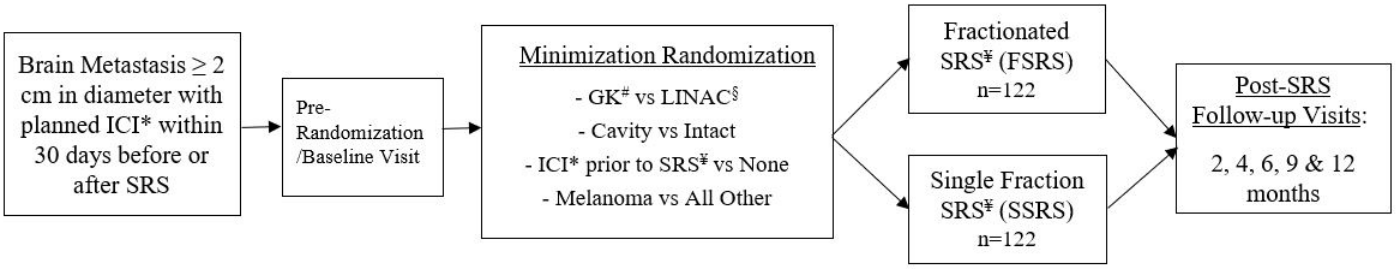
SCHEMA

HYPOFRACTIONATED RADIOTHERAPY VS SINGLE FRACTION RADIOSURGERY FOR BRAIN METASTASIS PATIENTS ON IMMUNOTHERAPY (HYPOGRYPHE)



ICI* = Immune check point inhibitor; agent targeted against the PD-1/PD-L1 axis
GK# = Gamma Knife
LINAC§ = Linear Accelerator
SRS¥ = Stereotactic radiosurgery
SSRS = Single Fraction SRS (SSRS)
FSRS = Fractionated SRS (FSRS)

Study Population: Melanoma, renal cell, non-small cell lung or breast cancer patients with brain metastases (≤ 15 metastases) currently receiving or planning to receive PD-1/PD-L1 targeted immune checkpoint inhibitor therapy within 30 days of SSRS/FSRS

Randomization of Intervention: 1:1 minimization randomization of FSRS vs SSRS with 4 prognostic factors of interest: radiosurgery platform (GK vs. LINAC), timing of immunotherapy relative to radiation (ICI within 30 days prior to Day 1 of SRS or not), surgical status (any resection cavity vs. intact metastases only), and predominant tumor type (Melanoma vs. All Others).

Assessments:

Pre-Rand./Baseline: MRI Brain, Physical Exam, Cancer History & Treatment, Concomitant Medications, Demographics & Health Behaviors, Patient-Reported Outcomes (MDASI-BT & GP5), Neurocognitive Evaluation (RAVLT, COWA & TMT) and Optional Blood Samples

SRS Treatment: MRI Brain, Treatment Summary, Concomitant Medications and Adverse Events

Post-SRS Follow-up:

2 & 9 month: MRI Brain, Physical Exam, Concomitant Medications, Adverse Events, Patient-Reported Outcomes (MDASI-BT & GP5) Neurocognitive Evaluation (RAVLT, COWA & TMT) and Optional Blood Samples (9 month visit only)

4, 6 &12 month: MRI Brain, Physical Exam, Concomitant Medications, Adverse Events and Patient-Reported Outcomes (MDASI-BT & GP5)

Sample Size: n=244 (n=122 FSRS arm; n=122 SSRS arm)

Primary Endpoint: Occurrence of a Grade 2 or higher Adverse Radiation Effect (ARE) within the first 9 months after SRS

Hypothesis: Reduction in Grade 2 or higher ARE from 22.5% with SSRS to 7.1% with FSRS (15.4% reduction)

4.0 PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 At least one intact brain metastasis or resection cavity ≥ 2 cm in diameter or ≥ 4 cc volume with no prior history of radiation therapy for brain metastasis.

- Both patients at initial diagnosis of brain metastases and patients known brain metastasis treated with systemic therapy alone are eligible
- Lesion volume will be approximated by measuring the lesion's three perpendicular diameters on contrast-enhanced, T1-weighted MRI and the product of those diameters will be divided by 2 to estimate the lesion volume (e.g., xyz/2). Alternatively, direct volumetric measurements via slice-by-slice contouring on a treatment planning software package can be used to calculate the total tumor volume.
- Any extent of non-CNS disease is allowed. There is no requirement for non-CNS disease to be controlled prior to study entry.

4.1.2 Age ≥ 18 years at the time of enrollment.

4.1.3 Total number of brain metastases (including resection cavities) ≤ 15 on diagnostic MRI; all lesions must be amenable to SSRS and FSRS as determined by the treating radiation oncologist. Treatment must take place at a facility credentialed by the Imaging and Radiation Oncology Core (IROC) for SRS and that offers both SSRS and FSRS as treatment options.

4.1.4 Total gross tumor volume must be ≤ 30 cc. Lesion volume will be approximated by measuring each lesion's three perpendicular diameters on contrast-enhanced T1 MRI and the product of those diameters will be divided by 2 (V = xyz/2). Direct volumetric measurements by contouring all lesions on all visible slices on treatment planning software is also acceptable. If there is a cavity, only gross residual disease within or adjacent to the cavity is counted toward the 30 cc total volume.

4.1.5 Ability to tolerate MRI brain with gadolinium-based contrast.

4.1.6 Pathologically confirmed melanoma, renal cell carcinoma, non-small cell lung cancer, or breast cancer.

4.1.7 Has received, is currently receiving, or is planned to receive immune checkpoint inhibitor therapy (defined as agent targeted to PD-1/PD-L1 axis) within 30 days of the planned first day of SSRS/FSRS. Dual ICI therapy with PD-1/PD-L1 and CTLA-4 targeted agents are allowed, but patients treated with a single agent CTLA-4 targeted agent only are ineligible.

4.1.8 Karnofsky Performance Status (KPS) ≥ 70. Refer to Appendix A.

4.1.9 Negative serum or urine pregnancy test within 14 days of randomization for women of child-bearing potential.

4.1.10 Ability to understand and the willingness to sign written informed consent.

4.1.11 Patients must be able to provide informed consent.

4.2 Exclusion Criteria

4.2.1 Prior fractionated, whole, or partial brain radiation therapy.

4.2.2 Prior courses of radiation therapy for brain metastases. Prior courses of SRS for benign tumors such as meningiomas, pituitary adenomas, schwannomas may be acceptable if the treatment is >2cm away from the site of a metastatic lesion that would be treated on this study. The study PI or a designated co-PI must review this type of case to confirm eligibility prior to enrollment.

4.2.3 Leptomeningeal carcinomatosis established by lumbar puncture cytology, or MRI imaging. In the absence of a clinical indication, a lumbar puncture is not required to confirm eligibility.

4.2.4 A brain metastasis that is 5 mm or less from the optic chiasm or optic nerves

4.2.5 Inability to tolerate brain MRI or receive gadolinium-based contrast

4.2.6 Planned or prior therapy with bevacizumab (or bevacizumab biosimilar) within 30 days of the planned first day of SRS as part of a systemic therapy regimen at study enrollment.

4.2.7 Serious intercurrent illness or medical condition judged by the local investigator to compromise the patient's safety, preclude safe administration of the planned protocol treatment, or would not permit the patient to be managed according to the protocol guidelines.