder of Year 1 and for Year 2, approximately every 6 months for Year 3, and approximately annually for Years 4-5 from the last treatment of concurrent mediastinal chemoradiation per study procedures defined in Section 5 are met. Some of these assessments will occur concurrently with adjuvant durvalumab administration. If subjects are no longer in the local area or otherwise not able to return for assessment, communications such as a telephone call or letter will be sent as follow up. Assessment of the disease by imaging for subjects who have not yet had documented disease progression will be performed at intervals as described in Section 7. Additionally, effort will be

made to continue to collect imaging assessments done per standard of care after disease progression in order to inform local/regional/distant control endpoints (described in Sections 12.2.6 – 12.2.9). Collection of imaging assessment data is not required after local/regional/distant progression, subsequent anti-cancer therapy is initiated or after the 60-month follow-up visit.

4.11 Active Follow-up

Subjects who discontinue study treatment for any reason, including progression, will move into Active Follow-up and continue completion of the Post-Concurrent Mediastinal Chemoradiation assessments as defined in the Study Calendar in Section 5 and the section above (4.10) up until completion of the 60-month follow-up visit. Post-Concurrent Mediastinal Chemoradiation assessments are required for all subjects at a minimum of through the 12-month follow-up visit. Subjects who have met endpoints for local/regional/distant control (e.g. disease progression locally, regionally and distally) or started subsequent anti-cancer therapy prior to the 60-month follow-up visit will move into Long-Term Follow-up per Section 4.12.

4.12 Long-term Follow-up

Subjects who have completed at a minimum of through the 12 month Active Follow-up visit with subsequent disease progression (locally, regionally and distally) or initiation of subsequent anti-cancer therapy **or** completion of the 60-month follow-up visit will move into Long-Term Follow-up.

Subjects in Long-Term Follow-up will be contacted approximately every 12 months for survival until the criteria for the final analysis is met. Phone contact is acceptable.

4.13 Subject Withdrawal and Off-Study

Subjects may withdraw consent at any time for any reason or be removed from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if for safety reasons or other reasons per investigator discretion.

In this trial, a subject may discontinue from study treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent for study participation.

A subject will be discontinued from the trial for any of the following reasons:

- The subject withdraws consent for participation on the study
- The subject is lost to follow-up
- Investigator’s decision to withdraw the subject from study
- Noncompliance with study treatment or procedure requirements per investigator’s discretion
- Subject death

In all cases, the reason for withdrawal and/or subject going Off Study must be documented in the subject's medical record and/or research record and recorded in the CTMS.

Subjects that are Off Study will not participate in any study related procedures, including data collection.

5. STUDY CALENDAR

Study Procedures	Screening[j]	During SBRT	During Concurrent Mediastinal Chemoradiation	One Month After Concurrent Mediastinal Chemoradiation[s]	Adjuvant Immunotherapy/ Post- Concurrent Mediastinal Chemoradiation Assessments	Active Follow-Up[t,bb]	Long-term Follow-Up [cc]
History and Physical Exam [a,r,dd]	X	X[n]	X[b]	X	X[z,aa]	X[aa]	
Performance Status Assessment [r,dd]	X	X[n]	X[b]	X	X[z,aa]	X[aa]	
PET/CT	X[k]				X 3 months after completion of concurrent mediastinal chemoradiation timepoint only		
CT Chest [d,q]	X[k]				X[w]		
Chest X-Ray	X[o]						
CT Abdomen/Pelvis [c,d]	X [k]				X Only if unable to obtain PET/CT at the 3 months after completion of concurrent mediastinal chemoradiation timepoint only		
Neuroimaging (MRI brain or CT head)[d]	X[k]						
Documentation of Biopsy of Primary Tumor and/or Nodes	X[e]						
CBC with differential	X		X[m]		X[z]		
Electrolytes	X[v]		X[m]		X[z]		
LFTs	X[v]				X[z]		
TSH, free T4, amylase, lipase, LDH and UA					X[z]		

Study Procedures	Screening[j]	During SBRT	During Concurrent Mediastinal Chemoradiation	One Month After Concurrent Mediastinal Chemoradiation[s]	Adjuvant Immunotherapy/ Post- Concurrent Mediastinal Chemoradiation Assessments	Active Follow-Up[t,bb]	Long-term Follow-Up [cc]
Pulmonary Function Testing [f]	X[l]				X[u]	X[u]	
Pregnancy Test [g]	X						
Toxicity Assessment [p]	X	X[n]	X [b]	X	X	X	
Quality of Life Assessment [h]	X	X		X	X	X	
Inflammatory Marker Analysis [i]	X	X	X		X 2-5 weeks after first durvalumab only		
Blood Correlatives for Potential Future Research [x]	X		X		X 2-5 weeks after first durvalumab only		
Archived Tumor Tissue[y]	X						
Survival Status						X	X

a: Includes vital signs and weight. Smoking history at screening visit only.

b: Weekly (treatment visits)

c: only required if unable to obtain PET/CT

d: should be performed with IV contrast unless approved by the Sponsor-Investigator

e: documentation of prior pathology of primary tumor and/or nodes is required

f: to include FEV1 and DLCO

g: serum or urine; within 14 days of enrollment for women of child bearing potential

h: QOL using the MDASI-LC, EORTC QLQ-C30 and EORTC QLQ-LC13 lung surveys will be obtained at six time points: 1) within 30 days prior to the initiation of SBRT, 2) after completion of SBRT but within 7 days prior to initiation of concurrent mediastinal chemoradiation (see Section 4.4 for details regarding the QOL time-point), 3) at One Month After Concurrent Mediastinal Chemoradiation Visit (± 7 days), 4) at 3 month follow-up (±60 days), 5) at 6 month follow-up (±60 days), and 6) at 12 month follow-up (±60 days). QOL may be administered in the clinic or over the phone.

i: Blood samples [(2) 10 ml EDTA tubes] for inflammatory marker analysis will be obtained at the following time-points: 1) prior to initiation of SBRT, 2) during SBRT (preferentially on the final day of SBRT but within the range of the day of the fraction before the final fraction of SBRT and 5 days after completing SBRT), and 3) during the course of concurrent mediastinal chemoradiation (preferentially in the final week of conventionally fractionated radiation therapy but within the range of two weeks before the final fraction of conventionally fractionated radiation therapy and one week after the last treatment of conventionally fractionated radiation therapy), 4) 2-5 weeks after the first dose of durvalumab (just prior to the 2nd dose of durvalumab); sample not required for subjects who have already received the second dose of durvalumab at the time of the amendment or for subjects who do not ultimately initiate

durvalumab for whatever reason.See Section 4.7.1.

j: Screening assessments to be performed within 30 days of enrollment unless otherwise specified

k: Within 90 days prior to enrollment

l: Within 6 months prior to enrollment

m: As clinically indicated as determined by the treating investigator

n. Any time prior to and during any of the SBRT treatments including the day of the last treatment

o. In subjects with a pleural effusion visible on CT scan, a chest x-ray is required to confirm that a pleuracentesis is not required, see Section 3.2 d

p. Baseline pre-existing symptoms and conditions present at the time of informed consent and prior to the first dose of study treatment should be documented. Toxicity assessment should start at study treatment initiation and continue up to 12 months after the last dose of concurrent mediastinal chemoradiation. **Collection requirements are as follows**: All AEs from initiation of study treatment until 90 days after last dose of protocol-directed durvalumab. After this time period, if less than 12 months has elapsed since last dose of concurrent mediastinal chemoradiation, AESIs (as defined in Section 10.3) until 12 months after last dose of concurrent mediastinal chemoradiation. For subjects who do not initiate protocol-directed durvalumab, AESI's starting on the date the decision is made that durvalumab will not be initiated through 12 months after last dose of concurrent mediastinal chemoradiation.

q. Imaging required at the following time-points: **3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48, 60 mos (+/- 60 days)** from completion of concurrent mediastinal chemoradiation. Imaging schedule only required for subjects who have not yet had disease progression (local, regional and distant) or started subsequent anti-cancer therapy. Additionally, effort will be made to continue to collect imaging assessments done per standard of care after disease progression in order to inform local/regional/distant control endpoints (described in Sections 12.2.6 – 12.2.9). Collection of imaging assessment data is not required after subsequent anti-cancer therapy is initiated.

r. Not required after 12 months of follow-up in subjects who have documented disease progression

s. Required for all subjects; may occur during adjuvant immunotherapy

t. All follow-up time points and procedures are timed from last treatment of concurrent mediastinal chemoradiation (+/- 60 days). If a current follow-up visit overlaps with the next follow-up time-point (within the 60 day window), one visit can be used for both time-points. This is allowed as long as all required assessments for both time-points are completed (e.g. if the 9-month visit occurs at 10 ½ months from last concurrent chemoradiation, all procedures required at the 12 month visit are required at this visit)

u 6- and 12-month follow-up visits only (+/- 60 days); additional time points as clinically indicated

v. At screening, a comprehensive metabolic panel (CMP) will be acceptable to meet electrolytes and LFTs requirement

w. Chest CT at 3 months not required if a post-mediastinal chemoradiation completion CT was performed prior to the 3-month follow-up time-point as part of standard of care

x. Correlative blood samples will be obtained for potential future analysis [(2) 10 ml EDTA tubes] and (2) 8.5 ml CPT tubes] at the following time-points: 1) prior to initiation of SBRT 2) during the course of concurrent mediastinal chemoradiation (preferentially in the final week of conventionally fractionated radiation therapy but within the range of two weeks before the final fraction of conventionally fractionated radiation therapy and one week after the last treatment of conventionally fractionated radiation therapy and 3) 2-5 weeks after the first dose of durvalumab (just prior to the 2nd dose of durvalumab); sample not required for subjects who have already received the second dose of durvalumab at the time of the amendment or for subjects who do not ultimately initiate durvalumab for whatever reason.. See Section 4.7.1.

y. Submit archived tumor specimen of tumor, if available. See Section 4.7.2. Tissue should not be submitted until the subject has been enrolled into the study.

z. All safety assessments for adjuvant durvalumab administration to be performed per treating investigator

aa. History and physical exam and performance status should be performed at the following time-points after completion of concurrent

mediastinal chemoradiation: **3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48, 60 mos** (±60 days). Subjects who have disease progression will be required to have these assessments performed up through the 12-month time-point. SAEs will be reported in subjects who have initiated durvalumab per Section 10.8.

bb**.** Subjects who discontinue study treatment for any reason, including progression, will move into Active Follow-up and continue completion of the Post-Concurrent Mediastinal Chemoradiation assessments until completion of the 60-month follow-up visit. Post-Concurent Mediastinal Chemoradiation assessments are required for a minimum of 12 months after last treatment of conconcurrent mediastinal chemoradiation. Subjects who have met end-points for local/regional/distant control (i.e. disease progression locally, regionally and distally) or have started subsequent anti-cancer therapy after 12 months of Active Follow-up but prior to the 60-month follow-up visit will move into Long-Term Follow-up per Section 4.1.2

cc. Subjects will move into Long-term Follow-up for either of the following: Completion of at minimum the 12-month Active Follow-up visit with subsequent disease progression (local, regional and distant) or initiation of subsequent anti-cancer therapy **or** completion of the 60 month Active Follow-up assessment (in absence of disease progression or initiation of subsequent anti-cancer therapy). Subjects will be contacted approximately every 12 months for survival until the criteria for the final analysis are met. Phone contact is acceptable.

dd. Office visits after enrollment may be performed virtually during the COVID-19 pandemic, per investigator discretion

6. TREATMENT PLAN

6.1 Radiation Therapy

6.1.1 Treatment Planning, Imaging and Localization Requirements

All subjects will be immobilized in a custom designed device in the appropriate position.

Radiation treatment planning CT or PET/CT scans (contrast preferred) will be required to define gross target volume (GTV) and clinical target volume (CTV). The treatment planning CT or PET/CT scan should be acquired with the subject in the same position and using the same immobilization device as for treatment. All tissues to be irradiated must be included in the CT scan. Planning CT scan will be done at ≤3 mm intervals from encompassing the region of interest with sufficient margin for treatment planning. Four dimensional CT is required for linac-based treatment with SBRT t account for tumor motion. Additional treatment planning scans may be performed during the course of radiotherapy as necessary. Imaging, including PET/CT, may be fused with the planning CT images to better visualize the anatomy when indicated.

Primary tumors will be classified as either central or peripheral for the purposes of SBRT treatment planning. Tumor within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi) will be classified as central. Central primary tumors must be at least 2 cm from involved nodal disease. All other primary tumors will be classified as peripheral and do not have a specified distance from involved nodal disease.

6.1.2 ***Target Contouring***

SBRT:

Primary Gross Tumor Volume (GTV_Primary) is defined as gross primary disease determined from imaging, clinical information, and/or endoscopic findings. The GTV will consist of the primary parenchymal tumor as visualized on CT and PET.

Primary Internal Gross Tumor Volume (IGTV_Primary): This will consist of the GTV_Primary plus an additional margin based on the 4D-CT image sets to account for tumor motion.

Clinical Target Volume (CTV_Primary): A margin of up to 5 mm will be added to the IGTV_Primary to account for microscopic extension of tumor at the discretion of the treating radiation oncologist. The addition of a CTV is encouraged for all primary tumors >3 cm. For tumors greater than 3 cm up to 5 cm, a 3 mm expansion is encouraged. For tumors greater than 5 cm, a 5 mm expansion is encouraged. All CTV expansions can be asymmetric and should not extend into uninvolved organs.

Primary Planning Target Volume (PTV_Primary): A 5 mm margin will be added to the CTV_Primary for setup error. In cases where a CTV expansion is not used, a 5 mm margin will be added directly to IGTV_Primary to create the PTV_Primary.

Mediastinal Radiotherapy:

Mediastinal Gross Tumor Volume (GTV_Med): This will consist of gross disease in the mediastinum, excluding the primary tumor, determined from imaging, clinical information, and/or endoscopic findings. The GTV will consist of the mediastinal disease as visualized on CT and PET scans, including any lymph node ≥ 1.5 cm in longest axis on CT scan or with an SUV of ≥ 3.0, consistent with abnormal on PET imaging.

<u>4DCT Planning</u>

Mediastinal Internal Gross Tumor Volume (IGTV_Med): This will consist of the GTV_Med plus an additional margin based on the 4D-CT image sets to account for tumor motion with respiration.

Mediastinal Clinical Target Volume (CTV_Med): A 5 mm margin without extending into uninvolved organs will be added to the IGTV_Med to account for microscopic extension of tumor. At the discretion of the treating radiation oncologist, the CTV_Med can be expanded beyond a 5 mm margin on the IGTV_Med to allow for the inclusion of regions of potential microscopic extension for the entire nodal level for any nodal station that has gross disease.

Mediastinal Planning Target Volume (PTV_Med): A 5 mm margin will be added to

the CTV_Med for setup error.

3D Planning

Mediastinal Clinical Target Volume (CTV_Med): A 5 mm margin without extending into uninvolved organs will be added to the GTV_Med to account for microscopic extension of tumor. At the discretion of the treating radiation oncologist, the CTV_Med can be expanded beyond a 5 mm margin on the GTV_Med to allow for the inclusion of regions of potential microscopic extension for the entire nodal level for any nodal station that has gross disease.

Mediastinal Planning Target Volume (PTV_Med): A 10 mm margin in the cranial-caudal direction and 8 mm margin in the radial circumferential direction will be added to the CTV_Med for setup error and to account for tumor motion with respiration.

6.1.3 ***Normal Structures***

SBRT:

The following normal structures will be contoured: lung (right and left to be contoured separately), spinal cord, esophagus, heart, brachial plexus, carina, great vessels, chest wall, ribs, trachea, skin, proximal bronchus, proximal bronchus + 2 cm.

Mediastinal Radiotherapy:

The following normal structures will be contoured: lung (right and left to be contoured separately), spinal cord, esophagus, heart, brachial plexus, carina.

6.1.4 ***Dose fractionation and Specification***

SBRT:

The prescription dose per fraction to the PTV_Primary will be 12.5 Gy/day to 50 Gy or 18 Gy/day to 54 Gy for peripheral tumors and 10 Gy/day to 50 Gy for central tumors. Subjects will be treated daily or every other day without a planned treatment break.

The primary tumor will be contoured for all subjects and the isocenter will be placed at the center of the primary tumor for all subjects.

Mediastinal Radiotherapy:

The prescription dose per fraction to the PTV_Med will be 2.0 Gy (RBE)/day to 60 Gy. Subjects will be treated daily, 5 days/week, without a planned treatment break.
The carina will be contoured for all subjects and the isocenter will be placed at

mid-carina for all subjects.

6.1.5 ***Treatment Planning***

Dose specifications:
Dose constraints for PTV_Primary:
At least 95% of the PTV will be encompassed by 100% of the prescription dose.

The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV $_{V100RX}$ = 95%) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (PTV $_{V90\%RX}$ > 99%).

Dose Constraints for PTV_Med:
At least 95% of the PTV will be encompassed by 95% of the prescription dose.

Normal tissue constraints:

Table 1 SBRT Maximum Dose Constraints

OAR	**3 Fractions**	**4 Fractions**	**5 fractions**
Spinal Cord	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	28 Gy (5.6 Gy/fx)
Esophagus	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	38 Gy (7.6 Gy/fx)
Brachial Plexus	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32.5Gy (6.5 Gy/fx)
Heart/Pericardium	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	38 Gy (7.6 Gy/fx)
Great Vessels	39 Gy (13 Gy/fx)	49 Gy (12.25 Gy/fx)	53 Gy (10.6 Gy/fx)
Trachea/Proximal Bronchi	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	50 Gy (10 Gy/fx)
Rib	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	57 Gy (11.4 Gy/fx)
Skin	30 Gy (10 Gy/fx)	36 Gy (9 Gy/fx)	38.5 Gy (7.7 Gy/fx
Stomach	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	35 Gy (7 Gy/fx)

*Rib dose in excess of the above constraints will be documented but is not a reason to necessitate subject withdrawal. In cases where the rib dose constraint will be exceeded, attempts should be made to keep the dose as low as achievable. For central tumors, every effort should be made to spare the contralateral wall of the adjacent organ at risk including the proximal bronchial tree, esophagus, or heart. Dose in excess of above constraints to those structures will be documented

but is not a reason to necessitate subject withdrawal.

Dose-volume histograms from the sum SBRT-Mediastinum plan should be performed for spinal cord, lungs, heart, and esophagus.

When assessing the composite plan of the primary tumor and of the mediastinum, the maximal spinal cord dose should not exceed 50 Gy (RBE) in 2 Gy/fraction equivalents. No more than 37% of the total lung volume minus GTV should receive greater than 20 Gy (RBE). The mean dose of the total lung volume minus GTV should be no greater than 20 Gy. No more than 50% of the total cardiac volume should receive greater than 40 Gy (RBE). The mean dose of the esophagus should be no greater than 34 Gy. All attempts should be made to minimize dose overlap of the SBRT course and the mediastinal course, particularly overlap of dose in the spinal cord, esophagus, brachial plexus, heart, great vessels, trachea, and proximal bronchus.

6.1.6 *Treatment Duration*

SBRT:

SBRT will be completed in 1-2 weeks.

Mediastinal Radiotherapy:

Concurrent mediastinal chemoradiation will in most instances be completed in under 8 weeks from the start of the course of chemoradiation. This may be extended if subjects require a break from treatment. Criteria for break would include any Grade 3 non-hematologic toxicity at Investigator discretion, Grade 4 hematologic toxicity at PI discretion, or Grade 4 non-hematologic toxicity.

6.1.7 *Equipment and Beam Delivery*

SBRT and Photons: A ≥ 6 MV photon beam will be used. 6 MV is preferred. IMRT is allowed and encouraged for mediastinal radiotherapy.

All treatments will be given with the subject in the appropriate immobilization device. Film or digital images will be taken prior to the initial treatment to verify the position of the subject and the aperture and as appropriate. A radiation oncologist will check the first film on all fields. A radiation therapist or radiation oncologist will check subsequent films taken before treatment. All set-up films will be permanently filed for all subjects.

6.1.8 *IGRT and Quality Assurance*

Daily portal films, and/or daily online radiographic imaging is required to be performed prior to each fraction of treatment. Volumetric imaging or continuous intermittent kV imaging and volume or fiducial match is required prior to each fraction of SBRT.

The first 3 cases from participating sites will have pretreatment review by the participating site PI or a participating site radiation oncology designee. The first 3 cases from Atrium Health will have pretreatment review by the coordinating center S-I or a coordinating center radiation oncology designee. Additionally, the first 3 cases from each treatment center within the coordinating center will have pretreatment review by the coordinating center S-I or a coordinating center radiation oncologist designee, and first 3 cases from each treatment center within the participating site will have pretreatment review by the participating site PI or a participating site radiation oncologist designee. Additional pretreatment reviews may be requested at the discretion of the coordinating center S-I. Central review will be supervised by the coordinating center S-I.

6.2 **Concurrent Chemotherapy**

A single platinum-based doublet chemotherapy regimen is to be administered during radiotherapy. The choice of the chemotherapy regimen is at the discretion of the treating physician. <u>One of the following recognized standard-of-care, protocol-allowed regimens must be given with radiation therapy:</u>

Paclitaxel (50 mg/m^2) intravenous over approximately 1 hour followed by
Carboplatin AUC = 2 mg/mL/min intravenous weekly (every 7 days) during radiotherapy
(Belani 2005) (NCCN 2014)
For 1 treatment cycle (approximately 6 weeks in duration)
Standard premedications with steroids, diphenhydramine, H2 receptor antagonist, and 5-HT3 receptor antagonist antiemetics must be administered per individual institutional guidelines.

<u>OR</u>

Etoposide (50 mg/m^2/d) intravenous on days 1 to 5 and days 29 to 33
Cisplatin (50 mg/m^2/d) intravenous on days 1, 8, 29, and 36
(Albain KS, et al. J Clin Oncol 2002; 20:3454-60) (NCCN 2014)
For 2 treatment cycles (each cycle is 4 weeks in duration)
Standard premedication with steroids and 5-HT3 receptor antagonist antiemetics must be administered per individual institutional guidelines.
Standard intravenous hydration (≥ 1.5 liters) must be administered in conjunction with cisplatin.

Chemotherapy regimens should not be switched after initiation unless approval is granted by the Sponsor-Investigator.

Filgrastim and pegfilgrastim may not be used during concurrent chemoradiotherapy.

Erythropoiesis-stimulating agents (epoetin alfa, darbepoetin alfa) may not be used during concurrent chemoradiotherapy.

Chemotherapy dosing for all subjects will be based on actual body weight prior to each cycle, in accordance with ASCO guidelines (Griggs JJ, et al. J Clin Oncol 2012;30:1553-61).

Chemotherapy scheduling modifications of +/- 48 hours are allowed. Concurrent chemotherapy treatment must begin within 48 hours of mediastinal radiation therapy initiation.

6.2.1 *Chemotherapy Drug Information*

All chemotherapy received on the protocol during the study treatment period will be commercially supplied.

Refer to package insert(s) for detailed pharmacologic, safety information and preparation/administration instructions for chemotherapy drugs. Chemotherapy will be administered per institutional guidelines. Please note that 1 treatment cycle (6 weeks in duration) is an example of a schedule, a 6-week duration is not required. Standard dose reductions will be used as required for drops in subject blood counts and other chemotherapy related toxicities, and will be performed under the direction of the treating investigator according to individual institutional guidelines. All dose modifications to study treatment will be done per treating physician discretion.

6.2.2 *Permitted Supportive Therapy*

All supportive therapy for optimal medical care will be given during SBRT and concurrent chemoradiation at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

6.2.3 *Non-Permitted Supportive Therapy*

Filgrastim, pegfilgrastim and erythropoiesis-stimulating agents (epoetin alfa, darbepoetin alfa) may not be used during concurrent chemoradiotherapy.

No other systemic or immunologic tumor-directed therapy may be administered while the subject is receiving protocol-directed therapy.

6.3 **Durvalumab**

All subjects will receive adjuvant immunotherapy with durvalumab until disease progression, unacceptable toxicity, or until a maximum of 12 cycles of durvalumab therapy has been administered. In the event of treatment delays, a full 12 months cycles of durvalumab should be admininstered.

6.3.1 **Supplier/How Supplied**

Durvalumab will be provided by AstraZeneca as a 500 mg vial concentrate for solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The label-claim volume is 10.0 mL. Durvalumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from visible particles. The investigational product will arrive with commercial labeling. The investigational product must be relabled with supplied investigational labels immediately upon receipt.

6.3.2 **Preparation**

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Please refer to local prescribing information for in-use storage conditions and times. Durvalumab will be prepared according to the most current version of the package insert.

6.3.3 **Storage and Stability**

Durvalumab does not contain preservatives, any unused portion must be discarded. Durvalumab vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product must be kept in original packaging until use to prevent prolonged light exposure. Administer infusion solution immediately once prepared. Please refer to most current package insert for information on prepared infusion stability.

6.3.4 **Accountability**

An adequate record of receipt, distribution, destruction, or return of this agent must be kept in the form of a Drug Accountability Form. The investigator, or responsible party designated by the investigator, will maintain a careful record of the inventory using the Drug Accountability Form**.** The investigational drug for this clinical trial shall only be dispensed by authorized personnel to subjects enrolled in this clinical trial.

6.3.5 **Destruction**

The investigator or designee is responsible for keeping accurate records of the clinical supplies received from AstraZeneca, including the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused product will be destroyed at the site according to site pharmacy policies or as dictated by the manufacturer. Used vials can be destroyed immediately after preparation. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.3.6 **Administration**

Durvalumab may be administered after concurrent mediastinal chemoradiation per physician discretion. Durvalumab should be administered through an IV line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter. Durvalumab should be administered as soon as possible after preparation, within the timeframes defined in Section 6.3.3. Do not co-administer other drugs through the same infusion line.

Do not co-administer other drugs through the same infusion line. The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials.

There are (2) different dosing schedules that may be administered, per investigator discretion. Dosing schedule may be switched after initiation of durvluamb, per investigator discretion.

Table 2: Q 2 Week Dosing

Drug	Dose	Route	Schedule[2]	Cycle Length
Durvalumab	10 mg/kg[1]	Intravenously (IV) over approximately 60 minutes[3]	D1 and D15	4 weeks (28 days)

[1] Calculated from most recent weight prior to durvalumab (baseline) during screening. Do not recalculate unless weight changes >10% from baseline weight.
[2] A +/- 3 day window is allowed
[3]If there are interruptions during the infusion, the total allowed time must not exceed 8 hours at room temperature

Table 3: Q 4 week Dosing[1]

Drug	Dose	Route	Schedule[2]	Cycle Length
Durvalumab	1500 mg (flat dose)	Intravenously (IV) over approximately 60 minutes[3]	D1	4 weeks (28 days)

[1] Schedule only allowed in subjects weighing 30 kg or more, if weight is less than 30 kg, subject should receive durvalumab per Table 2.
[2] A +/- 3 day window is allowed

[3]If there are interruptions during the infusion, the total allowed time must not exceed 8 hours at room temperature

6.3.7 Dose Modifications

All durvalumab dose modifications should be per the most current durvalumab package insert and Investigator's Brochure. Please also refer to the most current Toxicity Management Guidelines for guidance on durvalumab-related symptom management.

6.3.8 Reproductive Risks

Durvalumab can cause fetal harm when administered to a pregnant woman. Females of child-bearing potential should be advised to use effective contraception during treatment with durvalumab and for at least 3 months after the last dose of durvalumab. Women should not breastfeed during treatment with durvalumab and for at least 3 months after the last dose of durvalumab. If a subject becomes pregnant while on durvalumab, study treatment should be discontinued immediately.

6.3.9 Supportive Care

Subjects should be monitored for immune-mediated adverse reactions, signs and symptoms of infection, and infusion-related reactions. Supportive care for any durvalumab-related toxicities should implemented per the most current version of the durvalumab package insert. Please also refer to the Toxicity Management Guidelines for guidance on durvalumab-related symptom management.

6.4 Treatment Compliance

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol. At the discretion of the Sponsor-Investigator, a subject may be discontinued from the protocol for non-compliance with follow-up visits or treatment.

6.5 Duration of Therapy

Study treatment will continue until the subject completes protocol-directed therapy (protocol therapy includes SBRT, concurrent mediastinal chemoradiation and protocol—directed durvalumab). Reasons why study treatment may be discontinued early may include:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the protocol
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the Investigator.
- Study subject becomes pregnant

In all cases, the reason for study treatment discontinuation must be documented in the subject's medical record and/or research record and collected in the eCRF.

NOTE: In the event the criteria for the final analysis are met, and there are subjects who have not yet been discontinued from study treatment, they will continue to receive therapy until one of the above criteria applies.

7 STUDY ASSESSMENTS

7.1 History and Physical:

Subject undergoes history and physical per standard of care and is identified for study by the treating physician. Pathologic and radiologic review of available studies are performed per standard of care and at the discretion of the treating physician. Performance status is assessed per ECOG criteria. Vital signs including weight, temperature, blood pressure, heart rate, respiratory rate. These assessments are repeated after initiation of study treatment per the time-points indicated in Section 5.

7.2 Positron emission tomography-computed tomography:

Every effort will be made to obtain standard PET/CT at the timepoints indicated in Section 5. If PET/CT is not able to be performed, CT abdomen/pelvis may be performed instead as referenced below.

7.3 CT chest:

This will be performed utilizing standard imaging procedures at the timepoints indicated in Section 5. Imaging should be performed with IV contrast unless approved by the Sponsor-Investigator.

7.4 Chest X-Ray:

Chest x-ray will be performed at screening in subjects with a pleural effusion visible on CT scan to confirm that a pleuracentesis is not required.

7.5 CT abdomen/pelvis:

This will be performed utilizing standard imaging procedures at the time-points indicated in Section 5 if PET/CT is not performed. Imaging should be performed with IV contrast unless approved by the Sponsor-Investigator.

7.6 Neuroimaging:

MRI of the brain with contrast (preferred) or CT of the head with contrast should be performed utilizing standard imaging procedures at the time-point as indicated in Section 5. Imaging should be performed with IV contrast unless approved by the Sponsor-Investigator.

7.7 Documentation of biopsy of primary tumor and/or nodes:

All techniques that may have been used for biopsy to obtain tissue confirmation of non-small cell histology are allowed including bronchoscopy, percutaneous, and surgical biopsy. Repeat biopsy is not required but is permitted to document recurrence or failure.

7.8 Laboratory assessments:

Including CBC with differential, electrolytes, and LFTs. CBC with differential and electrolytes will be repeated after initiation of study treatment at the time-points identified in Section 5.

7.9 Pulmonary Function Testing:

Standard pulmonary function testing to include FEV1 and DLCO will be performed at the time-points as indicated in Section 5.

7.10 **Toxicity Assessment**

Baseline pre-existing symptoms and conditions present at the time of informed consent and prior to the first dose of study treatment should be documented. Toxicity assessment should start at study treatment initiation and continue at a minimum of up to 12 months after the last treatment of concurrent mediastinal chemoradiation. **Collection requirements are as follows**: All AEs from initiation of study treatment until 90 days after last dose of protocol-directed durvalumab. After this time period, if less than 12 months has elapsed since last dose of concurrent mediastinal chemoradiation, AESIs (as defined in Section 10.3) until 12 months after last dose of concurrent mediastinal chemoradiation. For subjects who do not initiate protocol-directed durvalumab, AESI's starting on the date the decision is made that durvalumab will not be initiated through 12 months after last dose of concurrent mediastinal chemoradiation.

7.11 **Quality of Life Assessment:**

Quality of life will be reported during the study by each subject using the MDASI-lung and EORTC QLQ-LC13 lung surveys at the time-points as indicated in Section 5.

7.12 **Biospecimen collection:**

Blood samples and archived tissue for correlatives will be collected at the time-points as indicated in Section 5.

8 TREATMENT-RELATED ADVERSE EVENTS

8.1 Adverse Events Related to Radiation

Possible <u>early</u> side effects:

- Skin changes which may include dryness, redness, burning, swelling, or peeling of the skin
- Decrease in weight, low blood counts, loss of appetite, nausea, diarrhea, and fatigue.
- Irritation of the esophagus causing pain when swallowing
- Swelling/inflammation of the lung causing pain, fever, cough, or shortness of breath or difficulty breathing
- Rare: Ulcerations of the skin in the irradiated area.

Possible <u>late</u> side effects, although rare:

- Changes in the color or texture of the skin or hair in the treated area
- Ulcers or scars on the skin in the treated area
- Scars or shrinking of the lung that could cause shortness of breath
- Narrowing of the esophagus that could cause swallowing problems
- Bone damage that may lead to small cracks (fracture) in the bone
- Damage to the heart muscle, heart sac, or arteries that may lead to heart attack or heart disease or the need for surgical correction

8.2 Adverse Events Related to Chemotherapy

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting, electrolyte imbalance, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased

liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase); hepatic failure, hepatic necrosis

- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness
- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights; blurred vision, scintillating scotoma
- Allergy: Anaphylactoid and urticarial reactions (acute); Stevens-Johnson Syndrome; flushing, rash, pruritus
  Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration); radiation recall reaction.

8.3 **Adverse Events Related to Durvalumab**

For complete information on safety, please refer to the latest version of the prescribing information for durvalumab, which can be found at www.imfinzihcp.com. Please also refer to the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 5 events reported across the durvalumab program.

- Immune-related reactions include, not limited to:
  - Pneumonitis/interstitial lung disease (ILD)
  - Hepatitis/increases in transaminases
  - Colitis
  - Endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus and diabetes insipidus, and pancreatitis)
  - Nephritis/increases in creatinine
  - Dermatologic reactions including rash/dermatitis (including pemphigoid)
  - Uveitis
  - Myocarditis
  - Myositis/polymyositis
  - Thrombocytopenia
  - Other rare or less frequent inflammatory events including neuromuscular toxicities (e.g., Guillain-Barrè, myasthenia gravis)

- Serious infections
- Infusion-related reactions, including hypersensitivity
- Embryo-fetal toxicities
- Cough/productive cough
- Dyspnea
- Diarrhea
- Abdominal pain
- Pruritis
- Fatigue

- Pyrexia
- Pneumonia
- Intestinal perforation

In monotherapy clinical studies, AEs at an incidence of ≥ 20% include events such as fatigue and decreased appetiate. Approximately 10% of participants discontinued the drug due to an AE.

9 DATA AND SAFETY MONITORING PLAN

9.1 Safety Monitoring

This protocol will be monitored according to the processes in effect for all Levine Cancer Institute investigator-initiated studies and the protocol-specific monitoring plan and will abide by institutional standard operating procedures. It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator, Statistician, and other team members as needed will meet regularly to monitor subject consents, enrollment and retention, safety data for all subjects [including adverse events, Adverse Events of Special Interest (AESI's), serious adverse events (SAE's)], and validity/integrity of the data. Documentation of these meetings will be kept with study records. The Sponsor-Investigator will submit data to the LCI Data and Safety Monitoring Committee according to the overarching LCI Data and Safety Monitoring Plan.

9.2 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the study protocol, institutional standard operating procedures (SOPs), and other applicable regulations and guidelines (e.g. GCP).

Subjects will be monitored by Levine Cancer Institute Research Monitors routinely for data quality. This monitoring will be done by comparing source documentation to the eCRFs. Any variation between the source documentation and the database will be discussed with the Sponsor-Investigator or appropriate research personnel.

The study database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by Sponsor- Investigator or appropriate research personnel. Only authorized personnel will make corrections to the study database and all corrections will be documented in an electronic audit trail.

10 SAFETY DATA COLLECTION, RECORDING AND REPORTING

Safety and tolerability, relationship to treatment and intensity will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. AE and AESIs as

defined in Sections 10.2 and 10.3 will be determined by the Investigator, documented in subject study charts and/or the medical record, and collected in the eCRF per Section 10.7.

10.1 **Unanticipated Problem Definition**

An UAP is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g. Investigator's brochure, informed consent) and the study population characteristics that is related or possibly related to participation in the research study and places the participant at an increased risk.

10.2 **Adverse Event Definition**

An adverse event or adverse experience is any untoward medical occurrence in a study subject who is treated on study that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study treatment, whether or not considered related to it. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a study drug in human clinical trials are also considered adverse events.

Pregnancy and/or elective abortions are not regarded as AEs unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication.

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study treatment should be considered pre-existing and should be documented in the subject's medical records and/or in the study chart.

The relationship to study intervention should be assessed using the following definitions:

"Not Related: Evidence exists that the AE has an etiology other than the study treatment (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered remotely or unlikely related to study treatment.

Related: A temporal relationship exists between the event onset and administration of treatment. It cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves and reappears upon re-challenge. It should be emphasized that ineffective study treatment should not be considered as causally related in the context of AE reporting. This includes events that are considered possibly, probably, or definitely related to study treatment."

The Investigator is responsible for verifying and providing source documentation for all collected adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

10.2.1 **Abnormal Laboratory Values/Clinical Results Defined as AEs**

An abnormal laboratory value or clincal result is considered to be an AE if the abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Requires treatment, delay or modification of study drug dose, or any other therapeutic intervention
- Grade 3 or higher, regardless of clinical significance

If a laboratory/clinical result abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be collected as an AE. If the laboratory abnormality/clinical result was not a part of a diagnosis or syndrome, then the abnormality should be collected as the AE.

10.3 **Adverse Events of Special Interest (AESI) Definition**

Adverse Events of Special Interest for this protocol are defined as non-hematologic adverse events Grade 2 or higher related to SBRT or concurrent mediastinal chemoradiation.

10.4 **Suspected Adverse Reaction Definition**

A SAR is an adverse event in which there is reasonable possibility that the study intervention caused the adverse event. The Investigator is responsible for judging whether it is a reasonable possibility that the study treatment caused the adverse event.

10.5 **"Unexpected" Definition**

An AE or SAR is to be considered unexpected if the event is not listed in the current Investigator Brochure and/or package insert or is not listed in the severity or specificity observed.

10.6 **Serious Adverse Event (SAE) Definition**

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

The following do not meet the criteria for seriousness per ICH definition but must be reported in the same manner as SAEs:

- New primary cancer
- Overdose (dose of durvalumab in excess of the protocol directed dose) of durvalumab
- Pregnancy exposure:
    - Pregnancies of a subject or pregnant partner that occur within 90 days after the last dose of durvalumab. Signed authorization from the pregnant partner must be obtained prior to reporting any pregnancy information.
- Hepatic function abnormality is associated with liver injury and impaired liver function defined as (possible Hy's Law case):
    - ALT ≥3 x ULN and total bilirubin ≥2 xULN (if fractionated and direct bilirubin >35%)
      or
    - ALT ≥3 x ULN and INR >1.5.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

10.7 AE and AESI Reporting

Toxicity reporting requirements are as follows:

All AEs from initiation of study treatment until 90 days after last dose of protocol-directed durvalumab. After this time period, if less than 12 months has elapsed since last dose of concurrent mediastinal chemoradiation, AESIs (as defined in Section 10.3) until 12 months after last dose of concurrent mediastinal chemoradiation. For subjects who do not initiate protocol-directed durvalumab, AESI's starting on the date the decision is made that durvalumab will not be initiated through 12 months after last dose of concurrent mediastinal chemoradiation.

10.8 Expedited Safety Reporting to the Sponsor-Investigator

SAEs, pregnancies including pregnant partners and AEs requiring expedited reporting as defined in Section 10.6 must be reported to the Sponsor-Investigator within 1 business day of awareness. SAEs will be captured from the time of study treatment initiation through 90 days (30 days for subjects who have not yet initiated protocol-directed durvalumab) after the date of the last study treatment administration or until the initiation of subsequent anti-cancer therapy (minimum reporting period of 30 days after last dose of study treatment). SAEs that are determined to be related to study treatment or a research procedure are reportable for the subject's duration of study participation. SAEs will be followed until clinical recovery is complete and laboratory tests have returned to baseline, until progression has been stabilized, or until there has been acceptable resolution of the event. This may at times cause the follow-up period for SAEs to be greater than 90 (or 30 for subjects who have not yet received protocol-directed durvalumab) days. The Sponsor-Investigator is responsible for following the

subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care and is being treated under another service.

The outcome of all pregnancies (including pregnant partners) should be followed up and documented. Written authorization must be obtained from a pregnant partner before any obtaining and reporting any information about the pregnancy to the sponsor.

10.9 Expedited Safety Reporting to AstraZeneca

Note: SAEs will only be reported to AstraZeneca on subjects who have initiated protocol-directed durvalumab. The following does not apply to subjects who have not yet initiated protocol-directed durvalumab.

SAEs determined to be related to protocol-directed durvalumab per the Sponsor-Investigator and all pregnancies as defined in Section 10.6 will be reported to AstraZeneca within 1 business day of Sponsor-Investigator awareness (both initial reports and follow-up reports).

All other SAEs (determined to be unrelated to protocol-directed durvalumab) including initial and follow-up information will be provided to AstraZeneca by the Sponsor-Investigator or designee in a quarterly line listing.

Death clearly resulting from disease progression should not reported to AstraZeneca as an SAE (but will be collected in the eCRF as an AE).

The SAE report and accompanying cover page should be sent via email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca.

10.10 Expedited Safety Reporting to the IRB

All events occurring during the conduct of a protocol and meeting the definition of an UAP or SAE will be reported to the IRB per IRB reporting requirements.

Protocol deviations will be reported promptly to the IRB per IRB reporting requirements.

11 MEASUREMENT OF EFFECT

11.1 Anti-tumor Effect – Solid Tumor

Response and progression will be evaluated in this study using a modification of the revised response evaluation criteria in solid tumors (RECIST) guideline version 1.1, allowing baseline scans to have occurred no more than 90 days prior to enrollment.

11.1.1 Definitions

Subjects will be evaluated for response based on pretreatment disease parameters below and follow up imaging at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48, and 60 months after the last treatment of concurrent mediastinal chemoradiation. Protocol-directed follow-up imaging will be discontinued for subjects who have documented disease progression. After PD, only imaging data from standard of care imaging will be collected until initiation of subsequent anti-cancer therapy.

11.1.2 **Disease Parameters**

Target lesions include the primary disease in the lung, mediastinum, and hilum. The sum of longest diameters of the primary lung tumor and other solid tumor lesions and shortest axis for involved lymph nodes that are PET avid in subjects who have PET/CT (and have a long axis ≥1 cm (lymph nodes must have short axis ≥ 1.5 cm) will be measured prior to treatment and on follow up imaging.

11.1.3 **Methods for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and no more than 90 days before the beginning of study treatment (enrollment).

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. The tumor measurements will be recorded on the eCRF.

11.1.4 **Response Criteria**

Response will be evaluated using RECIST 1.1 Criteria.

Complete Response:

- Target lesion: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Non-target lesion: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Partial Response:

- Target lesion: At least a 30% decrease in the sum of diameters of target, taking as reference the baseline sum diameters.
- Non-target lesion: Not applicable

Stable Disease:

- Target lesion: Neither sufficient shrinkage to qualify for a partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

- Non-target lesion: Not applicable.

Progressive Disease:

- Target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).
- Non-target lesion: *Unequivocal progression* (as described in RECIST version 1.1) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

Non-Complete Response / Non-Progressive Disease:

- Target lesion: Not applicable
- Non-target lesion: Persistence of one or more non-target lesion(s)

Table 4 Summary of RECIST 1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Response for this Category also requires
CR	CR	No	CR	Documented at least once ≥ 4 weeks from baseline
CR	Non-CR/Non-PD	No	PR	Documented at least once ≥ 4 weeks from baseline
CR	Not all evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least once ≥ 4 weeks from baseline
Not all evaluated	Non-PD	No	NE	NA
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and

NE = inevaluable.

Table 5 Time Point Response: Patients with Non-Target Disease Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/ Non-PD	No	Non-CR/ Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size

A total of 60 PFS1 evaluable subjects (section 12.3) will be enrolled to this study. The primary objective is to evaluate the 12-month progression free survival rate. The PACIFIC study[19] reported a lower limit of the 95% confidence interval for median PFS of 13 months for subjects on the arm receiving durvalumab; however, PFS was measured from end of chemoradiotherapy in the PACIFIC study while we derive PFS from enrollment to the study (start of SBRT treatment). As such we are assuming a 15-month median PFS (allowing two months for SBRT and chemoradiation) which corresponds to a 12-month PFS rate of approximately 60.0%. Therefore, a single-stage design will be used to test the hypothesis that the 12-month PFS rate is less than or equal to 0.60. If at least 42 of the 60 subjects are alive and progression free at 12 months, the null hypothesis will be rejected (based on an exact binomial test) and the study treatment regimen may be considered for further evaluation in this subject population. Assuming a one-sided alpha = 0.10 significance level, this sample size will provide at approximately 98% power to reject the null hypothesis, assuming the true 12-month PFS rate is 0.80. An increase in the PFS-12 rate of 0.20 in the context of this Phase II study is considered clinically relevant.

Note, since not all enrolled subjects will have received adjuvant durvalumab due to both initiation of enrollment to the study prior to regulatory approval of durvalumab and previous investigator discretion for decision to administer durvalumab was allowed,, we must also consider the inclusion of subjects who do not receive durvalumab. The CALGB 30105 study (Socinski MA, et al. J Clin Oncol. 2008;26(15):2457-63) reported a 12-month PFS of 54.8% for Arm A (carboplatin + paclitaxel). The lower bound of the 95% confidence interval for one year PFS was 38.7%. Therefore, we assume the null hypothesis for the subjects not receiving durvalumab to be 0.40 and the alternative is assumed to be 0.60. Therefore, including subjects who did not receive durvalumab will reduce the power from 98%. Table 6 shows the conditional power of the study design given the sample size of enrolled subjects who do not receive adjuvant durvalumab (N1).

Table 6

N1	Conditional Power
5	0.95472

6	0.94832
7	0.94124
8	0.93344
9	0.92489
10	0.91555
11	0.90539
12	0.89439
13	0.88254
14	0.86982
15	0.85622
16	0.84175
17	0.82641
18	0.81021
19	0.79319
20	0.77536

12.2 **Endpoint Definitions**

12.2.1 **1-Year Progression-Free Survival**

The primary endpoint is 1-year progression-free survival, which will be calculated from a recorded binary variable determined for each subject indicating whether or not the subject experienced disease progression or death from any cause within 1 year from study enrollment. Disease progression will be classified according to Section 11.1.4.

12.2.2 **Progression Free Survival**

Progression free survival (PFS) is defined as the duration of time from enrollment to the study to first occurrence of either progressive disease or death. Disease progression must be objectively determined as per Section 11.1.4, where the date of PD is the date of the radiologic assessment that identified RECIST-defined progressive disease. If the subject died without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not have documented disease progression, PFS will be censored at the date of last radiologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, PFS will be censored at the date of last

radiologic assessment prior to the commencement of subsequent therapy. Subjects who have an initial PFS event immediately following 2 or more consecutive missed assessments will be censored at the date of the last assessment prior to those missed assessments. For participants with only one missed assessment, the documented progressive disease status and assessment date will be used.

12.2.3 **Overall Survival**

Overall survival (OS) is defined as the duration of time from the date of enrollment to the study to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

12.2.4 **Radiologic Clinical Complete Response**

Radiologic clinical complete response will be recorded for each subject as a binary variable indicating whether or not the subject had no evidence of disease on PET/CT or CT scan approximately 3 months after the last treatment of concurrent mediastinal chemoradiation.

12.2.5 **Objective Response**

Objective response will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of CR or PR as determined per criteria described in Section 11.1.4.

12.2.6 **Local Control at 12 and 24 Months**

Local control (LC) is defined as the duration of time from enrollment to the study to first progression of the subject's primary lesions(s). If a subject dies prior to local progression, local control will be censored at the date of death. For surviving subjects with no documented local progression, local control will be censored at the date of the last radiologic assessment that evaluated the local tumor(s). For subjects who receive subsequent anti-cancer therapy prior to documented local progression, local control will be censored at the date of last radiologic assessment that evaluated the local tumor(s) prior to the commencement of subsequent therapy. Local control will be estimated at 12 and 24 months.

12.2.7 **Regional Control at 12 and 24 months**

Regional control (RC) is defined as the duration of time from enrollment to the study to first progression of the subject's regional lesion(s). If a subject dies prior to regional progression, regional control will be censored at the date of death. For surviving subjects with no documented regional progression, regional control will be censored at the date of the last radiologic assessment that evaluated the regional lesion(s). For subjects who receive subsequent anti-cancer therapy prior to documented regional progression, regional control will be censored at the date of last radiologic assessment that evaluated the regional lesion(s) prior to the commencement of subsequent therapy. Regional control will be estimated at 12 and 24 months.

12.2.8 **Locoregional Control at 12 and 24 months**

Locoregional control is defined as the duration of time from enrollment to the study to first progression of the subject's local and/or regional lesion(s), whichever occurs first. If a subject dies prior to locoregional progression, locoregional control will be censored at the date of death. For surviving subjects with no documented local and/or regional progression, locoregional control will be censored at the date of the last radiologic assessment that evaluated the locoregional lesion(s). For subjects who receive subsequent anti-cancer therapy prior to documented locoregional progression, locoregional control will be censored at the date of last radiologic assessment that evaluated the local and regional lesion(s) prior to the commencement of subsequent therapy. Locoregional control will be estimated at 12 and 24 months.

12.2.9 **Distant Control at 12 and 24 months**

Distant control defined as the duration of time from enrollment to the study to first metastatic progression. If a subject dies prior to metastatic progression, distant control will be censored at the date of death. For surviving subjects with no documented mestastic progression, distant control will be censored at the date of the last radiologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented metastatic progression, distant control will be censored at the date of last radiologic assessment prior to the commencement of subsequent therapy. Distant control will be estimated at 12 and 24 months.

12.2.10 **Quality of Life**

QOL will be assessed utilizing the MDASI-lung cancer and EORTC QLQ-C30, EORTC QLQ-LC13 lung surveys. Surveys will be obtained at the time points as indicated in Section 5.

12.2.11 **Safety Endpoints**

Safety endpoints will include radiation dosing administration (including dose of radiation received for both SBRT and mediastinal radiation, and other dosimetry parameters), incidence of AESIs, incidence of SAEs and deaths while on study. Toxicities will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Toxicities will be tabulated by type and grade separately for each phase of treatment. Selected adverse events for this objective will include the following:

- Grade 2 or higher radiation pneumonitis
- Grade 3 or higher pulmonary events

12.3 **Analysis Populations**

All subjects who receive at least one fraction of SBRT will be included in all efficacy and safety populations. The population evaluable for the primary endpoint (PFS1 evaluable population) will include all subjects in the efficacy population who have experienced a PFS event within one year

of enrollment or have at least one year of follow-up time from enrollment. Evaluation of the secondary endpoints will be conducted on the efficacy population. Analysis of objective response will be conducted on those subjects in the efficacy population with measurable disease present at baseline. For the exploratory analysis, the immune marker population will contain all subjects who received at least one fraction of SBRT and who had at least one blood sample drawn. The exploratory analysis of lung texture data will be conducted on the population of subjects who receive at least one fraction of SBRT and who also have available data from the lung texture analysis software.

12.4 Analysis Methods

12.4.1 Timing of Analysis

The primary analysis will occur when all subjects in the study have experienced a progression or when they have been on study for 1 year. Baseline characteristics and secondary endpoints will also be assessed at the time of the primary analyses. Updated analyses will be conducted after all subjects have been on study for at least 2 years or are off study otherwise. A final analysis will be conducted after the overall survival censoring rate reaches 30%, or after all surviving subjects have been followed for at least 5 years after last treatment of mediastinal chemoradiation or are off study otherwise, whichever occurs first.

12.4.2 Subject Disposition

An accounting of all consenting subjects will be provided at the end of the study. This will include a breakdown of subjects who consented, received study treatment, discontinued treatment early, died, and were lost to follow-up or withdrew consent.

12.4.3 Baseline Subject and Disease Characteristics

A summary of subject and disease-related characteristics will be completed.

12.4.4 Efficacy Analyses

12.4.4.1 Primary Analysis

The primary analysis will be to compare the progression free survival rate at one year in PFS1 evaluable subjects receiving the study treatment regimen to a relevant historical control rate. The frequency and proportion of subjects alive and progression free at 1 year will be calculated, along with a 95% Clopper Pearson confidence interval. A one-sided exact binomial test of proportions, with alpha = 0.05, will be carried out, testing the null hypothesis that the 1-year progression free survival probability is less than 40%. Based on the sample size calculations described in Section 12.1, if at least 42 subjects are alive and progression free at 1-year, the null hypothesis can be rejected.

12.4.4.2 **Secondary Analyses**

OS and PFS will be analyzed using Kaplan Meier techniques. Medians, 25th, and 75th percentiles will be estimated. Selected landmarks for OS and PFS at 1-year, 2-years, and 3-years will be obtained from the Kaplan Meier curves.. Clinical complete response and objective response rates will be estimated with proportions and associated 95% Clopper Pearson confidence intervals will be calculated.

Landmark local control, regional control, locoregional control, and distant control will be estimated along with 95% confidence intervals at 12 and 24 months using Kaplan Meier methods. Additionally, patterns of primary, locoregional, and distant failure will be derived from the local, locoregional, and distant control, respectively, and reported.

Total scores and subscales from the QOL surveys (MDASI-LC, EORTC QLQ-C30, EORTC QLQ-LC13 lung) will be summarized for each subject and evaluated over time (six time points). Change from baseline will be described for each post-baseline timepoint and individual trajectories will be examined graphically and with linear mixed models. The models will include subject as a random factor in order to account for within-subject correlation.

Note, secondary analyses may involve subsets of subjects based on the delivered dose of therapy.

12.4.5 **Safety Analysis**

Incidence rates for adverse events, treatment-emergent adverse events, SAEs, deaths, and complications recorded from the time of initiation of SBRT until the end of the collection period (defined in Sections 10.7 and 10.8) will be summarized as counts and proportions. For selected events, 95% Clopper Pearson confidence intervals will be calculated. Treatment-emergent adverse events are defined as follows:

- An adverse event that occurs after treatment start that was not present at the time of treatment start; or
- An adverse event that increases in severity after treatment start if the event was present at the time of treatment start.

The frequency and proportion of subjects with clinical symptoms of and receiving treatment with steroids for radiation pneumonitis (grade ≥ 2) within 6 months of the last treatment of concurrent mediastinal chemoradiation will be reported. Grade 3 or higher pulmonary events will also be summarized with frequencies and proportions. Additionally, radiation dosimetry parameters will be correlated with

the incidence of select adverse events. The continuous dosimetry data will be summarized with medians and ranges among those who did and did not experience the select adverse events.

12.4.6 **Exploratory Analyses**

The impact of baseline subject and disease characteristics on outcomes will be evaluated. Univariate models will be used to identify individual prognostic factors and multivariate models will be used to identify independent prognostic factors. Additionally, in an effort to determine inflammatory markers, changes in expression levels of chemokines and cytokines will be evaluated over time (prior to SBRT, during SBRT, and during mediastinal chemoradiation. Differentially expressed chemokines and cytokines will be correlated with toxicity endpoints, specifically to explore associations with radiation-induced lung toxicity.

Radiation fibrosis is a common radiologic observation after SBRT in the lung that often appears as partial lung atelectasis. This is a scarring effect usually in the lung tissue that surrounds the primary tumor and can change over time. Some patients have more fibrosis than others, and there are likely multiple factors that affect the level of fibrosis that occurs in patients. Fibrosis is likely a mechanism of small airway collapse from small airway radiation injury. Quantifying the amount of fibrosis and resulting effects on lung function has not been studied. Newer software is available to analyze CT scans and quantify as well as categorize lung texture. Provided sufficient sample sizes are available, post treatment CT scans will be evaluated utilizing lung texture analysis and lung density analysis software to quantify and categorize lung changes pre-SBRT versus post-SBRT, at CT scan time points, up to 24 months after SBRT treatment completion. The shift in distribution of the lung texture data over those time points will be calculated and will also be correlated with dose information from the treatment plan to evaluate if there are dosimetric causes of lung texture changes and small airway collapse. In addition, the effect of lung texture changes over time on selected outcomes, such as toxicity and PFT changes, will be evaluated. Further discovery-type evaluations of the predictive nature of lung texture changes as may also be carried out on an ad hoc basic.

13 **STUDY COMPLETION**

13.1 **Completion**

The study will be considered complete when one or more of the following conditions is met:

- All subjects have completed all study visits.
- All subjects have discontinued from the study.
- The IRB, LCI DSMC, Sponsor-Investigator discontinues the study because of safety considerations.

13.2 **Termination**

The study will be terminated when one or more of the following conditions occur:

If risk-benefit ratio becomes unacceptable owing to, for example:

- Safety findings from this study (e.g. SAEs)
- Results of parallel clinical studies
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The Sponsor-Investigator has the right to close the trial at any site and at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow- up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 5.9.

14 **RETENTION OF RECORDS**

Essential documentation (e.g. adverse events, records of study treatment receipt and dispensation), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

15 **ETHICAL AND LEGAL ISSUES**

15.1 **Ethical and Legal Conduct of the Study**

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. DSMC, IRB) will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the Investigators may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the investigator without discussion with the Sponsor- -Investigator at Levine Cancer Institute. However, the Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as

possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the protocol must be explained and documented by the Investigator.

The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Sponsor-Investigator is responsible for overseeing the treatment of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

15.2 **Confidentiality**

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

16 **PUBLICATION POLICY**

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the coordinating center Sponsor-Investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of the coordinating center study Sponsor- Investigator from Levine Cancer Institute. Any investigator involved with this study is obligated to provide the Sponsor- Investigator with all data derived from the study.

The Sponsor-Investigator will ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

REFERENCES

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APPENDICES

Appendix A. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Radiation Pneumonitis Grading

Grade 1 – asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2 – symptomatic; medical intervention indicated; limiting instrumental ADL
Grade 3 – severe symptoms; limiting self care ADL; oxygen indicated
Grade 4 – life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation)
Grade 5 – death

Appendix B. Quality of Life Questionnaires

MDASI-lung

EORTC QLQ-LC13