INDIANA UNIVERSITY
MELVIN AND BREN SIMON
COMPREHENSIVE CANCER CENTER

Study Title

*Ra*diosurgery *D*ose *Re*duction for Brain *M*etastases on *I*mmunotherapy (RADREMI):
A Prospective Pilot Study

Protocol Number:
IUSCC-0710

Principal Investigator:
Kevin Shiue, MD
535 Barnhill Dr. RT 041
Indianapolis, IN 46202
(317) 944-2524
KShiue@iuhealth.org
Radiation Oncology

Co-Investigator(s):
Paul Anthony, MD
Nasser Hanna, MD
Shearwood McClelland III, MD-Case Western Reserve University

Study Statistician:
Yong Zang, PhD

Support Provided By:
Radiation Oncology

Protocol Version Date:
January 10, 2024

TABLE OF CONTENTS

PROTOCOL SIGNATURE PAGE

*Ra*diosurgery *D*ose *Re*duction for Brain *M*etastases on *I*mmunotherapy (RADREMI):
A Prospective Pilot Study

VERSION DATE: ***10 January 2024***

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Indiana University Simon Comprehensive Cancer Center and keep a record for your files.

_____ _____

Signature of Investigator Date

_____

Investigator Name (printed)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

_____ ☐ Not Submitting to IRB

Expected IRB Submission Date

COMPLETE AND EMAIL COPY TO INDIANA UNIVERSITY SIMON COMPREHENSIVE CANCER CENTER CLINICAL TRIALS OFFICE

1. OVERVIEW

*Ra*diosurgery *D*ose *Re*duction for Brain *M*etastases on *I*mmunotherapy (RADREMI): A Prospective Pilot Study

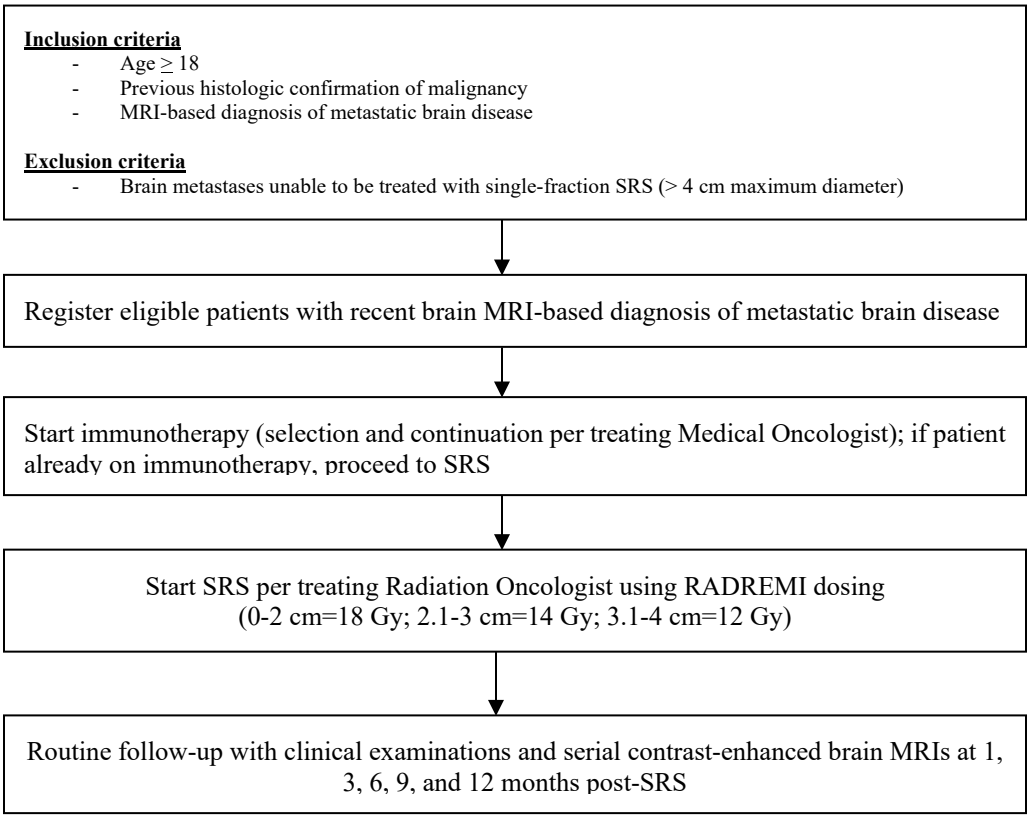
Principal Investigator: Kevin Shiue, MD
Co-Investigators: Ryan Rhome, MD PhD; Nasser Hanna, MD; Paul Anthony, MD, Shearwood McClelland III, MD (Case Western Reserve University)

Primary objective: To demonstrate 6 month symptomatic radiation necrosis (SRN) rates following ICI concurrent with dose-reduced SRS

Secondary objectives: 6-month local control (LC), 6-month radiographic radiation necrosis rates, 12-month SRN, 12-month LC, Differences in SRS and LC at 12-months for SRS modality, single versus multi-agent ICI, and melanoma versus non-melanoma brain metastases

Eligibility
- ≥ 18 years old
- Biopsy-proven primary malignancy
- Metastatic brain disease as visualized on brain MRI
- No previous whole brain radiation therapy (WBRT)
- Expected survival of 6+ months using ds-GPA

Sample size: 42



2. BACKGROUND & RATIONALE

Epidemiology

Occurring ten times more frequently than primary brain tumors, brain metastases are by far the most common intracranial malignancy (Nabors et al., 2017). Associated with a median overall survival of 4-5 months, brain metastases afflict more than 200,000 people annually in the United States, comprising up to 30% of adults with cancer (Pruitt et al., 2017; Gibney et al., 2012; Fife et al., 2004; Davies et al., 2011).

Treatment of Brain Metastases

In general, treatment of metastatic brain disease involves surgical resection, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and/or systemic therapy. While conventional systemic therapies alone are typically not sufficient to control intracranial disease due to the presence of the blood-brain barrier, newer studies suggest efficacy of immunotherapy – predominantly via immune checkpoint inhibitors (ICI). Recent Level I evidence in patients with metastatic melanoma indicates that the 6-month local control rate of brain metastases treated with multi-agent ICI alone (nivolumab + ipilimumab) is 57% (Tawbi et al., 2018), compared to the 24% rate of ipilimumab alone (Margolin et al., 2012), the 22% rate of pembrolizumab alone (Goldberg et al., 2016), or the 50% rate of ipilimumab + fotemustine (DiGiacomo et al., 2012). While the local control rate of multi-agent ICI is encouraging, it is important to remember that the 57% rate remains vastly inferior to the six-month local control rates of 87-91% achieved following single-fraction SRS administered via linear accelerator or Gamma Knife (Tawbi et al., 2018; Bernard et al., 2012; Minniti et al., 2017; Matsunaga et al., 2018). Candidates for SRS are typically patients with 1-10 brain metastases, while patients exceeding 10 brain metastases often receive WBRT instead of SRS (Yamamoto et al., 2014).

Morbidity of Standard-Dose Stereotactic Radiosurgery + Immunotherapy for Metastatic Brain Disease

A potential late toxicity of high-dose SRS for brain metastases is symptomatic radiation necrosis, which is associated with focal inflammation and intracranial edema at the irradiated site, often requiring steroid treatment (which is in itself counterproductive for optimizing efficacy of ICI; Kotecha et al., 2019) and/or craniotomy for resection of the necrosis in situations where the edema manifests as acute and potentially life-threatening neurologic deterioration. Albeit limited compared to the addition of SRS, the efficacy of multi-agent ICI alone in achieving local control of more than half of brain metastases (including a 26% complete response rate) at six months brings forth an important question: Are the doses of SRS currently being administered for brain metastases excessive given that a large proportion of the metastatic brain disease population is receiving systemic ICI treatment?

Prior to the widespread use of immunotherapy, the radiographic radiation necrosis rate of SRS for metastatic brain disease was less than 5% (with the symptomatic radiation necrosis rate less than 3%); however, a recent large study of 115 patients has indicated that in the current immunotherapy era, the true rate of symptomatic radiation necrosis with SRS + ICI is as high as 20% (Martin et al., 2018). Unfortunately, studies examining SRS + ICI have rarely reported radiation necrosis

rates, and the vast majority of those doing so have failed to report symptomatic radiation necrosis rates (Cohen-Inbar et al., 2017; Williams et al., 2017; Anderson et al., 2017; Yusuf et al., 2017; Chen et al., 2018). Only two studies have reported symptomatic radiation necrosis rates, revealing a range from 12-20% of treated patients (Skrepnik et al,. 2017; Martin et al., 2018). Unlike the majority of studies examining SRS + ICI, these two studies allow for determination of symptomatic radiation necrosis rates per patient rather than per treated lesion; for disease where it is common for patients to require treatment for multiple lesions, rates determined per patient will be substantially higher than those determined per treated lesion.

This is not a trivial consideration, as up to 1 in 5 patients treated with SRS for metastatic brain disease may develop symptomatic radionecrosis. This toxicity has the potential to affect outcomes in this patient population, given the proven association between steroid use and poorer overall survival for patients on ICI (Kotecha et al., 2019), and the side effect profile of bevacizumab when used to address symptoms. The paucity of studies examining symptomatic radiation necrosis following SRS in brain metastasis patients who are receiving immunotherapy is further exacerbated by the lack of detail in the literature regarding radionecrosis rates relative to immunotherapy and SRS administration, and the dearth of prospectively collected data (Lehrer et al., 2019). To date, only one study has reported the time from SRS to radiographic radiation necrosis rate (median: 14.7 months), with no studies reporting the time from SRS to symptomatic radiation necrosis (Skrepnik et al., 2017).

Proposed Solution to Metastatic Brain Disease Treatment-Related Morbidity

A potential solution to this problem involves dose-reduced SRS to a level which substantially reduces radionecrosis risk without sacrificing the approximately 80-85% six-month local control provided by the present dosing schema, which from RTOG 90-05 has remained 24 Gy for lesions 0-2 cm, 18 Gy for lesions 2.1-3 cm, and 15 Gy for lesions 3-4 cm (Shaw et al., 2000). To maintain a dosing schema less toxic than the RTOG 90-05 regimen while remaining within SRS doses established by Level I evidence to provide local control (Brown et al., 2017), we propose the following dose-reduced SRS protocol for this *Ra*diosurgery *D*ose *Re*duction for Brain *M*etastases on *I*mmunotherapy (RADREMI) prospective pilot study: 18 Gy (0-2 cm lesions), 14 Gy (2.1-3 cm lesions), and 12 Gy (3-4 cm lesions) for brain metastases patients receiving at least one immunotherapy agent. These doses are consistent with Level I evidence comparing SRS with whole brain radiation therapy for metastatic brain disease, which revealed that SRS doses of 12-20 Gy were sufficient to provide local control (Brown et al,. 2017). For perspective, it is important to remember that RTOG 90-05 was not a dose finding study, but rather a dose tolerance study; subsequent work has established improved local control compared to RTOG 90-05 while using lower doses than the RTOG 90-05 regimen (Shehata et al., 2004; Colaco et al., 2016). Given the efficacy of immunotherapy alone in treating melanoma brain metastases (Tawbi et al., 2018), it is reasonable to hypothesize that a lower SRS dose than the RTOG 90-05 schema will result in a combinatorial effect sufficient to provide local control without resulting in the 20% symptomatic necrosis rate seen with the present dosing schema (Martin et al., 2018).

Summary and Rationale

In summary, this study seeks to assess the efficacy and safety of radiosurgery dose reduction for brain metastases patients receiving immunotherapy. We hypothesize that: 1. Dose-reduced SRS will reduce the risk of radionecrosis compared to the 16% average rate per patient from the existing concurrent SRS + ICI literature (Skrepnik et al., 2017; Martin et al., 2018) with current SRS dose, and 2. Dose-reduced SRS demonstrates non-inferior efficacy (measured primarily through six-month local tumor control) compared to the 80% local control rate associated with the RTOG 90-05-established SRS dosing parameters. For the purposes of this study, radionecrosis will be defined as clinical symptomatology following SRS requiring steroid utilization and/or operative intervention in combination with imaging features strongly suggesting radionecrosis as demonstrated utilizing routine MRI, MR Perfusion, MR Spectroscopy, and/or PET imaging. Although the definition of concurrent SRS+ICI has varied greatly in the literature, ranging from 2 weeks to 4 months with some studies defining administration within 4 months as concurrent (Anderson et al., 2017; Chen et al., 2018); for the purposes of this study, concurrent therapy will be defined as ICI administered within 30 days of SRS. We also hope to explore SRS radionecrosis rates in multi-agent versus single-agent immunotherapy, as well as in melanoma versus non-melanoma brain metastases. Local control will be defined as a less than 20% increase in tumor size following SRS, as previously described using Response Assessment in Neuro-Oncology (RANO) criteria (Lin et al., 2015).

3. OBJECTIVE(S)

3.1 Primary Objective

To evaluate toxicity rates of brain metastasis after ICI concurrent with SRS at six months with regard to symptomatic radiation necrosis, defined as a 6-month rate of clinical symptomatology requiring steroid administration (i.e. Decadron), bevacizumab (Avastin), and/or operative intervention concomitant with advanced and routine brain imaging findings consistent with radiation necrosis.

3.2 Secondary Objectives

- 6-month local control
- 6-month radiographic radiation necrosis
- 12-month symptomatic radiation necrosis
- 12-month local control
- 12-month radiographic radiation necrosis
- 12-month local control rate by SRS modality
- 12-month local control rate by single versus multi-agent ICI
- 12-month local control rate by melanoma versus non-melanoma brain metastases
- 12-month symptomatic radiation necrosis rate by SRS modality
- 12-month symptomatic radiation necrosis rate by single versus multi-agent ICI
- 12-month symptomatic radiation necrosis rate by melanoma versus non-melanoma brain metastases

4. OUTCOME MEASURES

4.1 Primary Outcome Measure

6 month symptomatic radiation necrosis, defined as a 6-month rate of clinical symptomatology requiring steroid administration (i.e. Decadron) and/or operative intervention concomitant with advanced and routine brain imaging findings consistent with radiation necrosis. Follow-up MRIs will be fused with the planning scan for this assessment.

4.2 Secondary Outcome Measure

1. 6 month local control, defined as a 6-month rate of any new, recurrent or progressing (as defined by RANO criteria) tumor within the planning target volume compared to pre-SRS on any post-treatment MRI by 6 months. Follow-up MRIs will be fused with the planning scan for this assessment.
2. 6 month radiographic radiation necrosis, defined as brain imaging findings (MRI, MR Perfusion, MR Spectroscopy, and/or PET) consistent with radiation necrosis.
3. 12 month local control
4. 12 month symptomatic radiation necrosis
5. 12 month radiographic radiation necrosis
6. Evaluation of 12 month local control rate by SRS modality (Gamma Knife versus Linear Accelerator)
7. Evaluation of 12 month local control rate by single agent versus multi-agent ICI
8. Evaluation of 12 month local control rate by melanoma versus non-melanoma brain metastases
9. Evaluation of 12 month symptomatic radiation necrosis rate by SRS modality (Gamma Knife versus Linear Accelerator)
10. Evaluation of 12 month symptomatic radiation necrosis rate by single agent versus multi-agent ICI
11. Evaluation of 12 month symptomatic radiation necrosis rate by melanoma versus non-melanoma brain metastases

5. ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

1. Brain MRI-confirmed 1-10 solid tumor brain metastases (Yamamoto et al., 2014)
2. Biopsy-confirmed primary malignancy
3. ds-GPA estimated median survival of at least 6 months, for histologies not included in the ds-GPA, publications or noted online at brainmetgpa.com, the PI will use either published or validated data or their best clinical judgment to determine the patient's expected survival
4. Stereotactic radiosurgery candidate per treating Radiation Oncologist
5. ≥ 18 years old at the time of informed consent
6. Ability to provide written informed consent and HIPAA authorization
7. ALC > 800/ul (Ku et al., 2010)
8. Patients currently on cytotoxic chemotherapy are eligible
9. Patients receiving ICI up to 30 days prior to delivery of SRS are eligible

10. Patients having undergone operative resection for metastatic brain disease within 30 days of immune checkpoint inhibitor (ICI) administration are eligible.

5.2 Exclusion Criteria

1. Major medical illnesses or psychiatric impairments, which in the investigator's opinion will prevent administration or completion of the protocol therapy and/or interfere with follow-up
2. Patients unable to receive MRI Brain
3. Patients with more than 10 brain metastases on MRI Brain
4. Any lesion > 4 cm maximum diameter
5. Total volume of metastatic disease more than 30 cm^3
6. Previous whole brain radiation therapy
7. For Cohort 1: Previous stereotactic radiosurgery where the 50% isodose line overlaps with current treatment field
8. For Cohort 2: Patients whose treatment will have a dose overlap within the target from prior treatments of 20% or greater
9. Already receiving chronic dexamethasone (chronic = $\geq$ 2 weeks) prior to SRS
10. Not a radiosurgical candidate per Radiation Oncology discretion
11. Existing autoimmune disease
12. Patients who have an unknown primary
13. Histology not amenable for SRS (i.e. lymphoma). (Small Cell Lung Cancer IS amenable.)

6. STUDY DESIGN

This is a prospective multi-site, single arm, pilot study to determine the symptomatic radiation necrosis rate at 6 months utilizing dose-reduced stereotactic radiosurgery with immunotherapy for subjects with a diagnosis of 1-10 brain metastases from MRI and tissue diagnosis of primary malignancy.

7. PATIENT REGISTRATION

Potential patients will be identified and recruited per the recommendation of medical oncologists, tumor boards, Department of Radiation Oncology, outside physicians, or self-referral. No advertisement will be used to recruit subjects. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the eligibility criteria. Eligible patients who complete the Informed Consent Process will be registered in the OnCore® database and assigned a patient ID number. Regulatory files will be maintained by the Radiation Oncology Research Office. Applicable regulatory documents must be completed and on file prior to registration of any patients.

8. STUDY PROCEDURES

8.1 Cohorts Description

This study will be divided into 2 main cohorts as described below. Both cohorts will have the same procedures completed and will follow the same timelines up to the 6-month follow-up. After 6 months, subjects will be followed on the most recent calendar for up to 5 years post last SRS.

Cohort 1: All subjects initially screened and treated for this study.

Cohort 2: If a subject is treated and during follow-up scans new lesion(s) are found, they may be treated for those new lesion(s). These must be patients who have not had a negative outcome or end-point event while enrolled on Cohort 1. These subjects will be consented on a cohort specific consent and follow all procedures listed below.

Subjects may be treated multiple times, per procedures below.

8.2 Baseline/Screening Procedures

The following will be completed prior to radiosurgery:

1. Written informed consent and HIPAA authorization
2. Diagnostic MRI Brain
3. Medical history and clinical examination performed by physician from neurology, neurosurgery, medical oncology, or radiation oncology.
4. Absolute Lymphocyte Count (ALC) – total number of immune cells in mL of blood
5. Baseline ds-GPA, and KPS; for histologies not included in the ds-GPA, publications or noted online at brainmetgpa.com, the PI will use either published or validated data or their best clinical judgment to determine the patient's expected survival

8.3 Stereotactic Radiosurgery

Stereotactic radiosurgery will be delivered on all patients utilizing gamma knife or linear accelerator based techniques as per RADREMI dosing criteria (Section 10 Table 1) based on tumor diameter. All apparent, previously untreated brain metastases will be treated with radiosurgery at this time.

If any of the following occurs during the MRI Brain planning scan, the subject will be withdrawn from study, not treated on protocol, and replaced:

- The total number of brain metastases sums greater than 10. The subject will be withdrawn and not treated on protocol.

- The total volume of brain metastases is greater than 30 cm^3. The subject will be withdrawn and not treated on protocol.

8.4 Follow-Up

Following delivery of stereotactic radiosurgery, all patients will be monitored clinically and with serial MRI Brain scans to determine local control and rate of radiation necrosis. Additional imaging and testing may be performed as deemed necessary by the treating physician.

Initiation/continuation of immunotherapy, chemotherapy and/or other systemic agents will be per medical oncologist discretion.

8.5 One Month Follow-Up

A detailed medical history, toxicity assessment and physical examination including vital signs along with a brain MRI will be performed at 4 weeks after radiosurgery.

8.6 Long Term Follow up

Subjects will be followed approximately every 3 months (+/- 30 days) after SRS for 1 year. A detailed medical history (including necessity of any steroid administration), toxicity assessment and physical examination including vital signs will be performed at each visit. Each follow-up over this time period will also include a Brain MRI with the following sequences: without contrast, with contrast, FLAIR, Diffusion Tensor Imaging (DTI) and Perfusion Weighted Imaging (PWI). The MRI will be analyzed per RANO BM criteria (Section 11) for assessment of local control. The MRI will also be analyzed for radiation necrosis as discussed in Section 12. Neurologic status will be assessed using the Neurologic Assessment in Neuro-Oncology (NANO) scale (Nayak et al., 2017).

After the 1-year (12-month) follow-up period, subjects will be followed according to their treating physician per standard of care every 3-6 months. MRI Brain obtained during this time period may be used for assessment of primary and secondary endpoints; however, are not mandated to be obtained at particular time intervals. Patients who are unable to travel to Indiana University for follow-up appointments will have records sent to Indiana University at each follow-up.

From year 2-5, the follow up period will be determined by their treating physician per standard of care, generally every 3-6 months. MRIs will be obtained per treating physician discretion.

9. STUDY CALENDAR

	Baseline Screening*	**SRS (stereotactic radiosurgery) ***	**1 Month Follow Up[1*]**	**3 Month Follow Up[1*]**	**6 Month Follow Up[1*]**	**9 Month Follow Up[1*]**	**12 Month Follow Up[2*]**
	Within 30 days of SRS	Gamma Knife or Linear Accelerator (LINAC)	30 days post SRS	90 days post SRS	180 days post SRS	270 days post SRS	1 years post SRS
Radiation Oncology consult and consent	X						
Medical History (including steroid usage)	X		X	X	X	X	X
Physical Examination	X		X	X	X	X	X
Vitals: weight/ht. BP[7]	X	X	X	X	X	X	X
ds-GPA[5]	X						
Diagnostic MRI Brain[6]	X						
KPS	X						
MRI Brain Planning Scan[4]		X					
ALC	X						
Toxicity assessment			X	X	X	X	X[8]
MRI Brain with and without contrast[3]			X	X	X	X	X

Footnotes:

1. Variations of +/- 30 days from the scheduled visit are permitted
2. After 12-months post-SRS, subjects will be followed at physician's discretion, approximately every 3-6 months per standard of care. Any MRI Brain, physical exam or vitals obtained at these appointments will be gathered. However, if these procedures are not performed per standard of care, this will not be a deviation.
3. MRI Brain performed at Indiana University will have sequences including contrast, no contrast, FLAIR, DTI and PWI. If patient receives MRI Brain outside of Indiana University, a minimum of contrast, no contrast and FLAIR will need to be obtained and all sequences mentioned above are encouraged.
4. Variations of -30 days from the scheduled visit are permitted for linear accelerator based SRS, and may include the baseline screening MRI at the treating radiation oncologist's discretion.
5. Will be calculated using www.brainmetgpa.com tool
6. Diagnostic brain MRI is considered standard of care and will be performed as part of standard of care if subjects have not already undergone the procedure prior to enrollment.
7. Height is only required at the baseline screening visit.
8. After 12 months, only clinically relevant AEs will be recorded.

* Subjects may be treated multiple times. Subjects cannot be enrolled if the treatment will have a dose overlap within the target from prior treatments of 20% or greater. Once it is determined that they will receive treatment if they are in follow-up, they will be enrolled onto cohort 2 and re-start all procedures beginning with baseline screening.

TREATMENT DOSE AND DELIVERY

The total radiosurgery dose will be specified according to tumor size as noted in Table 1. All patients will be treated to this dose in one session.

Table 1: RADREMI Dose Criteria

Maximum Tumor Diameter	Prescribed Dose
≤ 20 mm	18 Gy
21 – 30 mm	14 Gy
31 – 40 mm	12 Gy

FDA-approved stereotactic localization procedures for imaging and treatment delivery will be used. With radiosurgery treatments using the Leksell Gamma Knife Perfexion®, target localization will be performed using the head frame coordinate system. The Leksell GammaPlan® will be used to generate the treatment plan with respect to the coordinate system created by localization. Target volume and isocenter determination will be based on an MRI Brain scan with the patient's head in a stereotactic frame. The imaging study used to deliver the radiosurgical treatment must be the same as used to determine the size of the metastatic lesion(s). Stereotactic MRI slice thickness may not exceed 3 mm. The target volume will include the enhancing portion of the metastatic lesion. Surrounding areas of edema will not be considered part of the target volume.

Linear accelerator based stereotactic localization will be performed using the Encompass® SRS thermoplastic mask immobilization system. The patient will undergo a 1mm slice thickness helical CT scan that will be fused with the MRI brain T1-weighted post-contrast axial scan used for target delineation. The CT-MRI fusion maximum correlation error must be less than 1.5mm. The imaging study used to deliver the radiosurgical treatment must be the same as used to determine the size of the metastatic lesion(s). Stereotactic MRI slice thickness may not exceed 3 mm. The target volume will include the enhancing portion of the metastatic lesion. Surrounding areas of edema will not be considered part of the target volume.

The dose will be prescribed to the isodose surface (50 – 90%), which encompasses the margin of the metastasis, as defined by the imaging studies. The 100% dose will be recorded for each patient.

For patients with multiple brain metastases, stereotactic radiosurgery will be delivered to each lesion that has not previously undergone stereotactic radiosurgery. The prescribed dose will be according to the RADREMI dosing schema as described in Table 1 above. Due to the volumetric summation constraint for the remaining metastases, no single lesion greater than 4cm will be allowed on study, and, therefore, the above dose prescriptions can be used. If any two lesions are within 0.8 to 2 cm of each other, the intervening midplane dose will not exceed 13 Gy. This may require treating each respective target with a lesser dose than dictated by the above table. This is designated to minimize toxicity in patients.

Isodose distributions must be calculated, and the prescription isodose line clearly designated, for each target lesion in all planes.

Table 2: Critical Structures [36]

Structure	Maximum critical volume above threshold	Threshold dose (Gy)	Max Point Dose (Gy)
Optic pathway	<0.2 cc	8	10
Brainstem	<0.5 cc	10	15
Cochlea	N/A	N/A	9
Medulla	<1.2 cc	7	

The dose to the above structures must meet constraints as designated by TG-101; the small size of the cochlea allows for only a max point dose and not a maximum critical volume above threshold or a threshold dose (Benedict et al., 2010). If the above constraints cannot be met utilizing the prescribed radiosurgery dose Table 1, then the highest dose to the target volume will be used such that constraints can be met. This will be considered a minor deviation.

10.1 General Concomitant Medication and Supportive Care Guidelines

For patients presenting with signs and symptoms relatable to peri-tumoral edema, including but not limited to nausea and headaches, dexamethasone will be prescribed at a dose level per clinician judgement.

For patients presenting with seizure, anti-seizure medication will be prescribed at a dose level per clinician judgement. No specific type of anti-seizure medication is recommended or prohibited.

Each patient will be given a prescription for 1mg Ativan to be taken approximately 30 minutes prior to the procedure, or otherwise at the physician's discretion.

10. RESPONSE ASSESSMENT IN NEURO-ONCOLOGY BRAIN METASTASES (RANO-BM)

11.1 Definitions Associated with RANO-BM (Lin et al., 2015)

1. **Measurable disease** is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 3 mm, and is visible on three or more axial slices that are preferably 1 mm or less apart with 0 mm skip (and ideally ≤ 1.5 mm apart with 0 mm skip).
    a. Additionally, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 3 mm for the lesion to be considered measurable.
        i. Note: Recording of the 2nd dimension is at the radiologist's discretion, if measurable.
    b. If the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least double the slice thickness. Interslice gaps, if present, should also be considered in the determination of the minimum size of measurable lesions at baseline.

2. **Non-measurable disease** includes all other lesions, including lesions with longest dimension less than 3 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

3. **Methods of measurement**

   The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Consistent use of imaging techniques across all imaging time points is important to ensure that the assessment of interval appearance, disappearance of lesions, or change in size is not affected by scan parameters such as slice thickness. Use of thin section imaging is particularly important for the assessment of lesions less than 3 mm in longest diameter or small changes in lesion size, or both.

   Gadolinium-enhanced MRI is the most sensitive and reproducible method available to measure CNS lesions selected for response assessment. MRI is strongly encouraged as the default standard imaging technique, although CT with and without contrast could be considered in specific circumstances (e.g., countries with limited medical resources or contraindication for MRI).

4. **Tumor response assessment**

   Only patients with measurable CNS disease at baseline should be included in protocols where objective CNS tumor response is the primary endpoint. For studies in which objective response is not the primary endpoint, the protocol must specify prospectively whether entry is restricted to those with measurable disease or if patients with non-measurable disease are also eligible.

   a. Assignment of CNS response is independent of systemic disease response. CNS lesions are to be assessed according to RANO-BM criteria, whereas non-CNS lesions would most typically be assessed according to RECIST 1.1 criteria.

   b. Generally, CNS lesions should initially be re-assessed by MRI at protocol-specified intervals 6–12 weeks apart, although there might be specific circumstances in which longer (or shorter) intervals are desirable. For patients who remain stable for extended periods of time, a longer interval between scans might be appropriate. All baseline assessments should be done as close as possible to the treatment start and no more than 4 weeks before the beginning of treatment.

   c. For previously treated lesions, we recommend documentation of how each lesion was previously treated (e.g., stereotactic radiosurgery, whole brain radiotherapy, surgical resection).

   d. When more than one measurable lesion in the CNS is present at baseline, all lesions up to a maximum of five CNS lesions should be identified as target lesions and will be recorded and measured at baseline. All measurements should be recorded in metric notation. Target lesions should be selected on the basis of

their size (longest diameter) and as those that can be measured reproducibly. For patients with recurrent disease who have multiple lesions, of which only one or two are increasing in size, the enlarging lesions should be prioritized as target lesions for the response assessment.

e. Lesions with prior local treatment (i.e., stereotactic radiosurgery or surgical resection) can be considered measurable if progression has occurred since the time of local treatment. However, careful consideration should be given to lesions previously treated with stereotactic radiosurgery, in view of the possibility of treatment effect, which is discussed below. Whether such lesions can be considered measurable should be specified prospectively in the clinical protocol. If lesions not previously treated with local therapies are present, these are preferred for selection as target lesions.

f. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters. All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be classified as present, absent, or unequivocal progression, and followed up.

11.2 Response assessment of target and non-target lesions

Please see Table 3 and Table 4 for a partial summary of this section.

1. While on study, all CNS target lesions should have their actual measurement recorded, even if very small (e.g., 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) to be assigned an exact measurement, a default value of 5 mm should be recorded on the case report form.

2. Lesions might coalesce during treatment. As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum longest diameter of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

3. New lesions can appear during treatment. The finding of a new CNS lesion should be unequivocal and not due to technical or slice variation. A new lesion is one that was not present on prior scans.

    i. If the MRI is obtained with slice thickness of 1.5 mm or less, the new lesion should also be visible in axial, coronal, and sagittal reconstructions of 1.5 mm or thinner projections.

    ii. If a new lesion is equivocal, for example because of its small size (i.e., ≤ 3 mm), continued therapy can be considered, and a follow-up assessment will clarify if it really is new disease. If repeated scans confirm a new lesion, progression should be declared using the date of the initial scan showing the new lesion.

iii. In the case of immunotherapy, however, new lesions alone cannot constitute progressive disease (see below).

4. The RANO-BM group acknowledges the case of patients who have been treated with stereotactic radiosurgery or immunotherapy-based approaches, for whom there has been radiographical evidence of enlargement of target and non-target lesions, which do not necessarily represent tumor progression. If radiographical evidence of progression exists, but clinical evidence indicates that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is needed to distinguish between true progression and treatment effect, in which case standard MRI alone is insufficient. The methods used to distinguish between true progression and treatment effect should be specified prospectively in the clinical protocol. Patients can be continued on protocol therapy pending further investigation with one or more of the following options.

   The scan can be repeated at the next protocol-scheduled assessment or sooner, and generally within about 6 weeks. An investigator can choose a shorter time interval if progressive symptoms or other clinical concerns arise. Continued tumor growth might be consistent with radiographical progression, in which case the patient should leave the study. Stabilization and shrinkage of a lesion can be consistent with treatment effect, in which case the patient can stay in the study. For patients with equivocal results even on the next restaging scan, the scan can be repeated again at a subsequent protocol-scheduled assessment or sooner, although surgery or use of an advanced imaging modality (in the case of stereotactic radiosurgery), or both, are strongly encouraged. Surgical pathology can be obtained via biopsy or resection.

   i. For lesions treated by stereotactic radiosurgery, additional evidence of tumor progression or treatment effect (radionecrosis) can be acquired with an advanced imaging modality, such as perfusion MRI, magnetic resonance spectroscopy, or ^{18}FLT or ^{18}FDG PET. Current recommendations suggest involving a multidisciplinary team to decide on the appropriate next step. Irrespective of the additional testing obtained, if subsequent testing shows that progression has occurred, the date of progression should be recorded as the date of the scan this issue was first raised.

      Patients can also have an equivocal finding on a scan (e.g., a small lesion that is not clearly new). Continued treatment is permissible until the next protocol-scheduled assessment. If the subsequent assessment shows that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

   ii. In patients receiving immunotherapy-based treatment, an initial increase in the number and size of metastases can be followed by radiographical stabilization or regression. This pattern might be related to the mechanism of action of immunotherapy, including immune infiltrates, and the time to mount an effective immune response. Thus, progressive disease should not be solely defined by the

appearance of new lesions but rather as a minimum 20% increase in the sum longest diameter of CNS target and new lesions, as unequivocal progression of existing enhancing non-target CNS lesions, as unequivocal progression of existing non-enhancing (T2/FLAIR) CNS lesions, or as clinical decline related to the tumor. If immune response-related radiographical changes are suspected, we advise to not change treatment until a short interval scan is obtained. If the subsequent assessment confirms that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

Note that the advanced imaging modalities discussed for treatment effect above have not been extensively studied with regards to immunotherapy-based approaches and therefore cannot be recommended to distinguish between tumor progression and immune-related changes at present.

5. In the absence of clinical deterioration related to the tumor, an increase in corticosteroid dose alone should not be used as a sole determinant of progression. Patients with stable imaging results and whose corticosteroid dose has increased for reasons other than clinical deterioration related to the tumor do not qualify as having stable disease or progression. These patients should be observed closely, and if their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease, but if further clinical deterioration related to the tumor becomes apparent, they will be considered as having progression.

   The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that patients who have a decrease in score on the Karnofsky performances scale from 100 or 90 to 70 points or less, a decrease of minimum 20 points from 80 or less, or a decrease from any baseline to 50 points or less, for at least 7 days, be considered as having neurological deterioration, unless this functional impairment is attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

Table 3. Response assessment of target and non-target lesions (Lin et al., 2015)
Target lesions
Complete response
Disappearance of CNS target lesion(s) sustained for at least 4 weeks; with no new lesions, no use of corticosteroids and patient is stable or improved clinically.
Partial response
At least a 30% decrease in the sum longest diameter of CNS target lesion(s), taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
Progressive disease
At least a 20% increase in the sum longest diameter of CNS target lesion(s), 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%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
Stable disease

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.
Non-target lesions
Non-target lesions should be assessed qualitatively at each of the time points specified in the protocol.
Complete response
Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
Non-complete response or non-progressive disease
Persistence of one or more non-target CNS lesion or lesions.
Progressive disease
Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

11.3 Other considerations

1. Volumetric criteria are currently experimental and the existing data is not strong enough to support the universal requirement of volumetric response criteria in clinical trials. Nevertheless, the RANO-BM working group believes that assessment and reporting of volumetric data and response will further research in this future and encourage its inclusion as a secondary endpoint when feasible. For investigators choosing to report volumetric response data, please note the following recommendations.

    i. Partial volumetric response should be defined as 65% or greater decrease in the sum volume of CNS target lesions, in addition to the corticosteroid and clinical status criteria outlined previously.

    ii. Volumetric response should be reported as a waterfall plot to provide a global sense of potential efficacy.

2. Response of non-CNS (extracranial) disease should be assessed separately from CNS (intracranial) disease.

3. Please refer to Table 5 for RANO-BM recommendations for bi-compartmental assessment of response, i.e. when considering local control and distant brain failure separately.

Table 4. Summary of the response criteria for CNS metastases proposed by RANO-BM

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥ 30% decrease in sum longest distance	< 30% decrease relative to baseline but < 20% increase in sum longest distance relative to baseline	≥ 20% increase in sum longest distance relative to nadir*

		relative to baseline		
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease
New lesion(s)^	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable#
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any#
*Progression occurs when this criterion is met.				
^A new lesion is one that is not present on prior scans and is visible in a minimum of two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression.				
#Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.				

Table 5. Sites of inclusion for assessment of bi-compartmental CNS outcomes.

	Local CNS lesions	Distant CNS lesions	Non-CNS lesions*
Bi-compartmental progression-free survival*	x	X	X
CNS progression-free survival	x	X	
Non-CNS progression-free survival*			X
CNS_{local} progression-free survival	x		
*Non-CNS disease is not assessed in the current protocol.			

11. RADIATION NECROSIS

12.1 Radiographic Radiation Necrosis

Assessment for radiation necrosis will be done based on the contrast-enhanced, FLAIR, Diffusion tensor imaging (DTI) and Perfusion weighted imaging (PWI) MRI sequences. Radiation necrosis is typically a contrast enhancing lesion with surrounding edema noted on contrast-enhanced MRI and FLAIR respectively; however, this is difficult to distinguish from recurrent tumor. Therefore, DTI and PWI sequences will be analyzed as well. DTI uses fractional anisotropy that reflects the preferential direction of water diffusion along white matter tracks. Fractional anisotropy in radiation necrosis is lower than that for recurrent tumor due to lack of normal axonal fibers or cells within the necrotic area as compared to partially functioning axonal fibers and cells associated with recurrent tumor (Shah et al., 2012). PWI

assesses intra-lesional and peri-lesional cerebral blood volume. Recurrent tumor is more likely to be associated with higher cerebral blood volume than radiation necrosis as radiation necrosis is devoid of vasculature. The percentage of signal recovery ≥ 76.3% has a sensitivity of 96% and specificity of 100% for radiation necrosis as noted on PWI. (Barajas et al., 2009).

12.2 Symptomatic Radiation Necrosis

Assessment for symptomatic radiation necrosis will be performed based on patients meeting criteria for radiographic radiation necrosis who require steroid administration, bevacizumab, and/or operative resection to treat symptomatic cerebral edema. These will be assessed at each post-SRS follow-up visit in conjunction with Brain MRIs.

12. CRITERIA FOR EVALUATION/REMOVAL FROM STUDY

Every subject should be encouraged to remain in the study. Possible reasons for early withdrawal may include, but are not limited to, the following:

1. Withdrawal of consent – Subject decides to withdraw from the study. This decision must be an "independent decision" that is documented in the source documentation
2. Principal Investigator and/or treating physician discretion – The Principal Investigator and/or treating physician may choose to withdraw a subject from the study if there are safety or other concerns.
3. Subject non-compliance.
4. Subject lost to follow-up.
5. Subject enrolled in hospice care.
6. Subject death.

13. STATISTICAL METHODS

14.1 General Considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. If any changes occur, they will be documented in the clinical study report. The statistical analysis methods are outline below.

14.2 Study Design

This is a single-arm pilot study without blinding.

14.3 Analysis Datasets

Enrolled Population
The enrolled population comprises all subjects who meet the eligibility criteria and are registered onto the study.

Safety Population
The safety population comprises all subjects who have received at least one dose of radiation. This set will be used for safety analysis.

Efficacy Population
The efficacy population comprises all subjects who have completed stereotactic radiosurgery. This population will be used for efficacy analysis.

14.4 Sample Size

An optimum one-stage design is planned. We specify a historical 6 month symptomatic radiation necrosis rate of 16% and an expected 6 month symptomatic radiation necrosis rate of 5%. Then, to achieve a power of 80% and control the type I error below 10%, a total of 40 patients evaluable for symptomatic radiation necrosis will be enrolled in the study. If at most 4 patients will experience symptomatic radiation necrosis in 6 months, the proposed dose reduction is claimed to be desirable. Otherwise, it is undesirable. We assume that at most 5% of the patients will not be evaluable for symptomatic radiation necrosis, which results in a total sample size of 42. In addition, we will add an interim analysis for the 6 month local control rate. When 20 patients have been enrolled in the study with their local control outcome being available, we will conduct a binomial exact test for the null hypothesis that the proposed method can maintain a 6 month local control rate of at least 75%. If p-value of this binomial test is less than 0.05, we will reject the null hypothesis and terminate this study earlier for futility.

14.5 Patient Characteristics and significant protocol violations

Baseline subject characteristics will be tabulated, such as demographics (age, race, gender), and disease characteristics (ds-GPA).

14.6 Disposition

The reasons for patient treatment and study discontinuation will be summarized.

14.7 Analysis of Primary Objectives

For the primary objective of 6 month symptomatic radiation necrosis for dose-reduced stereotactic radiosurgery concomitant with immunotherapy, the proportion of patients who have symptomatic radiation necrosis at 6 months will be calculated using Kaplan-Meier method along with a 95% confidence interval. Testing the observed proportion smaller than a baseline 6 month symptomatic radiation necrosis rate of 16% at a type I error rate of 5% using a one-sided binomial exact test will be done.

14.8 Analysis of Secondary Objectives

For the secondary objectives of 6-month local control, 6-month radiographic radiation necrosis, 12-month symptomatic radiation necrosis, 12-month local control, 12-month radiographic radiation necrosis and 12-month local control rate by SRS modality, Kaplan-Meier methods will be used to provide point estimate with 95% confidence intervals. The method of Klein et al., (Klein et.al., 2007) will be conducted for the group comparison.

14. MULTICENTER GUIDELINES

15.1 Study Documents

Each participating site must submit regulatory documents (informed consents, 1572s, Financial Disclosures, IRB approval documents, Continuing Reviews, Amendments, patient brochures or recruitment material etc.) to the Coordinating Center. The Coordinating Center will provide each site with a comprehensive list of the required documents prior to study start-up, throughout the duration of the study and upon study close-out. It is the responsibility of the participating site to maintain copies of all documentation sent to the Coordinating Center.

15.2 Study Initiation

Before activating the clinical trial at each participating site, the IUSCCC CTO Multicenter Clinical Research Coordinator, or designee, will ensure that:

- Full **Institutional Review Board (IRB) approval** has been obtained.
- Research staff at the participating site has been trained in data entry into *OnCore*®
- A **start-up meeting** with each institution has taken place via telephone conference. The start-up meeting will cover protocol details (including eligibility criteria, treatment plan, etc.), responsibilities of the participating investigators, and reporting procedures.
- A financial **conflict of interest statement** from each investigator has been obtained.

15.3 Patient Enrollment

After eligibility is confirmed by the participating site staff, a completed eligibility checklist, supporting source documentation, and signed consent will be sent to IUSCCC for verification. The Multicenter Clinical Research Coordinator, or designee, will assign the patient a study number and return the enrollment information to the site. The site staff will then register the patient in OnCore®. *Additional details of this process can be found in the Study Procedure Manual.*

15.4 Data Monitoring

All multicenter investigator initiated trials conducted at the IUSCCC are subject to data monitoring by the Multicenter Clinical Research Coordinator and the IUSCCC Compliance Office, or designee. External sites will be notified of upcoming monitoring visits and will be expected to provide the Multicenter Clinical Research Coordinator, IUSCCC Compliance Office, or designee, with de-identified source documents for remote monitoring of patients. Queries will be issued in OnCore® and a detailed monitoring report will be provided to the participating site. The IUSCCC will also forward any monitoring and/or auditing reports to the DSMC.

When a patient enrolled on this trial, or the trial itself, is selected for local monitoring or auditing, the participating site will forward the results to the Multicenter Clinical Research Coordinator, or designee. In addition, if a participating site patient is selected for local auditing by the IUSCCC DSMC, the site will be responsible for sending IUSCCC de-identified source documents.

15.5 Record Retention

Following closure of the study, each participating site will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

15. DATA FORMS AND SUBMISSION SCHEDULE

This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore®. The OnCore® database is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. OnCore® was developed by Forte Research Systems, Inc. and is used by the IUSCCC Clinical Trials Office (CTO) and supported by the Indiana Clinical and Translational Sciences Institute (CTSI). OnCore® properly used is compliant with Title 21 CFR Part 11.

OnCore® provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Comprehensive Cancer Center Data Safety Monitoring Committee.

16. PATIENT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Trials Office) and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

17. DATA AND SAFETY MONITORING PLAN

Moderate Risk Trials

Investigators will conduct continuous review of data and patient safety. **Monthly review meetings** for moderate risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Monthly** meeting summaries should include review of data, the number of patients, significant toxicities as described in the protocol, and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

If there are no patients on treatment or in follow-up, email communication will be used in lieu of a teleconference, or in the circumstance where a scheduling conflict does not permit phone attendance.

Data and Safety Monitoring Committee

The IUSCCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the principal investigator will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer

must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

Study Auditing and Monitoring
All trials conducted at the IUSCCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

Data Management/ Oncore Reporting Requirements
The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

Study Accrual Oversight
Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

Oncore Safety Reporting
In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information.
Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

Protocol Deviation Reporting
Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

18. REPORTING ADVERSE EVENTS

19.1 Definitions of Adverse Events

Adverse Event (AE)
An **adverse event** is defined as untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be **ANY** unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 5.0.

Serious Adverse Event (SAE)
A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 30 days of last study intervention
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Hospitalizations that are not considered SAEs are:
  - Hospitalization planned prior to study intervention
  - Hospitalization for elective treatment of a pre-existing condition unrelated to the study intervention

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

19.2 Determining Attribution to the Investigational Agent(s)

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational agent/intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

19.3 Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

Adverse events (AEs) will be recorded from the time of study intervention and until 12 months after the end of SRS treatment, regardless of whether or not the event(s) are considered related to treatment. After 12 months, AEs related to SRS or any AEs that are grade 4 or higher will be

recorded. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

All SAE's should be collected from study intervention until the 1-month follow up visit. SAEs related or possibly related to study treatment or a study procedure should be reported until the patient is off study. Any death occurring within 30 days after the study intervention must be reported as an SAE regardless of attribution.

Reporting to the IRB: Adverse Events will be reported to the IRB within 5 days from becoming aware of the event if they are: (1) unexpected, (2) related or possibly related to study participation, AND (3) suggests that the research places subject(s) or others at greater risk of harm than was previously known.

Reporting to the Data Safety Monitoring Committee (DSMC):

Regardless of study sponsorship, the DSMC chair and/or coordinator will review all expedited SAE reports through OnCore®. Expedited reports are completed per IRB guidelines and may include the IRB Prompt Reporting form, non-compliance form, AdEERS reports, MedWatch, and additional SAE forms as required by the sponsor. Submission of this information to the DSMC is additional to any other protocol-specified regulatory bodies (e.g., FDA, pharmaceutical company) to be notified.

When follow-up information is received, a follow-up expedited SAE reports monthly, and report findings to the DSMC quarterly.

19.4 Reporting to the IU Simon Comprehensive Cancer Center

Any serious adverse event or unanticipated problem occurring within 30 days of the treatment must be reported to the IU Simon Comprehensive Cancer Center within **1 business day** of notification or discovery of the incident, using the MedWatch Form 3500A (Mandatory Reporting) *or SAE Form*. SAEs that occur greater than 30 days from treatment must be reported to the IU Simon Comprehensive Cancer Center if the event is possibly, probably, or definitely related to the treatment. This form must be accompanied by a cover letter which: identifies the event, is signed by the local principal investigator or treating physician, includes the applicable study number and title, and contains the following:

- Site assessment of the event attribution to investigational product or study procedure
- Site assessment of event expectedness (expected vs. unexpected)
- Assessment of whether or not the research places subjects at a greater risk of harm than was previously known or recognized
- Assessment of the event's effect on the risk to benefit ratio
- Statement as to whether the informed consent statement should reflect changes in the potential risks involved
- Statement as to whether the event has been reported previously, and if so, whether the frequency is considered unusually high

Send to: IUSCCC Clinical Trials Office
ATTN: Multicenter coordinator/ *IUSCC-0710*
Fax: (317) 274-8022
E-mail: iusccsae@iupui.edu

The Multicenter Clinical Research Coordinator, or designee, will distribute the reports to all participating sites, as per section *19.5* below. Copies of all serious adverse event reports or unanticipated problems reports will be kept on file in the IU Simon Comprehensive Cancer Center Clinical Trials Office.

19.5 Coordinating Center Reporting Responsibilities

In addition to the responsibilities above, the Coordinating Center will also be responsible for reporting events to the FDA as required.

19.6 Reporting to Participating Sites

The Multicenter Clinical Research Coordinator, or designee, will distribute reports which are serious, unexpected and suspected to be associated with the study intervention (possibly, probably or definitely related) to all participating sites in the form of an Expedited Safety Report (external safety/IND report) within 15 calendar days from determination that the suspected adverse reaction qualifies for reporting. Copies of these Expedited Safety Reports will be kept on file in the IU Simon Comprehensive Cancer Center Clinical Trials Office.

19. Representation of Women and Minorities

Given the racial, ethnic, and gender diversity of the patient population at Indiana University, we expect the representation of women and minorities to be adequate, and consistent with their representations in the most recent United States census – this depiction of gender and racial representation is far more stringent than that demonstrated in vast majority of published immunotherapy and/or SRS series.

20. REFERENCES

1. Nabors LB, Portnow J, Ammirati M, et al. NCCN Guidelines Insights: Central Nervous System Cancers, Version 1.2017. J Natl Compr Canc Netw. 2017;15:1331-1345.

2. Pruitt AA. Epidemiology, treatment, and complications of central nervous system metastases. Continuum (Minneap Minn) 2017;23:1580–1600.

3. Gibney GT, Forsyth PA, Sondak VK. Melanoma in the brain: biology and therapeutic options. Melanoma Res 2012;22:177–183.

4. Fife KM, Colman MH, Stevens GN, Firth IC, Moon D, Shannon KF, et al. Determinants of outcome in melanoma patients with cerebral metastases. J Clin Oncol 2004;22:1293–1300.

5. Davies MA, Liu P, McIntyre S, Kim KB, Papadopoulos N, Hwu WJ, et al. Prognostic factors for survival in melanoma patients with brain metastases. Cancer 2011;117:1687–1696.

6. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med. 2018;379:722-730.

7. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012;13:459-465.

8. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol 2016;17: 976-983.

9. Di Giacomo AM, Ascierto PA, Pilla L, et al. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. Lancet Oncol 2012;13:879-886.

10. Bernard ME, Wegner RE, Reineman K, et al. Linear accelerator based stereotactic radiosurgery for melanoma brain metastases. J Cancer Res Ther. 2012;8:215-221.

11. Minniti G, Paolini S, D'Andrea G, et al. Outcomes of postoperative stereotactic radiosurgery to the resection cavity versus stereotactic radiosurgery alone for melanoma brain metastases. J Neurooncol. 2017;132:455-462.

12. Matsunaga S, Shuto T, Yamamoto M, et al. Gamma Knife radiosurgery for metastatic brain tumors from malignant melanomas: a Japanese multi-institutional cooperative and retrospective cohort study (JLGK1501). Stereotact Funct Neurosurg. 2018;96:162-171.

13. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 2014;15:387-395.

14. Kotecha R, Kim JM, Miller JA, et al. The impact of sequencing PD-1/PD-L1 inhibitors and stereotactic radiosurgery for patients with brain metastasis. Neuro Oncol. 2019 Feb 23. pii: noz046. doi: 10.1093/neuonc/noz046. [Epub ahead of print] PMID: 30796838.

15. Martin AM, Cagney DN, Catalano PJ, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. JAMA Oncol. 2018;4(8):1123-1124.

16. Cohen-Inbar O, Shih HH, Xu Z, Schlesinger D, Sheehan JP. The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab. J Neurosurg 2017;127:1007–1014.

17. Williams NL, Wuthrick EJ, Kim H, et al. Phase 1 Study of Ipilimumab Combined With Whole Brain Radiation Therapy or Radiosurgery for Melanoma Patients With Brain Metastases. Int J Radiat Oncol Biol Phys. 2017;99:22-30.

18. Anderson ES, Postow MA, Wolchok JD, Young RJ, Ballangrud Å, Chan TA, Yamada Y, Beal K. Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression; efficacy and safety of combined treatment. J Immunother Cancer. 2017;5:76.

19. Yusuf MB, Amsbaugh MJ, Burton E, Chesney J, Woo S. Peri-SRS Administration of Immune Checkpoint Therapy for Melanoma Metastatic to the Brain: Investigating Efficacy and the Effects of Relative Treatment Timing on Lesion Response. World Neurosurg. 2017;100:632-640.e4.

20. Chen L, Douglass J, Kleinberg L, et al. Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. Int J Radiat Oncol Biol Phys. 2018;100:916-925.

21. Skrepnik T, Sundararajan S, Cui H, Stea B. Improved time to disease progression in the brain in patients with melanoma brain metastases treated with concurrent delivery of radiosurgery and ipilimumab. Oncoimmunology 2017;6:e1283461

22. Lehrer EJ, Peterson J, Brown PD, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data. Radiother Oncol. 2019;130:104-112.

23. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys. 2000;47:291-298.

24. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18:1049-1060.

25. Shehata MK, Young B, Reid B, et al. Stereotatic radiosurgery of 468 brain metastases < or =2 cm: implications for SRS dose and whole brain radiation therapy. Int J Radiat Oncol Biol Phys. 2004;59:87-93.

26. Colaco RJ, Yu JB, Bond JS, et al. A contemporary dose selection algorithm for stereotactic radiosurgery in the treatment of brain metastases - An initial report. J Radiosurg SBRT. 2016;4:43-52.

27. Rock JP, Scarpace L, Hearshen D, et al. Associations among magnetic resonance spectroscopy, apparent diffusion coefficients, and image-guided histopathology with special attention to radiation necrosis. Neurosurgery. 2004;54:1111-1119.

28. Woody NM, Greer MD, Reddy CA, et al. Validation of the Disease-Specific GPA for Patients With 1 to 3 Synchronous Brain Metastases in Newly Diagnosed NSCLC. Clin Lung Cancer. 2018;19:e141-e147.

29. Etchells E, Darzins P, Silberfeld M, et al. Assessment of patient capacity to consent to treatment. J Gen Intern Med. 1999;14:27-34.

30. Ku GY, Yuan J, Page DB, et al. Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. Cancer. 2010;116:1767-1775.

31. Nayak L, DeAngelis LM, Brandes AA, et al. The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria. Neuro Oncol. 2017;19:625-635.

32. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med. Phys. 2010;37:4078-4101.

33. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015;16:e270-e278.

34. Shah R, Vattoth S, Jacob R, et al. Radiation necrosis in the brain: imaging features and differentiation from tumor recurrence. RadioGraphics. 2012;32:1343-1359.

35. Barajas RF, Chang JS, Sneed PK, et al. Distinguishing recurrent intra-axial metastatic tumor from radiation necrosis following gamma knife radiosurgery using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. AJNR Am J Neuroradiol. 2009;30:367–372.

36. Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med. 2007;26:4505-4519.

37. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int. J. Radiat Oncol Biol Phys. 2010;77:655-661.

38. Sperduto PW, Yang TJ, Beal K, et al. Estimating survival in patients with lung cancer and brain metastases, an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). JAMA Oncol. 2017;3:827-831.

39. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008;70:510-514.

40. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012;30:419-425.

41. Sperduto PW, Kased N, Roberge D, et al. Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases. Int J Radiat Oncol Biol Phys. 2012;82:2111-2117.

42. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012;30:419-425.

43. Villa S, Weber DC, Moretones C, et al. Validation of the new graded prognostic assessment scale for brain metastases: a multicenter prospective study. Radiat Oncol. 2011;6:23-31.

44. Venur VA, Ahluwalia MS. Prognostic scores for brain metastasis patients: use in clinical practice and trial design. Chin Clin Oncol. 2015;4:18-25.

21. APPENDICES

22.1 APPENDIX I - TOXICITY CRITERIA

NOTE: the attached Appendix I contains reference to the DCT/NCI Common Toxicity Criteria, Version 5.0, used to grade toxicities in reporting an "ADR" (adverse drug reaction) as described in Section 19.0 of this protocol. Other toxicity criteria (i.e., related to specialized treatments such as immunotherapy or BRMs) may be used as needed.

22.2 APPENDIX II- Performance Status

Appendix I

NCI Common Toxicity Criteria

Version 5.0
Due to the size of the latest version of the Common Toxicity Criteria, copies of this appendix are not included with this protocol document.

An electronic copy is available on the CTEP web site, http://ctep.cancer.gov/reporting/ctc.html

Appendix II

Performance Status Scales/Scores

ECOG or Zubrod		Karnofsky		Lansky	
Score	Activity	Score	Activity	Score	Activity
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.