NRG-BN014
SCHEMA

STEP 1 REGISTRATION

Financial clearance for proton therapy

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STEP 2 REGISTRATION

STRATIFY

- Histology (breast vs. NSCLC)
- Systemic disease status (active vs. stable or none)
- Intrathecal therapy, and/or immunotherapy, and/or targeted therapy including antibody drug conjugates used within 4 weeks prior to step 2 registration and/or planned for within 4 weeks after completion of RT (yes vs. no)

RANDOMIZE*

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Arm 1	**Arm 2**
Involved-field radiotherapy	Proton craniospinal irradiation (pCSI)

*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 adequate health that permits completion of the study requirements and required follow up.
- Patients must be able to undergo MRI scans with and without gadolinium contrast.

Notes: Per NCI guidelines, exceptions to eligibility 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.

Prior to STEP 1 REGISTRATION

3.2.1 Documentation of Disease

Patients with pathologically (histologically or cytologically) proven diagnosis of breast cancer or NSCLC.

3.2.2 Definition of Disease

- Patients must have newly diagnosed leptomeningeal metastasis established through at least one of the following:
  - Positive CSF cytology for malignancy
    - CSF cytology with suspicious cells is considered positive; CSF cytology with atypical cells is considered equivocal and not positive.
  - Patients with an equivocal CSF cytology result, or not suitable for CSF sampling, radiographic diagnosis of leptomeningeal metastasis with linear and/or nodular disease and documentation of typical clinical signs (EANO-ESMO Diagnostic Criteria Type IIA-IIC [Le Rhun 2023]) is required.
    - Patients with typical clinical signs of leptomeningeal metastasis may have one or more of the following symptoms and signs: headache, nausea, vomiting, mental status change, gait difficulty, cranial nerve palsy, diplopia, visual change, hearing loss, radicular weakness, radicular sensory change, urinary retention, saddle anesthesia, constipation, neck pain, and back pain.
  - For patients with prior history of immunotherapy or current immunotherapy, CSF sampling rather than just MRI enhancement is strongly recommended to exclude immune-related aseptic meningitis.

- Patients must be candidates for radiation therapy for the treatment of leptomeningeal metastasis.

3.2.3 Age ≥ 18

Prior to STEP 2 REGISTRATION
Note: Step 2 registration must occur no later than 30 calendar days after Step 1 registration.

3.2.4 Financial clearance for proton therapy treatment

3.2.5 Patients must have systemic disease evaluation through standard of care imaging for example CT chest/abdomen/pelvis or body PET/CT.

3.2.6 Karnofsky Performance Status ≥60

3.2.7 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.

3.2.8 Required Initial Laboratory Values

Adequate hematologic function defined as follows:

- Hemoglobin ≥8.0 g/dl (Note: the use of transfusion or other intervention to achieve Hgb ≥8.0 g/dl is acceptable)
- Absolute neutrophil count (ANC) ≥1,000/mm^3 (Note: the use of granulocyte-colony

stimulating factor or other intervention to achieve ANC ≥1,000/mm^{3}is acceptable)
- Platelets ≥100,000/mm^3 (Note: the use of transfusion or other intervention to achieve Platelets ≥100,000/mm^3 is acceptable)

Adequate hepatic function defined as follows:
- Total bilirubin ≤1.5 × institutional upper limit of normal (ULN) (patients with known Gilbert disease without other clinically significant liver abnormalities are not excluded)
- AST(SGOT) and ALT(SGPT) ≤3 × ULN

3.2.9 Prior Treatment
- No prior radiation therapy to the spinal cord with equivalent dose in 2Gy fractions (EQD2) more than 40Gy or cauda equina with EQD2 more than 50Gy using α/β ratio of 3
- No prior treatment for leptomeningeal metastasis (note: prior CNS treatment for other non-leptomeningeal disease is allowed)

3.2.10 Comorbid Conditions
- No history of unstable angina requiring hospitalization in the last 3 months;
- No history of myocardial infarction within the last 3 months;
- 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 active chronic obstructive pulmonary disease exacerbation or other acute respiratory illness precluding study therapy;
- No CTCAE v5.0 ≥ grade 2 encephalopathy.