NRG ONCOLOGY
Radiation Therapy Oncology Group

RTOG 1114

(ClinicalTrials.gov NCT #: 01399372)

Phase II Randomized Study of Rituximab, Methotrexate, Procarbazine, Vincristine, and Cytarabine With and Without Low-Dose Whole-Brain Radiotherapy for Primary Central Nervous System Lymphoma

Amendment 10: September 19, 2019

NRG ONCOLOGY GROUP

RTOG 1114

PHASE II RANDOMIZED STUDY OF RITUXIMAB, METHOTREXATE, PROCARBAZINE, VINCRISTINE, AND CYTARABINE WITH AND WITHOUT LOW-DOSE WHOLE-BRAIN RADIOTHERAPY FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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PHASE II RANDOMIZED STUDY OF RITUXIMAB, METHOTREXATE, PROCARBAZINE, VINCRISTINE, AND CYTARABINE WITH AND WITHOUT LOW-DOSE WHOLE-BRAIN RADIOTHERAPY FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Protocol Agent (1/31/13)

Agent	Supply	NSC #	IND #
Rituximab	Commercial	N/A	Exempt
Methotrexate (MTX)	Commercial	N/A	Exempt
Vincristine	Commercial	N/A	Exempt
Procarbazine	Commercial	N/A	Exempt
Cytarabine	Commercial	N/A	Exempt

Participating Sites(1/31/13)
(NOTE: This study is not open to Canadian sites, due to rituximab distribution.)
☒ U.S. Only
☐ Canada Only
☐ U.S. and Canada
☒ Approved International Member Sites

Document History

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PHASE II RANDOMIZED STUDY OF RITUXIMAB, METHOTREXATE, PROCARBAZINE, VINCRISTINE, AND CYTARABINE WITH AND WITHOUT LOW-DOSE WHOLE-BRAIN RADIOTHERAPY FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

SCHEMA

STRATIFY

RPA Class

Class 1: age ≤ 50

Class 2: age > 50 and KPS ≥ 70

Class 3: age >50 and KPS < 70

RANDOMIZE

Arm A (chemo only)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)		Ara-C Cycle 1	Ara-C Cycle 2
Arm B (chemo + low-dose WBRT)	R-MPV Cycle 1	R-MPV Cycle 2	R-MP Cycle 3 (no vincristine)	R-MP Cycle 4 (no vincristine)	Low-Dose WBRT (13 fx)	Ara-C Cycle 1	Ara-C Cycle 2

1 cycle = 28 days
(8 MTX doses total)

Patient Population: (See Section 3.0 for Eligibility)

- B-cell non-Hodgkin's lymphoma involving the brain, as demonstrated by contrasted MRI and histologic confirmation by one of the following within 6 weeks prior to registration:
  - A positive CSF cytology for lymphoma or a monoclonal lymphocyte population as defined by cell surface markers
  - A biopsy of the vitreous or uvea demonstrating non-Hodgkin's lymphoma
  - Brain biopsy

Required Sample Size: 89 patients

ELIGIBILITY CHECKLIST (4/17/14)
(page 1 of 3)

NRG Oncology Institution #
RTOG 1114
Case #

_____(Y) 1. Does the patient have B-cell non-Hodgkin's lymphoma involving the brain, as demonstrated by contrast-enhance MRI **and** histologic confirmation by one of the following within 6 weeks prior to registration?
- ____(Y/N) A positive CSF cytology for lymphoma or a monoclonal lymphocyte population as defined by cell surface markers
- ____(Y/N) A biopsy of the vitreous or uvea demonstrating non-Hodgkin's lymphoma
- ____(Y/N) Brain biopsy

_____ (Y) 2. Did the patient agree to submit tissue (ie, the original or duplicate cut H/E stained slides and immunohistochemistry studies) for central pathology review post-registration?

_____ (Y) 3. Did the patient show no evidence of systemic non-Hodgkin lymphoma as demonstrated by a CT scan of the chest, abdomen and pelvis within **6** weeks prior to registration?

_____ (Y) 4. Is the patient's age ≥ 18?

_____ (Y) 5. Did the patient have a history and physical examination within 6 weeks prior to registration?

_____ (Y/N) 6. Is the patient's Karnofsky performance status ≥ 50?
- _____ (Y) If no, is the patient's Karnofsky performance status ≥ 30.
- _____ (Y) Is the reason for the poor performance status due to neurologic deficit from primary CNS lymphoma? **Note that if the reason is other than primary CNS lymphoma, the patient is not eligible**.

_____ (Y) 7. Is there documentation of negative HIV-1 testing within 6 weeks prior to study registration?

_____ (Y) 8. Was a CBC/differential obtained within 2 weeks prior to study registration, with adequate bone marrow function per Section 3.1.8?

_____ (Y) 9. Does the patient have adequate liver function within 2 weeks prior to study registration per Section 3.1.9?

_____ (Y) 10. Does the patient have adequate renal function within 2 weeks prior to study registration per Section 3.1.10?

_____ (Y) 11. If the patient is a woman of childbearing potential or a male, has the patient agreed to practice adequate contraception during therapy?

_____ (Y) 12. Has the patient provided study-specific informed consent prior to study registration?

_____ (Y/N) 13. Did the patient have prior invasive malignancy per Section 3.2.1?
- _____ (Y) If yes, is patient disease free for a minimum of 3 years?

_____ (N) 14. Did the patient have prior treatment with chemotherapy or radiotherapy for lymphoma or chronic lymphocytic leukemia? Note: prior chemotherapy for a different cancer is allowable.

_____ (N) 15. Did the patient have prior cranial irradiation?

_____ (N) 16. Does the patient have a severe, active co-morbidity as defined in Section 3.2.4?

_____ (N) 17. Did the patient have a prior allergic reaction to any of the study drugs involved in this protocol?

_____ (Y) 18. Is the patient able to swallow pills?

The following questions will be asked at Study Registration:

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at VA or Military Hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization date

(≤50/>50) 18. Age

(≥70/<70) 19. Karnofsky performance status

_____ 20. Medical oncologist's name

_____(Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 22. Have you obtained the patient's consent for his or her bone marrow/eye biopsy to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 23. Have you obtained the patient's consent for his or her cerebrospinal fluid to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 24. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 25. Have you obtained the patient's consent for his or her buccal cells to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 26. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 27. Have you obtained the patient's consent for his or her bone marrow/eye biopsy to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 28. Have you obtained the patient's consent for his or her cerebrospinal fluid to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 29. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 30. Have you obtained the patient's consent for his or her buccal cells to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 31. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____(Y/N) 32. Did the patient agree to participate in the neurocognitive function/quality of life component?

_____ If no, please provide:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other: specify_____

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

Completed by _____ Date _____

1.0 INTRODUCTION

The optimal treatment for primary central nervous system lymphoma (PCNSL) remains controversial. Historically, WBRT and corticosteroids were considered a mainstay of treatment, achieving a median survival of 15-18 months and a 3% to 4% 5-year survival. In the 1990s, however, evidence emerged from retrospective studies that the addition of high-dose MTX improved survival in PCNSL. RTOG 93-10 played a pivotal role in testing that hypothesis, as the first prospective study demonstrating the value of adding MTX to WBRT (DeAngelis 2002). That study, enrolling 102 patients, achieved a median progression-free survival (PFS) of 24 months and overall survival (OS) of 36.9 months. However, radiotherapy-related neurotoxicity emerged as a major complication of treatment in that and other studies of chemoradiation, affecting 16% to 24% of patients (Abrey 2000; Omuro 2005). Such patients develop a progressive frontal-subcortical dementia that eventually leads to death. Elderly patients are at particular risk, with neurotoxicity rates affecting up to 100% of those patients achieving long-term survival.

Because of the risk of neurotoxicity, several studies tried to investigate the role of chemotherapy-only approaches in PCNSL. In a clinical trial of high-dose MTX (8g/m^2) given as single agent without WBRT, a shorter PFS was observed (median PFS: 13 months), but the OS did not seem to be compromised (median: 55 m) (Batchelor 2003). However, it was unclear whether such short PFS was related to deferring WBRT or to the use of a single-agent regimen rather than a combination of drugs, which may be more effective. In another study of chemotherapy-only treatment for newly diagnosed PCNSL utilizing MTX 5 g/m^2 and 5 other drugs, the PFS was substantially longer, particularly in young patients (median PFS: 20 months for the entire population and not reached in patients under age 60) (Pels 2003). However, the follow-up was relatively short (32 months), and when the same regimen was given without intrathecal (IT) chemotherapy in a second study by the same group, the median PFS was only 8 months (Pels 2009). Although it is possible that IT chemotherapy was important to improve disease control, it is unlikely that it would account for such a striking difference in outcomes. Therefore, results of the first study remain to be reproduced to confirm that an intensive chemotherapy-only regimen can replace WBRT in terms of disease control. In a retrospective study of 64 PCNSL patients younger than 60, patients who achieved a CR after induction chemotherapy were selected to receive maintenance therapy and no consolidation WBRT (Omuro 2010). The median PFS in those patients was 22 months, significantly below the expected for that population, but the 3-year OS was 69%, again suggesting that aggressive salvage therapy (in that study WBRT and/or high-dose chemotherapy with stem-cell rescue) was effective. Because approximately half of the patients required WBRT, neurotoxicity rates were reduced, but not eliminated.

More recently, a large randomized study conducted in Germany has been reported (Thiel 2010). The study was initially designed to evaluate the role of consolidation WBRT following chemotherapy with MTX (4 g/m^2). The protocol was then amended and ifosfamide was added. A total of 551 patients were enrolled, but due to high dropout rates, 318 were analyzed. The study found no statistically significant differences in PFS or OS. The median PFS in the chemotherapy only arm was 12 months versus 18 months in the WBRT arm (p=0.13); the OS was 37 versus 32 months (p=0.80). While remarkable for its size, this study is unfortunately limited by the high dropout rates, relatively inefficient and variable chemotherapy, underpowered non-inferiority design, and insufficient neurotoxicity evaluation. Regardless, findings seem to support the concept that omitting WBRT results in decreased PFS but not OS in PCNSL. It remains, however, unknown whether the potential reduction in WBRT-related neurotoxicity rates justifies the reduction in PFS and on the number of patients cured upfront. No prospective study has investigated the potentially negative impact of early relapses and salvage therapies on the cognitive function of long-term survivors and how that compares to the gains in decreased neurotoxicity rates. Nevertheless, chemotherapy-only treatments have become the preferred treatment strategy in the community.

As an alternative approach, a study lead by MSKCC investigated the use of reduced-dose WBRT in newly diagnosed PCNSL (Shah 2007). In that phase II trial, patients received 5-7 cycles of R-MPV (rituximab, MTX, vincristine, procarbazine). Patients achieving a CR after chemotherapy received dose-reduced WBRT (23.4 Gy), and all others received standard WBRT (45 Gy). Two cycles of high-dose cytarabine were administered after WBRT. The initial cohort of 30 patients has been published (Shah 2007). Among the 21 patients achieving a CR, 19 received the planned 23.4 Gy WBRT. With a median follow-up of 37 months, the 2-year OS and PFS was 67% and 57%, respectively, and no treatment-related neurotoxicity was observed (Correa 2009). Since then, the study has been amended to expand the sample size to 52 patients. Accrual has been completed, and a preliminary analysis (personal data) of

the first 45 patients seems to confirm results of the pilot study. Thirty-one of the 45 patients have received a reduced-dose of 23.4 Gy WBRT. For the entire population, the median PFS has been 40 months and the median OS has not been reached after a median follow-up of 46 months. These results suggest that reduced-dose WBRT achieves disease control that is comparable to full-dose WBRT and likely superior to chemotherapy-only approaches, and that neurotoxicity rates were substantially decreased. However, because the R-MPV-A regimen has not been tested without radiotherapy, it is unclear whether the excellent results are due to a better drug combination or to the addition of reduced-dose WBRT. Therefore, to further evaluate this regimen, we are proposing a randomized phase II study in newly diagnosed PCNSL. The experimental arm will consist of R-MPV followed by reduced-dose radiotherapy, followed by consolidation cytarabine. The control arm will consist of a chemotherapy-only approach, with R-MPV followed by cytarabine, without WBRT. At progression, in both arms, patients will be treated at investigator's discretion. However, to characterize the impact of both RT-related neurotoxicity and disease burden from relapses on cognitive function, all patients will undergo neuropsychological evaluation for 5 years, regardless of progression status.

This study will therefore test the following hypotheses:

- We hypothesize that the addition of low-dose WBRT to R-MPV-A chemotherapy improves progression-free survival (PFS) in newly diagnosed primary central nervous system lymphoma in comparison to R-MPV-A alone. The primary endpoint will be median PFS.
- We hypothesize that the use of low-dose WBRT will result in improved long-term cognitive function outcomes in comparison to full-dose WBRT by decreasing radiation therapy–related neurotoxicity rates. All consenting patients will undergo neuropsychological evaluation throughout the study and results will be compared to historical controls.
- We hypothesize that the addition of low-dose WBRT to R-MPV-A will result in improved long-term cognitive function outcomes in comparison to R-MPV alone by decreasing the cognitive deterioration resulting from early disease recurrence and multiple salvage therapies associated with chemotherapy-only approaches. To capture the cognitive dysfunction associated with disease burden from relapses and salvage treatments, we will perform neuropsychological follow-up in both arms for 5 years, regardless of disease status (including in patients with disease progression), and analyze results utilizing competing-risk methodology accounting for death.
- We hypothesize that the improved neurocognitive outcomes associated with R-MPV-A followed by low-dose WBRT will be achieved without compromising overall survival (OS). We will analyze OS in both arms and compare to historical RTOG data.

1.1 Health-Related Quality of Life and Neurocognitive Function

The literature on formal evaluation of cognitive function, neurotoxicity and QOL in PCNSL is limited. The term "neurotoxicity" has been used to characterize treatment related cognitive dysfunction, but studies reporting on different clinical trials have used subjective definitions of "neurotoxicity", ranging from noticeable cognitive changes found on a routine neurologic exam, to severe and fatal dementia.

The recognition of neurotoxicity as a severe complication of combined chemo-radiotherapy in PCNSL arose from studies conducted in the 90's (Abrey 2000, Deangelis 2002). None of these studies included formal measurements of cognitive function or quality of life. In these studies, which utilized full doses of WBRT, neurotoxicity was defined clinically as per investigator's assessment. Typically, neurotoxicity was defined as progressively severe cognitive dysfunction with frontal-subcortical type of dementia, with associated urinary incontinence and gait ataxia. These symptoms resembled disease recurrence, but imaging only showed leukoencephalopathy. Most patients developing these symptoms died from neurotoxicity in the absence of disease recurrence. These studies utilizing qualitative definitions of neurotoxicity reported cumulative rates of 15-30%, with elderly (>60 yo) at the highest risk (up to 80-100% of long-term survivors). However, there is no information on milder cognitive dysfunction and corresponding impact on quality of life. Moreover, length of followup and absence of competing-risk methodology further limits the interpretation and comparison of such results. In spite of the lack of accurate characterization in these trials, neurotoxicity rates were considered alarming enough to warrant

abandoning WBRT, at the expense of a decrease in PFS and in the number of patients cured upfront.

In an effort to characterize the impact of WBRT in cognitive function and QOL in PCNSL patients, Correa et al (manuscript under review) has retrospectively investigated 50 PCNSL survivors in a cross-sectional study. In that study, the 24 patients who received WBRT at some point throughout their disease course were compared to 26 patients who never received WBRT. Patients treated with WBRT had statistically significantly lower scores on tests of selective attention and memory, in addition to impairment in other domains that did not reach statistical significance. QOL was measured with the FACT-BR and showed significantly higher scores (21.2 vs 29.1; $p<0.003$) in patients who received WBRT. It must be noted that patients who received WBRT as salvage therapy were included in the WBRT group.

A smaller, cross-sectional, study in long-term young (<60y) PCNSL survivors treated with WBRT (Harder 2004) is available. That study evaluated neuropsychological assessment in addition to QOL as measured by the EORTC QLQ-C30 and BCM30 module, in comparison to a matched control group with hematologic malignancies treated with chemotherapy. Cognitive impairment was found in 63% of PCNSL, and only 47% of patients reported excellent QOL (score >5); moreover, several of the QOL subscores were significantly lower than the control population.

Taken together, these two cross-sectional studies depict the cognitive and QOL consequences of radiotherapy in PCNSL survivors, but because of their inherent selection bias and retrospective nature, they do not provide adequate historical controls for evaluation of cognitive function and QOL for future trials.

Conversely, the study conducted at MSKCC utilizing reduced-dose WBRT detailed above (Shah 2007, Correa 2009) is the single prospective report on cognitive function and quality of life. In that study, Correa demonstrated that the reduced doses of radiotherapy did not result in significant cognitive impairment. Among the patients who completed the 2y follow-up, there was a continuous improvement in most of the domains tested, particularly the executive domain ($p<0.05$), although a minor, non-significant decline in verbal memory domain was observed. QOL was evaluated with the FACT-BR, which showed significant improvement in comparison to baseline, and stability over the 2y period, with no late decline. A limitation of this study is that manifestations of radiotherapy-related neurotoxicity are cumulative over time, and longer followup would be necessary for full characterization of treatment-related effects.

As detailed above, evaluation of quality of life and neurocognitive function are important aspects of this present study, as they may be affected by tumor burden, both at initial presentation and at relapse, as well by initial and salvage treatments with chemotherapy and radiotherapy (Omuro 2005). Therefore, this study will incorporate comprehensive evaluation of these aspects, with all patients followed for 5 consecutive years regardless of tumor status.

NRG Oncology has been successfully incorporating quality of life and neurocognitive function evaluation in the multicenter setting. This is exemplified by RTOG 0825, examining the role of bevacizumab in addition to chemoradiotherapy in glioblastomas. Given the high rates of compliance and quality of data being acquired in that study, we will utilize a similar battery of tests, consisting of the following:

- EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/BCM20)
- Neuropsychological evaluation:
    - - Memory: Hopkins Verbal Learning Test-Revised (HVLT-R)
    - - Cognitive Processing Speed : Trail Making Test, Part A
    - - Executive Function: Trail Making Test, Part B
    - - Verbal fluency: Controlled Oral Word Association Test (COWAT)

The EORTC core Quality of Life Questionnaire (QLQ-C30) and a Brain Cancer Module (BCM20) were developed and validated for use in this patient population (Osoba 1996). Extensive health-related quality of life data were obtained during 1 randomized phase II study comparing temozolomide with procarbazine in patients with recurrent glioblastoma (Yung 2000). This study,

which used the EORTC QLC-C30/BCM20, demonstrated an improvement in most domains tested. In addition to the randomized phase II trial described above, the EORTC QLQ-C30/BCM20 has become the standard and has been used in many large cooperative group trials.

The neuropsychological evaluation used in this study consists of a battery of standard, largely validated neurocognitive tests, which have been successfully applied in brain tumor clinical trials (Groves 1999, Levin 2002). This battery has been demonstrated to be practical in terms of cost and burden to the patient, with good compliance in multicenter trials (Meyers 2004). This battery also shares most of the tests with an internationally recognized battery to be utilized in primary CNS lymphoma (Correa 2009). Each institution will undergo a training and certification process, which is already being used for RTOG 0825.

2.0 OBJECTIVES

2.1 Primary

To determine median progression-free survival (PFS) in both arms on an intent-to-treat basis. PFS will be defined as the interval from randomization to progression or death, whichever occurs first.

2.2 Secondary

2.2.1 To determine overall survival (OS) defined as the interval from randomization to death due to any cause.

2.2.2 To determine treatment-related neurotoxicity rates and disease-related cognitive deterioration in each arm, through the following methods:

- Prospective formal neuropsychological evaluation, utilizing competing-risk methodology to account for death as a competing risk to neurotoxicity or cognitive deterioration from relapsed tumor burden/salvage treatment.
- Incidence of clinically defined neurotoxicity as per investigator's assessment. **2.2.3** To determine if there exists differences between the two treatment arms in terms of health-related quality of life and symptoms over time.

2.2.4 To determine response (partial response [PR] and complete response [CR]) rate after MTX-based chemotherapy and after consolidation WBRT.

2.2.5 To determine chemotherapy-related toxicity, measured by CTCAE, v.4.0.

3.0 PATIENT SELECTION

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

3.1 Conditions for Patient Eligibility (10/28/13)

For questions concerning eligibility, please contact the study data manager.

3.1.1 B-cell non-Hodgkin's lymphoma involving the brain, as demonstrated by contrast-enhanced MRI and histologic confirmation by one of the following within 6 weeks prior to registration:

- A positive CSF cytology for lymphoma or a monoclonal lymphocyte population as defined by cell surface markers
- A biopsy of the vitreous or uvea demonstrating non-Hodgkin's lymphoma
- Brain biopsy

NOTE: Patients in whom the type of lymphoma could not be determined or is unknown (eg, not enough tissue for further analysis) are assumed to have a B cell lymphoma and are eligible.

3.1.2 The patient must agree to submit tissue (ie, the original H/E stained slides and immunohistochemistry studies) for central pathology review post-registration (See Section 10 for details).

3.1.3 No evidence of systemic non-Hodgkin lymphoma as demonstrated by a CT scan of the chest, abdomen and pelvis within 6 weeks prior to registration (Note: Bone marrow biopsy is not required for registration but must be obtained prior to start of treatment; see section 4.1)

3.1.4 Age ≥ 18

3.1.5 History and physical examination within 6 weeks of registration

3.1.6 Karnofsky performance status equal to 50 or higher, with the following exception

- Patients with **KPS 30 to 50** are eligible if the reason for the poor performance status is neurologic deficit from primary CNS lymphoma. (Patients with KPS 30 to 50 due to reasons other than primary CNS lymphoma are ineligible. Patients with **KPS under 30** for any reason are ineligible)

3.1.7 Patient must have documentation of negative HIV-1 testing within 6 weeks prior to study registration (Separate counseling and consent as per institutional guidelines)

3.1.8 CBC/differential obtained within 2 weeks prior to study registration, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.);

3.1.9 Adequate liver function within 2 weeks prior to study registration, defined as follows:

- Bilirubin < 2.0 mg/dl
- AST <2.5 times upper limit of normal

3.1.10 Adequate renal function within 2 weeks prior to study registration, defined as follows

- Serum creatinine < 1.5 mg/dl
- Calculated creatinine clearance (CrCl) > 50cc/min/1.73m^2, using the Cockcroft-Gault equation, as follows:

  Male: CrCl (ml/min) = (140-age) X (Actual weight in kg) / 72 x serum Creatinine (mg/dl).

  Female: CrCl (ml/min) = (140-age) X (Actual weight in kg) X 0.85 / 72 x serum Creatinine (mg/dl).

Note: A measured CrCl from a 24 hour urine collection may also be used.

3.1.11 Women of childbearing potential and male participants must agree to practice adequate contraception during therapy

3.1.12 Patient must provide study-specific informed consent prior to study registration

3.1.13 Patient must be able to swallow pills.

3.2 Conditions for Patient Ineligibility (10/28/13)

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible)

3.2.2 Prior treatment with chemotherapy or radiotherapy for lymphoma or chronic lymphocytic leukemia; note that prior chemotherapy for a different cancer is allowable; see section 3.2.1

3.2.3 Prior cranial irradiation

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

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Transmural myocardial infarction within the last 6 months;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
- Known pre-existing immunodeficiency as seen in organ transplant recipient.

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

3.2.6 Prior allergic reaction to any of the study drugs involved in this protocol.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (1/27/15)

See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation.

4.1.1 Bloods: CBC with white cell differential, creatinine, calculated creatinine clearance, BUN, electrolytes, LFTs (ALT, AST, bilirubin), and LDH within 2 weeks of start of treatment.

4.1.2 Routine urinalysis within 2 weeks of start of treatment.

4.1.3 Radiographic studies: Chest X-ray (PA and lateral), MR scan of brain with gadolinium within 2 weeks of starting chemotherapy.

4.1.4 A complete history and physical, including neurologic exam within 2 weeks of start of treatment

- History and physical must consist of full history, including history of present illness, review of systems, past medical history, family history, medication, complete physical and neurological examinations, KPS performance status, height/weight, BSA, corticosteroid use

4.1.5 Lumbar puncture should be performed within 6 weeks of start of treatment in all patients unless contraindicated on the basis of the patient's neurological condition. CSF should be analyzed for cytology, glucose, protein, cell count, and in some patients' oligoclonal bands and lymphocyte markers. (Note: A sample of CSF may be stored for research purposes, per Section 10, if the patient consents.)

4.1.6 Complete ophthalmologic exam including slit lamp within 2 weeks of start of treatment.

4.1.7 Bone marrow biopsy should be performed within 6 weeks of start of treatment and should be sent for routine lab studies. Patients must have the bone marrow biopsy performed prior to start of treatment, but may start treatment while results are awaited. Results should be submitted to NRG Oncology within 1 month of start of treatment. If results indicate presence of lymphoma in the bone marrow, the patient will be removed from study and additional treatment will be left at discretion of treating physician (see Section 11.5 for criteria for study removal). [Note: A bone marrow sample (can be residual) may be stored for research purposes, per Section 10, if the patient consents.]

4.2 Highly Recommended Evaluations/Management (1/31/13)

4.2.1 Hepatitis B Reactivation Prophylaxis

Chemotherapies, particularly rituximab, may result in reactivation of hepatitis B. Screening for hepatitis B is strongly recommended within 6 weeks pre-treatment and should follow institutional guidelines. Results are not needed for patient to start treatment. In patients at risk for hepatitis B reactivation, hepatitis B prophylaxis (e.g. entecavir) should be strongly considered. For reference, MSKCC guideline is as follows:

- Obtain HB surface antigen and HB core antibody. If both are negative, no further action is needed. If either test is positive, obtain HBV PCR and start entecavir 0.5 mg PO daily throughout treatment and for at least 6 months after completion; consider consulting a GI specialist for guidance.

5.0 REGISTRATION PROCEDURES (23-AUG-2019)

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 (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (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 (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- 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

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.

5.1 Regulatory Pre-Registration Requirements (19-SEP-2019)

NOTE: This study is not open to Canadian sites, due to rituximab distribution.

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

Sites 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 to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Requirements for RTOG 1114 site registration:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

- IRB/REB approved consent (International sites only: English Version and native language versions)
  ***Note**: Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology (described below).
- CTSU RT Facilities Inventory Form (if applicable)
- NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Imaging and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

Non-English Speaking Non-North American Institutions:
Translation of 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 Oncology 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.

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5.2 Pre-Registration Requirements for Neurocognitive Function Testing Certification
NOTE: Sites must offer English-speaking participants the opportunity to participate in the neurocognitive function component of this study

Institutions with patients participating in the quality of life/neurocognitive function components of this study must meet certification requirements for administering neurocognitive assessments. Upon review and successful completion of the Neurocognitive Certification, Dr. Denise Correa will notify both the certified examiner and CTSU that the examiner has successfully completed this requirement.

See Appendix IV for certification requirements.

5.3 Registration (8/25/15)
5.3.1 OPEN Registration Instructions

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster. All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org
Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

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

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. 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 web support for assistance with web registration: websupport@acr.org or call the 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.

6.0 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) Is Not Allowed

Protocol chemotherapy treatment must begin within 6 weeks following histologic diagnosis. (See Section 7)
The radiotherapy must start no earlier than 2 weeks and no later than 5 weeks following the end of R-MPV.

6.1 Dose Specifications

Following chemotherapy with R-MPV, all patients in arm B will receive cranial irradiation to a total dose of 2340 cGy (180 cGy per fraction X 13 administered daily over a period of 3 weeks).

The opposed lateral radiation fields will include the whole brain down to the level of C2 ("German helmet" shape) and will exclude the anterior two thirds of the orbit. Treatment will be delivered once daily, 5 fractions per week, over 2.5 weeks. Breaks in treatment should be minimized.

Patients in arm B with ocular involvement will be irradiated without orbital shielding to the full dose of 2340 cGy. If no ocular involvement is evident on initial exam then only the posterior one third of the orbit is to be included in the treatment portal (see 6.4 for details).

Doses are specified as the target dose that will be representative of the dose in the center of the target volume. For 2 opposed coaxial equally weighted beams, the target dose will be specified on the central ray at mid-separation of beams.

6.2 Technical Factors

Treatment shall be delivered with megavoltage machines. Photon beams with energies of between 6 and 10 mV are to be used. Source to skin distances must be at least 80 cm.

6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine position. Head immobilization with a thermoplastic mask or other appropriate device is encouraged. A radio opaque marker should be placed on the right and left soft tissue canthus. Simulation may include a dedicated radiotherapy simulator or a virtual simulation using a treatment planning CT.

6.4 Treatment Planning/Target Volumes

A left and right lateral equally weighted, opposed field arrangement is to be used. Custom blocks or a multi-leaf collimator are to be used to shape the fields such that the meninges are included. Care should be taken in shaping the fields at the skull base to avoid inadvertent shielding of the meninges in the region of the anterior temporal lobes and the cribiform plate. If no ocular involvement is evident on initial exam then only the posterior one third of the orbit is to be included in the treatment portal. (See Fig 1 below) If ocular involvement is evident on initial slit lamp exam the entirety of both eyes will be included in the treatment volume. (See Fig 2 below) The anterior field edge is to be made coplanar via a gantry rotation so as to avoid contralateral ocular divergence. The anterior, posterior, and superior field borders shall include 1-2 cm of “fall off”. The inferior border is the C2-3 inter-space.

Figure 1

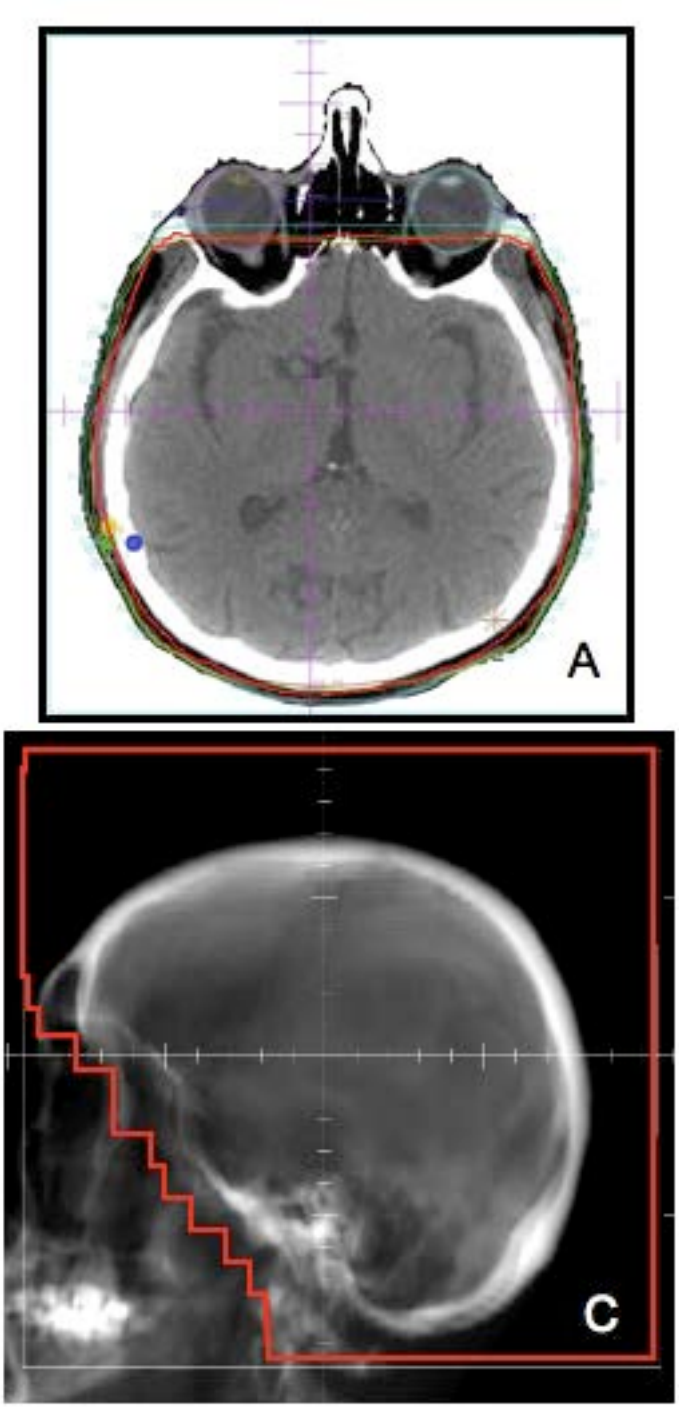
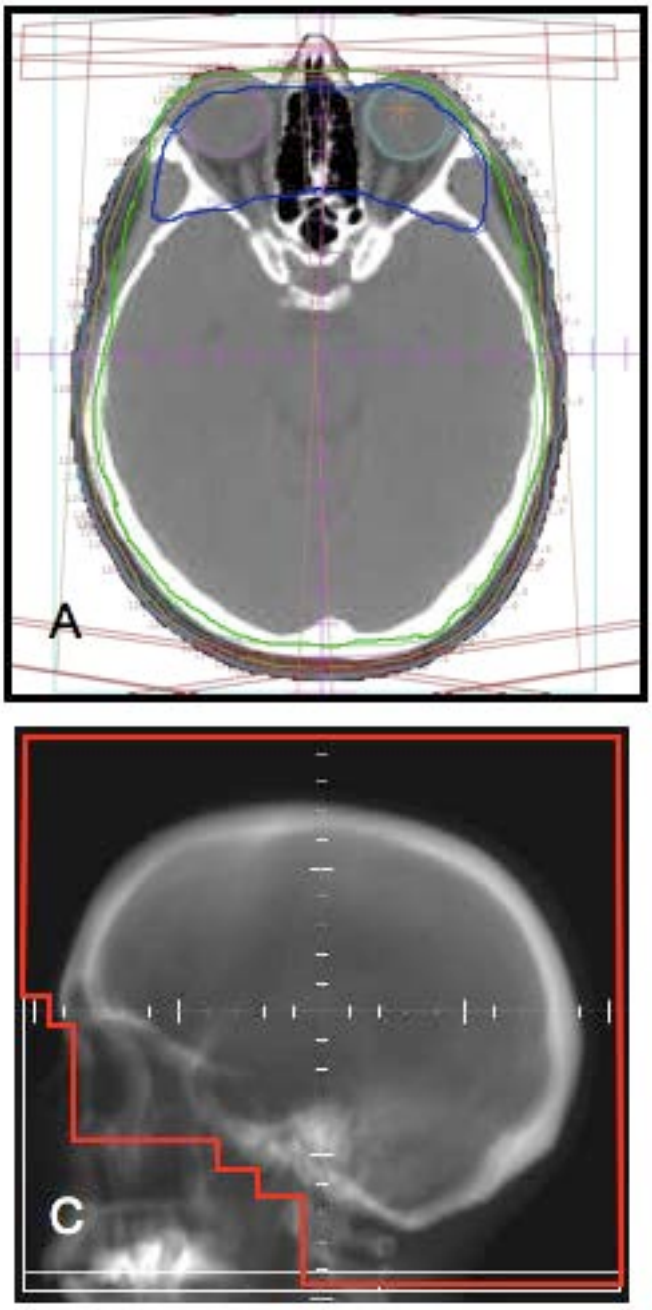


Figure 2



6.5 Documentation Requirements

For patients accrued to the protocol, treatment verification and documentation should be carried out, at least for the first treatment fraction, and more frequently, based on institutional policy; weekly verification is common. We suggest orthogonal images for documenting isocenter setup accuracy for the first fraction. These orthogonal images can be obtained with film or EPID.

6.6 Compliance Criteria

Radiotherapy will be continued without interruption if at all possible. If the sum total of radiotherapy interruptions exceeds 2 normally scheduled treatment days, the treatment will be considered an unacceptable deviation from the protocol and the patient will be considered inevaluable on final data analysis.

6.7 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chair, Joseph A. Bovi, MD, will perform an RT Quality Assurance Review only in the event that an adverse event warrants the collection of the RT data for review.

6.8 Radiation Therapy Adverse Events

6.8.1 Acute Reactions

All patients are likely to develop alopecia, erythema, and dry desquamation of the scalp within the treatment portal. Some patients may experience a headache, anorexia and or nausea. Middle ear congestion is commonly experienced following whole brain RT. Patients requiring treatment to the entire eye are likely to experience conjunctival irritation and may note dry eyes. All of the described acute effects are likely to be reversible with the exception of alopecia.

6.8.2 Late Reactions (> 90 days from RT start)

All patients are likely to have permanent partial or total alopecia corresponding to the treatment portal. Rarely, persistent middle ear effusion(s) requires myringotomy tube placement. There is a low risk of sensory neural hearing loss. All patients are at high risk of developing cataracts, which may or may not require treatment. The probability of cataract formation increases with post treatment survival time. The risk of cataract is greatest for patients who require treatment to the entire eye. All patients are at risk for developing neurocognitive dysfunction; the greatest risk is for patients > 60 years of age. There is a low risk of developing radiation necrosis of the brain, which may require surgery and/or extended use of steroids.

6.9 Radiation Therapy Adverse Event Reporting

See Sections 7.9 and 7.10

7.0 DRUG THERAPY

Protocol chemotherapy treatment must begin within 6 weeks following histologic diagnosis. The radiotherapy must start no earlier than 2 weeks and no later than 5 weeks following the end of R-MPV (See Section 6.0).

7.1 Treatment Arms (10/28/13)

7.1.1 Arm A (Chemotherapy-Only): Chemotherapy With Rituximab, Methotrexate (MTX), Procarbazine, Vincristine And Consolidation Cytarabine (R-MPV-A) Without WBRT

4 cycles of R-MPV (1 cycle = 28 days; vincristine not given during cycles 3 and 4), as follows:

Day	Agent	Dose
Day 1	Rituximab	500 mg/m^2
Day 2	MTX	3.5 g/m^2 (standard hydration/leucovorin support)
	Vincristine	1.4 mg/m^2, dose capped at 2.4mg. **Vincristine is given during cycles 1 and 2 only.**

Days 2-8	Procarbazine	100 mg/m^2/day
Days 10-14	Filgrastim* (Neupogen)	5 mcg/kg/ day SC (the use of filgrastim is mandatory)
Day 15	Rituximab	500 mg/m^2
Day 16	MTX	3.5 g/m^2 (standard hydration/leucovorin support)
	Vincristine	1.4 mg/m^2, dose capped at 2.4 mg. **Vincristine dose is given during cycles 1 and 2 only.**
Days 18-22	Filgrastim* (Neupogen)	5 mcg/kg/ day SC (the use of filgrastim is mandatory)

* Filgrastim should be discontinued if leucocytes > 20,000/mm^3, then re-started in the following cycle as planned. (See Section 9.1).

4 weeks (+/- 1 week) following cycle 4 day 28 of R-MP, 2 cycles of consolidation chemotherapy will be given as follows (1 cycle = 28 days):

Day	**Agent**	**Dose**
Days 1 and 2 of each cycle	Cytarabine	3 g/m^2/day
Day 4	Pegfilgrastim (Neulasta)**	6 mg SC

**The use of G-CSF is mandatory. Pegfilgrastim may be substituted for Filgrastim (5 mcg/kg/ day for 14 days); in this case, if leucocytes >20,000 mm^3, then Filgrastim should be discontinued (See Section 9.1).

7.1.2 Arm B: Chemotherapy Followed by Low-Dose WBRT Arm: Same Chemotherapy Regimen, With Low-Dose WBRT Given After R-MPV and Prior to Consolidation Cytarabine

4 cycles of R-MPV (1 cycle = 28 days; vincristine not given during cycles 3 and 4), as follows:

Day	**Agent**	**Dose**
Day 1	Rituximab	500 mg/m^2
Day 2	MTX	3.5 g/m^2 (standard hydration/leucovorin support)
	Vincristine	1.4 mg/m^2, dose capped at 2.4mg. **Vincristine is given during cycles 1 and 2 only.**
Days 2-8	Procarbazine	100 mg/m^2/d
Days 10-14	Filgrastim* (Neupogen)	5 mcg/kg/ day SC (the use of filgrastim is mandatory)
Day 15	Rituximab	500 mg/m^2
Day 16	MTX	3.5 g/m^2 (standard hydration/leucovorin support)
	Vincristine	1.4 mg/m^2, dose capped at 2.4mg. **Vincristine is given during cycles 1 and 2 only.**
Days 18-22	Filgrastim* (Neupogen)	5 mcg/kg/ day SC (the use of filgrastim is mandatory)

* Filgrastim should be discontinued if leucocytes > 20,000/mm^3, then re-started in the following cycle as planned. (See Section 9.1). In case of delayed MTX elimination, at the discretion of the treating physician, initiation of filgrastim may be delayed for up to 2 days in order to avoid administration of filgrastim in the setting of high methotrexate levels.

Following the 4 cycles of R-MPV, all patients will receive low-dose WBRT (see Section 6), except those with progressive disease on MRI.

4 weeks (+/- 1 week) after the end of WBRT, patients will receive 2 cycles (1 cycle = 28 days) of consolidation chemotherapy as follows:

Day	Agent	Dose
Days 1 and 2 of each cycle	Cytarabine	3 g/m^2/day
Day 4	Pegfilgrastim (Neulasta)**	6 mg SC

**The use of G-CSF is mandatory. Pegfilgrastim may be substituted for Filgrastim (5 mcg/kg/ day for 14 days); in this case, if leucocytes >20,000 mm^3, then Filgrastim should be discontinued (See Section 9.1).

7.2 Agents (10/28/13)

7.2.1 Rituximab

Rituximab 500 mg/m^2 will be given intravenously on the days specified in Section 7.1. Prior to rituximab infusion, patients will be premedicated as per institutional guidelines (recommended: lorazepam 0.5-1 mg intravenously, diphenhydramine l 25-50 mg intravenously or orally, acetaminophen 650 mg orally). meperidine 25-50 mg will be given to the patient prn rigors. Rituximab will be infused over approximately 5 hours or per institutional guidelines.

7.2.2 Methotrexate (MTX)

Methotrexate, 3.5 g/m^2, diluted in 500 cc D5W containing 50 mEq NaHCO3***** will be infused intravenously over approximately 2 hours on the days specified on Section 7.1.

***** In the event of national shortages of NaHCO3, methotrexate will be diluted in 500cc D5W and administered as above, with no NaHCO3 or substitutes added. In that event, the urine alkalinization protocol (see below) should be adjusted to compensate for the suppression of the 50 mEq NaHCO3 originally added to the methotrexate.

Standard pretreatment hydration and alkalinization of urine will be done per institutional guidelines or using the outlined standard pretreatment below. In the event of national shortages of NaHCO3, the use of substitutes considered suitable by the investigator (eg, sodium acetate, sodium citrate, etc) is allowed, but such substitutes should not be mixed together in the same IV bag with the methotrexate as stated above.

Example: Infuse 1 liter D5W + 100 mEq sodium bicarbonate over 4 hours and urine output should be > 150 ml/hour and urine pH > 7.5 prior to the start of the high-dose MTX). Prior to MTX administration, 1 mEq/kg of NaHCO3 in 50 cc D5W will be given. Oral NaHCO3 (2 tablets orally every 6 hours) will be given for the 3 days following MTX infusion to maintain urine pH > 7.0. If a patient is unable to take NaHCO3 by mouth or if adequate alkalinization of the urine is not accomplished, intravenous NaHCO3 will be started. 15 mEq NaHCO3 in 50 cc D5W are administered intravenously over 15 minutes every 6 hours; the frequency can be increased to every 4 hours if the urine pH remains < 7.0.

Leucovorin, 25 mg orally every 6 hours for 12 doses, (if a patient is unable to take oral leucovorin, it will be administered intravenously at 20 mg every 6 hours) will begin approximately 24 hours after MTX infusion and continue for 72 hours or until the MTX level is < 1 X 10^{-7}.

MTX levels, CBC and electrolytes (including BUN/Cr) will be obtained daily for 3 days following MTX administration until MTX is cleared. If MTX levels are toxic at 48 hours (>10^{-6} M), leucovorin will be increased to 40 mg orally or intravenously every 4 hours and total fluid intake will increase to 3000 cc/m^2. MTX levels > 1 X 10^{-7} M at 72 hours will dictate continuing leucovorin (40 mg orally/intravenously q 6 hours), hydration at 3000 cc/m^2/day and NaHCO3 (or per institutional guidelines) until MTX level is 1 X 10^{-7} M or less. Institutional guidelines for standard IV hydration and alkalinization post HDMTX will be used.

Note: Blood concentration levels of MTX must be reported in micromol/L on the treatment form (TF form) at the time of web data submission.

All patients will be instructed to maintain vigorous oral hydration throughout the MTX infusion and for 72 hours thereafter. For the first 24 hours after the MTX administration, total fluid intake should be at least 1500-1800 cc/m^2 and increased to 2000 cc/m^2 for the following 48 hours. Patients will be instructed to refrain from eating citrus fruit, drinking citrus fruit juices or taking vitamin C supplements during MTX administration and for the following 72 hours.

In case of significant delays in MTX elimination (see Section 7.8.1), the use of glucarpidase (carboxypeptidase G2) is permitted; in that case, leucovorin administration and hydration should be adjusted accordingly (See Section 9.1.8).

7.2.3 Vincristine

Vincristine 1.4mg/m^2 intravenously will be given during cycles 1 and 2 only (total of 4 doses) as specified in Section 7.1. Administration will be concomitant with systemic MTX. The vincristine dose should be capped at 2.4 mg maximum dose.

7.2.4 Procarbazine

Procarbazine 100mg/m^2/day orally for 7 days will be given during each cycle as specified in Section 7.1. Patients will be maintained on a tyramine-free diet during procarbazine administration.

7.2.5 Cytarabine

Two cycles (1 cycle = 28 days) of consolidation cytarabine 3 g/m^2/day for 2 days (total of 4 doses) will be given intravenously over approximately 3 hours, as specified in Section 7.1. The dose of cytarabine will be capped at 2 m^2 or a total dose of 6 g. The use of G-CSF is mandatory. Pegfilgrastim (Neulasta) 6 mg SC will be given subcutaneously on day 4 of each cycle. Pegfilgrastim may be substituted for Filgrastim (Neupogen) 5 mcg/kg/ day for 14 days; in this case, if leucocytes >20,000 mm^3, then Filgrastim should be discontinued.

7.3 Rituximab Agent Information (1/31/13)

Refer to package insert for detailed pharmacologic and safety information.

7.3.1 Formulation

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen present on the surface of both normal and malignant B-lymphocytes. Rituximab is provided as a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration; it is supplied at a concentration of 10 mg/ml in either 100 mg (10 ml) or 500 mg (50 ml) single-use vials. The product is formulated for intravenous administration in 9.0 mg/ml sodium chloride, 7.35 mg/ml sodium citrate dihydrate, 0.7 mg/ml polysorbate 80, and sterile water for injection. The pH is adjusted to 6.5.

7.3.2 Storage

Rituximab vials are stored at 2°–8° C (36°–46°F), should be protected from direct sunlight, and should not be used beyond expiration date stamped on the carton.

7.3.3 Adverse Effects

- Infusion reactions: Mild to moderate fever and chills/rigors occur in the majority of patients during the first rituximab infusion. Other frequent infusion reaction symptoms include nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion. The incidence of infusion reactions decreases with each treatment and responds to slowing or interruption of the infusion and supportive care.
- B-cell depletion with lymphopenia and risk of infection
- Grade 3 or 4 cytopenias including lymphopenia, neutropenia, thrombocytopenia, and anemia; rare instances of hemolytic anemia, aplastic anemia, and prolonged pancytopenia have been reported.
- Cardiac: Hypotension, rare cardiac failure
- Pulmonary: Serious effects include acute bronchospasm, acute pneumonitis presenting 1-4 weeks post-rituximab infusion, and bronchiolitis obliterans. More common effects include increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis.

- Immune/autoimmune events: uveitis, optic neuritis in a patient with systemic vasculitis, pleuritis in a patient with a lupus-like syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash
- Hepatitis B virus (HBV) reactivation: HBV reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of the rituximab and approximately one month after the last dose.
- Other less commonly observed events: Agitation, anorexia, arthritis, conjunctivitis, depression, dyspepsia, edema, hyperkinesia, hypertonia, hypesthesia, hypoglycemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness, neuritis, neuropathy, paresthesia, somnolence, vertigo, weight decrease

7.3.4 Contraindications

Contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product.

7.3.5 Supply

Commercially available

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.3.6 ***Non-Canadian International Institutions*:**

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.4 Methotrexate (MTX) Agent Information (1/31/13)

Refer to package insert for detailed pharmacologic and safety information.

7.4.1 Formulation

MTX is available in 20 mg, 50 mg, and 1 gm vials as a lyophilized preservative-free powder.

7.4.2 Storage

Once mixed, intravenous MTX will remain stable for 24 hours if kept refrigerated.

7.4.3 Adverse Effects

Systemic MTX can produce myelosuppression; GI toxicity, particularly mucositis; liver dysfunction, renal failure, and rarely, interstitial pneumonitis.

7.4.4 Contraindications

Contraindicated in patients with renal insufficiency, known hypersensitivity to methotrexate or to any component of this product.

7.4.5 Supply

Commercially available

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.4.6 ***Non-Canadian International Institutions*:**

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.5 Procarbazine Agent Information (1/31/13)

Refer to package insert for detailed pharmacologic and safety information.

7.5.1 Formulation

Capsules, containing the equivalent of 50 mg procarbazine as the hydrochloride, which is ivory, are supplied in bottles of 100.

7.5.2 Storage

Procarbazine is a white to pale yellow crystalline substance soluble but unstable in water or aqueous solution. Procarbazine can be stored at room temperature until expiration date.

7.5.3 Adverse Effects

Leukopenia, anemia, and thrombocytopenia occur frequently. Nausea and vomiting are the

most commonly reported side effects. Other less frequent gastrointestinal complaints include anorexia, stomatitis, dry mouth, dysphagia, diarrhea, and constipation. Pain, including myalgia and arthralgia, chills and fever, sweating, weakness, fatigue, lethargy, and drowsiness are often noted. Intercurrent infections, effusion, ascites, edema, cough and other respiratory symptoms are common. Bleeding tendencies such as petechiae, purpura, epistaxis, hemoptysis, hematemesis, and melena have been rare. Dermatitis, pruritus, herpes, hyperpigmentation, flushing, alopecia and jaundice have also been noted. Paresthesias and neuropathies, headache, dizziness, depression, apprehension, nervousness, insomnia, nightmares, hallucinations, falling unsteadiness, ataxia, footdrop, decreased reflexes, tremors, coma, confusion, and convulsions have been less common. Hoarseness, tachycardias, retinal hemorrhage, nystagmus, photophobia, photosensitivity, genitourinary symptoms, hypotension, and fainting have been rare. Isolated instances of diplopia, inability to focus, papilledema, altered hearing, and slurred speech have occurred. Coincidental onset of leukemia during procarbazine therapy has been reported in rare instances. Patients receiving procarbazine must avoid alcohol, aged cheese, and bananas.

7.5.4 Supply

Commercially available.

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.5.5 ***Non-Canadian International Institutions*:**

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.6 Vincristine Agent Information (1/31/13)

Refer to package insert for detailed pharmacologic and safety information.

7.6.1 Formulation

The dosage formulation is in 1 mg and 2 mg vials.

7.6.2 Storage

Vincristine should be stored in a refrigerator.

7.6.3 Adverse Effects

Vincristine is capable of producing paresthesias and numbness in the digits in its mildest form of toxicity ranging all the way to a profound weakness with loss or motor tone and foot drop in its extreme form. Other common side effects include constipation, abdominal pain, jaw pain and rarely, myelosuppression. Severe tissue damage can occur upon extravasation.

7.6.4 Supply

Commercially available.

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.6.5 ***Non-Canadian International Institutions*:**

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.7 Cytarabine Agent Information (1/31/13)

Refer to package insert for detailed pharmacologic and safety information.

7.7.1 Formulation

Cytarabine is available in 100, 500, 1,000 and 2,000 mg multidose vials for intravenous use.

7.7.2 Storage

The drug is stored unreconstituted at controlled room temperature, 15° to 30°C (59° to 86°F).

7.7.3 Adverse Effects

Cytarabine can cause myeolosupression, nausea, vomiting, cerebellar ataxia, lethargy, confusion, hepatic dysfunction, skin rash, conjunctivitis, chest pain, pancreatitis, pulmonary edema, alopecia, and painful hand-foot syndrome.

7.7.4 Supply

Commercially available.

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.7.5 ***Non-Canadian International Institutions*:**

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.8 Dose Modifications (4/23/12)

7.8.1 Days 1 and 15 of each cycle will be defined by the corresponding administration of rituximab. Toxicity assessment for the purposes of re-treatment and dose reduction will occur on days 1 and 15 of each cycle. Such toxicity assessment will be based on laboratory values obtained on the same day or the previous day. The treatment will start (or be resumed) when all of the following parameters are met:

For day 1:

- ANC >1,500/mm^3
- Platelets > 100,000/mm^3
- Creatinine < 2.0 mg/dl
- Calculated or measured creatinine clearance > 50 cc/min/1.73m^2
- All other non-hematologic toxicity related to the methotrexate or procarbazine resolved to grades 2 or lower

For day 15:

- ANC >1,200 /mm^3
- Platelets > 80,000/mm^3
- Creatinine < 2.0 mg/dl
- Calculated or measured creatinine clearance > 50 cc/min/1.73 m^2
- All other non-hematologic toxicity related to the methotrexate or procarbazine resolved to grades 2 or lower

For days 1 and 15, the use of G-CSF is permitted for achieving ANC parameters (See Section 9.1). The use of transfusion for achieving treatment parameters for platelets is not allowed

For patients not meeting treatment parameters for renal function (creatinine and creatinine clearance), hospital admission for intravenous hydration and nephrology consultation should be considered. In case of significant delays in methotrexate elimination, at the discretion of treating physician, the use of glucarpidase (carboxypeptidase G2) is permitted. In that case, leucovorin administration should be adjusted accordingly, following the manufacturer's recommendations or at discretion of treating physician.

If any of the parameters above are not met, patients should be re-evaluated twice per week until parameters are met. If parameters are not met after a 2-week delay, re-starting treatment at reduced doses may be considered, at the discretion of treating physician.

In addition to meeting these treatment parameters, the following modifications will be made in case of toxicities during the preceding cycle:

Toxicity Observed During the Previous Cycle

	Rituximab	Methotrexate	Procarbazine	Vincristine	Other Measures
Grades 3 or 4 ANC	No change	No change	Reduce to the following: - 1st occurrence: 75mg/m2/ day - 2nd occurrence: 50mg/m2/day - 3rd recurrence: discontinue;	No change	Increase duration of treatment with G-CSF for the following cycle; if pt on PCP prophylaxis, consider using pentamidine rather than

			consider decreasing methotrexate dose		Bactrim, dapsone, or atovaquone.
Grades 3 thrombocytopenia	No change	No change	Reduce to the following: - 1st occurrence: 75mg/m2/ day - 2nd occurrence: 50mg/m2/day - 3rd occurrence: discontinue; consider decreasing methotrexate dose	No change	If pt on PCP prophylaxis, consider using pentamidine rather than Bactrim, dapsone or atovaquone.

Grade 4 thrombocytopenia	No change	No change	Reduce to the following: - 1st occurrence: 50mg/m2/ day - 2nd occurrence: discontinue; consider decreasing methotrexate dose	No change	If pt on PCP prophylaxis, consider using pentamidine rather than Bactrim, dapsone or atovaquone.
Grades 3 or 4 creatinine	No change	Reduce to the following: - 1st occurrence: 2.6 g/m2 - 2nd occurrence: 1.7 g/m2 - 3rd occurrence: 1 g/m2 -4th occurrence: discontinue methotrexate	No change	No change	Consider nephrology consultation for guidance on increasing hydration throughout the cycle
Grade 3 or 4 ALT or AST	No change	No change (if toxicity is observed in spite of reductions in procarbazine, consider reduction in MTX dose)	Reduce to the following: - 1st occurrence: 75mg/m2/ day - 2nd occurrence: 50mg/m2/day - 3rd recurrence: discontinue; consider decreasing methotrexate dose	No change	
Grade 3 or 4 interstitial pneumopathy	No change	Consult pulmonary specialist, exclude other causes of pneumopathy, consider bronchoalveolar lavage to exclude PCP. If no other causes found and pneumopathy thought to be MTX-related, reduce dose to 1.7g/m2 (discontinue if worsening in spite of dose reduction)	No change	No change	
Grade 3 or 4 confusion	No change	Exclude other causes (toxic metabolic, seizures, tumor progression, hydrocephalus, etc). If confusion clearly associated with development of significant leukoencephalopathy, D/C MTX	No change	No change	
Grade 3 or 4 peripheral neuropathy	No change	No change	No change	Discontinue	

7.8.1.6 At the discretion of treating physician, doses may be increased back to earlier dose levels if no toxicity is observed.

7.9 Modality Review (1/31/13)

The Medical Oncology Co-Chair, Antonio Omuro, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the

review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Unacceptable Deviation, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

7.10 Adverse Events (07-AUG-2018)

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 web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.10.1 Adverse Events (AEs)

Definition of an 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). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012.

7.10.2 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.11 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.11.**Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

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.

7.10.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

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 following treatment with an agent under an NCI IND/IDE 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.

7.11 CTEP-AERS Expedited Reporting Requirements (07-AUG-2018)

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

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology 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 Oncology at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

- 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, and fax supporting documentation to NRG Oncology at 1-215-574-3191.
- 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.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and 3 Studies: Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the last administration of protocol treatment

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

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

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 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials:

None

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy (1/31/13)

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

9.1.1 Anticonvulsants

Patients presenting with seizures should be treated as needed for seizures control, preferably with non-enzyme inducing anticonvulsants such as levetiracetam. In case of nephrotoxicity, adjustments in level of levetiracetam should be considered, as appropriate.

Prophylactic use of anticonvulsants will be left at discretion of the treating physician but is usually not recommended.

9.1.2 Antiemetics

Prophylactic antiemetics will be used as per institutional guidelines. Prophylactic antiemetics should be used prior to administration of procarbazine (eg, ondansetron 8 mg orally prior to chemotherapy).

9.1.3 Anticoagulants

Use of anticoagulation is allowed as needed.

9.1.4 Hematopoietic Growth Factors

Prophylactic use of G-CSF (Neupogen or Neulasta) is mandatory (refer to Section 7.1 for details). In case of significant or persistent neutropenia, increasing the duration of G-CSF treatment or re-starting G-CSF for achieving treatment parameters is permitted, at the discretion of treating physician. Other therapeutic uses of G-CSF are permitted, at discretion of treating physician.

For days 1 and 15, the use of G-CSF is permitted for achieving ANC parameters. (The use of transfusion for achieving treatment parameters for platelets is not allowed; See Section 7.8.1).

9.1.5 Pneumocystis Jiroveci Pneumonia (PCP) Prophylaxis

PCP prophylaxis will be left to the discretion of treating physician. PCP prophylaxis is recommended in patients exposed to corticosteroids (until 1 month after the last dose) and in patients with lymphopenia. In patients with hematotoxicity, aerosolized pentamidine is preferred.

9.1.6 Bowel Regimen

Because of the risks of vincristine-related constipation and ileus, a prophylactic bowel regimen is highly recommended, as per institutional guidelines.

9.1.7 Hydration/Nephrology Consultation

For patients not meeting treatment parameters for renal function (creatinine and creatinine clearance), hospital admission for intravenous hydration and nephrology consultation should be considered.

9.1.8 Glucarpidase (carboxypeptidase G2)

In case of significant delays in MTX administration, the use of glucarpidase (carboxypeptidase G2) is permitted; in that case, leucovorin administration and hydration should be adjusted accordingly). following the manufacturer's recommendations or at the discretion of the treating physician.

9.1.9 Hepatitis B Reactivation Prophylaxis

Chemotherapies, particularly rituximab, may result in reactivation of hepatitis B. Screening for hepatitis B is strongly recommended and should follow institutional guidelines. In patients at risk for hepatitis B reactivation, hepatitis B prophylaxis (e.g. entecavir) should be strongly considered. Results are not needed for patient to start treatment. For reference, MSKCC guideline is as follows:

- Obtain HB surface antigen and HB core antibody. If both are negative, no further action is needed. If either test is positive, obtain HBV PCR and start entecavir 0.5 mg PO daily throughout treatment and for at least 6 months after completion; consider consulting a GI specialist for guidance.

9.2 Non-permitted Supportive Therapy (4/23/12)

9.2.1 See Section 7.8.1 for stipulations concerning platelet transfusion.

9.2.2 Antacids

It is recommended that proton pump inhibitors be used with caution or avoided during MTX treatment due to possible delays in elimination.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or quality of life assessment.

If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The NRG Oncology Biospecimen Bank also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of central review (mandatory for all cases, post-registration), tissue banking (recommended), and translational research (recommended).

10.2 Specimen Collection for Central Review (mandatory post-registration) (1/27/15)

The following material must be provided to the NRG Oncology Biospecimen Bank for Central Review:

10.2.1 All H & E stained slides and immunohistochemistry studies performed by local pathologist (unless not available per NOTE in Section 3.1.1) (slides can be a duplicate cut stained H&Es; they do not have to be the diagnostic slides).

10.2.2 A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.2.3 A Specimen Transmittal (ST) Form stating that the tissue is being submitted for Central Review. The Form must include the NRG Oncology protocol number and the patient's case number.

10.2.4 Central Review will be performed for every case by Dr Marc Rosenblum at Memorial Sloan-Kettering Cancer Center, New York, NY.

10.2.5 Submit material for central review to the NRG Oncology Biospecimen Bank per Section 10.3.8. The Biospecimen Bank will forward the material to Dr. Rosenblum at the end of trial enrollment. After central pathology review is complete, depending on the level of patient consent, Dr. Rosenblum will return remaining material to the Biospecimen Bank for banking or return the material to the submitting institution when requested by the submitting site. Sites must provide return airbills for all return requests.

10.3 Specimen Collection for Tissue Banking and Translational Research (07-AUG-2018)

For patients who have consented to participate in the banking/translational research component of the study.

The following must be provided in order for the case to be evaluable for the NRG Oncology Biospecimen Bank. Additional slides and blocks are not needed for banking if they were already submitted for central review. They can be used for both.

10.3.1 All H & E stained slides and immunohistochemistry studies performed by local pathologist as per 10.2.1 (Required).

10.3.2 At least one paraffin-embedded tissue block of the tumor or one 2-mm diameter core of tumor tissue, punched from the tissue block containing tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number and block ID (must correspond to one of the H&Es being submitted). **Note:** A kit with the punch, tube, and instructions (Appendix III) can be obtained free of charge from the Biospecimen Bank. Alternatively, 30 five micron unstained sections cut onto positive charged slides may be submitted. Slides, block or core must be clearly labeled with the pathology identification number and block ID that corresponds to the Pathology Report. All blocks, punches, unstained slides must be from the same block as one of the H&Es being submitted.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.3.3 Submission of frozen tumor tissue and/or bone marrow samples is strongly encouraged to maximize the information gained from this trial. When available, frozen samples should be sent on dry ice to the NRG Oncology Biospecimen Bank as indicated in Appendix III. The NRG Oncology Biospecimen Bank will supply kits for frozen tissue when requested. To request a kit, contact the Biospecimen Bank at NRGBB@ucsf.edu or by phone at 415-476-7864.

10.3.4 A Pathology Report documenting that the submitted slides, block or core contains tumor. The report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.3.5 Two tubes of whole blood and a buccal scraping are to be collected pre-treatment (obtained at any time prior to start of chemotherapy) should be collected and processed. Available frozen CSF and bone marrow samples can also be processed. See Appendix III for collection, processing, and kit instructions. Collection kits can be requested free of charge from the Biospecimen Bank at NRGBB@ucsf.edu. Please indicate if you need the CSF or bone marrow kits.

10.3.6 A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number.

10.3.7 Storage Conditions

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

10.3.8 Specimen Collection Summary

Specimens for Central Pathology Review (mandatory post-registration)			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
All H&E stained slides and immunohistochemistry studies of the primary tumor	Pre-treatment	Stained slides Pre-treatment	Slides shipped ambient
Specimens for Tissue Banking and Translational Research (recommended)			
All H&E stained slides and immunohistochemistry studies of the primary	Pre-treatment/submitted in conjunction with central review material above	Stained slides Pre-treatment	Slides shipped ambient

tumor			
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block or punch biopsy of block. Alternatively 30 unstained slides may be submitted	Block or punch shipped ambient
CSF specimen	Pre-treatment from unused portion of clinical sample	Frozen CSF	Sent frozen on dry ice via overnight carrier
Frozen Tumor Tissue (including eye biopsy)	Pre-treatment	Frozen tissue	Sent frozen on dry ice via overnight carrier
Frozen Bone Marrow Specimen	Pre-treatment from unused portion of clinical sample	Frozen bone marrow stored in the original vial. See appendix III for details	Sent frozen on dry ice via overnight carrier
Whole blood for DNA: 10-15 mL of anticoagulated whole blood in 2 EDTA tubes (purple/ lavender top) and mix	Pre-treatment. If site missed this collection, site can collect at any other timepoint or follow-up visit but must note this on the ST Form.	Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (6 to 10)	Whole blood sent frozen on dry ice via overnight carrier
Buccal Scrapings: brush/swab of oral mucosa placed place in RNAlater solution	Pre-treatment	Swab/RNAlater filled container frozen. Store frozen -70 º to -80º Celsius.	Swab/container sent on dry ice via overnight carrier

10.4 (07-AUG-2018) **Submit materials for Tissue Banking and Translational Research as follows:**

U. S. Postal Service Mailing Address: <u>For Non-frozen Specimens Only</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter St, room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): <u>For Frozen Specimens</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.5 Confidentiality/Storage (23-AUG-2019)

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

10.5.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient

withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

10.6 Translational Research Description (recommended but not required)

See Sections 10.3 and 10.4 for specimen collection details

10.6.1 Evaluation of DASL-Based Genome Wide Expression Profiling and Immunohistochemistry for the Molecular Characterization of PCNSL

Overview

Formalin-fixed and paraffin-embedded (FFPE) tissue from all consenting patients will be collected and analyzed utilizing the Illumina cDNA-mediated annealing, selection, extension, and ligation (DASL) assay, in addition to immunohistochemistry. With the support of the MSKCC Computational Biology Core, samples will be analyzed for the following:

- Comparison with previously described frozen tissue-based genome-wide expression profiling defined for both systemic NHL and PCNSL, seeking to determine whether a "brain-specific" molecular signature exists. Candidate genes will be validated through immunohistochemistry and RT-PCR.
- Characterization of a dedicated genome-wide based subclassification for PCNSL with prognostic implications in terms of PFS and OS.
- Evaluation of the prognostic value of standard prognostic markers utilized in NHL, including BCL-6, CD-10, MUM-1 and CD-138.

Rationale

We hypothesize that FFPE PCNSL samples can be used for genome-wide expression profiling utilizing the Illumina DASL assay.

Gene-expression studies in PCNSL have been limited by the small amount of available tissue for analysis (patients are typically diagnosed by biopsy) and lack of frozen tissue. Conversely, several genome-wide expression studies have been conducted in systemic NHL, which defined two molecular subclasses (germinal center B-cell like and activated B-cell like) with prognostic implications. An immunohistochemistry panel was developed to categorize DLBCL in these two categories, based on the expression of CD10/BCL-6 (markers of the germinal center B-cell like, associated with a better prognosis), and MUM-1/CD-138 (markers of the activated B-cell like, associated with a worse prognosis). Immunohistochemistry studies in PCNSL have been controversial. A study applying standard NHL immunohistochemistry-based prognostic markers panel to PCNSL samples found a relatively homogenous molecular pattern, with highly frequent expression of MUM-1 and rare expression of CD10 and CD-138; BCL-6 was expressed in 50%-70% of patients (Camilleri-Broet 2006). Several studies have examined the prognostic value of BCL-6 expression in PCNSL, with some studies reporting an association with a better prognosis and others reporting a worse prognosis (Levy 2008). Another study applied genome-wide expression profiling in PCNSL frozen tissue and generated a list of genes that seemed to constitute a « CNS signature » in PCNSL that was distinct from systemic NHL and normal brain (Rubenstein 2006). However, other studies found a discordant list of genes and, therefore, this subject remains unsettled. This trial offers the opportunity of collecting tissue from a relatively large number of patients for the studies described above, aiming at improving the molecular characterization of PCNSL. In addition to confirming or refuting the prognostic value of a standard NHL immunohistochemistry-based panel (BCL-6, CD-10, MUM-1 and CD-138), we will analyze genome-wide gene expression profiling utilizing the Illumina DASL assay. This analysis will seek to determine whether a PCNSL-specific molecular signature exists and to define a molecular subclassification for PCNSL that has prognostic implications. The DASL assay is ideal for use in PCNSL, as it requires much less RNA (200-500 ng) and generates robust gene expression data from FFPE samples, covering more than 24,000 annotated genes derived from RefSeq (Build 36.2, Release 22). After analysis, unused remaining tissue will be returned to either the NRG Oncology Biospecimen Bank or the submitting institution, depending on the level of patient consent.

10.6.2 Evaluation of Polymorphisms Influencing the Methionine Metabolism as Predictors of the Development of MTX-Related White Matter Changes and Neurotoxicity

Overview

Prior to start of treatment, a 5 mL blood sample will be obtained from all patients who consent for participation. Polymorphisms affecting the methionine metabolism will be evaluated through PCR, including the following: MTHFR c.677C>T, MTHFR c.1298A>C, Tc2 c.776C>G, DHFR c.594+59del19bp and ATIC c.346C>G. Results will be correlated with the development of white-matter changes on MRI as defined by central imaging review and neurocognitive data.

Rationale

We hypothesize that genetic variants of methionine metabolism predict the occurrence of white-matter changes and neurotoxicity resulting from MTX-based chemotherapy. MTX is a competitive inhibitor of several enzymes involved in folate and methionine metabolism. In a retrospective study, Linnebank et al evaluated 10 genetic variants influencing the methionine metabolism and correlated with the development of white-matter changes on the MRI in 68 patients undergoing MTX-based chemotherapy for PCNSL (Linnebank 2009). The authors found that the following polymorphisms were statistically significantly associated with white matter changes: the TT genotype of methylenetetrahydrofolate reductase c.677C>T (χ^2 = 8.67; p = 0.013; df = 2), the AA genotype of methylenetetrahydrofolate reductase c.1298A>C (χ^2 = 13.5; p = 0.001; df = 2), and the GG genotype of transcobalamin 2 c.776C>G (χ^2 = 19.73; $p < 0.001$). The relatively large sample in this present study, including one arm that will be treated with chemotherapy alone provides the opportunity of prospective validation of those findings. If confirmed, such polymorphism analysis would allow the identification of patients at risk for the development of MTX-related neurotoxicity that could be treated with a reduced number of treatment cycles in future studies.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix I. Details and exceptions appear below.

11.1.1 Follow-Up for Patients With Initial Involvement of the Eyes

All patients with initial involvement of the eyes on baseline evaluation should have a detailed follow-up evaluation including dilated fundus examination and color photographs of the posterior pole of the eye. Repeat ophthalmologic evaluation is not required for patients without evidence of ocular lymphoma at baseline or interval development of ocular symptoms.

11.1.2 Assessment of Radiographic Response

During treatment, MRI will be performed at the following time points:

- At baseline (≤ 2 wks prior to start of chemotherapy)
- During R-MPV: Day 28 of cycle 2; day 28 of cycle 4
- During cytarabine: cycle 1 day 1 (arm B only)
- Follow-up period: every 2 months, starting 26 days after the last dose of cytarabine for the first two years, then every 6 months till 5 years.

At each assessment, the radiographic response will be assessed as per IPCLG recommendations (Abrey, 2005), with modifications. Use of corticosteroid will be recorded in the radiographic assessment form and will be utilized for the response evaluation. Patients who previously had evidence of ocular lymphoma will require slit lamp re-examination. Patients with positive CSF cytology will require repeated lumbar puncture.

11.1.3 Neuroimaging Techniques

Standard MRI sequences should be obtained. Whenever possible, the exam should at least include T1 pre and post gadolinium **axial** sequences, FLAIR and T2 sequences. This will allow for evaluation of pre-contrast T1 hypersignal that may be misinterpreted as active, contrast enhancing disease. MRI scans will be performed with and without contrast and should be acquired in a plane that images both the anterior and posterior commissures (along the AC-PC line) and should cover the entire brain. The MRI scan should be comprised of at least 12 slices to encompass the intracranial contents from the cranial base to the convexity. A technique that utilizes 5 mm cuts with a 1 mm gap is preferred on the axial images.

Responses will be assessed at the time points corresponding to the imaging dates as detailed in Appendix I (during R-MPV: cycle 2, d28; cycle 4, d28; during cytarabine: cycle 1 day 1 (arm B only); follow-up period: every 2 months for the first 2 years and every 6 months during years 3-5. The following timepoints will be submitted for central review for confirmation of responses and correlative studies: baseline; cycle 2, d28; cycle 4, d28; cytarabine cycle 1 day 1 (arm B only); then every 6 months until year 5, starting 26 days after the last cytarabine dose. All efforts should be made to collect the MRIs regardless of patient progression status.

All neuroimaging obtained during the study should be submitted to NRG Oncology for central review and correlative studies.

11.2 Neurocognitive Function (NCF) Assessment
NOTE: Sites must offer English-speaking participants the opportunity to participate in the neurocognitive function component of this study.

If the patient consents to participate in the neurocognitive function component of the study, sites are required to administer the baseline NCF and functional assessments prior to the start of protocol treatment:

The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study must be pre-certified by Dr. Denise Correa See Section 5.2 and Appendix IV for details. The tests in the neurocognitive test battery were selected because they are widely used standardized psychometric instruments that have been shown to be sensitive to the impact of cancer and the neurotoxic effects of cancer treatment in other clinical trials (Meyers 2004). The tests have published normative data that takes into account age, and where appropriate, education and gender. The tests are given by certified site administrators, and the total time for the cognitive assessment is approximately 20 minutes, as follows:

Cognitive Domain Test Administration
Memory: Hopkins Verbal Learning Test-Revised (HVLT-R) – 5min
Cognitive Processing Speed: Trail Making Test, Part A – 3min
Executive Function: Trail Making Test, Part B- 5min
Verbal fluency: Controlled Oral Word Association (COWA)- 5min

11.2.1 Hopkins Verbal Learning Test-Revised (HVLT-R)
The patient is asked to recall a list of 12 words over three trials. After a delay of 20 minutes, the patient is asked to spontaneously recall the words. The patient is then asked to identify the list words from distractors. There are six alternate forms of this test to minimize practice effects. The test measures learning memory retrieval, and memory consolidation processes. This measure has been widely used in clinical trials (Benedict 1998).

11.2.2 Trail Making Test, Part A
This is a test of visual-motor cognitive processing speed, requiring the patient to connect dots in numerical order from 1 to 25 as fast as possible (Reitan 1992).

11.2.3 Trail Making Test, Part B
This test is similar to Trail Making Test Part A, with the additional requirement of shifting mental set (an executive function). The patient connects dots alternating numbers and letters as fast as possible (Reitan 1992).

11.2.4 Controlled Oral Word Association (COWA)
This is a test of phonemic verbal fluency. The patient is asked to produce as many words as possible in 60 seconds beginning with a specified letter. There are 2 alternate forms of this test (Benton 1989).

11.3 Quality of Life (QOL) Assessment (10/28/13)
NOTE: Sites must offer English-speaking participants the opportunity to participate in the quality of life component of this study.

11.3.1 EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/BCM20)
The EORTC QLQ-C30/BCM20 were developed and validated for use in this patient population. The QLQ-C30 is a 30-item self-report questionnaire that has patients rate the items on a 4-point scale, with 1 “not at all” to 4 “very much.” The instrument measures several domains, including

physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, pain, nausea and vomiting, and several single items (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact). The BCM20 consists of 4 scales comprised multiple items (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single items (headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs). The combined instrument takes an average of 8 minutes to complete by patients with primary brain tumors (Osoba 1996).

11.4 Measurement of Response

Response will be evaluated in this study using the international criteria proposed by the International PCNSL Study Group (Abrey 2005). In addition, MRI FLAIR or T2 sequences will be reviewed and scored for the development of white matter changes and leukoencephalopathy, for correlation with methionine metabolism polymorphisms and neuropsychological findings.

11.4.1 Radiographic Response (see Section 11 and Appendix I for assessment schedule)

CR requires the following:

- Complete disappearance of all enhancing abnormalities on gadolinium-enhanced MRI.
- If the patient had previous evidence of ocular lymphoma, no evidence of active ocular lymphoma as defined by absence of cells in the vitreous and resolution of any previously documented retinal or optic nerve infiltrates may be present. Chronic changes of the retinal pigment epithelium in the setting of a prior retinal or optic nerve infiltrate do not preclude the definition of a CR. (See Section 11.1 for patients with initial involvement of the eyes on baseline.)
- Negative CSF cytology. Given the reported disparity between cytologic specimens obtained from the ventricular system as opposed to lumbar puncture, it is recommended that a negative CSF cytology be confirmed from both spaces in patients with an Ommaya reservoir. Patients without significant CSF abnormalities at baseline do not require repeat CSF evaluation provided they have not developed interval symptoms that suggest leptomeningeal dissemination.
- At the time a CR is determined, the patient should have discontinued use of all corticosteroids for at least 2 weeks. Rare exceptions may be made for those patients receiving corticosteroids for another diagnosis (eg, panhypopituitarism).

CR/unconfirmed (CRu) includes those patients who fulfill the criteria for CR with the following features/limitations:

- Any patient who fulfills all criteria for CR but continues to require corticosteroid therapy at any dose should be considered an unconfirmed CR. This is critical because corticosteroids may be oncolytic in treating occult tumor. In addition, corticosteroids may decrease gadolinium enhancement on MRI.
- Some patients will have a small but persistent enhancing abnormality on MRI related to biopsy or focal hemorrhage. It is often difficult to ascertain whether this represents a residual nidus of tumor or scar tissue. Adjunctive radiologic studies such as single-photon emission computed tomography or positron emission tomography may be helpful, but often the nature of these abnormalities may only be determined by observing the patient with serial scans. If the type of abnormality does not change or slowly involutes over time without therapy and corticosteroids, it is reasonable to categorize it as a CR.
- Patients with a persistent minor abnormality on follow-up ophthalmologic examination (persistent nonmalignant cells in the vitreous, alteration of the retina/optic nerve that is not consistent with tumor infiltration) may be considered a CRu if this abnormality is unlikely to represent ocular lymphoma.
- Attentive review of T1 pre-gadolinium contrast sequences should be performed in order to differentiate contrast-enhancement from T1 pre-gadolinium hyperintensities, likely representing hydrated calcification and treated disease. Such T1 pre-gadolinium hyperintensities should not be considered when assigning response.

Partial response (PR) requires all of the following:

- A ≥ 50% decrease in the contrast-enhancing lesion seen on MRI as compared with baseline imaging.

- Corticosteroid dose is irrelevant to the determination of PR.
- Ophthalmologic examination should show a decrease in the vitreous cell count or retinal/optic nerve cellular infiltrate but may continue to show persistent malignant or suspicious cells. Color photos of the posterior pole of the eye should be obtained to document improvement in retinal/optic nerve infiltrates.
- CSF cytologic examination may be negative or continue to show persistent malignant or suspicious cells in patients with a ≥ 50% decrease in the primary brain lesion. In the setting of primary leptomeningeal lymphoma, PR is not recognized; all patients should be categorized as CR, CRu, stable disease, or progressive disease.
- No new sites of disease.

Stable disease is defined as less than a PR but not progressive disease.

Progressive disease requires the following:
- A more than 25% increase in the contrast-enhancing lesion seen on MRI as compared with baseline or best response (comparison should be made to the smallest of multiple lesions).
- Progression of ocular disease as indicated by an increase in the vitreous cell count or progressive retinal or optic nerve infiltration.
- Appearance of any new lesion or site of disease (ocular, leptomeningeal or systemic) during or at the end of therapy.

Relapsed disease (only applicable to patients with a prior CR, CRu) requires the following:
- Appearance of any new lesion.

Summary of Response Guidelines

Response	Brain Imaging	Corticosteroid Dose	Eye Examination*	CSF Cytology*
CR	No contrast enhancement	None	Normal	Negative
Cru	No contrast enhancement	Any	Normal	Negative
	Minimal abnormality	Any	Minor RPE abnormality	Negative
PR	50% decrease in enhancing tumor	Irrelevant	Minor RPE abnormality or normal	Negative
	No contrast enhancement	Irrelevant	Decrease in vitreous cells or retinal infiltrate	Persistent or suspicious
PD	25% increase in lesion Any new site of disease: CNS or systemic	Irrelevant	Recurrent or new ocular disease	Recurrent or positive

Abbreviations: CR, complete response; CRu, unconfirmed complete response; RPE, retinal pigment epithelium; PR, partial response; PD, progressive disease. *required if previously abnormal.

Evaluation of Leukoencephalopathy and White Matter Changes

In addition to response evaluation, each on-study MRI will be reviewed by the local investigators for the presence of white matter changes and leukoencephalopathy that may develop as a result from chemotherapy and/or radiotherapy. To that end, T2 or FLAIR sequences will be evaluated for presence of white matter hypersignal and rated as per the scale below (modified Fazekas scale, Correa 2009). All white matter hypersignal lesions, including those abnormalities thought to be a result from the tumor or surgery rather than chemotherapy or radiotherapy should be taken into consideration for rating purposes.

Modified Fazekas Scale:
Grade 0: No white matter change

Grade 1: Minimal patchy white matter foci
Grade 2: Start of confluence of white matter disease
Grade 3: Large confluent areas of white matter changes
Grade 4: Confluence of white matter changes with cortical and subcortical involvement
Grade 5: Leukoencephalopathy

11.5 Criteria for Discontinuation of Protocol Treatment (1/31/13)

Protocol treatment will be discontinued:

- In case of unacceptable toxicity
- Patient withdrawal of consent
- Tumor progression

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol. **All patients will be asked to be followed as specified above for a total of 5 years, regardless of disease status and duration of treatment.** History of tumor progression and salvage treatments will be recorded throughout 5 years.

If the patient is on active treatment for recurrent disease at the time a follow-up evaluation is due, the follow-up evaluation may be postponed and performed after salvage treatment has been completed. However, the subsequent evaluations should follow the original schedule and time points, as described in appendix 2, and defined from the time of original start of treatment. Therefore, all patients will have evaluations performed at same time points in the course of their disease, regardless of disease progression and salvage treatments.

Patients who are found to be ineligible (eg, bone marrow biopsy positive for the presence of lymphoma) will be removed from study and treated at the discretion of treating physician.

12.0 DATA COLLECTION (1/27/15)

Data should be submitted to:

NRG Oncology*
1818 Market Street, Suite 1720
Philadelphia, PA 19103

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

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

12.1 Summary of Data Submission (8/25/15)

Item	Due
Demographic Form **(A5)**	Within 2 weeks after registration
Initial Evaluation Form **(I1)**	Within 2 weeks after registration
Pathology Report **(P1)** [For studies with pathology]	Within 2 weeks after registration
Treatment Form **(TF)**	During treatment with R-MP(V) at the end of each 28 day cycle and during treatment with cytarabine at the end of each 28 day cycle.
Follow-up Form **(F1)**	Each 2 months starting 4 weeks after treatment for the first 2 years and the each 6 months for year 3 to 5. **See Section 11.5 for additional information.**
Quality of Life Assessments: EORTC QLQ30/BCM20	Within 2 weeks prior the start of treatment (baseline). During treatment with R-MP(V) on d28 of cycle 4. During follow-up each 6 months for 5 years.
Neurocognitive Assessments: HVLT-R	Within 2 weeks prior the start of treatment (baseline).

Trail Making Test Part A and B COWAT	During treatment with R-MP(V) on d28 of cycle 4. During follow-up each 6 months for 5 years.

***NOTE**. If a patient experiences disease progression during the study evaluation period, the neurocognitive and QoL assessment should be put on hold until the patient is clinically stable for 3 consecutive months, at which time the follow-up neurocognitive evaluation should be obtained. The next neurocognitive evaluation should be performed according to the next standard/planned protocol follow-up dates (the study calendar is not reset), but no sooner than 3 months from the previous neurocognitive evaluation.

Dosimetry Information	
MRI scans & reports (MR, ME)* See methods of submission below for scans	Pre-study, day 28 of R-MPV cycles 2 & 4, day 1 of cytarabine cycle 1 (arm B only), every 6mo for 5 yrs and at the time of progression
Radiology review form (SR)	As each scan time point listed above
Radiotherapy Form (T1)	Within 1 week of RT end
Complete Daily Treatment Record (T5)	Within 1 week of RT end
Composite Isodose Distribution (T6) in COLOR	Within 1 week of RT end

***NOTE:** Copies of simulation and port films and the complete RT daily treatment record for the (site) will be submitted to NRG Oncology ONLY if specifically requested.

Methods of scan submission

NRG Oncology can provide software (TRIAD) for installation on a PC at your site that collects, anonymizes and submits image sets from your MRI system or from your PACS. The images are "DICOM pushed" either from the MRI system or from the PACS to the PC on which the software is installed. This software anonymizes and encrypts images as they are transferred via FTP to the NRG Oncology image archive. For more information, see **https://triad.acr.org**.

TRIAD Image Submission software PC requirements:
1. Network capability to transmit data from a scanner to a linked workstation, PC, or PACS
2. A Windows XP PC available to transmit data (patient data, MR and PET image data) to NRG Oncology:
a. Operating System Windows XP Pro
b. Access to the Internet: Internet Explorer
c. Minimum of 50 GB available hard drive
d. At least 1 GB RAM
e. Ability to view PDF documents
3. Software utilities required:
a. Windows Installer 3.1
b. Microsoft .NET framework 2.0
c. MDAC Type 2.8
d. MS SQL 2005 Express

Please contact the TRIAD help desk (Triad-Support@ acr.org) regarding installation requirements and to arrange the installation of TRIAD software prior to first accrual.

For questions regarding image submission, call 215-574-3219

Scans can also be submitted on CD and mailed to HQ

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

Progression-free survival (PFS), defined as the interval from randomization to progression or death, whichever occurs first.

13.1.2. Secondary Endpoints

- Overall survival (OS), defined as the interval from randomization to death due to any cause
- Quality of life measured by the EORTC Quality of Life Questionnaire-Core/Brain Cancer Module(QLQ-C30/BCM20)
- Neurocognitive function measured by the Hopkins Verbal Learning Test-Revised(HVLT-R), Trail Making Test Part A, Trail Making Test Part B, Controlled Oral Word Association Test (COWAT).
- Response (partial response [PR] and complete response [CR]) rate
- Chemotherapy-related toxicity, measured by CTCAE, v.4.0.

13.2 Sample Size and Power Justification

The sample size calculation will address whether the addition of low-dose WBRT will improve the median PFS in comparison to a chemotherapy-only approach. The null hypothesis is that the median PFS for both arms is 12 months. The alternative hypothesis is that patients receiving low-dose WBRT will achieve a median PFS rate of 19 months. The study will be a randomized phase II screening trial as proposed by Rubinstein et al (2005). The randomization of experimental and standard arms is set as 1:1 and the randomization will occur after registration. Patients will be stratified according to MSKCC RPA status. With 84 eligible subjects (42 patients/arm), there will be 80% power to detect a 37% reduction in the hazard ratio to 0.63 at the significance level of 0.15 (one-sided). Analysis will be performed when 67 events are reported, expected to occur 18 to 25 months after trial closure. Guarding against up to a 5% ineligibility rate, the final targeted accrual for this study will be 89 cases.

13.3 Patient Accrual

The study is projected to accrue 3 cases per month. No accrual is expected during the first 2 months of trial activation as institutions obtain IRB approval; a total accrual of 6 patients is expected during the next 4 months; and thereafter monthly accrual is expected to reach 3 patients per month. Therefore, the target accrual of 89 cases should be completed within 33 months of study activation. If the average monthly accrual rate (excluding the first 6 months) is less than 1.5 patients, the study will be re-evaluated with respect to feasibility.

13.4 Stratification and Randomization

Patients will be stratified by the MSKCC RPA classification for PCNSL based on age and KPS as follows (Abrey 2006)

- Class 1: age ≤ 50
- Class 2: age > 50 and KPS ≥ 70
- Class 3: age > 5 0 and KPS < 70

The randomization will occur in a 1:1 ratio between the experimental arm and control arm in each stratum. Patients will be randomized in a permuted block design using the method of described by Zelen (1974).

13.5 Analyses Plans (07-AUG-2018)

13.5.1 Statistical Methods

Overall and Progression-Free Survival

OS and PFS rates will be estimated using the Kaplan-Meier method (Kaplan 1958), and differences between treatment arms will be tested by the log rank test (Mantel 1966). OS 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. PFS will be measured from the date of randomization to the date of first progression or death or, otherwise, the last follow-up date on which the patient was reported alive. Differences in observed severities of toxicities (grade 3+) between groups will be tested using a chi square test.

Multivariate analyses with the Cox proportional hazard model (Cox 1972) for OS and PFS will be performed with the stratification variables as fixed variables to assess the treatment effect adjusting patient-specific risk factors. The covariates evaluated for the multivariate models are: assigned protocol treatment, RPA risk class, and other prognostic factors. Proportional hazard assumptions will be checked using different graphical or time-varying coefficients testing methods. If the data clearly do not follow proportional hazards, other statistical models will be used to fit the data instead. Possible alternatives are to use the stratified Cox proportional hazard model, to use the accelerated failure model, or to partition the time axis into sections where proportional hazard assumption holds.

Analysis of Neurotoxicity and Impact on Cognitive Function and QOL

Evaluation of neurotoxicity will occur at two levels: formal evaluation of cognitive function through neuropsychological and QOL evaluation, as well as evaluation of neurotoxicity as clinically defined by the treating physician.

- Neuropsychological and QOL evaluation: In both arms, the cumulative incidence approach will be used to estimate the median time to neurocognitive failure to account for the competing risks of death. To that end, neurocognitive failure will be defined as the first cognitive failure on 2 or more of the following tests: the HVLT-R for Free Recall, Delayed Recall and Delayed Recognition; the COWA; and the Trail Making Test Part A or B. Cognitive failure for each test is defined as a change in a score that meets or exceeds the Reliable Change Index (RCI) value for each test indicating a performance that is worse than the patient's personal baseline score. In addition, the standardized test score will also be calculated for each test and to determine which tests are most sensitive to detect cognitive impairment/change. The cut-offs for standardized scores will be determined through receiver operating characteristic (ROC) methods.

  Gray's test will be used to test for a statistically significant difference in the distribution of neurocognitive failure times (e.g. neurocognitive failure at 3-year, 5-year) at the alpha=0.05 level (Gray RJ. 1988). Fine and Gray's proportional subdistribution hazard regression model (Fine and Gray, 1999) will be used to assess the effects of covariates on the progression.

  A similar approach will be used for symptom and HRQOL data. For the EORTC QLQ30/BN20, differences of at least 10 points will be classified as the minimum clinically meaningful change in a HRQOL measure. For example, an increase of 10 points or more on a functional scale would mean a moderate improvement, whereas a decrease of 10 points or more would be interpreted as moderate worsening. Furthermore, a rise in a symptom score means deterioration. Changes of less than 10 points will be regarded as no change or as clinically irrelevant, and changes of more than 20 points will be considered large effects.

  For the quality of life, symptom and neurocognitive function endpoints, the longitudinal data analysis will also be performed to assess if there exists difference over time across the two treatment arms using hierarchical formulation of the linear mixed model.

  Participation in the quality of life/neurocognitive function component is not mandatory in this study. However, if patients agree to participate in this component, adherence to the component assessment schedule will be encouraged through reminders from participating institutions. Completion of all scheduled assessment is part of the routine delinquency assessment for participating institutions. The Statistics and Data Management Center staff will monitor proportions of missing quality of life/neurocognitive function information in each treatment arm at different assessment points. In spite of these efforts, missing data is to a certain extent expected. The information from patients with missing data will be reviewed in to determine whether the data analyses will be biased. Patients with missing data will be reviewed for the distributions of treatment arms and patient characteristics. Mean scores on the primary items will be compared for patients with and without missing data at different assessment points to identify whether missing data was preceded by a significant decline in the scores. Mean scores by

assessment time for cohorts stratified by baseline score quartile will also be compared to investigate if the missingness is consistent with an ignorable missing data process (missing at random). If no missing data mechanism can be detected, the data will be analyzed assuming missing data is at random and the appropriate imputation for missing values will be conducted. The imputation methods may include: the missing value can be imputed from the variable mean of the completed cases, or it can be imputed from the mean conditional on observed values of other variables, or multiple imputation. If the missing data mechanism appears to be present, we will use appropriate analytic strategies to control for the potential bias and, if possible, to impute the missing data. The possible strategies for imputation and analyses will depend on the severity of the missing data problem and missing pattern. The imputation methods may include: worse-case scenario, use of mean response for individuals who withdraw from the trial from either all or similar (matched) patients remaining in the trial, last observation carry forward, or multiple imputation. The data can also are analyzed using pattern mixture models to estimate separate estimates for the outcome within strata based on the missing data pattern, and then combining estimates in a specialized way to yield appropriate an overall effect estimate (Little R and Rubin D. 2002). Sensitivity analyses based on the varying assumptions about the missing data mechanisms will also be conducted.

- Evaluation of clinically defined neurotoxicity: In addition to the formal evaluation of cognitive function and QOL as described above, information on the incidence of neurotoxicity as per the investigator's assessment will be collected in this study. The purpose of this analysis is to provide an estimate of neurotoxicity rate that can be compared to historical controls on the utilization of full-doses of WBRT, which have not included neuropsychological evaluation. In those studies, neurotoxicity was qualitatively defined by treating physicians.

  For a comparable assessment, in this study physicians will be asked to determine whether the patient is experiencing neurotoxicity at each clinical assessment throughout the 5 year followup. For this purpose, neurotoxicity will be defined as severe cognitive deterioration in comparison to post-treatment baseline, accompanied by psychomotor slowness and gait ataxia, and that cannot be accounted for by disease recurrence.

  Analysis will be descriptive, and the 3y and 5y cumulative incidence of neurotoxicity in each arm will be reported, accounting for death as a competing risk (as described above).

13.5.2 Interim Analysis to Monitor Study Progress

Interim reports with statistical analyses will be prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The reports will contain:

- the patient accrual rate with a projected accrual completion date;
- accrual by institution;
- the pretreatment characteristics of accrued patients;
- the frequency and severity of toxicities; and
- the results of any completed study chair modality reviews.

The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints (OS, PFS, treatment response). The NRG Oncology Data Monitoring Committee (DMC) will review the accrual to the study and the rate of adverse events on the study at least twice per year until the initial results of the study have been presented to the scientific community.

13.5.3 Interim Futility Analysis

The interim futility analysis will be performed when 50% of the required events (34 death or progression) are reported. The analysis will be performed on an intent-to-treat basis, with all eligible cases included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. The primary endpoint progression-free survival will be tested. The responsible statistician may recommend early reporting of the results and/or stopping accrual (if applicable) of the trial if the estimated hazard ratio favors the control arm (by any amount). The accrual rate, treatment compliance, safety of the treatments, and the

importance of the study are also considered in making such a recommendation. The results will be reported to the NRG Oncology DMC with the treatment blinded. The DMC will then make a recommendation about the trial to the NRG Oncology Group Co-Chairs.

13.5.4 Interim Efficacy Analysis

In July 2017, the result of the interim futility analysis mentioned in the section above was presented to the NRG Oncology DMC. At the request of the DMC, it was agreed upon that an interim efficacy analysis would be added at a later stage of the trial. This section addresses the method to be used for this interim analysis.

An interim efficacy analysis will be performed when 67% of the required events (45 deaths or progression events) are observed. At that time, if the PFS hazard ratio is in favor of the experimental arm with an estimated value of 0.50 or less, then the responsible statistician may recommend early reporting of the results. At 45 events, a hazd ratio of 0.50 corresponds to a Haybittle-Peto interim monitoring boundary p-value of 0.01. The results will be reported to the NRG Oncology DMC. The DMC will then render the final recommendation about the trial to the NRG Oncology Group Co-Chairs.

13.5.5 Analysis for Reporting the Initial Treatment Results

The final analysis will be performed on an intent-to-treat basis, such that all eligible cases on the study will be included in the arm to which they were randomized regardless of what treatment the patients actually received. The analysis to report the final results of treatment comparison between the experimental arm and the control arm will be undertaken when 67 events (death or progression) have been reported. A one-sided log-rank test at the 0.15 significance level will be performed to test the difference in PFS between the two treatment arms. If the P value is less than protocol-specified 0.15 (one-sided), the study statistician will reject the null hypothesis and conclude that the experimental arm has a better PFS than the standard arm, thereby supporting the development of a phase III trial comparing this regimen to the current standard at that time. All information reported in the interim analyses to monitor the study progress (Section 13.5.2) and treatment compliance with respect to radiation and chemotherapy will also be included in the final report.

13.5.6 CDUS Tracking

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

13.6 Gender and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we address this issue here; both men and women of all races and ethnic groups are eligible for this study. The following table lists the projected accrual for each racial and ethnic group based upon previous RTOG PCNSL trials.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	3	4
Not Hispanic or Latino	43	42	85
Ethnic Category: Total of all subjects	44	45	**89**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	1	2	3
Native Hawaiian or other Pacific Islander	0	1	1
White	42	41	83

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Racial Category: Total of all subjects	44	45	**89**

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APPENDIX I (8/25/15)
STUDY PARAMETER TABLES

Pretreatment Assessments

	≤6 wks prior to registration	≤2 wks prior to registration	≤2 wks prior to start of treatment
Histology confirmation See section 3.1.1 for details	X		
History/physical	X		X
Neurologic exam, KPS			X
MRI of brain, response assessment	X		X
History of corticosteroids use			X
CT chest, abdomen, pelvis	X		
Chest X-ray			X
Anti-HIV test	X		
CBC w/ diff & ANC, platelets, Hgb		X	X
Bilirubin, AST		X	X
ALT			X
LDH			X
Serum creatinine		X	X
Creatinine clearance		X	X
Electrolytes, BUN			X
Urinalysis			X
Serum or urine pregnancy test (if applicable)	X		
Complete ophthalmologic exam including slit lamp exam			X
Bone marrow biopsy see section 4.1 for details	Taken pre-treatment (≤ 6 weeks); submitted post-registration (< 1 month after start of treatment)		
Lumbar puncture see section 4.1 for details	Taken pre-treatment (≤ 6 weeks)		
Hepatitis B screening (recommended): see section 4.2 for details	Recommended (≤ 6 weeks) pre-treatment; results not needed for patient to start treatment		
Informed consent	X		
QOL assessment (for consenting pts)			X
NCF assessment (for consenting pts)			X
Tissue (H&E, immunohistochemistry, tissue block, unstained slides) for central path review	Taken pre-treatment; submitted post-registration		
Tissue (tumor, bone marrow, +/or eye biopsy) for banking/correlative studies (for consenting pts)	Taken pre-treatment; submitted post-registration		
CSF for banking/correlative studies (for consenting pts)	Taken pre-treatment; submitted post-registration. Remnant sample from clinical collection can be used.		
DNA for banking/correlative studies (for consenting pts)	Taken pre-treatment; submitted post-registration		
Buccal swab (for consenting pts)	Taken pre-treatment; submitted post-registration		

Assessments During Treatment

A window of + 3/- 2 days is acceptable for all on-study treatments and assessments. (It is NOT applicable to pre-treatment assessments.)

	R-MPV (cycles 1, 2, 3, 4)	**Consolidation Cytarabine (Cycles 1 &2)**
History/physical	d 1, 15	d 1
Neurologic exam, KPS	d 1, 15	d 1
MRI of brain, response assessment	Cycle 2, d28 Cycle 4, d28	Cycle 1 d 1 (arm B)
History of corticosteroids use	Cycle 2, d28 Cycle 4, d28	Cycle 1 d 1 (arm B)
CBC w/ diff & ANC, platelets, Hgb	d 1, 8, 15, 22	Repeat wkly throughout cycle
Bilirubin, AST	d 1, 15	
ALT	d 1, 15	
Serum creatinine	d 1, 15 (and then daily until MTX is cleared)	d 1
Creatinine clearance	d 1, 15	
Electrolytes, BUN	d 1, 15 (and then daily until MTX is cleared)	d 1
MTX levels	d3, 17 (and then daily until MTX is cleared Note: the administration of MTX is on d 2 and 16 (see Section 7.1)	
Urinalysis	D 1, 15	
QOL assessment (for consenting pts)	Cycle 4, d28	
NCF assessment (for consenting pts)	Cycle 4, d28	

Assessments During Follow-Up

A window of + 3/- 2 days is acceptable for all on-study treatments and assessments. (It is NOT applicable to pre-treatment assessments.)

	Q 2 m for 1st 2 yrs (starting 4 wks after cytarabine cycle 2, d 1)	**Q 6 m during years 3-5**
History/physical	X	X
Neurologic exam, KPS	X	X
MRI of brain, response assessment	X	X
Lumbar puncture	X*	X*
History of corticosteroids use	X	X
Complete ophthalmologic exam including slit lamp exam	Repeated if previously positive	Repeated if previously positive
QOL assessment (for consenting pts)	Q 6 months	X
NCF assessment (for consenting pts)	Q 6 months	X

***Performed at each MRI time point, until the second MRI showing CR (which confirms the CR status if tap still negative).**

NOTE. If a patient experiences disease progression during the study evaluation period, the neurocognitive and QoL assessment should be put on hold until the patient is clinically stable for 3 consecutive months, at which time the follow-up neurocognitive evaluation should be obtained. The next neurocognitive evaluation should be performed according to the next standard/planned protocol follow-up dates (the study calendar is not reset), but no sooner than 3 months from the previous neurocognitive evaluation.

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	**Normal; no complaints; no evidence of disease**
90	**Able to carry on normal activity; minor signs or symptoms of disease**
80	**Normal activity with effort; some sign or symptoms of disease**
70	**Cares for self; unable to carry on normal activity or do active work**
60	**Requires occasional assistance, but is able to care for most personal needs**
50	**Requires considerable assistance and frequent medical care**
40	**Disabled; requires special care and assistance**
30	**Severely disabled; hospitalization is indicated, although death not imminent**
20	**Very sick; hospitalization necessary; active support treatment is necessary**
10	**Moribund; fatal processes progressing rapidly**
0	**Dead**

APPENDIX III (07-AUG-2018)

APPENDICES FOR NRG ONCOLOGY BIOSPECIMEN COLLECTION *(as specified by the protocol)*.

NRG Oncology FFPE Specimen Plug Kit Collection
NRG Oncology Frozen Tissue and Bone Marrow Kit Instructions
NRG Oncology Blood Collection Kit Instructions
NRG Oncology Buccal Scrapings Specimen Kit Instructions

NRG Oncology CSF Collection Kit Instructions
Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter St, room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal (ST) Form has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
  - ○ Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking.
  - ○ Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - ○ Multiple cases/specimens may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - ○ Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - ○ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - ○ Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

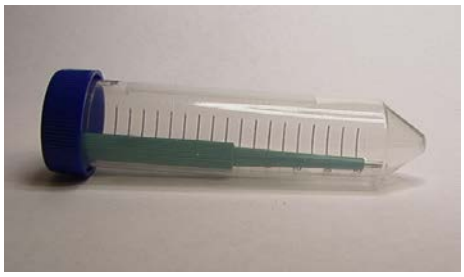
NRG ONCOLOGY FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper pathology specimen ID and block ID. DON'T remove specimen from the punch. Punches must be accompanied

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.
Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
USCF Box 1800
2340 Sutter St, room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens or Trackable shipments
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

NRG ONCOLOGY FROZEN TISSUE KIT INSTRUCTIONS

This Kit is for processing and shipping of frozen tissue specimens.

Kit contents:

- Biohazard pads/wipes 4" x 4" (orange)
- Five (5) 5-mL cryovials
- Disposable scalpel blades
- Disposable forceps
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Prepaid shipping label
- UN 3373 Label
- UN 1895 Dry Ice Sticker

Preparation and Processing of Fresh Frozen Tissue:

- ❑ On sterile cutting board, lay out the underpads.
- ❑ Keep biohazard wipes nearby to keep area clean throughout process.
- ❑ Label cryovials with NRG Oncology study and case numbers
- ❑ Using provided disposable scalpel, evenly cut tissue into 3 to 5 separate pieces (Note: if a frozen core was obtained, do not cut but send it whole).
- ❑ Use forceps to place each piece of tissue into individual 5-mL cryovials.
- ❑ Snap freeze tissue samples in liquid nitrogen, a dry ice slurry (dry ice with 95% ethanol or isopentane), or directly on dry ice.
- ❑ Once frozen, place all of the cryovials into biohazard bag
- ❑ Use NRG Oncology provided labels to label the bag (provided when patient is registered).

Storage and Shipping:

Freezing and Storage

- ❑ Store at -80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

  OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Place specimens and the absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7-10 lbs.—if appropriate; double-check temperature sample shipping temperature). Place Styrofoam cooler into outer cardboard box, and attach shipping label to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.*
- ❑ Send frozen specimens via overnight courier to the address below. Specimens should only be shipped Monday through Wednesday to prevent thawing due to delivery delays.
- ❑ Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen until ready to ship.
- ❑ For Questions regarding collection/shipping or to order a Frozen Tissue Kit, please contact the NRG Oncology Biospecimen Bank by **e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271**.

  Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
  NRG Oncology Biospecimen Bank, University of California San Francisco
  2340 Sutter St, room S341, San Francisco, CA 94115

NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of <u>whole blood</u> *(as specified by the protocol)*:

<u>Kit contents</u>:

- 2 Purple Top EDTA tubes for Whole Blood
- Ten (10) 1 ml cryovials
- Biohazard bags (1) and Absorbent shipping material (1)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal (ST) Form and Kit Instructions

<u>PREPARATION AND PROCESSING OF WHOLE BLOOD:</u>

<u>Whole Blood for DNA: 2 Purple Top EDTA tubes</u>

- ❑ Label as many 1ml cryovials (6 to 10) as necessary for the whole blood collected. Label them with 1NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (6 to 10) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

<u>Freezing and Storage</u>:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

  <u>OR</u>:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).

  <u>OR</u>:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

<u>Shipping/Mailing</u>:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

<u>(continued on next page)</u>

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

For questions, call 415-476-7864,e-mail: NRGBB@ucsf.edu, or Fax 415-476-5271

NRG ONCOLOGY BUCCAL SCRAPINGS SPECIMEN KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of Buccal Specimens.

Kit Contents

- One screw-top container filled with RNAlater
- Buccal brush/swab
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Return shipping label
- Specimen Transmittal (ST) Form

Preparation and Processing of Buccal Scrapings:

- Brush or swab the oral mucosa generously to collect cells.
- The swab with the specimen will then be placed into a cup/vial with RNAlater solution.
- Swish the swab in the solution to free the cells.
- The handle of the swab may be cut or bent to fit into the container.
- The specimen should then be stored frozen at -70 º to -80º Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with NRG Oncology study and case numbers, collection date/time, and time point collected (e.g., pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- ❑ Store at -80°C (-70°C to -90°C) until ready to ship. If a -80°C freezer is not available:
  - Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

  OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- ❑ For questions regarding ordering, collection, or shipping of a Buccal Collection Kit, please e-mail NRGBB@ucsf.eduor call 415-476-7864 or Fax 415-476-5271.

Shipping Address: FedEx/UPS/Courier address (all courier packages & frozen samples)
NRG Oncology Biospecimen Bank at UCSF
2340 Sutter St, room S341
San Francisco, CA 94115
Contact Phone 415.476.7864/Fax 415-476-5271

NRG ONCOLOGY CSFAND BONE MARROW COLLECTION KIT INSTRUCTIONS

This Kit contains:

- Five (5) 5mL cryovials
- Parafilm
- Sterile Disposable Pipette
- Biohazard bags

Cerebrospinal Fluid (CSF) and Bone Marrow Specimens:

Preparation for collecting **CSF and Bone Marrow:**

- Sterile CSF and bone marrow specimens will be collected according to individual site protocol.

Processing

- After CSF specimen has been obtained, use the following instructions:
  - Aliquot CSF using a sterile pipette into 5 different 5mL vials, each containing a minimum of 1mL
  - If CSF is already frozen, perform a controlled thaw and aliquot specimens according to above instructions. Indicate on paperwork if specimen had to be thawed/refrozen.
  - Bone marrow specimens will be collected following institutional SOPs for collection of frozen bone marrow specimens, and may be shipped in the original vial. While the provided cryovial can be used, specimens should not be aliquotted or thawed.

- Label the specimens with the NRG Oncology study and case number, collection date and time, and clearly mark specimen as “CSF” or “bone marrow”.
- If available, use parafilm to seal the aliquots and to prevent leakage.
- Place CSF and bone marrow samples into biohazard bag and seal the bag.
- Immediately freeze specimens at -80 ºC
- Store specimens frozen until ready to ship.

Storage:

- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

  - OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only).

  - OR:
  - Samples can be stored in liq. nitrogen vapor phase (ship out Monday-Wednesday only).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping Instructions for all specimens:

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

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

- **Sites must submit the required documentation with specimens. Specimens are shipped on Dry Ice to:**

  NRG Oncology Biospecimen Bank/University of California San Francisco (FedEx/UPS Courier address)
  2340 Sutter Street, rm 341
  San Francisco, CA 94115

(contact: 415-476-7864)

APPENDIX IV (8/25/15)

CERTIFICATION AND ADMINISTRATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY

STEP 1 – EXAMINER CERTIFICATION FOR RTOG 1114

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. Correa (See Section 5.1.4). Examiners who have completed the full certification procedure to perform these tests for RTOG 0525, 0534, 0614, 0834 or 0825 during the past 6 months do not need to complete the full certification procedure again, but the certification worksheet for 1114 must be faxed to Dr. Correa (fax number **646-888-3175)** for documentation purposes with information regarding the examiners 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 1114. Examiners who have not completed the full certification procedure for RTOG 0525, 0534, 0614, 0834 or 0825 within the past 6 months must complete the full certification procedure to be recertified to ensure continued familiarity with study procedures.

Prior to registering and/or testing a patient, potential examiners must:
(1) Read Section 11.2 of the protocol
(2) Read Appendix IV (Certification and Administration Procedures for the Neurocognitive Test Battery)
(3) Go to the NRG Oncology/RTOG web site and use your username and password to access the link entitled, "Neurocognitive Training Procedure Letter" on the **1114** forms section of the website. This letter will provide you with the web address for the training video.
(4) Obtain copies of the HVLT-R, TMT and COWA from the NRG Oncology/RTOG website
(5) Watch the training video
(6) Complete the training video post test
(7) Complete a "practice" assessment
(8) Complete the Certification Worksheet (Appendix V)
(9) All materials (i.e., post test, completed practice assessment and scoring forms, certification worksheet) must be faxed to Dr. Correa, 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 RTOG 1114. A certification approval notice will be sent to NRG Oncology for the registration process and to ensure that only RTOG 1114-approved examiners are testing subjects on protocol RTOG 1114.
(11) **After you are certified, please fax all neurocognitive test and summary forms for the first study patient you test on RTOG 1114 to Dr. Correa (646-888-3175) for centralized review.**

STEP 2 – ALTERNATE TEST FORMS/VERSIONS

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

TIME TABLE FOR COGNITIVE EVALUATIONS AND ALTERNATE FORMS TO BE USE AT EACH VISIT

TEST	≤2 wks prior to start of treatment	R-MPV (Cycle 4, d28)	Every 6 months up to year 5 (starting 4 wks after cytarabine cycle 2, d 1)
HVLT-R	Form 1	Form 2	Form 3 **
COWA	"C-F-L"	"P-R-W"	"C-F-L" ***

** HVLT-R: Continue to alternate order at subsequent 6-month intervals: Form 4. Form 5, Form 6, Form 1, Form 2, Form 3, Form 4, Form 5, Form 6

***COWA: Continue to alternate order at subsequent 6-month intervals: ‘P-R-W’, ‘C-F-L’, ‘P-R-W’,‘C-F-L’, ‘P-R-W’,‘C-F-L’,‘P-R-W’,‘C-F-L’, ‘P-R-W’.

STEP 3 — TEST INSTRUCTIONS AND ADMINISTRATION PROCEDURES
Additional comments:
1. Testing must be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.
2. Tests should be administered in the following order to every patient and at every study visit:
HVLT-R Part A (Learning Trials); Trail Making Test Part A; Trail Making Test Part B; COWA; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition).
3. You may fill the delay interval between COWA and HVLT-R Part B (Delayed Recall) with EORTC QLQ-C30/BCM20 questionnaire.
4. Follow the instructions on the Forms Packet Index before submission of forms to NRG Oncology.
5. Please keep all original test forms. In the event of questions, contact Dr. Correa. Copies of the test forms and summary sheets for the first case from each certified examiner must be faxed for review to Dr. Correa (646-888-3175 Additional test forms are not submitted to Dr. Correa nor to NRG Oncology. Results remain on file at the institution as source documentation pending request for submission by NRG Oncology or a study chair.
6. All test results are recorded on the Neurocognitive Evaluation Summary Form (CS), which is found in the Forms Packet. Study/case-specific labels must be applied to all forms.
7. Patients should not be given copies of their tests to avoid learning the material between test administrations.
8. Before dismissing the patient, thank the patient for his/her cooperation.
9. In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the Neurocognitive Evaluation Summary Form (CS).

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

[redacted]

[redacted]

2. TRAIL MAKING TEST [Timed Test]

[redacted]

[redacted]

[redacted]

3. CONTROLLED ORAL WORD ASSOCIATION (COWA) [Timed Test]

[redacted]

[redacted]

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

[redacted]

NCF/QOL ENDPOINT FLOW DIAGRAM

≤2 wks prior to start of treatment	R-MPV (Cycle 4, d28)	Every 6 months up to year 5 (starting 4 wks after cytarabine cycle 2, d 1)
NCF/QOL	NCF/QOL	NCF/QOL

NCF/QOL= neurocognitive function and quality of life battery

NOTE. If a patient experiences disease progression during the study evaluation period, the neurocognitive and QoL assessment should be put on hold until the patient is clinically stable for 3 consecutive months, at which time the follow-up neurocognitive evaluation should be obtained. The next neurocognitive evaluation should be performed according to the next standard/planned protocol follow-up dates (the study calendar is not reset), but no sooner than 3 months from the previous neurocognitive evaluation.

APPENDIX V

CERTIFICATION WORKSHEET FOR TEST ADMINISTRATOR

RTOG 1114

This worksheet must be completed and signed by the person requesting certification and submitted to Dr. Correa prior to the registration of any patients to RTOG 1114. Refer to Appendix IV for details.

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

_____ (Y/N) 2. Have you completed the full certification to perform the Neurocognitive Battery for RTOG 0525, 0534, 0614, 0834, or 0825 during the past 6 months?

_____ (Y) 3. Have you watched the Neuropsychological Test Administration video?

_____ (Y) 4. Have you completed and submitted the post test associated with the training video and a "practice" Neuropsychological Assessment?

PLEASE PRINT
Name of test administrator: _____

NRG institution number/name:_____

NCI code:_____

Telephone number of test administrator _____

Fax number of test administrator: _____

E-mail address of test administrator: _____

_____ _____
Signature of test administrator Date
(person who read Appendix IV, watched video and completed a "practice" Assessment)

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

Denise Correa, PhD; Phone 646-888-3177; FAX 646-888-3175; corread@mskcc.org

For Drs. Correa's/ Wefel's Use Only (*to fax to 215-569-0206, CTSU)*

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

Signature_____Date_____

APPENDIX VI

PATIENT'S MEDICATION DIARY

CTEP-assigned Protocol #_____

Local Protocol # _____

Today's date _____ **Agent: Procarbazine**

Patient Name_____(*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take procarbazine tablets for 7 days. You should take the tablets on an empty stomach at approximately the same time each day.
   Dose (each tablet contains 50 mg):

Day 1: take ___ tablets.
Day 2: take ___ tablets.
Day 3: take ___ tablets.
Day 4: take ___ tablets.
Day 5: take ___ tablets.
Day 6: take ___ tablets.
Day 7: take ___ tablets.

3. Record the date, the number of tablets of each size of tablet that you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottles of procarbazine tablets when you return for each appointment.

Day	Date	Time of dose	# of 50 mg tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				

Patient's signature

_____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total dose during this cycle_____
4. Total number of tablets taken this cycle _____
5. Physician/Nurse/Data Manager's Signature _____