HUNTSMAN CANCER INSTITUTE
UNIVERSITY OF UTAH

Phase I Study of Stereotactic Radiosurgery Dose Escalation for Brain Metastases

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Conformality Index
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration

Abbreviation or Term	Definition/Explanation
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GPA	Graded Prognostic Assessment
HR	Heart rate
hr	Hour or hours
i.e.	Id est (that is)
IEC	Independent ethics committee
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
PD	Pharmacodynamic(s)
PIV	Prescription Isodose Volume
PFS	Progression Free Survival
PR	Partial response
QC	Quality control
RPA	Recursive Partitioning Analysis
QTc	QT interval corrected
QTcF	QT interval corrected using Frederichia equation
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SD	Standard deviation or stable disease
SRS	Stereotactic Radiosurgery

Abbreviation or Term	Definition/Explanation
TV	Target Volume
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

All of these abbreviations may or may not be used in protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	Phase I Study of Stereotactic Radiosurgery Dose Escalation for Brain Metastases
Protocol Number	IRB# 71940
IND	N/A
Phase	Phase I
Design	Open label, prospective, single center, dose escalation study
Study Duration	3 years
Study Center(s)	Single Center; University of Utah Huntsman Cancer Institute
Objectives	Determine the maximum tolerated dose for stereotactic radiosurgery (SRS) treatment for patients with 1-5 brain metastases treated with SRS as the first line therapy for their CNS disease
Number of Subjects	Approximately 65 patients (5 patients per dose level in each of the four cohorts). Up to 117 patients may be enrolled depending on incidence of DLTs.
Diagnosis and Main Eligibility Criteria	Patients with 1-5 brain metastases, each less than or equal to 4 cm in greatest dimension, at least 3 cm apart, who will be treated with SRS as their first line of therapy for brain metastases.
Duration of administration	Single fraction radiosurgery
Reference therapy	The outcomes in this study will be reported against the dose escalation study RTOG 90-05 [1]
Statistical Methodology	No formal statistical comparison will be made

1 OBJECTIVES

1.1 Primary Objective

1.1.1 To determine the maximum tolerated dose of stereotactic radiosurgery (SRS) treatment for patients with 1 to 5 brain metastases who have not received prior brain radiotherapy.

1.2 Secondary Objectives

1.2.1 To assess the immediate, acute, and chronic central nervous system (CNS) toxicities of single fraction external beam irradiation at increased doses to brain metastases.

1.2.2 To evaluate response of the treated lesion(s) by volume assessment.

1.2.3 To evaluate distant brain failures outside of the treated site.

1.2.4 To evaluate overall survival of patients in this cohort for three years following SRS.

2 BACKGROUND

Metastatic disease to the brain is the most common cause of intracranial malignancy in adults with 170-200,000 new cases diagnosed per year in the United States.[2] Historically the incidence in cancer patients was quoted as 10-16%, however more recent data has shown an increase in the incidence to 20-40%.[3] This increase in incidence has been attributed to more frequent screening and use of MRI, as well as prolonged survival in patients with cancers that frequently metastasize to the brain such as breast and lung.[3,4] Patients who develop brain metastases have a survival in the range of 2-11 months depending on recursive partitioning analysis (RPA) or graded prognostic assessment (GPA) class.[4,5] The leading cancers in men in the United States are prostate, lung, and colorectal,[6] and in women, they are breast, lung, and colorectal.[6] The frequency of brain metastases in lung cancer is approximately 48%, breast 15%, colorectal 5% and there is also a high frequency of brain metastases in cancers of unknown primary, at 13%.[3] Melanoma also has a high propensity to metastasize to the brain and is quoted as the third overall most common disease causing brain metastases.[7,8] The frequency of brain metastases in melanoma was quoted as 9% by Arnold & Patchell.[3]

The management of brain metastases includes corticosteroids, surgery, radiotherapy, or the combination of modalities. Options for radiotherapy include whole brain irradiation in a fractionated course, or stereotactic radiosurgery (SRS), a high dose, single fraction treatment. In 1987, Strum et al. demonstrated the efficacy of single dose irradiation for solitary brain metastases in a retrospective study of 12 patients treated from 1984-1985 in Germany. These patients had tumors 1-3.5 cm in size which were deemed unresectable, and were treated with external beam radiation using a 15 MeV photon beam from a linear accelerator, with doses ranging 20-30 Gy to the tumor margin (80% isodose).[9] In one case of a patient with rapidly growing metastatic lesions, 42 mm, 25 Gy to the 50% isodose line was given and the patient suffered an inferior herniation and death within 15 hours. No other patient suffered undue side effects and no recurrences were observed.[9] In 1990 the

results of a randomized trial by Patchell et al. demonstrated that surgical resection followed by whole brain radiotherapy (36 Gy in 12 fractions) provided superior outcomes in local control and survival to biopsy and whole brain radiotherapy alone.[10] In 1998, a second randomized trial showed surgery followed by whole brain radiotherapy (54 Gy in 28 fractions) decreased recurrence rates when compared to surgery alone, although there was no added survival benefit.[11] The EORTC trial 22952-26001 published by Kocher et al. in 2010 demonstrated that for patients with 1-3 brain metastases, SRS and whole brain irradiation combined provided the best local control, SRS and surgery with whole brain irradiation were equivalent, and surgery alone provided the worst local control.[12] There was no survival benefit with the addition of whole brain irradiation in these patients.

The RTOG trial 90-05 was a dose escalation trial that established the maximum tolerated dose for brain tumors treated with SRS by size. For tumors $\leq$ 20 mm, 21-30 mm, and 31-40 mm the maximum tolerated doses were 24 Gy, 18 Gy, and 15 Gy respectively.[1] In this study, patients had either had cerebral or cerebellar tumors less than or equal to 40 mm and they were treated with prior whole brain or partial brain irradiation 3 months or more from enrollment. Patients with lesions $\leq$ 20 mm did not reach an unacceptable incidence of toxicity with 24 Gy. Of the 10 patients treated with this dose, no patient had acute toxicity and only 10% had chronic toxicity. Despite this, the dose was not escalated to 27 Gy because of investigators' reluctance to prescribe this dose. The toxicities reported in this study included grade 3 irreversible edema requiring inpatient administration of steroids and grade 4 radionecrosis requiring operation. The reported grade 4 and 5 toxicities were initially acute or chronic grade 3 or 4 toxicities that were ultimately fatal.[1]

Utilizing the size and dose parameters for SRS treatment for brain metastases outlined by RTOG 90-05 at our institution, of 126 patients evaluated in a recent analysis, 51% failed locally after initial therapy,[13] and whole brain radiotherapy or surgical resection did not affect the failure rate. Other studies have quoted local control rates upwards of 80% for melanoma patients;[14,15] therefore we hypothesize that dose escalation for brain metastases may provide better rates of local control. Other institutions have published their experiences of the safe and efficacious utilization of doses up to 30 Gy for radiosurgery,[16,17] and there is no real consensus on the appropriate dose ranges for patients that have not received prior brain radiation. In order to determine whether dose escalation would improve control, assessment of the safety of dose escalation must be addressed, as we propose to do in this study. The guidelines we follow in the proposed study are based on a trial where patients all had prior brain irradiation, either to the whole brain or to a partial volume, and the maximum tolerated dose for small lesions $\leq$ 20 mm was not reached. We hypothesize that patients who have not had prior brain irradiation will tolerate higher doses of single fraction SRS treatment to brain metastases with improved control rates.

3 STUDY DESIGN

3.1 Description

This is a Phase I dose escalation study aimed at determining the Maximum Tolerated Dose (MTD) of stereotactic radiosurgery (SRS) treatment and at evaluating the response rate, progression-free survival, overall survival, and toxicity of the treatment.

Patients will be assigned to one of four cohorts based on the size of their brain lesions (details of cohort assignment are provided in section 3.1.2). For each patient, a single lesion will be treated at experimental dose level (shown in Table 1), other metastases (if present) will receive standard SRS doses (shown in Table 2).

3.1.1 Dose escalation

A non-standard 5+4 design will be used for the dose escalation. For each cohort, an initial group of 5 patients will be accrued at dose level 1 and receive experimental treatment to one of their lesions.

- If 0 of 5 patients in a given cohort experience DLTs (as defined in section 3.2) within the first 12-16 weeks post treatment, the dose will be escalated by 2 Gy to the next dose level.
- If there are ≥ 2 DLTs in 5 patients from a given cohort within the first 12-16 weeks post treatment, the current dose will be declared as exceeding the MTD and no more patients will be treated with that dose.
- If there is exactly 1 DLT in 5 patients from a given cohort within the first 12-16 weeks post treatment, an additional 4 patients will be treated at that dose level.
    - If 0 DLTs are observed among the 4 additional patients, the dose will be declared below the MTD, and dose escalation will resume.
    - If there is ≥ 1 DLTs among the 4 additional patients, the current dose will be declared as exceeding the MTD and no more patients will be treated with that dose.

Escalation will continue until a defined maximum dose is reached or dose limiting toxicities (DLTs) are observed as discussed above.

Cohorts 1a, 1b, 2, and 3 are independent and enrollment may proceed simultaneously.

If dose level 1 for any cohort if found to exceed the MTD (as defined by ≥ 2 DLTs observed within the first 12-16 weeks post treatment in 5 to 9 patients treated at dose level 1), the cohort will be suspended and the data will be reviewed by the study chair and the DSMC. An amendment to the trial would be necessary prior to resuming enrollment on this cohort.

If the MTD for a particular cohort is exceeded during escalation (as defined by ≥ 2 DLTs in 5 to 9 patients from this given cohort within the first 12-16 weeks post treatment), the previous dose level will be defined as the MTD and no further escalation will be allowed.

Table 1: Experimental SRS doses for dose escalation

	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4
Cohort 1a Diameter: ≤ 10 mm Volume: ≤ 0.5236 cm^3	26 Gy	28 Gy	30 Gy	n/a
Cohort 1b Diameter: 11-20 mm Volume: 0.5237-4.1888 cm^3	26 Gy	28 Gy	30 Gy	n/a
Cohort 2 Diameter: 21-30 mm Volume: 4.1889-14.1372 cm^3	20 Gy	22 Gy	24 Gy	n/a
Cohort 3 Diameter: 31-40 mm Volume: 14.1373-33.5103 cm^3	17 Gy	19 Gy	21 Gy	23 Gy

Table 2: Standard SRS doses to be administered to lesions not selected for experimental treatment.

Maximum lesion diameter (mm)	**Corresponding volume (cm^3)**	**Standard SRS dose level (Gy)**
10	≤ 0.5236	24
20	0.5237-4.1888	24
30	4.1889-14.1372	18
40	14.1373-33.5103	15

3.1.2 Cohort assignment

Cohort assignments will be made by the Research Compliance Office based on **tumor volumes** (which will be calculated from the results of the SPGR MRI and brain CT scan).

- Patients with a single brain metastasis will be assigned to the cohort appropriate for the size of their lesion and will be treated with the experimental SRS dose mandated by the protocol.
- Patients with multiple brain metastases will be assigned to the cohort which allows for treatment of their largest lesion with the experimental SRS dose. Other lesions will be treated with standard SRS doses.
    - Should the cohort appropriate for the largest lesion be full and awaiting DLT assessment, a new cohort assignment will be made based on the size of the patient's second largest lesion (this process can be further repeated with other lesions of decreasing sizes if the appropriate cohorts are full).

- Should a patient have multiple lesions which all qualify for the same cohort which is full and awaiting DLT assessment, the patient will be considered ineligible.

3.2 Dose Limiting Toxicity

Dose Limiting Toxicities (DLTs) are defined as follows:

1. Any surgical intervention related to the lesion treated with the experimental dose of radiation.
2. Hospitalization for any toxicity related to the lesion treated with the experimental dose of radiation.
3. Inability to discontinue steroid use by the end of the DLT period (as defined below).
4. Seizures and need for anti-epileptic medication.

Patients will be followed for DLTs for 12 to 16 weeks following completion of SRS treatment. During this time there will be two office visits, one within 4-6 weeks of radiation treatment and the next 12-16 weeks post treatment. Determination of evaluability for DLT purposes can be made no sooner than 12 weeks post treatment and no later than 16 weeks post treatment. If applicable, dose escalation can occur only after **all** patients treated at a certain dose level have completed the 12-16 weeks post treatment visit (see details in section 3.1.1).

For patients who experience CNS toxicities, a diagnostic MRI scan or CT scan of the head is required. When correlated with the clinical picture, this will allow for identification of the lesion which is causing the toxicity (edema, hemorrhage, necrosis, new disease, etc.).

Patients who do not complete the 12-16 week DLT period for reasons other than a DLT will be considered non-evaluable and will be replaced. Replacement is at the discretion of the PI.

Any adverse event which occurs within 12 to 16 weeks post SRS treatment and meets DLT criteria will be reported to the DSMC as soon as it is discovered.

3.3 Number of Patients

We expect to enroll approximately 65 patients (5 patients per dose level in each of the four cohorts). Up to 117 patients may be enrolled depending on incidence of DLTs. Any patient who cannot complete the DLT period for reasons other than a DLT will be replaced.

3.4 Number of Study Centers

This study will be conducted at the Huntsman Cancer Institute (University of Utah).

3.5 Duration

We expect accrual for this study will take approximately 3 years.

4 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with signature in the patient research chart.

Patient No. _____

Patient's Initials: (L,F,M) _____

4.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

4.1.1 _____ Clinically confirmed brain metastases by CT or MRI criteria. If there is evidence of extra-cranial metastatic disease, it is preferable that the lesions be pathologically confirmed (see section 4.2.5 for excluded histologies) and reviewed by a University of Utah or Huntsman Cancer Hospital pathologist if the initial review was done at an outside facility.

4.1.2 _____ Prior brain surgery is allowed, although a lesion situated in the operative bed would not be selected to receive an experimental dose of SRS treatment. SRS should be delivered 4-6 weeks post-surgery if the patient had had a craniotomy for resection of a lesion. Enrollment of a patient with the goal of performing SRS outside of the 4-6 post-craniotomy window is at the PI's discretion.

4.1.3 _____ Patients must have 1-5 brain metastases total.

4.1.4 _____ Maximum tumor diameter ≤ 40 mm by CT or MRI measurement at the time of consultation/screening (for each metastatic lesion present in the brain).

4.1.5 _____ All metastatic lesions must be separated by a minimum of 3 cm as measured from the peripheral edges of the lesions which are in closest proximity to one another. If multiple lesions are present and are not all ≥ 3 cm away from each other, the patient will be deemed ineligible.

4.1.6 _____ Prior systemic therapy is allowed, although appropriate washout is required for patients who have been on BRAF inhibitors (at least 7 days).

4.1.7 _____ For subjects currently on active systemic cancer therapy, the treating medical oncologist should be consulted to ensure proper washout (if appropriate) periods prior to SRS.

4.1.8 _____ Patients must be at least 18 years of age.

4.1.9 _____ Karnofsky Performance Status (KPS) ≥ 60.

4.1.10 _____ Ability to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

4.1.11 _____ Women of child-bearing potential must have a negative pregnancy test within 10 days of study enrollment and must agree to use an acceptable method of birth control while receiving radiation and for 3 months after radiation. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 year.

4.1.12 _____ Men who are able to father a child must agree to use an acceptable method of birth control while receiving radiation, and for 3 months after radiation.

4.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

4.2.1 _____ Prior whole/partial brain irradiation or stereotactic radiosurgery.

4.2.2 _____ Brain lesions with a maximal diameter of > 40 mm in size on MRI imaging at the time of consultation/screening for protocol eligibility.

4.2.3 _____ Lesion located in anatomic regions that are not amenable to SRS, including the brain stem, optic apparatus, or eloquent cortex.

4.2.4 _____ Radiographic or cytologic evidence of leptomeningeal disease.

4.2.5 _____ Primary lesion with radiosensitive histology that includes the following: small cell carcinoma, germ cell tumors, lymphoma, leukemia, or multiple myeloma.

4.2.6 _____ Women of child-bearing potential who are pregnant or breast feeding.

4.2.7 _____ Patients with multiple lesions which by size criteria would be enrolled in a cohort which is full at the time of enrollment and the 12-16 week DLT period has not yet been reached.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____ _____ _____

Investigator Signature **Date** **Time**

5 TREATMENT PLAN

5.1 Radiation Therapy Preparation

- SPGR MRI & Diagnostic MRI of the brain will be obtained prior to simulation.
- BrainLab mask will be constructed at the time of simulation for patient immobilization during imaging procedures and treatment delivery.
- Treatment planning simulation will include obtaining a CT of the brain with 1.25 mm slice thickness, and will be fused to the SPGR MRI.
- The SPGR MRI will be fused to the simulation CT and verified by physicist as well as the treating physician.
- Target volume delineation and isocenter are based on the fused images.
- Target volume will include the primary tumor and any surrounding hemorrhage.
- The target volume will be calculated by volume (cm^3), as well as by maximum axial dimension (mm).
- All organs at risk will be contoured based off the SPGR MRI.
- The prescription dose will depend on the size of the target volume, maximum diameter in any one dimension, and the escalation dose the patient is enrolled to.

5.2 Radiation Therapy Treatment

5.2.1 Administration

SRS treatment will be administered via a Linear Accelerator, the Novalis.

5.2.2 Accountability and Compliance

The linear accelerator undergoes quality assurance testing by the medical physics department in radiation oncology per protocol.

5.2.3 Dose Prescription and Dosimetry Requirements

- At the time of treatment planning the volume of each lesion is re-calculated (based on the recent SPGR-MRI and brain CT scan) and the final dose prescription is made based on that volume.
- Dose will be prescribed to the greatest isodose line which completely encompasses 95% of the target volume, and 95% of the prescription dose covers at least 98.5% of the target volume.
- The maximum dose and isodose line prescribed to will be recorded for each patient.
- The maximum dose to the normal tissue will be assessed using a conformality index (CI).
    - CI = (PIV/PVTV)/(PVTV/TV)
        - TV: Target Volume

- PIV: Prescription Isodose Volume, total volume encompassed by prescription isodose line
- PVTV: TV encompassed by prescription isodose line

- The numerator measures the excess volume within the prescription isodose line that does not include the target volume, and the denominator measures the fraction of the target volume included in the prescribed isodose line
- Perfect conformality = 1

5.3 Prohibited Concomitant Medications

All medications which are considered necessary for the subject's welfare and which are not expected to interfere with the evaluation of the study treatment may be given at the discretion of the investigator.

The following concomitant medications/treatments will be captured in the research chart and electronic case report forms for this study:

- Concomitant medications used for the treatment of CNS-related adverse events.
- Concomitant medications used for the treatment of any SAE.
- Systemic chemotherapies or other treatments of the primary malignancy.

If a patient is receiving systemic chemotherapy or other treatment for the primary malignancy, the appropriate washout time pre- and post-SRS (if appropriate) should be reviewed with the medical oncologist (and the discussion documented in the patient's chart).

5.4 Duration of Therapy

Stereotactic radiosurgery will be administered in a single fraction.

Discontinuation of therapy will be for patients who develop a grade 3 or grade 4-5 CNS toxicity pre-treatment due to hemorrhage from metastases, seizure, or other CNS side effect from tumor burden. If a patient did not receive SRS treatment due to pre-treatment toxicity, as described, then an additional patient/lesion would be enrolled in that treatment cohort.

6 TOXICITIES AND DOSAGE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for adverse event and serious adverse event reporting.

6.1 Dose Modifications

Dose modifications are not allowed.

6.2 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

Surgery can be considered for patients post-treatment who have a symptomatic intraparenchymal hemorrhage or require prolonged use of steroids for symptom management.

If a patient develops one or more new brain metastases after receiving SRS treatment on protocol, the investigator may proceed with a second round of SRS (using standard of care doses) after discussion with and approval from the DSMC.

7 STUDY CALENDAR

Examination	Screening [a]	SRS treatment	4-6 Weeks post SRS	12-16 Weeks post SRS	Follow-up (Q3 months) [d]
Informed Consent	X				
Medical History	X				
Eligibility Criteria	X				
Vital Signs	X				
Physical Examination	X		X	X	X
KPS Performance Status	X		X	X	X
RPA Class	X				
GPA Score	X				
Neurological Exam	X		X	X	X
Pregnancy Test [b]	X				
Diagnostic MRI of the brain [c]	X		X	X	X
SPGR MRI of the brain [e]	X				
CT Simulation Scan	X				
Stereotactic Radiosurgery		X			
Assessment of Adverse Events			X	X	X
Concomitant medications			X	X	X

a ALL Pre-study/Screening procedures should be completed within 4 weeks of study enrollment – with the exception of the pregnancy test (if required) within 10 days.

b Pregnancy test must be done within 10 days of study enrollment for all women of childbearing potential and repeated as clinically indicated.

c Diagnostic MRI of the brain with intravenous contrast.

d Follow-up should occur per standard of care. It is expected that patients will be seen in follow-up approximately every 2-3 months the first year, 4-6 months the second year, and 6-12 months thereafter. Patients should be followed until death, or for three years following SRS, whichever comes earlier.

e SPGR MRI of the brain with intravenous contrast.

8 STUDY PROCEDURES

Prior to undergoing any study-specific procedure, patients must read and sign the current Institutional Review Board (IRB)-approved informed consent form. All on-study procedures are permitted within the time window indicated in the Study Calendar.

8.1 Screening Assessments

Pre-treatment assessment will include review of medical history, neurological history and exam, physical examination, vital signs, KPS status, GPA score, RPA class, pregnancy test (for women of child bearing potential) and a diagnostic and SPGR MRI of the brain with intravenous contrast.

8.2 Post Treatment Assessments

The first post-treatment assessment will be at approximately 4-6 weeks after radiotherapy, with the second assessment at 12-16 weeks post radiosurgery, and then every 2-3 months the first year, 4-6 months the second year, and 6-12 months thereafter, or clinically as per standard of care.

The visit will include a neurological exam and physical exam, adverse event assessment, KPS status, MRI of the brain with intravenous contrast, and disease assessment at each visit as clinically indicated.

Patients should be followed until the time of their death or for three years following SRS, whichever is sooner. Death should be determined as due to:

- Progression of treated brain tumor
- Progression of intracranial disease, but not experimental treated tumor
- Toxicity of protocol treatment
- Systemic progression
- Intercurrent disease, unrelated to treated tumor progression, progression of disease or toxicity of protocol treatment
- Unknown cause

Post-mortem examination of the brain should be obtained at the time of death if possible.

9 CRITERIA FOR EVALUATION AND ENDPOINT

9.1 Safety

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Physical Examination: complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs: blood pressure, respiratory rate, pulse rate and temperature will be obtained in the sitting position.

9.2 Stopping Rules

Refer to section 3.2 for definition and evaluation of Dose Limiting Toxicities.

Any dose limiting toxicity that occurs within the 12-16 weeks period following SRS treatment will be evaluated and reviewed by the PI and the DSMC for further determination of safety. Grade 4 or 5 toxicities are not expected as a result of SRS treatment, however, since patients enrolled on the study have metastatic disease to the brain, an appreciable percentage of patients are expected to pass away within a year of diagnosis of brain metastases. In such cases death is typically not attributable to radiation treatments but to progression of both systemic and intracranial disease.

9.3 Efficacy – Response Rates

Response of the lesion treated with the experimental SRS dose will be assessed by volumetric measurement on MRI imaging compared to pretreatment imaging (for the first post-treatment scan) and to NADIR (for subsequent scans). A lesion with growth of 25% or more from NADIR will be considered failure. Measurements similar to the NADIR measurements, or those with less than a 25% change will be considered stable. The lesions will be coded as either a failure or as a stable lesion; there will be no differentiation between a complete or partial response using this treatment.

If a patient has multiple brain metastases, the growth or stability of the lesions treated with standard SRS doses will also be recorded and monitored as above.

All metastases will be evaluated separately. Should the treating physician suspect a treated lesion is larger in size due to treatment effect and not true progression, appropriate follow up imaging will be ordered and the lesion will be coded as failed or stable as appropriate.

9.4 Progression – Distant Brain Failures

Should patients develop other metastatic lesions outside of the treated area, they will be coded as having a distant brain failure. The date of progression outside the treated area will be recorded and this will be utilized to determine progression free survival.

9.5 Overall Survival

Patients will be seen at regular follow-up intervals as defined in the study calendar. Should a patient pass away, their date of death will be recorded and overall survival analyses will be performed. If possible, the cause of death should be documented as well (see section 8.2 for detailed requirements). Patients will be followed for three years in this study to assess overall survival.

10 STATISTICAL CONSIDERATIONS

10.1 Dose escalation

This Phase I study follows a nonstandard 5+4 design with toxicity as the primary endpoint. A primary consideration of the statistical design is to provide 80% confidence that the true proportion of subjects with DLT at a putative “tolerated dose” is less than 30%.

The design will include an initial group of five patients (for each cohort), and if necessary, a second group of four patients, as described in details in section 5.2.4.

An 80% exact upper confidence bound will be constructed for proportion of MTDs associated with the dose level using the Clopper-Pearson method. Simulations will be used to adjust the upper confidence bound for the two stages of patient recruitment. Both upper confidence bounds will be reported. This design has the following statistical properties. If 0 DLTs are observed in a group of 5 then the one-sided 80% upper confidence bound for the proportion of subjects with DLT is 27.6%. If there is 1 DLT in a group of 9 subjects then the one-sided 80% upper confidence bound the proportion of subjects with DLT is 29.8%. If the true proportion of subjects with DLT is 10%, then there is an 80% probability that dose level will be declared to be below the MTD.

10.2 Secondary Endpoints

Response of the treated lesions is a binary endpoint and lesions will be determined to be stable or failed at follow up. The proportion of treated lesions that respond will be reported along with an exact 95% confidence interval, determined by the Clopper-Pearson method. As stated above, lesions will be measured volumetrically and determined to have failed if they have more than 25% volumetric growth. If hemorrhage is seen, this will also be recorded and coded separately. Kaplan Meier analysis will be used to analyze time to local failure.

For the secondary endpoint of distant brain failures, if a patient develops a new metastatic lesion outside of the treated region the date of presentation of that new lesion will be recorded and the patient will be coded as having failed outside the treated area. Kaplan Meier analysis will be used to determine progression free survival.

For the secondary endpoint of overall survival, patients will be coded as alive or deceased at last follow up to three years and date of death will be recorded. Kaplan Meier analysis will be used to analyze overall survival.

11 REGISTRATION GUIDELINES

Patients must meet all of the eligibility requirements listed in Section 4 prior to registration.

Study related screening procedures can only begin once the patient has signed a consent form. Patients must not begin protocol treatment prior to registration.

Treatment should start within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to: CTORegistrations@hci.utah.edu.

12 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of electronic forms for each patient that provides a record of the data generated according to the protocol. CRFs should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are

IRB approved. **Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.** These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

13.2 Institutional Review

The study will be approved by the Institutional Review Board of University of Utah.

13.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at the Huntsman Cancer Institute (HCI) and approved by the NCI to assure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a **Phase I study**. For each phase I study using an agent of potential risk a member of the DSMC will be assigned as the primary medical monitor. The primary medical monitor will be notified immediately of all SAEs. A formal report should be submitted to the primary medical monitor within 10 days. All serious adverse events (SAEs) occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC quarterly. Approval from the primary medical monitor is required for all dose escalations. The full committee will also review all grade 3 or greater toxicities for patients on treatment and within 30 day follow-up window (only if possibly, probably or definitely related).

13.4 Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for AE and SAE reporting. An electronic copy of the CTCAE Version 4.0 can be downloaded from: http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

13.4.1 Adverse Events (AE)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after treatment with SRS regardless of the relationship of the event to SRS treatment. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before SRS treatment are only considered adverse events if they worsen after SRS is delivered. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, require treatment, or are considered clinically significant by the investigator.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v4.0 (grade 1-5).
2. Its relationship to treatment (definite, probable, possible, unlikely, not related).
3. Its duration (start and end dates or if continuing at final exam).
4. Action taken (no action taken; medical intervention given; hospitalization or prolonged hospitalization).
5. Whether it constitutes an SAE.

All adverse events will be treated appropriately. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to SRS, the interventions required to treat it, and the outcome.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected in the patient's research chart and followed as appropriate. Only CNS-related toxicities (as assessed by the investigator) will be captured as AEs and recorded on the electronic case report form for this study.

Adverse event collection will begin immediately after SRS treatment and continue throughout the 12-16 weeks post treatment period and the follow-up period, and will end 3 years after completion of SRS treatment or at the time of the patient's death, whichever occurs the soonest.

All grade ≥ 3 CNS toxicities must be reported to the principal investigator and the DSMC via the RCO.

13.4.2 Serious Adverse Event (SAE)

Information about ALL serious adverse events (including non CNS-related events which meet seriousness criteria) will be collected, recorded, and reported as described in Section 13.5. A serious adverse event is an undesirable sign, symptom or medical condition which meets any of the following criteria:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.
- Causes congenital anomaly or birth defect.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control).
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the delivery of SRS.
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless of whether they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

The SAE reporting period for this study begins at the time of SRS treatment and ends 3 years after completion of SRS treatment or at the time of the patient's death, whichever occurs first.

13.5 SAE Reporting Requirements

SAEs must be reported to the DSMC, the FDA, the IRB according to the requirements described below.

A MedWatch 3500A form must be completed and submitted to compliance@hci.utah.edu **as soon as possible, but no later than 10 days of first knowledge or notification of event (5 days for fatal or life threatening event).** The

form can downloaded at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

DSMC Notifications:

- An HCI Research Compliance Officer (RCO) will process and submit the MedWatch form to the proper DSMC member as necessary for each individual study.
- The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the quarterly DSMC meeting.

FDA Notifications:

- Adverse events occurring during the course of a clinical study that meet the following criteria will be promptly reported to the FDA:
  - Serious
  - Unexpected
  - Definitely, Probably or Possibly Related to the investigational therapy
- Fatal or life-threatening events that meet the criteria above will be reported within 7 calendar days after first knowledge of the event by the investigator; followed by as complete a report as possible within 8 additional calendar days.
- All other events that meet the criteria above will be reported within 15 calendar days after first knowledge of the event by the investigator.
- The RCO will review the MedWatch report for completeness, accuracy and applicability to the regulatory reporting requirements.
- The RCO will ensure the complete, accurate and timely reporting of the event to the FDA.
- The MedWatch report will be submitted to the FDA through the voluntary reporting method by the Regulatory Coordinator.

IRB Notification:

- Events meeting the University of Utah IRB reporting requirements (http://www.research.utah.edu/irb/) will be submitted through the IRB's electronic reporting system within 10 working days.

13.6 Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

13.7 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant.
- Harmful (caused harm to participants or others, or place them at increased risk of harm, including physical, psychological, economic, or social harm).
- Possible serious or continued noncompliance.

13.8 FDA Annual Reporting

This study is IND exempt therefore there are no annual reporting requirements to the FDA.

13.9 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

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APPENDIX A – Tumor Assessment Worksheet

Patient's Name: _____ Patient's Study ID: _____

Patient's MRN: _____ Patient's consent date: _____

	CT sim/SPGR-MRI SRS Planning scan	4-6 Weeks Post SRS Scan	12-16 Weeks Post SRS Scan	Follow-up Scan __	Follow-up Scan __	Follow-up Scan __
Name of Measuring MD:						
Date of MRI:						
TARGET LESIONS*	**Volume (cm^3)**					
Lesion 1:						
Lesion 2:						
Lesion 3:						
Lesion 4:						
Lesion 5:						
INDIVIDUAL RESPONSES	**Change from NADIR / Response (F = failure, S = stable)**					
Lesion 1:	-					
Lesion 2:	-					
Lesion 3:	-					
Lesion 4:	-					
Lesion 5:	-					
MD signature: Date:						

*** Lesion 1 is the lesion selected to receive the experimental dose of SRS.**

APPENDIX B – Neurological Exam Worksheet

Patient's Name: _____ Patient's Study ID: _____

Patient's MRN: _____ Date of Visit: _____

Mental Status *(normal, abnormal, not examined)*		
Orientation *(person, place, year)*		
Attention *(days of week backwards, WORLD backwards, serial 7s)*		

Cranial Nerves *(normal, abnormal, not examined)*		
II (visual fields)		
II, IV, VI (EOM)		
V (sensation)		
VII (smile)		
IX (palate elevation)		
XII (shoulder shrug)		

Strength *(0 - 5, 5 is normal)*	***Left***	***Right***
Deltoid		
Biceps		
Triceps		
Wrist		
Hand Grip		
Hip Flexor		
Knee Flex		
Knee Extension		
Foot Flex		
Foot Extension		

Sensation *(normal, abnormal, not examined)*		
Light Touch	***Left***	***Right***
Leg		
Arm		

DTR *(0 - 3, 3 is normal)*	*Left*	*Right*
Brachiradialis		
Knee		

Cerebellar *(normal, abnormal, not examined)*	
Finger Tap	
Foot Tap	
Romberg	
Gait	
Tandem Gait	

I have completed this neurological exam. Only abnormal findings are indicated above. All other findings were normal.

Physician Signature: _____

Date Completed: _____

APPENDIX C – GPA & RPA Worksheet

Patient's Name: _____ Patient's Study ID: _____

Patient's MRN: _____ Date of Visit: _____

GPA indexes for patients with newly diagnosed brain metastases[4]

Diagnosis	Significant prognostic factors	GPA scoring criteria				
NSCLC SCLC		0	0.5	1	—	—
	Age	> 60	50-60	< 50	—	—
	KPS	< 70	70-80	90-100	—	—
	Extracranial metastases	Present	—	Absent	—	—
	Number of brain metastases	> 3	2-3	1	—	—
Melanoma Renal cell cancer		0	1	2	—	—
	KPS	< 70	70-80	90-100	—	—
	Number of brain metastases	> 3	2-3	1	—	—
Breast GI cancer		0	1	2	3	4
	KPS	< 70	70	80	90	100

RPA stages for patients with newly diagnosed brain metastases[5]

Stage	Characteristics	Median survival
I	KPS > 70, age < 65, primary controlled, no extracranial mets	7.1 months
II	All others	4.2 months
III	KPS < 70	2.3 months

Diagnosis: _____

Age: _____

KPS: _____

Extracranial mets: _____

Number of brain mets: _____

GPA score: _____

RPA class: _____

Physician Signature: _____

Date Completed: _____