DF/HCC Protocol #: *Assigned by the Office for Human Research Studies (OHRS) after submission for SRC and IRB review.*

DF/HCC Radiation Protocol Template: June 30, 2014

TITLE: Phase I/II Study of Stereotactic Body Radiotherapy (SBRT) for Pulmonary Metastases in Ewing Sarcoma, Rhabdomyosarcoma, and Wilms Tumors

***Principal Investigator (PI):**

Other Investigators:

Biostatistician:

Study Coordinator:

[redacted]

Responsible Research Nurse:

[redacted]

Study Exempt from IND Requirements per 21 CFR 312.2(b).

Original Protocol / Version Date: 23 February 2015

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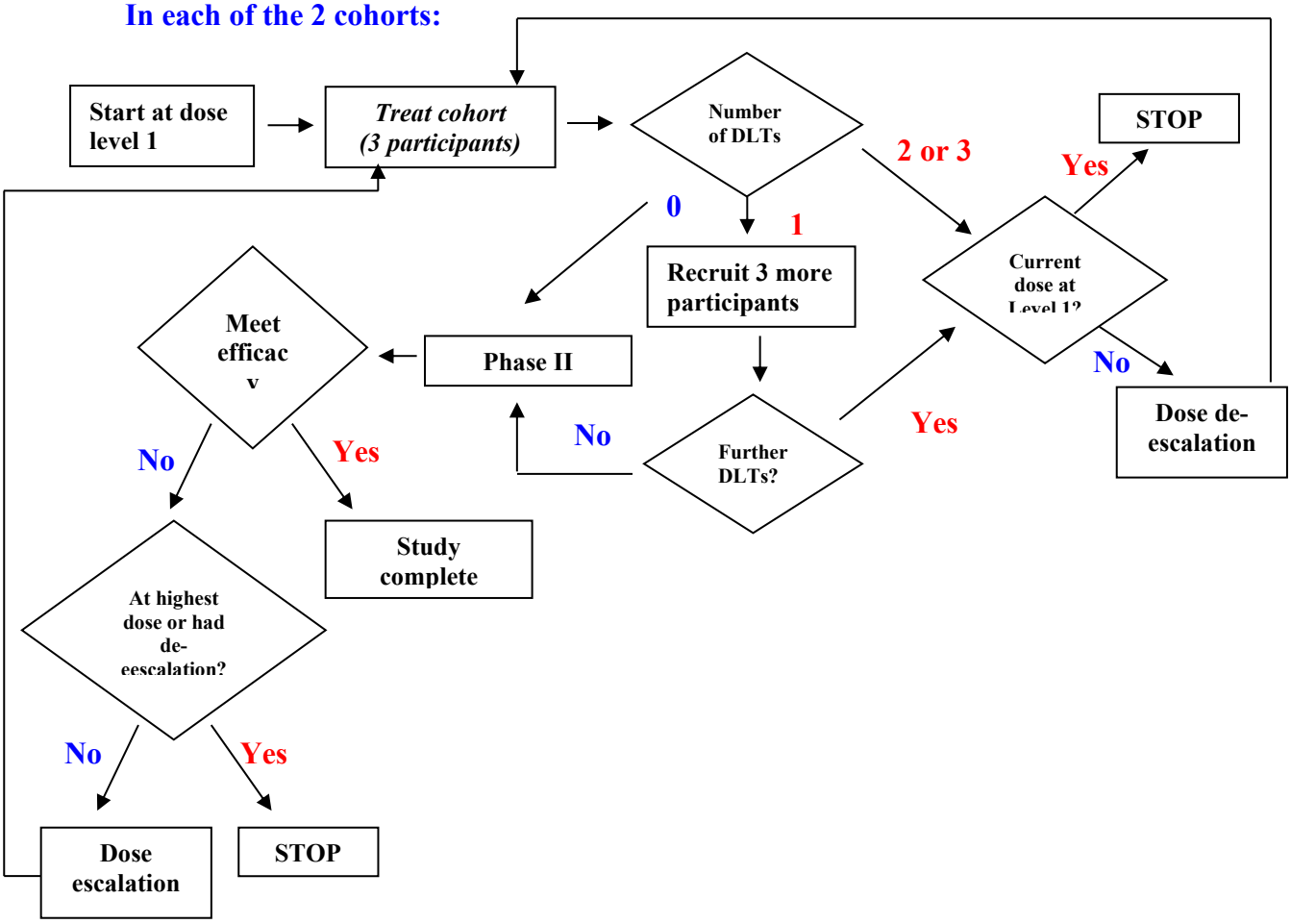
SCHEMA

Register → Simulation → Radiation Treatment (dose escalation by disease in Appendix A)

In each of the 2 cohorts:



Dose Levels (2 cohorts, 3 dose levels per cohort)

1) **Cohort 1 (Wilms/Renal tumor)**
   - **SBRT: begin at Dose level 1**

2) **Cohort 2 (Ewing sarcoma or rhabdomyosarcoma)**
   - **SBRT: begin at Dose level 2**

1. INTRODUCTION

1.1 Study Disease

The most common site of metastatic disease in Ewing sarcoma is the lung. The standard management of pulmonary metastases continues to include whole-lung radiotherapy. Although there are reports advocating the use of whole-lung radiotherapy, this approach has not been shown in randomized trials to improve survival [1, 2.] Localized Ewing sarcoma is curable with radiotherapy doses of 54-60 Gy, however whole-lung doses are limited because of lung toxicity. Patients who relapse after whole-lung radiotherapy also have few curative options. An alternative to whole-lung radiotherapy is stereotactic body radiotherapy (SBRT). SBRT can provide sustained control of tumor in the lung by delivering a tumoricidal dose while limiting dose to the normal lung. Similarly, the most common site of metastatic disease for Wilms and other primary pediatric renal tumors is the lung. Whole lung radiotherapy is used in some children with metastatic renal tumors. However, for those who had non-metastatic disease but relapse in the lung following completion of therapy, the efficacy of whole lung radiotherapy is unproven.

1.2 Rationale

SBRT is a well studied and commonly used method of conforming the radiation dose to the target volume in order to spare normal surrounding tissues. By doing so, doses to the target can be increased without causing excessive toxicity to surrounding tissues. SBRT is being used to treat adults with small inoperable lung cancers [3-5]. SBRT has been shown to be effective and well-tolerated.
Several regimens have been used and are summarized in the table below along with results of local control, follow-up and risk of grade 3 or greater toxicity. The table below was used at the American Association of Medical Dosimetrists (AAMD) annual meeting in Minneapolis in June 2010.

Table. — Selected Reported Results in the Use of Stereotactic Radiotherapy for Treatment of Peripheral Lung Cancers

Authors	Sample Size	Total Dose/# of Fractions (fx)	Local Control	Follow-up (mos)	≥ Grade 3 Toxicity
Uematsu et al[6]	50	50–60 Gy/5–10 fx	94%	60	0.0%
Onishi et al[7]	251	18–75 Gy/1–22 fx	86%	38	5.4%
Nagata et al[8]	45	48 Gy/4 fx	98%	30	0.0%
Timmerman et al[9]	37	60–66 Gy/3 fx	95%	24	5.4%
Baumann et al[10]	138	30–48 Gy/2–4 fx	88%	33	10.1%*
Zimmermann et al[11]	68	37.5 Gy/3 fx	88%	36	3.0%
McGarry et al[12]	47	54–72 Gy/3 fx	87%	15	–
Xia et al[13]	43	50 Gy/10 fx	95%	36	2.3%

*Some of the treated lesions were central in location, not peripheral, athough the report does not clarify whether a central tumor location led to increased risk of treatment toxicity.

SBRT has not routinely been used in the treatment of pulmonary metastases from Ewing sarcoma or from other malignancies in children, though there have been many studies published on its use in pulmonary metastases from adult cancers. Stereotactic radiotherapy to the brain has been used since 1992 to treat pediatric brain tumors and there is increasing interest in using this highly conformal technology in children [6].

2. OBJECTIVES

2.1 Study Design

This is a Phase I/II study. The purpose of this study is to find the lowest dose level with an acceptable safety profile and efficacy in this population. Therefore, the phase I and phase II designs will be run sequentially. Dose escalation in phase I does not go all the way to the MTD before moving to the phase II portion. If the dose being tested is found to be effective dose escalation will not continue. There are two cohorts that will use the same study design. One cohort will include patients with Wilms tumors or other primary renal tumors, and the other will include patients with Ewing sarcoma or rhabdomyosarcoma. Different dose levels will be used in the two cohorts, with non-renal tumor patients beginning at dose level 2 and renal tumor patients beginning at dose level 1. The two cohorts will be enrolling patients independently and simultaneously.

2.2 Primary Objectives

2.2.1 The primary aim of the Phase I portion is to determine the tolerability and safety of stereotactic body radiotherapy for pulmonary metastases in pediatric patients with Ewing sarcoma, rhabdomyosarcoma or Wilms tumor and other primary renal tumors. (See 11.1 for definitions.)

2.2.2 The primary objective of the Phase II portion is to evaluate disease response at 6 weeks post SBRT in this patient population. Response will be defined according to RECIST criteria.

2.3 Secondary Objectives

1. To determine the feasibility of SBRT in the pediatric population (including tolerability)
2. To document the safety of the treatment
3. To determine rate of relapse elsewhere in the lung
4. Best overall response

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

1. Diagnosis of Ewing sarcoma, rhabdomyosarcoma, osteosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, Wilms tumor or other primary renal tumor (including clear cell and rhabdoid)
2. Age ≤21years
3. Must be capable of treatment without general anesthesia
4. Lesion size 4 mm - 3 cm

5. Subjects who have lesions within 2 cm of central structures*, will be eligible on a case-by-case basis

   **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).*
6. Pulmonary metastases found at relapse (does not have to be first relapse); no more than 3 lesions per hemi-thorax will be treated but other lesions in the lung may be present
7. Greater than 5 weeks from doxorubicin at the time of consent, with radiation to be initiated no less than 6 weeks from doxorubicin
8. Informed consent/assent
9. Life expectancy > 3 months
10. Pulmonary function $FEV_1 \geq 50\%$ of predicted
11. Concurrent immunotherapy is allowed

3.2 Exclusion Criteria

1. Prior whole-lung or hemi-thorax irradiation of greater than 12 Gy received less than 6 months prior to consent (focal radiotherapy to the thorax is not an exclusion)
2. Lesion larger than 3 cm in diameter
3. Patients for whom surgery would be deemed appropriate rather than radiotherapy.

3.3 Inclusion of Women and Minorities

Females, minorities and other underrepresented populations are at risk to develop Ewing sarcoma and the other included malignancies and we will enroll any eligible patient in such groups. There is no reason to suspect any differential effect of this treatment. The eligibility criteria will not differentially affect the enrollment of these populations.

4. PRETREATMENT EVALUATIONS/MANAGEMENT

Eligible patients will be registered with the DF/HCC Office of Data Quality (ODQ). Registration must occur prior to initiation of therapy. Any participant not registered to the protocol before treatment begins will be deemed ineligible and registration denied. A member of the study team will confirm eligibility.

5. REGISTRATION PROCEDURES

5.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy.

Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

5.2 Registration Process for DF/HCC and DF/PCC Institutions

5.3 DF/HCC Standard Operating Procedure for Human Subject Research Titled *Stereotactic Body Radiotherapy (SBRT) for Pulmonary Metastases in Ewing Sarcoma, Rhabdomyosarcoma, and Wilms Tumors* (SOP #: REGIST-101) must be followed. General Guidelines for Other Participating Institutions

N/A

5.4 Registration Process for Other Participating Institutions

N/A

5.5 Stratification

Patients will be stratified into two groups by diagnosis: Wilms/Renal tumors are Cohort 1, Ewing sarcoma /rhabdomyosarcoma are Cohort 2

6. RADIATION THERAPY

6.1 Dose Specifications: 3D Conformal Radiotherapy (3DCRT) or IMRT

6.1.1 Treatment simulation: The patient will undergo simulation (treatment planning) in a standard stereotactic immobilization device. The simulation will be done using 4DCT to account for respiratory motion. A free-breathing CT scan will also be performed using 2.5-mm slices. Abdominal compression will be used if the tumor moves more than 1 cm with respiratory motion. This approach is the standard protocol for SBRT at our institution.

6.1.2 Contours: The tumor nodule or nodules will be contoured

6.1.2.1 Internal tumor volume (ITV): gross tumor plus margin for internal motion.

6.1.2.2 Planning target volume (PTV): will be ITV plus 5 mm

6.1.2.3 Organs at risk will be defined by the physician and/or the treatment planner:

- Total lung: total lung volume-ITV
- Heart: Defined from apex to first slice of great vessels
- Spinal cord
- Chest wall
- Skin
- Ribs abutting tumor
- Esophagus: defined 5 cm above and below PTV
- Proximal bronchial tree: defined from inferior 2 cm of trachea to lobar bronchi, to point of bifurcation into segments
- Brachial plexus

6.1.2.4 Dose Level 1 will be the starting dose for patients with Wilms/Renal tumor. Dose Level 2 will be the starting dose for patients with Ewing sarcoma/Rhabdomyosarcoma (non-renal). SEE APPENDIX: A.

Treatment will be delivered over 1- 2 weeks. Delivery of hypofractionated radiotherapy (i.e., using a small number of fractions) makes it challenging to determine normal-tissue dose constraints. However, we will use very conservative critical-structure dose limits based on those used in published experience in SBRT in adults. See Appendix B for UTSW Dose Constraints.

6.1.2.5 Dose Levels for each target lesion are as follows:

Dose level 1 – 8 Gy x 3
Dose level 2 – 10 Gy x 3
Dose level 3 – 12 Gy x 3

Non-renal tumor dose escalation scheme: Three participants with non-renal tumors will be treated starting at dose level 2. If no dose-limiting toxicities (DLTs, see definitions in 6.2) are seen, that cohort will move on to the phase II portion of the study. If one DLT occurs at the initial dose level, then 3 more patients will be accrued to that cohort. If no further DLTs occur in those 3 patients treated at the initial dose level, then that cohort will move on to the phase II portion of the study. In the phase II portion, if the efficacy criteria are not met, three more patients will be enrolled at the next dose level. Dose will be escalated to the next dose level (3) for the next three patients. If one DLT, an additional three patients will be enrolled at that current dose level. If two or three DLTs, no dose escalation will occur; if this is at the starting dose level 2, dose will be de-escalated to the next lower dose level for the next three patients, down to a minimum of dose level 1. If three patients are treated at dose level 2, three more at dose level 3, and there are still no DLTs, the dose will be held at level 3 for all additional non-renal tumor patients.

Renal tumor dose escalation scheme: Three participants with renal tumors will

be treated starting at dose level 1. If no dose-limiting toxicities (DLTs, see definitions in 6.2) are seen, that cohort will move on to the phase II portion of the study. If one DLT occurs at the initial dose level, then 3 more patients will be accrued to that cohort. If no further DLTs occur in those 3 patients treated at the initial dose level, then that cohort will move on to the phase II portion of the study. In the phase II portion, if the efficacy criteria are not met, three more patients will be enrolled at the next dose level. Dose will be escalated to the next dose level (2) for the next three patients. If one DLT, an additional three patients will be enrolled at that current dose level. If two or three DLTs, no dose escalation will occur; if this is at the starting dose level 1 (the lowest dose level), the study will be terminated. If three patients are treated at dose level 2, three more at dose level 3, and there are still no DLTs, the dose will be held at level 3.

6.1.2.6 Dose-escalation (please refer to Dose Schema section 6.1.2.5): The Phase I and Phase II portions will be done sequentially. If a dose level does not meet the safety criteria (none of three or no more than one out of six develops a DLT), and the next lower dose level does not meet the Phase II pre-specified criteria for efficacy, the study will be terminated. If two or more DLTs are observed at the starting dose level, the SBRT dose will be de-escalated to the next lower dose level; if this happens at dose level 1 (the lowest dose level), the study will be terminated.

The same Phase I/II design applies to both cohorts, Wilms and sarcoma patients, separately, except for the starting dose level in the Phase I portion. There are 3 dose levels (8, 10 and 12 Gy x 3) in this study. Patients with Wilms tumor or other renal tumors will start at dose level 1 (8 Gy x 3) and dose escalation will stop for this cohort at dose level 3 (12 Gy x 3). Ewing sarcoma and rhabdomyosarcoma patients will start at dose level 2 (10 Gy x 3).

6.1.2.7 Stopping rules: If two or more DLTs are observed at the starting dose level, the SBRT dose will be de-escalated to ther next lower dose level; if this happens at dose 1 (the lowest dose level), the study will be terminated.

6.2 Dose-limiting toxicities (DLTs)

DLTs are toxicities experienced between the start of the stereotactic radiotherapy and 6 months after radiotherapy. DLTs will be graded according to the CTEP active version of the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The current version is CTCAE v4.0.

For this study, DLTs are defined as follows:
The following grade 2 or higher toxicities:

- Myelitis
- Esophageal fistula, perforation, hemorrhage

The following grade 3 or higher toxicities considered to be a direct result of therapy:

- Pneumonitis
- Pericarditis, pericardial effusion
- Esophageal necrosis, stenosis, ulcer
- Dyspnea

The following grade 4 toxicities:

- Esophagitis
- Pericardial tamponade
- Pulmonary toxicity excluding infectious pneumonia
- Skin toxicity
- Hemoptysis/pulmonary hemorrhage

All grade 5 toxicities, including:

- Pulmonary toxicity including pneumonitis
- Excluding infectious pneumonia

6.3 Toxicities and Adverse Events

6.3.1 Toxicities

6.3.1.1 All patients will be seen weekly by their treating radiation oncologist or co-investigators (pediatric oncologist) while undergoing therapy. The following toxicities are expected and listed according to their likelihood and whether they are immediate or long term.

Evaluation of toxicity. All participants will be evaluable for toxicity from the time of their first treatment. Evaluation will be by the radiation oncology physician or by the patient's pediatric oncologist by physical examination and testing as indicated in the study calendar. Patients will be seen by the radiation oncologist for each treatment to assess toxicities and adverse events.

6.3.1.2 Immediate Toxicities

Common (>20%)

- Tiredness

- Hair loss in the treatment field
- Skin redness in the treatment field

Uncommon (10-20%)
- Inflammation of the lung

Rare (<10%)
- Nausea

6.3.1.3 Late Toxicities

Common (>20%)
- Scarring of the lung not requiring treatment (permanent)

Uncommon (10-20%)
- Shortness of breath (permanent)
- Skin dryness in the treatment field (permanent)
- Inflammation of the heart (duration weeks)
- Chest wall pain

Rare (<10%)
- Inflammation of the muscles of the chest wall (duration weeks)
- Scarring of the lung requiring treatment (permanent)
- Rib fracture
- Tumors caused by radiotherapy (lifelong)

Extremely rare (<5%)
- Spinal cord injury (permanent)
- Fatal inflammation of the lung

6.3.1.4 Clinical discretion may be used in managing radiotherapy-related side effects.

6.3.2 Adverse Event Reporting

6.3.2.1 Definitions

6.3.2.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment

or further diagnostic tests.

6.3.2.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death

- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

    - Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

6.3.2.1.3 Expectedness

Adverse events

6.3.2.1.3.1 Expected adverse event (toxicities)

Expected adverse events are those that have been previously identified as resulting from administration of stereotactic body radiotherapy. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list or is included in the informed consent document as a potential risk.
Please refer to Section 6.3.1 for a listing of expected toxicities.

6.3.2.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list or when it is not included in the informed consent document as a potential risk.

6.3.2.1.3.3 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

 Definite – The AE is clearly related to the study treatment.
 Probable – The AE is likely related to the study treatment.
 Possible – The AE may be related to the study treatment.
 Unlikely - The AE is doubtfully related to the study treatment
 Unrelated – The AE is unrelated to the study treatment

6.3.2.2 Procedures for AE and SAE Recording and Reporting

During the study investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points. AEs will be evaluated using the descriptions and grading scales found in the CTEP active version of the NCI TCAE located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The current version is CTCAE v4.0.

All AEs and SAEs, whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study specific case report forms.

Monitoring

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 6 months of the last study intervention should be followed to their resolution, until the investigator assess them as stable or determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

6.3.2.3 Reporting Requirements

All investigators are required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator (PI). The PI will be notified of all AEs and SAEs.

6.3.2.3.1 Reporting to Institutional Review Board (IRB)

SAEs will be reported directly to the DFCI IRB via the DFCI Office for Human Research Studies (OHRS). Copies of all SAE report forms will be sent to the PI:
Karen J Marcus, MD
Email: kmarcus@partners.org
Phone: 617-355-8399
Fax: 617-730-0211

6.3.2.3.2 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 6 months of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator and the DFCI IRB. SAEs include events meeting the criteria outlined in Section 6.3, as well as the following:

 Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
 All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
 All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Investigators must report each serious adverse event to the PI within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

Within the following 24-48 hours, the participating investigator must provide follow-up information on the SAE. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

6.3.2.3.3 Non-Serious Adverse Event Reporting
Non-serious adverse events will be reported to the PI on the toxicity case report forms.

6.3.3 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

7. OTHER THERAPIES

If systemic anti-cancer treatment is urgently required during the two weeks of study treatment, the subject will be removed from the study and replaced. However, patients will be allowed to receive concurrent immunotherapy.

During the Phase I portion, if clinically indicated, systemic therapy can be given and the subject will remain evaluable for the phase I (toxicity) portion. Surgery (other than to index lesions) will be allowed. These patients will be scored as unevaluable for response assessment.

During the Phase II portion, if systemic therapy is needed prior to the 6 week post-treatment assessment time, that subject but will be scored as UNEVALUABLE for response assessment but will be followed for toxicity. Surgery (other than to index lesions) is allowed if clinically indicated and the subject will remain evaluable.

However, if the reason for non-protocol surgery or chemotherapy is disease worsening of the index lesions, those patients would be scored as disease progression

Patients may receive Decadron orally prior to each fraction of radiotherapy per physician discretion.

8. TISSUE/SPECIMEN SUBMISSION

Not applicable.

9. PARTICIPANT ASSESSMENTS

Evaluation of response. All participants included in the study will be assessed for response to treatment, unless the subject received systemic therapy prior to the 6 week assessment.. Response in this study will be defined as disease control in the treated lesion at 6 weeks. We will continue to assess response and consider best overall response as a secondary objective.
Each participant will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

Disease control at 6 weeks will include complete response (CR), partial response (PR) and stable disease (SD).

Patients will be seen weekly during treatment for physical examination and assessment of acute side effects. They will then be seen at one month from the end of study treatment for physical examination, A CT at will be done at 6 weeks post completion of SBRT and then every three months with physical examination and CT scan of the chest during the first year, followed by every 6 months for the next year and then annually until year 5, as is considered standard of care. (See: Study Calendar)

The lesion or lesions treated will be measured as well as new lesions identified.
Pulmonary function tests will be done at 3 months post treatment, then at 9 months.

9.1 Response Criteria

9.1.1 Evaluation of Target Lesions (response will be measured using CT scans)

Complete Response (CR)
Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)
At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)
At least a 20% increase in the sum of the diameters of target lesions, taking as

reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions will not be considered progression.

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. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease). To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 6 weeks.

9.1.2 Evaluation of New Lesions

The appearance of new lesions will not be considered Progressive Disease (PD). The goal of this study is to evaluate the safety and efficacy of stereotactic radiotherapy to individual lesions. If subject develops new lesions, this would not impact the study results. For example, a new lesion might be amenable to SBRT. However, on this protocol such new lesions will not be treated.

9.1.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	**New Lesions**	**Best Overall Response**	**Remarks**
CR	Yes or No	CR	
PR	Yes or No	PR	
SD	Yes or No	SD	Documented at least once ≥6 wks. from study entry
PD	Yes or No	PD	No prior SD, PR or CR

Study Calendar

	Pre-study	Week 1	Week 2	One month (+/- 2 wks) post SBRT	Every 3 months (+/- 2 wks) after first assessment done 6weeks after SBRT during first year	Every 6 months (+/- 6 wks) during second year	Annually for the third, fourth, and fifth years
SBRT		x	x				
Informed consent	x						
History	x			x	x	x	x
Physical Exam	x	x	x	x	x	x	x
CT chest and tumor measurement	x			x (6 weeks post SBRT)	x	x	x
PFTS	x				x[a]		
CBC	x						
Adverse event reporting [b]		x	x	x	x	x	

[a] PFTs (pulmonary function tests) will be performed only at 3 and 6 months (+/- 2 wks) after SBRT.
[b] All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 6 months of the last dose of treatment

10. DATA COLLECTION

10.1 Study Documentation

After a participant is enrolled on the study, we will collect information about their diagnosis, treatment, and any side effects of treatment as well as demographic data. Information regarding the tolerability of SBRT in the study population and any information about disease relapse if it should occur after study treatment. Study participants will be assigned a study number by the study team and all information will be de-identified when analyzed. This de-identified data will be stored electronically in the ODQ system and protected by multiple firewalls that exist within the Partners network. Any paper records including Case Report Forms will be stored in an office secured by a lock that only study team members have access to.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

11 STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

A 3+3 study design will be used in the Phase I portion and patients will enter the study in sets of three for each cohort. For a given dose level, if none of three patients experiences a DLT, this dose level will move forward to the Phase II portion. However, if one patient experiences a DLT among the first three patients at any dose level, three more patients will be treated at that dose level. The dose level will enter the Phase II portion if no further DLT is observed following observation period of 6 months from treatment completion of third patient in the cohort. If a DLT is observed in any of the three additional patients, this dose level will not move forward to the Phase II portion and the dose will be de-escalated to the next lower level. If two or more patients experience a DLT among the first 3 patients, dose de-escalation will ensue, if applicable, without further testing of that dose level in the phase II portion. The table below shows the probability of entering the phase II portion for a dose level under different true DLT rates.

True DLT rate	5%	10%	15%	20%	30%	40%
Probability of entering phase II	0.97	0.91	0.81	0.71	0.49	0.31

Once a dose level enters the Phase II portion, a two-stage design will be used to evaluate efficacy. The first stage will accrue seven patients, including the patients enrolled at the same dose level in the Phase I portion. If at least two responses are observed among the seven patients, additional eight patients will be entered. If five or more responses are observed among the fifteen patients, there will be no further dose escalation and this dose level will be considered tolerable and effective for this patient population. With this design, the Phase II portion has 90% power to test the response rate of 50% vs. 20% based on a 0.14 level one-sided exact binomial test. The probability of stopping early is 0.58 if the true response rate is 20%; whereas if the true response rate is 50%, this probability is 0.06.

If a dose level examined in the Phase II portion does not meet the pre-specified criteria for efficacy, the next higher dose level will start in the Phase I portion until a dose level that meets both Phase I and Phase II criteria for safety and efficacy is found. If a dose level does not meet the safety criteria (none of three or no more than one out of six develops a DLT), and the next lower dose level does not meet the Phase II pre-specified criteria for efficacy, the study will be terminated. If two or more DLTs are observed at the starting dose level, the SBRT dose will be de-escalated to the next lower dose level; if this happens at dose level 1 (the lowest dose level), the study will be terminated. The same Phase I/II design applies to both cohorts, renal tumor (cohort 1) and Ewing patients (cohort 2), separately, except for the starting dose level in the Phase I portion.

11.2 Sample Size, Accrual Rate and Study Duration

We expect to accrue 3 patients per year in the renal tumor cohort (cohort 1) and 5 per year in the non-renal (Ewing/RMS) cohort (cohort 2). The maximum total accrual for a given dose level for both cohorts combined is 30. The accrual is expected to be completed in 5

years in the renal cohort and 2 years in the nonrenal cohort, for a dose level to be examined in both the Phase I portion and the Phase II portion.

11.3 Analysis of Primary Endpoints

This is a Phase I/II study to determine the lowest dose level of stereotactic body radiotherapy (SBRT) with an acceptable safety profile and efficacy in patients with relapsed Ewing sarcoma, rhabdomyosarcoma, soft tissue sarcoma or primary renal tumors (including Wilms tumor) who have limited pulmonary metastases. The primary objective of the Phase I portion is to evaluate the toxicity profile of each dose level and determine whether a given dose level could move forward to the Phase II portion. The primary endpoint of the Phase II portion is response to treatment (disease control at 6 weeks in the treatment field). The response rate along with the 95% two-stage confidence interval will be reported by dose level for each cohort. The Phase I and Phase II designs will be employed sequentially, i.e., a dose level will be examined in the Phase I portion for safety and then in the Phase II portion for efficacy if the Phase I safety criteria are met, to achieve the goal of balancing safety and efficacy in these rare tumor populations.

Given that the starting dose in the Phase I portion will be different for the patients with Wilms/renal tumor and the patients with relapsed Ewing sarcoma, rhabdomyosarcoma, soft tissue sarcoma, patients will be enrolled in two distinct cohorts, and escalate through the dose levels and enter the Phase II portion independently.

11.4 Analysis of Secondary Endpoints

Secondary endpoints include relapse elsewhere in the lung and toxicities, and these analyses will be performed by dose level. The method of Kaplan and Meier will be used to characterize time to relapse elsewhere in the lung. All patients who receive any part of the treatment will be monitored for toxicity, and the percent of patients with various toxicities will be tabulated for each dose level. Assuming a total of 15 patients treated at a dose level, if the true probability of a rare toxicity is 5%, the probability of observing 1 or more rare toxicities is 54%. A 90% confidence interval for any toxicity will be no wider than 46%.

12 REGULATORY CONSIDERATIONS

12.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

12.2 Informed Consent

All participants and their parents must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal assent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant's legally authorized representative, and by the person obtaining the consent if the participant is under the age of 10 years. If the participant is over the age of 10 years, they may provide verbal assent to participate and form must be signed and dated by the person obtaining the assent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

12.3 Study Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

12.4 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

12.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13 PUBLICATION PLAN

We plan to publish this study and, if the results are favorable, we will develop a Phase II protocol to follow the present one. The Principal Investigator will hold primary responsibility for publication of the study results.

We expect to make the results public within 24 months of the end of data collection. We plan to publish a report in a peer-reviewed journal, however we may submit an abstract prior to that publication submission. The abstract will meet the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of data collection.

REFERENCES

1. Paulusssen M, Aherns S, Burdach S, et al: Pulmonary metastatic (Stage IV) Ewing tumor: survival analysis of 171 patients from the EICESS studies. European Intergroup Cooperative Ewing Sarcoma Studies. Ann Oncol 9 (3):275-281, 1998.

2. Spunt SL, McCarville MB, Kun LE, et al: Selective use of whole-lung radiotherapy in Ewing sarcoma family of tumors and pulmonary metastases at the time of diagnosis. J PediatrHematolOncol 23(2):93-98, 2001.

3. Uematsu M, Shioda A, Suda A, Fukui T, Ozeki Y, Hama Y, Wong JR, Kusnao S. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience.Int J RadiatOncolBiolPhys 2001; 51:666-670.

4. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, Niibe Y, Karasawa K, Hayakawa K, Takai Y, Kimura T, Takeda A, Ouchi A, Hareyama M, Kokubo M, Hara R, Itami J, Yamada K, Araki T. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study.JThoracOncol.2007;2 (Suppl 3):S94-100.

5. McGarryRC, Papiez L, Williams M, et al: Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: Phase I study. Int J RadiatOncolBiolPhys 63:1010-1015, 2005.

APPENDIX A DOSE ESCALATION BY DISEASE

		Cohort 1: Wilms/Renal tumor	Cohort 2: Ewing sarcoma, Sarcoma and Rhabdomyosarcoma
Level 1	**8 Gy x 3**	**Starting dose level**	**De-escalation dose level**
Level 2	**10 Gy x 3**	**Next dose level**	**Starting dose level**
Level 3	**12 Gy x 3**	**Final dose level**	**Final dose level**

APPENDIX B UTSW DOSE CONSTRAINTS

One Fraction **Timmerman, 12-2008**

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	8 Gy	10 Gy	neuritis
Cochlea			9 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	10 Gy	15 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc <1.2 cc	10 Gy 7 Gy	14 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	10 Gy	14 Gy	myelitis
Cauda Equina	<5 cc	14 Gy	16 Gy	neuritis
Sacral Plexus	<5 cc	14.4 Gy	18 Gy	neuropathy
Esophagus*	<5 cc	11.9 Gy	15.4 Gy	stenosis/fistula
Brachial Plexus	<3 cc	14 Gy	17.5 Gy	neuropathy
Heart/Pericardium	<15 cc	16 Gy	22 Gy	pericarditis
Great vessels	<10 cc	31 Gy	37 Gy	aneurysm
Trachea and Large Bronchus*	<4 cc	10.5 Gy	20.2 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	12.4 Gy	13.3 Gy	stenosis with atelectasis
Rib	<1 cc	22 Gy	30 Gy	Pain or fracture
Skin	<10 cc	23 Gy	26 Gy	ulceration
Stomach	<10 cc	11.2 Gy	12.4 Gy	ulceration/fistula
Duodenum*	<5 cc <10 cc	11.2 Gy 9 Gy	12.4 Gy	ulceration
Jejunum/Ileum*	<5 cc	11.9 Gy	15.4 Gy	enteritis/obstruction
Colon*	<20 cc	14.3 Gy	18.4 Gy	colitis/fistula
Rectum*	<20 cc	14.3 Gy	18.4 Gy	proctitis/fistula
Bladder wall	<15 cc	11.4 Gy	18.4 Gy	cystitis/fistula
Penile bulb	<3 cc	14 Gy	34 Gy	impotence
Femoral Heads (Right & Left)	<10 cc	14 Gy		necrosis
Renal hilum/vascular trunk	<2/3 volume	10.6 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.4 Gy		Pneumonitis
Liver	700 cc	9.1 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	8.4 Gy		Basic renal function

Three Fractions **Timmerman**

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	15.3 Gy (5.1 Gy/fx)	17.4 Gy (5.8 Gy/fx)	neuritis
Cochlea			17.1 Gy (5.7 Gy/fx)	hearing loss
Brainstem (not medulla)	<0.5 cc	18 Gy (6 Gy/fx)	23.1 Gy (7.7 Gy/fx)	cranial neuropathy
Spinal Cord and medulla	<0.35 cc <1.2 cc	18 Gy (6 Gy/fx) 12.3 Gy (4.1 Gy/fx)	21.9 Gy (7.3 Gy/fx)	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	18 Gy (6 Gy/fx)	21.9 Gy (7.3 Gy/fx)	myelitis
Cauda Equina	<5 cc	21.9 Gy (7.3 Gy/fx)	24 Gy (8 Gy/fx)	neuritis
Sacral Plexus	<5 cc	21 Gy (7 Gy/fx)	24.6 Gy (8.2 Gy/fx)	neuropathy
Esophagus*	<5 cc	17.7 Gy (5.9 Gy/fx)	25.2 Gy (8.4 Gy/fx)	stenosis/fistula
Brachial Plexus	<3 cc	20.4 Gy (6.8 Gy/fx)	24 Gy (8 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	24 Gy (8 Gy/fx)	30 Gy (10 Gy/fx)	pericarditis
Great vessels	<10 cc	39 Gy (13 Gy/fx)	45 Gy (15 Gy/fx)	aneurysm