NRG ONCOLOGY
NRG-CC003
(ClinicalTrials.gov NCT #02635009 (11Aug2017)

RANDOMIZED PHASE II/III TRIAL OF PROPHYLACTIC CRANIAL IRRADIATION WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE FOR SMALL CELL LUNG CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Cancer Research Group; and SWOG.

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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
N/A				

Participating Sites:
☒ U.S.
☒ Canada
☒ Approved International Member Sites

Document History

	Version Date	Broadcast Date
Amendment 5	**July 1, 2022**	**N/A**
Amendment 4	April 13, 2021	N/A
Amendment 3	June 15, 2020	N/A
Amendment 2	February 14, 2019	N/A
Amendment 1	August 11, 2017	September 25, 2017
Activation	September 10, 2015	December 7, 2015
Pre-Activation	September 10, 2015	November 4, 2015

(14-FEB-2019)

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CONTACT INFORMATION (01-JUL-2022)		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: at 1-866-651-CTSU (2878) to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log in with a CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related): Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

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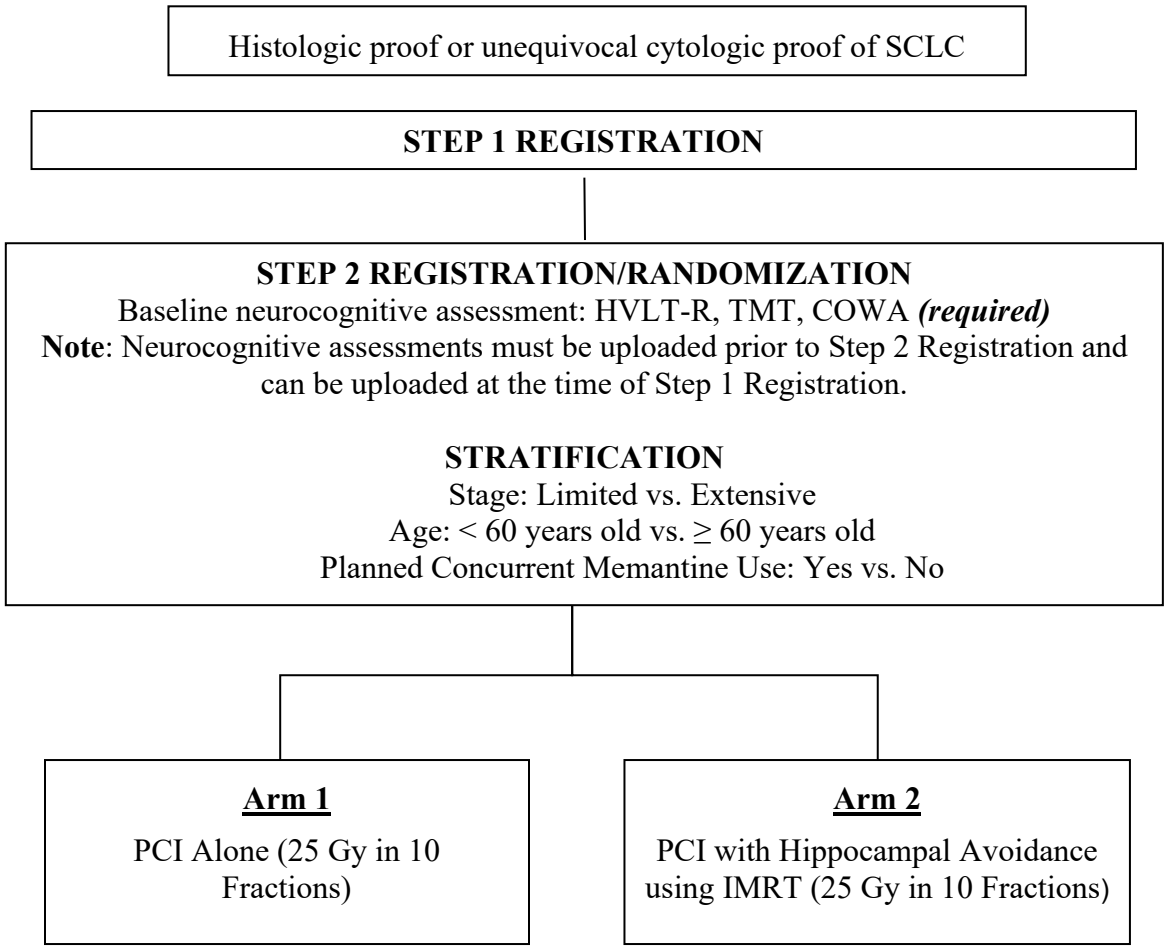
SCHEMA (11AUG2017)



NOTE: If the trial proceeds to the phase III component, all patients enrolled on the randomized phase II component will be included in the primary and secondary endpoint analysis of the phase III component.

1. OBJECTIVES

1.1 Primary Objective (11Aug2017)

1.1.1 *Randomized Phase II Component (Non-Inferiority):* Determine whether the 12-month intracranial relapse rate following HA-PCI is non-inferior to the rate following PCI for patients with SCLC.

1.1.2 *Phase III Component (Efficacy):* Determine whether HA-PCI reduces the likelihood of 6-month deterioration from baseline in HVLT-R delayed recall compared to PCI for patients with SCLC.

1.2 Secondary Objectives (15-JUNE-2020)

1.2.1 Compare time to cognitive failure, as measured by a battery of tests (HVLT-R, COWA test, and TMT Parts A and B), after PCI versus HA-PCI in SCLC.

1.2.2 Compare time to cognitive failure as separately measured by each test (HVLT-R for Total Recall and Delayed Recognition, COWA test, and TMT Parts A and B), after PCI versus HA-PCI for SCLC.

1.2.3 Compare patient-reported cognitive functioning and other quality of life domains (assessed by the EORTC QLQ-C30 and BN20) between PCI versus HA-PCI for patients with SCLC.

1.2.4 Compare overall survival after PCI versus HA-PCI for patients with SCLC.

1.2.5 Compare 12-month intracranial relapse rate (at completion of phase III) and time to intracranial relapse after PCI versus HA-PCI for patients with SCLC.

1.2.6 Evaluate adverse events according to CTCAE criteria.

1.2.7 Correlate changes in HRQOL domains with changes in cognitive testing outcomes following PCI versus HA-PCI for patients with SCLC.

1.2.8 Assess cost-effectiveness of HA-PCI (MRT) and PCI (3DCRT) using the EuroQOL-5D health state classification (EQ-5D-5L).

1.2.9 Correlate miRNA signatures with cognitive failure in SCLC patients who received PCI and HA-PCI

1.2.10 Evaluate APOE genotyping as potential predictor of neurocognitive decline, hippocampal atrophy after brain irradiation and/or differential benefit from hippocampal avoidance.

1.2.11 Evaluate baseline MR imaging biomarkers of white matter injury and hippocampal volumetry as potential predictors of cognitive decline and differential benefit from HA-PCI as compared to PCI.

1.3 Exploratory Objectives (01-JUL-2022)

1.3.1 Collect serum and whole blood for future translational research analyses.

1.3.2 Compare levels of hopefulness between PCI versus HA-PCI for patients with SCLC.

1.3.3 Feasibility of remote neurocognitive testing.

2. BACKGROUND

2.1 Rationale for Proposed Study

Cognitive Effects of Prophylactic Cranial Irradiation

Intracranial failure is a frequent problem in patients with small cell lung cancer (SCLC) (Hochstenbag 2000). The burden of brain metastases impacts on quality and length of survival. Multiple clinical trials of prophylactic cranial irradiation (PCI) in patients with

limited-stage SCLC (LS-SCLC) (Auperin 1999) and extensive stage SCLC (ES-SCLC) (Slotman 2007) have consistently shown a reduction in the incidence of brain metastases and a prolongation in survival with the use of PCI. These data provide compelling evidence for the use of PCI in SCLC.

However, a potential adverse effect of PCI can be cognitive toxicity. In a recent international phase III trial of standard-dose versus high-dose PCI for LS-SCLC (Le Pechoux 2009), patients from North America enrolled through the RTOG (RTOG 0212) underwent evaluation for cognitive toxicity and quality of life effects. Compared to patients receiving standard-dose PCI, patients receiving higher-dose PCI arms were found to have a 25% increase in the rate of chronic cognitive toxicity (Wolfson 2011). However, even among the patients receiving standard-dose PCI, 62% (95% confidence interval 50-74%) developed cognitive toxicity, with a 68% relative increase in the percentage of patients experiencing decline in memory function, assessed by the Hopkins Verbal Learning Test (HVLT) delayed recall. These data suggest that even standard-dose PCI is associated with relatively high rates of cognitive toxicity. Similar findings have been reported with the use of PCI for locally advanced non-small cell lung cancer. RTOG 0214 was a phase III comparison of PCI versus observation in patients with locally advanced non-small-cell lung cancer. Despite not reaching target accrual, this trial also demonstrated a significantly greater decline in HVLT total recall and delayed recall in the PCI arm at 3, 6, and 12 months follow-up (Sun 2011).

Observations of cognitive decline after PCI appear similar to those seen after whole-brain radiotherapy (WBRT) for brain metastases. Li, et al (2007) published a detailed analysis of the time course of cognitive decline in 8 prospectively measured domains in 208 brain metastases patients treated with 30 Gy of WBRT. They observed memory-related cognitive domains, specifically HVLT Total recall and delayed recall, as weakly associated with tumor reduction and most susceptible to early decline, even in patients with non-progressive brain metastases. Further evidence of the susceptibility of memory to cranial irradiation was recently demonstrated by Chang and colleagues (2009). They reported a single-institution phase III trial of stereotactic radiosurgery (SRS) with or without WBRT in patients with 1 to 3 brain metastases, with the principal objective of comparing cognitive decline between the 2 arms. Utilizing the HVLT-Revised (HVLT-R) as a cognitive metric for learning and memory, their study was halted early due to an interim observation of a 2-fold increase in the mean probability of HVLT-R Total Recall deterioration at 4 months (49%, SRS+WBRT, vs. 23%, SRS alone).

The sum of these PCI and WBRT findings suggests that memory-related cognitive domains may be differentially sensitive to the effects of cranial irradiation and that strategies meant to preserve these susceptible cognitive domains warrant further investigation.

Rationale for Hippocampal Avoidance during PCI

Emerging evidence suggests that the pathogenesis of radiation-induced cognitive deficit may involve radiation-induced injury to proliferating neuronal progenitor cells in the subgranular zone of the hippocampus (Mizumatsu 2003, Raber 2004). It has been found

that relatively small doses of radiation cause apoptosis in the subgranular zone of young rats and mice (Ferrer 1993, Nagai 2000, Mizumatsu 2003). On the other hand, little to no apoptosis is observed in other areas of the cerebrum (Nagai 2000). In particular, it has been noted that irradiation causes a sharp and prolonged decline in neurogenesis in the subgranular zone (Ferrer 1993, Abayomi 1996, Peissner 1999, Nagai 2000, Tada 2000, Monje 2002, Madsen 2003). Clinical studies suggest that radiation-induced damage to the hippocampus plays a considerable role in the cognitive decline of patients. In particular, deficits in learning, memory, and spatial processing observed in patients who have received cranial irradiation are thought to be related to hippocampal injury (Roman 1995, Abayomi 1996).

Moreover, irradiation of the hippocampus has been associated with pronounced cognitive impairment in the learning and memory domain in patients receiving radiation therapy for nasopharyngeal tumors (Lee 1989, Leung 1992), maxillary tumors (Sakata 1993), pituitary tumors (Grattan-Smith 1992), and base of skull tumors (Meyers 2000). In a recent study from our research group, patients treated with cranial irradiation for low-grade or benign brain tumors were prospectively evaluated with a battery of cognitive function tests up to 18 months post-treatment, and potential correlations between radiation dose to the hippocampus and cognitive function were assessed (Gondi 2013). In this analysis, a significant dose-response relationship was established, with dose to 40% of the hippocampus predicting an 18-fold increased risk of subsequent decline in a memory test similar to HVLT.

Monje and colleagues (2002) found that radiation injury to the hippocampus in Fisher 344 rats leads to structural alterations of the microenvironment of the "stem cell niche" of the hippocampus that regulates progenitor-cell fate; one consequence of this is decreased neurogenesis. Monje and colleagues (2003) went on to show that neurogenesis is inhibited by inflammation in the area surrounding the stem or progenitor cells. This inhibition occurred whether the inflammation was induced by radiation injury or by bacterial lipopolysaccharide. Hence, inflammatory injury of the hippocampus putatively represents a possible mechanism for the domain-wise differential effect in cognitive function, as well as the temporal sequence of events, following PCI.

We propose to use intensity modulated radiotherapy (IMRT) to conformally avoid the hippocampal region during PCI (HA-PCI) to reduce the dose to the hippocampus, thereby putatively limiting the radiation-induced inflammation of the hippocampal region and subsequent alteration of the microenvironment of the neural progenitor cells. We hypothesize that HA-PCI may delay or reduce the onset, frequency, and/or severity of cognitive decline, as measured with clinical cognitive tools.

<u>Feasibility and Preliminary Results of Hippocampal Avoidance</u>

HA-PCI poses important challenges in conformally avoiding the centrally located hippocampus, with its unique anatomic shape, while allowing for uniform dose delivery to the remainder of the brain. We have developed novel techniques to achieve HA-PCI using multiple IMRT delivery systems widely available at multiple academic and community radiation oncology practices. In recent dosimetric analyses, we and other

institutions have demonstrated the ability of these IMRT techniques to reduce mean dose received by the hippocampus by at least 80%, while providing acceptable coverage and homogeneity of radiotherapy to the remaining whole brain parenchyma (Gondi 2010, Hsu 2010). In addition, we have disseminated knowledge and provided experience with these techniques through RTOG 0933, a completed phase II trial of hippocampal avoidance during WBRT for brain metastases. In addition to accruing 113 patients in 19 months, this trial built a technological infrastructure at RTOG to credential 113 physicians and 84 RTOG sites spanning community, academic, and international institutions in the techniques of hippocampal contouring and hippocampal avoidance treatment planning.

As a single-arm phase II study with a pre-specified statistical comparison to a historical control of brain metastasis patients treated with WBRT without hippocampal avoidance, RTOG 0933 sought to provide preliminary observations on the potential cognitive benefit of hippocampal avoidance in the setting of WBRT for brain metastasis. This study successfully completed accrual in November 2012. The primary endpoint of RTOG 0933 was mean relative decline in HVLT-R delayed recall score from baseline to 4 months, defined as follows $\Delta HVLT_i = \frac{HVLT_B - HVLT_F}{HVLT_B}$, where B=baseline and F=follow-up with a positive change indicating a decline in function. Based upon historical control data of 30% mean relative decline in HVLT-R Delayed Recall at 4 months compared to baseline in patients treated with WBRT without hippocampal avoidance, RTOG 0933 hypothesized that hippocampal avoidance during WBRT would lead to a 50% relative improvement over historical control, with a mean relative decline of 15% or less.

RTOG 0933 demonstrated that hippocampal avoidance during WBRT was associated with a mean relative decline in HVLT-R Delayed Recall score from baseline to 4 months of **7.0%** (95% confidence interval (CI): -4.7% to 18.7%), which was highly significant in comparison to the historical control (p=0.0003) (Gondi 2014). The memory preservation benefit of hippocampal avoidance was maintained at 6 months follow up, with a mean relative decline in HVLT-R Delayed Recall score from baseline to 6 months of **2.0%** (95% CI: -9.2% to 13.1%). Similar memory preservation also was observed in the remaining HVLT-R domains. For instance, probability of HVLT total recall deterioration (defined as > 5 point drop in Total Recall score from baseline to follow-up assessment) was 19% at 4 months after HA-WBRT, which compared favorably to the 49% rate following SRS+WBRT in the Chang et al. study (Chang 2009) and 13.8% at 6 months after HA-WBRT, which compared favorably to the 28.6% rate following WBRT + memantine in RTOG 0614 (Brown 2013).

In addition to HVLT, RTOG 0933 included other assessments of memory function, including verbal learning memory (International Shopping List Task) and visuo-perceptual and spatial learning and memory (One Card Learning Test), both of which demonstrated no significant change from baseline following HA-WBRT (Caine 2014). HA-WBRT also was associated with preservation of patient-reported quality of life, assessed using the Functional Assessment of Cancer Therapy and its validated brain subscale and the Barthel Activities of Daily Living (Gondi 2014). Review of survival outcomes for RTOG 0933 found no difference in median PFS (5.9 months) and OS (6.8 months) compared to historical controls. Two grade 3 toxicities of fatigue and headache

were observed; there were no grade 4 or higher toxicities. Three patients (4.5%) experienced progression in the hippocampal avoidance region after HA-WBRT. This 4.5% risk of hippocampal/perihippocampal relapse was lower than prior published estimates of 8.6% (95% CI 5.7-11.5%) (Gondi 2010).

2.2 Significance of the Study (11Aug2017)

In spite of clinical evidence demonstrating an overall survival benefit from PCI (Auperin 1999, Slotman 2007), a recent study demonstrated that **40% of eligible LS-SCLC patients do not receive PCI** (Wu 2013). Concerns about cognitive toxicity from PCI—on the part of both patient and physician—were found to be the primary reasons for not receiving PCI, underscoring the importance of studying novel approaches to mitigating PCI-associated cognitive toxicity. Building upon extensive preclinical and clinical data supporting the memory-specificity and radiosensitivity of the hippocampal neural stem cell compartment, RTOG 0933 demonstrated **highly promising** memory-preservation results with the application of IMRT techniques to conformally avoiding the hippocampus during cranial irradiation. We propose a randomized study that addresses, in a placebo-controlled trial of SCLC patients receiving PCI, the hypothesis that hippocampal avoidance may prevent radiotherapy-induced memory toxicity.

2.3 Risk of Relapse in the Hippocampal Avoidance Region

The potential risk of attenuating the benefit of PCI due to the development of metastatic disease within the hippocampal avoidance region following HA-PCI for SCLC requires better definition, as such a comprehensive data set does not exist. Prior assessments of SCLC patients presenting with brain metastases have observed a 4.8%-10.5% incidence of brain metastases within the hippocampal avoidance region (Gondi 2010, Kundapur 2013). If we assume that the risk of developing brain metastasis in the hippocampal avoidance region scales in the same proportion as that at presentation, these data suggest that the absolute increase in risk of intracranial relapse following HA-PCI may be 10% or less. The Auperin meta-analysis of PCI trials for SCLC (Auperin 1999) demonstrated an overall survival benefit associated with a 23% absolute reduction in 12-month intracranial relapse rate with PCI as compared to no PCI. Given the effectiveness of salvage radiosurgery for intracranial relapse in SCLC (Wegner, Olson, et al. 2011; Serizawa, Ono, et al. 2002), should HA-PCI be associated with an elevated risk of intracranial relapse, we hypothesize that this risk will be sufficiently small so as to not compromise the established survival benefit of PCI for SCLC.

2.4 Proposed Seamless Randomized Phase II/III Study Design

To reliably address the objectives of both intracranial relapse and prevention of memory toxicity with HA-PCI, we propose a seamless randomized phase II/phase III study of PCI versus HA-PCI for patients with SCLC. With a primary endpoint of 12-month intracranial relapse risk, the phase IIR component will be designed as a non-inferiority study to determine if the relapse risk following HA-PCI is not inferior to that following PCI. If the pre-specified non-inferiority margin is not exceeded, then the trial will reactivate and transition to the phase III efficacy component, in which the cognitive function outcomes of patients enrolled on the phase IIR component will be utilized for

the primary endpoint analysis of the phase III trial. The primary endpoint of the phase III component will be HVLT-R delayed recall at 6 months post-treatment.

Structuring the proposed study as a seamless phase IIR/III design provides the following advantages:

1) An overall sample size of 304 randomized SCLC patients for this phase IIR/III remains feasible;
2) The use of concurrent rather than historical controls permits more accurate comparison of both phase IIR and phase III endpoints;
3) The trial closure when the phase IIR component reaches accrual provides sufficient follow-up time to assess 12-month intracranial relapse risk before proceeding with the phase III component;
4) Utilization of the cognitive outcomes data from the phase IIR component to address the phase III primary and secondary endpoints limits overall sample size, while providing greater power for the phase III endpoints.

To remain consistent with the memory-specific toxicity of cranial irradiation observed in prior clinical trials and memory-specific benefits of hippocampal avoidance demonstrated in RTOG 0933, this proposed phase IIR/III study will utilize HVLT-R, the same memory-specific measurement tool used in prior studies, as the primary endpoint of the phase III component.

HVLT-R incorporates 6 different forms, helping to mitigate practice effects of repeated administrations. Each form includes 12 nouns (targets) with 4 words drawn from 3 semantic categories, which differ across the 6 forms. The test involves memorizing a list of 12 targets for 3 consecutive trials (immediate recall), recalling the 12 targets after a 20-minute delay (Delayed Recall), and then identifying the 12 targets from a list of semantically related or unrelated items (delayed recognition). Raw scores are derived for total recall, delayed recall, and a delayed recognition discrimination index. Each patient will serve as her/his own control, as the difference in HVLT-R scores obtained at baseline and post-treatment intervals will be calculated with the Reliable Change Index (RCI) to define deterioration (Jacobsen 1991).

Other cognitive instruments, including the Controlled Oral Word Association (COWA) and the Trail Making Test (TMT) Parts A and B, also will be used to complement HVLT-R in defining the secondary endpoint of time to cognitive failure. This battery of instruments has been selected based on accepted standardization and psychometric principles, published normative data relative to routine demographics, relevance to general cognitive status, minimal practice effects, and brevity of the overall battery. Additionally, similar variations of this cognitive testing battery have been utilized in multiple cooperative group trials.

2.5 Translational Research: (15-JUNE-2020)

2.5.1 Comprehensive miRNA profiling of serum in limited stage small cell lung cancer patients undergoing PCI or HA-PCI for detection of biomarkers for cognitive decline

MicroRNAs (miRNAs) are short, non-coding RNA sequences and have been presented as potential biomarkers of neurodegenerative diseases in blood in the recent years (Danborg 2014). A recent twin study of circulating miRNAs in healthy individuals has shown that an epigenetic miRNA signature can be detected in serum of individuals with cognitive decline compared to genetically matched controls (Mengel-From 2018). Additionally, previous studies have linked circulating miRNAs to cognitive decline in Alzheimer's patients (Fransquet 2018). This study will seek to determine as a secondary objective whether miRNAs can be utilized as potential biomarkers of cognitive decline following HA-PCI vs. PCI.

2.5.2 Apolipoprotein E (APOE)

Genomic DNA will be extracted from 400 µL peripheral blood by using the blood DNA extraction kit (TIANGEN) according to the manufacturer's instructions. DNA will be diluted with nuclease free water to 8 ng/µL for *APOE* genotyping analysis. Direct sequencing of APOE will be performed using previously tested primer pairs (16). Cycle sequencing products will be run on an ABI 3730 XL DNA analyzer and the resultant chromatograms will be analyzed with FinchTV v1.4 (Geospiza, Seattle, WA). Insufficient DNA amplification can result from low concentrations of DNA or impure DNA. This will be corrected with re-extraction and/or re-purification of DNA. Positive controls will be added at the beginning and end of each plate of samples.

The APOE gene encodes for APOE and is located on chromosome 19. ApoE is involved in the uptake, transport and distribution of lipid, is expressed at high levels in the brain, and is believed to play an important role in neuronal repair and synaptic function (1, 2). APOE is polymorphic and has three major alleles, APOE2, APOE3, APOE4. The E4 allele has been associated with cognitive dysfunction after damaging events such as cardiac bypass surgery (3) and traumatic brain injury (4, 5). Additionally, testing of middle-aged E4 carriers reveals cognitive difficulties (6). Finally, the E4 allele is an established risk factor for Alzheimer's dementia (7). Data suggest that patients having the APOE4 isoform realize Alzheimer's dementia far earlier than those without it (8).

Preclinical studies have demonstrated an association between APOE4 and hippocampal neurogenesis and function. In one study, neurogenesis in the hippocampal dentate gyrus was studied in transgenic mice expressing APOE4 or APOE3 in the setting of environmental stimulation. Environmental stimulation increased neurogenesis in the dentate gyrus of APOE3-transgenic and wild-type mice, but triggered apoptosis in the dentate gyrus of APOE4-transgenic mice. These APOE-dependent effects on neurogenesis were specific to the hippocampal dentate gyrus and were not observed in the subventricular zone (9). Hippocampal responses to "negative" stimuli such as traumatic brain injury or irradiation also demonstrated similar APOE-dependence. In a

microarray analysis, Crawford et al. observed genomic changes consistent with a loss of reparative function and impaired neurogenesis in the hippocampus of APOE4-transgenic mice, compared to APOE3-transgenic mice (10). Villasana and colleagues irradiated APOE2-, APOE3-, and APOE4-transgenic mice and assessed hippocampal-dependent spatial learning and memory tasks. Irradiated APOE4-transgenic mice performed poorly on hippocampal-dependent tasks relative to sham-irradiated APOE4-transgenic mice and to all other transgenic mice (11). These preclinical data suggest that APOE4 plays a critical role in neurogenesis within the hippocampal dentate gyrus and in hippocampal-dependent memory function.

In clinical studies, APOE4 allele status has been linked with rates of progressive hippocampal atrophy, which in turn has been demonstrated to be a sensitive marker of early Alzheimer's dementia and predictive of cognitive decline. In one study by Mori and colleagues (12), 55 patients with probable Alzheimer's disease were followed with serial annual MRI scans. The status of the APOE4 allele significantly correlated with the rate of hippocampal atrophy, implicating APOE4 allele status as relevant to the progression of hippocampal atrophy in the setting of Alzheimer's dementia. Similar findings were observed by Van der Pol and colleagues in patients with mild cognitive impairment (13).

RTOG 0614 treated adult patients with brain metastases with 37.5 Gy of WBRT (+/- memantine), performed neurocognitive function testing at baseline, 8, 16, 24, and 52 weeks, and included an optional blood draw for APOE genotyping. APOE results were available for 45% (n = 227/508) of patients. No pretreatment differences were detected between patients with APOE available versus not available. Preliminary analysis demonstrated that 29.5% of brain metastasis patients receiving WBRT had one or more APOE4 alleles (14). Mixed effects modeling showed that APOE4 allele carriers exhibited greater declines in episodic memory as assessed by the HVLT-R total recall (Figure 1, p=0.0081), immediate recall (p=0.0382), and delayed recognition (p=0.0265), executive functioning as assessed by Trail Making Test Part B (p=0.021), and the summary neurocognitive Clinical Trial Battery Composite score (Figure 2, p=0.0254) after WBRT. A study by Correa et al (15) of patients with glioma found approximately the same distribution of patients (30%) with APOE4 alleles. As with our preliminary work, their findings suggest that glioma patients treated with brain irradiation may experience worsening in attention and executive functions several years after treatment, and that the APOE4 allele may modulate cognitive decline.

This study will validate these preliminary findings using centrally collected blood and serum specimens. This trial offer a unique opportunity to determine if the individual risk of neurocognitive toxicity following WBRT with or without hippocampal avoidance can be determined based on APOE genotyping and/or serum APOE levels. Using blood specimens, APOE genotyping will be performed to assess whether a subgroup of patients exists that is genetically predisposed to developing neurocognitive decline and/or differential neuroprotection from hippocampal avoidance. Another objective on this trial is hippocampal volumetric changes from pre- to post-treatment using centrally collected MR imaging and these changes will bed correlated with APOE genotyping.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

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

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception during the therapy (PCI alone or PCI with hippocampal avoidance) part of the trial.

3.1.3 Submission of serum and whole blood is strongly encouraged for all patients. Samples will be submitted for banking for the translational research portion of this protocol and for future studies. (See Section 10 for further details).

3.2 Eligibility Criteria (13-APR-2021)

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

Prior to Step 1 Registration

3.2.1 Histologic proof or unequivocal cytologic proof (fine needle aspiration, biopsy or two positive sputa) of SCLC within 250 days prior to Step 1 registration;

- High-grade neuroendocrine carcinoma or combined SCLC and NSCLC is permitted.

3.2.2 Patients must have received chemotherapy and be registered to Step 1 registration no earlier than 7 days and no later than 56 days after completing chemotherapy. **Note:**

- Post-chemotherapy restaging imaging must be completed no more than 56 days prior to Step 1 registration.
- For patients with extensive-stage small cell lung cancer who are being considered for consolidative thoracic radiotherapy after chemotherapy, concomitant administration of consolidative thoracic radiotherapy and protocol-specified prophylactic cranial irradiation with or without hippocampal avoidance is permitted.

3.2.3 Patients must have a gadolinium contrast-enhanced three-dimensional (3D), spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan (see section 11.3 regarding axial T2/FLAIR sequence). To yield acceptable image quality, the gadolinium contrast-enhanced three-dimensional SPGR, MP-RAGE or TFE axial MRI scan must use the smallest possible axial slice thickness not exceeding 1.5 mm. Sites may contact the Imaging Co-Chairs for further information or assistance if needed.

- This MRI must be obtained within 56 days prior to Step 1 registration.

Note: The MRI study is mandatory irrespective of randomization to the experimental or control arm of this study.

3.2.4 Prior to chemotherapy +/- thoracic radiotherapy, patients must be defined as limited-stage or extensive-stage SCLC after clinical staging evaluation involving the following:
a. History/physical examination;
b. CT of the chest and abdomen with contrast (does not have to be done if the patient has had a PET/CT scan prior to initiating chemotherapy or thoracic radiotherapy);
c. MRI of the brain with contrast or diagnostic head CT with contrast;
d. For patients without evidence of extensive-stage SCLC on chest and abdomen CT and brain MRI or head CT, a PET/CT or bone scan is required to confirm limited-stage SCLC.

3.2.5 After chemotherapy, patients must be restaged prior to Step 1 registration using the same diagnostic work-up as required pre-chemotherapy (see Section 3.2.4). Repeat PET/CT or bone scan is not required. Patients must have:
- History/physical examination within 30 days of Step 1 registration;
- No CNS metastases (Repeat MRI required; see Section 3.2.3 for details) within 56 days prior to Step 1 registration;
- No progression in any site;
- Radiographic partial or complete response to chemotherapy in at least one disease site within 56 days prior to Step 1 registration.
    - If PET/CT was obtained prior to chemotherapy, either a repeat PET/CT or CT of the chest and abdomen with contrast can be obtained for response assessment.
    - Patients who underwent resection for limited-stage SCLC prior to chemotherapy and have no radiographically evident disease for response assessment remain eligible if post-chemotherapy imaging demonstrates no progression.

3.2.6 Zubrod performance status 0-2 within 30 days prior to Step 1 registration;

3.2.7 Age ≥18;

3.2.8 Women of childbearing potential must have a negative qualitative serum pregnancy test ≤ 14 days prior to Step 1 registration.

3.2.9 Patients who are primary English or French speakers are eligible.

3.2.10 Patients must sign a study-specific informed consent prior to study entry.

<u>Prior to Step 2 Registration</u>

3.2.11 The following baseline neurocognitive assessments must be completed and uploaded within 10 calendar days after or at the time of Step 1 registration: HVLT-R (recall, delayed recall, and recognition), TMT (Parts A and B), and COWA. The neurocognitive assessments will be uploaded into the NRG Oncology RAVE System for evaluation by Dr. Wefel. Once the upload is complete, within 3 business days, a notification email will be sent to the site to proceed to Step 2 registration. At minimum, the HVLT-R delayed recall must be able to be scored (i.e. completed without error) in order to be eligible.

3.2.12 Patients must have a baseline raw score greater than 2 on the HVLT-R Delayed Recall, as determined by central assessment by the Neurocognitive Co-Chair, Dr. Wefel.

3.3 Ineligibility Criteria (14-FEB-2019)

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

3.3.1 Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields;

3.3.2 Radiographic evidence of CNS metastases;

3.3.3 Radiographic evidence of hydrocephalus or other architectural distortion of the ventricular system, including placement of external ventricular drain or ventriculoperitoneal shunt;

3.3.4 Planned concurrent chemotherapy during PCI;

- Concurrent atezolizumab permitted

3.3.5 Concomitant invasive malignancy or invasive malignancy within the past five years other than non-melanomatous skin cancer; history of *in situ* carcinoma (e.g. ductal carcinoma *in situ* of breast, *in situ* carcinoma of the cervix, vulva or larynx) is permitted**.**

3.3.6 Contraindication to MR imaging, such as implanted metal devices or foreign bodies or severe claustrophobia;

3.3.7 Severe, active comorbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Transmural myocardial infarction within the last 6 months;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- Uncontrolled, clinically significant cardiac arrhythmias;
- HIV positive with CD4 count < 200 cells/microliter;
  - **Note**: Patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to Step 1 registration.
  - **Note**: HIV testing is not required for eligibility for this protocol.

3.3.8 Pregnant or lactating women or women of childbearing potential and male participants who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the radiation treatment involved in this study may be significantly teratogenic.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (01-JUL-2022)

PRE-TREATMENT ASSESSMENTS

Prior to *Step 1* Registration *(calendar days; may also be required for eligibility)*	
Histo/cyto proof of SCLC	250
History/physical examination	30
Restaging imaging, per Section 3.2.5	56
MRI of the brain Thin slice MRI required as outlined in Section 3.2.3	56
Zubrod performance status	30
Serum pregnancy test, *(if applicable)*	14
Prior to *Step 2* Registration*(calendar days)*	
Baseline neurocognitive: HVLT-R, TMT, COWA ***(upload required to proceed to Step 2)***	7 (and within 10 days after or at time of Step 1 registration)
English or French must be the patient's primary language.	
Intention to use memantine concurrently with PCI or PCI with hippocampal avoidance	
Prior to Start of Treatment	
QOL: EORTC QLQ-C30 , BN20, AHS, and PHQ 2 (Must be completed in hard-copy)	
Cost-Effectiveness: EQ-5D-5L and WPAI Questionnaire. Patient diary must be given to patient prior to start of treatment.	
Whole blood and serum collection *(If patient consents)*	

ASSESSMENTS IN FOLLOW UP

Assessments	From start of PCI or HA-PCI:	
	At 3, 6, 12, 18 and 24 months	**q3 months until 12 months; q6 months until 3 years; thereafter annually until death**
History/physical examination		X
Zubrod performance status		X
Brain MRI w/ contrast or head CT with contrast Thin slice MRI (as outlined in Section 3.2.3) is not required in follow up		X
Required Neurocognitive: HVLT-R, COWA, TMT	X	
QOL: EORTC QLQ-C30, and BN20 (Can be completed online)*	X	
QOL: AHS and PHQ 2 (Can be completed online)*	At 6 months	
Cost-effectiveness: EQ-5D-5L*, Work Productivity & Activity Impairment (WPAI) Questionnaire and health resource utilization diary (The first diary must be given to patient prior to start of RT and is due at the end of RT. The next patient diary must be given to the patient when the previous diary is collected.)	At end of RT, 6, 12, and 24 months	
Serum collection *(If patient consents)*	At 3, 6, 12, and 18 months from start of PCI or HA-PCI	

***Note**: Patients have the option of completing quality of life (QOL) forms online from any location, including home, via VisionTree Optimal Care (VTOC) (see **Section 11.2** for details).

Definition of Disease Assessments

Intracranial relapse is defined as the development of a new brain metastasis as documented on brain MRI with contrast or head CT with contrast.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy (15-JUNE-2020)

Concurrent use of memantine is permitted but not required (see Section 5.4.1). Otherwise, no chemotherapy, hormonal therapy or other agent-based therapy will be permitted during or within 7 days before or after PCI or PCI with hippocampal avoidance except for atezolizumab as outlined in Section 3.3.4.

5.2 Radiation Therapy (15-JUNE-2020)

Protocol treatment must begin within 28 calendar days after randomization.

NOTE 1: Patients only can be enrolled by treating institutions that have passed pre-enrollment benchmark cases for HA-PCI treatment planning and that have at least one treating physician who has passed pre-enrollment benchmark cases for hippocampal contouring (credentialed physician). Each institution can have at most two credentialed physicians. Treating institutions and physicians credentialed for NRG-CC001 or RTOG 0933 also will be credentialed for NRG-CC003, since benchmark cases are similar between these trials. See Section 8.3 for further details.

NOTE 2: While credentialing has been limited to 2 physicians per institution, there is no limit on the number of physicians who can enroll patients. Any physician can accrue patients and develop the hippocampal contours and hippocampal avoidance IMRT plan (should the patient be randomized to the experimental arm). If a non-credentialed physician enrolls a patient, then a credentialed physician at the same site must review the contours/plan to ensure they meet protocol criteria, and both the treating physician and the reviewing credentialed physician must be entered on OPEN during case registration.

NOTE 3: The first patient enrolled or reviewed by a credentialed physician and institution in Arm 2 (HA-PCI) will require a Pre-Treatment Review. The patient cannot start treatment until they have received approval from the Imaging and Radiation Oncology Core (IROC)-Philadelphia RT. The Pre-Treatment Review process requires 5 business days from the receipt of complete data. If an unacceptable deviation occurs, the next case may require a Pre Treatment Review. See Section 8.3 for specifics on submission requirements.

NOTE 4: Credentialed physicians who have passed one (1) pre-treatment review of a patient enrolled on the hippocampal avoidance arm of NRG-CC001 will be permitted to enroll patients or serve as reviewing credentialed physician for patients enrolled on NRG-CC003 without pre-treatment case review. **Note**: If the institution has not enrolled a case on NRG-CC001, then one pre-treatment review is **required**.

5.2.1 Treatment Technology

This protocol requires photon treatment. 3DCRT is required in Arm 1. Field-in-field approaches to 3DCRT to optimize homogeneity are permitted for Arm 1. Inverse planned IMRT is not allowed for Arm 1. IMRT is required for Arm 2. Fixed-gantry IMRT, helical tomotherapy or VMAT can be used for Arm 2. All participating sites must be credentialed for IMRT.

Megavoltage beam of 6MV or greater must be used for Arms 1 or 2, with a minimum source-axis distance of 100cm. The exception is the use of the helical tomotherapy unit that has a source-axis distance of 85cm.

5.2.2 Immobilization and Simulation

Immobilization

Patients will be immobilized in the supine position using an immobilization device such as an Aquaplast mask over the head. Patients will be treated in the immobilization device.

Simulation Imaging

A non-contrast treatment-planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2.5 mm will be required. For patients enrolled on Arm 2 (HA-WBRT experimental arm), the axial slice thickness of the treatment-planning CT scan must match the MRI axial slice thickness as much as possible. The treatment-planning CT scan must be acquired with the patient in the same position and immobilization device as for treatment. This should be obtained within 28 days prior to initiating treatment.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-up

For Arms 1 and 2: Post-contrast gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) axial MRI scan and axial T2/FLAIR sequence acquisitions.

To yield acceptable image quality, the pre- (if performed) and post gadolinium contrast-enhanced three-dimensional SPGR, MP-RAGE, or TFE axial MRI scan must use the smallest possible axial slice thickness not exceeding 1.5 mm. These imaging sequences should be obtained with the patient in the supine position. The MRI is **required at baseline** as an eligibility criterion for enrollment in the study. Immobilization devices used for CT simulation and daily radiation treatments need not be used when obtaining these imaging sequences, but an attempt should be made to image the patient in as close to the same plane as the CT simulation as possible to facilitate fusion of the MRI and CT images.

Downloading MRI Protocol Documents:

If you don't currently have a three-dimensional SPGR, MP-RAGE, or TFE sequence on your scanner, many acceptable examples are available for download from the Alzheimer's Disease Neuroimaging Initiative (ADNI) *http://adni.loni.usc.edu/methods/documents/mri-protocols.*

Sites should contact the Imaging Co-Chairs for further information or assistance if needed.

Note: The MRI study is mandatory irrespective of randomization to the experimental or control arm of this study.

For Arm 2, the MRI for radiotherapy planning and treatment-planning CT should be fused semi-automatically for hippocampal contouring.

5.2.4 Definition of Target Volumes and Margins

For Arm 1, 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 digitally reconstructed radiograph (DRR) from the CT simulation scan. This flashing accounts for beam penumbra and day-to-day set-up variation.

For Arm 2, the following structures are required and must be named for digital RT data submission as listed in the table below. These structures must be contoured and submitted with the treatment plan. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	Description	Detailed Specification
CTV_2500	CTV to receive 25 Gy	The whole-brain parenchyma to the foramen magnum.
PTV_2500	PTV to receive 25 Gy	The CTV_2500 excluding the hippocampal avoidance region (see Section 5.2.5). No set-up margin is added.

5.2.5 Definition of Critical Structures and Margins

For Arm 1, care should be taken to minimize the dose to the lens. These can be contoured on the simulation CT and visualized on the DRR.

For Arm 2, all structures listed in the table below must be contoured and labeled for digital RT data submission as listed. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated. All structures should be contoured on the planning CT, using the fused MRI for guidance as described below. Due to variance in eye position between the CT and MRI, the lenses and optic nerves should be contoured using the CT dataset only.

Standard Name	Description	Descriptive Details
Hippocampi	Bilateral hippocampal contours	Bilateral hippocampal contours will be manually generated on the fused planning MRI/CT image set by the treating physician according to contouring instructions specified on http://www.rtog.org//corelab/contouringatlases/hippocampalsparing.aspx.
Hippocampi_5mm	Hippocampal avoidance region	Generated by three-dimensionally expanding the hippocampal contours by 5 mm.
Hippo_L	Left hippocampu	Bilateral hippocampal contours will be subdivided into Left and Right hippocampi.

	s	
Hippo_R	Right hippocampus	Bilateral hippocampal contours will be subdivided into Left and Right hippocampi.
Lens_L	Left lens	Due to variance in eye position between the CT and MRI, if possible, the left lens should be contoured using the CT dataset only.
Lens_R	Right lens	Due to variance in eye position between the CT and MRI, if possible, the right lens should be contoured using the CT dataset only.
OpticNerve_L	Left optic nerve	Due to variance in eye position between the CT and MRI, if possible, the left optic nerve should be contoured using the CT dataset only.
OpticNerve_R	Right optic nerve	Due to variance in eye position between the CT and MRI, if possible, the right optic nerve should be contoured using the CT dataset only.
OpticChiasm	Optic chiasm	Located above the pituitary fossa, the optic chiasm includes both anterior and posterior limbs. It is best visualized on SPGR/MPR/TFE T1 MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.

5.2.6 Dose Prescription

For Arms 1 and 2, one treatment of 2.5 Gy will be given daily over approximately 2 weeks for a total of 25.0 Gy (10 fractions). Treatment does not necessarily need to start on a Monday and it is acceptable for treatment to start later in the work-week.

For Arm 1, dose is specified as the target dose, which shall be the dose on the central x-ray at mid-separation for two opposed coaxial equally weighted beams. "Compensating beams" that block hot spots (these hot spots are typically present along midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve better dose homogeneity. All portals shall be treated during each treatment session.

For Arm 2, IMRT plan should be normalized such that 95% of the PTV_2500 volume receives prescription dose of 25 Gy in 10 fractions of 2.5 Gy per fraction. If ≥ 90% of the PTV_2500 volume receives prescription dose of 25 Gy it will be considered Variation Acceptable (See Section 5.2.7).

5.2.7 Compliance Criteria

Arm 1: There are no compliance criteria specific to radiation therapy planning or delivery.

Arm 2: The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do

not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is **required**.

Accuracy of MRI/CT fusion and hippocampal contouring will be assessed subjectively by central physician reviewer. If MRI/CT fusion or hippocampal contouring is not considered acceptable, this will be scored as a Deviation Unacceptable.

NOTE: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.

Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable	Notes
PTV_2500	$D_{2\%}$(Gy)	≤ 31.25 Gy	≤ 33.3 Gy	Dose to hottest 2% of PTV_2500
	$D_{98\%}$(Gy)	≥ 21 Gy	< 21 Gy	Dose to 98% of PTV_2500
	$V25_{Gy}$ (%)	≥ 95%	≥ 90%	Volume receiving prescription dose of 25 Gy

Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Notes
Hippocampi	$D_{100\%}$(Gy)	≤ 7.5 Gy	≤ 8.5 Gy	Dose to 100% of Hippocampus
	D_{max}(Gy)	≤ 13.5 Gy	≤ 15 Gy	Dose to hottest 0.03 cc volume of Hippocampus
OpticNerve_L	D_{max}(Gy)	≤ 25 Gy	≤ 36.0 Gy	Dose to hottest 0.03 cc volume of OpticNerve_L
OpticNerve_R	D_{max}(Gy)	≤ 25 Gy	≤ 36.0 Gy	Dose to hottest 0.03 cc volume of OpticNerve_R
OpticChiasm	D_{max}(Gy)	≤ 25 Gy	≤ 36.0 Gy	Dose to hottest 0.03 cc volume of

				OpticChiasm

Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	Notes
Interruptions	0 break days	1-3 break days	Unscheduled break days

5.2.8 Treatment Planning Procedures and Priorities

Arm 1: Three-dimensional approaches to radiotherapy planning will be used for patients enrolled in the PCI reference arm. There are no treatment-planning priorities.

Arm 2: Intensity-modulated radiotherapy will be used for patients enrolled in the PCI with hippocampal avoidance arm. In optimizing planning, the following treatment-planning priorities should be followed:

1. OpticChiasm
2. OpticNerve_L or OpticNerve_R
3. Hippocampus
4. PTV_2500
5. Lens_L or Lens_R

In the event that an OAR with higher priority than PTV_2500 cannot be constrained within Unacceptable Deviation limits, then D98% and/or V25Gy for PTV_2500 should be lowered to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits.

5.2.9 Dose Calculations

Arm 1: Primary dataset for dose calculation should be non-contrast treatment-planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2.5 mm. Dose matrix grid size must be ≤ 3 mm in sagittal and coronal directions.

Arm 2: Primary dataset for dose calculation should be non-contrast treatment-planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2.5 mm. Dose matrix grid size must be ≤ 3 mm in sagittal and coronal directions.

5.2.10 Patient-specific Quality Assurance (QA)

Arm 1: Patient-specific QA not required but should follow guidelines of enrolling institution.

Arm 2: Patient-specific QA is strongly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 4% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan. These QA data will not be collected but should be held by the institution and available for review if requested.

5.2.11 Daily Treatment Localization/IGRT

Verification orthogonal films or images are required. For all forms of IMRT dose delivery, orthogonal films or images that localize the isocenter placement shall be obtained. The length of the treatment field shall be indicated on these films.

5.2.12 Case Review

Arm 1: No case review will be performed.

Arm 2: Case reviews will be ongoing and performed remotely for all patients enrolled in Arm 2. Case reviews will be conducted by a team of Co-Chairs.

NOTE: The first patient enrolled in Arm 2 from each treating physician and institution will require a Pre-Treatment Review. The patient cannot start treatment until they have received approval from IROC-Philadelphia RT. The Pre-Treatment Review process requires 5 business days from the receipt of complete data. See Section 8.4 for specifics on submission requirements.

5.3 Surgery

Not applicable to this study.

5.4 General Concomitant Medication and Supportive Care Guidelines (11Aug2017)

5.4.1 Use of memantine is optional and left to the discretion of the treating physician.

However, intention to use memantine concurrently with PCI or PCI with hippocampal avoidance **must** be stated at time of Step 2 registration. In determining intention to use memantine, treating physicians would be advised to consult with the patient's pharmacy to determine memantine availability and coverage by the patient's insurance.

Both extended release memantine (Namenda XR) and twice-daily memantine dosing are allowed and should be administered per the package insert (see below). If memantine utilization is intended per the treating physician's discretion, then the treating physician is recommended to start memantine on the same day as PCI/HA-PCI and no later than before the fourth PCI/HA-PCI treatment.

Twice Daily Dosing Memantine

The target dose for memantine is 20 mg (10mg divided twice daily). Dose is escalated by 5 mg per week to target of 10 mg twice daily. Dose modifications are required in the setting of renal insufficiency, and the package insert should be reviewed.

	Daily AM Dose	**Daily PM Dose**
Week 1	5 mg	None
Week 2	5 mg	5 mg
Week 3	10 mg	5 mg
Weeks 4-24	10 mg	10 mg

Patients continue on memantine for 24 weeks.

Extended Release Memantine

The target dose for extended release memantine is 28 mg. Dose is escalated by 7 mg per week to target of 28 mg daily. Dose modifications are required in the setting of renal insufficiency, and the package insert should be reviewed (or follow institutional guidelines).

	Daily Dose Extended Release Memantine
Week 1	7 mg
Week 2	14 mg
Week 3	21 mg
Weeks 4-24	28 mg

Patients continue on memantine for 24 weeks.

5.4.2 Permitted Supportive/Ancillary Care and Concomitant Medications

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.

5.4.3 Prohibited Therapies

If memantine is prescribed, the treating physician should be aware that the clearance of memantine is reduced with alkaline urine conditions at pH 8 or higher. Urine pH can be made more alkaline with chronic use of carbonic anhydrase inhibitors (e.g. acetazolamide, brinzolamide, methazolamide, dorzolamide, topiramate) and sodium bicarbonate and hence, memantine should be used with caution with these medications. Concurrent use of memantine with other NMDA antagonists (e.g. amantadine, ketamine, or dextromethorphan) is discouraged and other medications should be considered.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

No information needed for patients unable to complete PCI.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

This trial involves no investigational or commercial agents.

7.2 Adverse Events and Serious Adverse Events (14-FEB-2019)

7.2.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Expedited Reporting of Adverse Events (11Aug2017)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP website, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Biostatistical/Data Management Center by phone, 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.3.1 Expedited Reporting Methods

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification

is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-hour notification must be followed by a complete report within 5 days.

- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. Contact NRG Oncology at 1-215-574-3191 for details to submit source documentation.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.3.2 Expedited Reporting Requirements for Adverse Events

Any Phase Study Utilizing Radiation Therapy (including chemoRT studies)[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 3 adverse events

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements: Not applicable

7.3.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.3.4 Secondary Malignancy

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

8. REGISTRATION AND STUDY ENTRY PROCEDURES

8.1 Investigator and Research Associate Registration with CTEP (01-JUL-2022)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**	**AB**
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval) or consenting/treating/drug shipment investigator in OPEN, must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

8.1.1 Cancer Trials Support Unit Registration Requirements

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/ Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, rostered on the NCI under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol specific requirements (PSRs);
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.
- Neurocognitive Function Testing Certification: See Section 8.2.
- IRB/REB Approved Informed Consent (International and Canadian sites only: English and native language versions*****)
  Note: International and Canadian Institutions must provide certification/verification of IRB/REB consent translation to NRG Headquarters (described below).

***Non-English Speaking Canadian and International Institutions:**
Translation of regulatory documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well. Sites are NOT permitted to translate the Neurocognitive Tests. For sites testing native French speakers, the French versions of the tests must be obtained from the NRG Oncology website just as the English versions are obtained from the NRG Oncology website.

Downloading Site Registration Documents:
Download the site registration forms from the NRG-CC003 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen;
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select NRG, and the protocol number (NRG-CC003).
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) in order to receive further instruction and support.

Checking Site's Registration Status:
Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with the site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

8.2 Pre-registration Requirements (15-JUNE-2020)

Neurocognitive Function Testing Certification

At least one Clinical Research Associate (CRA) must be credentialed to administer the neurocognitive assessments at each institution. Only a certified test administrator is permitted to administer the neurocognitive tests to study participants. Test administrators must meet certification requirements for administering neurocognitive assessments; see Appendix I in this protocol, the NRG-CC003 Neurocognitive Training Procedure Letter and the NRG-CC003 Test Instruction and Administration Procedures document on the CTSU website, www.ctsu.org. Upon review and successful completion of the Neurocognitive Certification process, Jeffrey S. Wefel, PhD, Neurocognitive Co-Chair, will notify both the certified examiner and CTSU that the examiner has successfully completed this requirement. The certified test administrator must be proficient in the language (English or French) in which the test is administered to the patient. Refer to the protocol-specific material on the CTSU website for certification requirements.

Note: Examiners who have completed the full certification procedure to perform these tests for RTOG 0534, 0834, 1114, NRG-BN001, or NRG-CC001 during the past 6 months do not need to complete the full certification procedure again, but the certification worksheet for NRG-CC003 (available on the CTSU website) must be sent along with information regarding the examiners prior certification (protocol number, date of certification) to Dr. Wefel for approval. If these criteria are met, the healthcare

professional responsible for test administration and CTSU will be notified of the test administrator's recertification status for NRG-CC003. Examiners who have not completed the full certification procedure for RTOG 0534, 0834, 1114, NRG-BN001, or NRG-CC001 within the past 6 months must complete the full certification procedure to be recertified to ensure continued familiarity with study procedures.

8.3 RT-Specific Pre-Registration Requirements (01-JUL-2022)

All sites must be IMRT credentialed. For detailed information on the specific technology credentialing requirements required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, the Imaging and Radiation Oncology Core (IROC) Houston will notify your institution and NRG Oncology Headquarters when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. The Regulatory Support System (RSS) will be updated so patients can be enrolled.

In order for a site to be eligible to enroll patients in this trial, the institution and its treating physicians must have passed benchmark testing for hippocampal contouring and Hippocampal Avoidance PCI (HA-PCI) treatment planning. **Benchmark testing is limited to two (2) physicians per site. Benchmark testing for hippocampal contouring and HA-PCI treatment planning is no longer available.**

A treating physician who has not participated in or passed benchmark testing can enroll and treat patients on study so long as the patient's contouring and HA-PCI treatment plan is reviewed by another physician who has passed benchmark testing at the treating site.

Treating physicians and institutions credentialed for RTOG 0933 (Phase II study of hippocampal avoidance during WBRT for brain metastases) or NRG-CC001 (Phase III study of memantine with or without hippocampal avoidance during WBRT for brain metastases) can enroll patients in this trial without having to repeat the Benchmark QA test. However, the first case they enroll on NRG-CC003 and that is randomized to Arm 2 (HA-PCI) will require pre-treatment review of hippocampal contouring and HA-PCI treatment before proceeding with protocol treatment.

While the trials limit credentialing to 2 physicians per site, the trials do NOT limit accrual to 2 physicians per site. Instead, we ask sites to enable any physician to accrue a patient to this study and to develop the hippocampal contours and hippocampal avoidance IMRT plan (should the patient be randomized to the experimental arm). However, we mandate that if a patient is enrolled by a non-credentialed physician, they ask one of the credentialed physicians at their site to review the contours/plan to ensure that they meet protocol criteria. When enrolling the patient, the system asks two questions: 1) Who is the enrolling the physician? and 2) Who is the credentialed physician who will be approving the contours? Again, these do not need to be the same physician.

To be Grandfathered from 0933 or CC001, complete a Credentialing Status Inquiry (CSI) Form (see the procedures and instructions table below) must be submitted in order to receive a letter and have RSS updated.

NRG-CC003			
RT Credentialing Requirements	**Web Link for Procedures and Instructions: http://irochouston.mdanderson.org**		
	Treatment Modality		**Key Information**
	3DCRT (Arm 1)	**IMRT Mandatory for all sites (Arm 2)**	
Facility Questionnaire		✓	The IROC-Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, go to http://irochouston.mdanderson.org/questionnaires.
Credentialing Status Inquiry Form (CSI)		✓	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Benchmark Cases		✓	In order for a site to be eligible to enroll patients in this trial, the institution and its treating physicians must have passed benchmark testing for hippocampal contouring and Hippocampal Avoidance PCI (HA-PCI) treatment planning. Benchmark testing for NRG CC003 is no longer available. EXCEPTION: Treating physicians and sites credentialed for RTOG 0933 (phase II study of hippocampal avoidance during WBRT for brain metastases) or NRG-CC001 (phase III study of memantine with or without hippocampal avoidance during WBRT for brain metastases) will not be required to pass Benchmark Testing for NRG-CC003. A CSI form should be submitted.
Phantom Irradiation		✓	An anthropomorphic phantom study provided by the IROC-Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC -Houston website under credentialing

			(http://irochouston.mdanderson.org).

8.3.1 Digital Radiation Therapy Data Submission Using Transfer of Images and Data
Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid Cancer Therapy Evaluation Program (CTEP) Identify and Access Management (IAM) (CTEP-IAM) account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD site user role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installations:
To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/,

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.4 Patient Enrollment (01-JUL-2022)

8.4.1 Oncology Patient Enrollment Network (OPEN)
The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/ randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;

- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN site staff should verify the following:

- The following baseline neurocognitive assessments have been completed prior to Step 2 registration: HVLT-R, TMT, and COWA (see Section 3.2.1 for details).
- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

To receive site reimbursement for specific tests and/or biospecimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: websupport@acr.org or call the NRG Registration Desk at 215-574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

9. DRUG INFORMATION

Not applicable for this study.

10. PATHOLOGY/BIOSPECIMEN

10.1 Biomarkers (15-JUNE-2020)

10.1.1 miRNA Profiling of Serum

Comprehensive miRNA profiling of serum of patients enrolled on trial will be performed using comprehensive miRNA microarray prior to PCI or HA-PCI and after PCI or HA-PCI for comprehensive analysis of miRNA alterations induced by PCI or HA-PCI and to correlate those results with neurocognitive decline.

Total RNA will be extracted from patient's serum using a dedicated miRNA kit (QIAGEN Total RNA) and hybridized to GeneChip™ miRNA 4.0 Array using samples obtained before and after irradiation.

Candidate miRNAs identified during the discovery phase will be validated using qPCR analysis on an independent subset of samples in triplicate.

10.1.2 Apolipoprotein E (APOE)

Genomic DNA will be extracted from 400 μL peripheral blood by using the blood DNA extraction kit (TIANGEN) according to the manufacturer's instructions. DNA will be diluted with nuclease free water to 8 ng/μL for *APOE* genotyping analysis. Direct sequencing of APOE will be performed using previously tested primer pairs (Haasl 2008). Cycle sequencing products will be run on an ABI 3730 XL DNA analyzer and the resultant chromatograms will be analyzed with FinchTV v1.4 (Geospiza, Seattle, WA). Insufficient DNA amplification can result from low concentrations of DNA or impure DNA. This will be corrected with re-extraction and/or re-purification of DNA. Positive controls will be added at the beginning and end of each plate of samples.

10.2 Biospecimen Submission Table (15-JUNE-2020)

10.2.1 Optional Specimen Submissions

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

See detailed specimen collection/processing/shipping instructions on the protocol-specific page of the CTSU website.

Optional Study: Correlation of biomarkers to the development of neurocognitive decline after brain irradiation
The specimens are being collected in order to be prepared to correlate biomarkers to the development of neurocognitive decline after brain irradiation (see Section 10.1 for further details).

- Required Form: ST form (include study #, case #, patient initials, NRG/NCI institution ID# and name, treatment time point of specimens)
- Biospecimen Kits: Available from the NRG Oncology Biospecimen Bank-San Francisco - send all kit requests by email to NRGBB@ucsf.edu
- Shipping days: Monday-Wednesday (U.S. sites); Monday-Tuesday (Canada and Non-North American).
- Shipping costs: One return label is provided for each case in the frozen Biospecimen kits provided by the bank. Batch shipping specimens from all timepoints from each case is encouraged.

For questions, contact:
NRG Oncology Biospecimen Bank-San Francisco
415-476-7864/FAX 415-476-5271
NRGBB@ucsf.edu

Specimen Type	**Collection Time Points**	**Collection Information and Requirements/ Instructions for Site**	**Shipping** *See the protocol-specific page of the CTSU website for detailed specimen collection and shipment instructions.*
Specimen 1: Serum-red top tube - centrifuge and aliquot	• Pre-Treatment: Prior to PCI or HA-PCI • At 3, 6, 12, and 18 months from start of PCI or HA-PCI	Frozen serum samples containing minimum 0.5 mL per aliquot in five (5) 1 mL cryovials Storage: -80°C and ship frozen	Serum sent frozen on dry ice via overnight courier to NRG Biospecimen Bank-San Francisco
Specimen 2: Whole blood for DNA- One 5ml purple EDTA tube – mix and aliquot	• Pre-treatment only: Prior to PCI or HA-PCI	Frozen whole blood samples containing a minimum of 1.0 mL per aliquot in three (3) 2 mL cryovials	Whole blood shipped frozen on dry ice via overnight courier to NRG Biospecimen Bank -San Francisco

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Patient-Reported Outcomes (14-FEB-2019)

In a recent secondary analysis of 2 prior RTOG PCI trials (RTOG 0212 and 0214), PCI was associated with a 2- to 3-fold increased risk of deterioration in patient-reported cognitive functioning, as assessed on the self-reported cognitive functioning subscale of the EORTC

QLQ-C30, at 6 months (PCI 45% vs. no PCI 18%) and 12 months (PCI 51% vs. no PCI 23%) (Gondi 2013). Thus, in determining whether HA-PCI will mitigate cognitive toxicity as compared to PCI, inclusion of this validated and sensitive patient-reported endpoint will complement information gained from the primary endpoint of HVLT-R Delayed Recall.

EORTC QLQ-C30

The EORTC QLQ-C30 is the instrument most frequently used to measure quality of life (QOL) in cancer patients, and BN20 is a supplemental questionnaire specifically developed for use with the general questionnaire (QLQ-C30) in patients with brain cancer. Both instruments have been used in previous RTOG PCI trials (RTOG 0212 and 0214) and have also been shown to be reliable and valid instruments in the setting of recurrent high-grade gliomas (Osoba 1996, Osoba 1997). In addition, QLQ-C30 has demonstrated adequate reliability in patients with lung and other cancer diagnoses (Osoba 1997; Aaronson 1993, Bergman 1992, Osoba 1994). Both the EORTC QLQ-C30 and BN20 instruments are copyrighted by the EORTC and translated and validated in 81 languages. No monetary charge is required for use in a non-commercial setting. Permission to use these QOL instruments for this proposed phase III PCI trial has been obtained.

EQ-5D-5L

The EuroQOL-5D health state classification (EQ-5D-5L) is a 2-part questionnaire that takes approximately 5 minutes to complete (Schultz 2002). The first part of the EQ-5D-5L consists of 5 items covering 5 dimensions including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 5 levels including: 1-no problems, 2-slight problems, 3-moderate problems, 4-severe problems, and 5-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 (3 to the 5th) health states to which unconsciousness and death are added (Badia 1998). The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm 10 point-interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale and best imaginable health state is scored as 100 at the top. Both the 5-item index score and the VAS score are transformed into a utility score between 0 "Worst health state" and 1 "Best health state". Either the index score or the VAS score can be used in the quality adjusted survival analysis, or enter the cost-utility equation, depending on the health state(s) of interest (Wu 2002).

Although developed in Europe, the EQ-5D has been used in the United States and Canada (Glick 1999, Johnson 1998, Johnson 1998b, Johnson 2000, Trippoli 2001). The EQ-5D web site, http://www.euroqol.org/, lists the languages in which the form has been validated. The Work Productivity and Activity Impairment (WPAI) Questionnaire, a validated instrument to assess work and productivity (Reilly 1993), will be used to assess both the patient and any caregiver lost wages and productivity. It consists of 6 questions utilizing a recall period of the last 7 days. The WPAI has 4 outcomes: absenteeism (work time missed), presenteesism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism + presenteeism), and activity impairment. These outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

Cost-Effectiveness

A health resource utilization diary will be used to measure the services consumed by the patient. The diary must be given to the patient at the beginning of the reporting period and the due dates for submission of the diary are provided in Section 4. For example, the first diary must be given to the patient prior to the start of RT and is due at the end of RT. This diary can also be completed by a caregiver. The institution must collect the caregiver's contact information so that the caregiver can be contacted if the diary is not completed by the patient. Note that this information will not be provided to NRG Oncology.

Hopefulness

The hippocampus has been implicated as a mediator of emotional regulation, especially during stress, e.g. cancer and the treatment of cancer (Godsil 2013). Indeed, smaller hippocampal volume has been correlated with greater vulnerability to psychological trauma (Gilbertson 2002). If the hippocampus functions, in part, as a neurophysiological "hope center" then protection of the structure in the HA-PCI arm is expected to preserve hopefulness among those treated with this experimental approach. We hypothesize that HA-PCI may allow maintenance of hopefulness as measured by the Adult Hope Scale (AHS).

The AHS was developed by Snyder and colleagues at the University of Kansas (1989). The tool, designed to be completed in approximately 5 minutes, assesses the core components of hope theory: goal-setting, path establishment, and agency (i.e. "motivation") to attain said goals by pursuing an established pathway. The instrument has been validated and utilized in oncology studies in which links between levels of hopefulness with post-traumatic growth and positive coping skills have been found (Ho 2012, Clayton 2008). To avoid the confounding effect of depression on hope, a 2-item tool (PHQ 2) will be administered to determine if underlying depression is present among subjects (Gilbody 2007). The PHQ 2 has already been used in a depression screening trial mounted by NRG Oncology (RTOG 0841) and was found to be remarkably robust in detecting depressive symptoms.

Data Collection

Collection of the EORTC QLQ-C30 and BN20 will occur at the same time points as cognitive assessments: baseline (prior to Step 2 registration) and at 3, 6, 12, 18, and 24 months from the start of treatment. The EQ-5D-5L will be collected at baseline (prior to Step 2 registration), at the end of RT, and at 6, 12, and 24 months from the start of treatment. The WPAI Questionnaire will be collected at the end of RT and at 6, 12, and 24 months from the start of treatment. The AHS and PHQ 2 will be collected at baseline and 6 months from the start of treatment. Such a data collection schedule will permit comparison of patient-reported QOL and cognitive outcomes, as well as early and long-term patient-reported QOL effects of HA-PCI as compared to PCI. RTOG 0212 and 0214 collected QOL data at 6 and 12 months. The compliance with quality of life data collection was 64%-67% at 6 months and 50%-56% at 12 months. To optimize data collection at the proposed time points, this trial will incorporate electronic data collection using VisionTree, a HIPPA-secure web-based technology that has demonstrated significantly improved data compliance (from 52% to 90%) as compared to historical standards within the RTOG network (Movsas 2011); see Section 11.2 below.

11.2 Optional Online Completion of Patient-Reported QOL Assessments (14-FEB-2019)

Missing data are a significant problem, particularly for QOL assessments. Unlike data for traditional endpoints, such as survival, QOL data can never be obtained retrospectively if it is not provided by the patient at the appropriate time point. This limits researchers' ability to accurately perform QOL statistical analyses and negatively impacts the clinical relevance of this effort. Typically, QOL forms are filled out in hardcopy (paper). To provide a more convenient method of completing QOL assessments, NRG Oncology is working with VisionTree Software, Inc., San Diego, CA. VisionTree offers patients on this study the option of completing their QOL forms online from any location that has a computer with Internet access, including the patient's home, and provides reminders to patients to complete the assessments.

VisionTree has developed a tool, VisionTree Optimal Care (VTOC), a HIPAA-secure, user friendly, web-based software system (Gorgulho 2005; Gorgulho 2007; Pedroso 2006). The VTOC tool contains a web-based system for global patient and trial administration access, which allows improved compliance and accuracy of data collection, validation, and reporting. It is compliant with the Title 21, Code of Federal Regulations, Part 11 statistical process control system and provides a mobile solution for clinical trials. QOL data are collected with Microsoft Excel and PDF export of reports. VTOC also has mobile messaging and e-mail reminders. Surveys can be "pushed" to patients for completion at timed intervals (see http://www.visiontree.com for details). This technology allows consenting patients on this study to fill out their QOL forms online from any location and to receive e-mail reminders to complete assessments. E-mail reminders also can be sent to research associates (RAs) at the appropriate institutions to remind them that a QOL time point window is about to close so that a patient can be contacted to fill out QOL information on time, before it becomes "missing data".

In a pilot RTOG study (RTOG 0828), the compliance rate of patients completing QOL assessments at 6 months significantly improved using electronic technology. Based on this pilot data, NRG Oncology is offering VisionTree as an option in other studies, including this one. Patients preferring to complete hardcopy QOL assessments can do so. The QOL forms completed via VTOC are identical to the hardcopy forms; this technology does not add to or change the QOL assessments in this study.

Patients without e-mail or Internet access are still able to complete hardcopy (paper) forms. Indeed, at any time, any patient may choose to fill out their QOL form using the hardcopy form. If the patient wishes to complete QOL assessments online, the patient must have an e-mail address that they consent to use for this purpose. Patients' e-mail addresses are necessary so that e-mail reminders may be sent to them to remind them to fill out QOL forms that are due. The patient's e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g. Yahoo!, Hotmail, or AOL).

The baseline QOL forms must be completed in hardcopy (on paper) prior to the start of treatment. In addition, the Adult Hope Scale (AHS) and PHQ 2 must be completed in hard

copy (on paper) at 6 months from the start of PCI or HA-PCI. All subsequent QOL forms can be completed by the patient online.

The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link: https://rtog.optimalcare.com - medical team. RA login information will be provided by VTOC after the first patient registered by the RA is randomized to the study. (Once login information is received, the RA can immediately set up future patients' accounts in VTOC after registration.) The patient's VTOC account must be set up within 14 days after randomization. VTOC will send patients e-mail reminders to complete QOL forms. The first reminder will be sent at the beginning of the window for completion of the form, with a second reminder sent halfway through the window, if the form has not yet been completed. A maximum of 3 reminders will be sent for each of the QOL assessment time points (subsequent to the baseline assessments). After the patient has completed all forms, a dialogue box will appear thanking the patient for completing the QOL form(s), and the patient will no longer receive reminders for that time point.

Patients will receive a login card (either printed or sent via e-mail) with which to log in using the secure, web-based VTOC portal. VTOC meets all HIPAA guidelines and is encrypted (via 128-bit SSL) for the security, privacy, and confidentiality of QOL information. It is similar to the secure login commonly used when performing online banking. The login card can then be kept and maintained by the patient.

Site Research Associates (RAs) will receive training in the use of VTOC via NRG Oncology webinars and educational sessions. Dates and registration for the VTOC webinars are found in the weekly NRG Oncology Broadcast. The RA or study administrator will be informed via the VTOC "At a Glance" form management system when QOL forms have been completed or when the window for a particular form has closed. If the site RA receives a notice that forms have not been completed, she or he will contact the patient to remind the patient to fill out the QOL form or inquire why the forms have not been completed. The RA will complete the cover page for each form that was not completed (either via VTOC or in hardcopy) and will submit the cover page.

The patient's e-mail address only will be used by NRG Oncology for this purpose. Patients will be sent e-mail reminders to complete QOL forms. A typical e-mail reminder would read: "Your Quality of Life forms for the study, NRG-CC003, are now due. Please go to http://www.optimalcare.com, use your secure login, and complete the online forms. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. If you have any questions, please e-mail or call your research associate at [insert RA e-mail address] or [insert RA telephone number]. Thank you for participating in this study." The reminders will be created by NRG Oncology and placed into a study template that will be sent to patients at customized intervals (at the time points when QOL forms are due). Reminders will be sent for each of the 4 QOL time points (following the baseline QOL forms, which are completed in hardcopy) until the form(s) is completed or the time window on that time point ends. After a patient has completed all forms in the VTOC portal, a dialogue box will appear that says "Thank you for completing your Quality of Life

forms," and the patient will no longer receive any remaining notices for that time point. The site RA or study administrator will be informed through the VTOC "At-A-Glance" form management system when QOL forms have been completed.

11.3 Imaging Biomarkers (14-FEB-2019)

MR imaging represents a potentially sensitive tool for monitoring cognitive injury from cancer therapies including cranial irradiation. Degree of white matter changes and hippocampal volumetry represent novel imaging biomarkers that may predict cognitive outcomes following neuro-protective strategies such as hippocampal avoidance. As exploratory objectives of this study, we plan to assess white matter injury and hippocampal volumetry on pre-treatment brain MRIs and correlate these imaging biomarkers with cognitive outcomes and potential differential benefit of HA-PCI versus PCI.

In other neurodegenerative conditions, MR imaging-defined white matter changes have been correlated with cognitive deterioration (Carmichael 2010, Breteler 1994). Sabsevitz, et al. (2013) demonstrated a strong and independent relationship between white-matter integrity prior to cranial irradiation and the volume and severity of these post-treatment white matter changes. However, correlation of pre-treatment T2/FLAIR white matter injury with cognitive and quality of life outcomes remains poorly understood. In addition, the ability of hippocampal avoidance to mitigate white matter injury has not been previously examined.

A number of studies have demonstrated that MR-defined hippocampal volumetry is a significant predictor for cognitive decline (Kantarci 2013, Fleischman 2013). Similarly, serial atrophy in hippocampal volume over time also has predicted for cognitive decline. Wang, et al (2013) found that hippocampal loss over time was significantly greater in patients with mild cognitive impairment compared with age-matched normal controls. Additionally, in a longitudinal study of 323 subjects with mild cognitive impairment, patients who had factors predictive for the development of Alzheimer's dementia had higher rates of hippocampal atrophy on serial MRI (van de Pol 2007). Thus, we hypothesize that smaller pre-treatment hippocampal volumes will predict for an increased risk of cognitive decline and that patients who experience serial decline in hippocampal volume, irrespective of pre-treatment volume, will be at a higher risk of cognitive decline. Using MR images obtained at baseline, we plan to quantify extent of MR-defined white matter changes and hippocampal volume pre-treatment, correlate these data with cognitive and quality of life outcomes, and evaluate differential benefit of HA-PCI as compared to PCI.

11.3.1 Technique, Timing and Central Submission

The study requires a SPGR, MP-RAGE, or TFE MRI scan without and with gadolinium contrast-enhanced T1-weighted acquisitions and standard T2-weighted FLAIR sequence acquisitions to be obtained within 56 days of Step 1 registration. The purpose of this baseline imaging study is to rule out intracranial metastases prior to enrollment and for hippocampal contouring should the patient be randomized to the HA-PCI experimental arm of this study. This imaging study will be submitted for centralized quality assurance review of hippocampal contouring and HA-PCI treatment planning. For this exploratory analysis of imaging biomarkers, the MRI scan also will be used to provide assessment of white matter changes and hippocampal volumetry at baseline prior to HA-PCI as compared to PCI. To yield acceptable image quality, the pre-contrast-enhanced should have a

resolution of 1 x 1 x 1.2 mm and should follow the protocols established by the Alzheimer's Disease Neuroimaging Initiative (ADNI). Performance of this sequence at a 3 Tesla field strength is recommended. Vendor-specific versions of this sequence are available for download from the ADNI website, http://www.adni-info.org/scientists/MRIProtocols.aspx . Sites may contact the Imaging Co-Chairs for further information or assistance if needed. MRI scans are non-invasive and provide no additional risk to the patient.

As exploratory objectives of this study, T2/FLAIR and SPGR, MP-RAGE or TFE sequences will be submitted for central analysis. Abnormal FLAIR volumes will be created in a semi-automated fashion by trained individuals using a consensus approach and blinded to the cognitive outcome data. Automated hippocampal volumetry will be performed on the pre-contrast SPGR, MP-RAGE or TFE sequences using FreeSurfer (Boston, MA). FreeSurfer has been widely used in multiple large multi-institutional trials and, for hippocampal volumetry in particular, has been shown to be highly accurate compared with expert manual tracing (Morey 2009).

Submission of imaging will be required on all patients. See Section 8.4 for specifics on submission requirements and procedures. All imaging will be anonymized by TRIAD to ensure patient confidentiality.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

For Arm 2 Only: A team of Co-Chairs will perform an RT Quality Assurance Review after IROC-Philadelphia has received complete data. These reviews will be completed remotely and will be ongoing. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as IROC-Philadelphia RT has received complete data for all cases enrolled, whichever occurs first. The scoring mechanism is: **Per Protocol**, **Acceptable Variation**, and **Unacceptable Deviation**.

13. DATA AND RECORDS

13.1 Data Quality Portal (01-JUL-2022)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.2 Data Submission/Data Reporting (01-JUL-2022)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is granted through the CTEP-IAM system and role assignments.

Requirements to access Rave via Medidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA role or CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must either click on the link in the email or log into iMedidata via the CTSU members' website under Data Management > Rave Home and click to accept the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the *Tasks* pane located in upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave accounts at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under in the Data

Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.3 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting. Submit digital RT data via TRIAD; see Section 8.3 for TRIAD account access and installation instructions.

All neurocognitive materials for every patient at every time point must be uploaded to Medidata Rave® within 7 days after test administration.

For reporting of second primary cancers or other report forms available in Rave: Indicate form for reporting in Rave; timeframes; add if loading of the pathology report is required.

Summary of Data Submission: Refer to the CTSU website for the data submission summary.

13.4 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design (13-APR-2021)

This is a randomized phase II/III study in which phase II patients will be used in the phase III analysis. The first phase will determine the safety of the treatment of interest, hippocampal avoidance during PCI using a non-inferiority design, compared to the current standard of care, PCI alone, while the second phase will test the efficacy of the treatment. For both phases, patients will be stratified according to stage (limited vs. extensive), age (<60 years old vs. ≥60 years old), and planned concurrent memantine use (yes vs. no). Patients will then be randomized 1:1 to PCI alone (25 Gy in 10 fraction) using IMRT or PCI with hippocampal avoidance (HA-PCI) using IMRT (25 Gy in 10 fractions) using a permuted block procedure (Zelen 1974). This study is prospective and not blinded. The total accrual for this study will be 392 patients as described in detail in Section 14.3.3. The analysis population is intent-to-treat, such that all randomized patients will be analyzed.

14.2 Study Endpoints (01-JUL-2022)

14.2.1 Phase II

- Primary Endpoint: 12 month intracranial relapse rate

14.2.2 Phase III

- Primary Endpoint: HVLT-R delayed recall deterioration status, defined using the Reliable Change Index (RCI) (Jacobson 1991, Chelune 1993) at 6 months from the start of treatment
- Secondary Endpoints:
  - Time to neurocognitive failure, where a failure is defined using the RCI criteria, as measured by HVLT-R, Controlled Oral Word Association (COWA) test, and Trail Making Test (TMT) Parts A and B
  - Preservation of neurocognitive function, *as measured by neurocognitive decline for HVLT-R, COWA test, TMT Parts A and B*, and Clinical Trial Battery Composite (CTB COMP) score
  - Patient-reported health-related quality of life (HRQOL), as measured by the EORTC Quality of Life Questionnaire (QLQ-C30) and BN20
  - Correlation of changes in HRQOL domains measured by the EORTC QLQ-C30 and BN20 with changes in cognitive function
  - Cost-effectiveness as measured by the EuroQOL-5D health state classification (EQ-5D-5L)
  - Overall survival
  - Intracranial relapse rate
  - Adverse events, as measured by the CTCAE v.4
  - Correlation of miRNA signatures with neurocognitive decline
  - Correlation of APOE genotyping with neurocognitive decline
  - Effect of baseline white matter injury and hippocampal volume on neurocognitive function
- Exploratory Endpoints:
  - Hopefulness as measured by the Adult Hope Scale (AHS)
  - Feasibility of Remote Neurocognitive Testing

14.3 Primary Objectives Study Design (15-JUNE-2020)

14.3.1 Primary Hypothesis and Endpoints

- *Phase II*
  The primary hypothesis of the phase II trial is that HA-PCI has a similar 12-month intracranial relapse rate compared to PCI for patients with small cell lung cancer (SCLC).
- *Phase III*
  The primary hypothesis for the phase III trial is that HA-PCI reduces the likelihood of 6-month deterioration from baseline in HVLT-R Delayed Recall compared to PCI for patients with SCLC.

14.3.2 How Primary Endpoints Will Be Analyzed

- *Phase II*
  The primary endpoint of the phase IIR portion of this study is the rate of intracranial relapse at 12 months. Patients who die prior to experiencing a relapse will be considered as not having a relapse. It will be compared between arms using a binomial test of difference in proportions at a significance level of 0.1. If the rate of relapse in the HA-PCI arm is significantly greater than that of the PCI only arm, this study will not continue to the phase III portion.

- *Phase III*
  The primary endpoint of the phase III portion of the study is deterioration, defined as a change in raw score ≥ 3 points (i.e. RCI criteria) from baseline to 6 months in the HVLT-R Delayed Recall score (Jacobson 1991, Chelune 1993). It will be compared using Fisher's exact test at a significance level of 0.05. Due to the inclusion of remote testing, sensitivity analyses will be conducted in which patients who completed the neurocognitive testing remotely will be considered missing.

14.3.3 Sample Size and Power Calculations:

- *Phase II*
  In the phase IIR portion of this study, the primary endpoint is the 12-month rate of intracranial relapse and the potential impact of HA-PCI compared to PCI. We anticipate that HA-PCI may have a higher rate of intracranial relapse compared to PCI alone due to potential relapse in the hippocampal avoidance region. In order to assess the safety of HA-PCI, a non-inferiority design will be used to determine if the relapse rate is similar to that of PCI only. In RTOG 0212, 22% of patients enrolled on the 2.5Gy in 10 fractions arm experienced a relapse at 12 months (Wolfson 2011). It is assumed that the PCI-only arm will have a similar 12-month relapse rate. The non-inferiority margin needs to be less than 23% due to results from Auperin's meta-analysis which found that a 23% absolute 12-month intracranial control benefit of PCI translated to an overall survival advantage (Auperin 1999). In RTOG 0933, although a different patient population, a relapse rate in the HA region of 4.5% was observed. Thus, a relapse rate of 4.5% higher in the HA-PCI is expected but more than 20% is of concern. The hypothesis to be tested is:

$$H_0: P(relapse)_{HA-PCI} - P(relapse)_{PCI} > 20\%$$
$$vs.\ \ H_A: P(relapse)_{HA-PCI} - P(relapse)_{PCI} = 4.5\%$$

  Using a non-inferiority margin of 20% and an assumed difference in proportions of 4.5% under the alternative, a 2-sample test of difference in proportions with a 1-sided alpha of 0.1 requires 164 patients to achieve 85% statistical power. Increasing this by 5% due to loss to follow up, **172 patients are required to ensure 164 evaluable patients** for the phase II portion of this study. If HA-PCI is associated with a < 20% absolute increase in 12-month intracranial relapse as compared to PCI, then HA-PCI will be deemed safe, and this trial will proceed to the phase III component.

- *Phase III*
  The sample size calculations will address the specific primary hypothesis that HA-PCI reduces probability of deterioration in HVLT-R Delayed Recall (from baseline to 6 months from the start of treatment). We do not expect improvement in HVLT-R Delayed Recall; at best, we anticipate a preservation of HVLT-R Delayed Recall. Data from RTOG PCI trial 0212 demonstrated deterioration, as defined by the RCI criteria (Jacobson 1991; Chelune 1993), in HVLT-R Delayed Recall in 29% of patients at 6 months following standard-dose PCI. We anticipate that HA-PCI will have a lower probability of deterioration, as defined by the RCI criteria, in HVLT-R Delayed Recall performance at 6 months as compared to PCI alone. Detecting a 14.5% absolute reduction in the probability of HVLT-R Delayed Recall deterioration due to HA-PCI suggests a 50% relative improvement. With alpha=0. 05 (1-sided), a total of **98 analyzable patients per arm** would ensure 80% statistical power to detect

a 14.5% absolute reduction in the probability of HVLT-R Delayed Recall deterioration at 6 months using a test of difference in proportions. In RTOG 0933, 4% of patients were ineligible and 31% were non-compliant at 6 months, with 2% not completing the HVLT prior to the start of treatment. In RTOG 0212, 5% of patients were deceased by 6 months on study. The sample size for this study therefore will be increased by 5% due to loss to follow up, 5% due to death, and 25% due to patient non-compliance. Thus, **the target sample size will be 392 randomized patients to ensure 196 randomized evaluable patients**. It is expected that some patients will score between 0 and 2 on the HVLT-R Delayed Recall prior to Step 2 registration and thus not be able to experience cognitive deterioration as defined by the RCI criteria. It also is expected that some patients may not complete all parts of the HVLT-R. These patients will not be able to register to step 2. It is assumed that 10% of registered patients will not be randomized to step 2.

Due to the higher than projected enrollment of patients with extensive-stage disease, the rate of death by 6 months is higher than initially estimated. Thus the number of evaluable patients will be increased by 5% due to loss to follow up, 20% due to death, and 25% due to patient non-compliance. Thus, **the target sample size will be 392 randomized patients to ensure 196 randomized evaluable patients**.

14.4 Study Monitoring of Primary Objectives

(Interim Analysis)

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

If the phase II null hypothesis is rejected, an analysis for the phase III primary endpoint, 6-month HVLT-R Delayed Recall deterioration, will occur at the time of the phase II analysis when all evaluable patients have at least 12 months of follow up. Due to potential non-compliance, it is estimated that about 70% of evaluable patients for phase III will be available for this interim analysis. HVLT-R Delayed Recall deterioration will be tested using a significance level of 0.05. The DMC will review the results from the interim analysis to decide if the study should be closed & reported early due to efficacy.

Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pre-treatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoints, time to neurocognitive failure, or any secondary endpoints, with the exception of reporting of adverse events.

14.5 Accrual/Study Duration Considerations (15-JUNE-2020)

14.5.1 Accrual Rate

RTOG 0933 is a completed phase II trial of hippocampal avoidance during WBRT for brain metastases. RTOG 0933 accrued 113 patients at an accrual rate of 6 patients per month with target accrual reached in 25% less time than initially projected. RTOG 0212 accrued 265 patients in 5 years at an accrual rate of 4.4 patients per month but did not include patients with extensive-stage small cell lung cancer. For this proposed trial, in which patients with extensive-stage small cell lung cancer will be permitted, accrual is expected to be higher. Thus, no accrual is expected for the first 4 months after activation then a total of 6 patients are expected in the next 2 months while sites, physicians, and clinical research associates are being credentialed. At this point, accrual is expected to increase to 6 patients per month for the duration of the study. This study will be monitored according to DCP accrual guidelines.

14.5.2 Accrual Goal

The accrual goal for phase II is 172 patients and for phase III, it is 392 patients.

14.5.3 Study Duration

The study is projected to be open to accrual for 56 months for both phases combined, including the 6 month ramp-up period specified in Section 14.5.1. Including the accrual hold for the phase II analysis, the phase III portion is projected to close to accrual approximately 70 months from activation.

The average monthly accrual has been 9 patients/month and the study is on track to complete earlier than initially projected. With the sample size increase, the phase III portion is projected to close as initially planned, approximately 70 months from activation.

14.5.4 Estimated Duration for Completion of Primary Endpoint

The projected time of analysis, 6 months from the start of treatment, is expected to occur about 8 months after study closure, or approximately 88 months from activation.

14.6 Secondary or Exploratory Endpoints (including correlative science aims) (15-JUNE-2020)

14.6.1 Secondary Hypotheses and Endpoints (phase III only):

- Evaluation time to neurocognitive failure, where a failure is defined using the RCI criteria, as measured by HVLT-R, Controlled Oral Word Association (COWA) test, and Trail Making Test (TMT) Parts A and B. It is hypothesized that the HA-PCI arm will result in a longer time to neurocognitive failure compared to the PCI only arm.
- Evaluate neurocognitive function, as measured neurocognitive decline by HVLT-R, COWA test, TMT Parts A and B, and CTB COMP (the arithmetic mean of the HVLT-R, TMT, and COWA outcomes). Specifically, it is hypothesized neurocognitive function will be preserved in the HA-PCI compared to the PCI only arm.

- Evaluate 6-month decline, defined as a reduction of 10% from baseline, in patient-reported cognitive function, as measured by the cognitive functioning subscale of the EORTC QLQ-C30. It is hypothesized that PCI will lead to a great likelihood of decline as compared to HA-PCI.
- Evaluate patient-reported health-related quality of life (HRQOL), as measured by the global QOL, physical functioning, role functioning, emotion functioning and social functioning domains on the EORTC Quality of Life Questionnaire (QLQ-C30) and BN20.
- Correlate changes in HRQOL domains measured by the EORTC QLQ-C30 and BN20 with changes in cognitive function
- Evaluate cost-effectiveness as measured by the EuroQOL-5D health state classification (EQ-5D-5L)
- Evaluate overall survival
- Evaluate intracranial relapse rate
- Evaluate adverse events, as measured by the CTCAE v.4
- Correlate cognitive failure with miRNA signatures. Specifically, it is hypothesized that microarray profiling of miRNAs in serum of individuals with LS-SCLC enrolled in NRG-CC003 who undergo PCI or HA-PCI will reveal miRNA signature correlating with cognitive decline.
- Correlate neurocognitive function with APOE genotyping. It is hypothesized that APOE genotyping will be predictive of neurocognitive decline after brain irradiation and MRI evidence of hippocampal volume loss after brain irradiation and APOE genotyping will identify patients who derive the most or least benefit from hippocampal avoidance.
- Correlate neurocognitive function with both FLAIR volume and hippocampal volume. It is hypothesized that hippocampal volume and abnormal FLAIR volume at baseline will be predictive of subsequent neurocognitive decline after brain irradiation and that baseline FLAIR volume and hippocampal volume will identify patients who derive the most or least neurocognitive benefit from hippocampal avoidance.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Time to Neurocognitive Failure

Neurocognitive failure is the first failure, defined as a neurocognitive decline using the reliable change index (RCI) on at least one of the following assessments: HVLT-R, TMT, or COWA (Jacobson 1991; Chelune 1993). The HVLT-R has 3 parts that will be analyzed separately for decline: Total Recall, Delayed Recall, and Delayed Recognition. The TMT has 2 parts that will be analyzed separately: Part A and Part B.

The cumulative incidence approach will be used to estimate the median time to neurocognitive failure to account for the competing risk of death. Gray's test will be used to test for statistically significant difference in the distribution of neurocognitive failure times (Gray 1988). The cause-specific Cox proportional hazards regression model will be used to evaluate the effect of stratification variables (age, stage, and planned concurrent memantine use) and other baseline characteristics, on time to neurocognitive decline (Cox 1972).

Neurocognitive Function

Preservation of neurocognitive function will be measured by the HVLT-R, COWA, and TMT. The HVLT-R has 3 parts that will be analyzed separately: Total Recall, Delayed Recall, and Delayed Recognition. The TMT also has 2 parts that will be analyzed separately: TMT Part A and TMT Part B. The COWA has a single outcome measure that will be analyzed. Standardized scores that adjust for age, education, and gender when necessary will be analyzed. For discrete time point analyses, the change from baseline to each follow-up time point (3, 6, 12, 18, and 24 months from the start of treatment) will be calculated and compared between treatment arms using a t-test or Wilcoxon-Mann-Whitney test, depending on the normality of the data. Neurocognitive decline using the reliable change index (RCI) for the HVLT-R, COWA, and TMT also will be compared between treatment arms at each follow-up time point using Fisher's exact test (Jacobson 1991; Chelune 1993).

A mixed effects model will be used to assess changes of standardized neurocognitive scores across time using all available data while adjusting for stratification variables and other baseline characteristics. Mixed models are a general class of models for analyzing repeated measures data, which allow modeling of the covariance among the repeated measures as well as random effects such as patient-specific intercepts and slopes and can incorporate fixed and time-varying covariates. Fixed effects will consist of stratification factors (age, stage, and planned concurrent memantine use) and potentially other baseline covariates. Since missing data is expected, patients with missing data will be compared to patients with complete data at each follow-up time with respect to baseline characteristics. If any of these characteristics are found to be significantly different, then they will be incorporated into the mixed effects model. Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 2010, Verbeke 2000). If missing data are MCAR or MAR, then a mixed model using maximum likelihood is sufficient because all available data can be used. A joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998). Due to the inclusion of remote testing, sensitivity analyses will be conducted in which patients who completed the neurocognitive testing remotely will be considered missing.

Health-Related Quality of Life

The primary HRQOL endpoint will be the decline in patient-reported cognitive function at 6 months, as measured by the cognitive functioning subscale of the EORTC QLQ-C30. Since higher scores indicate better functioning, a reduction of 10% from baseline indicates a decline in function. Additionally cognitive function decline at 3, 6, 12, 18 and 24 months will also be assessed and compared using Fisher's exact test. Decline from baseline to each time point (3, 6, 12, 18, and 24 months from the start of treatment) in the following subscales will also be assessed and compared using Fisher's exact test: global

QOL, physical functioning, role functioning, emotional functioning, and social functioning domains along with fatigue and pain items. Change from baseline to each follow-up time point will be assessed using Wilcoxon rank sum test or a t-test if normally distributed.

A mixed effects model will be used to examine the cognitive functioning data across time while adjusting for stratification factors and other baseline characteristics. Similar methods described for *Neurocognitive Function* above will be used.

Correlation of HRQOL with Neurocognitive Function

The domains of interest, global QOL, cognitive functioning, physical functioning, role functioning, emotional functioning, and social functioning as well as the two items, fatigue and pain, will each be correlated with the neurocognitive battery consisting of the 3 parts of the HVLT-R, COWA test, TMT Parts A and B, and the CTB COMP score. Pearson correlation coefficients will be used and treatment arms will be combined.

Cost-Effectiveness

Preference scores used to obtain quality-adjusted survival will be assessed from participant responses to the EuroQol-5D health state classification system (EQ-5D-5L) completed at the end of treatment and at 6, 12, and 24 months from start of treatment. Quality-adjusted life years (QALY's) will be assessed as the area under the preference-weighted survival curve. Cost will be assessed using a societal perspective. The primary cost-effectiveness outcome will be the pooled incremental cost-per QALY ratio for HA-PCI versus standard PCI. The incremental cost per QALY ratio will be calculated as the total cost of the HA-PCI minus total cost of standard PCI which will be divided by the quality adjusted survival of the patients treated with HA-PCI minus the quality adjusted survival of patients receiving standard PCI. The point estimates for the ratio will be based on the point estimates for the difference in costs and QALY's derived from the multivariable generalized estimating equations (GEE) or general linear model (GLM) analyses.

Price weights are required for translating the measured services into cost. Medical service price weights will generally be derived from Federal Fee Schedules (e.g. diagnosis related group payments for hospitalization, the Medicare Fee Schedule for physician fees, Medical Expenditure Panel survey data for emergency department visits, and the Federal Supply Schedule for concomitant medications). Hospital specific cost-to-charge ratios will be used to convert charges to costs. A health resource utilization diary will be used to measure the services consumed by the patient. The Work Productivity and Activity Impairment Questionnaire, a validated instrument to assess work and productivity, will be used to assess both patient and any caregiver lost wages and productivity. Both the diary and questionnaire are collected at the end of treatment, and 6, 12, and 24 months from the start of treatment. The method formulated by Glick, et al. (2015) will be followed for assessing the extent and mechanism of missingness of cost data and selecting an appropriate method for addressing it.

Parametric failure time models will be used for the analysis of survival. Standard diagnostics will be used to identify an appropriate survival distribution. Repeated

measure count models (Poisson, negative binomial, and zero-inflated negative binomial as appropriate) will be used to assess counts of services between the 2 groups. Assessed services include hospitalizations, nursing home or rehabilitation hospital admissions, emergency room visits, physician visits, travel, and other caregiver costs. Use of repeated measures models (for these count data and for costs) facilitates use of data from patients before they withdraw from the study or are lost to follow up. Repeated measure multivariable GEE and/or GLM will be used to analyze health care costs. Candidate predictor variables include but not necessarily limited to the follow-up period during which the data were collected and variables used to stratify the randomization. Separate multivariable analyses will be performed for the costs of the radiotherapy, hospitalizations, caregiver costs, foregone employment costs and long-term care. Where appropriate, two-part models will be used (part 1, estimation if any costs were incurred in a period; part 2 estimation of the magnitude of cost if any has been incurred in the period). If generalized linear models are used, links and families will be empirically fit to the data using diagnostic tests including the Modified Parks test, Pregibon-Link test, Hosmer-Lemeshow test, and Pearson's correlation test.

Parametric confidence intervals for the cost-effectiveness ratio as well as an acceptability curve will be derived using the point estimates of the difference in cost and QALYs, their standard errors and the correlation between the differences (Glick 2015). Standard errors and the correlation of the difference in cost and QALY's will be derived from a nonparametric bootstrap.

A standard 3% discount rate for both QALY and cost will be used (Libscomb 1996). The medical component of the consumer price index will be used to adjust for inflation. The effect of the discount rate on overall outcome of the trial will be tested in sensitivity analysis. The trial mandates follow up at predefined time points up to 2 years. The majority of cost drivers is expected to be identified by this time point and if significance patients are still living past the 3-year time point the important cost drivers can be modelled for further analysis.

Overall Survival

Overall survival rates will be estimated using the Kaplan-Meier method (Kaplan 1958), and differences between treatment arms will be tested using the log rank test (Mantel 1966). Overall survival will be measured from the date of randomization to the date of death, or, otherwise, the last follow-up date on which the patient was reported alive.

The Cox proportional hazard model (Cox 1972) will be performed with the stratification variables and other baseline characteristics as fixed variables to assess the treatment effect while adjusting for patient-specific risk factors.

Intracranial Relapse

The occurrence of intracranial relapse will be defined as the appearance of a brain metastasis in the brain. Intracranial relapse will be assessed at the time of the primary endpoint analysis, which is expected to occur once all patients have 6 months of follow up from the start of treatment. The cumulative incidence approach will be used to

estimate the median time to intracranial relapse to account for the competing risk of death. Time to intracranial relapse will be measured from the date of randomization to the date of intracranial relapse, death, or, otherwise, the last follow-up date on which the patient was reported alive. Gray's test will be used to test for statistically significant difference in the distribution of intracranial relapse times (Gray 1988). The cause-specific Cox proportional hazards regression model will be used to evaluate the effect of stratification variables (age, stage, and planned concurrent memantine use) and other baseline characteristics, on time to intracranial relapse (Cox 1972).The 12-month comparison in intracranial relapse rates between the treatment arms also will be assessed and compared using a test of proportions.

Relapse in the perihippocampal regions also will be evaluated at 12 months based on site review. Few events are expected based on the results of RTOG 0933 where only 4.5% of patients experienced progression in this region (Gondi 2013; Gondi 2014), although this was progression rather than relapse. A test of proportions will be used to compare the rates in each treatment arm at 12 months.

Adverse Events

Adverse events (AE) will be evaluated using the CTCAE v4.0. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm.

miRNA Signature

Three miRNA signatures, miR-151a-3p, miR-212-3p, and miR-1274b, will be assessed as both continuous and categorical (≤ median vs. > median) variables. Categorical miRNA signatures will be compared on pretreatment characteristics and treatment history (previous chemotherapy, previous radiation) and on memantine use using chi-square tests. Of primary interest is whether these signatures are correlated with time to neurocognitive decline. Gray's test will be used to test for statistically significant difference in the distribution of neurocognitive failure times (Gray 1988). The cause-specific Cox proportional hazards regression model will be used to evaluate the effect of each miRNA signature on time to neurocognitive decline (Cox 1972). Treatment arm, the interaction between each miRNA signature and treatment, and memantine use will also be examined. It's possible that memantine use will confound the results. Since any significant miRNA signature would require subsequent validation, a two-sided significance level of 0.05 will be used for each miRNA signature.

As additional exploratory analyses, each miRNA signature will be correlated with neurocognitive decline of each test (HVLT-R, TMT Parts A and B, and COWA) at each follow-up time point (3, 6, 12, 18, and 24 months from the start of treatment). If memantine use is found to confound the results, these analyses will be limited to patients who did not use memantine. Continuous miRNA signatures will be assessed using t-tests or Wilcoxon tests if data is non-normal using a two-sided significance level of 0.05. Categorical miRNA signatures will be assessed used chi-square tests, also at a significance level of 0.05. No multiplicity adjustments will be performed due to the exploratory nature of these assessments.

APOE Genotyping

APOE genotype, specifically APOE4 is of interest. Patients will be scored semi-quantitatively and categorically ordered into whether they carry or do not carry one or more APOE4 alleles. APOE genotyping will be assessed as a categorical variable: patients with one or more APOE4 alleles vs. those with no APOE4 alleles. Descriptive statistics by APOE4 status will be performed to determine the number of patients who received HA vs. those who did not, by neurocognitive compliance at each time point. Baseline neurocognition (HVLT-R Total Recall, Delayed Recall, and Recognition, TMT Parts A and B, COWA, and CTB Composite score) will be compared between patients with and without APOE4 using the t-test or Wilcoxon text if not normally distributed. Neurocognitive dysfunction, defined using RCI, will be compared between patients with and without APOE4 using a Chi-square test.

Longitudinal modeling will be used to determine the effect of APOE4 status on neurocognitive function across time using the standardized test scores that adjust for age, gender, and education when necessary. Specifically, mixed effects models utilizing maximum likelihood estimation will incorporate various covariates in addition to APOE4 status such treatment with HA and a treatment with HA by APOE4 interaction. Depending on the amount of missing data, a joint model may be considered that will model the repeated measures and time to missing assessment jointly.

Time to cognitive function failure, defined as the first failure on any neurocognitive test using RCI, will be assessed using cumulative incidence treating death as a competing risk. Patients with and without APOE4 allele will be tested using Gray's test. A cause-specific Cox model for time to cognitive function failure will be performed to assess the effects of HA treatment, APOE4 status, and treatment with HA by APOE4 interaction. If the proportional hazards assumption is violated, other methods, such an inclusion of a time-varying covariate will be used.

Radiographic Evaluation:

The effect of white matter injury and hippocampal volume (see Section 11.1 for more detail) on time to neurocognitive failure and baseline neurocognitive function will be examined. Both of these will be evaluated through MRI scans using auto-contoured and, only for hippocampal volume, physician-contoured scores. Concordance rates for white matter injury will be assessed using Kappa statistics. The auto-contoured scores will be used for the remaining analyses due to the number of physicians reviewing the scans. White matter injury is measured by FLAIR volume change and is a continuous variable. Hippocampal volume is measured as a continuous variable also. Both will be covariates considered in the Cox proportional hazards model to assess the impact on time to neurocognitive failure and the longitudinal modeling of neurocognitive function described in Section 14.6.2. Pearson correlation coefficients will be used to assess the effect of hippocampal volume and FLAIR volume change on baseline neurocognitive function, as measured by the HVLT-R, COWA, and TMT, separately for each arm.

An analysis will be conducted to determine if an appropriate cut-point for baseline hippocampal volume and baseline FLAIR volume exists to categorize neurocognitively deteriorated and not deteriorated patients. Receiver operating curves (ROC) will be used to determine area under the curve (AUC) for both volumes and sensitivity and specificity for cutpoints. Once a cutpoint is determined, it will be included as a covariate in longitudinal and cause-specific Cox models to determine the effect of the dichotomous hippocampal volume and FLAIR volume variables on neurocognition. These models will also assess the interaction between hippocampal volume/FLAIR volume and treatment with HA. The effect of hippocampal volume and FLAIR volume on the cumulative incidence of neurocognitive failure will be tested using Gray's test.

14.6.3 Power Calculations

Patient-reported cognitive function decline at 6 months

For patients with small cell lung carcinoma (SCLC) eligible for PCI, HA-PCI reduces decline in patient- reported cognitive functioning as assessed by the self-reported cognitive functioning scale within the EORTC QLQ-C30. Patient-reported cognitive function decline at 6 months will be assessed using the cognitive functioning subscale of the EORTC QLQ-C30 and compared between patients receiving HA-PCI and those receiving PCI only. Using data from RTOG 0212, 50% of patients experienced patient-reported cognitive functioning deterioration at 6 months from the start of treatment. The proposed sample size (N=198) would provide 94% power to detect a 50% relative reduction (PCI 50% vs. HA-PCI 25%) in the likelihood of decline in patient-reported cognitive functioning at 6 months using Fisher's exact test with a two-sided alpha=0.05.

Intracranial Relapse

As part of the phase III analysis, the phase IIR primary endpoint of 12-month intracranial relapse risk also will be assessed as a secondary endpoint. With an estimated 287 evaluable patients, as death and non-compliance will not be an issue for this specific analysis, and an assumed difference in proportions of 4.5% under the alternative, a 2-sample test of difference in proportions with a 1-sided alpha of 0.05 requires 80% statistical power to evaluate a non-inferiority margin of 17.2%.

Cost-Effectiveness

The clinical endpoint is the metric driving the power calculation for trial. With alpha=0.05 (1-sided) and 1 interim analysis for efficacy, a total of **98 analyzable patients per arm** would ensure 80% statistical power to detect a 14.5% absolute reduction in the probability of HVLT-R Delayed Recall deterioration at 6 months using a test of difference in proportions. The power to rule out cost-effectiveness ratios exceeding the maximum willingness to pay values described previously is of interest. This is given by the equation

$$Z_\beta = \sqrt{\frac{n(WQ - C)^2}{2(sd_c^2 + (Wsd_q)^2 - (2W\rho sd_c\, sd_q))}} - Z\alpha$$

where n is the number of patients in each arm, W is the maximum willingness to pay, Q is the effect difference, C is the cost difference, sd_c is the expected standard deviation for

the cost in each treatment group, sd_q is the expected standard deviation for the effect and ρ is the expected correlation of the difference in cost and effect. We base our estimate for our primary sample size analysis on an expected increase of discounted QALYs during 3 years of follow up of 0.14 (SD, 0.07), an expected increase in costs of $2441 (based on the expected difference in the costs of radiation therapy, and not reflecting potential cost offsets) (SD, 6000), a correlation of the difference in costs and QALYS of 0.05, a willingness to pay of $50,000 per QALY, a 2-tailed alpha of 0.05, and a sample size of 98 per treatment group. The power to conclude that the resulting ratio is acceptable exceeds 99%.

miRNA Signatures

This endpoint will be powered using categorical miRNA signatures using the median as a cut-point. All patients will be considered initially, but if memantine use confounds the results, it will be limited to only those who did not receive memantine. About 70% are expected to consent and submit blood which leaves approximately 138 of the planned 196 evaluable patients for this analysis. About 50% of patients are expected to receive memantine, reducing the number of evaluable patients to 69. The table below provides the statistical power to detect each of the specified HRs using a two-sided alpha=0.05 (Schoenfeld 1983).

Hazard Ratio	Statistical Power if n=69	Statistical Power if n=138
1.5	51.6%	76.9%
1.6	62.1%	86.7%
1.7	71.2%	92.9%
1.8	78.7%	96.5%
1.9	84.6%	98.3%

APOE Genotyping

Approximately 529 patients are expected to have APOE4 status determined from centrally collected blood on NRG-CC003 as well as NRG/RTOG 0933 and NRG-CC001 which will be combined for this analysis. This includes patients who have completed at least baseline neurocognitive testing. It is expected that 20% of patients (n=423) will either be non-compliant, have withdrawn consent, or died and thus have missing neurocognitive test scores at 2 months. The prevalence of APOE4 allele is assumed to be 30% based on results from a similar analysis on NRG/RTOG 0614 (14). Thus, there is 80% statistical power to detect a HR=1.35 in time to neurocognitive failure assuming a two-sided type I error of 0.05.

Radiographic Evaluation

Of the 98 evaluable patients, 10% are expected to be missing either the image or the correct image, resulting in 88 evaluable patients per arm. Using a Bonferroni-adjusted type I error of 0.025 to account for both FLAIR volume and hippocampal volume, there is 95% statistical power to detect a correlation coefficient of 0.4 between baseline FLAIR volume/hippocampal volume with 6 month change in HVLT-R total recall.

14.7 Exploratory Hypotheses and Endpoints (01-JUL-2022)

Hopefulness: The AHS and PHQ 2 are collected at baseline and at 6 months from the start of treatment. The AHS is a 12-item tool rated on an 8-point Likert scale. There are 2 subscales with scores calculated by the average of the item scores: agency (items 2, 9, 10, and 12) and pathway (items 1, 4, 6, and 8). The change from baseline to 6 months will be compared between arms using the t-test (or Wilcoxon test if not normally distributed) in the two subscale scores. These scores will be correlated with the EORTC- QLQ-C30 total score using a Pearson correlation coefficient.

Since hopefulness is closely tied with depression, the PHQ-2 will be used to assess depression between treatment arms. Scores range from 0-6, with scores ≥ 3 indicating depressive symptoms. The distribution of depression at baseline and 6 months will be compared between treatment arms using a chi-square test. There is also an overlap between "belief," "faith," and "hope" so it is hypothesized that religious people are more hopeful. A general linear model will be used to assess hopefulness, performed separately for the AHS subscale scores, between treatment arms while adjusting for depression, religion, and stratification factors.

Feasibility of Remote Neurocognitive Testing: During the COVID-19 pandemic, remote neurocognitive testing was permitted on NRG-CC003. The feasibility of conducting the remote testing will be assessed using descriptive measures, such as patient compliance, proportion of patients who attempted and completed remote testing, and frequency of disruptions. Since no outcome data (i.e. neurocognitive test outcomes, survival, etc.) will be reported, this endpoint will be analyzed prior to the meeting the primary endpoint.

14.8 Statistical Analysis Plan for Translational Research Endpoints (14-FEB-2019)

MiRNA levels detected by the microarray will be processed and normalized using R/Biocon-ductor statistical software and appropriate analytical packages. Data will undergo stringent quality control and will be normalized using quantile normalization. Normalized data will be used to detect differentially expressed miRNAs.

Correlation with cognitive decline will be carried out using regression analysis in R statistical software.

QPCR validation will be evaluated using standard delta-delta Ct.

14.9 Gender/Ethnicity/Race Distribution (15-JUNE-2020)

No differences across the patient subsets below are anticipated.

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	8	12	20
Not Hispanic or Latino	149	223	372
Ethnic Category: Total of all subjects	157	235	**392**
	Gender		
Racial Category	**Females**	**Males**	**Total**

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	1	3	4
Asian	2	3	5
Black or African American	11	13	24
Native Hawaiian or other Pacific Islander	1	2	3
White	142	214	356
Racial Category: Total of all subjects	157	235	**392**

REFERENCES (15-JUNE-2020)

Aaronson NK, Ahmedzai S, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 85(5): 365-76.

Abayomi OK. (1996) Pathogenesis of irradiation-induced cognitive dysfunction. *Acta Oncol*. 35(6): 659-663.

Arriagada R, Le Chevalier T, et al. (1995) Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst*. 87(3): 183-190.

Arriagada R, Le Chevalier T, et al. (2002) Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: Analysis of 505 randomized patients. *Ann Oncol*. 13(5): 748-754.

Auperin A, Arriagada R, et al. (1999) Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 341(7): 476-484.

Badia X, Herdman M, Kind P. (1998) The influence of ill-health experience on the valuation of health. *Pharmacoeconomics*. 13: 687-696.

Benedict HB, Schretlen D, et al. (2010) Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-form and Test-Retest Reliability. *Clinical Neuropsychologist*. 12(1): 43-55.

Bergman B, Sullivan M, et al. (1992) Quality of life during chemotherapy for small cell lung cancer. II. A longitudinal study of the EORTC Core Quality of Life Questionnaire and comparison with the Sickness Impact Profile. *Acta Oncol*. 31(1): 19-28.

Breteler MM, van Amerongen NM, et al. (1994) Cognitive correlates of ventricular enlargement and cerebral white matter lesions on magnetic resonance imaging. The Rotterdam Study. *Stroke*. 25: 1109-15.

Brown PD, Pugh S, et al. (2013) Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain raditherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol*. 15(10): 1429-37.

Caine C, Mehta MP, et al. (2014) CogState computerized memory tests in patients with brain metastases: secondary endpoint results of RTOG 0933. European Society for Radiotherapy and Oncology Annual Meeting, 2014.

Carmichael O, Schwarz C, et al. (2010) Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. *Arch Neurol*. 67: 1370-1378.

Chang EL, Wefel JS, et al. (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 10(11): 1037-1044.

Chelune GJ, Naugle RI, Luders H, Sedlak J, Awad IA. Individual change after epilepsy surgery: practice effects and base-rate information. *Neuropsychology.* 1993;7(1):41-52.

Christie LA, Acharya MM, et al. (2012) Impaired cognitive function and hippocampal neurogenesis following cancer chemotherapy. *Clin Cancer Res*. 18(17): 1954-65.

Clayton JM, Hancock K, Parker S, et al. (2008) Sustaining hope when communicating with termially ill patients and their families. *Psycho-Oncology*. 17: 641-659.

Clerx L, van Rossum IA, et al. (2013) Measurements of medial temporal lobe atrophy for prediction of Alzheimer's disease in subjects with mild cognitive impairment. *Neurobiol Aging*. 34(8): 2003-2013.

Colliot O, Chetelat G, et al. (2008) Discrimination between Alzheimer disease, mild cognitive impairment, and normal aging by using automated segmentation of the hippocampus. *Radiology*. 248(1): 194-201.

Conill C, Berenguer J, et al. (2007) Incidence of radiation-induced leukoencephalopathy after whole brain radiotherapy in patients with brain metastases. *Clin Translational Oncol.* 9, 590-595.

Cosentino S, Scarmeas N, et al (2008) APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. *Neurology*. 70:1842-9.

Cox DR. (1972) Regression models and life tables. *J Royal Stat Soc (series B)*. 34:187-229.

Csernansky JG, Wang L, et al. (2005) Preclinical detection of Alzheimer's disease: Hippocampal shape and volume predict dementia onset in the elderly. *Neuroimage.* 25(3): 783-792.

CuiY, Gondi V, et al. (2013) Credentialing in hippocampal sparing techniques for RTOG 0933: Quality assurance report. *IJORBP*. Submitted.

Danborg PB, Simonsen AH, Waldemar G, et al. (2014) The potential of microRNAs as biofluid markers of neurodegenerative diseases--a systematic review. *Biomarkers*. Jun;19(4):259-68.

Fairclough D. (2010) *Design and analysis of quality of life studies in clinical trials* (2nd ed.). Boca Raton, FL: Chapman & Hall/CRC.

Fairclough DL, Peterson HF, Cella D, Bonomi P. (1998) Comparison of several model-based methods for analysing incomplete quality of life data in cancer clinical trials. *Stat Med*. Mar 15-Apr 15;17(5-7):781-796.

Farrer LA, Cupples LA, et al (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA*. 278:1349-56.

Ferrer I, Serrano T, et al. (1993) X-ray-induced cell death in the developing hippocampal complex involves neurons and requires protein synthesis. *J Neuropathol Exp Neurol*. 52(4): 370-378.

Fleischman DA, Yu L, et al. (2013) Faster cognitive decline in the years prior to MR imaging is associated with smaller hippocampal volumes in cognitively healthy older persons. *Front Aging Neurosci.* 5: 21.

Fransquet PD, Ryan J. (2018) Micro RNA as a potential blood-based epigenetic biomarker for Alzheimer's disease. *Clin Biochem*. Aug;58:5-14.

Gorgulho A, De Salles A, Mattozo C, et al. *Definition of a Treatment Modality by the Patients Using a Decision- Making Software*. Poster presented at: Annual Meeting of the American Association of Neurological Surgeons; April 18-20, 2005; San Francisco, CA.

Gorgulho A, De Salles A, Mattozo C, et al. *VisionTree Software - Stereotactic Radiation vs. Conventional Surgery*. Paper presented at: Annual Meeting of the International Stereotactic Radiosurgery Society; June 23-27, 2007; San Francisco, CA

Gilbertson MW, Shenton ME, Ciszewski A, et al. (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience*. 5: 1242-1247.

Gilboody S, Richards D, Brealey S, Hewitt C. (2007) Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): A diagnostic meta-analysis. *J Gen Inter Med*. 22: 1596-1602.

Glick HA, Polsky D, Willke RJ, et al. (1999) A comparison of preference assessment instruments used in a clinical trial: Responses to the visual analog scale from the EuroQol EQ-5D and the Health Utilities Index. *Med Decis Making*. 19: 265-275, 1999.

Glick HAD, Sonnad JA, et al. (2015) *Analyzing censored cost, in Economic Evaluation in Clinical Trials.* HA Glick, Editor. Oxford: New York , NY. p. 123-139.

Godsil BP, Kiss JP, Spedding M, Jay TM. (2013): The hippocampal-prefontal pathway: The weak link in psychiatric disorders? *Eur Neuropsychopharmacol*. 23: 1165-1181.

Gondi V, Pugh SL, et al. (2014) Preservation of memory with conformal avoidance of the hippocampal neural stem cell compartment during whole-brain radiotherapy for brain

metastases (RTOG 0933): A phase 2 multi-institutional trial. *J Clin Oncol*. Oct 27 [Epub ahead of print].

Gondi V, Hermann BP, et al. (2013) Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *IJROBP*. 85(2): 348-354.

Gondi V, Paulus R, et al. (2013) Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: Pooled secondary analysis of radiation therapy oncology group randomized trials 0212 and 0214. *IJROBP.* 86(4): 656-664.

Gondi V, Tolakanahalli R, et al. (2010). Hippocampal-sparing whole-brain radiotherapy: a "how-to" technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. *IJROBP.* 78(4): 1244-1252.

Gondi V, Tome WA, et al. (2010) Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: safety profile for RTOG 0933. *Radiotherapy and Oncology*. 95(3): 327-331.

Grattan-Smith PJ, Morris JG, et al. (1992). Neuropsychological abnormalities in patients with pituitary tumours. *Acta Neurol Scand*. 86(6): 626-631.

Gray RJ. (1988) A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Statist*. 16:1141-1154.

Gregor A, Cull A, et al. (1997) Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer*. 33(11): 1752-1758.

Haasl RJ, Ahmadi MR, Meethal SV, et al. A luteinizing hormone receptor intronic variant is significantly associated with decreased risk of Alzheimer's disease in males carrying an apolipoprotein E epsilon4 allele. BMC Med Genet. 2008;9:37. Epub 2008/04/29. doi: 1471-2350-9-37 [pii] 10.1186/1471-2350-9-37. PubMed PMID: 18439297; PubMed Central PMCID: PMC2396156.

Ho SM, Judy WH, Kayan PB, et al. (2012) Hope-based intervention for individuals susceptible to colorectal cancer: A pilot study. *Familial Cancer*. 11: 545-551.

Hochstenbag MM, Twijnstra A, et al. (2000) Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. *J Neurooncol*. 48(3): 243-248.

Hsu F, Carolan H, et al. (2010) Whole brain radiotherapy with hippocampal avoidance and simultaneous integrated boost for 1-3 brain metastases: a feasibility study using volumetric modulated arc therapy. *IJROBP*. 76(5): 1480-1485.

Jack CR, Jr, Bernstein MA, et al. (2008) The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J Magn Reson Imaging*. 27(4): 685-691.

Jack CR, Jr, Petersen RC, et al. (1997). Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology*. 49(3): 786-794.

Jacobson NS, Truax P. (1991) Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 59:12-9.

Johnson JA, Coons SJ. (1998) Comparison of the EQ-5D and SF-12 in an adult U.S. sample. *Qual Life Res*. 7: 155-166.

Johnson JA, Coons SJ, Ergo A, et al. (1998b) Valuation of EuroQol (EQ-5D) health states in an adult U.S.sample. *Pharmacoeconomics*. 13: 421-433.

Johnson JA, Ohinmaa A, Murti B, et al. (2000) Comparison of Finnish and U.S.-based visual analog scale valuations of the EQ-5D measure. *Med Decis Making*. 20:281-289.

Kantarci KS, Weigand D, et al. (2013) MRI and MRS predictors of mild cognitive impairment in a population-based sample. *Neurology.* 81(2): 126-133.

Kaplan EL, Meier P. (1958) Nonparametric estimation from incomplete observations. *J Amer Stat Assoc*. 53:457-81.

Kundapur V, Ellchuk T, et al. (2013) Can hippocampus be spared in patients with small cell lung carcinoma during cranial radiation therapy? *J Clin Oncol*. 31: 7596S.

Langer CJ. Mehta MP. (2005) Current management of brain metastases, with a focus on systemic options. *J Clin Oncol*. 23(25): 6207-6219.

Le Pechoux C, Dunant A, et al. (2009) Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): A randomised clinical trial. *Lancet Oncol*. 10(5): 467-474.

Lee PW, Hung BK, et al. (1989) Effects of radiation therapy on neuropsychological functioning in patients with nasopharyngeal carcinoma. *J Neurol Neurosurg Psychiatry*. 52(4): 488-492.

Leung SF, Kreel L, et al. (1992) Asymptomatic temporal lobe injury after radiotherapy for nasopharyngeal carcinoma: incidence and determinants. *Br J Radiol*. 65(776): 710-714.

Levi O, Michaelson DM. (2007) Environmental enrichment stimulates neurogenesis in apolipoprotein E3 and neuronal apoptosis in apolipoprotein E4 transgenic mice. *J Neurochem*. 100:202-10.

Li J, Bentzen S, et al. (2008) Relationship between neurocognitive function and quality of life after whole-grain radiotherapy in patients with brain metastasis. *IJROBP.* 71: 64-70.

Li J, Bentzen S, et al. (2007) Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol*. 25(10): 1260-1266.

Libscomb, J., Weinstein, MC, Torrance, GW. (1996) *Time Preference, in Cost-effectiveness in Health and Medicine.* M. Gold, Siegel, JE, Russell, LB, Weinstein, MC, Editor. Oxford: New York, NY. p. 214-246.

Little RA. (1995) Modeling the Drop-out Mechanism in Repeated-Measures Studies. *J Am Stat Assoc*. 90(431):1112-1121.
Madsen TM, Kristjansen PE, et al. (2003) Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat. *Neuroscience*. 119(3): 635-642.

Mahley RW, Weisgraber KH, et al. (2006) Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci USA*. 103:5644-51.

Mantel N. (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports*. 5:163-70.

Mengel-From J, Feddersen S, Halekoh U, et al. (2018) Circulating microRNAs disclose biology of normal cognitive function in healthy elderly people - a discovery twin study. *Eur J Hum Genet*. Sep;26(9):1378-1387.

Meyers CA, Geara F, et al. (2000) Neurocognitive effects of therapeutic irradiation for base of skull tumors. *IJROBP*. 46(1): 51-55.

Mizumatsu S, Monje ML, et al. (2003) Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res*. 63(14): 4021-4027.

Monaco EM, Faraji AH, et al. (2013) Leukoencephalopathy after whole-brain radiotherapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. *Cancer*. 119(1): 226-32.

Monje ML, Mizumatsu S, et al. (2002)Irradiation induces neural precursor-cell dysfunction. *Nat Med*. 8(9): 955-962.

Monje ML, Toda H, et al. (2003) Inflammatory blockade restores adult hippocampal neurogenesis. *Science*. 302(5651): 1760-1765.

Morey RA, Petty CM, et al. (2009). A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes. *Neuroimage*. 45(3): 855-866.

Movsas B, Hunt D, et al. (2011) Electronic web-based technolog significantly improves quality of life data collection: Analysis of RTOG 0828. *IJROBP*. 81(2): S111.

Nagai R, Tsunoda S, et al. (2000) Selective vulnerability to radiation in the hippocampal dentate granule cells. *Surg Neurol*. 53(5): 503-506; discussion 506-507.

Osoba D, Zee B, et al. (1994) Psychometric properties and responsiveness of the EORTC quality of life questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. *Qual Life Res.* 3(5): 353-64.

Osoba D, Aaronson NK, et al. (1996) The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res*. 5(1): 139-50.

Osoba D, Aaronson NK, et al. (1997) Effect of neurologic dysfunction on health-related quality of life in patients with high-grade glioma. *J Neurooncol*. 34(3): 263-78.

Osoba D, Aaronson NK, et al. (1997b) Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. *Qual Life Res*. 6(2): 103-8.

Pedroso A, De Salles A, Mattozo C, et al. Decision Support Software Use For Patients: Immediate and Post Evaluation. Paper presented at: Annual Meeting of the Congress of Neurological Surgeons; April 28-29, 2006; Los Angeles, CA.

Peiffer AM, Leyrer CM, et al. (2013) Neuroanatomical target theory as a predictive model for radiation-induced cognitive decline. *Neurology*. 80(8): 747-753.

Peissner W, Kocher M, et al. (1999) Ionizing radiation-induced apoptosis of proliferating stem cells in the dentate gyrus of the adult rat hippocampus. *Brain Res Mol Brain Res*. 71(1): 61-68.

Pintilie M. (2002) Dealing with competing risks:Ttesting covariates and calculating sample size. *Statistics in Medicine.* 21(22):3317-3324.

Raber J, Rola R, et al. (2004) Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res*. 162(1): 39-47.

Redmond KJ, Hales RK, Anderson-Keightly H, et al. (2017) Prospective Study of Hippocampal-Sparing Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer. *IJROBP*. Jul 1;98(3):603-611.

Regine WF, Schmitt FA, et al. (2004) Feasibility of neurocognitive outcome evaluations in patients with brain metastases in a multi-institutional cooperative group setting: results of Radiation Therapy Oncology Group trial BR-0018. *IJROBP*. 58(5): 1346-1352.

Reilly MC, Zbrozek AS, Dukes E (1993) The validity and reproducibility of a work productivity and activity impairment measure. *PharmacoEconomics*. 4(5):353-365.

Rizopoulos D. (2012) *Joint models for longitudinal and time-to-event data with applications in R. Boca Raton, FL*: Chapman & Hall/CRC.

Roman DD, SP. (1995) Neuropsychological effects of cranial radiation: Current knowledge and future directions. *IJROBP.* 31: 983-998.

Sabsevitz DS, Bovi JA, et al. (2013) The role of pre-treatment white matter abnormalities in developing white matter changes following whole brain radiation: a volumetric study. *J Neuro-oncology.* DOI 10.1007/s11060-013-1181-8

Sakata K, Aoki Y, et al. (1993) Analysis of the results of combined therapy for maxillary carcinoma. *Cancer*. 71(9): 2715-2722.

Schoenfeld DA. (1983). Sample-size formula for the proportional hazards regression model. *Biometrics*. 39(2):499-503.

Schultz MW, Chen J, Woo HH, et al. (2002) A comparison of techniques for eliciting patient preferences in patients with benign prostatic hyperplasia. *J Urol*. 168: 155-159.

Serizawa T, Ono J, et al. (2002) Gamma knife radiosurgery for metastatic brain tumors from lung cancer: A comparison between small cell and non-small cell carcinoma. *J Neurosurg*. 97: 484-488.

Shaw E, Su J, et al. (1994) Prophylactic cranial irradiation in complete responders with small-cell lung cancer: Analysis of the Mayo Clinic and North Central Cancer Treatment Group data bases. *J Clin Oncol*. 12(11): 2327-2332.

Slotman B, Faivre-Finn C, et al. (2007) Prophylactic cranial irradiation in extensive small-cell lung cancer. *New England J Med*. 357(7): 664-672.

Snyder CR. (1989) Reality negotiation: From excuses to hope and beyond. *J Social and Clinical Psych.* 8: 130-157.

Stuschke M, Eberhardt W, Pottgen C, et al. (1999) Prophylactic cranial irradiation in locally advanced non-small-cell lung cancer after multimodality treatment: long-term follow-up and investigations of late neuropsychologic effects. *J Clin Oncol*. Sep;17(9):2700-9.

Swennen MHJ, Bromberg JE, et al. (2004) Delayed radiation toxicity after focal or whole brain radiotherapy for low-grade glioma. *J Neuro-Oncology*. 66: 333-339.

Sun A, Bae K, et al. (2011) Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: Neurocognitive and quality-of-life analysis. *J Clin Oncol*. 29(3): 279-286.

Tada E, Parent JM, et al. (2000) X-irradiation causes a prolonged reduction in cell proliferation in the dentate gyrus of adult rats. *Neuroscience.* 99(1): 33-41.

Takahashi T, Yamanaka T, Seto T, et al. (2017) Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. May; 18(5):663-671.

Teipel SJ, Grothe M, et al. (2013). Relevance of magnetic resonance imaging for early detection and diagnosis of Alzheimer disease. *Med Clin North Am*. 97(3): 399-424.

Trippoli S, Vaiani M, Lucioni C, et al. (2001) Quality of life and utility in patients with non-small cell lung cancer. Quality-of-life study group of the master 2 project in pharmacoeconomics. *Pharmacoeconomics* . 19: 855-863.

van de Pol LA, van der Flier WM, Korf ES, Fox NC, Barkhof F, Scheltens P. (2007) Baseline predictors of rates of hippocampal atrophy in mild cognitive impairment. *Neurology*. 69(15): 1491-7

Verbeke G, Molenberghs G. (2000) *Linear Mixed Models for Longitudinal Data*. New York, NY: Springer-Verlag.

Villasana L, Poage C, et al. (2008) Passive avoidance learning and memory of 56Fe sham-irradiated and irradiated human APOE transgenic mice. *Radiats Biol Radioecol*. 48:167-70.

Wassenberg MW, Bromberg JE, Witkamp TD, Terhaard CH, Taphoorn MJ (2001) White matter lesions and encephalopathy in patients treated for primary central nervous system lymphoma. *J Neuro-oncology*. 52 (1):73-80

Wegner RE, Olson AC, et al. (2011) Stereotactic radiosurgery for patients with brain metastases from small cell lung cancer. *IJROBP*. 81(3): e21-e27.

Welzel T, Niethammer A, et al. (2008) Diffusion tensor imaging screening of radiation induced changes in the white matter after prophylactic cranial irradiation of patients with small cell lung cancer: First results of a prospective study. *Amer J Neuroradiology.* 29: 379-383.

Welzel G, Steinworth S, Wenz F. (2005) Cognitive effects of chemotherapy and/or cranial irradiation in adults. *Strahlentherapie und Onkologie.* 181: 141-156.

Wolfson AH, Bae K, et al. (2011) Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: Impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *IJROBP*. 81(1): 77-84.

Wu AJ, Foster A, et al. (2013) Factors influencing utilization of prophylactic cranial irradiation in limited-stage small cell lung cancer. *J Thor Oncol*. 8(2): S539.

Wu AW, Jacobson KL, Frick KD, et al. (2002) Validity and responsiveness of the EuroQol as a measure of health-related quality of life in people enrolled in an AIDS clinical trial. *Qual Life Res*. 11: 273-282.

Zelen M. (1974) The randomization and stratification of patients to clinical tials. *J Chron Dis*. 27:365-375.

APPENDIX I: CERTIFICATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY (01-JUL-2022)

EXAMINER CERTIFICATION FOR NRG-CC003

Institutions with patients participating in the quality of life/neurocognitive function components of this study must meet certification requirements for administering neurocognitive assessments. The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study must be pre-certified by Dr. Wefel (see Section 8.2). Examiners who have completed the full certification procedure to perform these tests for RTOG 0534, 0834, 1114, NRG-BN001, or NRG-CC001 during the past 6 months do not need to complete the full certification procedure again, but the certification worksheet for NRG-CC003 must be faxed to Dr. Wefel for documentation purposes with information regarding the examiner's prior certification (protocol number, date of certification). If these criteria are met, each examiner and NRG Oncology will be notified of the examiner's recertification status for NRG-CC003. Examiners who have not completed the full certification procedure for RTOG 0534, 0834, 1114, NRG-BN001, or NRG-CC001 within the past 6 months must complete the full certification procedure to be recertified to ensure continued familiarity with study procedures. All certified test administrators are required to attest to their proficiency in the language (English or French) in which the test is administered to the patient. Only certified test administrators proficient in the primary language of the patient are permitted to test the patient.

Prior to registering and/or testing a patient, potential examiners must:

1) Read the protocol
2) Read this Appendix (Certification Procedures for the Neurocognitive Test Battery)
3) Go to the CTSU website (www.ctsu.org) and use your username and password to access the CC003 protocol. Access the "NRG-CC003 Neurocognitive Letter" from the Case Report Forms folder. This letter will provide you with the web address and study specific password for the training video.
4) Obtain copies of the NRG-CC003 Test Instruction and Administration Procedures document, Neurocognitive Assessment Packets (containing the HVLT-R, TMT and COWA), the NRG-CC003 Blank Forms (containing the Neurocognitive Function Coversheet), and the Training Video Post Test (attached to the NRG-CC003 Neurocognitive Letter) from the CTSU website.
5) Watch the training video.
6) Complete the Training Video Post Test.
7) Complete a "practice" assessment with the Neurocognitive Assessment packet.
8) Complete the Certification Worksheet (available on the CTSU website)
9) All materials (i.e., Training Video Post Test, completed practice assessment and Neurocognitive Function Coversheet, certification worksheet) must be scanned and emailed (NeuropsychologyResearch@mdanderson.org) or faxed (713-794-4999) to Dr. Wefel, who will review it and correct any procedural errors with the trainee.

10) If the trainee demonstrates competency, he/she will be notified of the certification approval to administer the tests to study subjects as part of NRG-CC003. A certification approval notice will be sent to NRG Oncology for the registration process and to ensure that only NRG-CC003-approved examiners are testing subjects on protocol NRG-CC003.
11) **All neurocognitive materials for every patient at every time point must be uploaded to Medidata Rave® within 7 days after test administration.**