Protocol #: LCI-LUN-SBRT-002

TITLE: Pilot study of SGRT alone vs. SGRT in combination with fiducials for breath hold SBRT treatments of the lung

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

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PROTOCOL SIGNATURE PAGE

PROTOCOL TITLE: Pilot study of SGRT alone vs. SGRT in combination with fiducials for breath hold SBRT treatments of the lung

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

_____ _____

Signature of Sponsor-Investigator Date

____John H Heinzerling, MD _____

Sponsor-Investigator Name (printed)

SYNOPSIS

TITLE	Pilot study of SGRT alone vs. SGRT in combination with fiducials for breath hold SBRT treatments of the lung
STUDY POPULATION	Stage I non-small cell lung cancer (NSCLC) and lung metastases
PHASE	Pilot
SUMMARY OF STUDY RATIONALE	Stereotactic Body Radiation Therapy (SBRT) is an effective therapy for non-surgical management of stage I non-small cell lung cancer and lung metastases. One challenge with SBRT treatments of the lung is accounting for respiratory associated motion of the tumor. One technique to reduce respiratory motion is to have patients hold their breath during radiation delivery, only delivering the treatment while the patient is at that point in the respiratory cycle. Often, this method requires use of implanted fiducial markers which are placed via invasive techniques. A newer technology called Surface Guided Radiation Therapy (SGRT) uses non-invasive surface monitoring of the patient to perform breath hold treatments. However, no clinical data exists for its use during SBRT treatments of the lung, and no comparison has been made with use of implanted fiducials. This study aims to compare SBRT treatments delivered with standard free breathing techniques to breath hold treatments utilizing either SGRT alone or SGRT in combination with implanted fiducials in attempt to compare reliability, effectiveness, and toxicity of these 3 techniques during SBRT treatments of primary lung tumors or lung metastases
STUDY DESIGN	This is a pilot study of patients undergoing SBRT treatment for primary and metastatic lung tumors that have ≥1 cm of respiratory associated motion. Subjects will be treated with standard SBRT doses. Subjects will be separated into 3 cohorts and treated either with 1) free breathing SGRT 2) breath hold SBRT utilizing SGRT alone, or 3) breath hold SBRT utilizing SGRT in combination with implanted fiducials
OBJECTIVES	<u>Primary Objective:</u> • To estimate the incidence of grade 2 or higher SBRT and fiducial-related pulmonary toxicities for subjects treated with SBRT who have tumors that move ≥1 cm in 3 different cohorts: 1) free breathing and SGRT 2) breath hold utilizing SGRT only; 3) breath hold utilizing SGRT in combination with implanted fiducials <u>Secondary Objectives:</u> • Estimate reliability of gated SBRT treatments utilizing SGRT vs. SGRT with fiducials • Estimate local control for SBRT in subjects treated in the three different cohorts • Estimate overall survival • Evaluate quality of life

	Safety Objective • Estimate acute and long-term grade 2 or higher non-hematologic toxicity related to SBRT/fiducials in subjects treated in the three different cohorts
KEY INCLUSION CRITERIA	• Presumed stage I non-small cell lung cancer or lung metastases to be treated with SBRT • Respiratory associated motion of ≥ 1cm as determined on Four-dimensional CT (4DCT) at the time of treatment planning. • Tumor size ≤ 7cm • ECOG PS ≤ 2
STATISTICAL CONSIDERATIONS	This is a pilot study with 45 evaluable subjects, with a goal of at least 15 evaluable in Cohorts 1 and 2
NUMBER OF SUBJECTS	45 evaluable

SCHEMA

Pilot study

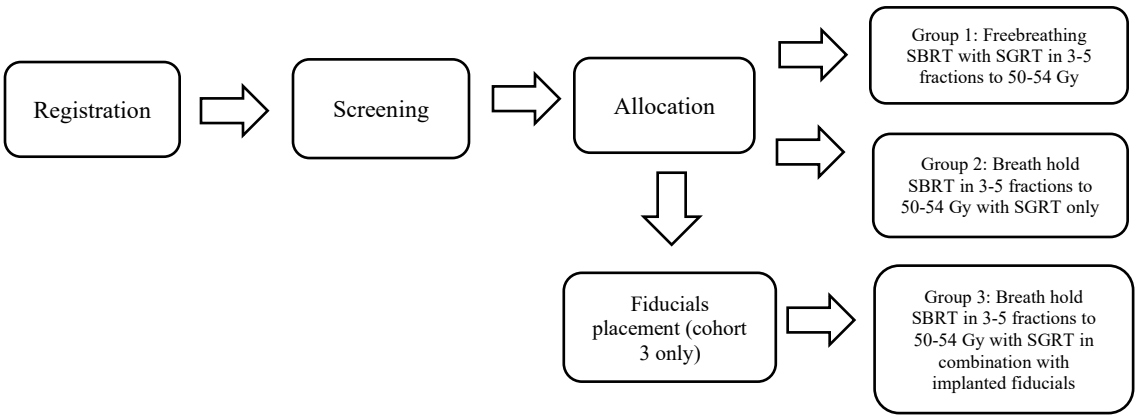


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1. BACKGROUND AND RATIONALE

1.1 SBRT and Lung Cancer Background

Surgical resection remains the standard therapy for patients with stage I non-small cell lung cancer (NSCLC) who are surgical candidates. Five-year survival rates range from approximately 60 to 70 percent. A newer approach that has been extremely effective in controlling lung primary and metastatic tumors is stereotactic body radiation therapy (SBRT). SBRT is an alternative as primary treatment for patients who are not candidates for or who refuse surgery.

SBRT delivers an ultra-high dose per fraction (typically >8-10Gy 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.[1] In prospective phase II studies, SBRT has been associated with local control rates of over 90% for patients with medically inoperable stage I NSCLC.[2] SBRT has also improved survival for medically inoperable patients with stage I NSCLC compared with conventionally fractionated radiotherapy.[3] SBRT also appears to be an effective and well tolerated local therapy for patients with limited metastatic disease within the lung. Local control rates in patients with lung metastases have also exceeded 90 percent using various dose fractionation schemes.[4]

One important aspect of quality delivery of ablative SBRT in the lung is respiratory motion management. Lung tumors often move relative to other thoracic structures during the respiratory cycle, and this motion can vary significantly depending upon the location of the tumor and patient characteristics.[5]

Respiratory motion management for lung SBRT can consist of several different techniques including suppression of respiratory motion with abdominal compression, tumor “tracking”, as well as treatment gating of tumor motion, otherwise known as respiratory gating.[6] Within respiratory gating, there are several technologies to assist in gating to allow the tumor within the lung to be treated at a specific timepoint of the respiratory cycle, including treatment of the patient with a breath hold technique. Respiratory gating or breath hold techniques may have advantages particularly for lung tumors that have greater quantity of respiratory motion by limiting the amount of normal lung that is exposed to high or intermediate doses of radiation. Current technologies that are already in routine use in SBRT treatments include respiratory gating utilizing implanted fiducials for verification of target position. Implanted fiducials, however, have many disadvantages including the need for invasive procedures for placement with associated complication risks, as well as additional costs to the patient.[7] In addition, there is

no current data suggesting a clinical benefit to fiducial based respiratory gating, such as lower toxicity rates or increased tumor control rates.

1.2 Investigational Treatment

SGRT (surface guided radiation therapy) represents a technology that can be utilized for non-invasive respiratory gating or breath hold SBRT and does not require risk-associated procedures or additional cost to the patient.[8] This technique utilizes non-ionizing visible light directed at the patient and has been utilized extensively for deep inspiration breath hold treatment of the breast. However, publications utilizing SGRT for breath hold treatments for smaller targets such as SBRT lung treatments are lacking outside of feasibility studies. SGRT also provides additional benefit beyond implanted fiducials in that it continuously monitors patient position during treatment, ensuring that there is no intrafraction motion.[9]

Implanted fiducials in the lung for SBRT treatments utilizing tumor tracking or gating have been utilized for many years to assist with tumor tracking or gating with results showing comparable efficacy and safety to standard free breathing SBRT.[10] While there have been publications on reliability and minimal migration of fiducials within the lung, there is not yet evidence that implanted fiducials improve clinical outcomes.

1.2.1 Clinical Safety

The clinical safety and efficacy of SBRT for primary and metastatic lung tumors has been well described with high rates of local control and low rates of pulmonary toxicities. However, toxicities do occur, and the rate of grade 2 or higher pulmonary toxicity can range from 10-25% depending on certain clinical characteristics. [2] Tumors that are larger in size, have greater respiratory motion, and are in the lower lobes of the lungs tend to have higher rates of pulmonary toxicity, creating a potential benefit to using gating or tracking techniques in these patients. In addition, placement of fiducials for tumor tracking or gating does appear to have reasonable safety and low complication rate.[11]

1.3 Study Rationale

The rationale for this study is to provide data and experience comparing two different techniques of breath hold SBRT treatments. The first technique will include SGRT, but with the assistance of implanted fiducials. Subjects will be treated with a breath hold technique utilizing SGRT but will also be imaged during treatment with fiducial match. The second technique will utilize SGRT for breath hold treatments without the assistance of implanted fiducials/continuous imaging. These subjects will undergo fast cone beam CT prior to, during, and after treatment to ensure reliable tumor position during SBRT and providing valuable data that SGRT is reliable for small internal target position during breath hold treatments. Both breath-hold groups will be compared to standard “free breathing” SBRT treatments to evaluate endpoints on clinical

efficacy and toxicity, providing valuable clinical data on use of these techniques in subjects with higher risk of toxicities.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To estimate the incidence of SBRT and fiducial related pulmonary toxicities for subjects treated with SBRT who have tumors that move ≥1 cm in 3 different cohorts: 1) free breathing with SGRT 2) breath hold utilizing SGRT only; 3) breath hold utilizing SGRT in combination with implanted fiducials.

2.1.2 Secondary Objectives

- Estimate reliability of gated SBRT treatments utilizing SGRT vs. SGRT with fiducials
- Estimate local control for SBRT in subjects treated in the three different cohorts
- Estimate overall survival.
- Evaluate quality of life

2.1.3 Safety Objective

- Estimate acute and long-term grade 2 or higher non-hematologic toxicities attributed to SBRT/fiducial implantation in subjects treated in the three different cohorts

2.1.4 Exploratory Objectives

- 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 SBRT 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.

2.2 Endpoints

2.2.1 Primary Endpoint

- Incidence of grade 2 or higher acute and late pulmonary toxicities related to SBRT or fiducials observed in the three cohorts as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0

2.2.2 Secondary Endpoints

- Reliability of gated SBRT treatments in cohorts 2 and 3 based on target position at the time of verification imaging prior to, during treatment, and at the end of treatment
- Local control (LC) is defined as the duration of time from enrollment to the study to first progression of the subject's treated tumor. LC will be estimated at 12 months (or 24 months) after enrollment.
- Overall survival is defined as the time from enrollment until death as a result of any cause.
- QOL will be evaluated via MDASI at various time points prior to and after treatment

2.2.3 Safety Endpoints

- Incidence of grade 2 or higher non-hematologic treatment-related toxicities observed in the three cohorts during SBRT treatment and through 12 months after last study treatment as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, incidence of SAEs, and deaths while on study therapy.

3. SUBJECT SELECTION

3.1 Subject Recruitment

Subjects will be recruited at Levine Cancer Institute (LCI).

3.2 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent with HIPAA authorization for release of personal health information.

2. Age ≥ 18 years at the time of consent. Because no dosing or adverse event data are currently available on the use of fiducials in combination with SBRT in subjects <18 years of age, children are excluded from this study.

3. ECOG Performance Status of ≤ 2.

4. Stage IA-IIB (T1a-T3bN0) presumed non-small cell lung cancer, carcinoid tumors, or lung metastasis that have ≥1 cm of respiratory associated motion measured on 4DCT at time of simulation for SBRT with or without respiratory motion suppression techniques. Histologic confirmation of malignancy is encouraged but not required.
    a) Primary or metastatic tumor ≤ 7 cm.

5. Subjects may be receiving systemic chemotherapy or other systemic agents prior to enrollment, but these agents must be stopped during SBRT treatments.

6. Females of childbearing potential (FCBP) must have a negative serum pregnancy test within 14 days prior to day 1 of treatment. NOTE: Females are considered of child-bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are postmenopausal (at least 12 consecutive months with no menses without an alternative medical cause).

   The effects of radiation on the developing human fetus are not well described. For this reason, 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. 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. FCBP must be willing to use a highly effective contraceptive method (i.e., achieves a failure rate of <1% per year when used consistently and correctly) from the time of informed consent until 5 days after last dose of SBRT. Contraceptive methods with low user dependency are preferable but not required (see table, adapted from:
   2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf

Table 1. Highly Effective Birth Control Methods

• combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  ○ oral
  ○ intravaginal
  ○ transdermal

• progestogen-only hormonal contraception associated with inhibition of ovulation
  ○ oral
  ○ injectable
  ○ implantable[1]

• intrauterine device (IUD) [1]
• intrauterine hormone-releasing system (IUS) [1]
• bilateral tubal occlusion[1]
• vasectomized partner [1,2]
• sexual abstinence [3]
[1] Contraception methods considered to have low user dependency [2] Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the FCBP trial participant and the vasectomized partner has received medical assessment of the surgical success [3] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

7. As determined by the enrolling physician, ability of the subject to understand and comply with study procedures for the entire length of the study

3.3 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Prior radiation to the chest that would overlap with the current radiation fields and determined by the treating physician to impede the treatment of the study malignancy.

2. Active ongoing pulmonary infection or pneumonitis that is requiring active treatment with antibiotics or steroids. Prior pneumonitis from drug or other therapies that has been treated within 15 days of first day of treatment.

3.4 Screen Failures

A subject who, for any reason (e.g., failure to satisfy the eligibility criteria or withdraws consent), terminates his/her study participation before receiving first dose of study therapy is regarded as a "screen failure." All screen failures will be tracked. The specific reason for screen failure (i.e. inclusion/exclusion criterion not met, if applicable) must be recorded in the CTMS/Subject Console/Eligibility tab.

4. REGISTRATION AND ALLOCATION

4.1 Sequence Number Assignment

Following informed consent, subjects will be registered by the LCI Data Coordinating Center and assigned a Sequence Number.

4.2 Treatment Allocation

This study contains 3 cohorts. Subjects will not be randomly assigned, but instead assigned based on two parameters. The first is the treating facility. For Cohorts 2 and 3, subjects must be treated at a facility that has both SGRT and a TruBeam linear accelerator capable of performing both triggered KV imaging and short arc cone beam CT. In addition, for Cohort 3, subjects who are identified as potential candidates prior to planned biopsy will be preferentially enrolled into Cohort 3 and either have fiducials planned to be placed at the time of biopsy or have had fiducials placed prior to consent per section 5.3.

5. TREATMENT PLAN

See Schema (page III).

This study is a prospective pilot study with 3 cohorts evaluating breath hold SBRT treatments of the lung with the use of SGRT with and without fiducial tracking compared to free breathing. Ideally, Cohorts 1 and 2 will have at least 15 subjects. In Cohort 1, subjects will be treated with "standard" free breathing SBRT with SGRT. In Cohort 2, subjects will be treated with breath hold SBRT utilizing SGRT only; and in Cohort 3, subjects will be treated with breath hold SBRT utilizing SGRT in combination with implanted fiducials.

This study will be opened as a single center study at LCI. Subjects will be enrolled over approximately 50 months.

Treatment will be administered on an outpatient basis.

5.1 Radiation Therapy

5.1.1 Treatment Planning, Imaging and Localization Requirements

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

Radiation treatment planning CT will be required to define gross target volume (GTV). The treatment planning CT 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. The 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 to account for tumor motion. In addition, for subjects in Cohorts 2 and 3, CT simulation will be performed at end expiration or breath hold position of the respiratory cycle as outlined in sections 5.2 and 5.3. 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.

Target 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.

5.1.2 Target Contouring

Gross Tumor Volume (GTV_Lung) 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 the

planning CT. For cohorts 2 and 3, GTV_Lung should be contoured on the breath hold CT attained at the time of simulation as detailed in section 5.2.

Internal Gross Tumor Volume (IGTV_Lung): This will consist of the GTV_Lung plus an additional margin based on the 4D-CT image sets to account for tumor motion. For cohorts 2 and 3, the IGTV is not generated.

Planning Target Volume (PTV_Lung): A 5 mm margin will be added to the IGTV_Lung for setup error for Cohort 1 and the GTV_Lung for Cohorts 2 and 3.

5.1.3 Normal Structures

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.

5.1.4 Dose Fractionation and Specification

The prescription dose per fraction to the PTV_Lung 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.

5.1.5 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	22.5Gy (7.5Gy/fx)	26Gy (6.5Gy/fx)	28Gy (5.6Gy/fx)
Esophagus	32.4Gy (10.8Gy/fx)	35.6Gy (8.9Gy/fx)	38Gy (7.6Gy/fx)
Brachial plexus	26Gy (8.6Gy/fx)	29.6Gy (7.4Gy/fx)	32.5Gy (6.5Gy/fx)
Heart/ pericardium	30Gy (10Gy/fx)	34Gy (8.5 Gy/fx)	38 Gy (7.6Gy/fx)
Great Vessels	45Gy (15Gy/fx)	49Gy (12.25Gy/fx)	53Gy (10.6Gy/fx)
Trachea/ Proximal Bronchi	43Gy (14.3Gy/fx)	47Gy (11.8Gy/fx)	50Gy (10Gy/fx)
Rib/Chest wall	50Gy (16.6Gy/fx)	54Gy (13.5Gy/fx)	57Gy (11.4Gy/fx)
Skin	33 Gy (11Gy/fx)	36Gy (9Gy/fx)	38.5Gy (7.7Gy/fx
Stomach	30 Gy (10Gy/fx)	33.2Gy (8.3Gy/fx)	35Gy (7Gy/fx)

*Dose in excess of the above constraints will be documented but is not a reason to necessitate subject withdrawal. In cases where the 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.

5.1.6 Treatment Duration

SBRT will be completed in 1-2 weeks.

5.1.7 Equipment and Beam Delivery

A ≥ 6 MV photon beam will be used. 6 MV is preferred. Intensity-modulated radiotherapy (IMRT) is allowed and encouraged for central tumors.

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.

5.1.8 **Image-guided Radiation Therapy (IGRT) and Quality Assurance**

Daily online radiographic imaging is required to be performed prior to each fraction of treatment. Volumetric imaging with cone beam CT and volumetric match prior to treatment is required. For Cohorts 2 and 3, please see sections 5.2 and 5.3 for specifics on daily IGRT requirements.

SBRT plans will be reviewed by the Sponsor-Investigator or a coordinating center radiation oncology designee.

5.2 SGRT

5.2.1 **Cohort 1-SGRT with free breathing**

For Cohort 1, subjects are to be set up and monitored with SGRT during treatments using the following procedures. Simulation and treatment will be performed with the subject free breathing. Abdominal compression can be utilized to decrease tumor motion to <1cm if desired. A four-dimensional CT scan will be obtained as described above. Treatment planning will be performed on the average CT generated from this four-dimensional CT scan. From the average CT, a reference surface region of interest (ROI) will be created in the Align RT software system and labeled "DICOM freebreathing". The ROI is defined as the chest starting superiorly below the chin, inferiorly down to xiphoid process and laterally down to the edge of the vacuum bag used for immobilization. During each SBRT treatment, the subject will be set up initially with Vision RT while free breathing utilizing the "DICOM freebreathing" reference surface. Cone beam CT will then be acquired and volumetric match of the target will be performed by the treating physician. Corresponding shifts will be performed, and a new reference "gated" capture will be immediately obtained and labeled "VRT freebreathing". The treatment will then commence and continue while the subject is within tolerance. The tolerance for the free breathing relative to the reference "VRT freebreathing" will be 3 mm translations and 1-degree rotations within a 2 second interval (to account for natural chest wall motion). If the subject is out of tolerance for more than 2 seconds on 3 separate occasions, the process can be repeated to ensure that no intrafraction motion has occurred.

5.2.2 **Cohort 2-SGRT with breath hold**

For subjects in Cohort 2 that will undergo SBRT treatments with breath hold technique utilizing SGRT without fiducials, the treatment procedures are outlined here. At the time of simulation, CT scans at either end inspiration or end expiration for treatment planning will be obtained. Subjects will be coached on breath hold and the corresponding respiratory waves will be observed utilizing either the bellows system, RPM, or Gate CT to monitor reproducibility and consistency of the subject at either end expiration or inspiration. The more

reproducible breath hold position will be chosen for treatment planning and delivery. A corresponding planning CT scan will be performed at either end expiration or end inspiration utilizing RPM, the bellows system, or Gate CT at ≤3 mm intervals. In addition, a four-dimensional CT scan will be performed with the subject free breathing. From the corresponding breath hold CT, a reference surface ROI will be created in the Align RT software system and labeled "DICOM breath hold". The ROI is defined as the chest starting superiorly below the chin, inferiorly down to xiphoid process and laterally down to the edge of the vacuum bag used for immobilization. In addition, a similar reference surface ROI will be created from the average CT of the freebreathing four-dimensional CT and labeled "DICOM freebreathing." Target contouring, treatment planning, dose calculation, and plan objectives and constraints are the same for this cohort as described above and will be performed on the corresponding breath hold CT.

During each SBRT treatment, the subject will be set up initially with Vision RT while free breathing utilizing the "DICOM freebreathing" reference surface. The subject will then be instructed to undergo breath hold as per the simulation procedure and the table is shifted so that the alignment of the subject is within 3mm translations and 2 degree rotations corresponding to the "DICOM breath hold" reference surface. An additional breath hold will be performed to ensure reproducibility prior to the treatment team leaving the vault. A breath hold will then be performed, and a short arc cone beam CT will be acquired while the subject is within tolerance of the "DICOM breath hold" reference surface. The tolerance for the breath hold relative to the reference will be 3 mm translations and 2-degree rotations. Volumetric match of the target on the short arc cone beam CT will then be performed by the treating physician. These shifts will be recorded in the treatment log. Prior to the shifts being applied, the subject will perform breath hold and while in tolerance of the DICOM breath hold reference surface, the shifts will be applied and immediately a new "non-gated" reference surface capture will be obtained and labeled "VRT breath hold". The subject will then be instructed to undergo breath hold and the treatment will commence and continue while the subject is within tolerance of the "VRT breath hold" reference surface. The beam will be automatically gated by the SGRT system so that if the subject's breath hold is not within tolerance, the beam will turn off. If the subject is unable to return to tolerance, then the treatment is stopped, and a breath hold is performed during which a new VRT breath hold reference surface is obtained. A short arc cone beam CT is obtained while the subject is in tolerance of the new VRT breath hold reference surface. Every effort should be made to obtain an additional short arc cone beam CT approximately midway through the treatment for validation of target position at the breath hold position. However, this should be performed per investigator discretion. Any additional shifts after short arc cone beam CT will be recorded in the treatment log.

5.2.3 **Cohort 3-SGRT with breath hold utilizing implanted fiducials**

Subjects in cohort 3 will have fiducial markers implanted in or near their lung tumor at the time of biopsy (see Section 5.3). The CT simulation process for these subjects will be identical to that for subjects in cohort 2. The markers will be identified in the subject's treatment plan for the purpose of intra-fraction monitoring, which will be performed in addition to the SGRT monitoring. However, the SGRT system will be used for gating the beam, not the fiducials. Each implanted fiducial will be identified in the treatment planning system as a marker and contoured. The marker will be placed at the center of the fiducial. The fiducial contours will also be expanded uniformly by 3 mm into separate structures that can be used to evaluate the magnitude of the fiducial offset from the planned location.

During each SBRT treatment, the subjects will undergo set up and breath hold procedures utilizing SGRT as outlined above, including recording of the shifts made after short arc cone beam CT (CBCT) in the treatment log. As with cohort 2, every effort will be made to obtain a short arc CBCT on these subjects to verify that the fiducials and surface monitoring are suitable surrogates for the tumor position. As with Cohort 2, this will be performed per investigator discretion. Once the volumetric tumor position is evaluated, the fiducial position should be within the 3mm expansion contour that was outlined during treatment planning. If a marker has migrated since the CT simulation and no longer has the same geometrical relationship to the other markers, then it may be excluded from tracking. The Varian TrueBeam linear accelerator uses kilovoltage (kV) imaging or "triggered imaging" to monitor the location of the fiducials during the treatment with the imaging software automatically identifying the fiducials and comparing the detected position to the expected position. The SGRT system will gate the beam and the fiducials will be used as confirmation of the tumor location. For the purpose of this study, the triggered images will be acquired every 15 seconds. If three consecutive kV images indicate the fiducials are more than 3 mm from the planned position (regardless of the SGRT breath hold result), or if the treating physician is concerned about the fiducial position at any timepoint during the treatment, the treatment can be stopped and the procedure can be repeated as per above as if the patient was out of tolerance, where a new "VRT breath hold" reference surface capture is obtained and then the short arc cone beam CT is obtained utilizing the new "VRT breath hold" with corresponding additional shifts recorded in the treatment log.

5.3 Fiducial placement

Fiducial placement will be performed per institutional standards.

5.4 Supportive Care

All supportive therapy for optimal medical care will be given during the study treatment period 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.

5.5 Concomitant Systemic Therapy

Concurrent systemic therapies with SBRT are not allowed during the SBRT course due to the potential for added toxicities. Systemic agents would be preferentially stopped one week prior to radiation start and held for one week after if they have radiosensitizing effects. Other systemic agents can be stopped prior to radiation start and administered the day after radiation completion if desired by the treating medical oncologist.

6. STUDY CALENDAR

Study Procedures	**Screening**	**During SBRT[4]**	**One month after SBRT[5]**	**Active follow-up Year 1[6]** (3, 6, 9, 12 months)	**Active follow-up Year 2[6]** (18 and 24 months)	**Yearly Long-term follow-up** (after 24 months)
Informed Consent	X[1]					
Medical history[7]	X[1]	X		X[14]		
Physical exam[7]	X[1]	X		X[14]		
ECOG Performance status	X[1]	X		X[14]		
CT chest[8]	X[2]			X	X[6]	
PFTs[9]	X[3]			X[3]		
Serum pregnancy test[10]	X					
Toxicity assessment[11]	X	X	X	X[14]		
Concomitant medications[12]	X					
Quality of Life Assessment[13]	X		X	X		
Overall survival[15]		X				

Key to Footnotes

[1] Screening window is within 30 days from enrollment. Exception is height which can have a window of up to 5 years prior to enrollment.

[2] Screening window is within 90 days from enrollment.

[3] Subjects should have baseline PFTs within 6 months of start of radiation. Follow up PFTs at 6-month visit only.

[4] The designated procedures must be performed at least once during SBRT.

[5] This visit should occur in subjects 30 days (±15 days) after treatment stops for whatever reason (toxicity, completion, or at discretion of the investigator).

[6] For subjects who had a complete response, partial response, or stable local disease and discontinue study therapy for reasons other than local progressive disease, every effort will be made to obtain imaging studies and tumor assessments as outlined in the Study Calendar until at least 24 months of radiographic follow-up after last SBRT or documented local progression, whichever occurs first. The last scan data collected must have been performed no earlier than 24 months from enrollment (i.e. the next scan performed after the subject has been enrolled for at least 24 months).

[7] Complete history at baseline only, thereafter focused history on symptoms/toxicity; physical exam to include evaluation by body system and weight. Height at screening only.

[8] Use of contrast is encouraged but optional at the discretion of the investigator. CT or CT portion of PET/CT from simulation may be used for the Screening requirement at the discretion of the investigator.

[9] To include FEV1 and DLCO. Follow up PFTs at 6 months only.

[10] Within 14 days prior to day 1 of treatment; only required for FOCBP as defined in Section 3.2.

[11] Baseline symptoms and toxicities will be recorded as referenced in section 7.1 Subsequent adverse events of special interest assessments should start at study treatment initiation and continue up to 12 months after the last treatment of SBRT. Toxicity assessment may be performed over the phone.

[12] Document all concomitant medications subject is taking at the time of consent only.

[13] QOL using the MDASI-LC lung surveys administered either via paper (preferred; either in-person or via mailed to the subject) or over the phone with research staff will be obtained at five time points:
1) within 30 days prior to the initiation of SBRT
2) at one Month after SBRT (±15 days),
3) at 3-month follow-up (±30 days),
4) at 6-month follow-up (±30 days), and
5) at 12-month follow-up (±30 days).

[14] Follow-up office visits may be performed virtually per investigator discretion (if weight is not performed due to a visit being conducted virtually, this will not be a deviation)

[15] **Survival:** All subjects will be followed for survival until death, lost to follow-up, consent withdrawal or until the criteria for the final analysis are reached. Survival assessment may be

conducted during clinic visit or via telephone. **Minimum Frequency after study treatment discontinuation:** Active-Follow-up Year 1 → at 3, 6, 9, 12 month time-points (± 30 days); Active Follow-up Year 2 → at 18 and 24 month time-points (± 30 days); Long-term Follow-up → yearly (± 60 days)

7. DETAILS ON STUDY PROCEDURES

Please also refer to the Study Calendar in Section 6.

7.1 Screening Procedures

- **Informed Consent:** No protocol-related assessments may be performed prior to obtaining informed consent.
- **Medical History:** A complete relevant medical history should be obtained, including documentation of any clinically significant pre-existing conditions.
- **Physical Examination and Performance Status:** Evaluation by body system, weight, height, and ECOG performance status.
- **Baseline Symptoms and Toxicities:** Document pre-existing symptoms including complications from fiducial placement and any toxicities present (per NCI CTCAE v5.0) at the time of informed consent and prior to the first dose of study treatment.
- **Concomitant Medications***:* Document any concomitant medications; concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.
- **CT chest:** This will be performed utilizing standard imaging procedures at the timepoints indicated in Section 6. Use of contrast is encouraged but optional at the discretion of the investigator. CT or CT portion of PET/CT from simulation may be used for the Screening requirement at the discretion of the investigator.
- **Pulmonary Function Tests:** Should include DLCO and FEV1.
- **Quality of Life:** QOL using the MDASI-LC lung surveys will be obtained.

7.2 Treatment Procedures

7.2.1 During SBRT treatment

- **Physical Examination and Performance Status:** Evaluation by body system, weight, and ECOG performance status
- **Medical history:** focused history on symptoms/toxicities
- **AEs:** Record adverse events of special interest as defined in **10.1.2** per NCI CTCAE v5.0

7.3 One Month after SBRT treatment

This visit should occur 30 days (±15 days) after last dose of study treatment. **NOTE:** this 30-day time period applies even if the subject is taken off study treatment and begins new anti-cancer treatment during this time period.

- **AEs:** Record adverse events of special interest as defined in **10.1.2**.
- **Quality of Life:** QOL using the MDASI-LC lung surveys will be obtained

7.4 Follow-up

The 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 at another institution.

If the subject cannot be contacted following three attempted phone calls over a period of 10 business days, the subject will be contacted in writing. Lost to follow-up is defined as four consecutive unsuccessful documented attempts (telephone and written) to contact the subject.

7.4.1 Active Follow-Up Year 1

Active follow-up during Year 1 will occur at the time-points indicated in Section 6 for the first year from the last administration of protocol-directed therapy or until death or consent withdrawal. Office visits may be performed virtually per investigator discretion.

- **Physical Examination and Performance Status:** Evaluation by body system, weight, and ECOG performance status.
- **Medical history:** Focused history on symptoms/toxicities.
- **AEs:** Record adverse events of special interest as defined in **10.1.2** for 12 months after last dose of SBRT.
- **CT chest** For subjects who had a complete response, partial response, or stable local disease and discontinue study therapy for reasons other than local progressive disease. This will be performed utilizing standard imaging procedures at the timepoints indicated in Section 6. Use of contrast is encouraged but optional at the discretion of the investigator.
- **Pulmonary Function Tests:** Should include DLCO and FEV1. At 6 months after radiation completion only.
- **Quality of Life:** QOL using the MDASI-LC lung surveys will be obtained at 3 month follow-up, at 6 month follow-up, and at 12 month follow-up.
- **Survival Assessment:** May be assessed by review of the medical record or via phone call.

7.4.2 Active Follow-Up Year 2

Active follow-up during Year 2 will occur at the time-points indicated in Section 6.

- **CT chest**: For subjects who had a complete response, partial response, or stable local disease and discontinue study therapy for reasons other than local progressive disease. This will be performed utilizing standard imaging procedures at the timepoints indicated in Section 6. Use of contrast is encouraged but optional at the discretion of the investigator.
- **Survival**: May be assessed by review of the medical record or via phone call.

7.4.3 Long-Term Follow-up

Long-term follow-up after Year 2 will occur at the time-points indicated in Section 6.

- **Survival**: May be assessed by review of the medical record or via telephone

7.5 Treatment Discontinuation Criteria

Study treatment will continue until completion of protocol-directed treatment per Section 5.1.6. Reasons a subject may discontinue study treatment early include:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw study consent
- 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

7.6 Off Study

Subjects will remain on study until the criteria for the final analysis have been met (Section 12.5.1). Reasons a subject may be removed early from the study include, but are not limited to:

- Subject non-compliance with study participation, in the opinion of the investigator
- The subject or legal representative (such as a legal guardian) withdraws study consent
- The subject is lost to follow-up
- Investigator's decision to withdraw the subject
- Subject death
- Early termination of the study

When subjects are removed from the study, the reason for study removal and date the subject was removed should be documented.

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

8. DATA AND SAFETY MONITORING PLANS

Data will be collected in electronic case report forms (eCRFs). Study personnel will be trained on data entry by the sponsor and provided protocol-specific eCRF guidelines.

This protocol will be monitored according to the processes in effect for all LCI investigator-initiated studies, the protocol-specific monitoring plan and will abide by applicable regulations and guidelines (e.g. Good Clinical Practice [GCP]). It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator and other sponsor-level team members will meet regularly to monitor subject consents, enrollment and retention, safety data, and timeliness/validity/integrity of the data. Documentation of these meetings will be kept with study records. The Sponsor-Investigator will submit reports to the LCI Data and Safety Monitoring Committee according to the institutional Data and Safety Monitoring Plan.

This study will be monitored to ensure the study is conducted in compliance with the study protocol, SOPs of the LCI and Atrium Health Office of Clinical and Translational Research (and/or other participating institutional SOPs), the FDA, and other applicable regulations and guidelines (e.g. GCP).

Investigators and/or their delegated study personnel will be required to be available during the monitoring visits.

9. ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a study subject who is administered any treatment or drug that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials are also considered adverse events. Adverse events may also include pre or post-treatment complications that occur as a result of protocol mandated procedures (e.g., invasive procedures such as biopsies).

An increase in grade to a pre-existing CTCAE toxicity grade present at the time of study treatment initiation will be recorded as an AE. Changes in vital signs, ECG, physical examination, and laboratory test results will be recorded as an AE if they are judged clinically significant by the investigator and/or require a medical intervention or dose modification.

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study treatment administration should be considered pre-existing and should be documented.

An AE does not include:

- relapse or progression of the underlying malignant disease;
- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); **NOTE:** the condition that leads to the procedure may be an adverse event;
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions);
- overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation

The severity of adverse events should be classified and recorded according to the CTCAE version 5.0.

9.1.2 Adverse Event of Special Interest (AESI)

Adverse Events of Special Interest for this protocol are defined as all non-hematologic adverse events grade 2 or higher related to SBRT or implantation of fiducials.

10.1.3 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the radiation treatment or intervention is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the study treatment and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by study treatment.

Causality assessment to study treatment is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study treatment, known mechanism of action or side effect profile of study treatment, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering study treatment as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with study treatment exposure
- One or more occurrences of an event not commonly associated with study treatment exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the Sponsor-Investigator could determine that there is *reasonable possibility* that the study treatment caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the study treatment group than in a concurrent or historical control group

9.1.3 Adverse Reaction

An adverse reaction means any adverse event caused by the treatment intervention. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the study treatment caused the event.

9.1.4 Serious AE or SAR

An AE or SAR is to be considered serious if the investigator deems it as such and the event results in any of the following outcomes:

- Death (fatal);
- Life-threatening situation (subject is at immediate risk of death);
- Persistent or significant disability/incapacity;
- Requires or prolongs inpatient hospitalization*;
- A congenital anomaly/birth defect in the offspring of a subject who received study drug;
- Based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the afore listed outcomes from occurring (e.g. intensive treatment in an emergency room without hospitalization, blood

dyscrasias or convulsions that do not result in hospitalization, development of drug dependency or drug abuse).

*Hospitalizations for study treatment administration, protocol-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events, will not be recorded as SAEs. Other hospitalizations planned at the beginning of the trial also do not need to be reported as a SAE.

Pregnancy
Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 30 days of the subjects last dose of study treatment should be recorded as SAEs.

9.1.5 Unexpected AE (AE or SAE) or SAR

An AE or SAR (whether serious or not) is considered unexpected if the specificity or severity of it is not consistent with the applicable treatment.

9.1.6 Unanticipated Problem (UAP)

An UAP is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g., IB 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. By this definition, any event that meets the criteria defined in Section 10.1.5 would meet the criteria for a UAP. However other events may also meet the criteria for a UAP, e.g., a lost or stolen laptop computer that contains sensitive study information.

9.2 Attribution

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

Table 2. Adverse effect relationship to study treatment	
Definite	The AE is ***clearly related*** to the treatment under investigation
Probable	The AE is ***likely related*** to the treatment under investigation
Possible	The AE ***possibly related*** to the treatment under investigation
Unlikely	The AE is ***doubtfully related*** to the treatment under investigation
Unrelated	The AE is ***clearly not related*** to the treatment under investigation

The investigator is responsible for verifying and providing source documentation for all AEs and assigning the attribution for each event for all subjects enrolled on the trial.

9.3 Timing and Reporting

9.3.1 Adverse Events of Special Interest

All AESIs from the time of D1 of study treatment up to 12 months after last dose of study treatment (including event name, grade, start/stop date and attribution) will be collected on the eCRF.

9.3.2 SAEs

After informed consent but prior to initiation of study treatment, only SAEs determined to be related and unexpected to a protocol-mandated intervention will be reported (e.g. SAEs related and unexpected to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of a SAE or a serious SAR, recording of the event must begin from day 1 of treatment and continue through the 30-day follow-up period after study treatment is discontinued. SAEs determined to be related to study treatment or procedures are reportable for the duration of the subject's participation in the trial.

It is the responsibility of the Sponsor-Investigator, investigators and the study conduct team to ensure SAEs are reported according to the Code of Federal Regulations (CFR), GCP, the protocol guidelines, IRB, and FDA policy.

9.3.2.1 Reporting to Sponsor-Investigator

All SAEs (whether considered related or not, expected or not) must be reported to the Sponsor-Investigator within 1 business day of awareness.

9.3.2.2 Reporting to the IRB

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

9.3.3 UAPs

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

10. DISEASE EVALUATION

10.1 Criteria used for Efficacy Evaluation

Response will be defined by an adaptation of RECIST 1.1 criteria. Only lesions treated by SBRT will be followed for response.

10.1.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements from **lung lesions treated by SBRT only** must be recorded in millimeters (or decimal fractions of centimeters).

10.1.1.1 Non-measurable Lesions

All other lesions, including small lesions (longest diameter <10 mm), are considered non-measurable disease. All non-measurable lung lesions **treated by SBRT only** must be recorded.

10.1.1.2 Target Lesions Treated with SBRT

All target lesions treated with SBRT should be identified and recorded and measured at baseline. A sum of the longest diameters for all lesions intended to be treated with SBRT will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

10.1.1.3 Non-target Lesions Treated with SBRT

All other lesions (or sites of disease) treated with SBRT including any measurable treated lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.1.1.4 Evaluation of Target Lesions Treated with SBRT

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Table 2. Evaluation of Target Lesions Treated with SBRT

Complete Response (CR)	Disappearance of all treated lesions.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of treated lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of treated 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.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

10.1.1.5 Evaluation of Non-target Lesions Treated with SBRT

Table 3. Evaluation of Non-target Lesions Treated with SBRT

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level.

Non-CR/ Non-PD	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the Sponsor-Investigator.

10.1.1.6 Evaluation of the Lesions Treated by SBRT

Table 4. Evaluation of the Lesions Treated by SBRT

Target Lesions	Non-Target Lesions	Overall Response
CR	CR	CR
CR	Non-CR/ Non-PD	PR
CR	Not evaluated	PR
PR	Non-PD/ or not all evaluated	PR
SD	Non-PD or not all evaluated	SD
Not all evaluated	Non-PD	NE
PD	Any	PD
Any	PD*	PD
Any	Any	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

11. STATISTICAL CONSIDERATIONS

11.1 Milestones

11.1.1 Registration Date

The date the subject signs the informed consent.

11.1.2 Enrollment Date

The date of first SBRT dose.

11.1.3 Treatment Discontinuation Date

The date the investigator makes the decision to discontinue subject from study treatment. See Section 7.4.3 for criteria for discontinuation of treatment.

11.2 Sample Size and Accrual

This pilot study is designed to evaluate the safety (primarily evaluating grade 2+ pulmonary toxicities) and preliminary efficacy of the three methods of SBRT administration (free breathing SGRT, SGRT with breath hold, and SGRT with breath hold + fiducials). This study is not powered for formal hypothesis testing. Analysis of 45 total evaluable subjects, with a goal of at least 15 evaluable in Cohorts 1 and 2, will provide adequate results to inform future studies.

11.3 Endpoints

11.3.1 Definition of Primary Endpoint

The primary endpoint is the occurrence of acute and late grade 2 or higher pulmonary toxicities which will be recorded as a binary variable determined for each subject indicating whether or not the subject had at least one grade 2 or higher pulmonary toxicity related to SBRT or implantation of fiducials. Acute toxicities are those that occur within 30 days of last dose of SBRT. Late toxicities are toxicities that occur after that time.

11.3.2 Definition of Secondary Endpoints

11.3.2.1 Reliability of gated SBRT treatments

Reliability of gated SBRT treatments is defined as the measured shift deltas that are determined utilizing SGRT vs SGRT + fiducials based on target position at the time of verification imaging (CBCT). This will be recorded as numerical values for each of the shift/rotational directions and the vector composites of the directional shifts. Reliability will be measured with each fraction.

11.3.2.2 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 treated tumor(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). Local control will be estimated at 12 and 24 months.

11.3.2.3 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.

11.3.2.4 Quality of Life

QOL will be assessed using the MDASI-LC lung survey. Surveys will be obtained at five time-points: 1) within 30 days prior to the initiation of SBRT 2) at one month after SBRT (±15 days),

3) at 3-month follow-up (±30 days), 4) at 6-month follow-up (±30 days), and 5) at 12-month follow-up (±30 days)

11.3.3 Definition of Safety Endpoints

Safety endpoints will include SBRT dosing administration (including dose/fractions received for SBRT), incidence of AESIs, incidence of SAEs, and deaths while on study therapy. Toxicities will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Toxicities will be tabulated by type and grade. Additionally, the results of PFTs will be captured at the study calendar time points.

11.4 Analysis Populations

All subjects who receive at least one fraction of SBRT will be included in all efficacy and safety assessments. Additionally, the local control population will include all subjects in the efficacy population who have at least 6 months of radiographic follow-up. Subjects in cohorts 2 or 3 (breath hold SGRT or breath hold SGRT + fiducials) will be included in the analyses for reliability. Exploratory analyses 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.

11.5 Analysis Methods

11.5.1 Timing of Analysis

The reliability analyses for subjects in cohorts 2 and 3 will occur when all subjects have completed their last treatment of SBRT on study. The primary analysis will occur once all subjects have 12 months of follow up since their last treatment of SBRT. Baseline characteristics and secondary endpoints will also be assessed at the time of the primary analyses. A final analysis will be conducted after all surviving subjects who are not lost to follow up or have not been withdrawn from the study have been followed for at least 2 years after last treatment of SBRT.

11.5.2 Disposition

A disposition, summary of all consenting subjects will be provided. This will include a summary of subjects who consented, were treated, discontinued treatment, died, and were lost to follow-up or withdrew consent.

11.5.3 Baseline Subject and Disease Characteristics

A summary of subject demographics and disease-related characteristics will be completed and selected previous treatment history will be assessed. Additionally, PTV volume and respiratory motion range will be captured for each subject.

11.5.4 Primary Analysis

The frequency and proportions of subjects with grade ≥ 2 pulmonary AESIs within 12 months of last treatment of SBRT will be reported for each cohort, and overall, along with 95% Clopper Pearson confidence intervals.

11.5.5 Secondary Analysis

Reliability, as captured by shift measurements, will be analyzed, and compared between cohorts given sufficient enrollment is achieved in cohort 3, using linear mixed models for repeated measures for each of the directions and the vector composites. Shifts will be modeled with main effects for cohort and fraction number (time), as well as a lesion-specific identifier as a random factor to account for within-lesion correlation. Additionally, baseline disease and treatment factors may also be included in the models.

OS will be analyzed in the efficacy population using Kaplan Meier techniques. Median, 25th, and 75th percentile will be estimated. Selected landmarks for OS at 1 year and 2 years will be obtained from the Kaplan Meier curves. Landmark local control will be estimated in local control population along with 95% confidence intervals at 12- and 24-months using Kaplan Meier methods. Local control and OS analyses will be stratified by disease type: primary lung versus metastatic lung lesions.

Total scores and subscales from the (MDASI-LC QOL survey will be summarized for each subject and evaluated over time (five 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. Provided sufficient survey completion rates are achieved, linear mixed models including cohort, time, and cohort by time interaction will be used. The models will include subject as a random factor in order to account for within-subject correlation.

11.5.6 Safety Analysis

SBRT dosing will be summarized quantitatively. Incidence rates for acute and long-term adverse events of special interest, SAEs, and deaths from the time of initiation of SBRT until 12 months after the last treatment of SBRT will be summarized as counts and proportions. For selected events, 95% Clopper Pearson confidence intervals will be calculated. PFT results will be summarized over time.

11.5.7 Exploratory Analysis

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 may also be carried out on an ad hoc basis.

11.5.8 Interim Analysis

No formal interim analyses are planned.

12. STUDY COMPLETION OR TERMINATION

12.1 Completion

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

- All subjects have died and/or are withdrawn from the study
- All subjects have discontinued from the study
- The IRB, FDA, LCI DSMC, or Sponsor-Investigator discontinues the study because of safety considerations
- The Sponsor-Investigator defines an administrative or clinical cut-off date

12.2 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 any interim analysis
    - Results of parallel clinical studies
    - Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity, or reproduction toxicity).
    - 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 decided 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.

13. STUDY MANAGEMENT

13.1 IRB Approval

The final study protocol and the final version of the informed consent form(s) must be approved in writing by the Sponsor IRB.

The Sponsor-Investigator is responsible for informing the Sponsor IRB of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB annually, as local regulations require.

13.2 Informed Consent

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

13.3 Protocol Adherence

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

13.4 Changes to the Protocol and/or Informed Consent

13.4.1 Amendments to the Protocol

If it is necessary for the study protocol to be amended and/or the informed consent revised, the amendment or a new version of the study protocol (amended protocol) and/or the revised informed consent must be approved by the Sponsor-Investigator, and the Sponsor IRB.

13.4.2 Emergency Modification

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, any site investigator who implements an emergency modification must notify the Sponsor-Investigator. 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.

13.5 Other Protocol Deviations

If a deviation occurs, the event should be reported to the Sponsor-Investigator promptly. Any IRB reportable event that occurs must be reported to the IRB per institutional policies and reported to the Sponsor-Investigator as soon as possible.

NOTE: Protocol deviations that, in the Investigator's judgment, potentially caused harm to participants or others or indicates that the participants or others are at an increased risk of harm, or has adversely impacted data integrity will be reported promptly to the IRB per IRB reporting requirements.

13.6 Retention of Records

Essential documentation (e.g. AEs, records of study drug 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.

13.7 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 GCP guidelines. The study will also be carried out in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6 and in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. DSMC, IRB, FDA) will be obtained for all participating centers before the 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. The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Title 21 of the CFR 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.

13.8 Confidentiality of Records

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.

13.9 Compliance with ClinicalTrials.gov

The Sponsor-Investigator is solely responsible for determining whether the trial and its results are subject to the requirements for submission to ClinicalTrials.gov (http://www.clinicaltrials.gov).

14. REFERENCES

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