Protocol Title:

A Feasibility Study of Stereotactic MRI-guided Adaptive Radiation Therapy (SMART) in One Fraction for Inoperable Primary or Metastatic Carcinoma (SMART ONE)

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Sponsor Investigator Signature Page

Title (2020-CHU-002) A Feasibility Study of Stereotactic MRI-guided Adaptive Radiation Therapy (SMART) in One Fraction for Inoperable Primary or Metastatic Carcinoma (SMART ONE)

This study protocol was subjected to critical review and has been approved by Miami Cancer Institute. The information it contains is consistent with the current/risk benefit evaluation of the study treatment as well as with the moral, ethical and scientific principles governing clinical research following the guidelines on Good Clinical Practice.

_____ _____

Michael Chuong, M.D. Date
Sponsor Investigator
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Investigator's Agreement

I have read this study protocol, including appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), Declaration of Helsinki (2013), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

Protocol Summary

Sponsor/Investigator: Michael Chuong M.D. Miami Cancer Institute

Study Treatment: Single-fraction Stereotactic Ablative Body Radiation Therapy (SABR)

Study Number: 2020-CHU-002

Title: A Feasibility Study of Stereotactic MRI-guided Adaptive Radiation Therapy (SMART) in One Fraction for Inoperable Primary or Metastatic Carcinoma (SMART ONE)

Study Center(s): Multi-Site

Investigators: Multi-site

Study periods (years):
Estimated last patient enrolled: Q3 2023
Estimated date last patient last visit: Q3 2024

Hypothesis:
Single-fraction SABR using daily MRI guidance with on-table adaptive replanning as needed is well-tolerated and able to be completed within a practical amount of time.

Objectives

Primary:
To determine feasibility and tolerability of SABR delivered in one fraction.
Feasibility will be achieved if all are true:

- •Successful completion of treatment to each lesion within 3 working days of intended treatment completion
- •Successful completion of treatment to each lesion within 90 minutes from the patient entering the treatment room until treatment completion
- •Image guidance verification of treatment delivery within 5 mm of the planned delivery

Tolerability will be achieved if all are true:

- •No greater than 4 of 30 patients experience grade 3 or higher acute toxicity within 90 days of completing SABR
- •No grade 5 toxicity is attributed to SABR

Secondary:

- •To assess 1-year local control
- •To assess 1-year overall survival
- •To assess acute and late toxicity
- •To assess patient-reported quality of life

STUDY DESIGN

This is a single arm, multi-site, feasibility study of single-fraction SMART for primary or metastatic carcinoma involving the lung, liver, adrenal gland, abdominal/pelvic lymph node, pancreas, and/or kidney.

This study will consist of a Baseline period (Day-28 to Day-1), Enrollment, Treatment period (Day 1 up to Day 3), and After treatment visits occurring 6 weeks (optional), 3 months, 6 months, 9 months, and 12 months after completion of Study Therapy.

All patients deemed eligible will receive single-fraction SABR therapy using MRI as image-guidance. A total of 1-10 total lesions may be treated on the study and each lesion will be treated either sequentially or concurrently in one fraction.

FACT-G Survey will be administered at baseline and every visit after completion of Study Therapy.

Safety assessment performed will include collection of Adverse Events (AEs), vital signs, and physical exam, ECOG and laboratory assessments.

CT scan of the Chest, Abdomen and Pelvis will be conducted at baseline, 6 weeks/ optional (± 1 week) after study therapy and every 3 months (± 1 week) until 12 months (± 1 week) after completion of SABR.

All AEs will be collected upon initiation of treatment and for a minimum of 100 days after completion of study treatment or until resolution, whichever occurs later. Any pregnancy that occur at the time of study participation are to be reported.

Number of Patients (planned): It is anticipated that approximately 30 patients will be enrolled and treated under this study protocol.

Sites: Up to five (5) US sites

Inclusion Criteria:

Patient will be eligible for study entry if all of the following criteria are met:

1. Subject must be ≥18 years of age at the time of study enrollment
2. Subject must have Biopsy-confirmed primary or metastatic carcinoma with involvement of the lung, liver, adrenal gland, pancreas, kidney, and/or abdominal/pelvic lymph node that would receive SABR
3. Any lesion that would receive SABR under this study protocol is no larger than 5 cm in greatest dimension
4. 1-10 total lesions that would receive SABR
5. If multiple lesions are treated, they must be at least 3 cm apart
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
7. Life expectancy at least 6 months
8. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Abstinence is acceptable if it's the patient preferred method. Should a woman become pregnant or suspect she is

pregnant while participating in this study, she must inform her treating physician immediately.

9. Patients receiving hormonal therapy or immunotherapy such as immune checkpoint inhibitor that had begun at least 4 weeks prior to SABR will be allowed.

Exclusion criteria:

Patients will not be eligible for study entry if any of the following criteria are met:

1. Subject has contraindication to having an MRI scan
2. Subject has central or ultra-central lung tumor that would receive SABR on this study, defined as a lesion located within 2 cm of the trachea and proximal bronchial tree
3. Subject has received cytotoxic chemotherapy or investigational agent within 2 weeks of SBRT
4. Subject has uncontrolled brain metastases, spinal cord compression, or leptomeningeal carcinomatosis
5. Subject has any unresolved toxicity (Common Terminology Criteria for Adverse Events version 5.0 > grade 2) from previous anti-cancer therapy
6. Any condition, therapy or lab abnormality in the opinion of the investigator that would interfere with patient safety, evaluation of study treatment or interpretation of study results
7. Subject has received prior radiation therapy that directly overlaps any radiation therapy given in this study
8. Subject has received radiation therapy that could lead to an unacceptably high risk of clinically significant normal tissue injury due to high cumulative normal tissue dose as determined by the investigator
9. Female subject who are pregnant or breastfeeding
10. Subject who has received vascular endothelial growth factor (VEGF) inhibitor such as bevacizumab within 4 weeks prior to study therapy or planned to receive it within 4 weeks after study therapy.

Radiation Therapy

1. **Simulation:** Both MRI and CT simulations scans must be performed in the treatment position. MRI simulation scans should be performed on the MRIdian Linac. Use of dummy MRI coils is permitted.

2. **Supplemental Oxygen:** At the treating physician's discretion, the patient may be simulated and treated with supplemental oxygen by nasal canula since this may improve the breath hold length and thus improve the treatment duty cycle efficiency. The oxygen flow rate will be at the treating physician's discretion although is suggested to be approximately 2-3 L/min.

3. **Daily MR image guidance:** The use of image guidance using MRI is mandatory. This will include a pre-treatment volumetric MRI using a TRUFI sequence that will be obtained prior to each delivered fraction.

4. **Target Volumes:**
   - Gross Tumor Volume (GTV) will ,include visible tumor as seen on MRI/CT
   - Clinical Target Volume (CTV) is optional and will be used at the discretion of the treating physician
   - Planning Target Volume (PTV) will be created from a 3-5 mm uniform expansion from the GTV/CTV

5. **Prescription dose and fractionation**
   Each lesion will be treated in one fraction. The prescription dose is dependent on the anatomic location of the lesion and based on previously published safety data.

6. **Treatment Planning** Step-and-shoot intensity modulated radiation therapy (IMRT) using 6 MV FFF photons will be used. Ideally, ≥95% of the PTV and ≥99% of the GTV/CTV should receive ≥100% of the prescribed dose. Hotspots of at least 120-130% of the prescription dose are permitted, and in fact are encouraged, if they are located within the GTV and not in organs at risk (OARs). For patients treated to multiple lesions, separate plans will be generated for each lesion if treated sequentially while one plan will be generated if all lesions are treated in the same session. The cumulative dose to OARs from all treatment plans should be assessed regardless of the number of lesions.

7. **Treatment delivery and on-table adaptive replanning** All patients will receive radiation therapy using photons on the MRIdian Linac system. For each delivered fraction, a volumetric MRI data set will be obtained using system integrated sequences. An estimated delivered dose will be calculated and saved using the software on the console (dose prediction). An adapted radiation therapy plan is created based on physician assessment of medical necessity. If required, adaptive replanning must be performed on the day of treatment delivery in order to achieve at least the same dose avoidance as the original plans. If multiple lesions are to be treated on this study, it is preferred that each one should be treated separately although it is permitted that multiple be treated concurrently.. During radiation dose delivery, continuous cine MR image acquisition in at least one principal plane is mandatory for soft tissue tracking and radiation beam gating.

Treatment Response Evaluation

Imaging Assessment Treatment response will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1.

Statistical Methods

Primary objective:
The point estimate for feasibility will be reported as a binary variable with its 95% confidence interval. The point estimate for tolerability will be reported as a binary variable with its 95% confidence interval.

Secondary objectives:
1-year local control (LC) will be assessed according to RECIST 1.1 criteria and will be estimated using the Kaplan-Meier method along with the corresponding 95% confidence interval from the time of study treatment.

1-year overall survival (OS) will be estimated using the Kaplan-Meier method along with the corresponding 95% confidence interval from the time of study treatment.

The proportion of patients who experience acute grade 3 or higher toxicity attributable to SABR will be determined along with the corresponding 95% confidence interval. For patients receiving SABR to multiple lesions, acute toxicity will be determined from the date of the initiation of SABR.

Patient-reported quality of life will be determined using the FACT-G survey instrument prior to and after SABR.

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1. BACKGROUND

1.1 Stereotactic ablative body radiation therapy (SABR)

Radiation therapy (RT) has historically been delivered using a fractionated approach, typically once daily over multiple weeks, based on classic radiobiological principles to optimize tumor cell kill and allow for normal tissue repair(1). This approach has served as the foundation for the field of radiation oncology and can achieve effective palliation or cure when typically used in a multi-disciplinary manner with systemic therapy and/or surgery.

Technological advances over the most recent decades have achieved increasingly conformal delivery of radiation dose such that there is better sparing of normal tissues, which in some cases may allow for an increase in dose delivered to the target(2-4). These advances include improvements in complex modulation of delivered dose, motion management for mobile tumors, and on-board imaging guidance capabilities(5, 6). A benefit of these improvements is the ability to deliver hypofractionated radiation therapy, or doses larger than approximately 2 Gy per fraction, in a fewer number of fractions. Extreme hypofractionation can be delivered using stereotactic body radiation therapy (SBRT) in 5 or fewer fractions(7). A unique radiological effect of delivering larger dose per fraction, such as >8 Gy, has been proposed(8).

Important to note is that the term stereotactic body radiotherapy (SBRT) is not synonymous with ablative radiation dose as non-ablative dose can be delivered with this technique; ablative dose is generally agreed to be a biologically effective dose (BED10) of at least 100 Gy. For example, SBRT for pancreas cancer is typically delivered with a non-ablative dose (i.e., 30-35 Gy in 3-5 fractions) due to the proximity of organs at risk including the small intestine, whereas SBRT for peripheral non-small cell lung cancer is commonly delivered a with ablative dose (i.e. 60 Gy in 5 fractions; BED10 = 132 Gy). Outcomes of ablative SBRT are generally superior to those of non-ablative SBRT as there are well-described dose response relationships that have been established for many cancers. The term stereotactic ablative body radiation therapy (SABR) was developed to more clearly communicate that an ablative dose is prescribed(9).

1.2 Single-fraction SABR

While SABR is delivered in as few as 1 but up to 5 daily fractions by definition, the vast majority of published outcomes data have used 3-5 fractions. Nonetheless, there are published prospective and retrospective studies for single-fraction SABR as summarized in a recently published critical review by Ng and colleagues(10). The most substantial supporting data for single-fraction SABR exists for early-stage peripheral non-small lung cancer (NSCLC) for which several randomized trials have been completed showing no significant difference in outcomes between singe- and multi-

fraction regimens(11,12). Despite these randomized data, the utilization of single-fraction SABR for early-stage NSCLC has been scarce. Safety and feasibility of single-fraction SABR has been demonstrated for other anatomic sites including the liver (13), lymph nodes (14), adrenal gland(15), and the kidney(16). Single-fraction SABR for locally advanced pancreas cancer has been prospectively evaluated (notably without intrafraction image guidance or daily adaptive replanning), and has been associated with increased gastrointestinal toxicity compared to fractionated SABR(17).

A single-fraction regimen should be at least isotoxic and isoeffective as compared to multi-fraction SABR for such an approach to be considered a reasonable alternative. Assuming that both are true, then there are several advantages of completing treatment in one fraction including reduced cost(18), potentially reduced lymphopenia(19), and increased patient convenience. One reason that clinicians may be hesitant to use single-fraction SBRT is concern about geographic miss, which stems from the lack of intrafraction evaluation of the tumor and internal anatomy using a linear accelerator using x-ray and/or CT-guidance(20). Furthermore, generous margins may be placed on the gross tumor to decrease the risk of a geographic miss, thereby increasing normal organ dose and potentially increasing the risk of more severe toxicity(21).

1.3 MR-guided radiation therapy

The recent develop of linear accelerators that use magnetic resonance (MR) instead of CT imaging for image guidance represents a tremendous advance in how radiation therapy is fundamentally delivered(22). MR guidance offers several important advantages including: 1) superior soft tissue imaging, 2) continuous intrafraction visualization, 3) tissue tracking and automatic beam triggering, and 4) the ability to perform on-table (or online) adaptive replanning(23). These technical capabilities have begun a transformation within the field of radiation oncology by facilitating better normal organ sparing, especially those in immediate proximity to the target, by permitting smaller margin expansions, treatment in breath hold, and daily on-table adaptive planning to account for intrafraction changes in internal and/or tumor anatomy(6). In fact, this technology is particularly well-suited for the delivery of SABR, especially in one fraction.

There is a growing body of literature describing favorable outcomes of MR-guided SABR for various cancers in diverse regions of the body, including the lung(24), breast(25), liver(26), pancreas(27), adrenal gland(28), kidney(29), lymph nodes(30), and prostate(31).

The collective published experience of MR-guided SABR has nearly exclusively used multi-fraction SABR although a recent report of single-fraction MR-guided SABR for lung tumors to 34 Gy was recently reported from The Netherlands suggesting feasibility and tolerance(32). However, treatment times were rather long although this can be explained by the decision of the investigators to perform on-table adaptive replanning prior to the start of treatment and then again half-way through; the clinical significance

of this is unclear and the total treatment time would be significantly reduced if treatment was not interrupted to adapt the plan a second time. Given the encouraging outcomes of single-fraction SABR delivered with CT-guidance, this study was designed to explore the feasibility and tolerability of single-fraction SABR using an MR-LINAC for various extracranial and extra-osseous tumors using on-table adaptive replanning, as needed. (33)

2. HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypothesis

Single-fraction SABR using daily MRI guidance with on-table adaptive replanning as needed is well-tolerated and able to be completed within a practical amount of time.

2.2 Primary objective

- To determine feasibility and tolerability of SABR delivered in one fraction

Feasibility will be achieved if all are true:

- Successful completion of treatment to each lesion within 3 working days of intended treatment completion
- Successful completion of treatment to each lesion within 90 minutes from the patient entering the treatment room until treatment completion
- Image guidance verification of treatment delivery within 5 mm of the planned delivery
- Tolerability will be achieved if all are true:
- No greater than 4 of 30 patients experience grade 3 or higher acute toxicity within 90 days of completing SABR
- No grade 5 toxicity is attributed to SABR

2.3 Secondary objectives

- To assess 1-year local control
- To assess 1-year overall survival
- To assess acute and late toxicity
- To assess patient-reported quality of life

3. STUDY DESIGN

This is a multi-site single arm feasibility study of single-fraction SMART for primary or metastatic carcinoma involving the lung, liver, adrenal gland, abdominal/pelvic lymph node, pancreas, and/or kidney. This study will consist of a Screening period (within 28 days from study therapy), Treatment period (Day 1 up to Day 3), and After treatment visits occurring at 6 weeks (optional), and every 3 months until 12 months after completion of study therapy.

All patients deemed eligible will receive single-fraction SABR therapy using MRI as image-guidance. A total of 1-10 total lesions may be treated on the study and each lesion will be treated sequentially in one fraction.

It is anticipated that approximately 30 patients will be enrolled and treated under this protocol at up to 5 sites in the US.

4. SITE AND INVESTIGATOR SELECTION

Investigators and sites will be selected and qualified by MCI for participation in this clinical investigation. Sites must have the facilities, specific technology, patient population and the ability to conduct research to fulfill the study requirements as determined by the sponsor investigator. The site must have written IRB approval for the study protocol and the informed consent form prior to enrolling any subjects.

5. PATIENT SELECTION

5.1 Inclusion criteria

1. ≥18 years of age at the time of study enrollment
2. Biopsy-confirmed primary or metastatic carcinoma with involvement of the lung, liver, adrenal gland, pancreas, kidney, and/or abdominal/pelvic lymph node that would receive SABR
3. Any lesion that would receive SABR is no larger than 5 cm in greatest dimension
4. 1-10 total lesions that would receive SABR
5. If multiple lesions are treated, they must be at least 3 cm apart
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
7. Life expectancy at least 6 months
8. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Abstinence is acceptable if preferred by patient. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must in form her treating physician immediately.

9. Patients receiving hormonal therapy or immunotherapy such as immune checkpoint inhibitor that had begun at least 4 weeks prior to SABR will be allowed.

5.2 Exclusion criteria

1. Contraindication to having an MRI scan
2. Central or ultra-central lung tumor that would receive SABR on this study, defined as a lesion located within 2 cm of the trachea and proximal bronchial tree
3. Cytotoxic chemotherapy or investigational agent within 2 weeks of SBRT
4. Presence of uncontrolled brain metastases, spinal cord compression, or leptomeningeal carcinomatosis
5. Any unresolved toxicity (Common Terminology Criteria for Adverse Events version 5.0 > grade 2) from previous anti-cancer therapy
6. Any condition, therapy or lab abnormality in the opinion of the investigator that would interfere with patient safety, evaluation of study treatment or interpretation of study results
7. Prior radiation therapy that directly overlaps any radiation therapy given in this study
8. Prior radiation therapy that could lead to an unacceptably high risk of clinically significant normal tissue injury due to high cumulative normal tissue dose as determined by the investigator
9. Female patients who are pregnant or breastfeeding.
10. Patients who have received vascular endothelial growth factor (VEGF) inhibitor such as bevacizumab within 4 weeks prior to study therapy or planned to receive it within 4 weeks after study therapy.

5.3. Patient recruitment

The patient's treatment team, the study investigator, or treating institution's research team will identify potential study participants. The site principal investigator may screen records of patients for the limited purpose of identifying patients who would be eligible for study enrollment and limited contact information may be recorded to contact the patient regarding study enrollment. However, it is expected that the patient's treatment team or investigator working in consultation with the treatment team will conduct the initial discussion of possible study enrollment with the patient. This recruitment process presents no greater than minimal risk to the privacy of screened patients. A (partial) limited waiver of authorization is requested for reviewing medical records to identify potential research participants, conversing with patients about possible enrollment, and handing of personal health information.

Both men and women in addition to individuals of all races and ethnic groups are eligible for this trial.

6. RADIATION THERAPY

6.1 Simulation

Fiducial markers are not needed for MRI-guided RT and therefore the placement of fiducial markers is not required prior to simulation.

Patients may be positioned in the supine position for simulation and treatment, although prone positioning may be considered using a belly board to displace the small bowel away from target lesion(s) in the abdomen and pelvis. There is not a requirement to use an immobilization device otherwise given the use of continuous infraction visualization with MRI.

At the treating physician's discretion, the patient may be simulated and treated with supplemental oxygen by nasal canula since this may improve the breath hold length and thus improve the treatment duty cycle efficiency. The oxygen flow rate will be at the treating physician's discretion although is suggested to be approximately 2-3 L/min.

Both MRI and CT simulations scans must be performed in the treatment position. It is preferred that MRI simulation be done prior to CT simulation with the CT scan deformably registered to the treatment planning MRI. MRI simulation scans should be performed on the MRIdian Linac. Use of dummy MRI coils is permitted. IV or oral contrast are not required for MRI simulation although Eovist may be used to better visualize hepatic lesions. While contrast may be used for CT simulation, it is not required as the MRI simulation scan is expected to be the primary scan used for contouring and treatment planning. Planning CT scan slice thickness should be 3 mm or less.

A 4D-CT simulation scan should be acquired at least for lesions in the chest and upper abdomen to assess the extent of tumor motion.

For patients with targets in the upper abdomen (e.g., pancreas, adrenal gland) it is recommended that patients have nothing by mouth (NPO) at least 2 hours prior to simulation or treatment. For patients with targets in the pelvis, reproducible bladder and rectal filling should be attempted, as per the discretion of the treating physician.

Arm position will be dependent on the location of the target lesion(s). To improve patient comfort and reproducibility it is preferred that both arms be positioned down at the sides, as close to the body as possible, if appropriate, based on the location of the target lesion(s) the discretion of the treating physician. Positioning both arms down may significantly limit beam angles for treating some lesions, especially those that are very lateral, and therefore positioning the ipsilateral arm above the head while keeping the contralateral arm down to the side should be considered. Both arms may be positioned above the head, as needed.

For patients receiving SABR to multiple lesions in different anatomic locations, several MRI and CT simulation scans may be required especially if the arm positioning will be different for treatment of various lesions. For example, while both arms may be placed down at the sides for treating a para-aortic lymph node, at least one arm may need to be raised above the head for treating a lateral lung lesion.

6.2 Motion management

Motion management must be employed for moving targets. Breath hold treatment, which is strongly preferred, may be either in inspiration or expiration at the discretion of the treating physician, based on patient tolerance, reproducibility, and proximity of the target to OARs. Patients who will be treated in breath hold should be able to reproducibly hold their breath such that a high quality 17-25 second volumetric MRI scan can be obtained with minimal motion artifact.

Patients may be treated using free breathing gating and it is strongly recommended that an MRI-compatible abdominal compression device be used to limit diaphragmatic excursion and tumor motion.

6.3 Daily MR image-guidance

The use of image-guidance using MRI is mandatory. This will include a pre-treatment volumetric MRI using a TRUFI sequence that will be obtained prior to each delivered fraction. Alignment should be to soft tissue including the target lesion.

6.4 Target Volumes

6.4.1. Gross Tumor Volume (GTV)

This will include visible tumor as seen on MRI/CT.

6.4.2 Clinical Target Volume (CTV)

The use of a CTV is optional and at the discretion of the treating physician.

It is suggested that the CTV should be an expansion of 2-5 mm from the GTV, edited out of anatomic barriers to microscopic tumor spread.

6.4.3 Planning Target Volume (PTV)

It is preferred that a 3 mm uniform expansion from the GTV/CTV define the PTV. However, a 5 mm uniform expansion will also be permitted.

6.5 Prescription dose and fractionation

Each lesion will be treated in one fraction.

The prescription dose is dependent on the anatomic location of the lesion and based on previously published safety data.

- Lung (30-34 Gy. BED10 = 120-149.6 Gy)
- Liver (35-40 Gy; BED10 = 157.5-200 Gy)
- Pancreas (25 Gy; BED10 = 93.6 Gy)
- Kidney (25 Gy; BED10 = 93.6 Gy)
- Adrenal gland (25 Gy; BED10 = 93.6 Gy)
- Abdominal/pelvic lymph node (25 Gy; BED10 = 93.6 Gy)

If a CTV is used, then it will be prescribed the same dose as the GTV.

6.6 Organs at risk and constraints

THORACIC			
Structure	**Contouring**	**Constraint**	
Spinal cord	Spinal canal extending ≥2 cm cranial and caudal to the PTV	≤0.03 cc ≤0.35 cc ≤1.2 cc	14 Gy 10 Gy 7 Gy
Skin	Outer 5 mm of the body surface extending ≥2 cm cranial and caudal to the PTV	≤0.03 cc ≤10 cc	26 Gy 23 Gy
Lungs (right and left)	Combined right and left lungs minus GTV	≤1500 cc ≤1000 cc	7 Gy 7.4 Gy
Proximal trachea	Trachea extending ≥2 cm cranial to the PTV or ≥5 cm cranial to the carina (whichever is most cranial) extending caudally to the cranial aspect of the proximal bronchial tree	≤0.03 cc 4 cc	20.2 Gy 10.5 Gy
Proximal bronchial tree	Distal 2 cm of the trachea, carina, right/left main stem bronchi, right/left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right/left lower lobe bronchi; lobar bronchi contour will not extend into the segmental bifurcation	≤0.03 cc 4 cc	20.2 Gy 10.5 Gy

Heart	Superiorly at the level of the bifurcation of the pulmonary artery inferiorly to the apex of the heart, including the pericardium	≤15 cc ≤0.03 cc	16 Gy 22 Gy
Great vessels	Aorta and vena cava (not the pulmonary artery/vein) extending ³2 cm cranial and caudal to the PTV	£10 cc ≤0.03 cc	31 Gy 37 Gy
Chest wall	2 cm radial expansion of the ipsilateral lung excluding mediastinal soft tissue, anterior vertebral body, and any extension outside of the external body contour; extended 2 cm cranial and caudal of the PTV	≤0.03 cc ≤5 cc ≤1 cc	30 Gy 27 Gy 22 Gy
Ribs	Bone and marrow of the ribs as seen on bone windows within 5 cm of the PTV to not include the intercostal spaces	≤0.03 cc ≤1 cc	30 Gy 22 Gy
Brachial plexus	Subclavian and axillary vessels starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib	≤0.03 cc ≤3 cc	17.5 Gy 14 Gy
Esophagus	All muscular layers extending ≥2 cm cranial and caudal to the PTV	≤0.03 cc ≤10 cc	12.4 Gy 11.2 Gy
Stomach	From the gastroesophageal junction to the pylorus	≤0.03 cc ≤10 cc	12.4 Gy 11.2 Gy

ABDOMEN/PELVIS			
Structure	**Contour**	**Volume**	**Dose**
Liver - GTV	Entire liver minus GTV	≤700 cc	9.1 Gy
Spinal cord	Spinal canal extended ≥2 cm cranial and caudal to the PTV	≤0.03 cc ≤0.35 cc ≤1.2 cc	14 Gy 10 Gy 7 Gy
Skin	Outer 5 mm of the body surface extending ≥2 cm cranial and caudal to the PTV	≤0.03 cc ≤10 cc	26 Gy 23 Gy

Chest wall	2 cm radial expansion of the ipsilateral lung excluding mediastinal soft tissue, anterior vertebral body, and any extension outside of the external body contour; extended 2 cm cranial and caudal of the PTV.	≤0.03 cc ≤5 cc ≤1 cc	30 Gy 27 Gy 22 Gy
Esophagus	All muscular layers extending ≥2 cm cranial and caudal to the PTV	≤0.03 cc ≤10 cc	12.4 Gy 11.2 Gy
Stomach	From the gastroesophageal junction to the pylorus	≤0.03 cc ≤5 cc ≤10 cc	12.4 Gy 11.2 Gy 9 Gy
Duodenum	From the pylorus to 4th part of duodenum	≤0.03 cc ≤5 cc ≤10 cc	12.4 Gy 11.2 Gy 9 Gy
Small bowel	Small bowel loops from the jejunum to 2 cm caudal to PTV	≤0.03 cc ≤5 cc ≤10 cc	12.4 Gy 11.2 Gy 9 Gy
Large bowel	Large bowel loops ≥2 cm cranial and caudal to the PTV	≤0.03 cc ≤5 cc ≤10 cc	18.4 Gy 11.2 Gy 9 Gy
Kidney (right and left)	Entire right and left kidneys	Mean V10	7 Gy 33%
Rectum	From the rectosigmoid junction to anal canal	≤0.03 cc ≤5 cc ≤10 cc	18.4 Gy 11.2 Gy 9 Gy
Bladder	Entire bladder	≤15 cc	11.4 Gy

6.7 Treatment planning

Step-and-shoot intensity modulated radiation therapy (IMRT) using 6 MV FFF photons will be used. Ideally, ≥95% of the PTV and ≥99% of the GTV/CTV should receive ≥100% of the prescribed dose. However, depending on the proximity of the normal organs, especially gastrointestinal (GI) luminal structures, that may not be achievable without violating normal organ constraints. If the proximity of OARs results in a clinically significant reduction in dose to the GTV on the original plan, defined as ≤80% receiving ≥100% of the prescribed dose and/or ≤90% receiving ≥90% of the prescribed dose, then multi-fraction SBRT off study should be considered although will not be required. If patients remain on study in this scenario, then attempts should be made to optimize the internal anatomy on the day of treatment to improve target dose coverage as much as reasonably possible, for example ensuring appropriate bladder, rectal, or stomach filling.

Hotspots of at least 120-130% of the prescription dose are permitted, and in fact are encouraged, if they are located within the GTV and not in organs at risk (OARs).

Meeting all OAR constraints should be prioritized, even at the expense of target volume coverage, while secondarily optimizing target volume coverage.
For patients treated to multiple lesions, separate plans will be generated for each lesion. A planning CT dataset that includes all targets and relevant critical structures in the imaging study should be obtained when possible. The cumulative dose to OARs from all treatment plans should be assessed. If multiple lesions are treated, then OAR dose constraints as described in section 6.6 should be considered to be cumulative constraints that should be met in total across all treatment plans regardless of the number of lesions treated.

For targets in the abdomen and pelvis, a PRVGI should be created that is defined as the union of the stomach + duodenum + small bowel + large bowel contours with a 5 mm uniform expansion. If there is any overlap of the PRVGI with the PTV then a PTVopt should be created, which is the PTV minus any overlap of the PRVGI. The treatment plan should be prescribed to the PTVopt instead of the PTV, ensuring that all OAR constraints are met. The dose to the overlapped region of the PTV and PRVGI should be as high as possible while meeting all OAR constraints, although no minimum coverage will be required. If there is not overlap of the PRVGI with the PTV then the treatment plan should be prescribed to the PTV.

6.8 Treatment delivery and on-table adaptive replanning

All patients will receive radiation therapy using photons on the MRIdian Linac system for alignment, dose prediction, tracking, gating, and on-table adaptive planning when clinically indicated.

For each delivered fraction, a volumetric MRI data set will be obtained using system integrated sequences; the preferred sequence is a balanced gradient echo most similar to Siemens True FISP scan with T2*/T1 weighted image-characteristics with at least a 1.5 x 1.5 x 3.0 mm image matrix resolution. The external contour of the patient should be inside the field of view where there are beam angles that will be used for treatment.

The target volume will be rigidly aligned to a reference position by virtual couch movement in cranio-caudal, left-right and anterior-posterior direction to optimally align with the planned treatment isocenter. Depending on operator assessment, these shifts are then executed, and treatment is initiated.

If optimal target to isocenter alignment cannot be achieved, system integrated deformable image registration between the primary treatment image data (used for simulation and treatment planning) and the respective fraction MRI dataset will be performed. Original plan contours are propagated onto the respective fraction MRI dataset. If on-table adaptive planning is clinically indicated, then all tumor volumes and

critical structures within 3 cm radially and 2 cm cranial-caudal from the surface of the PTV will be re-contoured as needed on the volumetric high-quality MRI data set.

An estimated delivered dose will be calculated and saved using the software on the console (dose prediction). An adapted radiation therapy plan is created based on physician assessment of medical necessity. General guidelines to establish medical necessity include but are not limited to the following:

- Any OAR constraint is violated. The same constraints used to develop the original plan will be used to on the day of treatment to determine the need to create an adapted plan.
- Reduction in GTV and/or PTV covered by the prescription isodose compared to the original plan.
- Favorable shift in the relation between GTV and dose-limiting OARs, such that adaptive planning would likely improve the coverage of the GTV.

For patients treated to multiple lesions, adaptive replanning may be required in order to ensure that cumulative dose to OARs meets constraints. As the original treatment plans are required to cumulatively meet all OAR constraints, adaptive replanning must be performed on the day of treatment delivery in order to achieve at least the same dose avoidance as the original plans.

Adaptive dose re-planning does not need to be performed if the dose prediction shows compliance with minimum dose coverage of the GTV and adherence to upper dose/volume limits of all OARs.

If multiple lesions are to be treated on this study, it is recommended that each one should be treated separately as treatment of multiple lesions may significantly prolong total treatment time, which may be poorly tolerated by the patient. However, treatment of multiple lesions on this trial during the same session is permitted if the treating physician believes that treatment would be completed within a feasible amount of time.

During radiation dose delivery, continuous cine MR image acquisition in at least one principal plane (suggested sagittal, but at the discretion of the treating physician) is mandatory for soft tissue tracking and radiation beam gating. To this end, a tracking slice of 7-10 mm thickness will be positioned to include a cross-sectional cut of the target for intra-fractional soft tissue tracking. The tracking/gating volume will be preferably delineated based on the GTV, or otherwise on a well visualized surrogate in proximity to the GTV.

The software should be set so that if 5% or more of the tracked target extends outside of the boundary the beam will gate off. For soft tissue tracking and gating, a minimum cine frame rate of 4 frames/second is mandatory throughout dose delivery although higher frame rates (e.g., 8 frames/second) may be used if available.

During study treatment, a time log will be used to record the following events, at a minimum:

- Patient enters the treatment room
- Volumetric scan initiated
- Target volume/OAR contouring started
- Target volume/OAR contouring ended
- Predicted dose calculation completed
- Treatment plan re-optimization finalized (if performed)
- Treatment delivery started
- Treatment delivery completed

6.9 Treatment plan storage

All clinically approved plans, structures delineated for dose prediction, predicted doses, as well as all adapted radiation therapy plans will be saved and stored in the MRIdian associated software. All initial plans, structures delineated initially and on-table, predicted dose, and adapted plan data are to be backed up for permanent storage and potential later analysis.

6.10 Additional radiation therapy

It is permissible for radiation therapy to be delivered to lesions other than those that are treated on this study. This could be to other lesions that are present at the time that SABR is delivered as part of this study, or new lesions that may appear after the completion of SABR on this study. However, additional radiation therapy should be avoided that would directly overlap or be in proximity to a lesion that previously received radiation therapy on this study that could significantly increase the risk of potentially severe toxicity. It is strongly recommended that additional radiation therapy not be delivered off study to lesions within the same organ or otherwise within 3 cm of a lesion treated on this study so that any toxicity related to study therapy can be accurately assessed. Otherwise, if it is medically necessary to deliver additional radiation therapy off study, especially if there are no reasonable treatment alternatives, and if the treating physician believes that the risk of severe toxicity is reasonably low and justified by the potential benefit of radiation therapy then it would be permissible to deliver additional radiation therapy regardless of location.

6.11 Systemic therapy

There will not be any cytotoxic chemotherapy, targeted systemic agents, and/or investigational agent administered within 2 weeks prior to or following delivery of

radiation therapy on this study, provided that the patient does not have any ongoing grade 2 or higher toxicity from any prior treatment.

If a lesion is to be treated in the abdomen or pelvis, it is required that vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab not be given at least 4 weeks prior to or after study therapy because of a potentially increased risk of GI toxicity.

Hormonal therapy or immunotherapy such as immune checkpoint inhibitors that had begun at least 4 weeks prior to SABR will be allowed, provided there are no grade 2 or higher toxicities ongoing as a result of such therapies.

6.12 Additional local therapy

Surgery, percutaneous ablation, or other local therapy should not be planned to any lesion treated on this study at the time of patient enrolment. However, in the event of local tumor progression then such therapies may be considered.

7. STUDY PROCEDURES

7.1 Informed Consent

Investigators or their authorized designees will be responsible for obtaining a signed informed consent form and authorization to use and disclose protected health information prior to conduct any study-specific procedures.

7.2 Screening and Enrollment Procedures

Subject eligibility for the study will be determined after the screening process. The site investigator or qualified designee will review all inclusion and exclusion criteria to ensure that the subject qualifies for the trial.

The screening package will be uploaded in the Oncore Subject Console or sent by email to theMCI Multi-site Program. The following documents should be included:

- Signed Informed Consent Form
- Signed HIPAA form
- Eligibility Form signed by the Investigator
- Copy of redacted screening laboratory tests results
- Copy of redacted pathology report confirming diagnosis
- Copy of redacted imaging report.

- RECIST 1.1 evaluation
- Additional relevant documents or communications confirming subject eligibility.

The MCI multi-site program designee will review the submitted documents in order to verify documentation of patient eligibility.

Upon confirmation of eligibility, the Coordinating Center will provide authorization to the site study team to register the subject in OnCore.

Subjects will be considered enrolled after they have given informed consent and passed eligibility criteria. The date of enrollment will be the date all eligibility criteria has been confirmed by the MCI Multi-site Program.

8. PATIENT ASSESSMENTS

All evaluations should be completed as detailed below and per the study calendar in Section 8.4 of this protocol.

8.1 Screening assessments

All screeningprocedures must be done after the subject signs the informed consent. Assessments completed as part of the standard of care before patient signs the Informed Consent Form can be used for screening purposes as long as the test/procedure meets the protocol-required timelines. Note that source documents must identify the standard of care tests/procedures used for screening and must be reviewed by the investigator for clinical significance. Obtaining Informed Consent, FACT-G, RECIST 1.1 evaluation and confirming subject eligibility must be performed by a delegated study team member.

Screening assessments include:

- Signed informed consent
- Medical History and cancer history and therapy
- Physical Examination
- Vital signs (blood pressure, heart rate, temperature, oxygen saturation via pulse oximetry, weight)
- ECOG Performance Status
- Concomitant Medication
- Complete blood count (CBC) with differential and Comprehensive Metabolic Panel (CMP) Note: Laboratory tests must be reviewed and documented by the investigator or sub-investigator for clinical significance to confirm eligibility of the potential research subject.

- Imaging: CT scan of the chest, abdomen, and pelvis (IV and/or oral contrast as per physician discretion)
- RECIST measurements
- FACT-G survey
- Urine pregnancy test in women of childbearing potential (within 14 days of first day of study therapy)
- SAE
- Confirm Eligibility

8.2 During Study Therapy

The following will be assessed on each day of radiation therapy after treatment delivery:

- ECOG Performance Status
- Vital Signs
- Adverse Events / SAE
- Concomitant Medications
- Complete Study Time Log

8.3 After Study Therapy Completion

After completion of SABR, an optional visit at 6 weeks (+/-14 days), can be performed as per treating physician criteria.

The following will be assessed every three (3) months until 12 month (+/- 28 days) after completion of SABR.

- Physical Examination
- ECOG Performance Status
- CBC
- CMP
- Imaging: CT scan of the chest, abdomen, and pelvis (IV and/or oral contrast as per physician discretion)
- RECIST 1.1
- Adverse Events / SAE
- Concomitant Medications
- FACT-G Survey

Assessments completed as part of the standard of care visits can be used for after treatment visits as long as the test/procedure meets the protocol-required timelines. Note that source documents must identify the standard of care tests/procedures used for this visit and must be reviewed by the investigator for clinical significance. FACT-G and RECIST 1.1, concomitant medications and adverse events evaluation must be performed by a delegated study team member.

Remote visits:In the case when an in-person clinic visit is not possible, remote visits will be allowed only for “After Study Therapy” completion visits. When a remote visit occurs, all research specific assessments including the FACT-G questionnaire, concomitant medications, and adverse events will be collected by a delegated study team member.

8.4 Study Calendar

Procedures	**Screening** (within 28 days prior to Study Therapy)	**During Study Therapy**[1]	**After Therapy Completion** (Optional visit) 6 weeks (+/-14 days)	**After Therapy Completion** 3m,6m,9m,12m (+/-28 days)
Signed Informed Consent	X			
Medical History/ Prior Cancer History and Therapy	X			
Physical Exam	X		X	X
Vital Signs[2]	X	X		
ECOG Performance status	X	X	X	X
Concomitant Medication	X	X	X	X
CBC W/ Differential	X		X	X
CMP	X		X	X
Urine pregnancy test[3]	X			
Imaging [4]	X		X	X
RECIST 1.1	X		X	X
FACT-G Survey	X		X	X
Adverse Events/SAE[5]	X	X	X	X
Confirm Eligibility	X			
Study Time log completion[6]		X		
Off Study[7]		X	X	X

1. Assessments will be collected each day after receiving study treatment as per the standard of care or per protocol.
2. Vital signs include blood pressure, heart rate, temperature, oxygen saturation via pulse oximetry, weight.
3. Pregnancy test in women of childbearing potential is performed at baseline within 14 days of enrollment.
4. CT scan of the chest, abdomen, and pelvis (IV and/or oral contrast as per physician discretion). Please refer to section 9 of the protocol. If a patient has a contraindication to contrast for a CT scan, then an alternate scan should be considered such as PET/CT or MRI.
5. Only SAEs assessed by the investigator as related to any protocol-specific procedure or therapy will be collected and reported.
6. Study time log should be completed during study treatment visit a as per this protocol Appendix B.
7. Off Study Form to be completed during the 12 months After Therapy Completion Visit or earlier if applicable.

9. TREATMENT RESPONSE EVALUATION

9.1 Imaging assessment

Patients should have CT scans of the chest, abdomen, and pelvis at 6 weeks (±14 days) if the six weeks visit is being performed, at 3 months (± 28 days), 6 months (± 28 days), 9 months (± 28 days), and 12 months (± 28 days) after completion of SABR delivered on this study, or more often as clinically indicated. IV and/or oral contrast should be used as per treating physician discretion and should be strongly considered if doing so would be critical for clearly visualizing the treated lesion to assess local response.

If a patient has a contraindication to contrast for a CT scan, then an alternate scan should be considered such as PET/CT or MRI.

Treatment response will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1.

9.2 Definitions for disease assessment

- Measurable lesions: Lesions that can be accurately measured in at least one dimension with longest diameter at least 10 mm.
- Malignant lymph nodes: A lymph node will be considered measurable if it measures at least 15 mm in short axis.
- Non-measurable lesions: All other lesions <10 mm or lymph nodes <15 mm in short axis.
- Target lesions: Target lesions should be identified and measured at baseline. Target lesions include measurable lesions up to a maximum of two lesions per organ and up to five lesions in total that are representative of all involved organs. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and are to undergo reproducible repeated measurements. If the largest lesion does not lend itself to reproducible measurement, it should not be considered a target lesion and instead the next largest lesion that can be measured reproducibly should be selected. A sum of the longest diameters for all target lesions 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.
- Non-target lesions: All other lesions (or sites of disease) including any measurable 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.

9.3 Definitions of Disease Response

Definition of response in target lesions:

- **Complete Response (CR)**: Disappearance of all target lesions
- **Partial Response (PR)**: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
- **Local Progressive Disease (LPD)**: At least a 20% increase in the sum of the diameters of target lesions compared to baseline sum of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). The sum must also demonstrate an absolute increase of at least 5 mm in addition to the relative increase of 20%.
- **Distant Progressive Disease (DPD)**: The appearance of at least 1 new lesion.
- **Stable Disease (SD)**: Neither sufficient decrease to qualify as a PR or sufficient increase to qualify as PD, taking as reference the smallest sum diameters while on study.

Definition of response in non-target lesions:

- **Complete Response (CR)**: Disappearance of all target lesions
- **Progressive Disease (PD)**: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
- **Incomplete Response/Stable Disease (SD)**: Persistence of one or more non-target lesions

9.4 Evaluation of best overall response

Best overall response is the best response recorded from the start of radiation therapy until disease progression or recurrence, taking as reference for progressive disease the smallest measurements recorded since SABR.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	PR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10. QUALITY OF LIFE ASSESSMENT

The FACT-G patient-reported quality of life (QOL) assessment instrument will be completed by all patients at the following time points:

- Screening6 weeks (±14 days) after completion of SABR if the six weeks visit is being performed.
- 3 months (± 28 days) after completion of SABR
- 6 months (±28 days) after completion of SABR
- 9 months (±28 days) after completion of SABR
- 12 months (±28 days) after completion of SABR

11. SAFETY ASSESSMENT

Safety parameters evaluated during this study will include AEs, vital signs, physical examination findings and clinical laboratory values. All safety parameters will be performed in accordance with the study calendar (Section 8.4).

11.1 Adverse Event definition, Assessment and Reporting

An Adverse Event (AE) is defined as any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.
The term AE is used to include both serious and non-serious AEs related to the radiation therapy specifically delivered on this study. It should be noted that additional radiation therapy is permitted by this study protocol to other lesions than what is being treated on this study; the treating physician should use best clinical judgment about whether any AE may be related specifically to the treatment delivered on study.

The Investigator or qualified designee will assess each subject to evaluate for potential or new worsening AEs as specified in the Schedule of Assessment and more frequently if clinically indicated.

Adverse Events (AEs) will be graded and recorded throughout the trial using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria.

A causal relationship between the radiation therapy delivered on this study and the AE should be determined with the treating physician using best clinical judgment to select one of the following for each AE:

- *Definitely related:* There is a definite relationship between study treatment and the AE. An alternative cause is highly unlikely. There is a strong time-based relationship between study treatment and the AE.
- *Probably related:* There is a reasonable probability that the AE is likely to have been caused by study treatment. The AE has a timely relationship to the study

treatment and follows a known pattern of response, but a potential alternative cause is possible.
- *Possibly related:* There is a possible relationship between the AE and study treatment. There may not be a known pattern of response and an alternative cause is more likely. A possible relationship between the AE and study treatment cannot be reasonably ruled out.
- *Unrelated*: There is not a reasonable causal relationship between study treatment and the AE. For example, the unrelated AE may be due to disease progression and not study treatment.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, or reported by the patient), will be collected and recorded in the eCRF, upon initiation of treatment and for a minimum of 100 days after completion of radiation therapy or until resolution or stabilization or reported as SAEs if they become serious.

11.2 Serious adverse event definition and reporting

A serious adverse event (SAE) is an AE occurring during any study phase that fulfills one or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

It is important to note that hospital admission for a planned medical/surgical procedure or disease treatment is not considered a SAE.

Only SAEs assessed by the investigator as related to any protocol-specific procedure or therapy will be collected and reported.

The investigator at each site must review source documentation and describe pertinent information, provide a causality assessment of the event documented in OnCore. The SAE form generated in OnCore must be printed, signed and dated by the investigator.

The study team will submit all SAEs to the MCI Multisite Research Program by email to: MCIMultisiteResearch@baptisthealth.net within 24 business hours of becoming aware of the initial event.

After receipt of the initial report, the Sponsor-Investigator or designee will review the information and, if necessary, contact the site study team to obtain further information.

Information to be reported in the description of each adverse event may include, but is not limited to:

- Subject ID
- Disease/histology
- Protocol number and title
- Date of the AE occurrence
- Describe the nature of the AE (i.e., dermatitis)
- The grade of the AE determined by CTCAE V5.0
- Relationship of the AE to treatment
- Whether the AE was expected or unexpected
- The intervention to address the AE
- A description of the subject's condition
- Outcome
- Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form

The PI's signature and date are required on this report.

If an ongoing SAE change in its intensity or relationship to study treatment or if new information becomes available, a follow-up SAE report should be sent within 72 business hours to MCI Multisite Research Program using the same procedure used for transmitting the initial SAE report.

Any local incident, experience or outcome that is (a) unanticipated in terms of nature, severity, or frequency given the research procedures that are described in the protocol-related documents, such as the IRB approve protocol and informed consent document; and the characteristics of the subject population being studied; and (b) Suggest that the research places subject(s) or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research, are considered Unanticipated Problems (UPs) involving risks to subjects or others.

All Safety Reports that meet the following criteria are considered UPs involving risk to subjects: Unexpected, related or possibly related to participation in the research as determined by Sponsor Investigator and is Serious.

UPs must be submitted to MCI Multisite Program following the SAEs reporting procedures.

All SAEs and UPs will be reported to IRB of record in accordance with its policies and procedures.

11.3 Management of adverse events

Supportive care should be given according to routine clinical practice to manage AEs.

11.4 Data Safety Monitoring Committee

The MCI Data Safety and Monitoring Committee (DSMC) will monitor this clinical trial according to the MCI Data and Safety Monitoring Plan (DSMP). In its oversight capacity, the MCI DSMC bears responsibility for suspending or recommending continuation of this study.

DSMC oversight of study conduct includes ongoing review of adverse event data, and periodic review of feasibility and tolerability of study treatment. The guidelines appearing in Section 11 of this protocol are offered for DSMC consideration in assessing adverse events and study objectives. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action.

The DSMC will review toxicity outcomes after the first 4 patients are enrolled and have at least 90 days of follow-up after completion of study therapy.

If any grade 3-5 toxicity is reported, the DSMC will determine if such toxicity is related to treatment. If the DSMC deems that toxicity rates are excessive then it can, at its discretion, recommend cessation of the trial, dose adjustment, or exclusion of certain treatment sites that are deemed as high-risk for complications.

11.5 Early study closure

If >4 patients have grade 3+ toxicity within 90 days of treatment completion, or if any patient has grade 5 toxicity as a result of study therapy, then the study will close as tolerability will not have been demonstrated.

11.6 Pregnancy

If it becomes known that a subject is pregnant or may have been pregnant at the time of study participation, the investigator must immediately notify MCI Multisite Research Office via email to MCIMultiSiteResearch@baptisthealth.net, the PI (Michael Chuong, MD at (786) 527-8140, and the Institutional Review Board of record (BHSF-IRB at (786) 596-9280), and the patient will be discontinued from study participation.

11.7 Overdose or misadministration of radiation

Overdose or misadministration of radiation is defined as the accidental or intentional administration of any dose of radiation considered excessive and medically important. All occurrences of overdose or misadministration must be reported as an SAE.

12. PATIENT DISCONTINUATION AND REPLACEMENT

12.1 Patient discontinuation

Permanent withdrawal of a patient from the study will occur when any of the following occur pertaining to the subject in question:

- Patient withdraws consent or is lost to follow-up.
- Patient becomes pregnant or has the intent to become pregnant.
- Patient is non-compliant with requirements of this study (i.e., refusal to adhere to scheduled visits) that in the opinion of the investigator warrants study withdrawal.
- AE occurs that in the opinion of the investigator is a contraindication to further treatment on study.
- Study closure.
- Death

If a patient is thought to be lost to follow-up, at least 3 documented attempts must be made to contact the patient before deemed lost to follow up. Any subject that is permanently discontinued from study participation will still be followed for safety and will also continue to have protocol-specified follow up evaluation, unless the subject withdraws consent, is lost to follow-up or enrolled in another clinical study.

Subjects who do not return to the treating institution for evaluations required by the study protocol will be offered telephone follow up every 3 months.

12.2 Patient replacement

Any patient that discontinues participation in this study for any reason other than unacceptable toxicity or progressive disease before the initial efficacy evaluation (CT scan 6 weeks after SABR lesion) may be replaced. These cases will be recorded and accounted for in the report of the trial.

13. STATISTICAL METHODS

13.1 Evaluation of study objectives

13.2 Primary objectives

The point estimate for feasibility will be reported as a binary variable with its 95% confidence interval. Feasibility will be achieved if all are true:

- Successful completion of treatment to each lesion within 3 working days of intended treatment completion
- Successful completion of treatment to each lesion within 90 minutes from the patient entering the treatment room until treatment completion. Any machine downtime during treatment delivery should be recorded and will not be included when assessing the time for completion of treatment.
- Image guidance verification of treatment delivery within 5 mm of the planned delivery

The point estimate for tolerability will be reported as a binary variable with its 95% confidence interval. Tolerability will be achieved if all are true:

- No greater than 4 of 30 patients experience grade 3 or higher acute toxicity within 90 days of completing SABR
- No grade 5 toxicity is attributed to SABR

13.3 Secondary objectives

1-year local control (LC) will be assessed according to RECIST 1.1 criteria and will be estimated using the Kaplan-Meier method along with the corresponding 95% confidence interval from the time of study treatment

1-year overall survival (OS) will be estimated using the Kaplan-Meier method along with the corresponding 95% confidence interval from the time of study treatment

The proportion of patients who experience acute grade 3 or higher toxicity attributable to SABR will be determined along with the corresponding 95% confidence interval. For patients receiving SABR to multiple lesions, acute toxicity will be determined from the date of the initiation of SABR.

Patient-reported quality of life will be determined using the FACT-G survey instrument prior to and after SABR.

13.4 Sample size determination

For this study, a sample size 30 is assessed pragmatically and not based on hypothesis testing. Table 1 shows 90% and 95% confidence intervals for different feasibility rates.

Sample size	Feasible cases	Feasibility rate	90% CI	95% CI
30	27	90%	76% - 97%	73% - 98%
30	24	80%	64% - 91%	61% - 91%
30	21	70%	53% - 83%	51% - 85%

Following criteria will be implemented for this feasibility study to advance to a phase II/III trial:

1. Grade ≥3 toxicity in no greater than 4 out of 30 patients
2. No grade 5 toxicity
3. Treatment feasibility rate of at least 80%

With a sample size of 30, if the true underlying grade 3 toxicity rate is 10.5%, the probability of no greater than 15% of patients in the sample (maximum 4 out of 30) suffering a grade 3 or higher acute toxicity is 80%. In other words, if the true underlying grade 3 toxicity rate is 10.5%, the probability of satisfying the specified tolerability threshold for escalation to a phase II/III trial is 80%. If the true underlying grade 3 toxicity rate is 21.4%, the probability of no greater than 15% of patients (maximum 4 out of 30) should suffer a grade 3 or higher acute toxicity is 20%. In other words, if the true underlying grade 3 toxicity rate is 21.4%, the probability of satisfying the specified tolerability threshold for escalation to a phase II/III trial is 20%.

With a sample size of 30, if the true underlying feasibility rate is 83.9%, the probability of at least 24 out of 30 patients satisfying the feasibility criteria is 80%. In other words, if the true underlying feasibility rate is 83.9%, the probability of satisfying the specified feasibility threshold for escalation to a phase II/III trial is 80%. If the true underlying feasibility rate is 71.3%, the probability of at least 24 out of 30 patients satisfying the feasibility criteria is 20%. In other words, if the true underlying feasibility rate is 71.3%, the probability of satisfying the feasibility tolerability threshold for escalation to a phase II/III trial is 20%.

13.5 Accrual and study duration

It is anticipated that approximately 30 patients will be enrolled and treated in this study. The expected accrual is an average of 1 patient at each participating site per month and a total of 2 patients per month across all participating sites. We expect study accrual to be completed in 15 months.

14. ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

Study procedures may begin once IRB approval is secured and other details (e.g., study supplies, clinical trial agreements) are in place.

14.2 Informed consent

All subjects must sign informed consent to participate in and register for this study. Investigators or their authorized designees will be responsible for obtaining informed consent and authorization to use and disclose protected health information prior to conduct any study-specific procedures.

All subjects will be informed about the following:

- Study aims
- Possible adverse effects
- Study procedures
- Confidentiality of patient data
- Medical records potentially being reviewed by authorized individuals other than the treating physician

Patients should be given the opportunity to ask questions and be allowed time to review the information provided. It will be explained to each patient that participation is voluntary and that subjects have the right to refuse participation at any time during the study. If any patient refuses to participate in this study, it will not affect the patient's subsequent care quality.

The written informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and investigator.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed document must be given to the patient.

15. DATA MANAGEMENT

The Miami Cancer Institute (MCI) Multisite Research Program will be responsible for all data management.

The trial will use Advarra Electronic Data Capture (EDC) system for all data collection. A web-based training for all eCRF users will be provided by MCI Multi-site research office.

All data entered must be verifiable by source documentation or any discrepancy should be explained, and corrections should be dated, initialed and explained (if necessary) and should not obscure the original entry.

Principal investigators are responsible for the accuracy, completeness, legibility and timelines of data reported to coordinating center in the eCRF/EDC and all required reports.

15.1 MONITORING, AUDITING AND QUALITY ASSURANCE

Routine monitoring or audit activities for this study will be conducted by the MCI OCR Office of Research Integrity authorized personnel in accordance with current FDA Regulations, ICH GCP guidelines, site's Standard Operating Procedures (SOPs), IRB and the respective local and national government regulations. The general scope of such visits would be to inspect study data including but not limited to, regulatory requirements, source documentation, original medical records/files and eCRF completion, as applicable, following a risk-based monitoring approach.

The study will be monitored based on procedures established in the Risk-Based Monitoring Plan at the time of protocol activation. A series of monitoring forms, tools and templates including:

MCI Clinical Research Monitoring/Audit Deficiencies Guidance and Summary

Monitoring Letters are utilized to ensure standard and consistent monitoring practices. The monitoring frequency may also be adjusted as per the monitor's discretion based on accrual rate, trial complexity, major deficiency findings, visit rating and safety reporting.

To ensure compliance with current federal regulations and the ICH GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, and duly authorized representatives of any entity providing support for this trial.

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