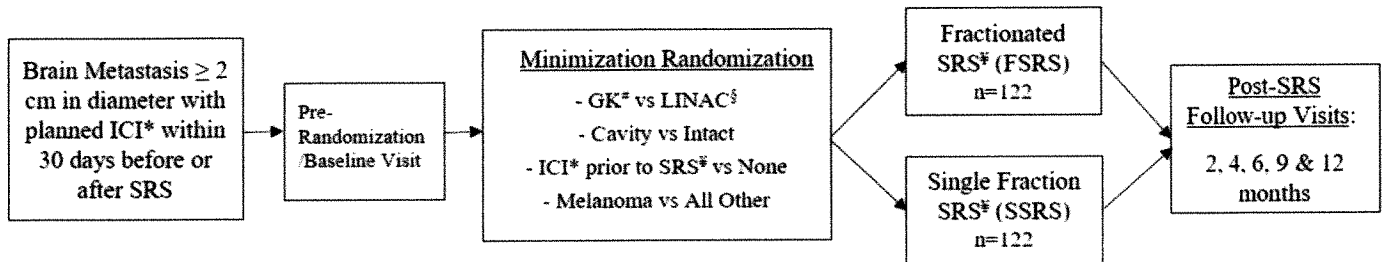


SCHEMA**HYPOFRACTIONATED RADIOTHERAPY VS SINGLE FRACTION RADIOSURGERY FOR BRAIN METASTASIS PATIENTS ON IMMUNOTHERAPY (HYPOGRYPHE)**

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)