NRG-CC009
SCHEMA

STEP 1 REGISTRATION

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STEP 2 REGISTRATION/RANDOMIZATION

Baseline neurocognitive function (NCF) tests: HVLT-R, TMT, COWA (***required***)
Note: NCF testing scores must be uploaded into Rave prior to Step 2 Registration and can be uploaded at the time of Step 1 Registration

STRATIFY
Disease-Specific Graded Prognostic Assessment (DS-GPA)[2]:
1. 0.5-2.0
2. 2.5-4.0

Prior exposure to NCF testing on SWOG S1827[3]:
1. Yes
2. No

RANDOMIZE[1]

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Arm 1	**Arm 2**
Stereotactic radiosurgery (SRS)	Whole brain radiotherapy with hippocampal avoidance (HA-WBRT)+ Memantine

[1]Randomization is 1:1

[2]See Appendix III for DS-GPA

[3]Note: Patients who enrolled on SWOG S1827 (MAVERICK) trial of brain MRI surveillance with or without prophylactic cranial irradiation (PCI) and develop brain metastases on the brain MRI surveillance alone arm will be eligible for this trial. Since the SWOG S1827 trial includes NCF testing of patients, this stratification factor is included to balance treatment arms with respect to percentage of patients with prior exposure to NCF testing on SWOG S1827.

HVLT-R=Hopkins Verbal Learning Test-Revised; TMT=Trail Making Test, COWA=Controlled Oral Word Association

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Notes: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

Inclusion of Women and Minorities

NIH policy requires that women 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. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf

3.1 Eligibility Criteria

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

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of small cell lung cancer within 5 years of registration. If the original histologic proof of malignancy is greater than 5 years, then pathological (i.e., more recent) confirmation is required (e.g., from a systemic or brain metastasis);

- Patients with *de novo* or recurrent small cell lung cancer are permitted.

3.1.2 Ten or fewer brain metastases ≤3cm in largest diameter and outside a 5-mm margin around either hippocampus must be visible on contrast-enhanced MRI performed ≤21 days prior to study entry.

- Brain metastases can be diagnosed synchronous to the initial diagnosis of small cell lung cancer or metachronous to the initial diagnosis and management of small cell lung cancer.
- The total tumor volume must be 30 cm^3 or less. 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.
- Brain metastases must be diagnosed on MRI, which will include the following elements:

REQUIRED MRI ELEMENTS

- Post gadolinium contrast-enhanced T1-weighted three-dimensional (3D) spoiled gradient (SPGR). Acceptable 3D SPGR sequences include magnetization-prepared 3D gradient recalled echo (GRE) rapid gradient echo (MP-RAGE), turbo field echo (TFE) MRI, BRAVO (Brain Volume Imaging) or 3D Fast FE (field echo). The T1-weighted 3D scan should use the smallest possible axial slice thickness, not to exceed 1.5 mm.

- Pre-contrast T1 weighted imaging (3D imaging sequence strongly encouraged).
- A minimum of one axial T2 FLAIR (preferred) or T2 sequence is required. This can be acquired as a 2D or 3D image. If 2D, the images should be obtained in the axial plane.

ADDITIONAL RECOMMENDATIONS

- Recommendation is that an axial T2 FLAIR (preferred) sequence be performed instead of a T2 sequence.
- Recommendation is that that pre-contrast 3D T1 be performed with the same parameters as the post-contrast 3D T1.
- Recommendation is that imaging be performed on a 3 Tesla (3T) MRI.
- Recommendation is that the study participants be scanned on the same MRI instrument at each time point.
- Recommendation is that if additional sequences are obtained, these should meet the criteria outlined in Kaufmann et al., 2020.
- If additional sequences are obtained, total imaging time should not exceed 60 minutes.

See Appendix IV for a summary of key imaging requirements, and contact the Principal Investigators and Imaging Co-Chairs for further information or assistance if needed.

3.1.3 History/physical examination within 28 days prior to registration;

3.1.4 Age ≥ 18;

3.1.5 Karnofsky Performance Status of ≥70 within 28 days prior to registration;

3.1.6 Adequate renal function within 28 days prior to registration defined as follows:

- Creatinine clearance ≥30 ml/min

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

3.1.7 Following the diagnosis of brain metastases, patients can initiate and treat with systemic (chemotherapy and/or immunotherapy) before enrollment only if their brain metastases are asymptomatic and not located in eloquent locations (e.g., brainstem, pre-/post-central gyrus, visual cortex). However, within 21 days prior to enrollment, brain MRI must be repeated to confirm eligibility.

- Patients with symptomatic brain metastases and/or brain metastases in eloquent locations (e.g., brainstem, pre-/post-central gyrus, visual cortex) are eligible for enrollment on the trial; however, the specific treatment approach of starting with systemic therapy alone and delaying brain radiation is not recommended for these patients.

3.1.8 Concurrent immunotherapy with brain radiation (SRS or HA-WBRT) is permitted.

3.1.9 Negative urine or serum pregnancy test (in women of childbearing potential) within 14 days prior to registration. Women of childbearing potential and men who are sexually active must use contraception while on study.

3.1.10 Patients may have had prior intracranial surgical resection. Patients must have completed prior intracranial surgical resection at least 14 days prior to registration.

3.1.11 Because neurocognitive testing is the primary goal of this study, patients must be proficient in English or French Canadian.

3.1.12 The patient must provide study-specific informed consent prior to study entry.

- Patients with impaired decision-making capacity are not permitted on study.

3.2. Eligibility Criteria Prior to Step 2 Registration

3.2.1 The following baseline neurocognitive tests must be completed within 21 days prior to Step 2 registration: HVLT-R, TMT, and COWA. The neurocognitive tests will be uploaded into RAVE for evaluation by Dr. Wefel. Once the upload is complete, within 1 business day a notification will be sent via email to the RA to proceed to Step 2.
NOTE: Completed baseline neurocognitive tests can be uploaded at the time of Step 1 registration.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Planned infusion of cytotoxic chemotherapy on the same day as SRS or HA-WBRT treatment. Patients may have had prior chemotherapy. As noted in 3.1.8, concurrent immunotherapy is permitted.

3.3.2 Prior allergic reaction to memantine.

3.3.3 Intractable seizures while on adequate anticonvulsant therapy; more than 1 seizure per month for the past 2 months.

3.3.4 Patients with definitive leptomeningeal metastases.

3.3.5 Known history of demyelinating disease such as multiple sclerosis

3.3.6 Contraindication to MR imaging such as implanted metal devices that are MRI-incompatible, allergy to MRI contrast that cannot be adequately addressed with pre-contrast medications, or foreign bodies that preclude MRI imaging. (Questions regarding MRI compatibility of implanted objects should be reviewed with the Radiology Department performing the MRI).

3.3.7 Current use of (other NMDA antagonists) amantadine, ketamine, or dextromethorphan

3.3.8 Radiographic evidence of hydrocephalus or other architectural change of the ventricular system resulting in significant anatomic distortion of the hippocampus, including placement of external ventricular drain or ventriculoperitoneal shunt.

- Mild cases of hydrocephalus not resulting in significant anatomic distortion of the hippocampus are permitted

3.3.9 Prior radiotherapy to the brain, including SRS, WBRT, or PCI

3.3.10 Severe, active co-morbidity defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Chronic obstructive pulmonary disease exacerbation or other acute respiratory illness precluding study therapy at the time of registration
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects