RADIATION THERAPY ONCOLOGY GROUP

RTOG 0614

A RANDOMIZED, PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF MEMANTINE FOR PREVENTION OF COGNITIVE DYSFUNCTION IN PATIENTS RECEIVING WHOLE-BRAIN RADIOTHERAPY

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SCHEMA

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<tr>
<th>S</th>
<th>RPA Class a:</th>
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<tr>
<td>T</td>
<td>1. Class I</td>
</tr>
<tr>
<td>R</td>
<td>2. Class II: with controlled systemic disease</td>
</tr>
<tr>
<td>A</td>
<td>Prior therapy:</td>
</tr>
<tr>
<td>T</td>
<td>1. None</td>
</tr>
<tr>
<td>I</td>
<td>2. Radiosurgery or surgical resection**</td>
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<td>F</td>
<td>Y</td>
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</table>

| R | A | N | D | O | M | I | Z | E |
|---|---|---|---|---|---|---|---|
| Arm 1 | WBRT 37.5Gy/15 fractions + memantine * |
| Arm 2 | WBRT 37.5Gy/15 fractions + placebo* |

* Memantine/placebo to be administered during and after WBRT for a total of 24 weeks. See Section 7.0 for details.

**Radiosurgery or surgical resection within 8 weeks of randomization, otherwise stratify to none.

a See Appendix IV.

Patient Population: (See Section 3.0 for Eligibility)
Pathologically proven solid tumor malignancy and brain metastases. Patients must be classified as RTOG RPA class I or RPA class II with controlled systemic disease for 3 months or more prior to study entry. Prior surgical resection and/or radiosurgery are allowed. Prior systemic therapy must be completed > 14 days prior to study entry.

Required Sample Size: 536
<table>
<thead>
<tr>
<th>Case #</th>
<th>____ (Y/N)</th>
<th>1. Is there histologically or cytologically confirmed diagnosis of solid tumor malignancy within 5 years of registration?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>____ (Y)</td>
<td>If no, and the original proof of malignancy is greater than 5 years, is there a more recent pathological confirmation (e.g., from a systemic metastasis or brain metastasis)?</td>
</tr>
<tr>
<td></td>
<td>____ (Y)</td>
<td>2. Has a diagnostic contrast-enhanced brain MRI (or contrast CT for patients unable to have an MRI) been performed within ≤28 days prior to study entry?</td>
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<tr>
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<td>____ (Y/N)</td>
<td>3. Is there stable systemic disease (i.e. no evidence of systemic disease progression within 3 months or more)?</td>
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<td></td>
<td>____ (Y)</td>
<td>If no, did the patient have brain metastases at initial presentation?</td>
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<tr>
<td></td>
<td>____ (Y)</td>
<td>4. Karnofsky Performance Status of ≥70 within 28 days prior to study entry?</td>
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<td></td>
<td>____ (Y)</td>
<td>5. Age ≥ 18?</td>
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<tr>
<td></td>
<td>____ (Y)</td>
<td>6. Serum creatinine and total bilirubin obtained ≤28 days prior to study entry?</td>
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<td></td>
<td>____ (Y)</td>
<td>7. Serum creatinine ≤ 3 mg/dL (265 μmol/L) ≤28 days prior to study entry?</td>
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<tr>
<td></td>
<td>____ (Y)</td>
<td>8. Creatinine clearance ≥ 30 ml/min ≤ 28 days prior to study entry?</td>
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<tr>
<td></td>
<td>____ (Y)</td>
<td>9. Total bilirubin ≤ 2.5 mg/dL (43 μmol/L) ≤ 28 days prior to study entry?</td>
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<td></td>
<td>____ (Y)</td>
<td>10. BUN &lt; 20 mg/dL ≤ 28 days prior to study entry?</td>
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<td></td>
<td>____ (Y)</td>
<td>11. Were the complete history and general physical examination performed ≤ 28 days prior to study entry?</td>
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<tr>
<td></td>
<td>____ Y/N/A</td>
<td>12. Negative serum pregnancy test ≤7 days prior to study entry?</td>
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<tr>
<td></td>
<td>____ (Y)</td>
<td>13. MMSE score ≥18 performed ≤28 days prior to study entry?</td>
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<tr>
<td></td>
<td>____ (Y)</td>
<td>14. Systemic chemotherapy received ≥14 days prior to study entry?</td>
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<tr>
<td></td>
<td>____ (N)</td>
<td>15. Is chemotherapy planned to be administered ≤14 days after completion of RT?</td>
</tr>
<tr>
<td></td>
<td>____ (N)</td>
<td>16. Prior therapy for brain metastasis ≤14 days or &gt;56 days prior to study entry?</td>
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<tr>
<td></td>
<td>____ (N)</td>
<td>17. Prior cranial radiotherapy (other than up to 3 WBRTs per Section 6.1)?</td>
</tr>
<tr>
<td></td>
<td>____ (Y)</td>
<td>18. Did patient sign study specific informed consent prior to study entry?</td>
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<td></td>
<td>____ (N)</td>
<td>19. Pregnant or lactating women?</td>
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<td></td>
<td>____ (Y)</td>
<td>20. Women of childbearing potential or men who are sexually active and willing/able to use medically acceptable forms of contraception?</td>
</tr>
<tr>
<td></td>
<td>____ (N)</td>
<td>21. Prior allergic reaction to memantine?</td>
</tr>
</tbody>
</table>

(Continued on the next page)
The following questions will be asked at Study Registration: (3/28/08)

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?
3. Is the patient eligible for this study?
4. Date the patient provided study-specific, informed consent prior to study entry?
5. Patient’s Initials (First Middle Last) [If no middle initial, use hyphen]
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
11. Gender
12. Patient’s Country of Residence

(Continued on the next page)
RTOG Institution # __________
RTOG 0614  ELIGIBILITY CHECKLIST (3/28/08)
Case # __________ (page 3 of 3)

_________  13. Zip Code (U.S. Residents)
_________  14. Patient’s Insurance Status
_________  15. Will any component of the patient’s care be given at a military or VA facility?
_________  16. Calendar Base Date
_________  17. Registration/randomization date: This date will be populated automatically.
_________  18. Medical oncologist
_________ (Y/N)  19. Blood/urine/CSF kept for cancer research?
_________ (Y/N)  20. Blood/urine/CSF kept for medical research?
_________ (Y/N)  21. Allow contact for future research?
_________ (Y/N)  22. Will the patient participate in the Quality of Life component (FACT-Br) of this study?

If no, please provide the reason from the following:
  1) patient refused due to illness
  2) patient refused for other reason: specify_______
  3) not approved by institutional IRB
  4) tool not available in patient’s language
  5) other reason: specify______

_________ (I, II)  23. RPA class.
_________ (Y/N)  24. Did the patient have radiosurgery or surgical resection ≤8 weeks prior to randomization?
_________ (Y/N)  25. Is patient currently receiving WBRT?

_______ (Y) If yes, will patient be able to receive study drug by Day 3 of radiation?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ____________________________ Date ____________________________
1.0 INTRODUCTION

1.1 Neurocognitive Effects of Cranial Radiotherapy

Radiotherapy is a proven curative and palliative therapeutic tool in the treatment of a wide variety of primary and metastatic brain tumors in adults. Recent advances in multi-modality therapy have led to improvement in survival for many cancer patients. As survival has improved, more attention has been directed toward long-term treatment-related morbidity. Specifically, the effect of radiotherapy on the long-term cognitive performance of these patients is a major concern. Because the morbidity caused by cranial irradiation can be devastating, the radioresponse of normal CNS tissues has been extensively studied and reviewed.1-8

Late delayed effects generally appear greater than 6 months after irradiation and are usually irreversible and often progressive.4 Late delayed injury is generally localized to the white matter and is thought to be secondary to vascular injury, demyelination, and ultimately necrosis. Symptoms vary depending on type and location of injury. Symptoms of diffuse white matter injury range from mild lassitude to progressive memory loss and dementia.1 Combined therapy leukoencephalopathy can be similar to diffuse white matter injury but can also include ataxia, confusion, dysarthria, seizures and ultimately incapacitating dementia or death.9 Risk of deficit after cranial radiotherapy is associated with high radiation dose, large fraction-size, larger field-size, use of concurrent chemotherapy, and extremes of age at time of treatment.5,10-12 Elderly patients with vascular comorbidities (diabetes, hypertension, atherosclerosis) appear to be at particular risk.13

Brain metastases are the most common form of intracranial tumor in adults, with an annual incidence approximately 10 times greater than primary brain tumors.14-16 Brain metastases are an increasingly important cause of morbidity and mortality in cancer patients, occurring in approximately 10 to 30 percent of adult patients.17,18 It is estimated that each year in the United States there are between 98,000 and 170,000 new cases of brain metastases.17,18 This number may be increasing due to the ability of magnetic resonance imaging (MRI) to detect small metastases and prolonged survival due to improvement in systemic therapy.17-19

Historically, patients with brain metastases had very limited survival. The median survival of patients with untreated brain metastases is approximately one month. The addition of steroids increases survival to two months. Historically, whole brain radiation therapy (WBRT) improved survival to three to six months.20-22 However, subgroups of patients exist in which prolonged survival is possible. A recursive partitioning analysis of prognostic factors from RTOG brain metastases trials has been performed on 1200 patients from three consecutive RTOG trials that tested several different dose fractionation schemes and radiation sensitizers. Three prognostic classes were identified and correlated with median survival. Class 1 patients had a Karnofsky performance score 70 or higher, were less than 65 years of age with a controlled primary tumor and no extracranial metastases. Median survival was 7.1 months. 23 Data is accumulating for other favorable subgroups of patients such as those with single brain metastasis and limited extracranial disease who are treated with surgery and WBRT. These patients have a median survival of approximately 10 to 16 months.24-28 Because of advances in the diagnosis and management of this condition, most patients receive effective palliation and the majority do not die from the metastases.29

Whole brain radiotherapy is the most common treatment for brain metastasis. Unfortunately, WBRT is associated with cognitive impairment in long term survivors, especially in the elderly. In a retrospective review of 70 patients treated with postoperative radiation therapy using greater than 3 Gy fractions, 11 percent showed evidence of progressive, debilitating dementia within 5 to 36 months of treatment.30 In a more recent study using more conventional fractionation, 33% of patients developed late neurocognitive toxicity with a median follow up of 10 months. Memory impairment was the most common symptom (50%). Actuarial rate of neurocognitive toxicity at 2 years was 49% and 20% of patients were documented to have a decline in their Karnofsky Performance Status (KPS) of greater than 10%.31 Recently, the first large, prospective study to evaluate cognitive function for patients with brain metastasis was performed. Meyers and coworkers used a battery of cognitive tests at baseline, monthly for 6 months, then every 3 months until death to assess cognitive function before and after WBRT. Interestingly, 90% of patients were impaired (1.5 SD below age-matched normative standards) in one or more cognitive test at baseline, and impairment correlated with bulk of disease. The majority of
patients in this study experienced cognitive decline after WBRT, with 59% experiencing a greater than 2 SD decline in their performance in one or more tests at 6 months.\textsuperscript{32} As expected, with formal neurocognitive testing the rate of cognitive impairment is significantly higher than previous retrospective reports suggest. With more long-term survivors, it has become increasingly important to minimize toxicity and maintain quality of life in patients with brain metastasis.

Although a neurocognitive conceptual framework for understanding the effects of radiotherapy is currently very limited,\textsuperscript{13} it is becoming increasingly clear that the pathophysiology of late RT injury is dynamic, complex and a result of inter- and intra-cellular interactions between the vasculature and many of the parenchymal cell lines.\textsuperscript{33} The vascular hypothesis of radiation-induced injury attributes accelerated atherosclerosis and mineralizing microangiopathy that result in vascular insufficiency and infarction to radiation injury and inflammation. Histologic studies reveal that death of endothelial cells begins during radiotherapy and this process continues over the next few months. Platelets adhere to the exposed matrix leading to the formation of platelet clusters and thrombi. Over weeks to months small vessels become partially or fully occluded by thrombi. Also during this period, thickening of the basement membranes and replacement of the lumen by collagen results in damage to large and small vessels. Taken together, these mechanisms result in a picture similar to the small vessel disease seen with vascular dementia.\textsuperscript{34}

Hippocampal-dependent functions of learning, memory, and spatial information processing seem to be preferentially affected by RT.\textsuperscript{35,36,37} Radiation exposure induces a microglial inflammatory response in the neurogenic region of the hippocampus that appears to inhibit neurogenesis of stem cells.\textsuperscript{37} Monje and co-workers conclude that repairing the neural microenvironment, including restoring the balance of signaling and blockade of neurotransmitters, is fundamental to any therapeutic intervention and the key first step to treating radiation-induced cognitive decline.\textsuperscript{33}

### 1.2 Memantine and Treatment of Neurocognitive Toxicity

Treatment of cognitive sequelae of cranial radiation is limited at this time. Methylphenidate has been used in a few small series of patients exhibiting neurobehavioral slowing with limited response.\textsuperscript{38-40} Patients who develop psychomotor slowing, decline in executive functioning, or general apathy may particularly benefit.\textsuperscript{38} A recent small, phase II trial using donepezil for brain irradiated patients with cognitive dysfunction showed limited improvements in quality of life and cognitive function at 24 weeks of therapy.\textsuperscript{41,42} Because treatment of cognitive decline after radiation in limited, effort must be directed at preventing the detrimental effects of cranial radiation. Recently, memantine (Namenda\textsuperscript{TM}), an N-methyl-D-aspartate (NMDA) receptor antagonist, has proven to be effective in the treatment of vascular dementia. Due to memantine’s mechanisms of action, limited toxicity, and potential for neuroprotection, memantine has inherent advantages over the previous agents used to treat dementia.

Glutamate is the principle excitatory amino acid neurotransmitter in cortical and hippocampal neurons.\textsuperscript{43} One of the receptors activated by glutamate is the NMDA receptor, which is involved in learning and memory.\textsuperscript{44} Excessive NMDA stimulation can be induced by ischemia and lead to excitotoxicity, suggesting that agents that block pathologic stimulation of NMDA receptors may protect against further damage in patients with vascular dementia.\textsuperscript{45} Thus, NMDA receptor antagonists such as memantine may be neuroprotective and prevent neuronal injury associated with radiation-induced ischemia. In addition, the physiologic function of the remaining neurons could be restored, resulting in symptomatic improvement.\textsuperscript{46} Pre-clinical in vitro and in vivo data support this hypothesis. Protection from excitotoxicity has been shown in cerebrocortical neurons, cerebellar neurons, and retinal neurons.\textsuperscript{47-49} In a rat model of stroke, memantine given as long as 2 hours after an ischemic event reduces the amount of neuronal injury by 50%.\textsuperscript{47,50}

Memantine has been shown to improve cognition in patients with mild to moderate vascular dementia and patients with moderate to severe Alzheimer’s type dementia. In a large, randomized trial for patients with suspected vascular dementia and MMSE (mini-mental status examination) scores of 12-20, 20 mg of memantine a day for 28 weeks (patients were started at 5 mg a day the first week, then escalated to 10 mg a day for one week, then 15 mg a day for one week, and then on week 4, the final escalation to 20 mg a day) was shown to significantly improve cognitive performance, intellectual function, reduce disturbing behavior and improve MMSE scores.\textsuperscript{51} A similar trial for patients (patients on the memantine arm were again started at
5 mg a day and dose escalated with weekly increments of 5 mg, thus reaching 20 mg daily on week 4, dosage split to 10 mg BID) with suspected vascular dementia and MMSE scores of 10-22 confirmed these results. In addition, patients with white matter lesions and deep lacunes but no larger lesions experienced greater therapeutic benefit, suggesting the subgroup of patients with small-vessel disease responded better to memantine than other types of dementia.\textsuperscript{52} In both trials, cognitive function of patient in the placebo arm continued to decline while patients receiving memantine stabilized or improved.\textsuperscript{51,52} Memantine was well-tolerated in this group of elderly patients with multiple co-morbidities and polypharmacy. Adverse event rates with memantine were similar to placebo, and more patients taking placebo than memantine discontinued the study medication.\textsuperscript{51,52}

In summary, evidence regarding pathogenesis of radiation-induced cognitive injury has recently been localized to the hippocampus and to primarily involve learning and memory. The vascular hypothesis of radiation-induced injury attributes accelerated atherosclerosis and mineralizing microangiopathy that result in vascular insufficiency and infarction to radiation injury and inflammation. Both mechanisms of radiation induced injury are particularly suited to potential therapeutic intervention with NMDA receptor antagonists which are thought to reduce inflammation and prevent progression of vascular dementia as well as potentially alter the neurochemical microenvironment to allow for neurogenesis in the hippocampus. Although memantine has been shown to improve cognition in patients with Alzheimer's type and vascular dementia, especially those with small vessel disease, this will be the first trial evaluating the drug's efficacy for cognitive deficits in brain irradiated patients. Furthermore, although neuroprotective properties of memantine have been hypothesized,\textsuperscript{53,54} this will be the first trial to evaluate the utility of memantine as a neuroprotective agent from the vascular injury and cognitive dysfunction caused by radiation. Anecdotal experience using memantine in Primary Central Nervous System Lymphoma (PCNSL) patients with cognitive dysfunction after radiation has shown dramatic clinical improvement.\textsuperscript{55}

1.3 Neurocognitive Function Assessment (3/28/08)

Neurocognitive status plays a very important role in neuro-oncological practice and clinical trials. Despite technological and therapeutic developments, patients with primary and metastatic brain tumors continue to suffer limited survival. The combination of limited therapeutic success and the effects of the tumor and its treatment upon the emotional, cognitive, and behavioral function have led to consideration of health-related quality of life and neurocognitive function as outcome endpoints in addition to the traditional clinical and radiological endpoints. This respective combination of patient-centered and disease-centered outcomes becomes very important in the comparative assessment of new therapies, especially when survival-equivalent therapies result in different neurocognitive and Health-Related Quality of Life (HRQOL) outcomes.

Most of the cancer clinical trials in general and the neuro-oncological trials in particular are concerned with the assessment of the toxic effects of treatment upon the target and other organ functions. Assessment of the possible effects of combination of anti-cancer and protective therapies, as proposed in this study, upon neurological and cognitive functions is an attractive paradigm that is worth pursuing.

Neurocognitive status has been shown to be of predictive prognostic value in patients with recurrent malignant glioma.\textsuperscript{56} Moreover, decline in neurocognitive status during treatment has also been shown to be predictive of treatment failure long before any radiological, clinical, or HRQOL deterioration.\textsuperscript{57}

RTOG 0018 is a Phase II trial to evaluate feasibility of cognitive testing of brain metastasis patients receiving WBRT in the cooperative group setting. Fifty-nine patients were accrued at 14 sites between 2000 and 2001. Cognitive testing was performed before WBRT, at end of WBRT, and 1 month after WBRT (37.5Gy in 15 fractions). The feasibility and utility of a battery of neurocognitive tests with a certification process for its administration by multiple RTOG institutions have been demonstrated. The battery required less than 45 minutes to administer. The battery included the MMSE, Hopkins verbal learning test (learning and short-term memory), Verbal Fluency/Controlled Word Association Test (language, executive/frontal skills), Ruff 2 and 7 (neglect, attention, concentration), Trail Making Test (visuospatial, speed, sequencing), Profile of Mood States - Short Form (mood/fatigue). Compliance pre-WBRT was excellent with > 90% of
patients completing assessment. Compliance at the completion of WBRT was also excellent with > 84% of patients completing testing. At one month after WBRT > 78% of patients completed assessment with most non-compliance being due to patient-related factors such as decline in performance status. In conclusion, greater than 90% of data was considered valid and usable thus confirming the feasibility of cognitive testing of brain metastasis patients receiving WBRT in the cooperative group setting.\textsuperscript{58}

Recently, the first large, multinational prospective study to evaluate cognitive function for patients with brain metastasis was performed. Meyers and coworkers used a battery of cognitive tests at baseline, monthly for 6 months, then every 3 months until death to assess cognitive function before and after WBRT. The cognitive battery was similar to that used in RTOG 0018 and included, HVLT (recall, recognition, delayed), COWA (verbal fluency), pegboard (fine motor), TMT (executive and visual motor). Patients were considered impaired if their baseline z-score was $\geq 1.5$ SD below age-matched normative standards. Patients were considered to experience cognitive decline if they tested $\geq 2$SD below their baseline performance. 401 patients were enrolled in the study. Compliance with testing was 87-98% baseline and 77-87% at 6 months. In this trial, 90.5% of patients impaired at baseline with 42.4% impaired in 4 or more tests. Impairment was found to correlate with bulk of disease. The majority of patients experienced cognitive decline during the period of study evaluation with 59% experiencing cognitive decline in one or more tests at 6 months.\textsuperscript{32} This large randomized trial including a similar cognitive battery to that proposed for this trial again confirms the feasibility, in terms of both burden and utility, of prospective cognitive testing of brain metastasis patients receiving WBRT.

In this trial, we will use the battery used by Meyers et al in RTOG 0525 (HVLT, COWA, and TMT A and B), the Cognitive Functioning Subscale of the Medical Outcomes Scale (MOS) (self-report), and the MMSE, which has been used in previous randomized trials with memantine (and innumerable brain metastases trials) and shown to be correlated with cognitive outcome.\textsuperscript{51, 52}

While limited research exists as to the best methods to measure cognitive impairment, at least one study, using the cognitive functioning subscale of the Medical Outcomes Scale\textsuperscript{59} in 68 persons with high-grade glioma has demonstrated that use of self-report questions of cognitive functioning correlate significantly with objective measures in patients with highly malignant brain tumors. Klein et al reported the measurement of self-reported cognitive status using the 6-item Medical Outcomes Cognitive Scale in 68 newly diagnosed persons with GBM and the comparison of those results to a neurocognitive battery.\textsuperscript{60} This finding suggests that persons with metastatic brain tumors likely can also monitor their own cognitive status at least for a period of time. The MOS-C measures difficulty with reasoning and problem-solving, slowed reaction time, forgetfulness, and problems with concentration. The MOS scale has been extensively tested in thousands of ill patients. Significantly moderate correlations were noted between attentional functioning, information processing capacity and graphamotor speed and the self-reports of cognitive status. Furthermore, the self-reports of cognitive status were also significantly correlated with mental health and social functioning, indicating the possible effects of cognitive dysfunction on Quality of Life (QOL). This study will explore, over time, the relationship between objective measurement and self-reported measurement of cognitive status in persons with brain metastases.

In the current trial, patients will undergo a battery of neurocognitive assessments. The feasibility of neurocognitive testing in the cooperative group setting has been evaluated by the RTOG\textsuperscript{58} and in multi-institutional trials.\textsuperscript{32} This study will use the validated tools utilized in the previous RTOG studies (RTOG 0212, 0424, 0525) as well as the Functional Assessment of Cancer Therapy-Brain (FACT-Br) to assess quality of life. Patients will return at 8, 16, and 24 weeks for repeat neurocognitive testing and repeat brain imaging. Primary outcome measure will be cognitive function (specifically memory) at 24 weeks. Exploratory cognitive data for patients surviving 12 months will also be collected.

Five tests will be used to assess neurocognitive function. Three of these tests (i.e. Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association, Trail Making Test Parts A and
B) are to be administered by a certified examiner (a health care professional such as a physician, nurse, or data manager certified to administer the tests). The MMSE will be administered by a health care professional but s/he does not need to be certified to administer the test. The self-report of cognitive function (i.e. the Medical Outcomes Cognitive Scale) can be completed by the patient or with the assistance of the examiner and does not require pre-certification.

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Assessment</th>
<th>Time to Administer (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>Hopkins Verbal Learning Test-Revised</td>
<td>5</td>
</tr>
<tr>
<td>Visual-Motor Scanning Speed</td>
<td>Trail Making Test Part A</td>
<td>5</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Trail Making Test Part B</td>
<td>5</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>Controlled Oral Word Association</td>
<td>5</td>
</tr>
<tr>
<td>Global Function</td>
<td>Mini-Mental Status Examination</td>
<td>5</td>
</tr>
<tr>
<td>Cognitive Function (self-report)</td>
<td>Medical Outcomes Cognitive Scale</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td></td>
<td><strong>30</strong></td>
</tr>
</tbody>
</table>

1.3.1 Summary of Measures (3/28/08)

- **Hopkins Verbal Learning Test - Revised (HVLT-R):** The patient learns 12 words read to them 3 times; free recall is tested after each learning trial. Delayed recall is evaluated after 20 minutes. Following the delayed recall trial, the patient completes a recognition test to determine if an impairment of delayed recall is due to a retrieval deficit or to a consolidation deficit. Entire test requires about 5 minutes to complete.

- **Trail Making Test (TMT):** This is a measure of visuospatial scanning, attention, sequencing, and speed Part A and executive function in Part B. Patients must “connect the dots” either in a numbered sequence or alternating letters and numbers. Generally Part A and Part B require less than 5 minutes, and Part A is discontinued at 3 minutes, Part B at 5 minutes, to reduce burden on patients with significant cognitive impairment.

- **Controlled Word Association Test (COWAT):** The patient produces as many words as possible in 1 min. (each) for a specific letter (C, F, L or P, R, W). Requires about 5 min to complete. Assesses language and executive/frontal skills.

- **Mini-Mental Status Examination (MMSE):** This is a brief, standardized tool to grade patients’ global cognitive function. The MMSE begins with an assessment of orientation to place and time. Next is a test of memory (immediate recall) by having the subject immediately repeat the names of 3 objects presented orally. Following this the patient subtracts sevens serially from 100. The subject is then asked to recall the three items previously repeated (delayed recall). The final section evaluates aphasia and apraxia by testing naming, repetition, compliance with a 3-step command, comprehension of written words, writing, and copying a drawing. The maximum score that can be obtained for the entire MMSE is 30 points.

- **Cognitive Functioning Subscale of the Medical Outcomes Scale (MOS)(Self-report):** This 6-item, self-report measure is designed to measure day-to-day cognitive functioning of which the patient would be aware, including difficulty with problem-solving, slowed reaction times, forgetfulness, and concentration. Reliability and validity have been reported for patients with cancer. Scale is based on multiple choice questions asking about cognitive function where the item is present 1=all of the time to 6=none of the time. Scored in five steps (data cleaning, changing out of range values to missing, item re-calibration and skip pattern recording, reverse scoring of items so that the highest score reflects the best health state, transforming scores linearly to a common metric with a range of 0-100, averaging across items in the same scale). Completion time is estimated to be less than 5 minutes.

1.4 Quality of Life Assessment (6/17/08)

The Functional Assessment of Cancer Therapy-Brain (FACT-Br) is a commonly used instrument measuring general quality of life (QOL) reflecting symptoms or problems associated with brain malignancies across 5 scales: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); functional well-being (7 items); and concerns relevant to patients with brain tumors (23 items). Patients rate all
items using a five-point rating scale ranging from "not at all" to "very much." The measure yields information about total QOL, as well as information about the dimensions of physical well-being, social/family well-being, emotional well-being, functional well-being, and disease-specific concerns. Six additional experimental items request information regarding how much each dimension affects QOL, using a "0" (not at all) to "10" (very much so) rating scale. The FACT scale is able to distinguish metastatic from non-metastatic disease, \( F(1,334) = 5.38, p < .05 \). It also distinguishes between stage I, II, III and IV disease, \( F(3,308) = 2.94, p < .05 \), and between inpatients and outpatients from different centers, \( F(2,411) = 17.0, p < .001 \). On the FACT-G, sensitivity to disease status was restricted to the Physical (p < .01) and Functional (p < .001) subscales. Concurrent validity is supported by strong Pearson correlations with the Functional Living Index - Cancer (.79) and a patient-completed version of the QOL Index (.74). Initial evidence for construct validity is supported by: 1) moderate to high correlations with mood state as measured by the Taylor Manifest Anxiety Scale (.57) and a shortened version of the Profile of Mood States (.69); 2) moderate correlation with activity level (negative direction of coefficient because of reverse scaling) as measured by the Eastern Cooperative Oncology Group five-point rating (-.56), and a small correlation with social desirability as measured by a shortened version of the Marlowe-Crowne Social Desirability Scale. The FACT is written at the 4th grade reading level, and patients can complete it in 5-10 minutes. The FACT has been translated into 26 languages, and translations are accessible at the FACIT web site, http://www.facit.org/translation/licensure.aspx.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Time to Administer (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life (self-report)</td>
<td></td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy - Brain</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td><strong>10</strong></td>
</tr>
</tbody>
</table>

The self-report of quality of life can be completed by the patient or with the assistance of the examiner and does not require pre-certification.

2.0 OBJECTIVES (3/28/08)

2.1 Primary Objective

Determine whether the addition of memantine to WBRT preserves cognitive function, specifically memory as measured by the Hopkins Verbal Learning Test-Revised for delayed recall (HVLT-R delayed recall), over that of placebo and WBRT in patients with brain metastases at 24 weeks from the start of drug treatment.

2.2 Secondary Objectives

2.2.1 Determine whether the addition of memantine preserves cognitive function, specifically memory as measured by the HVLT-R-delayed recall at 8 weeks, 16 weeks and 12 months from the start of drug treatment.

2.2.2 Determine whether the addition of memantine increases time to neurocognitive failure as measured by cognitive decline on a battery of tests: the HVLT-R for free recall, delayed recall, and delayed recognition; the Controlled Word Association Test (COWAT); the Trail Making Test Parts A and B (TMT); the Medical Outcomes Scale-Cognitive Functioning Subscale (MOS); and the Mini-Mental Status Examination (MMSE). (3/28/08)

2.2.3 Evaluate the potential benefit of memantine in change and overall quality of life, as measured by the Functional Assessment of Cancer Therapy-Brain (FACT-Br).

2.2.4 Determine whether the addition of memantine increases progression-free survival.

2.2.5 Determine whether the addition of memantine increases overall survival.

2.2.6 Compare adverse events between the treatment arms according to the CTCAE v3.0 criteria.

2.2.7 Collect serum, plasma, buffy coat cells, urine, and CSF for future translational research analyses.
3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of solid tumor malignancy 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 metastasis or brain metastasis).

3.1.2 Brain metastases must be visible on contrast-enhanced MRI or a contrast enhanced CT for patients unable to have an MRI performed ≤28 days prior to study entry (an allowed exception, regarding ability to image brain metastases, would be patients who had undergone radiosurgery or surgical resection and are planning adjuvant WBRT do not have to have visible disease but do need a baseline MRI). Patients unable to undergo MR imaging because of non-compatible devices can be enrolled, provided the contrast-enhanced CT scans are obtained and are of sufficient quality.

3.1.3 Patients must have stable systemic disease (i.e. no evidence of systemic disease progression ≥3 months prior to study entry). Patients who have brain metastases at initial presentation are eligible and do not need to demonstrate 3 months of stable scans.

3.1.4 Karnofsky Performance Status of ≥70 within 28 days prior to study entry.

3.1.5 Age ≥ 18

3.1.6 Serum creatinine and total bilirubin obtained ≤28 days prior to study entry; with adequate kidney and liver function defined as follows:
   a. Serum creatinine ≤ 3 mg/dL (265 μmol/L) and creatinine clearance ≥30 ml/min;
   b. Total bilirubin ≤ 2.5 mg/dL (43 μmol/L)

3.1.7 BUN < 20 mg/dL ≤28 days prior to study entry.

3.1.8 MMSE score ≥18 within 28 days prior to study entry.

3.1.9 Patient must provide study specific informed consent prior to study entry.

3.1.10 Patients may have had prior therapy for brain metastasis, including radiosurgery and surgical resection. Patients should have completed prior therapy at least 14 days but no longer than 56 days prior to study entry.

3.1.11 Patients receiving systemic therapy are eligible for this study if given >14 days prior to study entry and given no sooner than >14 days post RT completion.

3.1.12 Negative serum pregnancy test (in women of childbearing potential) ≤7 days prior to study entry.

3.1.13 Women of childbearing potential and men who are sexually active must practice adequate contraception.

3.1.14 Complete history and general physical examination ≤ 28 days prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Uncontrolled systemic disease (evidence of systemic disease progression within 3 months or more)

3.2.2 Systemic chemotherapy ≤14 days prior to study entry or ≤14 days after completing radiotherapy

3.2.3 Prior cranial radiotherapy (a patient may have already received up to 3 WBRT treatments and still be registered and randomized on the protocol as long as WBRT parameters meet protocol requirements). As noted above, prior radiosurgery is allowed.

3.2.4 Severe, active co-morbidity, defined as follows:

   3.2.4.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months

   3.2.4.2 Transmural myocardial infarction within the last 6 months

   3.2.4.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

   3.2.4.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration

   3.2.4.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects

   3.2.5 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.

3.2.6 Prior allergic reaction to memantine.
3.2.7 Current alcohol or drug abuse (may exacerbate lethargy/dizziness with memantine).
3.2.8 Chronic short-acting benzodiazepine use (may exacerbate lethargy/dizziness with memantine).
3.2.9 Intractable seizures while on adequate anticonvulsant therapy —more than one seizure per month for the past 2 months.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT
Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management
4.1.1 The sites are required to administer the neurocognitive assessments before the start of drug treatment: Hopkins Verbal Learning Test, Controlled Oral Word Association, Trail Making Test Parts A and B), MMSE, Medical Outcomes Cognitive Scale.
4.1.2 Detailed neurological examination and physical examination within 7 days prior to beginning protocol treatment.
4.1.3 Steroid and anti-convulsant doses must be documented.
4.1.4 If the patient consents to participate in the Quality of Life component of the study, sites are required to administer the baseline quality of life questionnaire for the Functional Assessment of Cancer Therapy-Brain (FACT-Br).
4.1.5 If the patient consents to participate in the translational research component of the study, sites are required to collect peripheral blood (serum/plasma/buffy coat) and urine at baseline.

4.2 Highly Recommended Evaluations/Management
4.2.1 Re-staging to confirm stability of systemic disease evaluated clinically, radiographically, and/or serologically, as appropriate for the underlying malignancy

5.0 REGISTRATION PROCEDURES
5.1 Preregistration Requirements (3/28/08)
Examiners for neurocognitive function must go through the certification procedures outlined in Appendix VI. Examiners who have been certified to perform these tests for RTOG 0525 or RTOG 0424 during the past 6 months do not need to be recertified, but the certification worksheet must be faxed to Dr. Meyers/ Dr. Wefel for documentation purposes. See Section 11.2.

5.2 Preregistration Requirements for Shipment of Memantine/Placebo:
5.2.1 U.S. sites and Canadian sites must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206) prior to registration of the institution’s first case:
   - IRB approval letter;
   - IRB assurance number;
   - Health Canada’s TPD forms.

5.2.2 Note: International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form_1-2007.pdf.

Approved international sites fax copies of the documentation below to RTOG Headquarters (215-574-0300) prior to registration of the institution’s first case:
   - IRB approval letter;
   - Federalwide Assurance (FWA) number.

5.2.3 For the initial shipment of memantine/placebo:
All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. International institutions must submit the SASF and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300). This must be done prior to registration of the institution’s first case.
5.3 Registration

5.3.1 Online Registration (3/28/08)

Patients can be registered only after eligibility criteria are met. Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) Is Not Allowed

Protocol whole brain radiotherapy (WBRT) must begin ≤14 days from study entry

6.1 Dose Specifications (7/15/08)

Protocol whole brain radiotherapy (WBRT) must begin within 14 days following registration; if day 14 falls on a holiday or weekend, it is acceptable to begin treatment the next business day. A patient may have already received up to 3 WBRT treatments before starting memantine or placebo as long as WBRT parameters meet protocol requirements. For patient eligibility, patients should only be registered and randomized if there is sufficient time to ensure study drug can be available by day 3 of WBRT. One treatment of 2.5 Gy will be given daily 5 days per week (15 fractions) for a total of 37.5 Gy over three weeks. All portals shall be treated during each treatment session. Doses are specified as the target dose which shall be the dose on the central ray at mid-separation for two opposed coaxial equally weighted beams.
“Compensating beams” that block hot spots (these hot spots are typically present along the midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve better dose homogeneity.

6.2 **Technical Factors**

Treatment shall be delivered with megavoltage machines of energy ranging from 4MV up to and including 10 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Partial brain conedown, stereotactic, electron, particle or implant boost are not permissible.

6.3 **Localization, Simulation, and Immobilization**

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility. The target volume shall include the entire cranial contents, with flashing beyond skin and a minimum margin of 0.75 cm on the skull base as visualized on the simulator or portal films to account for beam penumbra and day-to-day set-up variation. ‘Helmet’ portals with customized immobilization and shielding are permitted.

6.4 **Critical Structures**

Care should be taken to minimize the dose to the lens and orbits.

6.5 **Documentation Requirements**

Copies of simulation and port films and the complete RT daily treatment record and calculations will be submitted to RTOG Headquarters ONLY if specifically requested.

6.6 **Radiation Adverse Events**

Acute, ≤ 90 days from treatment start: Expected adverse events include hair loss, erythema of the scalp, headache, nausea and vomiting, lethargy, and transient worsening of neurological deficits. Reactions in the ear canals and on the ear should be observed and treated symptomatically. Late, > 90 days from treatment start: Possible adverse events include radiation necrosis, cognitive dysfunction, visual difficulties, accelerated atherosclerosis, and radiation-induced neoplasms. If significant increase in reaction of the normal tissue occurs, it should be noted and reported to the study Principal Investigator, Paul Brown, MD.

6.7 **Radiation Adverse Event Reporting**

See Section 7.0 for Adverse Event Reporting.

7.0 **DRUG THERAPY**

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Protocol treatment must begin ≤14 days from study entry. Drug therapy should start the same day as WBRT, and can start no later than the third day of WBRT.

7.1 **Code Breaks**

The decision to break the code must be based on a life-threatening event or extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment.

During business hours (8:30 AM to 4 PM ET), call RTOG Headquarters at 215-574-3150 and ask to speak to the Study Statistician. For after hours, weekends, and holidays, call 215-459-3576.

7.2 **Treatment**

7.2.1 Memantine or placebo should start the same day as WBRT. If WBRT must be started urgently, memantine or placebo must start no later than the third day of WBRT. See Section 7.2.2 for dose.

7.2.2 **Dose definition**

The target dose for memantine (or placebo) is 20 mg (10mg divided twice daily). Dose is escalated by 5 mg per week to target of 10 mg twice daily (i.e., 5 mg a day for week 1, then 5 mg BID for week 2, then 10 mg in AM and 5 mg in PM for week 3, then 10 mg in AM and 10 mg in PM by week 4).
<table>
<thead>
<tr>
<th>Week</th>
<th>Daily AM Dose</th>
<th>Daily PM Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>5 mg</td>
<td>None</td>
</tr>
<tr>
<td>Week 2</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Week 3</td>
<td>10 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Weeks 4-24</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

Patients continue on memantine or placebo for duration of study (24 weeks).

7.2.3 Administration
Memantine or placebo is administered by mouth.

Memantine is well absorbed after oral administration and absorption is not affected by food. Memantine plasma protein binding is low (45%) and the volume of distribution is 9 to 11 L/kg. Memantine undergoes partial hepatic metabolism, with about 50% of an administered dose excreted unchanged in the urine. Memantine is metabolized into 3 polar metabolites: the N-glucuronide conjugate (25%) 6-hydroxy memantine, and 1-nitroso-deaminated memantine. The metabolites have minimal NMDA receptor antagonist activity. Approximately 1% of memantine in humans is metabolized to 1-amino-3-hydroxymethyladamantan.

Fluctuations in a patient's intake of protein and carbohydrate may affect the side-effect profile of memantine, according to results of a crossover trial of 12 healthy male volunteers. High plasma concentrations of memantine are associated with a higher probability of side effects; plasma concentration is dependent on elimination, primarily via the kidneys. More alkaline urine results in reduced renal clearance and excretion of memantine, compared with that of more acidic urine. During treatment with memantine, diets should be kept relatively stable.

The terminal elimination half-life of memantine is 60 to 80 hours.

7.2.4 Duration of treatment
Memantine (or placebo) is to be administered from the start of WBRT through the duration of the study (24 weeks). Missed doses should be documented but patients should not try to make up missed doses. Memantine (or placebo) should be continued through the duration of 24 weeks regardless of disease status (i.e., if a patient progresses in the brain as long as study drug is tolerated study drug should be continued).

7.3 Memantine (Namenda)
See the package insert for further information.

7.3.1 Drug(s) description, packaging and storage

7.3.1.1 Description: (7/15/08)
Memantine hydrochloride belongs to the low to moderate affinity, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist class of drugs. Persistent activation of NMDA receptors by glutamate was believed to contribute to the symptoms of Alzheimer's disease. Memantine hydrochloride inhibits the excitotoxic action of glutamate by blocking the NMDA receptor. This prevents exposure of the neuron to an excessive influx of calcium, which is thought to be one of the mechanisms responsible for neuronal death. Memantine hydrochloride while blocking NMDA under pathologic conditions, rapidly dissociates from the receptor during the normal phasic activity required for learning and memory. It showed low to negligible affinity for GABA,
benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca2+, Na+ or K+ channels.

7.3.1.2 Storage:
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

7.3.2 How drug is supplied (3/28/08) (7/15/08)
Memantine (Namenda™) and placebo will be supplied by Forest Labs, Jersey City, NJ. The drug will be distributed by a vendor, I.V. Solutions, Inc., under contract to RTOG.

Memantine and placebo will be supplied to patients on study free of charge.
The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

The Study Agent Shipment Form must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. Note: International sites must receive written approval of submitted LOI Forms from RTOG Headquarters prior to submitting documents to local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form_1-2007.pdf

Approved international institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). This must be done prior to registration of the institution’s first case. The drug supply will not be shipped by I.V. Solutions, Inc. until the patient has been registered. The shipment of the entire 24-week supply of drug will occur at randomized. I.V. Solutions, Inc. generally ships drug Mondays through Thursdays. It will be shipped 2nd day courier. Canadian and International shipments may require additional time. If the confirmation of registration email is received by IVS before noon, the drug will be sent out that same day. Confirmations received in the afternoon may not be sent until the following day. RTOG will notify I.V. Solutions, Inc. to initiate this shipment after registration of the patient. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.

Unused supplies at the sites will be returned directly to I.V. Solutions, Inc. Additional questions about supply and delivery should be directed to:

Angel Corradino, R.Ph
I.V. Solutions, Inc.
162 North Main Street
Old Forge, PA 18518
(570) 457-9201
Fax (570) 457-0465
ivspublic@choiceonemail.com

7.3.3 Accountability: Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

7.3.4 Known Adverse Events
Memantine is well-tolerated with incidence of adverse effects in clinical trials being similar to placebo. Most commonly reported adverse events include dizziness (7%), headache (6%), constipation (5%), hypertension (4%), coughing (4%), pain (3%), and dyspnea (2%). Symptons of pharmacologic toxicity appear to be dose dependent and include hallucinations, nervousness, changes in behavior, tremor, and other central nervous system symptoms. Other reactions to monitor include akathisia, restlessness, increased motor activity, insomnia, and depression.

Memantine is U.S. Food and Drug Administration’s Pregnancy Category: Category B (All Trimesters). 64

7.3.5 Drug Interactions
Concomitant use of drugs that make the urine alkaline may increase plasma concentration of memantine with a possible increase in adverse events. Examples of drugs that increase urine pH include: acetazolamide, dichlorphenamidine, methazolamide, sodium bicarbonate. Coadministration of drugs that use the same renal cationic system may result in altered plasma levels of memantine and the coadministered drug. Examples of drugs that use the same renal cationic system include: cimetidine, ranitidine, hydrochlorothiazide, nicotine, quinidine. If possible, patients should avoid use of medications that use the same renal cationic system.
and/or increase urine pH. If the medications must be used, patients should be monitored for
signs of memantine toxicity including lethargy, hallucinations, tremor, agitation and insomnia.
Concomitant use of other NMDA-receptor antagonists may also increase probability of adverse
events and should be avoided (e.g., amantadine, ketamine, dextromethorphan).  

7.3.6 Human pharmacokinetics
Peak Concentration at target dose 22.08 nanogram (ng) /mL ± 5.07 ng/ml and was found to
rise in subjects with renal impairment. Time to Peak Concentration is 3 to 7 hours and was
found to increase in subjects with renal impairment. Area Under the Curve 1941 nanograms
(nanogram) hour/mL. The mean AUC increased in 8 subjects with mild renal impairment (mean
creatinine clearance, CrCl, 60.9 milliliters (mL) per minute ± 7.9), 8 subjects with moderate
(mean CrCl, 41.6 mL per minute ± 5), and 7 subjects with severe (mean CrCl, 20.1 mL per
minute ± 5.7) renal impairment, respectively, compared to healthy subjects (mean CrCl, 93.5
mL per minute ±13.4) following the oral administration of 10 mg twice daily of memantine HCl.
In healthy subjects (n=8) the AUC (0-12) was 954 nanograms (ng) hour/mL ± 199 ng hour/mL,
in renally impaired individuals, the AUC (0-12) increased to 1083 ng hour/mL ± 297 ng hour/mL
(mild), 1504 ng hour/mL ± 327 ng hour/mL (moderate), and 990 ng hour/mL ± 267 ng hour/mL
(severe).  

7.4 Dose Modifications
Approximately 50% of memantine is metabolized by the liver, the remained 50% is excreted
unchanged by the renal system. A dosage reduction to 5 milligrams (mg) orally twice daily is
recommended in patients with severe renal impairment (creatinine clearance (CrCl), 5 to 29
milliliters/minute (mL/min)). Therefore the eligibility criteria is for creatinine clearance ≥ 30 ml/min
and no dosage adjustment is needed in patients with mild (CrCl greater than 50 to 80 mL/min) or
moderate (CrCl 30 to 49 mL/min) renal impairment.

Creatinine should be evaluated at each follow-up evaluation (8, 16, 24, and 52 weeks). Protocol
treatment will be dose modified based on criteria outlined in the dose modification table.

<table>
<thead>
<tr>
<th>% Calculated Dose</th>
<th>BUN(mg/dL)</th>
<th>5-29</th>
<th>&lt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 20</td>
<td>10 mg by mouth twice daily</td>
<td>5 mg by mouth twice daily Recheck value weekly; If CrCl not &gt; 29 (mL/min) by 3 weeks, continue at reduced dose throughout protocol treatment</td>
<td>HOLD STUDY DRUG Recheck value weekly; If CrCl not &gt; 5 (mL/min) by 3 weeks, discontinue protocol treatment</td>
</tr>
<tr>
<td></td>
<td>HOLD STUDY DRUG Recheck value in one week; If BUN not &lt; 20 mg/dL by 3 weeks, discontinue protocol treatment</td>
<td>HOLD STUDY DRUG Recheck value in one week; If BUN not &lt; 20 mg/dL by 3 weeks, discontinue protocol treatment</td>
<td>HOLD STUDY DRUG Recheck value in one week; If BUN not &lt; 20 mg/dL by 3 weeks, discontinue protocol treatment</td>
</tr>
<tr>
<td>&gt;20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* For males: CrCl = [140-age (years)] · Weight (kg)/[72 · serum creatinine (mg/dL)]
For females: CrCl = 0.85 · [140-age (years)] · Weight (kg)/[72 · serum creatinine (mg/dL)]

7.5 Chemotherapy
See Section 9.1.

7.6 **Modality Review**
The Principal Investigator, Paul Brown, M.D., will perform a Medication Assurance Review of all patients who receive placebo or memantine in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of treatment information data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable.** A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

7.7 **Adverse Events (3/28/08)**
This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, MedDRA, version 9.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.7.1 **Adverse Events (AEs)**
**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). **[CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]**

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.8 also must be reported via AdEERS.**

**NOTE:** If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.7.2 **Serious Adverse Events (SAEs)** — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

**Definition of an SAE:** Any adverse drug experience occurring at any dose that results in any of the following outcomes:
- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to
prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.7.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA  19103</td>
</tr>
</tbody>
</table>

7.8 AdEERS Expedited Reporting Requirements
CTEP defines routine AE reporting requirements for phase 2 and 3 trials as described in the table below. Important: All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1),
Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days\(^1\) of the Last Dose of the Investigational Agent/Placebo in this Study

<table>
<thead>
<tr>
<th>Unrelated</th>
<th>Unexpected and Expected</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5(^2)</th>
<th>Grades 4 &amp; 5(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlikely</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td></td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certain</td>
<td></td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>24-Hour; 5 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td></td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a non-CTEP IND require reporting as follows:

- AdEERS 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events

- AdEERS 10 calendar day report:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 5 expected events

\(^2\) Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” – A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND:

Not applicable.

8.0 SURGERY

Not applicable.

9.0 OTHER THERAPY

9.1 Chemotherapy

16 RTOG 0614
9.1.2 Patients may not receive chemotherapy within 14 days prior to study entry. Patients may receive chemotherapy after the completion of WBRT but must be started at least 14 days after RT completion.

9.1.3 Dose/duration is at the discretion of the treating physician. However, caution is recommended with the use of platinum-containing agents and other chemotherapeutics known to cause renal dysfunction. Kidney function should be checked regularly in patients receiving renotoxic agents and dose modifications to study drug should be made according to Section 7.4.

9.2 Permitted Supportive Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication.

9.2.1 Anticonvulsant usage and dosage should be noted at the time of study entry, at each follow-up evaluation, and at any changes in medication use.

9.3 Non-permitted Supportive Therapy
Chronic short acting benzodiazepine may increase the risk of lethargy and cognitive disturbance with memantine. Specific examples would be valium and ativan used other than one time for testing anxiety (e.g. claustrophobia for MRI).

10.0 TISSUE/SPECIMEN SUBMISSION (3/28/08)
The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, serum, plasma, buffy coat, and urine (strongly recommended) and CSF (recommended when feasible if patient consents, see Appendix I) will be submitted to the RTOG Biospecimen Resource for the translational research portion of this protocol and for banking for future studies. See Section 10.4.

10.1 Specimen Collection for Tissue Banking for Translational Research
Strongly recommended for patients who have consented to participate in the blood/urine/CSF component of the study
Serum, plasma, buffy coat, and urine will be collected prior to start of drug treatment, 8 weeks, 16 weeks, 24 weeks, and 52 weeks. CSF will be collected at time of resection, when feasible and if patient consents. See Section 10.4.1.6.

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.1.1 A Specimen Transmittal Form clearly stating that serum, plasma, buffy coat, and urine or CSF is being submitted for the RTOG Biospecimen Resource. It should state on the form that it is for translational research. The form must include the RTOG protocol number and patient’s case number.

10.1.2 Serum Collection
Serum specimens will be collected in red-top tubes (5-10 mL tubes). See Appendix VIII for detailed instructions.

10.1.2.1 After allowing the serum to clot, keep serum tubes refrigerated (4° - 8° C) until processing (tubes may be on ice up to 2 hrs). Centrifuge specimens at approximately 2500 RPM in a standard clinical centrifuge at for 10 minutes.

10.1.2.2 Using sterile techniques to avoid contamination, aliquot 0.5-1 mL serum into cryovials and freeze. Take great care to collect only serum and avoid collecting any solid particulate matter before transferring serum into the cryovials.

10.1.2.3 Label each aliquot with RTOG study protocol and case numbers, the date and time of collection, specimen type (serum) and the time point collected.

10.1.2.4 Place specimens in freezer or ship immediately on dry ice per Appendix VIII instructions.

10.1.3 Plasma Collection
For plasma collection, specimens will be collected in tubes containing EDTA (purple/lavender top tubes). See Appendix VIII for detailed instructions.

10.1.3.1 After collecting the specimens, invert the tubes multiple times to mix the blood thoroughly with the EDTA anticoagulant.

10.1.3.2 After thoroughly mixing, centrifuge specimens at approximately 2500 RPM in a standard clinical centrifuge for 10 minutes.

10.1.3.3 Using sterile techniques to avoid contamination, aliquot 0.5-1 mL plasma into cryovials and freeze. Take great care to collect only plasma and avoid collecting any solid particulate matter before transferring plasma into the cryovials.

10.1.3.4 Label each aliquot with RTOG study protocol and case numbers, the date and time of collection, specimen type (plasma) and the time point collected.

10.1.3.5 Place specimens in freezer or ship immediately on dry ice per Appendix VIII instructions.

10.1.4 Buffy Coat Collection

For buffy coat collection, specimens will be collected in tubes containing EDTA (purple/lavender top tubes). See Appendix VIII for detailed instructions.

10.1.4.1 Carefully remove plasma from the collection tubes (as in Section 10.1.3.3).

10.1.4.2 Using a pipette, remove the buffy coat layer and place into cryovials and freeze.

10.1.4.3 Label each aliquot with RTOG study protocol and case numbers, the date and time of collection, specimen type (i.e. buffy coat) and the time point collected.

10.1.4.4 Place specimens in freezer or ship immediately on dry ice per Appendix VIII instructions.

10.1.5 Urine Collection

See Appendix IX for detailed instructions for collection and shipping. For urine collection, a minimum of 10 mL urine should be collected in a sterile collection cup labeled with patient ID, date and time of collection, and placed into a freezer for storage.

10.1.6 CSF Collection

See Appendix X for detailed instructions. At least 10 ml of CSF stored at -20°C shall be placed in a sterile transport tube. The sample needs to be shipped via overnight courier in an insulated box with dry ice where it will be stored at the RTOG Biospecimen Resource at -70°C until ready for analysis. The Specimen Transmittal Form must document the date of collection of the CSF; the RTOG protocol number, the patient’s case number, and method of storage, for example, stored at -20°C.

10.1.7 Specimen Shipping

All patient specimens should be shipped to the RTOG Biospecimen Resource at UCSF. Follow shipping instructions in Appendix VIII for blood, in Appendix IX for urine, in and Section 10.1.6 and Appendix X for CSF.

Submit materials to:

**Mailing address:** For all non-frozen materials
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, RM 223
San Francisco, CA 94143-1800

**Courier address (FedEx/DHL, etc.):** For frozen specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

**Telephone:** 415-476-RTOG (7864)
**Fax:** 415-476-5271
RTOG@ucsf.edu

10.1.8 Specimen Collection Summary
Specimens taken from patient:  Submitted as:  Shipped:

5-10 mL of whole blood in red-top tube and centrifuge for serum  Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials  Serum sent frozen on dry ice via overnight carrier

5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for plasma  Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials  Plasma sent frozen on dry ice via overnight carrier

5-10 mL of anticoagulated whole blood in EDTA tubes (purple/lavender top) and centrifuge for buffy coat  Frozen buffy coat samples in 1 mL cryovials  Buffy coat sent frozen on dry ice via overnight carrier

10-25 mL clean-catch urine  A minimum of 5 mL unpreserved urine in a sterile collection container  Urine sent frozen on dry ice via overnight carrier

10-25 mL of CSF in sterile transport tube  Frozen CSF samples aliquotted into 5mL vials, each containing a minimum of 1 mL  CSF sent frozen on dry ice via overnight carrier

10.2 Reimbursement
RTOG will reimburse submitting institutions $100 per case for serum/plasma, $300 for buffy coat, $50 for urine, and $300 for CSF. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in December/January and June/July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.3 Confidentiality/Storage
(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/tissuebank/tissuefaq.html for further details.)

10.3.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.3.2 Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

10.4 Translational Research
Serum, plasma, buffy coat, and urine collection are highly recommended, CSF is recommended when feasible. Samples will be used for the purposes of the current protocol and stored samples will be kept for future studies of the cognitive effects of radiotherapy.

10.4.1 Rationale
Little data exists on methods of measuring neurocognitive decline in vivo in patients receiving radiation from brain metastasis, an extensive amount of investigations have been performed in Alzheimer’s disease (AD). Because the mechanisms of neurocognitive decline are similar, correlative studies proposed are largely based on the information from the AD research. It is hypothesized that a dichotomy exists as to which patients receiving WBRT for brain metastasis will manifest neurocognitive decline. Decline maybe secondary to disease related neurocognitive deficits, genetic predisposition, and treatment related toxicity. A variety of measures (imaging, genetic, and serum markers) will be analyzed to predict patients at risk for developing neurocognitive decline. When feasible, CSF will also be analyzed. Based on the current literature, the following represent the possible tests that may be associated with outcome and are under consideration for analysis in this trial.

10.4.1.1 Imaging
Brain MRI is to be performed prior to start of drug treatment and at 8, 16, 24, and 52 weeks. Radiographic findings will be analyzed in relation to neurocognitive performance to evaluate the role of disease progression in test performance. Brain imaging may be a reliable marker for measurement of cognitive decline. Poorer memory decline may be a result of persistent or progressing disease or changes in the limbic system structures, particularly the hippocampus.\textsuperscript{67,68}

10.4.1.2 Genetic Markers

Amyloid precursor gene mutations are known factors that are related to dementia in Alzheimer’s patients. One in particular, apolipoprotein E epsilon4 (apoE4) has been associated with not only AD, but also age associated memory impairment (AAMI) and mild cognitive impairment (MCI).\textsuperscript{67} This allele is present in 16% of the general population and 50% of patients with late onset AD.\textsuperscript{69} Given the similar mechanisms of dementia between AD and radiation induced dementia (e.g. vascular or metabolic)\textsuperscript{69}, apoE4 genotyping may prove to be a predictor of radiation induced neuronal damage. The apoE4 protein binds rapidly and tightly to beta amyloid. Normally beta amyloid exists in a soluble form. However, when bound by apoE4 protein, beta amyloid becomes insoluble and is more likely to be deposited in plaques which may lead to changes in microvasculature, ultimately leading to neurocognitive decline. Further, patients with just one copy of the apoE4 allele have demonstrated accelerated hippocampal volume loss which can also compromise neurocognitive function.\textsuperscript{70} Patients with apoE2 and apoE3 alleles, on the contrary, tend to have ¼ the risk of developing Alzheimer’s disease. It is felt that the E2 and E3 alleles are able to facilitate repair and protection from neuronal damage.

10.4.1.3 Inflammatory Markers

Markers of inflammation are elevated with aging and their increase has been associated with cognitive decline.\textsuperscript{71,72} Epidemiological and retrospective data reveals an improvement in neurocognitive function with the use of NSAID’s in patients with AD, hence, supporting an inflammatory process involved in neurocognitive decline.\textsuperscript{69} Chronic inflammation as a result of mass effect from tumor or treatment related inflammation may be associated with neurocognitive deficits and can be measured in serum. Interleukin 1 (IL-1), Interleukin 6 (IL-6), and Tumor Necrosis Factor (TNFalpha) are proinflammatory cytokines that are a measure of inflammation and have been shown to be elevated in patients with AD\textsuperscript{69,73-76}

10.4.1.4 Oxidative Stress

It is widely accepted that oxidative stress plays a critical role in the manifestation of AD.\textsuperscript{77,78} Decreased cerebral perfusion results in decreased oxygen and glucose delivery that eventually leads to energy deprivation which is the cause of oxidative stress in the brain.\textsuperscript{68} Oxidative stress from either tumor or radiation may be a predictor and excellent measure of neurocognitive decline. Isoprostanes are one of the best described indicators of oxidative stress and can be measured in vivo.\textsuperscript{80}

10.4.1.5 Hormone and Growth Factors

Aging and memory decline is associated with the disruption of hormone regulation, including glucocorticoids, gonadal steroids, and growth hormone.\textsuperscript{61} Cortisol, human chorionic gonadotropin (hCG), insulin-like growth factor-1 (IGF-1), and neuronal growth factor (NGF), have all recently been associated with cognitive decline in Alzheimer’s disease.\textsuperscript{67,81,82} High cortisol levels, for example, are associated with decrease in hippocampal volume and impaired memory.\textsuperscript{83}

10.4.1.6 CSF Analysis

For patients where resection is planned, an effort will be made to acquire CSF for potential future analysis. Because the CSF is in direct contact with the brain, CSF biomarkers may provide the most accurate assessment of changes in neurocognitive function. Three such biomarkers have been extensively studied in AD and are of interest in this study include total Tau (T-tau), phospho-tau (P-tau), and the 42 amino acid form ß-amyloid (Aß42).\textsuperscript{54}
11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II.

11.2 Neurocognitive Evaluation

11.2.1 Certification (3/28/08)

All examiners must go through the certification procedures outlined in Appendix VI. This requires reviewing the test materials and administration procedures, watching a training video that is accessed on a password protected website [contact Dr. Meyers (cameyers@mdanderson.org) or Dr. Wefel (jwefel@mdanderson.org) for instructions on how to access the website], taking a post-test, performing a practice assessment, and scoring the tests. All of the materials (certification worksheet, post-test, neurocognitive tests and neurocognitive summary form) are then faxed to Dr. Christina Meyers and Dr. Wefel for review. See Appendix VII. Examiners who have been certified to perform these tests for RTOG 0525 or RTOG 0424 during the past 6 months do not need to be recertified, but the certification worksheet must be faxed to Dr. Meyers/Wefel for documentation purposes. Examiners certified for RTOG 0525 or RTOG 0424 more than 6 months prior must be recertified to ensure continued familiarity with study procedures.

11.2.2 Summary of Measures (3/28/08)

Five tests will be used to assess neurocognitive function. Three of these tests (i.e. Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association, Trail Making Test Parts A and B) are to be administered by a certified examiner (a health care professional such as a physician, nurse, or data manager certified to administer the tests). The MMSE will be administered by a health care professional but s/he does not need to be certified to administer the test. The self-report of cognitive function can be completed by the patient or the examiner and does not require pre-certification.

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Assessment</th>
<th>Time to Administer (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>Hopkins Verbal Learning Test-Revised</td>
<td>5</td>
</tr>
<tr>
<td>Visual-Motor Scanning Speed</td>
<td>Trail Making Test Part A</td>
<td>5</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Trail Making Test Part B</td>
<td>5</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>Controlled Oral Word Association</td>
<td>5</td>
</tr>
<tr>
<td>Global Function</td>
<td>Mini-Mental Status Examination</td>
<td>5</td>
</tr>
<tr>
<td>Cognitive Function (self-report)</td>
<td>Medical Outcomes Cognitive Scale</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td></td>
<td><strong>30</strong></td>
</tr>
</tbody>
</table>

- **Hopkins Verbal Learning Test- Revised (HVLT-R):** The patient learns 12 words read to them 3 times; free recall is tested after each learning trial. Delayed recall is evaluated after 20 minutes. Following the delayed recall trial, the patient completes a delayed recognition test to determine if an impairment of delayed recall is due to a retrieval deficit or to a consolidation deficit. Entire test requires about 5 minutes to complete.

- **Trail Making Test (TMT):** This is a measure of visuospatial scanning, attention, sequencing, and speed Part A and executive function in Part B. Patients must “connect the dots” either in a numbered sequence or alternating letters and numbers. Generally Part A and Part B require less than 5 minutes, and Part A is discontinued at 3 minutes, Part B at 5 minutes, to reduce burden on patients with significant cognitive impairment.
• **Controlled Word Association Test (COWAT):** The patient produces as many words as possible in 1 min. (each) for a specific letter (C, F, L or P, R, W). Requires about 5 min to complete. Assesses language and executive/frontal skills.

• **Mini-Mental Status Examination (MMSE):** This is a brief, standardized tool to grade patients’ global cognitive function. The MMSE begins with an assessment of orientation to place and time. Next is a test of memory (immediate recall) by having the subject immediately repeat the names of 3 objects presented orally. Following this the patient subtracts sevens serially from 100. The subject is then asked to recall the three items previously repeated (delayed recall). The final section evaluates aphasia and apraxia by testing naming, repetition, compliance with a 3-step command, comprehension of written words, writing, and copying a drawing. The maximum score that can be obtained for the entire MMSE is 30 points.

• **Cognitive Functioning Subscale of the Medical Outcomes Scale (MOS)(Self-report):**

  This 6-item, self-report measure is designed to measure day-to-day cognitive functioning of which the patient would be aware, including difficulty with problem-solving, slowed reaction times, forgetfulness, and concentration. Reliability and validity have been reported for patients with cancer. Scale is based on multiple choice questions asking about cognitive function where the item is present 1= all of the time to 6=none of the time. Scored in five steps (data cleaning, changing out of range values to missing, item re-calibration and skip pattern recording, reverse scoring of items so that the highest score reflects the best health state, transforming scores linearly to a common metric with a range of 0-100, averaging across items in the same scale). Completion time is estimated to be less than 5 minutes.

### 11.3 Quality of Life Evaluation (6/17/08)

The Functional Assessment of Cancer Therapy-Brain (FACT-Br) is a commonly used instrument measuring general quality of life (QOL) reflecting symptoms or problems associated with brain malignancies across 5 scales: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); functional well-being (7 items); and concerns relevant to patients with brain tumors (23 items). Patients rate all items using a five-point rating scale ranging from "not at all" to "very much." The measure yields information about total QOL, as well as information about the dimensions of physical well-being, social/family well-being, emotional well-being, functional well-being, and disease-specific concerns. Six additional experimental items request information regarding how much each dimension affects QOL, using a "0" (not at all) to "10" (very much so) rating scale. The FACT-G is able to distinguish metastatic from non-metastatic disease, $F(1,334) = 5.38, p < .05$. It also distinguishes between stage I, II, III and IV disease, $F(3,308) = 2.94, p < .05$, and between inpatients and outpatients from different centers, $F(2,411) = 17.0, p < .001$. On the FACT-G, sensitivity to disease status was restricted to the Physical ($p < .01$) and Functional ($p < .001$) subscales. Concurrent validity is supported by strong Pearson correlations with the Functional Living Index - Cancer (.79) and a patient-completed version of the QOL Index (.74). Initial evidence for construct validity is supported by: 1) moderate to high correlations with mood state as measured by the Taylor Manifest Anxiety Scale (.57) and a shortened version of the Profile of Mood States (.69); 2) moderate correlation with activity level (negative direction of coefficient because of reverse scaling) as measured by the Eastern Cooperative Oncology Group five-point rating (-.56), and a small correlation with social desirability as measured by a shortened version of the Marlowe-Crowne Social Desirability Scale. The FACT is written at the 4th grade reading level, and patients can complete it in 5-10 minutes. The FACT has been translated into 26 languages, and translations are accessible at the FACIT web site, http://www.facit.org/translation/licensure.aspx.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Time to Administer (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life (self-report)</td>
<td>10</td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy - Brain</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td>10</td>
</tr>
</tbody>
</table>

The self-report of quality of life can be completed by the patient or the examiner and does not require pre-certification.
11.4 **Measurement of Response**

Patients will undergo brain MRI prior to study entry and at 8, 16, 24, and 52 weeks or at onset of clinical deterioration.

11.4.1 **Criteria for CNS Progression**

11.4.1.1 **Assessment:**

The treating radiation oncologist will measure and calculate the bidimensional product for each of the 1-3 largest brain metastases identified at baseline. The bidimensional product is defined as the largest dimension multiplied by the second largest dimension that is perpendicular to it (the largest dimension). This value will be recorded on the baseline form and every subsequent follow-up form. The appearance (yes/no) of any new brain metastases will be recorded on all follow-up forms.

Please note: patients who have had radiosurgery or surgical resection and are planning adjuvant WBRT may not have measurable disease and therefore follow-up studies will be focusing on the development of new metastases or recurrence.

11.4.1.2 **Definition of CNS Progression**

CNS progression will be defined as a defined increase (see below) in perpendicular bi-dimensional tumor area for any of the 1-3 tracked brain metastases, or the appearance of any new brain metastasis on a follow-up MRI.

For lesions smaller than 1 cm in maximum diameter, a maximum increase of 50% in perpendicular bi-dimensional treatment area will be necessary to score as progression. This caveat is included to account for potential variability in measurement, which will be most susceptible to proportionate errors at smaller sizes. For greater than 1 cm lesions, the definition will use a 25% rule for change.

11.5 **Criteria for Discontinuation of Protocol Treatment**

Unacceptable adverse event to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and RTOG Headquarters data management must be notified;

- A delay in protocol treatment > 4 weeks.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.
## 12.0 DATA COLLECTION

Data should be submitted to:

**RTOG Headquarters**
1818 Market Street, Suite 1600
Philadelphia, PA  19103

*If a data form is available for web entry, it must be submitted electronically.*

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

### 12.1 Summary of Data Submission (3/28/08)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1) [For studies with pathology]</td>
<td></td>
</tr>
<tr>
<td>Mini-Mental status Exam (MS)</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive Evaluation Summary Form (NP) (HVLT-R,TMT, COWAT)</td>
<td></td>
</tr>
<tr>
<td>Medical Outcomes Scale (QL)</td>
<td></td>
</tr>
<tr>
<td>Functional Assessment of Cancer Therapy: FACT-Br (PQ)</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment Form (TF)**

- Mini-Mental status Exam (MS)
- Neurocognitive Evaluation Summary Form (NP) (HVLT-R,TMT, COWAT)
- Medical Outcomes Scale (QL)
- Functional Assessment of Cancer Therapy: FACT-Br (PQ)

For protocols involving RT QA without Initial Review:

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosimetry Information</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy form (T1)</td>
<td>Due within 1 week of completion of RT</td>
</tr>
</tbody>
</table>

**Follow-up Form (F1)**

- Every 3 months for 1 year, then every 4 months for 1 year, then every 6 months for 2 years and then annually.

**For protocols involving RT QA without Initial Review:**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosimetry Information</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy form (T1)</td>
<td>Due within 1 week of completion of RT</td>
</tr>
</tbody>
</table>

**For protocols without RT QA:**

*NOTE: Copies of simulation and port films and the complete RT daily treatment record and calculations will be submitted to RTOG Headquarters ONLY if specifically requested.*
13.0 **STATISTICAL CONSIDERATIONS (3/28/08)**

13.1 **Study Endpoints**

13.1.1 **Primary Endpoint**

Cognitive function, specifically memory, 24 weeks from the start of drug treatment as measured by the Hopkins Verbal Learning Test- Revised for delayed recall (HVLT-R-delayed recall)

13.1.2 **Secondary Endpoints**

13.1.2.1 Cognitive function, specifically memory, 8 weeks, 16 weeks, and 12 months from the start of drug treatment as measured by the HVLT-R-delayed recall

13.1.2.2 Neurocognitive failure, defined as the first cognitive failure on any of the following battery of tests:

1. HVLT-R for free recall, delayed recall, and delayed recognition;
2. Controlled Word Association Test (COWAT);
3. Trail Making Test Parts A and B (TMT);
4. Medical Outcomes Scale-Cognitive Functioning Subscale (MOS);
5. Mini-Mental Status Examination (MMSE)

13.1.2.3 Quality of Life (QOL) as measured by the Functional Assessment of Cancer Therapy Brain subscale (FACT-Br)

13.1.2.4 Progression-free survival

13.1.2.5 Overall survival

13.1.2.6 Adverse events based on CTCAE v3.0

13.1.2.7 Collection of serum, plasma, buffy coat cells, urine, and CSF for future translational research analyses

13.2 **Sample Size**

13.2.1 **Stratification and Randomization:** Patients will be stratified before randomization with respect to RPA class (Class I vs. Class II with controlled systemic disease) and prior surgical therapy (none vs. radiosurgery or surgical resection). The treatment allocation scheme described by Zelen\(^85\) will be used because it balances patient factors other than institution. Within each stratum, patients will be randomized in a 1:1 ratio to placebo or memantine in addition to WBRT.

13.2.2 **Sample Size Derivation:** The sample size calculations will address the specific primary hypothesis that the use of memantine during WBRT (Arm 1) will result in a statistically significant reduction in cognitive decline as compared to placebo during WBRT (Arm 2). We do not expect memantine to improve cognitive function; at best, we anticipate a preservation of cognitive function.

Meyers et al reported in a previous phase III brain metastases trial that patients treated only with WBRT saw a mean score in the HVLT-R-delayed recall decline by 0.87 from 7.04 at baseline to 6.17 at 24 weeks, with a standard deviation of 3.19. Based upon Meyers’ results, we expect patients receiving placebo (Arm 2) to experience a similar decline in cognitive function. We expect patients receiving memantine (Arm 1) to experience a statistically significant smaller decline in cognitive function from baseline (pre-drug treatment) to 24 weeks:

\[ H_0: \Delta \mu_1 \geq \Delta \mu_2 \text{ vs. } H_A: \Delta \mu_1 < \Delta \mu_2 \]

where \( \Delta \mu \) is the mean decline in HVLT scores from baseline to 24 weeks for patients in arm i.

The change scores will not be normally distributed, and will be compared using the nonparametric Wilcoxon rank sum test. Based on a one-sided Wilcoxon rank sum test with alpha=0.025, 221 patients per arm would be required to have 80% statistical power to detect a mean difference of 0.87 in the HVLT-R change scores between the two treatment arms\(^86\). Powering to detect an even smaller decline than hypothesized for this study may result in detecting a difference that is not clinically meaningful. If patients on Arm 1 have an equal or larger decline than patients on Arm 2, the memantine treatment will not be considered beneficial.

Assuming that 20% of patients may be ineligible, or die prior to the 24 week assessment, the target sample size for randomization will be 536.

13.3 **Patient Accrual**

This trial will be open concurrently with RTOG 0320, a three-arm phase III trial of patients with non-small cell lung cancer primaries and 1-3 brain mets. However, the RTOG has shown in the
past the ability to accrue simultaneously to multiple brain metastases trials even when there were overlapping patient populations. RTOG 0118 and RTOG 0119 jointly accrued 227 patients in the 14 months when both were open to new patient entries (average of 16 per month). Based on patient accrual in previous RTOG brain metastases studies, there will be negligible accrual during the initial six months while institutions are obtaining IRB approval. As this trial is not limited to patients with lung cancer primaries, we would then expect a uniform accrual rate of 12 patients per month. We expect to complete accrual in 4.25 years (51 months). The total duration of the study is expected to be 5 years from the time the first patient is entered to the final analysis with 24 weeks of follow-up for each patient.

The RTOG Data Monitoring Committee (DMC) will begin evaluating patient accrual semi-annually following the anticipated quiet period. If the average monthly accrual rate for the trial in the fifth and sixth quarters after study activation (i.e., in months 13-18) is less than 20% of the rate projected in the paragraph above (i.e., less than 3 patients per month), the study will close to further accrual. If the average monthly accrual rate is greater than 20% but less than 50% of projected (i.e., less than 6 patients per month), the trial will be placed on probation for six months. If the average monthly accrual rate at the end of the probationary period is less than 50% of projected, the study will close to future accrual.

13.4 Power Calculations for Selected Secondary Endpoints

13.4.1 Neurocognitive Failure
The median time to neurocognitive failure has been shown by Meyers et al to be 7.4 weeks (monthly hazard rate = 0.41) for patients with brain metastases treated with WBRT alone and prospectively tested with similar neurocognitive tests. Assuming that the failure times are exponentially distributed; a one-sided log-rank test with alpha 0.025 that accrues 221 patients per arm with 12 months of follow-up would ensure 98% statistical power to detect a 33% relative reduction in the monthly hazard rate with the use of memantine (corresponding median time to neurocognitive failure of 11.1 weeks).

13.4.2 Overall Survival
Gaspar et al report in a previous recursive partitioning analysis of RTOG brain metastases patients a median survival of 7.1 months for RPA Class I patients (monthly hazard rate=0.10). Wronksi et al report in a retrospective analysis of brain metastases patients treated with surgery in addition to WBRT a median survival of 16.2 months (monthly hazard rate=0.04). Assuming that the failure times are exponentially distributed, a one-sided log-rank test with alpha 0.025, that accrues 221 patients per arm with 12 months of follow-up would ensure at least 85% statistical power to detect a 33% relative reduction in the monthly hazard rate with the use of memantine in either case (corresponding to a median survival time of 9.9 months or 23.1 months, respectively).

13.5 Analysis Plan
All eligible patients who are randomized to the study will be included in the comparison of treatment arms, regardless of treatment compliance (intent-to-treat analysis).

13.5.1 Scoring of Neurocognitive Assessments

13.5.1.1 HVLT-R Delayed Recall
Patient scores on the HVLT-R delayed recall section have an integer range from 0 to 12 with lower scores indicating declining cognitive function. The score is the number of words a patient can recall from a list of 12 words. The change in score from baseline to 24 weeks ranges from -12 to 12. Change scores from 1 to 12 indicate declining cognitive function. A change score of 0 indicates preserved cognitive function. Change scores from -1 to -12 indicate improved cognitive function and are not expected.

13.5.1.2 HVLT-R Free Recall
Patient scores on the HVLT-R free recall section have an integer range from 0 to 36 with lower scores indicating declining cognitive function. The score is the number of words a patient can recall from a list of 12 words in three trials.

13.5.1.3 HVLT-R Delayed Recognition
Patient scores on the HVLT-R delayed recognition section have an integer range from -12 to 12 with lower scores indicating declining cognitive function. The score is the number of correctly identified words from the list of 12 words minus the number of incorrectly identified words from the list of 12 words.

13.5.1.4 COWAT
Patient scores on the COWAT are non-negative integer values with lower scores indicating declining cognitive function. The score is the number of words a patient identifies that begin with a specified letter.

13.5.1.5 TMT
Patient scores on the TMT-A are time values ranging from 0 to 3 minutes and scores on the TMT-B are time values ranging from 0 to 5 minutes with higher times indicating declining cognitive function. Patients are timed to connect the dots in a numbered sequence or alternating letters and numbers.

13.5.1.6 MOS
Patient scores on the MOS are self-reported and have a continuous range from 0-100 with lower scores indicating declining cognitive function. The score is the weighted average of the patient’s response to a six-item questionnaire.

13.5.1.7 MMSE
Patient scores on the MMSE have an integer range from 0 to 30 with lower scores indicating declining cognitive function. The score is based on the patient's response to an 11-item questionnaire.

13.5.2 Primary Endpoint
The primary endpoint is decline in cognitive function, specifically memory, from baseline (pre-treatment) to 24 weeks from the start of drug treatment as measured by the Hopkins Verbal Learning Test- Revised for delayed recall (HVLT-R-delayed recall).

Patients who die prior to the 24 week assessment will be analyzed separately. If these patients are not equally distributed between the two treatment arms, we will conduct a sensitivity analysis to determine the impact of the exclusion.

Imputation methods will be used to determine values for all alive patients missing the 24 week assessment. Multiple imputation procedure provides a valid strategy for dealing with missing data sets, properly reflecting the uncertainty due to missing values. In the propensity score method, logistic regression model will be used to generate a propensity score for each live patient indicating the probability of that observation being missing given patient baseline cognitive function and treatment group. The observations are then grouped based on these propensity scores, and an approximate Bayesian bootstrap imputation is applied to each group.

We hypothesize that patients receiving memantine (Arm 1) will experience a statistically significant smaller decline in cognitive function than patients receiving placebo (Arm 2):

\[ H_0: \Delta \mu_1 > \Delta \mu_2 \text{ vs. } H_A: \Delta \mu_1 \leq \Delta \mu_2 \]

where \( \Delta \mu \) is the mean decline in HVLT-R scores from baseline to 24 weeks for patients in arm 1.

The one sided Wilcoxon rank sum test will be used to test the hypothesis at the 0.025 significance level. Subgroup analyses based on the stratification variables, RPA class and prior surgical therapy, will also be conducted.

13.5.3 Secondary Endpoints:
13.5.3.1 Cognitive decline:
Decline in cognitive function, specifically memory, from baseline to 8 weeks, 16 weeks, and 12 months from the start of treatment as measured by the HVLT-R-delayed recall will be assessed in addition to the primary endpoint of 24 weeks.

In addition to comparing the change scores at specific time points, overall trends in cognitive function will be modeled using the general linear mixed-effect model.

13.5.3.2 Time to neurocognitive failure:
Neurocognitive failure is defined as the first cognitive failure on any of the following five tests: the HVLT-R for immediate recall, recognition, and delayed recall; the COWAT; the TMT Parts A and B; the MOS; and the MMSE. Cognitive failure for each test is defined as a post-treatment score that is at least 2 standard deviations worse than the patient’s personal baseline score.

The cumulative incidence approach will be used to estimate the median time to neurocognitive failure to account for the competing risks of disease progression and death. Patients that experience disease progression and receive non-protocol treatment or patients that die prior to experiencing a neurocognitive failure will be censored accordingly. Gray’s test will be used to test for a statistically significant difference in the distribution of neurocognitive failure times at the alpha=0.025 level. The null and alternative hypotheses are:

\[ H_0: S_1(t) < S_2(t) \quad \text{vs.} \quad H_A: S_1(t) \geq S_2(t) \]

where \( S_i(t) \) is the distribution of survival times for patients in arm \( i \).

In addition, the Cox proportional hazards regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference. Unadjusted ratios and ratios adjusted for stratification variables and other covariates of interest will be computed.

### Quality of Life (Functional Assessment of Cancer Therapy-Brain)

The FACT-Br includes the four domains on the general fact—physical well-being (7 items), social well-being (7 items), emotional well-being (6 items), functional well-being (7 items)—and the 23-item brain subscale. Patient scores on the FACT-Br subscale range from 0 to 92 with lower scores indicating declining quality of life. The change scores from pretreatment to 24 weeks will be compared between the treatment arms. A mean difference of 5 points represents a clinically meaningful change (CMC). A difference of less than 5 points between the treatment arms will not be considered meaningful, even if it has statistical significance. If the baseline scores are not distributed similarly between the treatment arms, the percent change scores will be used to adjust for these varying baseline values. A 5 point CMC corresponds to varying percentage changes, depending on the baseline values. The null and alternative hypotheses are:

\[ H_0: \Delta \mu_1 < \Delta \mu_2 \quad \text{vs.} \quad H_A: \Delta \mu_1 \geq \Delta \mu_2 \]

where \( \Delta \mu_i \) is the mean change in FACT score from baseline to 24 weeks for patients in arm \( i \).

Assuming that the data are normally distributed, the two sample t-test assuming equal variances will be used to test the hypothesis at the 0.025 significance level. If normality assumptions are not met, the Wilcoxon rank sum test will be used to test the hypothesis.

In addition to change in QOL at 24 weeks from the start of drug treatment, overall trends in quality of life will be described with longitudinal data analysis. The FACT-Br will also be collected at 8 weeks, 16 weeks, and 12 months from the start of drug treatment. Specifically the general linear mixed-effect model will be used to describe the change trend of FACT-Br scores over time between the treatment arms. The model allows for adjustments using stratification variables (RPA Class and prior therapy) and other covariates of interest. Missing data will be addressed similar to the primary endpoint.

### Progression-Free Survival

Disease progression is defined in detail in Section 11.4.1.2 and includes an increase of at least 50% for lesions less than or equal to 1cm, an increase of at least 25% for lesions greater than 1cm, or appearance of any new brain metastases. Death will also be considered a failure. The median time to disease progression will be estimated using the Kaplan-Meier approach. The stratified log-rank test will be used to test for a statistically significant difference in survival distributions with alpha=0.025. The null and alternative hypotheses are:

\[ H_0: S_1(t) < S_2(t) \quad \text{vs.} \quad H_A: S_1(t) \geq S_2(t) \]

where \( S_i(t) \) is the distribution of survival times for patients in arm \( i \).
In addition, the Cox proportional hazards regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference. Unadjusted ratios and ratios adjusted for stratification variables and other covariates of interest will be computed.

13.5.3.5 Overall Survival

The median overall survival time will be estimated using the Kaplan-Meier approach. The stratified log-rank test will be used to test for a statistically significant difference in survival distributions with alpha=0.025. The null and alternative hypotheses are:

\[ H_0: S_1(t) < S_2(t) \quad \text{vs.} \quad H_A: S_1(t) \geq S_2(t) \]

where \(S_i(t)\) is the distribution of survival times for patients in arm \(i\).

In addition, the Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference. Unadjusted ratios and ratios adjusted for stratification variables and other covariates of interest will be computed.

13.5.3.6 Incidence of Adverse Events

Adverse events are reported according to CTCAE v3.0. Differences in incidence rates at 24 weeks between the two treatment arms will be tested using the one-sided chi-square test at the 0.025 significance level. Univariate logistic regression will be used to model the distribution of acute adverse events. Multivariate logistic regression will be used to model the distribution of acute adverse events, adjusting for covariates, including, but not limited to treatment arm, RPA class, prior surgical therapy, and age. Both unadjusted and adjusted odds ratios and their respective 95% confidence interval will be computed.

13.5.3.7 Translational Research Analyses

Serum, plasma, buffy coat cells, urine, and CSF will be collected for exploratory analyses detailed in Section 10.5. Stored samples will be kept for future studies of the cognitive effects of radiotherapy.

13.5.4 Early Stopping Rules for Excessive Adverse Events

Memantine is well-tolerated with incidence of adverse effects being similar to placebo in previous clinical trials. Seizures and lethargy are expected adverse events in addition to those detailed in Section 7.3.4. We expect \(\leq 5\%\) of patients in each treatment arm to experience a grade 3 or higher (3+) seizure, cognitive disturbance, and/or somnolence (depressed level of consciousness) adverse event that is possibly, probably, or definitely related to treatment within 24 weeks from the start of treatment (CTCAE v3.0). A rate of 20% in each treatment arm is considered unacceptable and indicates that the treatment is not tolerable. The following table provides the stopping boundaries that will be utilized on the first 40 evaluable patients (eligible patients that received at least 1 dose of memantine) in each treatment arm. The first stage will utilize one-third of the patients permitting an earlier formal evaluation of treatment tolerability. These boundaries were calculated by the method of Fleming for a two-stage design in which the significance level and the statistical power were set at 0.062 and 0.93, respectively. The null and alternative hypotheses are:

\[ H_0: p_i \geq 0.20 \quad \text{vs.} \quad H_A: p_i \leq 0.05 \]

where \(p_i\) is the proportion of patients with excessive adverse events (intolerable treatment).

<table>
<thead>
<tr>
<th>Step</th>
<th>Total Number of Evaluable Patients</th>
<th>Upper Limit of Patients With Intolerable Treatmenta</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>5</td>
</tr>
</tbody>
</table>

\(a\) If the number is equal to or above the limit, the trial will be temporarily closed.

If drug treatment is deemed intolerable due to an excessive number of adverse events at either step, the trial would be temporarily closed to accrual while the study statistician, study chairs, and the RTOG group chair review the documented adverse events and make a recommendation to the RTOG Data Monitoring Committee (DMC) regarding the future of the study. The RTOG DMC will make the final decision regarding the future course of action for the study.
13.6 **Interim Reports to Monitor the Study Progress**

Interim reports with descriptive statistics will be prepared twice a year until the initial paper reporting the treatment results has been accepted for publication. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events. The interim reports will not contain results from the treatment comparisons with respect to the primary or secondary endpoints. This study will also be monitored by the Clinical Data Update System (CDUS) version 3.0. Quarterly CDUS reports are submitted electronically.

13.7 **Reporting the Initial Treatment Results**

The primary hypothesis of this study is whether the use of memantine during whole brain radiation therapy will significantly reduce the decline in neurocognitive function at 24 weeks from the start of treatment compared to WBRT alone. This final analysis will occur after each patient has been potentially followed for at least 24 weeks. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. The primary hypothesis of treatment benefit will be compared using the Wilcoxon rank sum test after imputing for missing values as specified in the analysis plan. Also, where feasible, treatment comparisons with respect to all endpoints will be compared within each racial and ethnic category.

13.8 **Gender and Minorities**

In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of women and minorities will be examined during the interim reports. Based on accrual statistics from RTOG 0118, a brain metastases trial, the projected accrual by gender, race, and ethnicity is shown below:

<table>
<thead>
<tr>
<th>Projected Distribution of Gender and Minorities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td><strong>Ethnic Category</strong></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
</tr>
<tr>
<td><strong>Racial Category</strong></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Black or African American</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
</tr>
</tbody>
</table>
REFERENCES


RTOG 0614


64. Forest Pharmaceuticals, Inc. Namenda ® Product Information, 2005


This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have cancer that has spread to the brain.

Why is this study being done?
The purpose of this study is to compare the effects, good and/or bad, of memantine with a placebo on memory and thinking in participants receiving whole brain radiotherapy. Doctors hope that memantine will be effective in preventing thinking problems after whole brain radiotherapy, although there is no proof of this yet. In this study, you will get either memantine or the placebo. You will not get both. In addition, we want to find out what effects, good and/or bad, memantine has on participants and their brain tumors. Memantine is currently used to help with thinking and memory for people with different types of dementia. A placebo is a non-active substance that looks the same as, and is given the same way as, an active drug being tested. The effects of the active drug are compared to the effects of the placebo.

How many people will take part in the study?
About 536 people will take part in this study.

What will happen if I take part in this research study?
Before you begin the study …
You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

• A physical and neurologic examination to evaluate the tumor
• Blood test
• For women of childbearing age, a pregnancy test in which blood is drawn through a needle into a tube
• An MRI of the brain with contrast or a CT if you are unable to have an MRI

You will need to answer questions measuring your memory and thinking that take about 30 minutes to complete.

All of these tests and procedures can be performed on an outpatient basis; no hospitalization is necessary.

In some patients with cancer that has spread to the brain, chemotherapy is used in addition to radiation therapy. This is not allowed for 14 days before participating in this study, during the three weeks of radiation therapy, and for 14 days following completion of radiation therapy.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

• A physical and neurologic examination within 14 days prior to beginning drug treatment then during weeks 8, 16, and 24 and at 12 months to evaluate the tumor and the effects of treatment
• Blood test prior to drug treatment and on weeks 8, 16, and 24 and at 12 months
• An MRI of the brain on weeks 8, 16, and 24 and at 12 months

All of these tests and procedures can be performed on an outpatient basis; no hospitalization is necessary.

You will need these tests and procedures that are being done to see how the study is affecting your body.

• A 30 minute testing session to measure your memory and thinking abilities by asking you to answer questions and follow a few directions. This will be done during weeks 8, 16, and 24, and at 12 months.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group. Neither you nor your doctor will know which group you will be in.

If you are in group 1 (often called "Arm A") you will receive radiation therapy once a day, five days a week (Monday to Friday) for three weeks, for total of fifteen treatments. In addition, you will begin taking memantine (by mouth) while you are receiving radiation therapy. You will continue taking memantine for 24 weeks or until your doctor tells you to stop. You will start with 5 mg by mouth once a day. Seven days later you will increase the dose to 5 mg by mouth twice a day. Seven days later you will increase the dose to 10 mg by mouth in the morning and 5 mg in the evening, and 7 days later to 10 mg by mouth twice a day.
If you are in group 2 (often called "Arm B") you will receive radiation therapy once a day, five days a week (Monday to Friday) for three weeks, for total of fifteen treatments. In addition, you will begin taking placebo (by mouth) while you are receiving radiation therapy. You will continue taking placebo for 24 weeks or until your doctor tells you to stop. You will start with 5 mg by mouth once a day. Seven days later you will increase the dose to 5 mg by mouth twice a day. Seven days later you will increase the dose to 10 mg by mouth in the morning and 5 mg in the evening, and 7 days later to 10 mg by mouth twice a day.

<table>
<thead>
<tr>
<th>Dosing Chart</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily AM Dose</td>
<td>Daily PM Dose</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>5 mg</td>
<td>None</td>
</tr>
<tr>
<td>Week 2</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Week 3</td>
<td>10 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Weeks 4-24</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

When you are finished taking **memantine or placebo** you will continue to follow with your doctor for regular exams, tests or procedures that are part of regular cancer care. You will be followed as long as you live or until you do not wish to participate in the study.

How long will I be in the study?

You will be receiving study treatment for approximately 6 months. After you are finished taking memantine or placebo, the study doctor will ask you to visit the office for follow-up exams at one year, every 4 months the following year, then every 6 months for the next 2 years, and then annually for as long as you live.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the memantine. In some cases, side effects can be serious, long lasting, or may never go away. As with any experimental study, there also is a risk of death.
You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the whole brain radiotherapy include those which are:

**Likely**
- Hair loss, which may be permanent
- Dry mouth and/or change in taste
- Headaches
- Nausea and/or vomiting
- Scalp reddening or tanning and irritation (Your skin will be examined once a week during radiation therapy)
- Memory loss, which can occur in the first few months after whole brain radiotherapy and may be permanent
- Tiredness

**Less Likely**
- Temporary worsening of tumor symptoms such as seizures or weakness
- Drainage of clear fluid from the ears or plugging of the ears with decreased hearing
- Behavioral change and/or increased sleepiness (occurring four to ten weeks after radiation therapy is complete and lasting for several days up to two weeks)
- Cataracts and eye damage with the possibility of impaired vision

**Rare but serious**
- Severe local damage to or death of normal brain tissue, which may require surgery to remove
- Hardening of the arteries in the brain which may lead to strokes
- A second new cancer caused by radiation, in the brain or nearby organs
- Eye damage with the possibility of permanent blindness

Risks and side effects related to the memantine include those which are:

Memantine is well-tolerated and is not associated with frequently occurring side effects.

**Less Likely**
- dizziness
- headache
- constipation
- pain
- shortness of breath
- high blood pressure
- coughing
- nervousness
- changes in behavior
- tremor
- restlessness
• inability to obtain enough sleep
• depression
• tiredness, lack of energy

**Rare but serious**
• seeing or hearing things that aren’t there
• increased seizure frequency

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. You need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the study?**

Taking part in this study may or may not make your health better. While doctors hope memantine will be effective in preventing thinking problems after whole brain radiotherapy, there is no proof of this yet. We do know that the information from this study will help doctors learn more about memantine as a treatment for people with cancer that has spread to the brain. This information could help future cancer patients.

**What other choices do I have if I do not take part in this study?**

Your other choices may include:
• Getting treatment or care for your cancer without being in a study
• Taking part in another study
• Getting no treatment
• Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

**Will my medical information be kept private?**

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.
Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Radiation Therapy Oncology Group
- Forest Labs, the drug manufacturer

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The manufacturer, Forest Laboratories, will provide the placebo and memantine free of charge for this study. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the (drug).

The study agent, memantine or placebo, will be provided free of charge while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.
What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, __________________ [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at __________________ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety Monitoring Committee will be regularly meeting to monitor safety and other data related to this study. The Committee members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ [telephone number]. [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]
Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.

You can say “yes” or “no” to [each of] the following study[ies]. Below, please mark your choice [for each study].

Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This “Quality of life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete questionnaires prior to drug treatment, then during weeks 8, 16, and 24 and at 12 months. Each questionnaire takes about 10 minutes to fill out.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this part of the study, the only thing you will be asked to do is fill out these questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the Quality of Life Questionnaires.

YES     NO
Consent Form for Use of Blood/Urine/CSF for Research

About Using Blood/Urine/CSF for Research

You are going to have blood tests as part of your cancer care. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the blood that is left over for future research. In addition, we would like to collect urine before you start drug treatment, at 8, 16, and 24 weeks and 12 months. If you agree, this blood and urine will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: http://www.rtog.org/tissue%20for%20research_patient.pdf

Some patients may need to have surgery as part of their treatment for cancer that has spread to the brain. If that becomes necessary, your doctor may ask to use some of the fluid covering the brain called the cerebral spinal fluid (CSF) for further research.

Your blood, urine, and CSF may be helpful for research. The research that may be done is not designed specifically to help you. It might help people who have cancer and other diseases in the future. Reports about research done with your blood, urine, and/or CSF will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over blood, urine, and CSF for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your blood, urine, and CSF can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood, urine, and CSF. Then any blood, urine, and CSF that remains will no longer be used for research and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the doctor/institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue and specimens are used for genetic research (about diseases that are passed on in families). Even if your tissue and specimens are used for this kind of research, the results will not be put in your health records.

Your tissue and specimens will be used only for research and will not be sold. The research done with your tissue and specimens may help to develop new products in the future.

Benefits

The benefits of research using tissue and specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.
Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My blood/urine/CSF may be kept for use in research to learn about, prevent, or treat cancer.
   Yes   No

2. My blood/urine/CSF may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
   Yes   No

3. Someone may contact me in the future to ask me to take part in more research.
   Yes   No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ________________________________

Date ________________________________
# APPENDIX II

## STUDY PARAMETER TABLE

<table>
<thead>
<tr>
<th>Prior to Study Entry</th>
<th>Prior to Drug Treatment</th>
<th>Drug Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 28 days prior to study entry</td>
<td>Within 7 days prior to study entry</td>
<td>Within 14 days of study entry</td>
<td>Week 8’</td>
</tr>
<tr>
<td>Neurologic exam</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>History/physical</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>MMSE</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Brain MRI/CT</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Performance status</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Creatinine, CrCl</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>BUN</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Serum pregnancy test (if applicable)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Tumor response eval</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Adverse event evaluation***</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Neurocognitive/ QOL assessment**</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Translational specimen collection</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

*Weeks from start of drug treatment

**MMSE ≥18 for eligibility; additional MMSE administered with other neurocognitive evaluations after study entry

***Additionally, as needed based on reporting requirements

****No other formal evaluations required by study

Patients will continue to undergo formal evaluation as outlined above even if tumor progression (i.e. if tumor progression before week 24, patient will still undergo formal evaluation at week 24 and 52 weeks).
APPENDIX III

ZUBROD PERFORMANCE SCALE

0  Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

1  Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2  Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3  Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4  Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).

5  Death (Karnofsky 0).

KARNOFSKY PERFORMANCE SCALE

100  Normal; no complaints; no evidence of disease

90  Able to carry on normal activity; minor signs or symptoms of disease

80  Normal activity with effort; some sign or symptoms of disease

70  Cares for self; unable to carry on normal activity or do active work

60  Requires occasional assistance, but is able to care for most personal needs

50  Requires considerable assistance and frequent medical care

40  Disabled; requires special care and assistance

30  Severely disabled; hospitalization is indicated, although death not imminent

20  Very sick; hospitalization necessary; active support treatment is necessary

10  Moribund; fatal processes progressing rapidly

0  Dead
APPENDIX IV
RTOG RPA CLASSIFICATION SYSTEM

Class I: KPS ≥ 70 (Zubrod 0-1);
age < 65 years;
no extra-cranial metastases; and
controlled primary malignancy
(controlled primary malignancy is defined clinically, radiographically, and/or serologically, as appropriate for the underlying malignancy during the previous 3 months or longer).

Class II: for this study defined as all eligible patients which do not fall into RPA Class I; in other words, patients with
KPS ≥ 70
controlled primary malignancy
(controlled primary malignancy is defined clinically, radiographically, and/or serologically, as appropriate for the underlying malignancy during the previous 3 months or longer).
age ≥ 65;
extra-cranial metastases

Class III: not eligible for study entry
KPS < 70
Memantine/placebo will be shipped by I.V. Solutions, Inc. only to institutions that have identified a single individual as responsible for receipt and accountability of shipments. Sites must review Section 5.0 of the protocol to assure that all pre-registration requirements have been met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG website, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. Approved international institutions must submit the SASF and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300). This must be done prior to registration of the institution’s first case. The SASF must be processed before the institution is approved to receive drug. Institutions should allow adequate time (7-10 days) to process the form before calling to register the first case. Patient registration, not submission of the SASF, triggers the initial drug shipment. See Section 7.0 under “Drug Ordering and Accountability” for details regarding anticipated shipment and delivery timeframes.
The tests that constitute the neurocognitive function (NCF) battery were selected because they are widely used standardized psychometric instruments that have been shown to be sensitive to the neurotoxic effects of cancer treatment in other clinical trials.\(^1,2\) NCF function has been demonstrated to predict tumor progression\(^3\), and independently predict survival for patients with CNS tumors\(^4-6\). This battery has also been demonstrated to be practical in terms of cost and burden to the patient with good compliance in multi-center trials\(^5\). They are widely used, standardized psychometric instruments with published normative data that takes into account age, and where appropriate, education, gender and handedness. The tests were also selected to minimize the effects of repeated administration. These tests are to be administered by a certified examiner and require 25 minutes or less to complete.

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Test</th>
<th>Time to Administer (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>Hopkins Verbal Learning Test–Revised(^7)</td>
<td>8</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Controlled Oral Word Association(^8)</td>
<td>5</td>
</tr>
<tr>
<td>Visual-motor processing speed</td>
<td>Trail Making Test Part A(^9)</td>
<td>5</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Trail Making Test Part B(^9)</td>
<td>7</td>
</tr>
</tbody>
</table>

**Total time: 25 minutes**

**Statistical Considerations**

We will use various models including the Cox proportional hazards model and mixed and hierarchical linear models. Alternatively, we can use multilevel modeling to detect differences between the two groups over time. These repeated measure analyses can also be supplemented with a psychometric analysis of changes in test performance using the Reliable Change (RC) Index.\(^10\) The difference between the pre-treatment baseline and follow-up assessments will be evaluated by the RC index. This index is derived from the standard error of measurement (SEM) for each test in the battery. The SEM is calculated from the test-retest reliability (r) and the standard deviation of test scores (SD): SEM=SD(1- r)\(^{1/2}\). The standard error of difference is then calculated: SEdiff=[2(SEM2)]\(^{1/2}\). A reliable change (RC) in test scores from baseline to follow-up is considered significant if it is within ± (1.64)(SEdiff), a 90% confidence interval. For each subject, the difference between the pre-treatment baseline and each follow-up assessment will be coded (according to the RC index) as 1 (deterioration), 2 (no change), and 3 (improved). Frequency tables will show the percentage of patients in each treatment protocol who show meaningful losses or gains in the various test domains over the course of the study. Treatment group differences can be compared using chi-square analysis and Cochran's and Mantel-Haenszel statistics.
Appendix VI References


APPENDIX VI (continued)

STEP 1 – EXAMINER APPROVAL FOR RTOG 0614

Prior to testing a patient, potential examiners must:

(1) Read Appendix VI (Administration Procedures for the Neurocognitive Test Battery)

(2) Watch the training video available on a password protected website. Please contact Dr. Meyers (cameyers@mdanderson.org) or Dr. Wefel (jwefel@mdanderson.org) for instructions on how to access the website.

(3) Complete the training video post test

(4) Complete a “practice” assessment

(5) Complete the Certification Worksheet (Appendix VII)

All materials (i.e., post test, complete practice assessment and scoring forms, certification worksheet) must be faxed to Drs. Meyers/Wefel, who will score it and review any procedural errors with the trainee. If the trainee demonstrates competency, he/she will be notified of the approval to administer the tests to study subjects as part of RTOG 0614. An approval notice will be sent to CTSU for their records and to ensure that only RTOG 0614 approved examiners are testing subjects on protocol RTOG 0614.

STEP 2 – ALTERNATE TEST FORMS/VERSIONS

Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. See the table below for the versions to be administered at pre-entry and subsequent sessions. The forms should continue to be alternated in this order for the duration of the study. The forms packet will contain alternate versions of these neuropsychological tests.

<table>
<thead>
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Additional comments:

1. Testing should be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.

2. Tests should be administered in the following order to every patient and at every study visit:
   - HVLT-R Part A (Learning Trials); Trail Making Test Part A; Trail Making Test Part B; COWA; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition). After completion of these tests the MMSE may be administered.

3. You may fill the delay interval between COWA and HVLT-R Part B (Delayed Recall) with QOL questionnaires.

4. Follow the instructions on the Forms Packet Index before submission of forms to RTOG.

5. Please keep all original test records. In the event of questions, contact Dr. Wefel (phone: (713)563-0514; fax: (713)794-4999; email: jwefel@mdanderson.org) or Meyers (see Appendix VII or Protocol Title page for contact information for Dr. Meyers). Copies of the test forms and summary sheets for the first case from each site must be reviewed by Dr. Meyers. Additionally, test results are not submitted to Dr. Wefel or Meyers nor to RTOG Headquarters. Results remain on file at the institution as source documentation pending request for submission by RTOG or a Study Chair.

6. All test results are recorded on the Neurocognitive Evaluation Summary Form (CS), which is found in the Forms Packet. Study/case specific labels must be applied to all forms.

7. Patients should not be given copies of their tests to avoid learning the material between test administrations.

8. Before dismissing the patient, thank him/her for their cooperation. Remind the patient of their next appointment and that these tests will be repeated.

9. In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the data summary form.
1. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

This test has three parts and six alternate forms:

Part A - Free Recall: Complete the three learning trials first

Part B - Delayed Recall: Complete after a 20 minute delay that includes administration of Trail Making Tests and COWA

Part C - Delayed Recognition: Complete immediately after Delayed Recall

Part A – Free Recall: Trial 1

Examiner: “I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?”

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (for example, “intrusion”), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: Trial 2

Examiner: “OK. Now tell me as many of those words as you can remember.”

- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (for example, “intrusion”), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 3. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: Trial 3

Examiner: “I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me.”

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (for example, “intrusion”), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- Do not tell the respondent that recall of the words will be tested later.
- Record the time on the clock that you complete 'Part A – Free Recall' (for example, 10:00am) on the designated space on the HVLT-R form.
APPENDIX VI (continued)

2. TRAIL MAKING TEST [Timed Test]

Part A – Sample: The Sample for Part A must be completed/attempted by each patient and every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table). Give the patient a black pen and say:

Examiner: “On this page (point) are some numbers. Begin at number 1 (point to 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4), and so on, in order, until you reach the end (point to the circle marked END). Draw the lines as fast as you can. Ready, begin.”

If the patient completes Sample A correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it. The following explanations of mistakes serve as illustrations:

• “This is where you start (point to number 1)”
• “You skipped this circle (point to the circle omitted)”
• “You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END”

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on he copy. Then say:

Examiner: “Remember, begin at number 1 (point to 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4) and so on, in order, until you reach the circle marked END (point). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin.”

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part A – Test: After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:

Examiner: “Good! Let’s try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (point) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4) and so on, in order, until you reach the circle marked END (point). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin.”

• Start timing as soon as the instruction is given to “begin”
• Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
• The patient must complete the test in 3 minutes or less
• DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED “END”
• If the patient does not complete the test within 3 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number reached on the test.
• If the patient successfully completes the test collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds. Then say, “That’s fine. Now we’ll try another one.”

Part B – Sample: The Sample for Part B must be completed/attempted by each patient and every assessment. Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:

Examiner: “On this page (point) are some numbers and letters. Begin at number 1 (point to 1) and draw a line from 1 to A (point), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the end (point to the circle marked END). Remember, first you have a number (point to 1), then a letter (point to A), then a number (point to 2), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin.”

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it.
APPENDIX VI (continued)

The following explanations of mistakes serve as illustrations:

- “You started with the wrong circle. This is where you start (point to number 1)”
- “You skipped this circle (point to the circle omitted)”
- “You should go from number 1 (point) to A (point), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3) and so on, until you reach the circle marked END (point)”

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner: “Now you try it. Remember, begin at number 1 (point to 1) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3) and so on, in order, until you reach the circle marked END (point). Ready, begin.”

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part B – Test:

After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

Examiner: “Good! Let’s try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (point) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the circle marked END (point). Remember, first you have a number (point to 1), then a letter (point to A), then a number (point to 2), then a letter (point to B), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin.”

- Start timing as soon as the instruction is given to “begin”
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
- The patient must complete the test in 5 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED “END”
- Collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds
- If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.
- At the top of both Sample forms and Test forms please write: patient initials, RTOG case number, date of evaluation, institution name, name of certified tester, and the certified tester’s phone number.
APPENDIX VI (continued)

3. **CONTROLLED ORAL WORD ASSOCIATION TEST (COWAT) [Timed Test]**
This test has three parts (letters) and two alternate forms.

Examiner: “I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say ‘Rochester’ or ‘Robert’. Also, do not use the same word again with a different ending, such as ‘Eat,’ and ‘Eating.’

“For example, if I say ‘s,’ you could say ‘son,’ ‘sit,’ ‘shoe,’ or ‘slow.’ Can you think of other words beginning with the letter ‘s’?”

Wait for the patient to give a word. If it is a correct response, say “good”, and ask for another word beginning with the letter “s”. If a second appropriate word is given, proceed to the test itself.

If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.

If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring sheet.

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

Examiner: “That is fine. Now I am going to give you another letter and again you say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP.”

“You will have a minute for each letter. The first letter is ‘___’” (see scoring sheet).

“Allow exactly one minute for each letter”

- If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., “Tell me all the words you can think of that begin with a “c”).
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing one minute for each.

Recording and Scoring:

- The record sheet provides lines on which the patient’s responses can be entered (e.g., write in the word that is said by the patient). If his/her speed of word production is too fast to permit verbatim recording, a “+” should be entered to indicate a correct response.
- Patient responses, including incorrect responses, should be recorded verbatim. Incorrect responses should be struck through with a single line, initialed and dated.
- If the patient provides more responses than there are lines on the record sheet, place check marks in the boxes to indicate correct responses only.
- Count all the correct responses. The number of correct words should be indicated below each column on the recording sheet and on the summary data form that is sent to the RTOG.

Comments on scoring:

- Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.
- The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word (e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs) are not considered correct responses.
• Patients often give both a verb and a word derived from the verb or adjective (e.g., fun-funny; sad-sadness). These are not considered correct responses. On the other hand, if the word refers to a specific object (e.g., foot-footstool; hang-hanger), it would be counted as a correct answer.
• Many words have two or more meanings (e.g., foot; can; catch; hand). A repetition of the word is acceptable if the patient definitely indicates the alternative meaning to you.
• Slang terms are OK if they are in general use.
• Foreign words (for example, pasta; passé; lasagna) can be counted as correct if they can be considered part of the lexicon of the relevant language, the criterion being their listing in a standard dictionary of that language. All incorrect and repeated responses MUST be crossed out with one single line, initialed and dated. Additionally, all duplicate entries that have been verified to have different meanings must be marked “ok”, initialed and dated. Refer to the descriptions above for guidelines for acceptability. Add the total number of correct responses in each column and input the totals where indicated on the COWA worksheet.
• If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Tests Discontinued/Not Done CRF.

4. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

Part B – Delayed Recall

- **DO NOT READ THE WORD LIST AGAIN.**
- Record the time on the clock that you start ‘Part B – Delayed Recall’ (for example, 10:20am) on the designated space on the HVLT-R form.
- Administer ‘Part B – Delayed Recall’ after completing all Trail Making Tests and the COWA. There should be at least 20 minutes between ‘Part A’ and ‘Part B’ of the HVLT-R. If the time is too short, allow the patients to complete a questionnaire.

Examiner: “**Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember.”**

- Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.
- If a word is said that is not in the list (for example, “intrusion”), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, record the number of words that were correctly recalled on the summary form.

Part C – Delayed Recognition

Examiner: “**Now I’m going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I’d like you to say “Yes” if it was on the original list or “No” if it was not. Was [word] on the list?”**

- Read the words from the top of the columns down.
- Check either the “Y” (Yes) or “N” (No) box next to each word to indicate the patient’s response.
- Guessing is allowed.
- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Tests Discontinued/Not Done CRF.
- The score for this portion of the HVLT-R is the number of list words (i.e., words that in CAPS) correctly identified (“yes” response) minus the number of non-list words (i.e., words in lower case) incorrectly identified (“yes” response). Therefore, the actual score can range from –12 (no list words identified and all non-list words identified) to +12 (all list words identified and no non-list words identified).
APPENDIX VII (3/28/08) (6/17/08)
Certification Worksheet for Test Administrator

RTOG 0614
A RANDOMIZED, PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF MEMANTINE FOR PREVENTION OF COGNITIVE DYSFUNCTION IN PATIENTS RECEIVING WHOLE-BRAIN RADIOTHERAPY

This worksheet must be completed and signed by the person requesting certification and submitted to Drs. Meyers/Dr. Wefel prior to the registration of any patients to RTOG 0614. Refer to protocol Section 11.2 for details.

1. Have you reviewed the Administration Procedures for the Neurocognitive Test Battery in Appendix VI of the protocol?
   (Y) ____________

2. Have you watched the Neuropsychological Test Administration video?
   (Y) ____________

3. Have you completed and submitted the post test associated with the training video and a “practice” Neuropsychological Assessment (See Section 11.2)?
   (Y) ____________

__________________________________________
Signature of test administrator
(person who read Appendix VI, watched video and completed a “practice” Assessment)

__________________________________________
Date

__________________________________________
Printed name of test administrator

__________________________________________
Institution number/Name

__________________________________________
Telephone number of test administrator

__________________________________________
Fax number of test administrator

If you have any questions regarding the certification, please contact Dr. Meyers or Dr. Wefel. Once you have completed this form, please attach both the Neuropsychological Assessment forms from the “practice” subject and the training video post test and submit to:

Christina A. Meyers, Ph.D.           Jeffrey S. Wefel, Ph.D.
Phone (713) 792-8296               Phone (713) 563-0594
FAX (713) 794-4999           FAX (713) 794-4999
cameyers@mdanderson.org           jwefel@mdanderson.org

For Dr. Meyers’ or Dr. Wefel’s Use Only  (to fax to 215-569-0206, CTSU)

(Y/N) ____________ The above individual has been certified for administering the neurocognitive assessments for this study.

__________________________________________
Signature

__________________________________________
Date
Instructions for use of serum, plasma, or buffy coat collection kit (collected as required by protocol):

This kit includes:
- Ten (10) 1 ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Shipping label(s)

Serum:
- Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “serum”.

Process:
1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. Aliquot a minimum of 0.5 ml serum (optimal 1ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, timepoint collected, and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at –70 to –80°C Celsius.
5. Store serum at –70 to –80°C Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma:
- Using three (3) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “plasma”.

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
3. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot a minimum of 0.5 ml plasma (optimal 1 ml) into each cryovial labeled with RTOG study and case numbers, collection date/time, timepoint collected and clearly mark specimen as “plasma”.
5. Place cryovials into biohazard bag and immediately freeze at –70 to –80°C Celsius.
6. Store plasma at –70 to –80°C Celsius until ready to ship.
7. Ship on dry ice.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Buffy coat:

For a visual explanation of Buffy coat, please refer to diagram below.

- Using one (1) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) “buffy coat”.

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APPENDIX VIII (3/28/08)
RTOG 0614
BLOOD COLLECTION KIT INSTRUCTIONS
APPENDIX VIII (continued)

Process:
1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at room temperature.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is performed.
3. Carefully remove plasma close to the buffy coat and set plasma aside (can be used to send plasma samples – see above instructions).
4. Remove the buffy coat cells carefully and place into cryovials labeled “buffy coat” (it is okay if a few packed red cells are inadvertently collected in the process). Clearly mark the tubes with date/time of collection and timepoint collected.
5. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
6. Store buffy coat samples frozen (-70 to -80° Celsius) until ready to ship.
7. Ship on dry ice.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Shipping/Mailing:
- Ship specimens overnight Monday-Wednesday to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted.
- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and buffy coats together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with dry ice (4-5lbs/2-2.5kg minimum). Ship ambient specimens in a separate envelope/cooler. Place specimen bags into the Styrofoam cooler, and attach shipping label to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.
- For questions regarding collection, shipping or to order a Blood Collection Kit, please contact the RTOG Biospecimen Resource (contact information below).
- All specimens will be shipped as follows:

  **Mailing address:** For all non-frozen materials
  RTOG Biospecimen Resource
  University of California San Francisco
  Campus Box 1800
  1657 Scott Street, RM 223
  San Francisco, CA  94143-1800

  **Courier address (FedEx/ DHL, etc.):** For frozen specimens
  RTOG Biospecimen Resource
  University of California San Francisco
  1657 Scott Street, Room 223
  San Francisco, CA  94115

  **Telephone:** 415-476-RTOG (7864)
  **Fax:** 415-476-5271
  RTOG@ucsf.edu
URINE COLLECTION KIT INSTRUCTIONS

This Kit contains:
- One (1) Sterile Urine collection cup
- Biohazard bags
- Shipping label(s)

Urine Specimens:

Preparation for collecting Urine:
- A clean catch urine specimen will be collected.

Process:
- To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
  - Place the cap on the collection cup and tighten the container. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Label the specimen with the RTOG study and case number, collection date and time, timepoint of collection, and clearly mark specimen as "urine".
- If available, use parafilm to seal the cap of the urine cup and to prevent leakage.
- Place urine cup into biohazard bag and seal the bag.
- Immediately freeze urine sample at -20°C.
- Store specimens frozen at -20°C until ready to ship.

Shipping Instructions for all specimens:

Urine Specimens: Urine cups must be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag). Urine specimens may be sent in batches, if within 30 days of collection. Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (4-5 lbs/2-2.5 mg minimum). Seal the box with plastic tape. All RTOG paperwork should be placed in a plastic bag, sealed, and taped to the outside of the Styrofoam box. Pack the Styrofoam box in a cardboard box. Note: Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box "biohazard".

Send specimens by overnight express to the address below. Specimens only should be shipped Monday through Wednesday to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted. Samples received thawed will be refrozen and held. A notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date, if possible.

Notes:
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag
- Sites must submit the required documentation with specimens. All specimens will be shipped as follows:

Mailing address: For all non-frozen materials
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, RM 223
San Francisco, CA 94143-1800

Courier address (FedEx/ DHL etc.): For frozen specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Telephone: 415-476-RTOG (7864)
Fax: 415-476-5271
RTOG@ucsf.edu
This Kit contains:
- Five (5) 5mL vials
- Parafilm
- Biohazard bags
- Shipping label(s)

Cerebrospinal Fluid (CSF) Specimens:
Preparation for collecting CSF:
- A sterile CSF specimen will be collected according to individual site protocol.

Processing
- After CSF specimen has been obtained, use the following instructions:
  - Aliquot CSF using a sterile pipette into 5 different 5mL vials, each containing a minimum of 1mL
  - If CSF is already frozen, perform a controlled thaw and aliquot specimens according to above instructions. Indicate on paperwork if specimen had to be thawed/refrozen.
- Label the specimens with the RTOG study and case number, collection date and time, and clearly mark specimen as “CSF”.
- If available, use parafilm to seal the aliquots and to prevent leakage.
- Place CSF aliquots into biohazard bag and seal the bag.
- Immediately freeze specimens at -20ºC or lower.
- Store specimens frozen at -20ºC or lower until ready to ship.

Shipping Instructions for all specimens:

CSF Specimens: Specimens should be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag). Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (4-5 lbs/2-2.5 kg minimum). Seal the box with plastic tape. All RTOG paperwork should be placed in a plastic bag, sealed, and taped to the outside of the Styrofoam box. Pack the Styrofoam box in a cardboard box. Note: Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box “biohazard”.

Send specimens by overnight express to the address below. Specimens only should be shipped Monday through Wednesday to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted. Samples received thawed will be refrozen and held. A notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date, if possible.

Notes:
- Sites must submit the required documentation with specimens. All specimens will be shipped as follows:
  - Mailing address: For all non-frozen materials
    RTOG Biospecimen Resource
    University of California San Francisco
    Campus Box 1800
    1657 Scott Street, RM 223
    San Francisco, CA 94143-1800
  - Courier address (FedEx/ DHL etc.): For frozen specimens
    RTOG Biospecimen Resource
    University of California San Francisco
    1657 Scott Street, Room 223
    San Francisco, CA 94115

  - Telephone: 415-476-RTOG (7864)
  - Fax: 415-476-5271
  - RTOG@ucsf.edu