NRG-CC001
A Randomized Phase III Trial Of Memantine and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Patients With Brain Metastases

SCHEMA

STEP 1: REGISTRATION

STEP 2: RANDOMIZATION
Baseline neurocognitive assessment: HVLT-R, TMT, COWA (required)
NOTE: Neurocognitive assessments can be uploaded at the time of Step 1 registration.

STRATIFICATION
RPA Class: (see Appendix III)
1. Class I
2. Class II
Prior therapy:
1. None
2. Radiosurgery or surgical resection*

Arm 1
WBRT 30 Gy/10 fractions
+ Memantine**

Arm 2
WBRT with Hippocampal Avoidance using IMRT 30 Gy/10 fractions
+ Memantine**

*Radiosurgery or surgical resection within 8 weeks of Step 1 registration; otherwise stratify to None.
**Memantine to be administered during and after WBRT or WBRT with hippocampal avoidance for a total of 24 weeks.
3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG Oncology/RTOG web site). For radiation therapy-related eligibility questions, please contact IROC Philadelphia RT (via the contact list on the NRG Oncology/RTOG web site).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other 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.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up. Patients must be willing to complete neurocognitive assessments at pre-specified time points outlined in the protocol.

3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception during the therapy (i.e. WBRT and memantine) part of the trial.

3.1.3 Submission of serum, plasma, whole blood and urine is strongly encouraged for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. Samples will be submitted for banking for the translational research portion of this protocol and future studies. (See details in Sections 9 and 10.)

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 Brain metastases outside a 5-mm margin around either hippocampus must be visible on contrast-enhanced MRI performed ≤21 days prior to Step 1 registration. An allowed exception, regarding ability to image brain metastases, would be that patients who had undergone radiosurgery or surgical resection and are planning adjuvant WBRT do not have to have visible disease but do need a pre-surgery MRI or CT scan demonstrating brain metastases. However, the brain metastases could not have been within 5 mm of either hippocampus.

3.2.2 Patients **must** have a gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) axial MRI scan with standard axial and coronal gadolinium contrast-enhanced T1-weighted sequence and axial T2/FLAIR sequence acquisitions. To yield acceptable image quality, the gadolinium contrast-enhanced three-dimensional SPGR, MP-RAGE, or TFE axial MRI scan should use the smallest possible axial slice thickness not exceeding 1.5 mm. The associated coronal and sagittal contrast-enhanced T1 sequences can be up to 2.5 mm in slice thickness. This MRI must be obtained ≤21 days prior to step 1 registration. The vendor specific MRI protocols are available for download from the Alzheimer’s Disease Neuroimaging Initiative (ADNI), http://www.adni-info.org/scientists/MRIProtocols.aspx.

3.2.3 Patients must provide study-specific informed consent prior to registration.

**Prior to Step 2 Registration:**

3.2.4 The following baseline neurocognitive assessments must be completed prior to Step 2 registration: HVLT-R, TMT, and COWA. The neurocognitive assessment will be uploaded into a folder in the NRG RAVE System for evaluation by Dr. Wefel. Once the upload is complete, a notification will be sent to the RA to proceed to Step 2. **Note:** Completed baseline neurocognitive assessments can be uploaded at the time of Step 1 registration.

3.2.5 Pathologically (histologically or cytologically) proven diagnosis of solid tumor malignancy within 5 years prior to Step 2 registration.

3.2.6 History and physical examination within 28 days prior to Step 2 registration

3.2.7 Age ≥ 18;

3.2.8 Karnofsky Performance Status of ≥70 within 28 days prior to Step 2 registration;

3.2.9 Adequate renal function ≤28 days prior to Step 2 registration defined as follows:
   - Serum creatinine ≤ 3 mg/dL (265 μmol/L) and creatinine clearance ≥30 ml/min
   - BUN within institutional upper limit of normal (e.g. < 20 mg/dL)

3.2.10 Adequate hepatic function ≤28 days prior to Step 2 registration defined as follows:
   - Total bilirubin ≤ 2.5mg/dL (43μmol/L)

3.2.11 Patients may have had prior therapy for brain metastasis, including radiosurgery and surgical resection. Patients must have completed prior therapy by at least 14 days prior to Step 2 for surgical resection and 7 days for radiosurgery.

3.2.12 Negative serum pregnancy test (in women of childbearing potential) ≤14 days prior to Step 2. Women of childbearing potential and men who are sexually active must practice adequate contraception while on study.

3.2.13 Patients who are primary English or French speakers are eligible.
3.3 Ineligibility Criteria

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

3.3.1 Prior external beam radiation therapy to the brain or whole brain radiation therapy.
3.3.2 Planned cytotoxic chemotherapy during the WBRT only; patients may have had prior chemotherapy.
3.3.3 Radiographic evidence of hydrocephalus or other architectural distortion of the ventricular system, including placement of external ventricular drain or ventriculoperitoneal shunt.
3.3.4 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.
   - Severe hepatic disease defined as a diagnosis of Child-Pugh class B or C hepatic disease.
   - Renal tubular acidosis or metabolic acidosis.
   - HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to registration. Note also that HIV testing is not required for eligibility for this protocol.
3.3.5 Pregnant or lactating women, or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the medication involved in this study has unknown effects on the unborn fetus.
3.3.6 Prior allergic reaction to memantine.
3.3.7 Current alcohol or drug abuse (may exacerbate lethargy/dizziness with memantine).
3.3.8 Intractable seizures while on adequate anticonvulsant therapy—more than 1 seizure per month for the past 2 months.
3.3.9 Patients with definitive leptomeningeal metastases.
3.3.10 Patients with brain metastases from primary germ cell tumors, small cell carcinoma, unknown primary, or lymphoma.
3.3.11 Contraindication to MR imaging such as implanted metal devices or foreign bodies.
3.3.12 Contraindication to gadolinium contrast administration during MR imaging, such as allergy or insufficient renal function.
3.3.13 Current use of (other NMDA antagonists) amantadine, ketamine, or dextromethorphan.