Update #11

**ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY**

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**PROTOCOL UPDATE TO CALGB 51101**

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**A RANDOMIZED PHASE II TRIAL OF MYELOABLATIVE VERSUS NON-MYELOABLATIVE CONSOLIDATION CHEMOTHERAPY FOR NEWLY DIAGNOSED PRIMARY CNS B-CELL LYMPHOMA**

*This study is open to FACT-accredited institutions only.*

| | | | |
|---|---|---|---|
| [X] | **Update:** | [ ] | **Status Change:** |
| [ ] | Eligibility changes | [ ] | Activation |
| [ ] | Therapy / Dose Modifications / Study Calendar changes | [ ] | Closure |
| [ ] | Informed Consent changes | [ ] | Suspension / temporary closure |
| [X] | Scientific / Statistical Considerations changes | [ ] | Reactivation |
| [ ] | Data Submission / Forms changes | | |
| [X] | Editorial / Administrative changes | | |
| [ ] | Other: | | |

***IRB approval (or disapproval) is required within 90 days. Expedited review is allowed. Please follow your IRB of record guidelines.***

**UPDATES TO THE PROTOCOL:**

**Cover Page**

- [redacted]

**Section 2.2 (Secondary Objective)**

Section 2.2.10 has been revised to read: "To analyze tumor tissue for gene mutational analysis via whole exome sequencing, copy number aberrations, and expression profiles, and to correlate these profiles with treatment outcomes (CALGB 151113)."

**Section 10.2 (Biomarker Correlative Science Companion Study [CALGB 151113])**
In Section 10.2.2, the first sentence has been revised to read: "Tumor tissue will also be analyzed for whole exome sequencing, copy number aberrations, and gene expression profiles in order to validate genetic prognostic markers and gene expression profiles in order to validate gene signatures associated with…"

**Section 14.4 (Sample Size Modification)**
A new final paragraph has been added to describe the revised final analysis timing due to low event rate as of protocol Update #11.

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**UPDATES TO THE MODEL CONSENT:**

No changes have been made to the model consent.

**Replacement protocol and model consent documents have been issued.**
**This study remains closed to new patient accrual.**

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**ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL**

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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

# CALGB 51101

## A RANDOMIZED PHASE II TRIAL OF MYELOABLATIVE VERSUS NON-MYELOABLATIVE CONSOLIDATION CHEMOTHERAPY FOR NEWLY DIAGNOSED PRIMARY CNS B-CELL LYMPHOMA

*This study is open to FACT-accredited institutions only.*

***Clinicaltrials.gov Identifier: NCT01511562***

Study Chair

[redacted]

[redacted]

SWOG Co-chair

[redacted]

[redacted]

Lymphoma Committee Chair

[redacted]

Transplant Committee Chair

[redacted]

Imaging Committee Chair

[redacted]

Health Outcomes Committee Chairs

[redacted]

Neuro-Oncology Committee Chair

[redacted]

Pathology Committee Chair and Correlative Study Co-Chair

[redacted]

Neurocognitive/Quality of Life Study Co-Chair

[redacted]

Imaging Study Co-Chair

[redacted]

Primary Statistician

[redacted]

Secondary Statistician

[redacted]

Data Coordinator

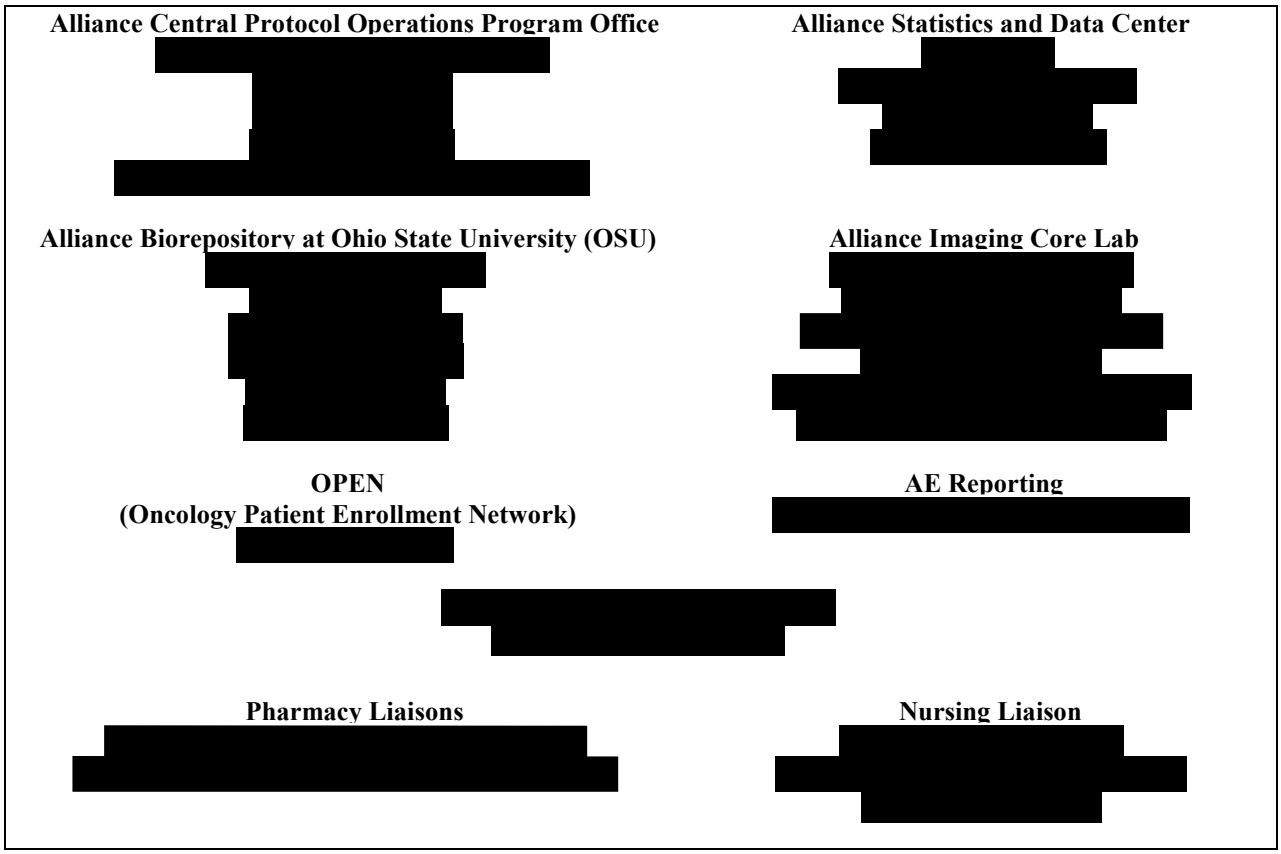
[redacted]

Protocol Coordinator

[redacted]

**Participating NCTN Groups:** ALLIANCE/Alliance for Clinical Trials in Oncology, ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, SWOG/SWOG, and NRG/NRG Oncology.

**Protocol Resources:**



## CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION

| For regulatory requirements: | For patient enrollments: | For study data submission: |
|---|---|---|
| Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.<br><br>Regulatory Submission Portal: (Sign in at [redacted] and select the Regulatory Submission sub-tab under the Regulatory tab.)<br><br>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instructions and support.<br><br>Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance. | Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at [redacted]<br><br>Contact the CTSU Help Desk with any OPEN-related questions at [redacted] | Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. |
| The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page of the CTSU Member website located at [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS. | | |
| **For clinical questions (i.e. patient eligibility or treatment-related)** contact the Study PI of the Lead Protocol Organization. | | |
| **For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU website is located at** [redacted] | | |

**A RANDOMIZED PHASE II TRIAL OF MYELOABLATIVE VERSUS NON-MYELOABLATIVE CONSOLIDATION CHEMOTHERAPY FOR NEWLY DIAGNOSED PRIMARY CNS B-CELL LYMPHOMA**

*Schema page 1 of 1*

**Eligibility Criteria**

Diffuse large B-cell lymphoma confined to the CNS; diagnosis by brain biopsy or resection, CSF, or vitreous fluid

No evidence of NHL outside of CNS; no history of NHL

No prior chemotherapy or radiation therapy for lymphoma

Age 18 – 75 years

Karnofsky Performance Scale ≥ 30 (≥ 50 for patients ages 60-70)

Non-pregnant and non-nursing

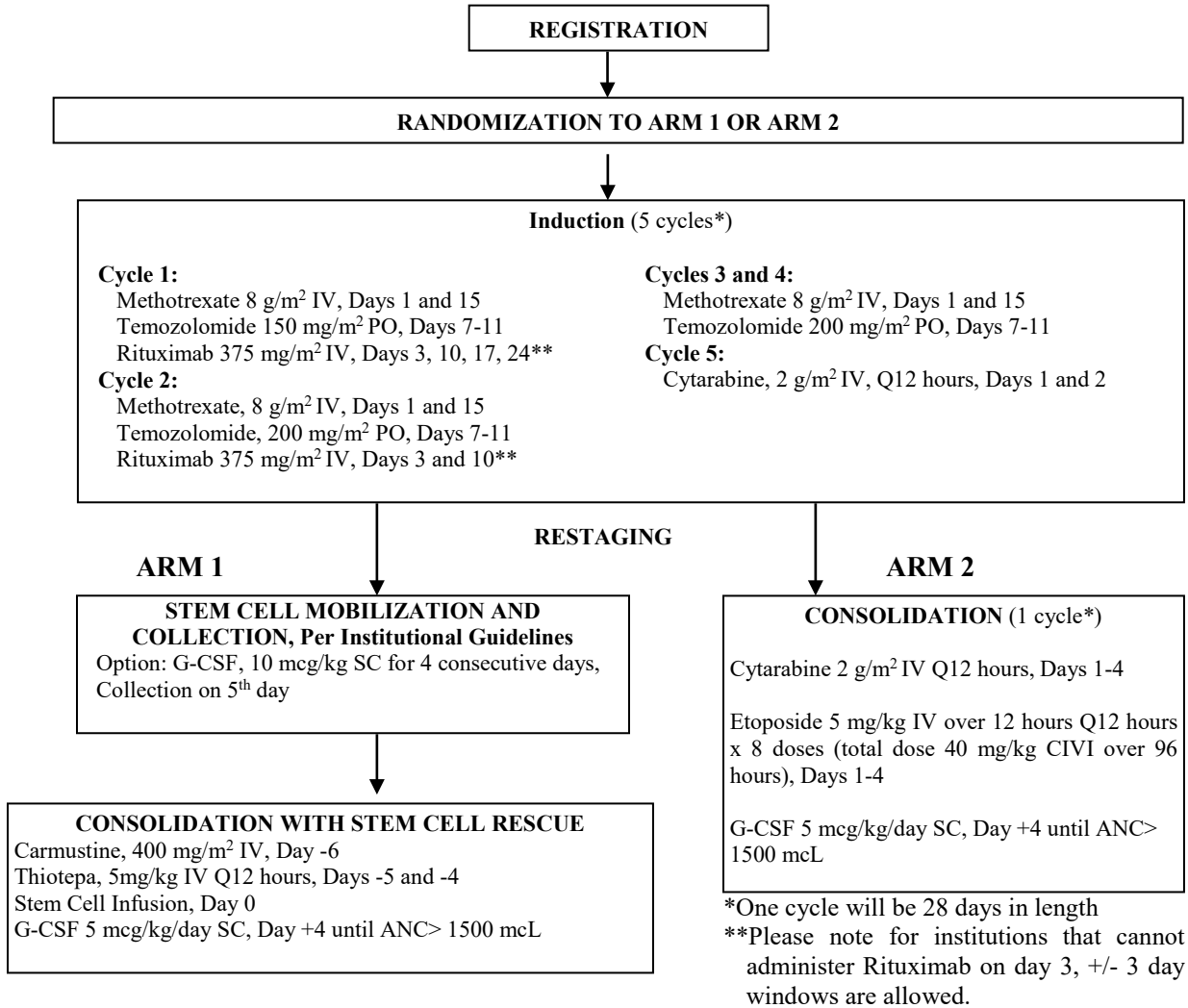
Negative HIV serology

Negative HCV serology

No history of organ transplantation or ongoing immunosuppressant therapy

**Required Laboratory Values**

| | |
|---|---|
| ANC: | ≥ 1500/mcL |
| AST & ALT: | ≤ 2 x ULN |
| Total bilirubin: | ≤ 3 mg/dL |
| Platelets: | ≥100,000/mcL |
| CrCl: | ≥ 50 mL/min |




*One cycle will be 28 days in length

**Please note for institutions that cannot administer Rituximab on day 3, +/- 3 day windows are allowed.

## TABLE OF CONTENTS

# 1.0 INTRODUCTION

## 1.1 Background

Primary central nervous system lymphoma (PCNSL), an uncommon form of extranodal non-Hodgkin lymphoma (NHL), is a potentially curable cancer. However, the 5-year survival rates for PCNSL are inferior to those achieved for other forms of extranodal NHL. An estimated 1,927 cases of PCNSL were diagnosed each year in the U.S. from 2004 to 2006 and the number of cases is expected to increase further with the aging of the U.S. population [1]. The optimal treatment approach for newly diagnosed PCNSL patients has yet to be defined, partially due to the lack of data from prospective randomized trials. Age and performance status are important prognostic factors in patients with PCNSL [2]. The International PCNSL Collaborative Group (IPCG) has established consensus guidelines for extent of disease evaluation, neurocognitive assessment, and tumor response in the newly diagnosed PCNSL patient population [2, 3].

Historically, whole brain irradiation was an integral component of therapy for newly diagnosed PCNSL. However, the limitations of treating PCNSL initially with whole brain irradiation alone are clear. Despite maximization of radiation dose, median survival has remained in the range of 10-18 months. A plateau in survival has been achieved with current therapy using methotrexate-based regimens plus whole brain irradiation. This approach results in a median survival of approximately 40 months with a 22% five-year survival [4]. These results are in contrast to the treatment outcome of patients who have localized non-CNS NHL who have at least a 75% rate of long-term disease-free survival with combined modality therapy [5]. Moreover, regimens that include whole brain irradiation are associated with a significant risk of long-term neurotoxicity. The median age of persons diagnosed with PCNSL is 60 [1]. The majority of patients aged 60 or over who are treated with whole brain irradiation will exhibit clinically measurable neurotoxicity [4]. It is also recognized that a significant proportion of patients under the age of 60 who are treated with whole brain irradiation will also manifest symptoms and signs of neurotoxicity. Preliminary reports suggest that when lower doses of whole brain irradiation are administered with chemotherapy the risk of neurotoxicity may be lower, although these reports have yet to be confirmed [6]. In one study reduction of whole brain irradiation compromised survival in the PCNSL patient population [7]. Moreover, preclinical studies indicate that even single fractions of whole brain irradiation may lead to irreversible injury to neural progenitor cell populations [7]. Therefore, there has been significant interest in developing alternatives to whole brain irradiation in the induction and consolidation treatment phases for PCNSL patients.

## 1.2 Induction Chemotherapy for PCNSL

Deferral of whole brain irradiation and use of chemotherapy alone in the newly diagnosed PCNSL patient population is a strategy used by an increasing number of clinicians [8]. Primary central nervous system lymphomas exhibit a unique responsiveness to methotrexate compared to systemic lymphomas [9, 10]. High-dose methotrexate-based therapies currently represent the most effective regimen in this disease. A univariate analysis of a retrospective series of 226 patients diagnosed with PCNSL suggests that use of high-dose methotrexate is the only treatment-related factor with independent positive prognostic value after adjustment for age, performance status and CSF protein level. Treatment with regimens that included high-dose methotrexate were associated with significantly better overall survival compared with other treatments ($p<0.0007$) [9]. High-dose methotrexate treatment results in prolonged cytotoxic CSF concentrations that are comparable to those achieved with intrathecal administration of the drug [11]. Although the optimal dose and administration schedule of methotrexate remain a topic of debate it appears that doses > 3 g/m$^2$ every 14-21 days are preferable in this patient population. Toxicity is acceptable with moderate nausea and reversible nephrotoxicity being the most common early side effects. Delayed toxicities such as brain necrosis and dementia, which are observed in patients receiving whole brain irradiation, are rare in patients treated with single-

agent high-dose methotrexate. In a multicenter phase II study of high-dose methotrexate (8 g/m$^2$) alone in patients with newly diagnosed PCNSL, the complete response (CR) proportion was 52%, the progression-free survival was 12.8 months, the overall survival was 55.4 months and the disease-specific survival was 72.3+ months. The median number of cycles to achieve CR was 6 in this study. Five of 25 of these patients had not relapsed after a median follow-up of approximately 7 years. Less than half of these patients experienced CTC grades 3 or 4 toxicities [8, 12]. A subsequent randomized study (IELSG 20) of methotrexate monotherapy versus methotrexate + cytarabine in 79 newly diagnosed PCNSL patients demonstrated a higher overall and complete radiographic response proportion in the combination arm versus methotrexate alone, 69% and 46% versus 41% and 18%, respectively. Hematologic and infectious complications were more common in the methotrexate and cytarabine arm compared to the methotrexate monotherapy arm [3]. Based on these and other studies methotrexate has emerged as the foundation of the chemotherapy regimens for patients with newly diagnosed PCNSL.

Rituximab, a chimeric anti-CD20 monoclonal antibody, is a potentially attractive therapeutic agent for PCNSL since at least 90% of CNS lymphomas express CD20. Rituximab enhances the efficacy of cytotoxic therapy in the treatment of diffuse large cell lymphoma (the most common histologic subtype in PCNSL) [13]. While penetration of this macromolecule into the CNS is limited, there are several facts that support the notion that rituximab may be a beneficial agent for PCNSL therapy. During the first weeks of treatment of PCNSL, the tumor is associated with an abnormal vasculature devoid of a normal blood-brain-barrier. After 5 weeks of treatment, blood-brain permeability values approach the level of normal brain [14]. Compromise of the blood-brain barrier through tumor cell angiotropism and by the elaboration of cytokines may contribute to this increased permeability [15]. Rituximab can be reproducibly detected in the CSF of patients with PCNSL who are treated systemically with this drug [16-18]. In individual case reports complete and partial responses have been described in patients with either PCNSL or post-transplant lymphoproliferative disorder (PTLD) involving the CNS who have been treated with intravenous rituximab [16, 17]. In a pilot study of 12 patients with relapsed or refractory PCNSL treated with rituximab alone (375 mg/m$^2$ weekly x 8 doses), radiographic responses were observed in 5 patients (4 CR, 1 PR) and the median progression-free and overall survival in the responding patients was 7.6 months and 47 months, respectively [19]. Finally, there is minimal toxicity associated with rituximab treatment of PCNSL, nor is there overlapping toxicity with the co-administration of rituximab and high-dose methotrexate (8 g/m$^2$) or cytarabine [16].

Temozolomide is an oral alkylating agent that is highly lipophilic and thus exhibits good CNS penetrance. Based on these properties it is an attractive candidate drug for use in PCNSL. In a phase II study of 23 patients with relapsed PCNSL who were treated with temozolomide alone, radiographic responses were observed in 6 patients (5 CR, 1 PR) and the median progression-free survival was 2 months (range 0.4 to 36 months) [20]. In a study of 17 elderly PCNSL patients (ages 62-90) treated with single-agent temozolomide, 8/17 (47%) achieved a complete radiographic response with a median progression-free survival of 5 months and a median overall survival of 21 months [21]. In another study of elderly PCNSL patients, temozolomide and methotrexate (3 g/m$^2$) were administered to 23 patients and 55% of patients achieved a complete radiographic response with a median progression-free survival of 8 months and a median overall survival of 35 months [22]. In a study of temozolomide and rituximab for relapsed and refractory PCNSL patients, 8/15 patients achieved radiographic responses; the median progression-free survival was 7.7 months and the overall survival was 14 months [23]. In another study of 8 patients with newly diagnosed or relapsed CNS lymphoma, temozolomide and rituximab were administered together for 4 weeks followed by 8 monthly cycles of temozolomide alone. Seven (5 CR, 2 PR) patients achieved a radiographic response with a median progression-free survival of 6 months and median overall survival of 8 months [24]. These phase II studies demonstrate that temozolomide alone or in combination with rituximab or methotrexate has objective activity

against PCNSL and provides a strong rationale for assessment of a combination regimen containing all of these agents in this patient population.

The combination of methotrexate, temozolomide, and rituximab (MTR) as induction chemotherapy has been utilized successfully in both the single center and the multicenter setting as induction therapy in PCNSL. In a single-center study MTR was administered as induction therapy to newly diagnosed (10) or relapsed (6) PCNSL patients with 10/10 (9 CR, 1 PR) and 6/6 (4 CR, 2 PR) radiographic responses, respectively [25]. In a multicenter phase II study (CALGB 50202) MTR was administered to 46 newly diagnosed PCNSL patients. In this latter study, 63% of patients achieved a complete radiographic response [26]. As noted above, each of the drugs in the MTR regimen has been studied in single-agent trials with objective efficacy observed in the PCNSL patient population.

### 1.3 Consolidation Chemotherapy for PCNSL

The optimal consolidation regimen for PCNSL has yet to be established. Whole brain irradiation is associated with a high frequency of neurotoxicity, especially in patients over the age of 60 [27]. Study results from the largest prospective, randomized trial conducted in the newly diagnosed PCNSL population regarding the role of whole brain irradiation (*G-PCNSL-SG-1*) have yielded conflicting interpretations [28]. In the intent to treat analysis of this study, whole brain irradiation as consolidation improved progression-free survival but not overall survival. Lower doses of whole brain irradiation have been advocated but there is no proof that such a strategy is associated with a lower incidence of neurotoxicity [28]. Deferral of whole brain irradiation and use of chemotherapy is associated with a lower incidence of neurotoxicity and may be as effective as regimens that contain whole brain irradiation. Chemotherapy alone is associated with promising 2-year progression-free survival proportions of 30-57% [3, 26, 29]. However, the optimal consolidation chemotherapy for the PCNSL patient population has yet to be defined.

In the phase II CALGB 50202 study consolidation consisted of etoposide and cytarabine. This regimen has been used effectively as a salvage regimen for PCNSL patients [30]. Good diffusion of cytarabine and etoposide in the CNS has been demonstrated. High-dose cytarabine achieves effective levels in brain parenchyma and CSF. Regimens that include cytarabine are also associated with improved survival in PCNSL on univariate analysis ($p<0.04$) [31]. Neurotoxicity with high-dose cytarabine is preventable when doses are reduced in accordance with serum creatinine levels [32]. There is no cross-resistance between cytarabine, etoposide and methotrexate. This regimen is efficacious in patients with Burkitt lymphoma and initial CNS disease [33]. Moreover, the combination of high-dose cytarabine plus etoposide appears to be feasible and safe in the multicenter setting. In a study of 128 patients with AML treated with autologous stem cell transplantation in first remission, only two patients experienced transient neurotoxicity related to high-dose cytarabine but both recovered completely [34]. In CALGB 50202 the treatment was associated with reversible grade IV myelotoxicity but was feasible and reasonably well tolerated in the multicenter setting [26]. Moreover, this consolidation strategy was associated with excellent 2-year progression-free survival (55%) and 2-year overall survival (71%).

### 1.4 HDT/ASCT for Newly Diagnosed PCNSL

Although the studies are relatively small and non-randomized, high-dose therapy and autologous stem cell transplant (HDT/ASCT) is associated with promising long-term OS results for PCNSL patients. The avoidance of whole brain irradiation appears to preserve cognitive function in long-term survivors. HDT/ASCT studies for PCNSL are summarized in Table 1. Demonstration that HDT/ASCT is superior to consolidation non-myeloablative chemotherapy could rapidly change the standard of care for the newly diagnosed PCNSL patient population under the age of 70 (> 50% of all PCNSL patients in the United States).

HDT/ASCT was initially studied in the PCNSL patient population in the setting of relapsed or refractory disease [30]. Investigators administered a salvage regimen consisting of cytarabine or etoposide followed by conditioning therapy with thiotepa, busulfan, and cyclophosphamide [30]. Based on promising median PFS and OS results of 41 and 58 months, respectively, this strategy was next employed in the newly diagnosed PCNSL population, initially in combination with whole brain irradiation. Although initial results in this setting were disappointing using the BEAM conditioning regimen [35], subsequent studies employed regimens with potentially better CNS penetration including busulfan, thiotepa, and carmustine [36-38]. Recent studies with the latter agents have eliminated whole brain irradiation and the median PFS and OS achieved in these studies are promising. In a multicenter phase II study of newly diagnosed PCNSL patients, induction therapy with high dose methotrexate (HD-MTX), high dose cytarabine, and thiotepa was followed by a conditioning chemotherapy regimen consisting of carmustine (400 mg/m²) and thiotepa (2 x 5 mg/kg) followed by ASCT. Whole brain irradiation was then given as consolidation. With a median follow-up of 63 months, the 5-year OS was 69% for all patients and 87% for those completing HDT/ASCT [39]. In a follow-up trial this protocol was modified with intensification of the chemotherapy and restriction of whole brain irradiation only for patients who did not achieve CR after induction therapy. Seven of 11 patients were in CR following ASCT and 3 in PR upon ASCT received whole brain irradiation as consolidative treatment. After a median follow-up of 25 months, 3-year OS was 77%. None of the patients suffered from severe neurotoxicity during the follow-up period [40]. In summary, HDT followed by ASCT is likely to assume an increasingly important role in patients with PCNSL in the newly diagnosed and relapsed setting. ASCT may be effective in patients with poor prognostic features as well [41].

| **Reference** | **N** | **Median Age** | **Induction regimen** | **Conditioning regimen** | **WBI** | **CRR [%]** | **FU [mos]** | **Survival** | **TRM** |
|---|---|---|---|---|---|---|---|---|---|
| Columbat et al 2006 [42] | 25 | 51 | MBVP +i.t. AraC | BEAM | yes | 44% | 34 | 4-y EFS: 46% | 4% |
| Abrey et al 2003 [35] | 28 | 53 | MTX AraC | BEAM | no | 18% | 27 | mEFS: 9 mo | 0% |
| Stewart et al 2004 [36] | 11 | 56 | MTX | Thiotepa Busulfan Cy | yes | 82% | 22 | 3-yr OS: 61% | 18% |
| Illerhaus et al 2006 [39] | 30 | 54 | MTX (8g) AraC/TT | Thiotepa (10mg/kg) BCNU | yes* | 76% | 63 | 5-yr OS: 69% | 3% |
| Monte-murro et al 2007 [37] | 23 | 55 | MTX (8g) | Bu / TT (10mg/kg) | yes* | 69% | 15 | 2-yr OS: 48% | 13% |
| Illerhaus et al 2008 [40] | 13 | 54 | MTX (8g) AraC/TT | TT (20mg/kg) /BCNU | no | 54% | 25 | 3-yr OS: 77% | 0% |

*AraC, cytarabine; ASCT, autologous stem cell transplantation; BCNU, carmustine; BEAM (regimen), carmustine, etoposide, cytarabine, and melphalan; Bu, busulfan; Cy, cyclophosphamide; IFO, ifosfamide; i.t., intrathecal; MBVP (regimen), methotrexate, carmustine, etoposide, and methylprednisolone; OS, overall survival; TRM, treatment-related mortality; TT, thiotepa; WBI, whole-brain irradiation.*

*Only for patients not achieving a complete remission

### 1.5 Inclusion of Women and Minorities

It is the intent of Alliance to enroll patients regardless of gender or race. Both men and women of all races and ethnic groups are eligible for this study. In the development of this protocol, the possibility of inherent gender or racial/ethnic differences in treatment response has been considered.

| PLANNED ENROLLMENT REPORT | | | | | |
|---|---|---|---|---|---|
| **Racial Categories** | **Ethnic Categories** | | | | **Total** |
| | **Not Hispanic or Latino** | | **Hispanic or Latino** | | |
| | **Female** | **Male** | **Female** | **Male** | |
| American Indian/ Alaska Native | 0 | 0 | 0 | 0 | 0 |
| Asian | 3 | 3 | 0 | 0 | 6 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 0 | 0 | 2 |
| Black or African American | 3 | 3 | 0 | 0 | 6 |
| White | 38 | 47 | 2 | 1 | 88 |
| More Than One Race | 5 | 1 | 1 | 1 | 8 |
| **Total** | 50 | 55 | 3 | 2 | 110 |

## 2.0 OBJECTIVES

### 2.1 Primary Objective

To compare the two-year progression-free survival (PFS) of patients treated with the myeloablative consolidation treatment strategy of HDT/ASCT versus those treated with non-myeloablative consolidation chemotherapy with cytarabine and etoposide

### 2.2 Secondary Objectives

**2.2.1** To compare the two-year event-free survival (EFS) of patients treated with consolidation HDT/ASCT versus those treated with consolidation chemotherapy consisting of etoposide and cytarabine

**2.2.2** To compare the overall survival (OS) of patients treated with the consolidation HDT/ASCT versus those treated with consolidation chemotherapy consisting of etoposide and cytarabine

**2.2.3** To assess the toxicities associated with consolidation HDT/ASCT versus consolidation consisting of etoposide and cytarabine

**2.2.4** To determine diffusion MRI metrics ($ADC_{mini}$, $ADC_{25\%}$, and $ADC_{mean}$) prior to induction chemotherapy, after one full induction chemotherapy cycle, and at the end of induction chemotherapy as a predictor of response and outcome (CALGB 581101)

**2.2.5** To determine brain FDG-PET metrics (tumor SUV and tumor versus background SUV) prior to induction chemotherapy, after one full induction chemotherapy cycle, and at the end of induction chemotherapy as a predictor of response and outcome (CALGB 581101)

**2.2.6** To determine whether low baseline ADC measurements are associated with shorter PFS and OS (CALGB 581101)

**2.2.7** To determine whether reduction in tumor SUV by > 25% on brain FDG-PET/CT after one cycle of induction therapy is associated with improved PFS and OS (CALGB 581101)

**2.2.8** To determine which IHC-based biomarkers are predictive of an adverse prognosis (CALGB 151113)

**2.2.9** To determine which IHC-based biomarkers are predictive of a favorable prognosis (CALGB 151113) for BCL6 (B-cell CLL/lymphoma 6), and STAT 6 (signal transducer and activator of transcription 6, interleukin-4 induced)

**2.2.10** To analyze tumor tissue for gene mutational analysis via whole exome sequencing, copy number aberrations, and expression profiles, and to correlate these profiles with treatment outcomes (CALGB 151113)

**2.2.11** To determine whether CSF proteome is a predictor of outcomes (prognostic marker) irrespective of treatment arm [43] (CALGB 151113) for (IL-10 (interleukin 10) and C3 (complement component 3)

**2.2.12** To assess the neurocognitive function of patients treated with consolidation HDT/ASCT versus those treated with consolidation chemotherapy (etoposide and cytarabine) as measured by serial administration of the International PCNSL Collaborative Group (IPCG) neurocognitive battery and evaluate the long-term survivorship differences between the two arms (CALGB 71105)

**2.2.13** To assess the quality of life of patients treated with consolidation HDT/ASCT versus those treated with consolidation etoposide and cytarabine as measured by the EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTC-QLQ30/BCM20), and to evaluate the long-term survivorship differences between the two arms (CALGB 71105)

## 3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to a patient entering this protocol:

- Psychiatric illness that would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease, which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with prior or concurrent malignancies other than surgically cured CIS of the uterus or cervix and carcinoma of the skin without evidence of disease for ≥ 5 years.
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives, or double barrier method (diaphragm plus condom).
- Patients must be considered to be a suitable candidate for high dose chemotherapy and autologous stem cell transplant at the time of initial evaluation based on medical history, physical examination, and available basic laboratory tests. Specific testing for organ function is not required, but if available, these tests may be used to judge suitability.

## 4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the Alliance Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

### 4.1 Documentation of Disease

Diagnosis of primary CNS diffuse large B-cell lymphoma confirmed by one of the following:

Brain biopsy or resection

Cerebrospinal fluid

Vitreous fluid

### 4.2 Other Lymphomas

Patients must have no evidence or history of non-Hodgkin lymphoma (NHL) outside of CNS.

### 4.3 Previous Treatment

Patients must have no prior chemotherapy or radiation therapy for lymphoma.

### 4.4 Age

Patients must be between the ages of 18 and 75 years.

### 4.5 Karnofsky Performance Scale

Patients must measure Karnofsky Performance Scale ≥ 30 (≥ 50 for patients ages 60-70).

### 4.6 Pregnancy and Nursing Status

Patients must be non-pregnant and non-nursing. Due to the unknown teratogenic potential of this regimen, pregnant or nursing patients may not be enrolled. Women of childbearing potential must have a negative serum or urine pregnancy test 10-14 days prior to registration. In addition, women and men of childbearing potential must commit to use an effective form of contraception throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives, or double barrier method (diaphragm plus condom).

### 4.7 HIV

Patients must have negative HIV serology.

### 4.8 Hepatitis

Patients must have negative HCV serology. All patients must be screened for hepatitis B infection before starting treatment. Those patients who test positive for hepatitis B should be closely monitored for evidence of active HBV infection and hepatitis during and for several months after rituximab treatment. PCNSL patients with a history of hepatitis B infection should be treated with entecavir or lamivudine (physician discretion for choice of drug) as antiviral prophylaxis to prevent hepatitis B reactivation.

### 4.9 Organ Transplant or Immunosuppressant Therapy

Patient must have no history of organ transplantation or ongoing immunosuppressant therapy.

### 4.10 Required Initial Laboratory Values:

| | |
|---|---|
| ANC | ≥ 1500/mcL |
| AST and ALT | ≤ 2 x upper limit of normal (ULN) |
| Total bilirubin | ≤ 3 mg/dL |

| | |
|---|---|
| Creatinine clearance | ≥ 50 mL/min |
| Platelet count | ≥ 100,000/mcL |

# 5.0 REGISTRATION/RANDOMIZATION, DATA SUBMISSION, HISTOLOGY REVIEW, AND CORRELATIVE SCIENCE SAMPLE SUBMISSION

## 5.1 Registration Requirements

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required.

Registration must occur prior to the initiation of therapy.

Registration to the optional correlative science companion studies will be performed at the time registration occurs to the treatment study. Registration to both the treatment study and the correlative studies will not be completed if eligibility requirements are not met for both trials.

### 5.1.1 Quarterly Teleconference

Institutional PIs will be invited and strongly encouraged to participate in quarterly teleconference calls with the study team to discuss patient enrollment and protocol treatment questions.

## 5.2 CTEP Registration Procedures

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 [redacted]. 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) [redacted] Documentation requirements per registration type are outlined in the table below.

| Documentation Required | IVR | NPIVR | AP | A |
|---|---|---|---|---|
| FDA Form 1572 | ✔ | ✔ | | |
| Financial Disclosure Form | ✔ | ✔ | ✔ | |
| NCI Biosketch (education, training, employment, license, and certification) | ✔ | ✔ | ✔ | |
| HSP/GCP training | ✔ | ✔ | ✔ | |
| Agent Shipment Form (if applicable) | ✔ | | | |

| Documentation Required | IVR | NPIVR | AP | A |
|---|---|---|---|---|
| CV (optional) | ✔ | ✔ | ✔ | |

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

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at <[redacted]

## 5.3 CTSU Site Registration Procedures

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

**IRB Approval:**

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participation roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

### 5.3.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the CALGB-51101 protocol page located on the CTSU members' website.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen

- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol #CALGB-51101
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

### 5.3.2 Requirements for CALGB 51101 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

### 5.3.3 Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

### 5.3.4 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal:
[redacted] (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:
[redacted]

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instructions and support.

### 5.3.5 OPEN Access Requirements and Procedures

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 < [redacted] >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

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 in the Rave database. OPEN can be accessed at [redacted] or from the OPEN tab on the CTSU members' side of the website at [redacted] To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or

investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: 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 OPEN tab of the CTSU members' side of the CTSU website at [redacted] or at [redacted] For any additional questions contact the CTSU Help Desk at [redacted]

## 5.4 Registration to Companion Studies CALGB 151113, 581101, and 71105

There are three correlative science companion studies within CALGB 51101:

CALGB 151113, Exploratory Analyses of Biomarkers as Potential Predictors of Outcome for Primary CNS B-cell Lymphoma

CALGB 581101, Imaging Markers of Outcome After Chemotherapy in Patients with Newly Diagnosed Primary CNS B-cell Lymphoma

CALGB 71105, Neurocognitive Function and Quality of Life in Patients with Primary CNS B-cell Lymphoma

The companion studies 151113 and 71105 must be offered to all patients enrolled on CALGB 51101, although patients may opt not to participate. The companion study 581101 is only available at limited access institutions. Please see the study website for a list of limited access institutions that may register patients to 581101. The full descriptions of the companion studies are found in Section 10.0.

If a patient answers "yes" to Model Consent Question #1, then the patient should be registered to CALGB 71105 at the same time that s/he is registered to the treatment trial (51101) with assessment data submitted per Section 5.11.

If a patient answers "yes" to Model Consent Question #2, then the patient should be registered to CALGB 151113 at the same time that s/he is registered to the treatment trial (51101) with samples submitted per Section 5.9.

If a patient is being treated at a CALGB 581101 limited access institution, and the patient answers "yes" to Model Consent Question #6, then the patient should be registered to CALGB 581101 at the same time that s/he is registered to the treatment trial (51101) with images submitted per Section 5.10.

## 5.5 Stratification Factors

After registration, randomization will occur according to the following three stratification factors (see Section 14.1):

Age < 51 years

Age ≥ 51 years and Karnofsky Performance Status (KPS) score ≥ 70

Age ≥ 51 years and KPS < 70

## 5.6 Data Submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < [redacted] >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login [redacted]) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at [redacted] or by contacting the CTSU Help Desk at [redacted]

### 5.6.1 Routine Adverse Event Data Submission

**Common Terminology Criteria for Adverse Events:** This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for routine toxicity and adverse event (AE) reporting. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. Please note that AE reporting stops at disease progression.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting. For this trial the following forms are used for routine AE reporting in Rave:

| | |
|---|---|
| *Adverse Event Form: Solicited* | Required at each assessment according to the Required Data Table (Section 6.0) |
| *Adverse Event Form: Other* | Required if any event occurs that is not pre-populated on *Adverse Event Form: Solicited* |
| *Adverse Event Form: Late* | Required if any event occurs after the 24 month requirements |

For reporting of secondary cancers or other report forms available in Rave:

| | |
|---|---|
| *Malignancy Screening Form* | Submission (regardless of whether screening took place) required every 6 months from the start of treatment while on study |
| *Institutional Contact Information* | One time optional form available at baseline |
| *Family Cancer History Form* | One time optional form available at baseline |
| *Patient Cancer History Form* | One time optional form available at baseline |
| *New Malignancy Form* | Required if a new malignancy is diagnosed |

### 5.7 Specimen Registration and Tracking

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

### 5.8 Histologic Review

**Submission of a tissue block is critical for confirmation of lymphoma diagnosis.** High quality hematoxylin and eosin staining and any required confirmatory studies (such as immunohistochemistry and in situ hybridization) may be done most efficiently from the tissue block in laboratories of the Alliance Central Protocol Operations Program Office.

Within 60 days of registration, send a formalin-fixed, paraffin-embedded block of well-fixed lymphoma tissue containing adequate material for histologic confirmation of diagnosis. A block at least 1 cm x 1 cm x 2 mm is preferable, although smaller is acceptable if no other block is suitable. If only one block exists, and the tissue is sufficiently large, it is acceptable to split the block into two and submit one. Contact [redacted] with questions.

**For patients in whom diagnosis was based on a fluid sample** (CSF, vitreous), submission of the diagnostic slide for digital microscopy scanning and copy of pathology report (include consultative pathology reports) is preferred.

**Samples should be logged and shipped via the BioMS system, see Section 5.7 for instructions.** The requested tissue block should be labeled with the protocol number (51101), institutional surgical pathology number, patient study ID number, institution, date of acquisition, and tissue source. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens. In addition to the pathology specimen and the shipping manifest, send a copy of the pathology report (include consultative pathology reports, if available) to the Alliance Central Protocol Operations Program Office.

Failure to submit pathology materials **within 60 days** of patient registration will be considered a major protocol violation.

If a patient has consented to participate in the biomarker correlative science research proposed (Model Consent Question #2), only one tissue block need be submitted to accommodate both histologic confirmation of diagnosis and correlative science studies (see Section 5.9.1).

The Alliance has instituted special considerations for the small percentage of institutions whose policies prohibit release of any blocks. If, due to institutional policy, a block cannot be sent, please call [redacted] obtain a protocol for submission of representative tissue from your institution.

Please note if a patient is positive in flow cytometry, slides do not need to be submitted.

## 5.9 Sample Submission for Correlative Study 151113

All participating institutions must ask patients for their consent to participate in the biomarker correlative science companion study CALGB 151113 (Model Consent Question #2) planned for CALGB 51101, although patient participation is **optional**. Rationale and methods for the scientific components of this study are described in Section 10.2.

For patients who consent to participate in CALGB 151113, the following specimens will be collected prior to initiation of therapy.

| | **Time Point** | |
|---|---|---|
| **Sample Type** | **Pre-Treatment** | **Ship to:** |
| **FFPE Tissue*** | 1 block | Biorepository |
| **CSF Sample**** (black top) | 2 to 3 mL | Biorepository |

* Only for patients whose diagnosis is based on biopsy or resection.

** Only in patients who have undergone a lumbar puncture for diagnostic or treatment-related purposes. A separate lumbar puncture for CSF sample collection for CALGB 151113 should NOT be performed.

### 5.9.1 Paraffin-Embedded Tissue Block Submission

Send a formalin-fixed, paraffin-embedded block of well-fixed lymphoma tissue. A block at least 1 cm x 1 cm x 2 mm is preferable, although smaller is acceptable if no other block is suitable. If only one block exists, and the tissue is sufficiently large, it is acceptable to split the block into two and submit one. Contact [redacted] with questions.

Samples should be logged and shipped via the BioMS system, see Section 5.7 for instructions. The requested tissue block should be labeled with the protocol number (51101), institutional surgical pathology number, patient study ID number, institution, date of acquisition, and tissue source. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens. In addition to the pathology specimen and the shipping manifest, send a copy of the pathology report (include consultative pathology reports, if available) to the Alliance Biorepository at Ohio State University (OSU).

The Alliance has instituted special considerations for the small percentage of institutions whose policies prohibit release of any blocks. If, due to institutional policy, a block cannot be sent, please call [redacted] to obtain a protocol for submission of representative tissue from your institution.

### 5.9.2 CSF Sample Submission

For patients who have undergone a lumbar puncture for diagnostic or treatment-related purposes, and who consent to participate (Model Consent Question #2), a 2 to 3 mL sample of cerebrospinal fluid (CSF) will be collected prior to initiation of therapy. These will be collected in black top culture tubes (Corning Falcon® catalogue number 352045) and stored at negative -20° C, for no longer than 3 days, until shipped on dry ice.

### 5.9.3 Shipping FFPE Tissue and CSF Samples

Ship samples by overnight courier Monday through Thursday. Do not ship specimens on Fridays or Saturdays. Ship specimens to the Alliance Biorepository at Ohio State University (OSU).

## 5.10 Image Submission for Correlative Study CALGB 581101

All limited access institutions must ask patients for their consent to participate in the imaging correlative science companion study CALGB 581101 (Model Consent Question #6) planned for CALGB 51101, although patient participation is **optional**. A list of limited access institutions for 581101 is available on the CALGB 51101 study page on the Alliance website. Rationale and methods for the scientific components of this study are described in Section 10.1.

For patients who consent to participate in CALGB 581101 (Model Consent Question #6), imaging studies will be conducted and submitted at the following time points:

| | Time Point | | | |
|---|---|---|---|---|
| **Imaging Study** | **Prior to study** | **Within 7 days prior to day 1 of cycle 2** | **Post induction cycle 5** | **Submit to:** |
| **Diffusion MRI** | A | X | C | ICL |
| **FDG-PET Brain**[1] | B | X | D | ICL |

1 Institutions that are able to perform the brain FDG-PET/CT are strongly encouraged to do so, as this is an important component of this study. Institutions that are not able to perform the brain FDG-PET/CT due to institutional or financial constraints may be excused from the brain FDG-PET/CT imaging requirement.

A Within 14 days prior to day 1 of cycle 1

B Within 21 days prior to day 1 of cycle 1

C Within 7 days after the last day of induction cycle 5

D Within 28 days after the last day of induction cycle 5

### 5.10.1 Diffusion MRI and FDG-PET/CT Submission

Data must be electronically submitted to the Imaging Core Lab (ICL) by either web transfer or FTP transfer.

The complete MR imaging data and PET/CT scans will be submitted to the ICL in digital DICOM format. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by the ICL. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the patient study ID number and protocol number. The de-identified digital images may be burned to a CD and then transferred to a PC-based system.

For PET/CT the following complete data sets must be sent:

1) CT data, and

2) Emission data with CT attenuation correction.

The above entire PET/CT imaging data in DICOM format together with the CALGB 581101 Form must be submitted to the ICL within no more than 3 business days once the image acquisition is completed at the site. The CALGB 581101 Form is found on the CALGB 51101 study website under Supplemental Materials. The ICL will notify the site and the Alliance imaging committee within 24 hours of the data receipt as well as within 72 hours of the quality check report.

Diffusion MRI analysis will be performed at University of California San Francisco by [redacted] laboratory. The de-identified and complete MR imaging data including diffusion MRI will be transferred from the ICL to [redacted] laboratory using either a CD or via a secure FTP site.

Send an e-mail notification to [redacted] to inform the ICL of the data submission once the data transfer is completed.

#### 5.10.1.2 Web Transfer

Any PC with Internet access and a web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to the ICL via [redacted] The standard Web Transfer information will be provided separately through the specific trial e-mail [redacted] per the request by participating sites before their first data submission.

#### 5.10.1.3 FTP Transfer

Any FTP software can be used to initiate access to the secure FTP Server of the ICL. The standard FTP access information will be provided separately through the specific trial e-mail [redacted] per the request by participating sites before their first data submission.

For any questions or problems regarding the data transfer to the ICL, call the ICL IT group at [redacted] for help.

### 5.11 Data Submission for Neurocognitive and Quality of Life Correlative Study CALGB 71105

All participating institutions must ask patients for their consent to participate in the neurocognitive and quality of life correlative science companion study CALGB 71105 (Model Consent Question #1) planned for CALGB 51101, although patient participation is **optional**. Rationale and methods for the scientific components of this study are described in Section 10.3.

Both the quality of life and neurocognitive assessments are to be completed at the following time points:

- Within 2 weeks prior to the start of treatment (baseline)

- Within 7 days prior to the start of induction cycle 5
- Every 6 months for up to 5 years (starting 6 months post-treatment completion); then every 12 months for the subsequent 5 years (for up to 10 years of follow-up)

Send a copy of each assessment to the following fax for quality assurance review:

[redacted]

For patients with evidence of disease progression during the study period, a neurocognitive evaluation will be performed at the time of radiographic progression and prior to initiation of additional therapy.

Please see Section 10.3.3 for instructions on accessing, training, and administering the neurocognitive and quality of life assessments.

## 6.0 REQUIRED DATA

Guidelines for Pre-Study Testing

To be completed within 14 DAYS before registration:

- All blood work
- History and physical, including height weight, KPS, vital signs

| Tests & Observations | Prior to Study | Day 1 Induction Cycles 1-5 | Time of Restaging Post Cycle 5 | Consolidation Day 1* | Follow-Up** |
|---|---|---|---|---|---|
| Medical history | X | X | K | X | X |
| Physical examination | X | C | K | X | X |
| Neurological examination[9] | X | C | K | X | X |
| Pulse, blood pressure | X | C | K | X | X |
| Height | X | | | | |
| Weight/body surface area | X | C | K | X | X |
| ECOG performance status | X | C | K | | X |
| Drug toxicity assessment | | X | K | X | X |
| Echocardiogram (transthoracic) | | | R | | |
| Pulmonary function test (with DLCO) | | | R | | |
| **Laboratory Studies** | | | | | |
| Creatinine clearance[1] | X | C, D | | N | |
| CBC, differential, platelets | X | E | K | O,P | X |
| Serum creatinine, BUN | X | E | K | O | X |
| Serum electrolytes, Ca++ | X | E | K | O | X |
| Serum methotrexate | | F | | | |
| AST, ALT, ALK Phos, total bilirubin | X | G | K | O | X |
| LDH | X | | | | X |
| Serum or urine βHCG*** | X | | | | |
| HBsAg, HBsAb, HB core antibody | X | | | | |
| HCV | X | | | | |
| HIV | X | | | | |
| CMV antibody**** | X | | | | |
| **Staging** | | | | | |
| Contrast-enhanced brain MRI with tumor measurements[8] | X | H | L | | X |
| Lumbar puncture[2] | X | I | M | | I |
| Ophthalmological examination[3] | X | J | M | | J |
| Testicular ultrasound[4] | Q | | | | |
| KPS | X | C | K | | |
| Bone marrow aspirate and biopsy | A | | | | |
| PET/CT, CT, or MRI of chest/abdomen/pelvis[5] | A | | | | |
| Histological review[6] | B | | | | |
| MMSE[7] | X | | K | | X |

* For Arm 1, day -6 (start of carmustine); for Arm 2, day 1 of consolidation chemotherapy.

** Every 3 months for the first 2 years after completion of therapy, then every 6 months for the next 3 years, then annually for the next 5 years. Total follow up is a maximum of 10 years from date of registration.

*** βHCG is only required for women of childbearing potential

**** All institutions may follow institutional guidelines for the CMV antibody assessment

1 Estimated creatinine clearance using Cockcroft-Gault formula for all cycles.

2 Lumbar puncture should be performed in all patients deemed safe for procedure

3 Ophthalmological examination should be performed by an ophthalmologist and must include slit lamp examination

4 Male patients

5 FDG-PET/CT is recommended; body and brain FDG-PET/CT should be done the same day with single contrast injection (only for limited access sites that are able to complete the brain FDG-PET/CT, as well as patients enrolled on the correlative study CALGB 581101, see Sections 5.10 and 10.1). If the patient is receiving inpatient care, CT alone with IV contrast or whole body MRI is sufficient.

6 See Section 5.8.

7 Mini-Mental Status Examination (0-30)

8 Collect 2 perpendicular measurements per lesion, with a maximum of 6 lesions

9 The Neurological Examination may be performed by any physician.

A Within 28 days prior to registration

B To be submitted within 60 days of registration

C Prior to each dose of methotrexate. Use initial weight unless > 10% difference from baseline.

D Within 48 hours prior to day 1 of cytarabine in cycle 5

E Within 48 hours prior to day of each induction cycle and daily while inpatient for methotrexate cycles

F Daily methotrexate levels should be obtained beginning 24 hours after the start of the methotrexate infusion and until methotrexate concentration is < 0.10 mcM.

G Every other day while inpatient for methotrexate cycles and prior to each Temozolomide course in cycles 1-4

H Within 7 days after completion of induction cycle 1 only

I In patients with positive/suspicious/atypical cytology, flow cytometry, or IgH PCR demonstrating a monoclonal cell population, the lumbar puncture should be repeated (if deemed safe) after completion of all induction therapy and after completion of all consolidation therapy. In patients with negative CSF at baseline, lumbar puncture does not need to be repeated.

J In patients with positive slit lamp examination or positive/suspicious/atypical cytology or flow cytometry or IgH PCR demonstrating a monoclonal cell population, the slit lamp examination should be repeated after completion of all induction and after completion of all consolidation therapy. In patients with negative slit lamp examination or vitreous fluid, the slit lamp examination should only be repeated after completion of all consolidation therapy.

K Within 7 days prior to day 1 of consolidation, both Arm 1 and Arm 2

L Within 7 days after the last day of induction cycle 5

M Within 21 days prior to day 1 of consolidation, and only if positive at baseline (contrast-enhancing lymphoma on spine MRI; positive ocular examination for lymphoma; positive, suspicious, or atypical cytology; positive flow cytometry; positive IgH PCR)

N In Arm 2, prior to starting cytarabine and etoposide

O Every day while inpatient and receiving etoposide/cytarabine or carmustine/thiotepa

P Consolidative therapy is to begin as soon as blood counts are permissible (ANC ≥ 1500 and platelets ≥ 100,000), but no earlier than 4 weeks and no later than 12 weeks after day 1 of cycle 5 of induction therapy. In patients who do not have sufficient blood counts at week 4, weekly CBC with differentials are required. Treatment is to start as soon as counts are permissible, however, if 12 weeks or more has passed, then the patient will go off study.

Q If the patient has a negative PET/CT that includes the testicles, testicular ultrasound is not required.

R For Arm 1 only, PFT and echocardiogram are to be performed at time of restaging post induction cycle.

## 7.0 TREATMENT PLAN

Protocol treatment is to begin within 7 days of registration (unless otherwise specified by Study Chair) and within 28 days of pathological diagnosis. Questions regarding treatment should be directed to the Alliance Study Chair. It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday.

Each cycle will be 28 days in length.

Arm 1 and Arm 2 receive the same induction therapy (cycles 1-5).

### 7.1 Induction Chemotherapy (Cycles 1 and 2)

Pneumocystis prophylaxis with cotrimoxazole double strength by mouth twice a day, two times per week beginning prior to initiation of therapy. Cotrimoxazole will continue unless ANC ≤ 500/mcL. **Cotrimoxazole is not to be given within 48 hours prior to initiation of methotrexate and until methotrexate concentration is < 0.10 mcM.** If patients are allergic to sulfa drugs or if the treating physician has a preference for non-sulfa prophylaxis, dapsone, atovaquone or aerosolized pentamidine may be substituted.

Dosing for all drugs on induction chemotherapy cycles 1 and 2 is based on actual body weight.

#### 7.1.1 Methotrexate 8 g/m$^2$ IV (dose adjusted for creatinine clearance, see below) over 4 hours on days 1 and 15 of cycle 1 and cycle 2.

Each methotrexate dose will be followed by leucovorin rescue (see Section 7.1.2).

Salicylates, non-steroidal anti-inflammatory drugs, sulfonamides, and penicillins are not to be used within 48 hours prior to the initiation of methotrexate and until methotrexate concentration is < 0.10 mcM. Patients will be hospitalized for high-dose methotrexate administration.

Recommended hydration before and after methotrexate includes IV fluids at rate of 500 mL/hour over 2 hours, then 150 mL/hour to assure a urine output > 100 mL/hour for at least 4 hours prior to methotrexate. Continue hydration during methotrexate administration and leucovorin rescue. Add 50-150 mEq $NaHCO_3$ per liter of fluid to achieve and maintain a urine pH ≥ 7 or per institutional guidelines. Check urine pH with every void or per institutional standard of care.

Methotrexate dose~~s~~ will be based on CrCl calculated by the Cockcroft-Gault formula as follows:

$$\frac{(140\text{-age}) \times \text{weight in kg.}}{72 \times \text{serum creatinine}} \times \begin{array}{l}0.85 \text{ for females} \\ 1.0 \text{ for males}\end{array}$$

- Note: In markedly obese patients, the Cockcroft-Gault formula will tend to overestimate the CrCl. (Adipose tissue tends to contribute little creatinine requiring renal clearance.)

If CrCl is greater than 100 mL/min, then no dose adjustment is necessary. If CrCl is less than 100 mL/min, then the methotrexate dose is reduced by the fraction of CrCl below 100 mL/min (i.e., methotrexate dose = 8 g/m$^2$ x CrCl/100).

#### 7.1.2 Leucovorin Rescue and Serum Methotrexate Levels

Leucovorin 100 mg/m$^2$ IV every 6 hours beginning 24 hours after the start of each methotrexate dose (for all patients, regardless of methotrexate level). Continue leucovorin until serum methotrexate level ≤ 0.10 mcM. Daily methotrexate levels are

to be obtained beginning 24 hours after the initiation of methotrexate and until methotrexate concentration is < 0.10 mcM. The leucovorin dose is adjusted based on serum methotrexate levels as follows:

| Methotrexate Level | Leucovorin Dose* |
|---|---|
| **24 Hours:**<br>> 10 mcM | 100 mg/m$^2$ IV q 6 hours until level is ≤ 0.10 mcM |
| **48 Hours:**<br>>1 mcM | 100 mg/m$^2$ IV q 3 hours until level is ≤ 0.10 mcM |
| **60 Hours:**<br>>2 mcM | 200 mg/m$^2$ IV q 3 hours until level is ≤ 0.10 mcM |
| **72 Hours:**<br>**> 0.1** mcM | 100 mg/m$^2$ IV q 6 hours until level is ≤ 0.10 mcM |

* When methotrexate level is ≤ 0.5 mcM, the leucovorin dose may be administered orally (instead of IV) and continued until methotrexate level is ≤ 0.10 mcM. The oral dose is 10 mg/m$^2$ every 6 hours (may be rounded up to within 5% of the calculated dose).

If the patient's creatinine is stable and there is evidence of appropriate clearance of methotrexate, and if the methotrexate level is decreasing for two consecutive time points below 1 mcM, then pharmacokinetic calculation may be performed to predict the time point when methotrexate level will be < 0.10 mcM. The patient may then be discharged to home with oral leucovorin rescue until the serum methotrexate level is predicted to be < 0.10 mcM.

Please note that the above are guidelines, and treating physicians may follow their own institutional guidelines set for administration of leucovorin including the dose and schedule.

**7.1.3 Rituximab 375 mg/m$^2$ IV (maximum infusion rate 400 mg/hour) on days 3, 10, 17, 24 of cycle 1, and days 3 and 10 of cycle 2 (i.e., a total of 6 doses).**

Suggested premedications include acetaminophen 650 mg by mouth and diphenhydramine 25-50 mg IV or by mouth.

Please note for institutions that cannot administer Rituximab on day 3, +/- 3 day windows are allowed.

**7.1.4 Temozolomide 150 mg/m$^2$/day (rounded to the nearest 5 mg) by mouth on days 7-11 of cycle 1.**

In cycle 2 days 7-11, temozolomide will be increased to 200 mg/m$^2$/day.

**7.2 Induction Chemotherapy (Cycles 3 and 4)**

Pneumocystis prophylaxis with cotrimoxazole double strength by mouth twice a day, two times per week beginning prior to initiation of therapy. Cotrimoxazole will continue unless ANC ≤ 500/mcL. **Cotrimoxazole is not be given within 48 hours prior to initiation of methotrexate and until methotrexate concentration is < 0.10 mcM.** If patients are allergic to sulfa drugs or if the treating physician has a preference for non-sulfa prophylaxis, dapsone, atovaquone or aerosolized pentamidine may be substituted.

Dosing for all drugs on induction chemotherapy cycles 3 and 4 is based on actual body weight.

**7.2.1 Methotrexate 8 g/m$^2$ IV (dose adjusted for CrCl, see Cockcroft-Gault formula in Section 7.1.1) over 4 hours on days 1 and 15 of cycles 3 and 4.**

Salicylates, non-steroidal anti-inflammatory drugs, sulfonamides, and penicillins are not be used within 48 hours prior to the initiation of methotrexate and until methotrexate concentration is < 0.10 mcM. Patients will be hospitalized for high-dose methotrexate administration.

Recommended hydration before and after methotrexate includes IV fluids at rate of 500 mL/hour over 2 hours, then 150 mL/hour to assure a urine output > 100 mL/hour for at least 4 hours prior to methotrexate. Continue hydration during methotrexate administration and leucovorin rescue. Add 50-150 mEq $NaHCO_3$ per liter of fluid to achieve and maintain a urine pH ≥ 7 or per institutional guidelines. Check urine pH with every void or per institutional guidelines.

**7.2.2 Leucovorin Rescue and Serum Methotrexate Levels**

Leucovorin 100 mg/m$^2$ IV every 6 hours beginning 24 hours after the start of methotrexate (for all patients, regardless of methotrexate level). Leucovorin should continue until serum methotrexate level ≤ 0.10 mcM. Daily methotrexate levels should be obtained beginning 24 hours after the initiation of methotrexate and until methotrexate level is < 0.10 mcM. The leucovorin dose is adjusted based on serum methotrexate levels as noted in Section 7.1.2.

When methotrexate level is ≤ 0.5 mcM, the leucovorin dose may be administered orally (10 mg/m$^2$) until methotrexate level is ≤ 0.10 mcM.

Please note that the above are guidelines and treating physicians may follow their own institutional guidelines set for administration of leucovorin.

**7.2.3 Temozolomide 200 mg/m$^2$/day (rounded to the nearest 5 mg) by mouth on days 7-11 of cycles 3-4.**

## 7.3 Induction Chemotherapy (Cycle 5)

Induction cycle 5 is to begin no earlier than 4 weeks and no later than 8 weeks after day 1 of cycle 4.

G-CSF is allowed.

In order to receive induction cycle 5, patients must have the following:

serum creatinine < 2.0 mg/dL or a 24 hour creatinine clearance must be > 50 mL/min,

total bilirubin < 2 x ULN,

AST < 3 x ULN,

ANC > 1000/mcL without G-CSF,

no less than 1 week since receiving G-CSF,

platelets > 100,000/mcL, and

neither active infection nor a need for ongoing antibiotics.

Cytarabine 2 g/m$^2$ (corrected body weight) IV every 12 hours (or twice a day) as a 2-hour infusion on days 1 and 2.

Corticosteroid ophthalmic preparation to begin 6-12 hours before the first dose of cytarabine and continuing at least 48 hours after the last high-dose to prevent conjunctivitis.

Dose should be based on corrected weight, calculated as ideal body weight + 25% of the difference between actual and ideal body weight. If actual weight is less than ideal weight, use actual body weight. If the patient's actual weight is >150% of ideal, then the corrected weight is ideal body weight x 1.125. (See Appendix II for ideal body weight table.)

In patients exhibiting signs or symptoms of cerebellar dysfunction, induction cycle 5 with cytarabine will be omitted, but patients may receive all other therapy. If the treating physician believes the patient has signs of cerebellar dysfunction, they should contact the study chair.

## 7.4 Restaging

Restaging will occur after completion of induction cycle 5. Patients who achieve a complete response, complete response unconfirmed, partial response, or stable disease will proceed to consolidation therapy. Patients with progressive disease will be removed from protocol therapy. (See Section 12.0 for definitions of response.)

## 7.5 Arm 1 Consolidation Therapy

Consolidative therapy is to begin as soon as blood counts are permissible (ANC ≥1500 and platelets ≥100,000), but no earlier than 4 weeks and no later than 12 weeks after day 1 of cycle 5 of induction therapy. In patients who do not have sufficient blood counts at week 4, weekly CBC with differentials are required. Treatment is to start as soon as counts are permissible, however, if 12 weeks or more has passed, then the patient will go off study.

Conditioning regimen may be administered per institutional standards; experienced sites may administer conditioning chemotherapy as 'outpatient' and admit to hospital only at the point of stem cell infusion.

### 7.5.1 Stem Cell Mobilization

Between 3 and 5 weeks after day 1 of cytarabine induction cycle 5, patients randomized to Arm 1 will proceed to stem cell mobilization per participating institution guidelines. The target goal is a CD34+ cell dose > 5 x $10^6$/kg (actual body weight) and the minimum CD34+ cell dose is 2 x $10^6$/kg. The following are suggestions, not protocol requirements. Stem cell mobilization may begin with daily **G-CSF injections at 10 mcg/kg SC per day for four consecutive days with planned stem cell collection on day 5.** If stem cell yield of day 1 collection is less than 1 x $10^6$ CD34+ cells/kg then the G-CSF dose can be increased to 15 mcg/day. In general, process 12-18 L of blood over 3-4 hours each leukapheresis at flow rates of 70-90 mL/minute. If CD34 cell yields are low at first, it is recommended that 1-2 days be skipped until WBC is 20,000-40,000/□L. Cells should be frozen according to institutional standards and practices. If stem cell mobilization is unsuccessful (<2 x $10^6$/kg CD34+ cells), then contact the Study Chair or Co-Chair. A remobilization of peripheral blood stem cells or a pelvic bone marrow harvest may be permitted.

### 7.5.2 High-Dose Therapy with Stem Cell Rescue

All drug chemotherapy doses are based on corrected body weight. Between 2 to 4 weeks after the last day of successful stem cell collection, patients will be admitted for high-dose therapy with stem cell rescue. Stem cell rescue requires adequate peripheral blood stem cell collection with CD34 cell dose > 2 x $10^6$/kg (actual body weight or study chair-approved alternative).

Prior to high dose therapy, patients must have serum creatinine < 2.0 mg/dL, total bilirubin < 2 x ULN and AST < 3 x ULN and neither active infection nor need for ongoing antibiotics.

**7.5.2.1** **Carmustine 400 mg/m$^2$** IV infused over 2 hours on day -6.

**7.5.2.2** **Thiotepa 5 mg/kg IV** infused over 2 hours, every 12 hours, on days -5 and -4.

**7.5.2.3** **Infusion of autologous peripheral blood stem cells on day 0.** Peripheral blood stem cells should be thawed in a 37° C water bath and immediately infused intravenously. If autologous pelvic marrow is infused, premedicate with 25 g mannitol IV 6 hours after infusion.

**7.5.2.4** **G-CSF 5 mcg/kg subcutaneous** daily starting on day +4 until ANC >1500/mcL on two separate occasions or >5000/mcL once. If actual weight is < 60 kg, use 300 mcg/dose; if actual weight is 60-99 kg, use 480 mcg/dose; if actual weight is 100-130 kg use 600 mcg/dose; if actual weight is >130 kg, use 780 mcg/dose.

### 7.5.3 Infection Prophylaxis

**Levofloxacin 500 mg by mouth daily** or other IV or oral antibiotic as per institutional preference beginning when ANC drops to ≤ 500/mcL and continuing until ANC >500/mcL.

**Fluconazole 200 mg by mouth daily** or other IV or oral antifungal as per institutional preference beginning on day 6 and continuing until ANC ≥ 500/mcL.

Acyclovir 200 mg by mouth three times a day or 2 mg/kg IV twice a day (actual body weight) rounded to the next highest 25 mg or other IV or oral antiviral as per institutional preference beginning on day 6 and continuing for 6 months.

### 7.5.4 Carmustine Pneumonitis Surveillance

Surveillance for carmustine pneumonitis should occur in the post-autologous stem cell treatment period, especially the first 4 months.

## 7.6 Arm 2 Consolidation Therapy

Consolidative therapy is to begin as soon as blood counts are permissible (ANC ≥1500 and platelets ≥100,000), but no earlier than 4 weeks and no later than 12 weeks after day 1 of cycle 5 of induction therapy. In patients who do not have sufficient blood counts at week 4, weekly CBC with differentials are required. Treatment is to start as soon as counts are permissible, however, if 12 weeks or more has passed, then the patient will go off study.

In order to receive consolidation therapy in Arm 2, patients must have: serum creatinine < 2.0 mg/dL or a 24 hour CrCl must be >50 mL/min; total bilirubin < 2 x ULN; AST < 3 x ULN; ANC > 1000/mcL without G-CSF; platelets > 100,000/mcL; have neither active infection nor a need for ongoing antibiotics (other than those used for pneumocystis prophylaxis).

One cycle of therapy will be considered 28 days. It is strongly advised that consolidation therapy for Arm 2 be administered on an inpatient hospital service.

**Pneumocystis prophylaxis with cotrimoxazole double strength by mouth twice a day, two times a week (or equivalent)** should begin prior to initiation of therapy. Cotrimoxazole will continue through consolidation, unless ANC ≤ 500/mcL. If patients are allergic to sulfa drugs, or if the treating physician has a preference for non-sulfa prophylaxis, dapsone, atovaquone or aerosolized pentamidine may be substituted.

In patients exhibiting signs or symptoms of cerebellar dysfunction, cytarabine will be omitted from consolidation therapy.

**7.6.1 Cytarabine 2 g/m$^2$ (corrected body weight) IV over 2 hours every 12 hours x 8 doses, on days 1-4**

Corticosteroid ophthalmic preparation to begin 6 – 12 hours before the first dose of cytarabine and continuing at least 48 hours after the last high-dose to prevent conjunctivitis.

Dose should be based on corrected weight, calculated as ideal body weight + 25% of the difference between actual and ideal body weight. If actual weight is less than ideal weight, use actual body weight. If the patient's actual weight is >150% of ideal, then the corrected weight is ideal body weight x 1.125. (See Appendix II for ideal body weight table.)

**7.6.2 Etoposide 5 mg/kg IV (corrected body weight) over 12 hours every 12 hours x 8 doses (total dose 40 mg/kg CIVI over 96 hours) on Days 1-4**

Dose should be based on corrected weight, calculated as ideal body weight + 25% of the difference between actual and ideal body weight. If actual weight is less than ideal weight, use actual body weight. If the patient's actual weight is >150% of ideal, then the corrected weight is ideal body weight x 1.125. See Appendix II for ideal body weight table.

**7.6.3 G-CSF 5 mcg/kg/day subcutaneous beginning on day +4 and continuing either until ANC ≥ 500 mcL for two consecutive days or ≥ 1500/mcL for one day. For G-CSF, if actual weight is < 60 kg, use 300 mcg/dose; if actual weight is 60-99 kg, use 480 mcg/dose; if actual weight is 100-130 kg use 600 mcg/dose; if actual weight is > 130 kg, use 780 mcg/dose.**

**7.6.4 Infection Prophylaxis**

**Levofloxacin 500 mg by mouth daily** or other IV or oral antibiotic as per institutional preference beginning when ANC drops to ≤ 500/mcL and continuing until ANC >500/mcL.

**Fluconazole 200 mg by mouth daily** or other IV or oral antifungal as per institutional preference beginning on Day 6 and continuing until ANC ≥ 500/mcL.

**Acyclovir 200 mg by mouth three times a day or 2 mg/kg IV twice a day** [actual body weight] rounded to the next highest 25 mg or other IV or oral antiviral as per institutional preference beginning on day 6 and continuing for 6 months.

## 8.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

| Drug | Starting Dose | Dose Level -1 | Dose Level -2 |
|---|---|---|---|
| Methotrexate (actual weight) | 8 g/m$^2$ | 6 g/m$^2$ | 4 g/m$^2$ |
| Temozolomide cycle 1 (actual weight) | 150 mg/m$^2$ | 100 mg/m$^2$ | N/A |
| Temozolomide cycles 2-4 (actual weight) | 200 mg/m$^2$ | 150 mg/m$^2$ | 100 mg/m$^2$ |
| Cytarabine (induction cycle 5, corrected weight) | 2 g/m$^2$ | 1 g/m$^2$ | N/A |

### 8.1 Hematologic Toxicity

**8.1.1 Hematologic Toxicity/Methotrexate Dose Modifications**

Decrease methotrexate by one dose level if ANC is ≤ 500/mcL for three or more days, platelets ≤ 25,000/mcL, and/or febrile neutropenia (defined as temperature ≥ 38.5°C

[101°F] sustained for more than one hour concomitant with an ANC <500/mcL). The reduced methotrexate dose should be used for all subsequent doses.

#### 8.1.2 Hematologic Toxicity/Temozolomide Dose Modifications

Growth factors cannot be used to induce elevations in neutrophil count for the purposes of administration of temozolomide on time.

Based on blood counts obtained within two days prior to day of treatment, the following dose modifications should be made:

For grade 3 or 4 ANC, delay temozolomide until ANC improves to ≤ grade 2, then decrease temozolomide by 1 dose level for all subsequent cycles.

For grade 3 or 4 thrombocytopenia, delay temozolomide until platelets improve to ≤ grade 2, then decrease temozolomide by 1 dose level for all subsequent cycles.

Patients who require dose reductions to a dose level <100 mg/m$^2$/day will discontinue temozolomide.

#### 8.1.3 Febrile Neutropenia During Consolidation Chemotherapy

Febrile neutropenia is expected during consolidation with the combination of cytarabine + etoposide or carmustine + thiotepa. Prophylactic antibiotics and G-CSF are utilized during this cycle of therapy. No dose modifications will be made for febrile neutropenia during consolidation therapy.

### 8.2 Hepatic Dysfunction

#### 8.2.1 Hepatic Dysfunction/ALT/AST Toxicity

ALT/AST should return to within 3 x upper limit of normal prior to next dose of MTX treatment. No dose adjustment is needed based on transient transaminitis regardless of grade.

#### 8.2.2 Hepatic Dysfunction/Total Bilirubin

Give the following dose reduction of methotrexate based on total bilirubin obtained within 2 days prior to treatment:

| Total Bilirubin (mg/dL) | Methotrexate Dose Reduction |
|---|---|
| < 1.5 | Starting Dose |
| ≥ 1.5 but <3.0 | Level -1 |
| ≥ 3.0 but <5.0 | Level -2 |
| ≥ 5.0 | Stop |

#### 8.2.3 Hepatic Toxicity

For grade 3 or 4 ALT, AST, or Total Bilirubin on day 7 and considered at least possibly related to Temozolomide, skip Temozolomide for that cycle.

### 8.3 Neuropsychiatric Toxicity

If cytarabine neurotoxicity develops or is suspected during its administration (dysmetria, dysdiadokinesis, truncal/gait ataxia, dysarthria, and/or cerebral psychiatric abnormalities not explainable by other medications or tumor location), stop cytarabine immediately.

### 8.4 Gastrointestinal Toxicity

Mucositis, dysphagia, and diarrhea: For grade 3 or 4 oral ulceration or diarrhea, hold all therapy and delay the next treatment until mucositis or diarrhea improves to ≤ grade 2. Resume methotrexate with one dose level reduction for the next dose.

### 8.5 Renal Dysfunction

#### 8.5.1 Renal Dysfunction/Methotrexate Dose Modifications

The CrCl will be estimated by method of Cockcroft Gault formula prior to every cycle. If CrCl is greater than 100 mL/min, then no dose adjustment is necessary. If CrCl is less than 100 mL/min, then the methotrexate dose is adjusted by the fraction of CrCl below 100 mL/min (i.e., methotrexate dose = 8 g/$m^2$ x CrCl/100). Treatment will proceed with rituximab, temozolomide and methotrexate as scheduled.

Delayed serum clearance (>3 days after infusion) may occur and mandates accelerated rescue and continued hydration and alkalinization. A minimum of 7 days should have elapsed from serum clearance (methotrexate level ≤ 0.10 mcM) prior to start of next methotrexate dose.

#### 8.5.2 Renal Dysfunction/Cytarabine Dose Modifications

Give the following cytarabine dose reductions for renal dysfunction based on serum creatinine on any day of induction or arm 2 consolidation high-dose cytarabine administration.

For creatinine 1.5-2 mg/dL or an increase of 0.5-1.2 mg/dL over baseline, decrease cytarabine by 1 dose level. For creatinine > 2.0 mg/dL or an increase of ≥ 1.3 mg/dL over baseline, omit the cytarabine dose.

### 8.6 Pulmonary Toxicities

#### 8.6.1 Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) presents as hypoxemia, dyspnea, fever and/or pulmonary infiltrates at the time of granulocyte engraftment. Bronchoalveolar lavage (BAL) reveals alveolar blood, which increases with serial lavages and is negative for infection. This is an uncommon complication of any high-dose conditioning regimen and is potentially fatal. Sensitivity to the diagnosis must be high and initiation of corticosteroids must be prompt in order to prevent death. Once DAH is suspected or confirmed, methylprednisolone 1000 mg IV twice a day is started for a minimum of 3 days. If the patient responds, then the methylprednisolone dose is halved every 3 days until a 3 to 4 week course is completed.

#### 8.6.2 Carmustine Pneumonitis

Carmustine pneumonitis complicates 10-60% of stem cell transplants in which 450-600 mg/$m^2$ of carmustine is administered. The incidence is related to carmustine dose and is expected to be about 10% in this study where the carmustine dose is capped at 400 mg/$m^2$. Although it can occur up to one year from administration, it is most frequent one-and-a-half to four months after carmustine is received. Presenting features are dry cough, dyspnea, fatigue, a "tight" feeling in the chest, hypoxemia, pulmonary infiltrates, and/or an absolute >10% drop in the percentage predicted diffusing capacity of the lung for carbon monoxide (DLCO). Anyone suspected of having carmustine pneumonitis should have 0.5 mg/kg (actual body weight) prednisone started by mouth twice a day followed by evaluations such as chest X-ray, pulmonary function tests with DLCO, sputum analysis, bronchoalveolar lavage, etc. If carmustine pneumonitis is suspected or

confirmed, then high-dose prednisone is continued for 10-14 days followed by a corticosteroid taper over 8 weeks. Carmustine pneumonitis is potentially fatal but uniformly reversible if prednisone is started early in the inflammatory phase. Therefore a high degree of sensitivity to and surveillance for this complication is warranted.

### 8.7 Other Non-Hematologic Toxicity Dose Modifications

#### 8.7.1 Temozolomide Dose Modifications for Other Non-Hematologic Toxicities

If at any time a patient experiences grade 3 or 4 non-hematologic toxicity considered at least possibly related to temozolomide, decrease temozolomide by one dose level for all subsequent cycles. Patients who require a dose reduction to a dose level < 100 $mg/m^2$/day will have temozolomide discontinued.

**8.7.2 All non-hematologic grade 2, 3 and 4 toxicities must have resolved to at least grade 1 prior to repeat dosing or grade 2 if, in the treating physician's opinion, the non-hematologic toxicity does not warrant further delay. Please contact the Study Chair to discuss delays in therapy caused by the need to delay temozolomide. If a temozolomide dose were to be delayed, a 4-week interval must occur between successive courses of temozolomide.**

### 8.8 Dose Modification for Non-Obese and Obese Patients

High-dose chemotherapy can adversely impact the outcomes of obese patients when dosing is performed according to actual body weight. Therefore, drug dosing for induction cycle 5 cytarabine (both arms) and for consolidation etoposide and cytarabine (arm 2) will be determined using a corrected weight. Patient ideal body weight is derived from Appendix II using frame size and height. The corrected weight is calculated using the following formula with all weights in kg:

Corrected weight = (0.25)(actual weight-ideal weight) + (ideal weight)

Doses are then based on corrected weight or BSA calculated using corrected weight.

For patients whose actual weight is >150% of their ideal, their "actual" weight will be capped at 150% of ideal (i.e., their corrected weight will be 112.5% of ideal). For patients whose actual weight is less than ideal, use their actual weight as the corrected weight.

## 9.0 ANCILLARY THERAPY

### 9.1 Supportive Care

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc. when appropriate per institutional guidelines. For CMV negative patients, use CMV negative blood products. In addition, all blood products should be leukofiltered and irradiated to reduce/prevent alloimmunization and transfusion graft-versus-host disease.

### 9.2 Steroids

Steroids may be used in the management of symptoms related to mass effect from lymphoma or to manage pulmonary toxicity. Steroids should be tapered as soon as possible.

### 9.3 Anticonvulsants

Administration of anticonvulsants is at the discretion of the treating physician. In accordance with the practice parameters described by the American Academy of Neurology, the use of prophylactic anticonvulsants should be avoided [44]. In patients with no history of a seizure, it

is recommended that anti-convulsants started before/after biopsy or craniotomy should be tapered after the first postoperative week [44].

### 9.4 Palliative Radiation

Palliative radiation therapy may not be administered.

### 9.5 Alliance Policy Concerning the Use of Growth Factors

#### 9.5.1 Epoetin (EPO)

**The use of an erythropoiesis-stimulating agent (ESA) is allowed. If an ESA is used, it should be within the context of the most current ASCO guidelines [45].**

#### 9.5.2 G-CSF

1. The use of G-CSF is allowed. G-CSF is required during HDT/ASCT (Arm 1) and etoposide and cytarabine (Arm 2) consolidation due to the intense nature of the treatment.
2. Elsewhere in the protocol, G-CSF may NOT be used
   a. to avoid dose reductions, delays or to allow for dose escalations specified in the protocol,
   b. prophylactically because of concern about myelosuppression from prior chemotherapies, and
   c. for the treatment of febrile neutropenia the use of colony-stimulating factors should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of colony-stimulating factors may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines [46]. Investigators should therefore use their own discretion in using the colony-stimulating factors in this setting. The use of colony-stimulating factors (G-CSF) must be documented and reported on the Ancillary Therapy form.
   d. If G-CSF is used, it must be obtained from a commercial source~~s~~.

## 10.0 CORRELATIVE SCIENCE COMPANION STUDIES

The images obtained for the embedded correlative science companion imaging study CALGB 581101 will be analyzed once funding is obtained for this study. In addition, the samples obtained for the embedded correlative science companion biomarker study CALGB 151113 will be analyzed once funding is obtained for this study.

### 10.1 Imaging Correlative Science Companion Study (CALGB 581101)

Imaging Markers of Outcome After Chemotherapy in Patients with Newly Diagnosed PCNSL

CALGB 581101 has two components, an MRI study and a FDG-PET/CT study. CALGB 581101 is open to limited access institutions only. Please see the study website for the list of limited access institutions that may register patients to CALGB 581101. Patients enrolled through the limited access institutions who answer 'Yes' to Model Consent Question #6 may be registered to CALGB 581101. Limited access institutions are required to offer patients participation in CALGB 581101. However, patients at the limited access institutions who are participating in the treatment study CALGB 51101 may opt not to participate in the imaging correlative study CALGB 581101. Patients who consent to participate in CALGB 581101 are consenting to participate in both the MRI and the FDG-PET/CT portions of the study. Limited access institutions that are able to perform the brain FDG-PET/CT are strongly encouraged to do so, as this is an important component of this study. Limited access institutions that are not

able to perform the brain FDG-PET/CT due to institutional or financial constraints may be excused from the brain FDG-PET/CT imaging requirement. Limited access institutions unable to participate in the brain FDG-PET/CT component of the imaging study are still required to participate in the MRI component. A maximum number of 25 patients per treatment arm will be enrolled on the MRI study. There is no maximum number of patients per treatment arm in the PET study.

### 10.1.1 Background

#### 10.1.1.1 Diffusion MRI Background

Diffusion-weighted imaging (DWI) is a noninvasive MR imaging technique that produces *in vivo* images of the brain based on differential rate of water diffusion or Brownian motion within the extracellular space. DWI is an essential tool to diagnose acute infarction in the brain due to its ability to detect early changes in altered water diffusion due to cellular cytotoxic damage. DWI has also been used in neuro-oncology to assess tumor biology. Specifically, the apparent diffusion coefficient (ADC) values derived from DWI have been shown to correlate with glioma grade [47, 48], tumor cellularity [49], and treatment response [50-56]. One study also suggests that ADC values may be helpful in predicting clinical outcome in immunocompetent patients with primary CNS lymphoma [29].

#### 10.1.1.2 Brain FDG-PET/CT Background

FDG-PET/CT is a standard test for the staging and response assessment of patients with systemic lymphoma [57]. It is also a useful test in the systemic staging of patients with primary CNS lymphoma (PCNSL). In one study, 8 of 42 patients showed sites of abnormal FDG uptake outside the brain [58]. Six of these 8 patients underwent biopsy (three lymphoma, one second primary, one benign adenoma, one inconclusive). Eleven patients in the study also underwent FDG-PET/CT of the torso at the time of CNS relapse; systemic lymphoma was noted on PET in three cases (27%). Of note, CT scans of the torso were entirely negative in these three individuals.

The utility of FDG-PET/CT for assessing the primary disease site in PCNSL has been investigated in a number of studies. Early data showed tumor to normal (T:N) tissue uptake ratios in the range of 1.2 – 3.5; the normal tissue region was placed in the contralateral hemisphere in the identical location as the PCNSL [59]. A subsequent study reported standardized update value (SUV) in PCNSL in the range of 4.3 – 10.7 and T:N ratios of 1.4 – 3.0, indicating that these lesions are usually well recognized on PET (one small 4 mm was not identified in this study) [60]. A study in 13 patients reported SUVs in the range of 6.6 – 23.2 (mean 13.9 +/- -5.6) and T:N ratios of 0.8 – 5.2 (mean 2.7 +/- 1.2) [61]. All primary lesions were clearly identified on PET. A retrospective analysis in 28 patients with PCNSL showed clearly increased FDG update in 75% of lesions at baseline [62].

The intensity of FDG update (measured by SUV) in PCNSL at baseline may have prognostic value. In a study of 17 patients, the SUVmax at baseline ranged from 6.3 to 23.3 [63]. Eight of the 17 patients showed moderate FDG update (SUVmax < 12) and 9/17 showed high uptake (SUVmax > 12). The median survival time was > 26 months in the group with moderate update, and 12 months in the group with high uptake. Both OS and PFS were significantly shorter for patients for high baseline SUV. The treatment regimen was uniform in all patients.

Few data are available regarding the potential utility of FDG-PET/CT for response assessment in PCNSL [62-64]. One study evaluated 8 patients undergoing

chemotherapy; FDG-PET/CT was true negative in 5 out of 8 and true positive in 3 out of 5 [60]. Another study found persistent elevated FDG uptake in 50% of patients during response assessment or scans obtained for clarification of nonspecific MRI findings; these data were helpful in guiding patient management [62].

In summary, there are sufficiently promising data to warrant further exploration of FDG-PET/CT in PCNSL for identifying patients with better or worse prognosis, and for response assessment. However, because the available data are still limited, FDG-PET/CT at this time cannot be used to guide patient management. Accordingly, the use of FDG-PET/CT in the current trial is exploratory. If successful, the data may potentially be useful for future risk and response adapted therapy trials.

### 10.1.2 Methods

#### 10.1.2.1 Diffusion MRI Methods

Diffusion MRI sequences ($ADC_{mini}$, $ADC_{25\%}$, and $ADC_{mean}$) will be obtained prior to induction therapy, and post cycles 1 and 5 of induction therapy in a subset of patients in each arm (25 per arm) [29]. These sequences will be obtained as part of the baseline and routine cranial MRI studies for each patient. The diffusion MRI parameters needed for ADC calculation are

b=0 and 1000 s/mm$^2$,

2-5 mm slice thickness without gap (whole brain coverage),

Spin-echo, and

Echo planar imaging.

#### 10.1.2.2 Brain FDG-PET Methods

Brain FDG-PET/CT will be obtained prior to induction therapy in a subset of patients in each arm. The same brain FDG-PET/CT will also be obtained after cycles 1 and 5 of induction chemotherapy. In addition to serial SUV measurements (baseline and scan after 4 weeks), we will also investigate changes in ratios of tumor FDG uptake versus uptake in contralateral white matter and normal cortex. No clear threshold is established for reliable response prediction and assessment in this setting. A decline in tumor SUV by at least 25% from baseline will be considered consistent with metabolic response in the week 4 scan. We hypothesize that individuals with greater decline in tumor SUV (or greater decline in tumor versus background ratios) in the 4 week scan will have a better outcome.

Parameters to be recorded include SUV in PCNSL and a contralateral identical region, as well as physiologic FDG uptake in various other brain regions (e.g. contralateral thalamus, contralateral frontal and parietal cortex), and presence or absence of crossed cerebellar diaschisis. SUVmax and its variations (mean, peak) will be measured within a volumetric region of interest completely encompassing the lesion or normal brain region. The use of SUV thresholds (e.g. 42% and 75% will be explored [60, 65].

FDG-PET/CT findings will not be used to guide patient management. Nevertheless, we tentatively define CR as no residual abnormal uptake (non-detectable or equal to contralateral white matter), PR as decline in SUV by at least 25% and similar decline in T:N ratio, PD as increase in SUV and T:N ratio by at

least 25%, and SD as minor changes in FDG uptake not meeting aforementioned criteria.

### 10.1.3 Diffusion MRI Procedures, Interpretation, and Analysis

#### 10.1.3.1 Diffusion MRI Procedures

Diffusion MRI data will be processed on an offline workstation to generate apparent diffusion coefficient (ADC) maps. Regions of interest (ROIs) outlining the contrast enhancing tumor region on post-contrast T1-weighted images will be performed. ADC maps will be co-registered with the post-contrast T1-weighted images containing the ROIs. The ADC values (mean, minimum, maximum, and $25^{th}$ percentile) of the entire contrast-enhancing tumor will be measured. Tumor ADC 25% greater than the median value of 692 will be considered high ADC patient cohort. Based on our preliminary data, approximately 60% of patients are expected to be in the high ADC cohort.

#### 10.1.3.2 Diffusion MRI Interpretation and Analysis

Pre-therapy baseline tumor ADC25% $< 692$ and $\geq 692$ will be designated into low and high-ADC groups, respectively. The difference in ADC values will be measured between 1) baseline and after one cycle of induction therapy, 2) baseline and after five cycles of induction therapy, and 3) after one and five cycles of induction therapy.

Clinical outcomes (time-to-progression and overall survival) difference between low and high-ADC groups will be determined. In addition, we will determine whether changes in ADC during and after therapy predict clinical outcomes.

### 10.1.4 Brain FDG-PET Imaging Procedures, Interpretation, and Analysis

18F-FDG PET/CT imaging MUST be performed according to the protocol criteria at both baseline and follow-up.

#### 10.1.4.1 FDG-PET/CT Institutional Requirements for Participation and Credentialing Procedures for FDG-PET/CT Imaging

All limited access institutions that may participate in CALGB 581101 have been previously credentialed by the Alliance Imaging Core Lab (ICL). In order for a limited access institution to participate in CALGB 581101, the ICL must be contacted at [redacted] to arrange for a credentialing update.

The ICL regularly performs team telephone calls as well as virtual site visits, and serves as a consultant to help the local sites resolve questions with regard to adherence to the acquisition and reconstruction protocol.

#### 10.1.4.2 FDG-PET/CT Imaging Timelines

For 581101 PET/CT imaging, the following brain PET/CT images will be collected digitally for evaluation and archival:

Baseline (within 21 days prior to day 1 of induction therapy)

Prior to cycle 2 of induction chemotherapy (within 7 days prior to day 1 of cycle 2)

After cycle 5 of induction chemotherapy (within 28 days after the last day of induction cycle 5)

#### 10.1.4.3 Patient Preparation

Patients should avoid any strenuous exercise for 24 hours prior to the PET scan and fast for no less than 4 hours prior to the injection of FDG. Patients must have a fasting blood glucose level ≤ 200 mg/dL prior to FDG injection. In patients presenting with fasting glucose > 200 mg/dL, an initial attempt may be made to lower blood glucose level according to local institutional guidelines. If the first attempt to control the blood glucose level fails (i.e., glucose remains > 200 mg/dL), then the patient will not be included in the FDG imaging study.

Patients should be adequately hydrated with plain water. Weight (kg), height (cm), and blood glucose (mg/dL) will be measured and recorded prior to the injection of FDG.

Patients should wait in a warm room to avoid false positive brown fat FDG uptake. Following FDG injections, patients should rest in a warm, quiet, and dimly lit (or dark) room during the FDG uptake period. FDG will be synthesized and prepared in accordance with the institution's standard procedures or obtained from a commercial supplier.

#### 10.1.4.4 FDG Dosing and Administration

The administered activity of FDG should be based on the PET/CT system manufacturer's recommendation. The recommended FDG activity is 6-10mCi, bolus injection followed by a saline flush (per institutional procedure). Pre-injection FDG syringe dose, FDG dose injected and post-injection FDG dose residual and corresponding time should be documented on form CALGB 581101.

#### 10.1.4.5 FDG-PET/CT Imaging Acquisition

Brain PET/CT at all time points (baseline, prior to induction cycle 2, and at the end of induction therapy) MUST start 60-80 minutes after FDG injection. The timing should stay the same for follow-up PET/CT scans from the baseline (no more than a ± 10 minute difference). It is critical that follow-up PET/CT scans will be performed in an identical way to the baseline scan, with the same scanner and same patient preparation. Preferably, patients should be scheduled for baseline and follow-up scans at the same time of day (AM or PM) to improve reproducibility.

The field of view is to encompass the brain (top of skull to skull base/upper neck). The head should be placed in a head holder and in the same position for all scans. The low dose CT will be done according to the institutional practice patterns, but using no less than 120kV, 120mA. The CT data will be used for attenuation correction of PET emission data.

For the emission scanning, the acquisition should be performed in 3D mode in accordance with the manufacturer's recommendations. The emission scan must be corrected for scatter, random events, and dead-time losses using the manufacturer's recommended procedure. The image reconstruction will be performed using the manufacturer's recommended parameters.

Images should be attenuation-corrected using CT data.

### 10.1.5 MRI and FDG-PET/CT Data Submission

Both the MR and FDG-PET/CT images will be submitted to the ICL. Please see Section 5.10.1 for MRI and FDG-PET/CT image storage and submission procedures.

### 10.1.6 Virtual Conferences and Training

The Alliance ICL enables Internet-based visual and virtual conferences [redacted] that allow the simultaneous display of images (desktop presentations/desktop applications such as PowerPoint) and mutual communication between participating sites and the ICL in a secure manner (SSL-encoded). The ICL will set up virtual meetings for problem solving and site training when necessary.

## 10.2 Biomarker Correlative Science Companion Study (CALGB 151113)

Exploratory Analyses of Biomarkers as Potential Predictors of Outcome for Primary CNS B-Cell Lymphoma

### 10.2.1 Immunohistochemistry

Based on prior studies, it is hypothesized that a number of IHC-based biomarkers will be predictive of an adverse prognosis: P-STAT-6, STAT-6 (signal transducer and activator of transcription 6, interleukin-4 induced) [66-69]. These markers arose from gene expression profiling studies carried out by [redacted] that identified IL-4 pathway as important in CNS lymphoma. Activation of this pathway as measured by phospho-STAT6 expression was found as a predictor of adverse outcome in primary CNS B-cell lymphoma [66]. Thus, we intend to validate this finding prospectively in a uniformly treated patient population. In an exploratory manner, we also will study total STAT6 to determine whether total levels can yield similar information given the lability of phosphoproteins [70].

Conversely, it is hypothesized that BCL-6 (B-cell CLL/lymphoma 6) will be predictive of a favorable prognosis. Data generated from a prior study by [redacted] has identified the germinal center B-cell marker BCL6 as a marker of favorable outcome in primary CNS lymphoma. Approximately 20% of cases lacked BCL6 expression by immunohistochemistry and median survivals were significantly decreased (101 months versus 12.7 months, P=0.002) compared to cases that expressed BCL6 [69]. Recent studies have not replicated this data; however, methodological and scoring issues confound the results [71]. Thus, prospective assessment using methods originally described [69] are required to validate this potential biomarker.

A tissue microarray (TMA) will be constructed from cases with sufficient representative material. TMAs are constructed by removing two 1 mm diameter tissue cores from the lymphoma tissue block using a specially designed instrument (Beecher Instruments, Sun Prairie, WI). The resulting tissue array can contain 100 cases in a single tissue block, and allows rapid, high throughput analysis of markers by immunohistochemistry or *in situ* hybridization. The original tissue block remains intact with only a small amount of tissue removed with no significant distortion. Given the generally small nature of CNS lymphoma biopsies, whole tissue section staining will be performed in cases judged insufficient for TMA construction.

For BCL6, automated staining using Pg-B6p (DAKO) will be performed with nuclear immunoreactivity in 10% as the cutoff [69]. pSTAT6 and STAT6 staining using pSTAT6 antibodies from Upstate Biotechnology as previously described with positive staining will be defined as high cellularity areas expressing pSTAT6 [66]. Total STAT6 will be assessed using monoclonal anti-STAT6 (Clone 253906, R&D Systems) and scored similarly. Immunostains will be performed in the laboratories of [redacted]

Other candidate protein biomarkers of prognosis may be considered and tested.

### 10.2.2 Genomic and Expression Profiling

Tumor tissue will also be analyzed for whole exome sequencing, copy number aberrations, and gene expression profiles in order to validate genetic prognostic markers and gene expression profiles in order to validate gene signatures associated with germinal center B, activated B-cell, or type 3 large B-cell lymphoma and signatures [66] of primary CNS lymphoma [72]. Aneuploidy versus diploid dichotomy was found in one study [73] and del 6(q) was found at very high frequency (75%) [74] suggesting the potential presence of a tumor suppressor gene. Verification of these findings, and their potential clinical correlates is needed. Furthermore, use of higher resolution techniques and/or sequence analysis may provide more detail on important genetic changes in primary CNS lymphoma. DNA will be purified from diagnostic tumor specimens (formalin-fixed paraffin-embedded) and genomic aberrations will be analyzed using either sequencing methods or hybridization methods such as Illumina genotyping/copy number chip.

### 10.2.3 Circulating Protein Marker Analyses

We will validate candidate diagnostic and prognostic protein biomarkers in the CSF using ELISA methods. We will evaluate CSF protein and metabolites as biomarkers of prognosis. Candidate molecules include IL-10 (interleukin 10) and C3 (complement component 3) which have been identified using proteomic techniques and for which ELISA methods have been established in CSF [43]. We have used metabolic profiling to identify lactate and TCA cycle intermediates as selectively upregulated in the CSF of patients with CNS lymphoma, and it is hypothesized that these may be prognostic [75, 76].

## 10.3 Neurocognitive and Quality of Life Correlative Science Study (CALGB 71105)

Neurocognitive Function and Quality of Life in Patients with Primary CNS B-Cell Lymphoma

### 10.3.1 Background

Cognitive dysfunction in PCNSL patients is related to multiple factors including the effects of the tumor itself, age, and the delayed adverse effects of whole brain radiation therapy (WBRT) and HD-MTX either combined or alone [77]. Delayed treatment-related cognitive dysfunction has been recognized as a significant problem as effective treatment for PCNSL has increased survival rates [4, 77, 78]. Neurotoxicity is considered the most frequent complication among long-term survivors [79], and often interferes with the patient's ability to function at premorbid levels, despite adequate disease control [80, 81].

A review of the literature [27] indicated that in the three published cross-sectional studies that assessed cognitive outcome after treatment with WBRT + HD-MTX [80-82], there was evidence of cognitive impairment in the majority of patients. Quality of life assessment showed lower scores in cognitive emotional and social functioning in patients compared to controls [81], and reduced rates of employment [82]; however, the retrospective designs limited the ability to determine the specific contribution of disease and treatment. In prospective studies, including patients treated with WBRT and blood brain barrier disruption (BBBD) chemotherapy, the results were more equivocal with subsets of patients showing cognitive decline [83, 84]. Preliminary findings from a recent prospective study involving PCNSL patients treated with rituximab, MTX, vincristine and procarbazine (R-MPV), reduced-dose WBRT and high-dose cytarabine showed pre-treatment (baseline) impairments in executive function, verbal memory and motor speed. There was a significant improvement in cognitive function after induction chemotherapy and cognitive function remained relatively stable up to two years

following treatment completion; assessment of quality of life showed significant improvement after induction therapy and between the 6- and 12-month follow-up periods [6, 85].

To avoid the neurotoxic effects of WBRT, studies have explored the use of HD-MTX alone particularly in patients who are 60 years of age and older [3, 86]. Recent studies suggest that HD-MTX alone can be efficacious and reduce delayed neurotoxicity [8, 28, 87, 88]. However, disease relapse is relatively common and many patients require salvage therapy with WBRT or high-dose chemotherapy [8, 89]. Studies that assessed cognitive outcome after treatment with HD-MTX alone were mostly prospective, and reported either stable or improved cognitive performance in the majority of patients [87, 90-93]. Correa et al (2003) studied fourteen patients (mean age=54 years, SD=6.8) prior and at 6-month intervals subsequent to treatment with induction HD-MTX followed by myeloablative BEAM chemotherapy and autologous stem cell rescue [94]. Patients performed in the impaired range (i.e., test scores ≤ 1.5 SD below normative means) at baseline in attention and executive function, psychomotor speed, memory, and language. Improvement was observed in the seven patients available for post-induction follow-up, particularly in attention and executive functions. Cognitive performance remained stable (but within 1 SD below normative means) in three patients 18 months post-transplant (all patients had a CR). Patients did not complete all follow-up assessments due to disease progression or acute non-neurologic toxicity. Overall, in some studies, methodological problems limited the ability to discern the specific contributions of the disease and treatment to cognitive outcome [27]. As chemotherapy alone regimens have been used more frequently in the treatment of PCNSL, it is relevant to assess whether this therapy is associated with cognitive adverse effects.

In light of the recognized relevance of studying cognitive outcome and quality of life in PCNSL patients and the paucity of multicenter systematic studies in the literature, this study offers a unique opportunity to incorporate a comprehensive evaluation of these domains. We plan to use the core neuropsychological test battery proposed by the International PCNSL Collaborative Group (IPCG) to evaluate patients longitudinally for up to 10 years [27].

We hypothesize that in both treatment arms, there will be an improvement in cognitive function after induction chemotherapy followed by relatively stable cognitive performance in patients without evidence of disease progression – i.e. no cognitive decline after consolidation chemotherapy or HDT/ASCT in the absence of disease progression. Furthermore, we hypothesize that in both treatment arms, patients with relapsed disease requiring salvage therapy will have less preserved long-term cognitive function than patients without history of relapse.

### 10.3.2 IPCG Assessment

NOTE: English-speaking participants will be eligible to participate in the neurocognitive assessment component of this study. All eligible patients enrolled onto CALGB 51101 should be offered to participate in this correlative study.

The tests in the IPCG neurocognitive test battery are standardized psychometric instruments shown to be sensitive to the impact of cancer and the adverse effects of cancer treatment in studies of PCNSL patients [80, 85]. The tests have published normative data that takes into account age, and where available, education. The tests are given by trained and certified site administrators, and the total time for the assessment is approximately 45 minutes.

The IPCG test battery consists of the following:

Neuropsychological Evaluation:

Attention/Executive Function:
- Brief Test of Attention
- Trail Making Test, Part A & B

Verbal Memory:
- Hopkins Verbal Learning Test-Revised (HVLT-R)

Motor Speed:
- Grooved Pegboard Test

The quality of life evaluation consists of the following:

EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/BCM20)

The EORTC QLQ30/BCM20 were developed and validated for use in patients with brain tumors [95]. These questionnaires have been used in many large cooperative trials within the RTOG and other clinical studies [96]. This quality of life component follows the methodology used in past clinical trials to assess change, and the purpose of this component is in part to investigate how possible changes in quality of life may impact patient outcomes.

**Timetable for cognitive functions:**

| Tests | Time points | | |
|---|---|---|---|
| Cognitive and QOL tests | ≤ 2 weeks prior to treatment start | Induction therapy cycle 4, day 28 | Every 6 months up to year 5 (starting 6 months after treatment completion) then every 12 months for 5 years (for up to 10 years of follow-up) |

IMPORTANT: For patients with evidence of disease progression during the study period, a neurocognitive evaluation will be performed at the time of radiographic progression and prior to initiation of additional therapy. Subsequent follow-up will occur as described above. The treatment regimen at relapse will be considered in the long-term neurocognitive analyses.

Two of the cognitive 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 following is a timetable for cognitive evaluations and alternate forms to be used at each data collection time point.

**Alternate forms to be used at each visit:**

| Test | ≤ 2 weeks prior to treatment start | Induction therapy cycle 4, day 28 | Every 6 months up to year 5 (starting 6 months after treatment completion) then every 12 months for 5 years (for up to 10 years of follow-up) |
|---|---|---|---|
| HVLT-R | Form 1 | Form 2 | Form 3* |
| TRAILS B | Form 1 | Form 2 | Form 2** |

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

** TRAILS B: Continue to alternate order at subsequent 6-month intervals: Form 1, Form 2, Form 1, Form 2, etc.

### 10.3.3 CALGB 71105 Training and Certification Procedures

If the patient consents to participate in the neurocognitive function component of the study (Model Consent Question #1), sites are required to administer the baseline cognitive and quality of life assessments prior to the start of protocol treatment, and at the subsequent intervals specified. The healthcare professional (e.g., nurse, research assistant, psychologist) who is responsible for test administration in this study must be pre-certified by [redacted]

Institutions with patients participating in the quality of life/neurocognitive function (NCF) components of this study must meet certification requirements for administering neurocognitive assessments. The healthcare professional responsible for test administration in this study at each site must be pre-certified by [redacted]

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

(1) Contact [redacted] in order to obtain the training and certification materials, and test forms and test materials including:

Neurocognitive Administration Instructions Manual
Web address for the training video
Cognitive and QOL Test Forms
Grooved Pegboard and stopwatch
Test Summary Form
Certification Worksheet

All of these materials will be mailed to the participating sites.

(2) Read the entire Neurocognitive Administration Instruction Manual

(3) Log on to the video website and enter the specified logon and password. Watch the training video.

(4) Administer a practice assessment on a "non-patient volunteer"

(5) Complete the Test Summary Form and the Certification Worksheet

(6) Fax all materials pertaining to the practice assessment (i.e., practice test forms, summary form, and certification worksheet) to [redacted] The materials will be reviewed and corrections to any procedural errors will be made and re-reviewed with the tester.

(7) The tester will be notified of the certification approval to administer the tests to study subjects as part of CALGB 51101. A certification approval notice will be sent to the Alliance and to the Cancer Trials Support Unit (CTSU) for the registration process and to ensure that only approved examiners are testing subjects on protocol 51101.

(8) All neurocognitive test and summary test forms for the first study patient at each site should be sent via fax to [redacted] for review. In addition, send a copy of each assessment performed of each patient registered on study via fax to [redacted] for review.

(9) During the study period, enter the data from the summary test form for each assessment performed on each patient into Medidata Rave. Keep all original test forms at a secure location at your site.

If you have any questions please contact [redacted]

## 11.0 DRUG FORMULATION, AVAILABILITY AND PREPARATION

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

### 11.1 Methotrexate

Please refer to the FDA-approved package insert for more information.

*Availability*

Methotrexate is commercially available for the preparation of high dose (i.e., > 1g/$m^2$, as in this study) as a powder for reconstitution in vials containing 1000 mg. Solutions for injection that contain preservatives should not be used for the preparation of high doses

*Storage & Stability*

Intact vials should be stored at room temperature and protected from light. Reconstituted solutions (50 mg/mL) are stable for 7 days at room temperature. Solutions further diluted for IV infusion are stable for 24 hours at room temperature.

*Preparation*

Methotrexate powder for injection should be reconstituted with 19.4 mL of D5W or NS for a final concentration of 50 mg/mL, or according to institutional procedures. The desired volume should then be withdrawn and further diluted in 500 mL D5W or NS for IV infusion. The infusion solution should be protected from light. NaHCO3 50-150 mEq per liter of fluid may be added to the infusion solution to maintain urinary alkalinization (pH ≥ 7). Please note the information provided above are guidelines, institutions may follow their own institutional guidelines in place of this preparation.

*Administration*

Methotrexate will be administered as an IV infusion over 4 hours. Urine output and urinary alkalinization should be adequate before beginning methotrexate, as described in Sections 7.1.1 and 7.2.1. Additional NaHCO3 may be added to the infusion solution to maintain urinary alkalinization (pH ≥ 7).

*Toxicity*

Toxicities associated with methotrexate include myelosuppression (neutropenia, thrombocytopenia, anemia) GI toxicities (nausea, vomiting, diarrhea, mucositis, anorexia), dermatologic (rash [including erythema multiforme and exfoliative dermatitis], photosensitivity, alopecia), and ocular irritation. In addition, transient elevations in hepatic enzymes are frequently seen with high doses of methotrexate, such as the dose used in this protocol. Precipitation of methotrexate and its 7- hydroxy-metabolite in an acidic urine can lead to renal tubular obstruction with resultant delayed administration of the drug and enhanced toxicity (myelosuppression, mucositis). This is seen with high doses (≥ 1 g/$m^2$) and is prevented with hydration and urinary alkalinization.

### 11.2 Leucovorin

Please refer to the FDA-approved package insert for more information.

*Availability*

Leucovorin is commercially available in 50 mL vials containing 10 mg/mL; and in 50 mg, 100 mg, and 350 mg vials of lyophilized powder for reconstitution. Follow the manufacturer's labeling for reconstitution of vials containing powders. Leucovorin is also available in 5 mg, 10 mg, 15 mg, and 25 mg tablets. In the case of leucovorin shortage, please refer to the Leucovorin Shortage memorandum posted on the Alliance website.

*Storage & Stability*

Store intact vials and tablets at room temperature between 15° and 25°C (59° and 77°F). Protect from light and moisture. Solutions reconstituted with bacteriostatic water are stable for at least 7 days at room temperature.

*Preparation*

Reconstitute with bacteriostatic or sterile water for injection according to package insert instructions. If reconstituted with sterile water for injection, use immediately. If bacteriostatic water for injection is used, the solution is stable for 7 days.

*Administration*

Leucovorin is administered IV by bolus injection or short infusion. If leucovorin is required every 3 hours, a continuous infusion may be used if institutional preference. Oral administration is allowed at doses of 10 mg/m2, provided that methotrexate level is ≤ 0.1 mcM as described in Section 7.2.3. Leucovorin is to begin 24 hours after the start of each methotrexate dose.

*Toxicity*

The only adverse events usually associated with leucovorin are allergic reactions. These are extremely uncommon.

### 11.3 Temozolomide

Please refer to the FDA-approved package insert for more information.

*Availability*

Temozolomide is available in 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsules.

*Storage and Stability*

Temozolomide capsules should be stored at controlled room temperature.

*Administration*

The capsules are administered orally and should not be chewed. They should be swallowed whole with a glass of water. Procedures for handling and disposal of anticancer drugs should be considered.

*Toxicities*

Myelosuppression (including neutropenia, lymphopenia, leukopenia, anemia, an thrombocytopenia), has been reported in patients receiving temozolomide and is a dose-limiting side effect. Thrombocytopenia and leukopenia reach grade 2 or higher in up to 40% of patients on temozolomide therapy. Leukocyte/platelet nadirs usually occur in 3 weeks (about day 22) with a 5-day schedule, although leukocyte nadirs may be seen slightly later (day 29). Dose-limiting thrombocytopenia has persisted for 7 to 42 days, whereas recovery from leukopenia may be quicker. Bleeding has been infrequent with temozolomide therapy. In one large trial

involving adult patients with malignant glioma, the predominant effect was lymphopenia, which reached grade 3 and grade 4 in 41% and 15%, respectively, receiving a 5-day schedule of temozolomide. Corresponding incidences of neutropenia were 2% and 4%. The incidence of grade 3 or 4 thrombocytopenia was 11%. The incidence of myelosuppression may be higher with the use of a dose intense regimen. Opportunistic infections (e.g., pneumocystis jiroveci pneumonia (PCP)) have been reported with the use of temozolomide. Rarely, aplastic anemia and secondary leukemia have been described with temozolomide.

Hepatic toxicity: Mild transaminase elevations (up to 40% of patients) and hyperbilirubinemia (up to 19%) have been reported; increases in alkaline phosphatase have also occurred in some patients. Grade 4 increases in bilirubin have been seen rarely. Cases of hepatic injury, including fatal hepatic failure, have been reported in patients receiving Temozolomide. Hepatic toxicities has been reported several weeks or more after initiation of treatment with Temozolomide or after discontinuation.

Fatigue is among the most commonly reported adverse effect with the use of temozolomide in clinical trials, and is clearly drug-related. Fatigue with temozolomide therapy may be moderate to severe. The estimated incidence is 34%.

Nausea and vomiting occur in up to 75% of patients with temozolomide therapy, but is not usually severe (mostly grade 1 or 2). These symptoms have often been limited to day 1 of the first cycle of temozolomide. Standard antiemetics have been effective in most patients. The estimated incidence is 42% to 53%. Bedtime administration of temozolomide may help to minimize nausea and vomiting.

### 11.4 Rituximab

Please refer to the FDA-approved package insert for more information.

*Availability*

Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL.

*Storage and Stability*

Intact vials should be stored under refrigeration. Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

*Preparation*

The desired dose of rituximab should be diluted in 0.9% NaCl or D5W to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

*Administration*

Initial infusion rate is 50 mg/hr. If tolerated, the rate may be increased by 50 mg/hr every 30 minutes, to a maximum of 400 mg/hr. If this rate of escalation is tolerated, the second and subsequent infusions can begin at a rate of 100 mg/hr and increase in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hour.

*Toxicity*

The most severe serious adverse events associated with rituximab include severe infusion reactions, tumor lysis syndrome, and severe mucocutaneous reactions. Severe infusion reactions consisting of hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock may be fatal. Most reported fatal reactions occurred within 24 hours of the first dose of rituximab.

Tumor lysis syndrome resulting in renal failure has been described, and occasional fatalities noted. Tumor lysis syndrome is more likely in patients with high numbers of circulating malignant cells (≥ 25,000/μL).

Severe mucocutaneous reactions associated with rituximab include Stevens-Johnson syndrome and toxic epidermal necrolysis. The onset of these reactions has been from 1-3 weeks.

Less severe infusion reactions are common with rituximab. These include fever, chills, and dyspnea. The mechanism of rituximab infusion reactions is thought to be secondary to release of cytokines. If a reaction occurs, then the infusion should be stopped until the symptoms resolve, and then restarted at a 50% slower rate.

Recent reports describe hepatitis B reactivation with fulminant hepatitis, hepatic failure and death in some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after starting rituximab and approximately 1 month after the last dose.

Exacerbation or reactivation of other viral infections has also been reported with rituximab. Recent reports describe JC virus reactivation leading to progressive multifocal leukoencephalopathy (PML) in patients who were receiving rituximab. Patients presenting with new neurologic findings (e.g., major changes in vision, unusual eye movements, loss of balance or coordination, confusion) should be evaluated for PML.

### 11.5 Cytarabine

Please refer to the FDA-approved package insert for more information.

*Availability*

Cytarabine is commercially available as a powder for reconstitution in 100 mg, 500 mg, 1 g and 2 g vials, or a preservative free solution of 20 mg/mL (5 mL and 50 mL vials) and 100 mg/mL (20 mL vials).

*Storage and Stability*

Intact vials of cytarabine should be stored at room temperature. Vials of solution should be protected from light. Reconstituted solutions and solutions further diluted for infusion are stable at room temperature for up to 8 days.

*Preparation*

Cytarabine powder should be reconstituted with water for injection or 0.9% NaCl, to a concentration of 100 mg/mL. Diluents with bacteriostat should not be used to reconstitute high doses such as those used in this study (e.g., ≥ 1 g/m$^2$). Solutions are further diluted in 0.9% NaCl or D5W for IV infusion.

*Administration*

Each dose of cytarabine will be administered IV over 2 hours.

*Toxicity*

The most common adverse events reported with cytarabine ("usual dosage" i.e., ≤ 200 mg/m$^2$) include hematologic, gastrointestinal, dermatologic, and hepatic toxicities. Myelosuppression includes neutropenia, thrombocytopenia, and anemia. Cytarabine is considered highly emetogenic. In addition to nausea and vomiting, diarrhea and mucositis are reported in > 10% of patients. Alopecia is common. Rash, including palmar-plantar erythrodysesthesia (hand-foot syndrome) is also reported. Mild jaundice and elevations in transaminases are also reported in

> 10% of patients. Fever (non-infectious) is also reported among the most common adverse events associated with cytarabine.

Less commonly, a "cytarabine syndrome" or "ara-C syndrome" has been reported. The syndrome may be characterized by fever, myalgia, bone pain, rash, malaise, chest pain, and, rarely, pericarditis.

In addition to the above, the following adverse events have been described with high-dose (≥ 1 g/m$^2$/day) cytarabine. Neurologic toxicity is primarily cerebellar (nystagmus, dysarthria, disdiadochokinesia, ataxia, abnormal gait) but cerebral toxicity (somnolence, confusion, psychosis, seizures) may also be seen. Ocular toxicity, including photophobia and conjunctivitis are described with high-dose cytarabine. A steroid ophthalmic preparation should be administered, beginning 6-12 hours before the first dose of cytarabine and continuing for 48 hours after the last "high dose," to prevent conjunctivitis. Pulmonary edema has been rarely reported in association with high-dose cytarabine.

### 11.6 G-CSF

Please refer to the FDA-approved package insert for more information.

*Availability*

G-CSF is commercially available in 1 mL and 1.6 mL vials containing 300 mcg and 480 mcg G-CSF, and in prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL.

*Storage and Stability*

Intact vials and prefilled syringes should be stored in the refrigerator at 2°-8° C (36°-46° F). Do not freeze.

*Administration*

In Arm 1, is given for mobilization at a dose of 10 mcg/kg/day SC. In both Arm 1 and Arm 2, G-CSF may be used for neutropenia.

*Toxicity*

The most common adverse event associated with G-CSF is bone pain. Bone pain is usually reported as mild or moderate and, if necessary, may be treated with nonopioid or opioid analgesics.

### 11.7 Carmustine

Please refer to the FDA-approved package insert for more information.

*Availability*

Commercially available as a powder for reconstitution in vials containing 100 mg carmustine. Each vial is packaged with a vial of diluent (3 mL absolute ethanol).

*Storage and Stability*

Intact vials should be stored in the refrigerator (2°-8°C). Un-reconstituted vials are stable for 7 days at room temperature. Reconstituted solutions with ethanol diluent are stable for 24 hours under refrigeration and protected from light. Further diluted solutions for administration are stable for 48 hours under refrigeration and protected from light, but are stable only for 4-6 hours at room temperature and protected from light.

*Preparation*

Reconstitute each vial with 3 mL absolute ethanol diluent. Further dilute in 500 – 1000 mL D5W or NS. Solutions for infusion should be prepared in glass or non-PVC plastic containers and protected from light.

*Administration*

In Arm 1, carmustine is infused IV over 2 hours.

Toxicity

Hypotension and facial flushing occur frequently during administration. These effects are related to the alcohol diluent. Arrhythmias and encephalopathy may also be seen. High dose carmustine is considered highly emetogenic. Onset of nausea and vomiting is within 2-4 hours of drug administration. Myelosuppression is expected with high dose therapy, as is alopecia. Late effects include nephrotoxicity and interstitial pneumonitis. Interstitial pneumonitis should be treated with steroids as described in (Section 8.6.2). Veno-occlusive disease of the liver is a complication associated with multiple drugs given in SCT regimens.

### 11.8 Thiotepa

Please refer to the FDA-approved package insert for more information.

*Availability*

Thiotepa is commercially available as a powder for reconstitution in vials containing 15 mg or 30 mg.

*Storage and Stability*

Intact vials should be stored under refrigeration and protected from light at all times. Reconstituted solutions are stable for 28 days under refrigeration and 7 days at room temperature. Solutions further diluted for infusion in D5W are stable for 14 days under refrigeration and 3 days at room temperature; infusion solutions in 0.9% NaCl are stable for 48 hours under refrigeration and 24 hours at room temperature.

*Preparation*

Reconstitute each vial with sterile water for injection concentration of 10 mg/mL.

Drug should be further diluted in D5W to a concentration of 5 mg/mL for IV infusion, using a 0.22 micron filter.

*Administration*

Thiotepa will be infused over 2 hours in Arm 1.

*Toxicity*

Adverse events associated with thiotepa are myelosuppression (neutropenia, thrombocytopenia), oral mucositis, hyperpigmentation, and CNS toxicity. CNS toxicity is more prominent at high doses in stem cell transplants, and may include confusion, inappropriate behavior, and somnolence. CNS toxicities reported at lower doses include dizziness, fatigue, and headache.

### 11. 9 Etoposide

Please refer to the FDA-approved package insert for more information.

*Availability*

Etoposide is commercially available in 5 mL, 25 mL, and 50 mL vials containing 20 mg/mL.

*Storage and Stability*

Unopened vials should be stored at room temperature and protected from light. Solutions diluted to a concentration of 0.2 or 0.4 mg/mL (in D5W or NS) are stable for 96 and 24 hours, respectively, at room temperature under normal light.

*Preparation*

The dose of etoposide should be diluted in D5W or 0.9% NaCl to a final concentration of ≤ 0.4 mg/mL.

*Administration*

Etoposide will be administered IV, over 96 hours, in Arm 2.

Toxicity

Myelosuppression is expected with high dose etoposide. GI toxicities associated with high dose etoposide include severe nausea and vomiting, and mucositis. Hypotension is associated with shorter infusion times (e.g. 30 minutes).

## 12.0 CRITERIA FOR RESPONSE, PROGRESSION AND RELAPSE

### 12.1 Definitions of Response

Response will be defined using the modified IPCG criteria as noted below [97].

| Response | CNS imaging | Corticosteroid dose | Eye exam | CSF cytology |
|---|---|---|---|---|
| CR | No enhancing disease | None | Normal | Negative |
| uCR | No enhancing disease | Any | Normal | Negative |
| | Minimal enhancing disease | Any | Minor RPE abnormality | Negative |
| PR | 50% decrease in enhancement | N/A | Minor RPE abnormality or normal | Negative |
| | No enhancing disease | N/A | Decrease in vitreous cells or retinal infiltrate | Persistent or suspicious |
| PD | 25% increase in enhancement | N/A | Recurrent or new disease | Recurrent or positive |
| | Any new site of disease | | | |
| SD | All scenarios not covered by responses above | | | |

Abbreviations: CR, complete response; uCR, unconfirmed complete response; PR, partial response; PD, progressive disease; RPE, retinal pigment epithelium.

#### 12.1.1 Complete Response (CR):

A complete response is defined as disappearance of all contrast-enhancing CNS (brain and spine if latter abnormal at baseline) disease, absence of any systemic corticosteroids prescribed to treat lymphoma (prophylactic steroid eye drops, topical steroids, corticosteroid antiemetics and steroids prescribed for non-disease reasons [e.g. asthma exacerbation, dermatologic or rheumatologic conditions] are allowed and not considered in the definition of CR), resolution of abnormal ocular findings on ophthalmological examination, negative CSF cytology.

#### 12.1.2 Complete Response Unconfirmed (CRu)

An unconfirmed complete response is defined as CR but with either residual requirement for any corticosteroid dose or minimally enhancing abnormality on CNS imaging or minor abnormalities on ophthalmological examination.

#### 12.1.3 Partial Response (PR):

A partial response is defined as >50% reduction in contrast-enhancing CNS (brain and spine if latter abnormal at baseline) disease either with minor abnormalities on ophthalmological examination or normal ophthalmological examination OR disappearance of all contrast-enhancing CNS (brain and spine if latter abnormal at baseline) but only reduction of vitreous cells or retinal infiltrates or residual suspicious or positive CSF cytology.

#### 12.1.4 Stable Disease (SD)

All scenarios not covered by definitions of CR, CRu, PR or PD.

#### 12.1.5 Progressive Disease (PD)/Recurrence:

Progressive disease is defined as > 25% increase in contrast-enhancing CNS (brain and spine if latter abnormal at baseline) disease, appearance of any new, measurable (>/= 10mm) contrast-enhancing disease or recurrent or new ocular or CSF disease.

## 13.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

### 13.1 Duration of Treatment

#### 13.1.1 (CR, CRu, PR, SD)

Patients will be assessed for response after 4 cycles of methotrexate/temozolomide/rituximab and 1 cycle of cytarabine (5 cycles of remission induction therapy) per modified IPCG criteria [97]. Patients who achieve a complete response (CR), complete response/unconfirmed (CRu), partial response (PR) or stable disease (SD) will proceed to consolidation therapy with either etoposide and cytarabine or HDT/ASCT, depending on the initial randomization.

#### 13.1.2 (PD)

At any point during protocol therapy, remove any patient with progressive disease (PD). Document details, including tumor measurements, on flow sheets.

### 13.2 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.

- Document the reason(s) for discontinuation of therapy on the Off Treatment form.
- Follow the patient for relapse, progression, survival, and secondary malignancy or new primaries.

## 14.0 STATISTICAL CONSIDERATIONS

### 14.1 Randomization

Randomization will be stratified by

age < 51 years,

age ≥ 51 years and KPS ≥ 70, and

age ≥ 51 years and KPS < 70.

The use of this simple prognostic model consisting of age and performance status has been validated in the multicenter setting [2].

### 14.2 Sample Size / Power Calculation

A total of 160 patients (80 per arm) will be randomized between the control and experimental arms with 50:50 allocation proportions. The randomization will be conducted at registration, i.e. before induction therapy. Assuming that 80% of randomized subjects will achieve a radiographic response (CR, CRU, or PR) or stability (SD) and 5% will withdraw or will be ineligible, approximately 120 patients will be eligible for proceeding to either HCT/ASCT or chemotherapy. Further assumptions of this sample size calculation are as follows.

1) For the patients who have CR, CRU, iPR, or SD from the induction therapy, we hypothesize a two-year PFS of 50% for the control arm, based on CALGB 50202 [26]. We will be highly interested in the experimental arm if its two-year PFS is 70% or higher.
2) For the patients who develop tumor progression during induction therapy, we assume three months of median PFS.
3) We assume exponential distributions for PFS.
4) We expect an accrual rate of 6 patients per month. The patients will be followed for an additional three years after the completion of patient accrual.

Under these assumptions, the intent to treat (ITT) analysis using the log-rank test with a one-sided alpha=10% will have 90% power to compare two-year PFS of 50% and 70% between the two arms. The final analysis will be conducted when 95 events (progressions or deaths) are observed, which is expected to occur approximately 63 months after study activation.

### 14.3 Analysis Plan for Primary Endpoint

#### 14.3.1 Interim Analysis

An interim analysis for futility testing will be conducted when 20 events are observed, which is expected to occur approximately 1.5 years after study activation. The study will be closed early because of futility if the one-sided p-value is larger than or equal to $c_1$=0.691 (or equivalent if the standardized log-rank statistic is smaller than -0.5).

#### 14.3.2 Final Analysis

The final analysis will be conducted when 60 events (progressions or deaths) are observed from the patients who proceed to either HDT/ASCT or chemotherapy (or about 95 events from all the eligible patients). All randomized patients will be included in the final data analysis based on intent-to-treat analysis. The experimental therapy will

be accepted for further investigation if the one-sided p-value is smaller than 0.1. The critical value c at the final analysis will be obtained by solving 1-alpha=P($Z_1 > c_1$, $Z > c$) with respect to c, where ($Z_1$, Z) is a bivariate normal random vector with means 0, variances 1 and correlation coefficient $r=(v_1/v)^{1/2}$, and $v_1$ and v are variance estimates of the log-rank test at the interim and final analyses, respectively. Through simulations, the two-stage design is found to have about 9.7% of type I error and 87% power.

A secondary analysis will be conducted using the stratified log-rank test adjusting for the stratification factor. We will also conduct a secondary analysis including only the patients who proceeded to either HDT/ASCT or chemotherapy. The latter analysis will be more powerful than the primary analysis based on ITT by excluding the patients who will receive the induction therapy only. The secondary analyses will be conducted only at the final analysis time.

## 14.4 Sample Size Modification

Due to the lower than expected accrual rate, the accrual goal was lowered from 160 to 110 with update #09, when approximately 95 patients were registered. We recalculate the power of the new sample size assuming a median PFS of 2 years for the control arm and 4.5 years for the experimental arm, and an expected accrual rate of 4 patients per month, with other design parameters the same as before: (i) 50:50 randomization, (ii) 5% of withdrawal, (iii) 80% of randomized subjects achieve a radiographic response (CR, CRU, or PR) or stability (SD) and proceed to the allocated treatments, (iv) a median PFS of 3 months for the patients who develop tumor progression during induction therapy, (v) 2 years of additional follow-up, and (vi) modified intent to treat (ITT) analysis to exclude ineligible patients.

Under these assumptions, a sample size of N=110 guarantees 84% of power by the log-rank test with a one-sided alpha=10%. The final analysis will be conducted when 64 events (progressions or deaths) are observed, which is expected to occur approximately 52 months (=28 months for patient accrual + 24 months for additional follow-up) after study activation. Since this sample size modification occurred after the interim analysis that was planned by the original design was conducted and concluded to proceed to the second stage, there will be no more interim analysis.

**As of protocol Update #11, the following change has been made:**

**Revised final analysis timing due to low event rate:**

This study closed to accrual May 2 2017, having registered 113 patients. A total of 108 patients are considered evaluable for the primary analysis, excluding 4 patients who never started treatment and 1 ineligible patient. As of March 2020, the pooled event rate was lower than that specified by the study design. According to the study design, we would have expected 64 events needed to trigger the final analysis in May 2019. However, with a median follow-up of 42 months (IQR 34 to 56), the observed number of events is 50. Considering data maturity and ability to provide a timely final analysis, the final analysis will be performed when all patients have been followed for at least 36 months, which is expected in May 2020.

## 14.5 Monitoring for Adverse Events and Study Feasibility

### 14.5.1 Adverse Event Monitoring

About 10% of patients are expected to experience grade 3 or higher unexpected toxicities from the consolidation therapies. We consider 30% of 3 or higher unexpected toxicities from the consolidation therapies too high. Each time both the experimental and control groups enroll 10 additional patients, adverse events (AEs) will be monitored. We will consider suspension of the study for a protocol amendment if, in either of the study arms, 5 or more of the first 10 patients experience any unexpected grade 3 or higher toxicities (≥5/10), ≥7/20, ≥8/30, or ≥10/40. This monitoring rule has

a 1.1%, 32.5%, and 83.4% probability of rejecting each arm due to toxicity if the grade 3 or higher unexpected toxicity rate is 10%, 20%, and 30%, respectively.

#### 14.5.2 Study Feasibility

We expect (1) about 75% of patients will achieve SD or better response from the induction therapy and continue to the randomized arms, and (2) about 5% of patients with SD or better response from the induction therapy will withdraw from the randomized arms. We will perform interim analyses to check these assumptions as follows:

The study will be stopped for feasibility if (1) among the first 80 randomized patients the overall observed proportion of patients receiving the randomized therapy is less than 65%, or (2) among the first 80 patients eligible to receive randomized treatment (i.e., patients achieving SD or better) the observed non-adherence (due to withdrawal) rates differ between the arms by more than 10%. These rules have stopping probabilities of (1) 85%, 20% and 3% if the true probability to continue to the randomized therapy is 60%, 70% and 75%, respectively, or (2) 2.2% and 88% if the true probabilities of non-adherence in two arms are (5%, 5%) and (5%, 25%), respectively.

### 14.6 Secondary Endpoints

#### 14.6.1 The event-free survival (EFS) and the overall survival (OS) will be estimated for each arm by the Kaplan-Meier method, and compared between the two arms using the log-rank test. We will also conduct a multivariate analysis of these outcomes adjusting for the predictors, such as age and KPS.

#### 14.6.2 Toxicity data will be summarized by grade and attribution for induction therapy and for each of HCT/ASCT and chemotherapy consolidation arms. The toxicity rate will be compared between the arms using Fisher's exact method.

### 14.7 Correlative Science Companion Study Analyses

#### 14.7.1 Exploratory Analyses on Genomic and Proteomic Studies of FFPE Tissue, CSF Specimens, and Whole Blood Specimens (151113)

We assume that specimens will be available from about 80% of patients. IHC-based markers will be associated with PFS and OS. In a previous study (CALGB 50202), [redacted] observed amplification of STAT6 in about 50% of PCNSL patients. With 66 (=82 eligible patients x 0.8), we will have about 90% power to detect a median PFS of 1.5 years vs. 4.5 years between STAT6 amplification and non-amplification groups by the log-rank test with two-sided 5% alpha.

We will also investigate the impact of del 6q on PFS and OS. Cady et al observed a del 6q frequency of 45% in a prior study [98]. At first this analysis will be conducted within each treatment arm. Assuming a del 6q prevalence of 40%, this analysis will have about 88% power to detect a median PFS of 1.5 years vs. 4.5 years between del 6q+ and del 6q- groups by the log-rank test with two-sided 5% alpha.

These analyses will be conducted by stratifying the treatment allocation. A multivariate analysis will be conducted adjusting for the stratification factors together with the treatment arm and the interaction between treatment and marker value.

#### 14.7.2 Diffusion MRI Metrics (581101)

In order to determine diffusion MRI metrics ($ADC_{mini}$, $ADC_{25\%}$, and $ADC_{mean}$) prior to induction chemotherapy, after the first cycle of induction chemotherapy, and after the last cycle of induction chemotherapy as a predictor of response and outcome, ADC

values ($ADC_{mini}$, $ADC_{25\%}$, and $ADC_{mean}$) will be collected at baseline (pretreatment) and post induction cycles 1 and 4 during treatment from the 25 patients per arm. An inverse correlation between ADC values and cellular density will be investigated using scatter plots and correlation coefficients. Others have observed a correlation coefficient of about 0.5 [29]. We will have 75% and 96% power to detect a true correlation coefficient of 0.5 with n=25 and 50 (by combining the two arms), respectively, with a two-sided alpha=5%.

ADC values will be correlated with PFS, EFS, and OS using Jung et al, 1995 [99]. This approach is to investigate the global association between a continuous marker and a survival endpoint by calculating the log-rank test statistics between low and high marker value groups using all possible cutoff values for the marker. The testing distribution will be approximated using a permutation method [100]. Multivariate analyses adjusting for other predictors will be conducted using Cox regression method.

These analyses will be conducted for each arm. If the treatment effect is not significant, the data from the two arms will be combined for pooled analyses. We will consider transforming (e.g. log transformation) the positive measurements, like ADC values and cellular density, for variance stabilization and symmetry of the distributions.

### 14.7.3 FDG-PET Metrics (581101)

There is no clear threshold established for reliable response prediction and assessment for FDG-PET in the setting of PCNSL. Tentatively, a decline in tumor SUV by at least 25% from baseline will be considered consistent with metabolic response on the 4-week scan. We hypothesize that patients with > 25% decline in tumor SUV (or greater decline in tumor versus background ratios) on the 4-week brain FDG-PET scan will have a better prognosis. The association between decline in tumor SUV and metabolic response on the 4-week scan will be tested using Fisher's exact test.

### 14.7.4 Cognitive and Quality of Life Evaluation (71105)

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.

Neurocognitive decline will be defined as the first cognitive failure on 2 or more of the following tests: Digits Forward and Backward (WAIS-III); Brief Test of Attention; the HVLT-R for Free Recall, Delayed Recall and Recognition; the Trail Making Test Part A or B; and the Grooved Pegboard Test (average of left and right hand scores). 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 baseline score.

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.

To capture possible cognitive dysfunction associated with disease burden from relapses and salvage treatments, we will perform neurocognitive follow-up in both arms for at least the initial 5 years, regardless of disease status (including in patients with disease progression). Additionally, yearly cognitive follow-ups will be performed from years 5-10. Longitudinal data analysis will be performed to assess if there is a difference over time (i.e. change rate) across the two treatment arms using a generalized estimating equation (GEE), based on working independent correlation structure [101]. In this analysis, the 6-month observation will be used as the baseline. The treatment regimen

received subsequent to disease progression will also be considered in the longitudinal data analyses. The data may be transformed to improve the linearity of the longitudinal trend and normality of the marginal distribution. If no linear trend seems to fit the trend, we will compare the areas under the fitted trend.

The pattern of missing data (i.e. missing probabilities at measurement times) will be investigated for each arm. If the missing probabilities are similar between arms, we will apply the GEE method without imputing missing data [101]. However, if the missing trend is different, we will consider using Rubin-type (1978) multiple imputation method. Most missing data in this study is expected be monotone missing. We will test the similarity of missing pattern by comparing the time to missing data between two arms using the log-rank test.

Similar approaches will be used for the EORTC QLQ30/BCM20. Differences of at least 10 points will be classified as the minimum clinically meaningful change in a health-related quality of life (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. This approach has been used in several multi-center trials.

From CALGB 50202, which has a similar patient population to this study, we observed a 5-year survival rate of 62%. Assuming that about 80% of the living patients will be participating in this HRQOL study at any time and OS has an exponential distribution, the expected missing probability is 27%, 34%, 40%, 45%, and 50% at year 1, 2, 3, 4, and 5, respectively. We assume monotone missing pattern in this power calculation. For dependency structure of longitudinal data, we assume a continuous autoregressive correlation model with correlation coefficient rho=0.65 between two repeated measurements of 1 year apart. With a maximum of 10 measurement times (0.5 year, 1 year, 1.5 years, 2 years, 2.5 years, 3 years, 3.5 years, 4 years, 4.5 years, and 5 years), we assume a linear trend in an HRQOL measure (possibly after a transformation such as logarithm) whose difference in mean level becomes 0.3 times the standard deviation (SD) of the error terms after 1 year.

With n=82 patients in two arms, we have 88% power to detect this amount of difference in change rate between two arms by the GEE test with two-sided alpha=5% using the working independent correlation structure. For example, for EORTC QLQ30/BCM20, the SD was observed to be about 30 from brain cancer patients [102]. Thus, if the time trend in mean functional scale splits by 9 (=0.3 x SD) points between two arms after about 1 year post-induction, then we will have 88% power. The first study results will be reported at 5 years.

### 14.8 Accrual and Follow-up

A total of 110 patients (55 per arm) will be randomized between the control and experimental arms with 50:50 allocation proportions. We expect an accrual rate of 4 patients per month. The patients will be followed for a maximum of 10 years after registration.

Based on the power calculation, the study is expected to last for approximately 52 months (28 months for patient accrual plus 24 months for additional follow-up).

### 14.9 CDUS Reporting

The Alliance Statistics and Data Center will submit quarterly reports to CTEP by electronic means using the Clinical Data Update System (CDUS).

## 15.0 EXPEDITED ADVERSE EVENT REPORTING

Investigators are required by Federal Regulations to report serious adverse events as defined below. Investigators are required to notify the Alliance Central Protocol Operations Program Office, the Study Chair, and their Institutional Review Board (IRB) if a patient has a reportable serious adverse event. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site [redacted] All reactions determined to be "reportable" in an expedited manner must be reported using the CTEP Adverse Event Expedited Reporting System (CTEP-AERS).

### 15.1 CALGB 51101 Reporting Requirements

CALGB 51101: Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND trial within 30 Days of the Last Administration of a Commercial Agent [1]

**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.

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

**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 require reporting as follows:

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

- All Grade 4, and Grade 5 AEs that are at least possibly related to treatment

**Expedited 10 calendar day reports for**:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization, that are at least possibly related to treatment
- Grade 3 adverse events that are at least possibly related to treatment

Effective Date: July 25, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Commercial Agents in a Non-IND trial:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Grade 3/4 myelosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Febrile neutropenia and hospitalization from such do not require CTEP-AERS.
- Grade 3/4 nausea or vomiting and hospitalization resulting from such do not require CTEP-AERS, but must be reported as part of study results.
- Grade 3/4 neurotoxicity and hospitalization resulting from such do not require CTEP-AERS, but must be reported as part of study results.
- **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. In CTCAE version 5.0, 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 unless otherwise specified.

- Treatment expected adverse events include those listed in Section 11.0, in the package inserts for all agents, and in the CAEPR for rituximab (see Section 15.2). In the ASAEL column of the rituximab CAEPR, grade 3-5 events are NOT exceptions to CTEP-AERS reporting.
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., cooperative group data reporting (see Section 5.6)
- In CTCAE v5.0, pregnancy loss is defined as "Death in utero," and any pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC as currently CTEP-AERS recognizes this event as a patient death.

  A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.,* radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

## 16.0 REFERENCES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## APPENDIX I IDEAL BODY WEIGHT TABLE FOR CORRECTED BODY WEIGHT FORMULA

| | Height (Feet/Inch) | Small Frame (kg) | Medium Frame (kg) | Large Frame (kg) |
|---|---|---|---|---|
| MEN | | | | |
| | 5’2” | 54 | 59 | 64 |
| | 5’3” | 56 | 60 | 65 |
| | 5’4” | 57 | 62 | 67 |
| | 5’5” | 59 | 63 | 69 |
| | 5’6” | 60 | 65 | 71 |
| | 5’7” | 62 | 67 | 73 |
| | 5’8” | 64 | 69 | 75 |
| | 5’9” | 66 | 71 | 77 |
| | 5’10” | 68 | 73 | 79 |
| | 5’11” | 70 | 75 | 81 |
| | 6’0” | 72 | 77 | 84 |
| | 6’1” | 74 | 79 | 86 |
| | 6’2” | 76 | 82 | 88 |
| | 6’3” | 78 | 84 | 90 |
| | 6’4” | 79 | 86 | 93 |
| WOMEN | | | | |
| | 4’10” | 45 | 49 | 54 |
| | 4’11” | 46 | 50 | 55 |
| | 5’0” | 47 | 51 | 57 |
| | 5’1” | 49 | 53 | 58 |
| | 5’2” | 50 | 54 | 59 |
| | 5’3” | 51 | 55 | 61 |
| | 5’4” | 53 | 57 | 63 |
| | 5’5” | 54 | 59 | 64 |
| | 5’6” | 56 | 61 | 66 |
| | 5’7” | 58 | 63 | 68 |
| | 5’8” | 59 | 65 | 70 |
| | 5’9” | 61 | 67 | 72 |
| | 5’10” | 64 | 69 | 74 |
| | 5’11” | 65 | 70 | 76 |
| | 6’0” | 67 | 72 | 79 |

## APPENDIX II PERFORMANCE STATUS CRITERIA

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |