NRG-BN013
SCHEMA

STRATIFY

- Presence of symptomatic brain metastasis (yes vs. no)*
- Use of targeted or immunotherapy or antibody drug conjugates ± 4 weeks (yes vs. no)**
- Number of intracranial metastasis (1 vs. 2-4 vs. 5+ lesions)

RANDOMIZE***

↓ ↓

Arm 1	**Arm 2**
Stereotactic Radiosurgery (SRS) 1-2 cm: 22-24 Gy in 1 fraction >2-3 cm: 18-20 Gy in 1 fraction	Fractionated Stereotactic Radiosurgery (FSRS) 1-2 cm: 30 Gy in 3 fractions >2-3 cm: 27 Gy in 3 fractions

* Corticosteroids counted with the exceptions of:
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
- Systemic corticosteroids at physiologic doses not to exceed >10 mg/day of prednisone or its equivalent (e.g. for autoimmune disease)
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

** Use within 4 weeks prior to registration or planned for within 4 weeks after completion of SRS/FSRS

*** Randomization is 1:1

3. ELIGIBILITY CRITERIA

3.1 On Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. Investigators should consider all relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

Physicians should consider the following when evaluating if the patient is appropriate for this protocol:

- Patients must have the adequate health that permits completion of the study requirements and required follow-up period.
- Patients must be able to undergo MRIs given the primary endpoint of the study for response assessment and evaluation.
- Please see section 5.2.1 for guidance on systemic therapy during SRS/FSRS.

Notes: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility see protocol cover page.

NIH Participant Population Inclusion Policy

NIH policy requires that participants regardless of gender identity and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Participants of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf

3.2 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Documentation of Disease

Pathologically (histologically or cytologically) proven diagnosis of one of the following solid tumor malignancies within 5 years prior to registration:

- non-small cell lung cancer
- melanoma
- breast cancer
- renal cell carcinoma
- gastrointestinal cancer

If the original histologic proof of malignancy is greater than 5 years, then more recent pathologic confirmation (e.g., from a systemic site or brain metastasis) or unequivocal imaging confirmation of extracranial metastatic disease (e.g. CT of the chest/abdomen/pelvis, PET/CT, etc.) is required.

3.2.2 Definition of Disease

- Patients must have at least 1 and up to 8 total intact brain metastases detected on a contrast-enhanced MRI (see Appendix I for imaging guidelines) performed ≤ 21 days prior to registration.
- At least 1 of the up to 8 lesions must be a study eligible lesion, defined as lesion with a maximum diameter as measured on any orthogonal plane (axial, sagittal, coronal) of ≥ 1.0 cm and ≤ 3.0 cm.
- All brain metastases must be located outside of the brainstem and ≥5 mm from the optic nerves or optic chiasm and ≤ 3.0 cm in maximum dimension.

  Note: brainstem metastases per the MRI within 21 days of registration are an exclusion criterion; however, if the MRI used for treatment planning performed within 7 days of SRS/FSRS reveals a brainstem metastasis, the patient remains eligible if the patient is considered an appropriate radiosurgery candidate per the local investigator.
- Patients must have a diagnosis-specific graded prognostic assessment ≥1.5 (see Appendix II).
- No more than 2 lesions planned for resection if clinically indicated
- No known leptomeningeal disease (LMD)
  - Note: For the purposes of exclusion, LMD is a clinical diagnosis, defined as positive CSF cytology and/or unequivocal radiologic or clinical evidence of leptomeningeal involvement. Patients with leptomeningeal symptoms in the setting of leptomeningeal enhancement by imaging (MRI) would be considered to have LMD even in the absence of positive CSF cytology. In contrast, an asymptomatic or minimally symptomatic patient with mild or nonspecific leptomeningeal enhancement (MRI) would not be considered to have LMD. In that patient, CSF sampling is not required to formally exclude LMD, but can be performed at the investigator's discretion based on level of clinical suspicion.

3.2.3 Age ≥ 18 years

3.2.4 Karnofsky performance status (KPS) ≥ 60

3.2.5 Not Pregnant and Not Nursing

Negative urine or serum pregnancy test (in persons of childbearing potential) within 14 days prior to registration. Childbearing potential is defined as any person who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal

3.2.6 Prior Treatment

No prior radiotherapy to the brain (partial or whole brain irradiation, SRS, FSRS, or prophylactic cranial irradiation [PCI])

3.2.7 Comorbid Conditions

- New York Heart Association Functional Classification II or better (NYHA Functional Classification III/IV are not eligible) (Note: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification);
- No active infection currently requiring IV antibiotic management;
- No hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
- No chronic obstructive pulmonary disease exacerbation or other acute respiratory illness precluding study therapy;