

IIT2012-03-Lill-DRBEAT
A Phase IIA Study of the Addition of Temozolomide
to a Standard Conditioning Regimen for
Autologous Stem Cell Transplantation in Relapsed and Refractory Central
Nervous System (CNS) Lymphoma
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11/21/2016	Amendment to eligibility criteria and procedures

Principal Investigator Signature

Date

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PROTOCOL SYNOPSIS

Title:

A Phase IIA Study of the Addition of Temozolomide to a Standard Conditioning Regimen for Autologous Stem Cell Transplantation in Relapsed and Refractory Central Nervous System (CNS) Lymphoma

Study Design:

This is a Phase IIA, single institution trial with therapeutic intent to evaluate the safest and most efficacious dose of temozolomide when incorporated into a conditioning regimen (DRBEAT) for autologous hematopoietic stem cell transplant for relapsed or refractory primary central nervous system B cell lymphomas (PCNSL).

Patients who have relapsed or are refractory after therapy would be referred for stem cell evaluation and enrolled in this intent-to-treat, single-arm, prospective study. These referred patients would receive an open-ended induction therapy (to be determined in consultation between the referring physician and the study consultants). Subsequently, imaging would be obtained on the brain (MRI unless contraindicated) to assess response to induction therapy. The CNS imaging would also allow for determination of baseline prior to beginning the transplant regimen. In addition, neurocognitive testing will be performed to evaluate any effects from transplantation on neurologic function. The conditioning regimen would involve the use of chemotherapy already employed in lymphoma and, in many cases, transplantation. The patients who have responded would then receive the transplant.

Over the course of patient follow-up and therapy, toxicities will be evaluated, particularly as the investigators will be assessing the target dose of temozolomide. Overall, the major criteria for a dose-limiting toxicity (DLT) for this study will be any grade 3 or 4 nonhematologic toxicity from a list of commonly expected toxicities associated with autologous transplantation and temozolomide. The major DLT of temozolomide has been noted to be grade 4 hematologic toxicity. Grade 4 hematologic toxicity, defined by neutropenia of $<0.5 \times 10^9/L$ (along with febrile neutropenia) and thrombocytopenia $<25.0 \times 10^9/L$ is an expected outcome in all patients undergoing stem cell transplantation. Therefore, grade 4 hematologic toxicities lasting longer than 3 weeks for neutropenia (and febrile neutropenia) or 4 weeks for thrombocytopenia will also be used as a DLT in the context of this study. The investigators will evaluate all other grade 4 toxicities as per the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Accrual Goal and Expected Time Period:

The target accrual for this study is 20 patients over approximately over a 7-year period. Subjects will be considered off study once all follow up has been completed or one year after enrollment of the last subject, whichever come first.

Summary of Eligibility Criteria:

Patients ≥ 18 years of age and ≤ 75 years of age with PCNSL (based on World Health Organization (WHO)) criteria with relapse following therapy for primary CNS B cell lymphoma or refractory disease in spite of therapy for CNS lymphoma or has developed secondary B cell CNS lymphoma. These patients must be fit for autologous stem-cell transplantation.

Specific Aim:

The aim of this Phase IIA trial is to determine an effective and safe dose of temozolomide orally administered to patients with relapsed primary CNS lymphoma over the 5 days preceding autologous stem-cell transplantation.

Treatment Description:

Currently a standard regimen for autologous stem cell transplantation in B cell lymphomas is the RBEAM regimen which incorporates rituximab (R), BCNU (B), etoposide (E), Ara-C (A) and melphalan (M) as a conditioning regimen prior to Autologous Peripheral Blood Stem Cell Transplant (PBSCT). We plan to study the DRBEAT regimen. The D represents decadron, a steroid which is used as a standard pre-medication in the RBEAM regimen. The D is simply added to the name. The main difference between the RBEAM regimen and the DRBEAT regimen will be the replacement of melphalan with temozolomide. Temozolomide will be given as a daily dose over five days starting on D -5 of the Autologous PBSCT. A dose escalation design will be used to determine the target dose for this study.

Statistical Considerations:

Kaplan-Meier estimates of progression-free survival and overall survival which will be compared with the historical average of our clinical population, estimated at 41.1 months and 18.3 months, respectively will be used to determine efficacy.¹ The safest dose will be defined to be the dose level of temozolomide that when administered to a patient results in a 40% probability that a dose limiting toxicity of non-hematological \geq Grade 3 toxicities or a Grade 4 hematological toxicity (as per the CTCAE) will be manifest within 3 weeks post transplantation (this study will allow for 4 weeks for platelet counts $<25,000/\text{ul}$ as they tend to recovery more slowly than neutrophils). The dose escalation will follow a Bayesian method permitting precise determination of the therapeutic working-dose while directly controlling the likelihood of an overdose. The method, known as EWOC (Escalation With Overdose Control), is the first dose-finding procedure to directly incorporate the ethical constraint of minimizing the chance of treating patients at unacceptably high doses.

Abstract:

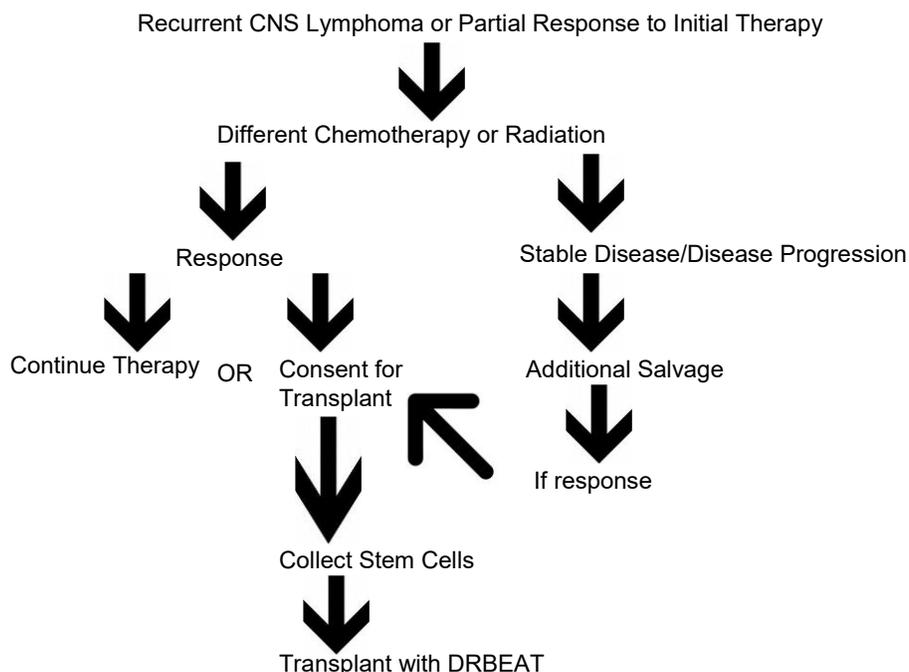
Currently there is no standard of care for relapsed primary central nervous system (CNS) lymphoma. After high-dose methotrexate or radiation therapy, the best approach to relapsed disease is undefined. Autologous stem cell transplantation is considered an effective therapy for relapsed disease. We commonly use the regimen RBEAM as a conditioning regimen in this patient population prior to transplantation. The melphalan used in this combination is not thought to have much CNS penetration. Temozolomide, an alkylating agent known to penetrate the CNS and approved by the FDA for brain tumors is used periodically for relapsed/resistant CNS lymphomas. We plan to evaluate the role of temozolomide in conjunction with high-dose chemotherapy/autologous stem-cell transplantation in relapsed primary CNS lymphoma, refractory primary CNS B-cell lymphoma, and secondary CNS B-cell lymphoma. The hope is that the conditioning regimen we will call DRBEAT will significantly improve the survival of patients with relapsed CNS lymphoma.

Patients who have relapsed or are refractory PCNSL after therapy or have systemic B cell lymphoma with relapse involving the CNS would be referred for stem cell evaluation and offered participation in this single-arm, prospective study. Referred patients will receive an open-ended induction therapy (to be determined in consultation between the referring physician and the study consultants). Subsequently, imaging would be obtained on the brain (MRI unless contraindicated) to assess response to induction therapy. The CNS imaging would also allow for determination of baseline disease prior to beginning the transplant regimen. The conditioning regimen would involve the use of chemotherapy already employed in lymphoma and, in many

cases, transplantation. Currently a standard regimen for autologous stem cell transplantation in B cell lymphomas is the RBEAM regimen which incorporates rituximab (R), BCNU (B), etoposide (E), Ara-C (A) and melphalan (M). We plan to study the DRBEAT regimen. The D represents decadron, a steroid already used as a premedication in the RBEAM regimen. The D is simply added to the name. The main difference between the RBEAM regimen and the DRBEAT regimen will be the replacement of melphalan, which is not thought to have much CNS penetration, with temozolomide, an alkylating agent known to penetrate the CNS, approved by the FDA for brain tumors, and used periodically for relapsed/resistant CNS lymphomas.

The goal of this study will be to determine the efficacy of DRBEAT and the safest dose for temozolomide for this DRBEAT regimen. Efficacy will be assessed by analysis of one-year progression-free and overall survival. Safety will be assessed using a dose escalation design for temozolomide's use to determine the target dose and also to evaluate any and all acute treatment related toxicities. During the course of patient follow-up and therapy, toxicities will be evaluated, particularly as the investigators will be determining the target dose of temozolomide. Overall, one of the major criteria for dose-limiting toxicity (DLT) for the study will be any Grade 3 or 4 non-hematologic toxicity from a list of commonly expected toxicities associated with autologous transplantation and temozolomide. The major DLT of temozolomide has been noted to be Grade 4 hematologic toxicity. Grade 4 hematologic toxicity, defined by neutropenia of $<0.5 \times 10^9/L$ (along with febrile neutropenia) and thrombocytopenia $<25.0 \times 10^9/L$ is an expected outcome in all patients undergoing stem cell transplantation. Therefore, Grade 4 hematologic toxicities lasting longer than 3 weeks for neutropenia (and febrile neutropenia) or 4 weeks for thrombocytopenia will be used as a DLT in the context of this study. The investigators will evaluate all other Grade 4 toxicities as per the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

SCHEMA



LIST OF ABBREVIATIONS

AE	Adverse Event
ACS	American Cancer Society
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
Ara-C	Cytarabine
ASCT	Autologous Stem Cell Transplantation
BBB	Blood Brain Barrier
BCNU	Carmustine
BM	Bone Marrow
BSA	Body Surface Area
CBC	Complete Blood Count
CD20	B-cell marker (cluster of differentiation)
CD34	stem-cell marker (cluster of differentiation)
CHF	Congestive Heart Failure
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone chemo regimen
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Research
CMV	Cytomegalovirus
CNS	Central Nervous System
CNSL	Central Nervous System Lymphoma
CR	Complete Remission
CRF	Case Report Form
CSMC	Cedars-Sinai Medical Center
CT	Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAH	Diffuse Alveolar Hemorrhage
DLBCL	Diffuse Large B Cell Lymphoma
DLT	Dose Limiting Toxicity
DFS	Disease-Free Survival
DMSO	Dimethyl Sulfoxide
DRBEAT	Dexamethasone, rituximab, BCNU, etoposide, Ara-C, temozolomide transplant conditioning regimen
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr Virus
EFS	Event-Free Survival
EORTC	European Organization for Research and Treatment of Cancer
EWOC	Escalation With Overdose Controls
FCR	Fludarabine, Cyclophosphamide, Rituximab
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GBM	Glioblastoma Multiforme
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte-Macrophage colony stimulating factor
GI	Gastrointestinal
HBV	Hepatitis B Virus
HCT	Hematopoietic Cell Transplantation

HCT-CI	Hematopoietic Cell Transplantation Comorbidity Index
HL	Hodgkin's Lymphoma
HIV	Human Immunodeficiency Virus
HTLV	Human T-Lymphotropic Virus
HSV	Herpes Simplex Virus
IL11	Interleukin 11
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention to Treat
IV	Intravenous
IVPB	Intravenous Piggy-Back
JCO	Journal of Clinical Oncology
LDH	Lactate Dehydrogenase
LH	Luteinizing Hormone
MD	Medical Doctor
MDS	Myelodysplastic Syndrome
MI	Myocardial Infarct
M1-M6	Classifications for acute myelogenous leukemia
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MTX	Methotrexate
NCIC	National Cancer Institute of Canada
NHL	Non-Hodgkin's Lymphoma
NRM	Non-Relapse Mortality
OS	Overall Survival
PO	(Per) Oral
PBSC	Peripheral Blood Stem Cell
PCNSL	Primary Central Nervous System Lymphoma
PD	Progressive Disease
PFS	Progression Free Survival
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Remission
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RCHOP	Rituximab, Cyclophosphamide, Adriamycin, Vincristine, Prednisone
RCVP	Rituximab, Cyclophosphamide, Vincristine, Prednisone
RN	Registered Nurse
RROT	Regimen Related Organ Toxicities
SAE	Serious Adverse Event
SCOEPS	Safety Committee On Early Phase Studies
SD	Stable Disease
SOP	Standard Operating Procedure
TLS	Tumor Lysis Syndrome
TMA	Thrombotic Microangiopathy
TRM	Transplant-Related Mortality
TSH	Thyroid Stimulating Hormone
VOD	Venoocclusive Disease
VZV	Varicella Zoster Virus
WBRT	Whole Brain Radiotherapy

DEFINITIONS

Disease-Free Survival (DFS): The time interval between the date of attaining a first complete remission and the date of relapse. Deaths not associated with relapse will be censored at the date of death. Incomplete data resulting from patients who are lost to follow-up will be censored at the date they were last known to be alive. Patients who have not died prior to study termination will be censored at the latest date known to be alive.

Dose Limiting Toxicity (DLT): Please see a more detailed discussion in Section 4.5.2.

Event-Free Survival (EFS): The time from diagnosis to tumor relapse, progression, or death and acute treatment related toxicity.

Enrollment: When a patient has signed informed consent, the study site has confirmed the eligibility of the patient, and the Screening and Enrollment Case Report Forms have been sent and approved by the study Coordinator at the Coordinating Center.

Non-Relapse Mortality: Death that occurs after therapy, from any cause except a cause associated with relapse.

Overall Survival (OS): The time interval between the date of transplant in the study and the date of death from any cause. Incomplete data resulting from patients who are lost to follow-up will be censored at the date they were last known to be alive. Patients who have not died prior to study termination will be censored at the latest date known to be alive.

Progression-Free Survival (PFS): The time interval between the date of attaining the maximal response to therapy prior to initiation of experimental therapy (DRBEAT) and the date of progression or renewed growth of disease. Incomplete data resulting from patients who are lost to follow-up will be censored at the date they were last known to be alive. Patients who have not died prior to study termination will be censored at the latest date known to be alive.

Target Dose: The dose at which the probability of a DLT is $\leq 40\%$. It will be determined by an adaptive dose-finding design described in Section 6 of this protocol.

Transplant-Related Mortality: Death that occurs within 3 months post-transplant, from any cause except a cause associated with relapse.

1. OBJECTIVES

The goal of this study is to determine an effective and safe dose of temozolomide to incorporate into the DRBEAT regimen. Efficacy of DRBEAT will be determined by:

- 1) One-year progression-free survival, defined as the time interval from maximal response from therapy to tumor re-growth, progression, or death.
- 2) Overall survival, defined as the time interval between the date of transplant and the date of death from any cause.

An adaptive dose escalation design will be used to determine the target dose for temozolomide. All acute treatment related toxicities will be described.

2. BACKGROUND

2.1 Primary Central Nervous System Lymphomas (PCNSL)

PCNSLs are lymphomas that arise within the brain, eyes, leptomeninges, or spinal cord in the absence of systemic lymphoma.² They make up 1% of Non-Hodgkin lymphomas (NHL) and 3-5% of primary brain tumors. Patients with an immunocompromised immune system tend to have a higher incidence of PCNSL but PCNSL may affect immunocompetent patients as well. Over the past 20 years, Cedars-Sinai Medical Center has seen 195 cases of CNS lymphoma for an average of approximately 10 a year. In 2008, 11 cases of CNS lymphoma were seen and treated at the institution (internal data). The incidence of the disease lends itself to seeking better modalities of therapy here at our institution but also in the medical community as a whole.

Approximately 20-30% of CNS lymphoma cases are cured. Over the years, the modality of therapy has evolved. Whole-brain radiotherapy (WBRT) had been the recommended therapy for PCNSL for decades. However, due to toxicity concerns and the goal of improving survival, chemotherapeutic agents have been used as well. More recently, high-doses methotrexate (MTX), a chemotherapeutic agent with known capability in penetrating the blood-brain barrier (BBB), has been used both alone and in combination with WBRT. Excellent results have been achieved with complete response rates ranging from 29-81%.

2.2 Hematopoietic Cell Transplants (HCT, also known as High-Dose Chemotherapy) for PCNSL

Despite the efficacy of MTX and WBRT, relapses still occur. One of the modalities of therapy used for relapsed PCNSL has been autologous stem cell transplantation (ASCT). ASCT incorporates the storage of a patients' hematopoietic stem cells (HSC). Patients then receive extremely high doses of chemotherapy that would otherwise not have been given due to concerns that pancytopenia would develop and persist for months, resulting in high risk of death. However, in ASCT, patients' stored HSCs are re-infused to allow for rapid blood count recovery. This strategy is employed for several malignancies including relapsed lymphomas, leukemias, and germ cell tumors. ASCT is considered standard-of-care therapy for relapsed and refractory diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma (HL). Long term complete remission rates in DLBCL and HL may approach 50%.

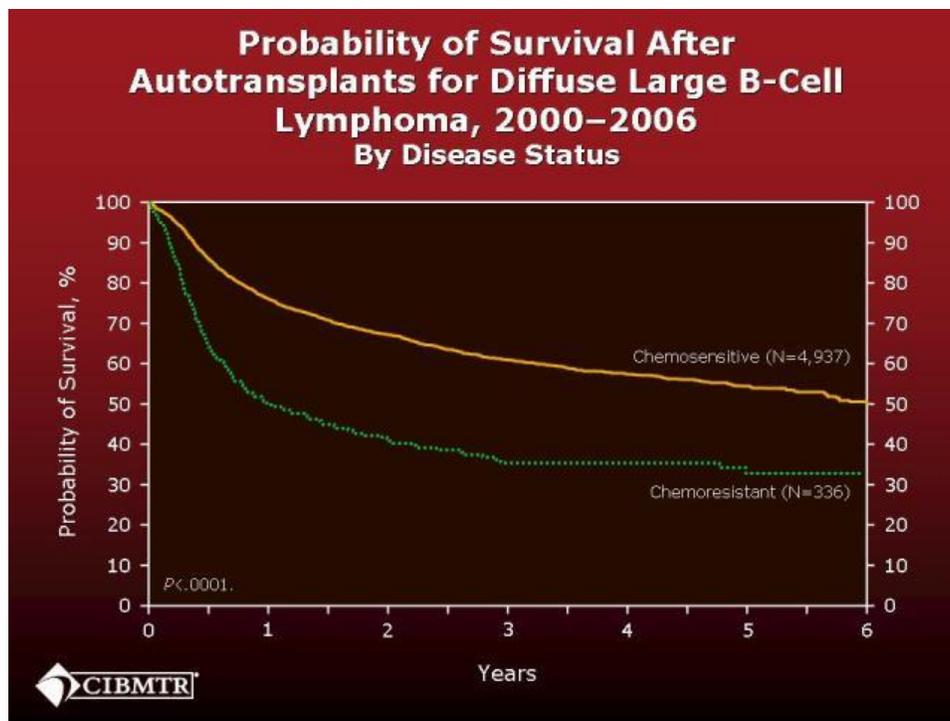
ASCT has been studied as well for PCNSL. The rationale is that higher doses of chemotherapy are better able to penetrate the BBB. Several combinations of chemotherapy for ASCT have been investigated. These include:

- 1) Cytarabine-Etoposide (CYVE) as induction/salvage therapy followed by Thiotepa, Busulfan, and Cyclophosphamide (TBC) as consolidation for ASCT. Phase I study results had 26/27 patients achieving complete response (CR). Median progression free survival (PFS) was 41 months and overall survival (OS) was 58 months. This regimen was for refractory/relapsed disease.³⁻⁴

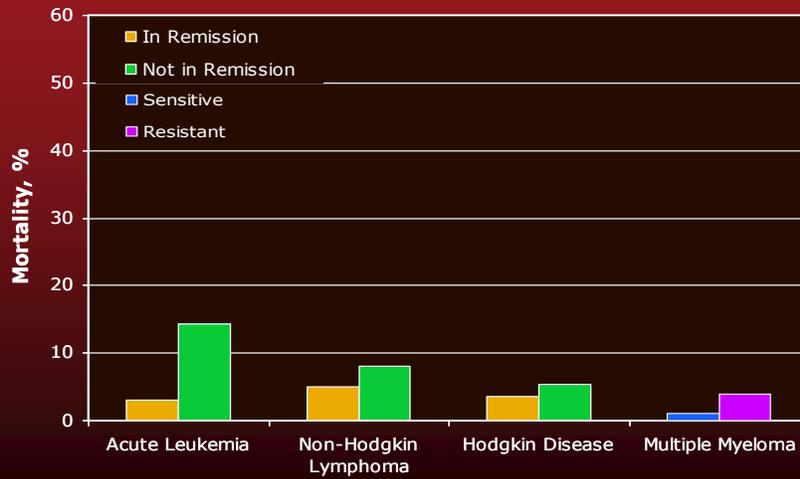
- 2) MTX-based induction chemotherapy followed by ASCT using the BEAM conditioning protocol (BCNU, etoposide, cytarabine, and melphalan) or thiotepa-based conditioning. These studies had favorable results but some incorporated WBRT, confounding the impact ASCT may have had on response.
- 3) MTX-cytarabine followed by BEAM.⁵
- 4) MVBP-based (methotrexate, etoposide, carmustine, and methylprednisolone) induction chemotherapy. If complete or partial response, this was followed by BEAM.⁶

Based on results from these studies, autologous hematopoietic stem cell transplantation may be considered a standard-of-care option for patients with relapsed or refractory primary CNS lymphomas.

The question of which transplant conditioning regimen is best for CNS lymphomas is difficult to determine without head-to-head studies. However, the above noted regimens do not include new therapies that have been developed within the past decade. We plan to use two such therapies in a combination conditioning regimen called DRBEAT. The “D” represents dexamethasone, which is already given as a premed for various chemotherapeutic agents in “BEAM.” The “R” represents rituximab and the “T” represents temozolomide. Our study design will be to dose escalate temozolomide to find an effective and safe dose within the context of the transplant regimen DRBEAT.



100-day Mortality after Autologous Transplantation, 2004-2005



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2.3 Autologous Transplant Conditioning Regimen Rationale:

2.3.1 The BEAM Regimen

Autologous stem cell transplants have been performed for relapse/refractory lymphomas for over 30 years. One of the best-known, and most often used, regimens used as conditioning prior to re-infusing autologous stem cells is the BEAM regimen. The BEAM regimen was devised in the 1980s and due to its consistent efficacy across various studies and institutions; it has become one of the primary, standard conditioning regimens. The BEAM regimen consists of the following:

- 1) Carmustine (BCNU) given on day -6 prior to the re-infusion of stem cells at a dose of 300 mg/m² IVPB once infused over 2 hours
- 2) Etoposide given on day -5 to day -2 at a dose of 100 mg/m² IVPB over 2 hours every 12 hours for 8 doses total
- 3) Cytarabine (Ara-C) given on day -5 to day -2 at a dose of 200 mg/m² IVPB over 30 minutes every 12 hours for 8 doses total
- 4) Melphalan given on day -1 at a dose of 140 mg/m² IV push for one dose over 5 minutes.

Follow-up data from the initial BEAM study revealed excellent efficacy for relapsed/refractory disease.⁷ In this study, 107 patients with relapsed or resistant intermediate-/high-grade non-Hodgkin's lymphoma received BEAM followed by ABMT between 1981 to 1993. The 5-year overall survival and progression-free survival rates were 41% and 35% respectively. Patients with chemo-sensitive disease had a 5-year survival rate of 49% at 5 years compared to 13% for those with chemo-resistant disease. Mortality due to transplant-related complications was approximately 7% in this regimen although improvements in supportive care over the past 10-20 years have significantly improved mortality rate in the setting of autologous stem cell transplantation. Our mortality rate here at Cedars-Sinai for autologous transplants is <3%.

The PARMA study, published the same year as Mills' study confirmed the benefits of chemotherapy followed by high-dose chemotherapy (such as/similar to BEAM) and autologous stem cell transplantation/rescue compared to chemotherapy alone (but not high-dose chemotherapy).⁸ This randomized trial studying lymphoma patients with relapsed or refractory disease had a median follow-up time of 63 months. The response rate was 84 percent after bone marrow transplantation and 44 percent after chemotherapy without transplantation. At five years, rate of event-free survival was 46 percent in the transplant group and 12 percent in the group receiving chemotherapy without transplantation ($p = 0.001$), and the rate of overall survival was 53 and 32 percent, respectively ($p = 0.038$). This study cemented and firmly established the role of autologous stem cell transplantation in lymphoma and it is thus recognized as the next line of therapy for relapsed/refractory disease for both non-Hodgkin Lymphoma and Hodgkin Lymphoma in the most recent National Comprehensive Cancer Network (NCCN) guidelines.⁹

2.3.2 Use of BEA

The rationale for this study is to replace in the BEAM regimen melphalan with temozolomide (hence BEAT) and to add rituximab. Thus we must first demonstrate that that we are at least administering an efficacious myeloablative regimen and not under treating the patients in our study.

The BEA regimen has been used for further consolidation in acute myeloid leukemia (AML) for patients with core binding factor (CBF, a prognostic molecular marker) AML status post induction and consolidation. Nakasone et al were able to show the efficacy and tolerability of the BEA regimen.¹⁰ Fourteen AML patients received the autologous transplant. Results showed that 92.9% \pm 6.9% EFS for the 14 autologous patients. The five-year overall survival for the 14 patients was 100%. Neutrophil recovery was achieved at a median of 13 days (11-36 range). Platelet recovery of $>20,000/\text{ul}$ was achieved at a median 27.5 days (range 12-217 days) and to $>50,000/\text{ul}$ at a median of 4 months (range 15-378 days). Five autologous transplant patients had Varicella Zoster Virus (VZV) reactivation which all resolved with acyclovir. These infections occurred at a median of 130 days after autologous transplant (range 85-567 days). One case of myelodysplastic syndrome (MDS) occurred after an autologous transplant.

The BEA regimen was also used as a conditioning regimen for autologous hematopoietic stem cell transplantation for 60 patients with de novo AML (from M1-M6).¹¹ No patient had engraftment failure. The average day to granulocyte engraftment to $500/\text{ul}$ was 15 days (range 8-44 days) which was not affected by whether they received GCSF. Median time to last platelet transfusion (platelets were transfused up above $20,000/\text{ul}$) was 24 days (range 0-180 days). A total of 13 out of 60 (22%) continued to be platelet transfusion dependent for >3 months and 7 of these 13 (54%) relapsed within 5 months of transplantation.

Three and five year DFS in those transplanted in first remission was 78.6% and 70.7%, respectively. Median survival without relapse was 17 months (range 4-73 months). A total of 9 patients relapsed, 8 (89%) within 12 months of transplant. Median interval of remission was 5 months (range 3-13 months).

From the above data, one can see that BEA is tolerable and efficacious. Thus, using BEA as a base therapy would allow one to test the use of temozolomide in a dose-dense fashion via dose escalation, knowing that at least a minimum level of efficacy is being obtained against the PCNSL via the BEA autologous transplant conditioning regimen.

2.4 Rituximab Use as Part of HCT Regimen for PCNSL

2.4.1 Adding Rituximab to BEAM:

Rituximab is a monoclonal antibody that targets CD20 positive cells. It is routinely used in all B cell lymphomas that express CD20 on the cell surface. The use of rituximab was established in the late 1990's. A landmark therapeutic study published in the New England Journal of Medicine firmly established rituximab's survival benefit.¹² "Previously untreated patients with diffuse large-B-cell lymphoma, 60 to 80 years old, were randomly assigned to receive either eight cycles of CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) every three weeks (197 patients) or eight cycles of CHOP plus rituximab given on day 1 of each cycle (202 patients)." Complete response rate was significantly higher in the group that received CHOP plus rituximab than in the group that received CHOP alone (76 percent vs. 63 percent, $p = 0.005$). Event-free and overall survival times were significantly higher in the CHOP-plus-rituximab group ($p < 0.001$ and $p = 0.007$, respectively) with a median follow-up of two years. The addition of rituximab to standard CHOP chemotherapy significantly reduced the risk of treatment failure and death (risk ratios, 0.58 [95% CI: 0.44, 0.77] and 0.64 [95% CI: 0.45, 0.89], respectively). Clinically relevant toxicity was not significantly greater with CHOP plus

rituximab. The conclusion from this study was that the addition of rituximab to the CHOP regimen increases the complete-response rate and prolongs event-free and overall survival in elderly patients with diffuse large-B-cell lymphoma, without a clinically significant increase in toxicity.

Rituximab is now included as part of the BEAM conditioning regimen (hence RBEAM) in all of Cedars-Sinai's transplant regimens for B cell lymphomas expressing CD20. Rituximab is routinely used in nontransplant settings as well. It is combined with CHOP for diffuse large B-cell lymphoma, RCVP (rituximab, cyclophosphamide, vincristine, and prednisone) for low-grade or follicular lymphomas, FCR (fludarabine, rituximab, and cyclophosphamide) for CLL, and so forth.

2.4.2 Use of Rituximab for CNS Lymphomas:

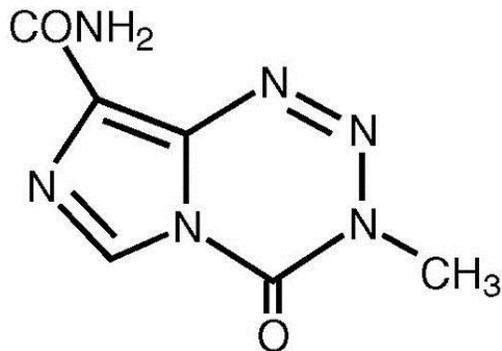
The utility of rituximab in diffuse large B-cell lymphomas is well known. Its use and efficacy in CNS B cell lymphomas has also been documented. Rituximab's use in CNS lymphoma was noted at the 2000 meeting of the American Society of Clinical Oncology.¹³ This study was the first to use rituximab as a single agent in refractory PCNSL. Rituximab was measurable within the CNS and radiographic evidence of response was noted in patients. Rituximab has also been administered intraventricularly. Rituximab was injected into an Ommaya reservoir and cytologic responses were observed, some even complete.¹⁴

The next natural extension was the use of rituximab in combination with other agents in refractory CNS lymphomas. This has occurred in combination with temozolomide, the use of which in CNS lymphomas will be discussed below. Wong and his colleagues at Harvard have demonstrated the efficacy of combination rituximab and temozolomide in PCNSL as has Memorial Sloan-Kettering Cancer Center.¹⁵⁻¹⁶ In the Enting paper, 53% of patients with recurrent or refractory PCNSL had an objective response rate to the combination of rituximab and temozolomide. All patients in Wong's study exhibited at least a partial response.

2.5 Use of Temozolomide and the Use of Temozolomide for CNS lymphomas

2.5.1 Background on Temozolomide:

TEMODAR is an alkylating agent and chemotherapeutic drug that contains temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of C₆H₆N₆O₂ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5) and labile at pH >7; hence TEMODAR can be administered orally and intravenously. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazene-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Information on temozolomide formulation from Prescriber information:

TEMODAR Capsules: Each capsule for oral use contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide.

The inactive ingredients for TEMODAR Capsules are as follows:

TEMODAR 5 mg: lactose anhydrous (132.8 mg), colloidal silicon dioxide (0.2 mg), sodium starch glycolate (7.5 mg), tartaric acid (1.5 mg), and stearic acid (3 mg).

TEMODAR 20 mg: lactose anhydrous (182.2 mg), colloidal silicon dioxide (0.2 mg), sodium starch glycolate (11 mg), tartaric acid (2.2 mg), and stearic acid (4.4 mg).

TEMODAR 100 mg: lactose anhydrous (175.7 mg), colloidal silicon dioxide (0.3 mg), sodium starch glycolate (15 mg), tartaric acid (3 mg), and stearic acid (6 mg).

TEMODAR 140 mg: lactose anhydrous (246 mg), colloidal silicon dioxide (0.4 mg), sodium starch glycolate (21 mg), tartaric acid (4.2 mg), and stearic acid (8.4 mg).

TEMODAR 180 mg: lactose anhydrous (316.3 mg), colloidal silicon dioxide (0.5 mg), sodium starch glycolate (27 mg), tartaric acid (5.4 mg), and stearic acid (10.8 mg).

TEMODAR 250 mg: lactose anhydrous (154.3 mg), colloidal silicon dioxide (0.7 mg), sodium starch glycolate (22.5 mg), tartaric acid (9 mg), and stearic acid (13.5 mg).

TEMODAR® (temozolomide) Capsules, TEMODAR® (temozolomide) for Injection TEMODAR® (temozolomide) Capsules, TEMODAR® (temozolomide) for Injection

The body of the capsules are made of gelatin, and are opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, and ferric oxide.

TEMODAR 5 mg: The green cap contains gelatin, titanium dioxide, iron oxide yellow, sodium lauryl sulfate, and FD&C Blue #2.

TEMODAR 20mg: The yellow cap contains gelatin, sodium lauryl sulfate, and iron oxide yellow.

TEMODAR 100 mg: The pink cap contains gelatin, titanium dioxide, sodium lauryl sulfate, and iron oxide red.

TEMODAR 140 mg: The blue cap contains gelatin, sodium lauryl sulfate, and FD&C Blue #2.

TEMODAR 180 mg: The orange cap contains gelatin, iron oxide red, iron oxide yellow, titanium dioxide, and sodium lauryl sulfate.

TEMODAR 250mg: The white cap contains gelatin, titanium dioxide, and sodium lauryl sulfate.

For this proposed study, the investigators plan to initiate the study with the PO formulation. There is however the possibility of subsequently transitioning in the future to the IV formulation of temozolomide (see Appendix C). Each vial of temozolomide contains 100 mg of sterile and pyrogen-free temozolomide lyophilized powder for intravenous injection. The inactive ingredients are: mannitol (600 mg), L-threonine (160mg), polysorbate 80 (120mg), sodium citrate dihydrate (235mg), and hydrochloric acid (160mg).¹⁷

2.5.2 Clinical Experience of Temozolomide:

Early studies showed that temozolomide could penetrate the CSF. One of the earliest experiences of temozolomide with CNS malignancies was in its use against glioblastoma (GBM) as well as anaplastic astrocytoma. A pilot trial studying 2002 combined temozolomide and radiation in newly diagnosed GBM patients after maximal surgical debulking. Due to encouraging results in phase II studies, a large randomized phase III therapeutic study by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) was initiated. Almost 600 patients were randomized to radiation alone or temozolomide and concomitant radiation followed by maintenance temozolomide. Median survival in the combined modality group was 15 months compared to 12 months for radiation alone.¹⁸ Based on

these results, combined-modality therapy incorporating radiation with temozolomide became the standard-of-care therapy for GBM.¹⁹

Because of temozolomide's efficacy in penetrating the CNS in GBM, the natural progression of thought was what its role could be in CNS lymphomas. As noted earlier, initial therapy for PCNSL consists of chemotherapy with a high-dose methotrexate based regimen or whole brain radiation with the chemotherapy based regimens becoming more of the initial option in patients. This is based on data from numerous studies, one of which was published in the Journal of Clinical Oncology in 2003.²⁰

Use of temozolomide alone in patients with recurrent PCNSL has shown reasonable response rates (31%) with minimal toxicity, primarily hematologic. The combination of temozolomide with rituximab as noted above has been noted to be efficacious with tolerable toxicity as well.

2.5.3 Clinical Experience of Temozolomide dosing

The determination of an effective and safe dose of temozolomide is the objective of this study. The starting dose has been determined based on published studies. Normally in GBM therapy, temozolomide is administered at 75 mg/m² daily for 42 days concomitant with focal radiotherapy (RT; 60 Gy administered in 30 fractions) followed by maintenance temozolomide for 6 cycles. Focal RT includes the tumor bed or resection site with a 2- to 3-cm margin. No dose reductions are recommended during the concomitant phase in GBM therapy; however, dose interruptions or discontinuation may occur based on toxicity. The temozolomide dose is normally continued throughout the 42-day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, common toxicity criteria (CTC) nonhematological toxicity \leq Grade 1 (except for alopecia, nausea, and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing is interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria.

Four weeks after completing the temozolomide plus radiation phase, temozolomide is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m² once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose can be escalated to 200 mg/m², if the CTC nonhematologic toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea, and vomiting), and absolute neutrophil count (ANC) is $\geq 1.5 \times 10^9/L$, and the platelet count is $\geq 100 \times 10^9/L$. The dose remains at 200mg/m² per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Thus the maximum recommended dose of temozolomide is 200 mg/m² per day for 5 days for a total dose over the 5 day period of 1000 mg/m².

Doses of 500, 750, 1000, and 1250 mg/m² (administered as a single dose) have been evaluated clinically in patients.⁴²⁻⁴⁴ Other doses have been studied as well by the manufacturers in their initial studies on the drug: "Dose-limiting toxicity was hematologic and was reported with any dose but is expected to be more severe at higher doses. An overdose of 2000 mg per day for 5 days was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia, multi-organ failure, and death. There are reports of patients who have taken more than 5 days of treatment (up to 64 days), with adverse reactions reported including bone marrow suppression, which in some cases was severe and prolonged, and infections and resulted in death." (from Temodar package insert)

The study from Rudek et al from 2004 used temozolomide in a dose escalation study for solid tumors. They started at 500 mg/m² administered as a single dose every 28 days. Neutropenia and thrombocytopenia were the dose limiting toxicities at 1000 mg/m² once every 28 days. Thus, Rudek et al felt the MTD was 750 mg/m² once per cycle. In another study, doses were escalated as well, and it was determined that 300 mg/m²/day for 3

consecutive days (900 mg/m² total) was the maximum tolerated dose due to myelosuppression as the dose limiting toxicity.⁴³ Dhodapkar's group noted an MTD of 250 mg/m²/day for 5 days which equals 1250 mg/m² total for a cycle of therapy. The DLT again was hematologic.⁴⁴ Thus all these data seem in line with a MTD of around 1250 mg/m² as a potential starting point for our study.

We also obtained data from the manufacturers via the Investigator's Brochure which was initially submitted to the FDA to obtain an investigational new drug approval (IND) for use in brain tumors. The data from this brochure available via the company and available to the FDA via the initial application for FDA approval of temozolomide, provides additional support for dosing rationale. (Investigator's brochure). The brochure cites a phase 2 SPRI study (C93-169) that the DLT of temozolomide occurred at 1000 mg/m² administered as a single dose for two subjects and the DLT was hematologic.

The starting dose given over five days (days -5 to -1 prior to stem cell reinfusion) for our proposed study should at least be equal to a total of 1250 mg/m² (250mg/m² per day x 5 days). The rationale for this is that hematologic toxicity should not factor as a dose limiting toxicity in our proposed study as this is an expected and anticipated side effect of high dose chemotherapy with stem cell rescue and Grade 4 hematologic toxicity should be rectified after the administration of the cryopreserved stem cells of the subjects in the study. Thus we are looking at a range of 250 mg/m² per day for 5 days (cumulative total dose of 1250 mg/m²) to start with but we cannot approach 1000 mg/m² per day for 5 days (cumulative total dose of 5000 mg/m²) as that resulted in multiorgan failure according to manufacturer data.

On February 27th, 2009, the FDA granted approval for intravenous temozolomide. The IV form was noted to be bioequivalent to the oral form when administered over 90 minutes. There was local irritation as the main adverse event of the infusions. The manufacturers performed randomized, multicenter studies confirming the bioavailability and bioequivalence of the PO and IV formulations which led to the IV formulation approval (Investigator brochure).

2.6 Replacement of Melphalan and Melphalan's Toxicities

The question arises regarding the replacement of melphalan for temozolomide. The primary reason for the replacement is CNS penetration. Initial studies in rats and rhesus monkeys showed that the levels of temozolomide in the brain and cerebrospinal fluid were approximately 30-40% of the plasma concentration.²¹ Data with human subjects have shown that with regard to temozolomide levels the ratio of CSF to plasma were 28-30%. Maximum CSF temozolomide concentrations were reached within 1-2 hours post-dose. Levels taken post doses on days 1 and 5 indicated lack of temozolomide accumulation.²² On the other hand, penetration of melphalan into the CSF is low, with a CSF to plasma concentration ratio up to 10%.²³ On the other hand, the other cytotoxic, traditional chemotherapeutic agents in the DRBEAT regimen have better CNS penetration. For example, cytarabine's ability to penetrate the CNS is certainly higher than melphalan with a reported CSF to plasma ratio ranging from 40-50% to as high as 76%.²⁴⁻²⁶ Etoposide's median CSF to plasma ratio has been noted as 30%.²⁷ BCNU's CSF to plasma ratio has been noted as high as 70%.²⁸ Thus it would appear that of all the agents to eliminate and replace in the BEAM regimen, melphalan would make the most logical sense, especially when factoring in toxicities as well.

The other major question is how much more toxic or less toxic temozolomide is compared to melphalan, the drug it is replacing in the transplant regimen. Both melphalan and temozolomide are categorized in the alkylating agent group. These agents tend to have similar toxicity profiles. Alkylating agents form molecular bonds with nucleic acids, proteins, and other molecules of low molecular weight. The alkylating agents are electrophiles or generate electrophiles in vivo to produce polarized molecules with positively charged regions which then interact with electron-rich regions of cellular molecules and act on DNA to produce their cytotoxic

effects. Alteration of coded DNA information results in inhibition of inaccurate replication of DNA causing mutation and cell death. There are several classifications of chemotherapeutic agents within the alkylating agent category. Melphalan is considered as nitrogen mustard derivative and is certainly not a benign drug.²⁹ Temozolomide is also an alkylating agent under the new category of alkylating agents known as the imidazotetrazines. Compounds in this group are structurally and functionally similar to DTIC (dacarbazine) which is in the alkylating agent category of the triazenes.²¹ Both agents have several side effects. Temozolomide is a reasonable replacement medication for CNS penetration reasons as noted above but also because of toxicity. It's toxicity in relation to melphalan is either relatively equal or even less toxic than melphalan and potentially more suitable in relation to its effects on the bone marrow. For example, because it does not result in chemical cross-linking of DNA strands, it is less toxic to the hematopoietic progenitor cells in the bone marrow than the nitrosureas (carmustine, lomustine), platinum compounds, and procarbazine, which do cross-link DNA.²¹ Melphalan has also been noted to cross-link DNA.³⁰ The overall themes of toxicity of the alkylating agents are as follows:³¹

- a) Inhibit hematopoiesis
- b) Suppress immune system
- c) Injure intestinal epithelium and gonadal tissue
- d) Epithelial pulmonary injury, pneumonitis, and pulmonary fibrosis
- e) Renal tubular injury and bladder toxicity
- f) Teratogenic and carcinogenic (such as leukemia).

The following data on melphalan is available from the FDA and the product label.

ADVERSE REACTIONS to MELPHALAN³²

Hematologic: The most common side effect is bone marrow suppression. White blood cell count and platelet count nadirs usually occur 2 to 3 weeks after treatment, with recovery in 4 to 5 weeks after treatment. Irreversible bone marrow failure has been reported.

Gastrointestinal: Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral ulceration occur infrequently. Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported. Hepatic veno-occlusive disease has been reported.

Hypersensitivity: Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving melphalan for Injection for myeloma. These reactions were characterized by urticaria, pruritus, edema, and in some patients, tachycardia, bronchospasm, dyspnea, and hypotension.

Miscellaneous: Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, vasculitis, alopecia, hemolytic anemia, allergic reaction, pulmonary fibrosis, and interstitial pneumonitis.

OVERDOSAGE

Overdoses resulting in death have been reported. Overdoses, including doses up to 290 mg/m², have produced the following symptoms: severe nausea and vomiting, decreased consciousness, convulsions, muscular paralysis, and cholinomimetic effects. Severe mucositis, stomatitis, colitis, diarrhea, and hemorrhage of the gastrointestinal tract occur at high doses (>100 mg/m²). Elevations in liver enzymes and veno-occlusive disease occur infrequently. Significant hyponatremia caused by an associated inappropriate secretion of ADH syndrome

has been observed. Nephrotoxicity and adult respiratory distress syndrome have been reported rarely. The principal toxic effect is bone marrow suppression.

Carcinogenesis: Secondary malignancies, including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating agents (including melphalan). Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantitation of the risk of acute leukemia, myeloproliferative syndrome, or carcinoma is not possible. Published reports of leukemia in patients who have received melphalan (and other alkylating agents) suggest that the risk of leukemogenesis increases with chronicity of treatment and with cumulative dose. In one study, the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome after oral melphalan therapy was 19.5% for cumulative doses ranging from 730 to 9,652 mg. In this same study, as well as in an additional study, the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome after oral melphalan therapy was less than 2% for cumulative doses under 600 mg. This does not mean that there is a cumulative dose below which there is no risk of the induction of secondary malignancy. The potential benefits from melphalan therapy must be weighed on an individual basis against the possible risk of the induction of a second malignancy. Adequate and well-controlled carcinogenicity studies have not been conducted in animals. However, intraperitoneal (IP) administration of melphalan in rats (5.4 to 10.8 mg/m²) and in mice (2.25 to 4.5 mg/m²) 3 times per week for 6 months followed by 12 months post-dose observation produced peritoneal sarcoma and lung tumors, respectively.

Mutagenesis: This is not as much an issue with the transplant patient population as we will be checking urine pregnancy tests and emphasizing the risk to babies. Melphalan has been shown to cause chromatin or chromosome damage in humans. Intramuscular administration of melphalan at 6 and 60 mg/m² produced structural aberrations of the chromatid and chromosomes in bone marrow cells of Wistar rats.

Impairment of Fertility: Melphalan causes suppression of ovarian function in premenopausal women, resulting in amenorrhea in a significant number of patients. Reversible and irreversible testicular suppression have also been reported. The other chemotherapies in a transplant regimen may impair fertility as well.

Pregnancy: This is not as much an issue with the transplant patient population as we will be checking urine pregnancy tests and emphasizing the risk to babies. Pregnancy Category D. Melphalan may cause fetal harm when administered to a pregnant woman. While adequate animal studies have not been conducted with IV melphalan, oral (6 to 18 mg/m²/day for 10 days) and IP (18 mg/m²) administration in rats was embryolethal and teratogenic. Malformations resulting from melphalan included alterations of the brain (underdevelopment, deformation, meningocele, and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the mandible and tail, as well as hepatocele (exomphaly). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

3. Eligibility Criteria

3.1 Informed Consent

Potential subjects will be informed about the study and given an opportunity to review the consent form at their leisure prior to making a decision regarding their participation. One of the study investigators will be available to meet with potential subjects to address any questions or concerns they may have about the study. In the consent conference, all potential risks associated with the use of chemotherapy will be discussed with the patient as objectively as possible.

Once all of their questions have been addressed and the individual is willing to participate in the study, one of the study investigators will obtain their informed consent.

An individual subject may potentially be withdrawn from the study if, for whatever reason, his or her safety or confidentiality is compromised.

Subjects may withdraw at any time if they so wish and this would not affect the quality or intent of their care.

3.2 Patient Inclusion Criteria

1. Patients ≥ 18 years of age and ≤ 75 years of age.
2. Patients must have CNS involvement with a mature B-cell Non-Hodgkin's Lymphoma, (WHO criteria)
3. Patients must meet one of the below criteria:
 - a. Patients who have achieved a CR or PR after initial therapy for CNS B-cell lymphoma.
or
 - b. Patients with relapsed or progressed disease following therapy for CNS B-cell lymphoma who have achieved a subsequent CR or PR following salvage chemotherapy
or
 - c. Patients who are initially refractory to therapy for CNS B-cell lymphoma but who have achieved a CR or PR following a salvage chemotherapy regimen
or
 - d. Patients who have developed a CNS relapse from systemic B-cell NHL, and have evidence of chemotherapy sensitive lymphoma.
4. Patients fit for autologous stem cell transplantation
5. Patients able to understand and willing to sign a written informed consent document.

3.3 Patient Exclusion Criteria

1. Patients whose life expectancy is severely limited by diseases other than malignancy.
2. Karnofsky Performance Score < 60
3. Patients who are pregnant or breastfeeding
4. Patients who are HIV seropositive.
5. Patients who have an uncontrolled infection (presumed or documented) with progression after appropriate therapy for greater than one month.

6. Patients with symptomatic coronary artery disease, uncontrolled congestive heart failure. Left Ventricular Ejection Fraction is not required to be measured, however if it is measured, patient is excluded if ejection fraction is <30%.
7. Patients requiring supplementary continuous oxygen. DLCO is not required to be measured, however if it is measured, patient is excluded if DLCO <35%.
8. Patients with clinical or laboratory evidence of liver disease will be evaluated for the cause of liver disease, its clinical severity in terms of liver function and histology, and for the degree of portal hypertension. Patients with any of the following liver function abnormalities will be excluded:
 - a. Fulminant liver failure.
 - b. Cirrhosis with evidence of portal hypertension or bridging fibrosis.
 - c. Alcoholic hepatitis.
 - d. Esophageal varices.
 - e. A history of bleeding esophageal varices.
 - f. Hepatic encephalopathy.
 - g. Uncorrectable hepatic synthetic dysfunction evidenced by prolongation of the prothrombin time.
 - h. Ascites related to portal hypertension.
 - i. Chronic viral hepatitis with total serum bilirubin >3 mg/dL.
 - j. Symptomatic biliary disease.
9. Patients with non-B-cell lymphomas or brain tumors that are not lymphomas are
 - i. Excluded from the study. Non-B-cell lymphomas include: any T-cell lymphoma,
 - ii. NK-cell lymphomas, and Hodgkin lymphomas.
10. Patients for whom an insufficient number of stem cells (<2 X 10⁶/kg) have been
 - i. collected

4.0 Trial Procedures

Procedures	Screening (up to 2 months prior):	Conditioning Phase Day:						Transplant Day: 0	Follow Up: (post-transplant date unless otherwise indicated)								
		-6	-5	-4	-3	-2	-1		Weekly (1-4 weeks <i>post- discharge</i>) ^a	Day 90-100	6m ^b	9m ^b	12m ^b	15m ^b	18m ^b	21m ^b	24m ^b
Complete Medical/Family and Menstrual History	X																
Review of Medical Records	X																
Physical Exam (including: measurements of weight, vital signs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Labs (including: CBC and Chemistry panel)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky status	X								X	X	X	X	X	X	X	X	X
HIV Testing	X																
Height	X																
MRI	X								X	X	X	X	X	X	X	X	X
PET/CT ^{cd}	X								X			X		X		X	X
Bone Marrow Biopsy	X																
Neurocognitive Testing ^e	X									X		X		X		X	X
Dexamethasone		X	X	X	X	X	X										
Rituximab		X															
BCNU (carmustine)		X															
Etoposide			X	X	X	X											
Ara-Cytarabine			X	X	X	X											
Stem Cell Transplant								X									
Informed consent	X																
Temozolomide			X	X	X	X	X										
Adverse Events ^f		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Post-progression Survival Status ^g																	X

^a Window is ± 2 days for weekly follow-up visits post-discharge (4 visits over 4 weeks).

^b Window for follow-up visit post-transplant is ± 30 days.

^c If a patient's history shows systemic involvement of the lymphoma, PET/CTs are required at the indicated time points. If patient only has primary CNS involvement, PET/CTs will only need to be done if clinically indicated by the treating physician.

^d This is the recommended schedule for PET/CTs in follow-up, however time points may vary depending on treating physician's assessment.

^e Neurocognitive testing is suggested to be performed prior to patients' induction therapy and again at screening prior to the study conditioning regimen. Neurocognitive testing prior to induction therapy is not required for study participation; however, this data will be collected if this test is performed. This test is not required during follow-up, but suggested to be collected at the appropriate time points if treating physician deems it necessary.

^f Only AEs graded 3 or 4 will be collected.

^g Subjects who progress will be followed for survival only. No other data will be collected.

4.1 Post induction Imaging and Determination of Response Including Definitions of Response

Please see section 4.7 for further details on response and imaging.

For the following sections in section 4 (4.2 and on) a large portion of the information delineated is modified from Standard Operating Procedures (SOP) of the Cedars-Sinai Medical Center Blood and Marrow Transplantation Service, authors primarily Dr. Stephen Lim, Dr. Yuliya Linhares, Dr. Ronald Paquette, Noah Merin, and Dr. Michael Lill.

<http://web.csmc.edu/resources/policies/bone/>

4.2 Determination of Candidacy for Transplantation

The determination of candidacy for transplantation will be determined based on recommended guidelines and standard operating procedures (SOP) formulated and written by Dr. Stephen Lim, Dr. Yuliya Linhares, Dr. Ronald Paquette, Noah Merin, and Dr. Michael Lill at Cedars-Sinai Medical Center.

4.3 Mobilization and Collection of Stem Cells

4.3.1 Background on Stem Cell Mobilization:

Background information on stem cell mobilization and procedures inherent in the process are delineated in full as part of the SOP formulated and written by Dr. Stephen Lim, Dr. Yuliya Linhares, Dr. Ronald Paquette, and Noah Merin, and Dr. Michael Lill at Cedars-Sinai Medical Center.

4.3.2 Stem Cell Collection Goals

The optimal target CD34 cell dose is $\geq 5 \times 10^6$ CD34 positive cells/kg of recipient weight. The minimal CD34 cell dose is 2×10^6 CD34 cells/kg.

The rare cases that do not achieve goal stem cell collection levels will be discussed on a case-by-case basis at the transplant committee meeting each week. Remobilization may be performed with the addition of plerixafor (Mozobil) to increase the likelihood of obtaining the target dose.

4.3.3 Preprocedure

Stem cell transplantation preparation will occur as per institutional standards.

4.4 Schedule of DRBEAT regimen and Temozolomide Dosing

4.4.1 DRBEAT Scheduling

Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0
Outpatient	Inpatient					
APAP: 650mg PO Diph: 25mg IV Dex: 10mg IV Rituxan IV	Dexamethasone- 20mg IVPB daily x 6 doses (Day -6 thru -1) as part of the regimen Rituximab-375mg/m2 IVPB once (Day -6) BCNU (Carmustine)-300mg/m2 IV over 2hr once (Day -6) Etoposide (VP-16- 100mg/m2 IV over 2hr q12hr x8 doses (Day -5 thru -2) ARA-C (Cytarabine)-200mg/m2 IV over 30min q12hr x8 doses (Day -5 thru -2) Temozolomide- Modified mg/m2 <u>per protocol</u> PO daily x5 doses(Day -5 thru -1)					Autologous Transplant
	Dex: 10mg IV Ond: 8mg IV	Investigational study medication: Temozolomide --Modified mg/m2 per protocol **Every patient will have a different modified dose assigned**				
	Carmustine IV					
	Dex: 20mg IV Ond: 8mg IV	Dex: 20mg IV Ond: 8mg IV	Dex: 20mg IV Ond: 8mg IV	Dex: 20mg IV Ond: 8mg IV	Dex: 20mg IV Ond: 8mg IV	
	Temozolomide PO	Temozolomide PO	Temozolomide PO	Temozolomide PO	Temozolomide PO	
	HOLD Breakfast until 2 hours after Temozolomide administration					
	Etoposide IV	Etoposide IV	Etoposide IV	Etoposide IV		
	ARA-C IV	ARA-C IV	ARA-C IV	ARA-C IV		
	Ond: 8mg IV	Ond: 8mg IV	Ond: 8mg IV	Ond: 8mg IV		
	Etoposide IV	Etoposide IV	Etoposide IV	Etoposide IV		
	ARA-C IV	ARA-C IV	ARA-C IV	ARA-C IV		
Difference between BEAT and BEAM 1 Replacement of Melphalan with Temozolomide given as a daily dose from (Day -5 thru Day -1) 2 Dexamethasone pre-meds is to be given in the morning pre-Temozolomide instead of the evening (Day -5 thru Day-2) 3 Additional Ondansetron is added as pre-med with the PM chemo doses (Day -5 thru Day -2) Additional steps/precaution relating to Temozolomide 1. Pill identification: exact count of each dosage strength is necessary prior to each dose 2. Lot number documentation of each dose prior to each dose (as this is a clinical trial utilizing commercial supply) 3. Complete oral Temozolomide administration within 1 hour. Give as divided doses (based on pill burden) 15 minutes apart. 4. At higher study doses, patients may vomit back up the pills. In this case, chemotherapy precautions should be applied and pill identification must be conducted.						

The schedule for the DRBEAT regimen will for the most part be very similar to scheduling of RBEAM. Rituximab would be given on Day -6 prior to the reinfusion of stem cells. Carmustine would also be given on Day -6. This would be followed by etoposide and cytarabine on Days -5 to -2. Melphalan would be replaced by temozolomide which would be given via divided doses over five days once daily on an empty stomach on days -5 to -1 prior to the transplant. Dexamethasone 20 mg IV would be given daily for the high nausea-inducing propensity of these combined agents (and dexamethasone has antilymphocytic properties as well).

Normally, patients admitted to our hospital for autologous stem cell transplantation obtain a room in the evening. During the first day of therapy (which would be day -6 prior to transplant), the patients most often receive rituximab in the cancer center while they are waiting for the bed to become available. The BCNU is given that evening of admission (day -6). The following morning, the cytarabine and etoposide are given (day -5). Usually etoposide will be given first followed by cytarabine. In the morning of the second day of admission (day -5), the temozolomide will be given. It causes less nausea on an empty stomach and will preferably be given prior to dinner. In the evening of the second day of admission, the second doses of q12 hour cytarabine and etoposide will be administered. This pattern will repeat itself over a total of 4 days (day -5 through day -2 of transplant). On day -1, one final dose of temozolomide will be administered. A typical anti nausea regimen at our institution for RBEAM is 8 mg of zofran IV prior to BCNU and 8 mg of zofran IV daily on the other pre-transplant days as well. As needed dosing of nausea meds may also be given, usually zofran. Due to concerns regarding nausea and vomiting with temozolomide, consideration will be given to increasing the standing daily dose of zofran depending on how well patients tolerate the initial dose.

4.5 Temozolomide Dosing (Please refer to appendix C for IV administration of Temozolomide)

Temozolomide comes in several dosing strengths: 5, 20, 100, 140, 180, 250mg. Doses will be rounded up to the nearest 5mg, as recommended by manufacturer). If the dosing is exactly in between, the dose will be rounded up to the nearest 5 mg dose. For example if a patient has a body surface area (BSA) of 2.25m², the calculated dose would be 562.5 mg but the dose to be given will be 565mg (i.e. three 180mg capsules and one 20mg capsule and one 5mg capsule)

If patient vomits within 60mins after Temozolomide administration, collect vomit and INTACT capsules only. Identify capsules with pharmacist. Pharmacist will call Dr. Linhares, Dr. Paquette, Dr. Merin, Dr. Rudnick or Dr. Lill for replacement dose, and replacement dose will be entered in eMAR titled “ Temozolomide Replacement dose “ and will be re-dispensed.

If replacement dose is administered, HOLD BREAKFAST THAT DAY.

If patient vomits after the replacement dose, call MD. No further replacement dose will be administered.

The dose for the first patient in the trial will be 250 mg/m²per day for 5 days as previous data indicates this to be a safe dose. Subsequent per patient dosing will be determined by DLT's experienced, illustrated below. Please see section 6.1 for further dosing schema clarification.

Because it takes 3 weeks to resolve toxicity, a patient may be accrued to the trial before the responses of all previously treated patients have been determined. It will be at the PI's discretion whether to treat the newly accrued patient at the dose level determined on the basis of the currently available data or to wait until one or

more toxicities are resolved. In this case, however, no more than 3 patients will be treated at the same dose level.

4.5.1 Implementation of Subject Dose Assignment

After a patient is consented to participate in the study and has met all enrollment criteria, the attending physician, the PI, and the biostatistician will discuss via conference call the exact dosing of temozolomide assigned to the patient. Based on the results of reported DLT's from previous patients, the EWOC statistical modeling will be performed to determine the next dose level. Written confirmation of the agreed upon dose will be sent via e-mail to all study staff members from the biostatistician, a copy of which will be added to the study regulatory binder.

4.5.2 Dose Limiting Toxicity

Dose Limiting Toxicity (DLT) will include Grade 3 (excluding grade 3 hematologic) and Grade 4 toxicities as per the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The CTCAE defines Grade 4 adverse events as life-threatening consequences in which urgent intervention is indicated. Please refer to http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae4.pdf for a full detailing of the CTCAE.⁴⁵

These toxicities as well as any others noted on physical exams and labs will be applied the scrutiny of whether the adverse event's etiology is:⁴⁶

- 1) Unclear/No Judgment Possible
- 2) Not related to temozolomide therapy
- 3) Possibly related to temozolomide therapy
- 4) Probably related to temozolomide therapy
- 5) Definitely related to temozolomide therapy

Because this study explores the safety of adding temozolomide to a base regimen of BEA, the focus will be to explore toxicities above and beyond those seen in BEA or RBEAM. As such, close scrutiny of toxicities commonly encountered with temozolomide is essential. As per the product label of temozolomide, which is based on extensive prior studies, the most common adverse reactions ($\geq 10\%$ incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, coordination abnormal, viral infection, amnesia, and insomnia. The most common Grade 3 to 4 hematologic laboratory abnormalities ($\geq 10\%$ incidence) that have developed during treatment with temozolomide are: lymphopenia, thrombocytopenia, neutropenia, and leukopenia. Allergic reactions have also been reported. Mortality due to transplant in the first 100 days (usually secondary to infection or organ toxicity from chemotherapy) is approximately $< 5\%$.⁴⁷

Grade 3 or 4 hematologic toxicities related to temozolomide will not be as much of a concern in this proposed study because the procedure of high dose chemotherapy followed by stem cell rescue would largely alleviate the myelosuppressive toxicity of temozolomide. We will certainly be reporting Grade 3 and 4 hematologic toxicity. These toxicities will not be considered dose-limiting and unexpected (and part of the stopping rules) unless neutropenia/leukopenia lasts longer than 21 days and thrombocytopenia lasts for a period greater than 28 days. By definition, neutropenia will be considered a neutrophil count that fails to climb $> 0.5 \times 10^9/L$, and

thrombocytopenia will be a platelet count that fails to climb $>25 \times 10^9/L$. Other nonhematologic Grade 3 and 4 toxicities that will be considered unexpected will include allergic, auditory, cardiac, coagulopathic, endocrine, hepatobiliary, renal, and certain musculoskeletal complications. Alopecia and insomnia will not be reported as they are not gradable toxicities, alopecia is universal in all patients for transplant, and insomnia includes the confounding factor of a 3+ week hospital stay and is universal among transplant patients.

Common gradable (unless otherwise noted) toxicities that will be evaluated that are secondary to temozolomide include:

- 1) Constipation
- 2) Diarrhea (need to delineate from high-grade diarrhea seen often in transplants)
- 3) Vomiting
- 4) Asthenia
- 5) Fever
- 6) Headache (no grade 4 definition)
- 7) Dizziness (no grade 4 definition)
- 8) Ataxia (no grade 4 definition)
- 9) Amnesia (no grade 4 definition)
- 10) Seizures
- 11) Hemiparesis (no specific CTCAE grading)
- 12) Rash
- 13) Fatigue (no grade 4 definition)
- 14) Hematologic toxicities

If a nonhematologic grade 3 or 4 adverse event or a grade 4 hematologic adverse event (as we will be monitoring patients closely for signs of engraftment after the transplant) is probably related to the study drug, our research team will decide whether this was indeed the DLT. This would help determine the target dose for the drug. It may be acceptable if no more than 40% of patients enrolled in the study get the above mentioned toxicities.

Only grade 3 or 4 adverse events will be collected.

As noted, mortality at 100 days status post transplant is expected to be approximately 5% with autologous stem cell transplant for B cell lymphoma. This is consistent with institutional data using BEAM or RBEAM. A percentage of 10% or higher would be considered an indication to stop the trial

4.5.3 Discouraged Concomitant medications:

Temozolomide has been studied in combination with other drugs. Drugs known to interact with temozolomide and which may decrease its oral clearance is valproic acid. Whenever possible, any patients we have with seizure disorders who are on this agent will be switched to a different antiseizure medication.

4.6 Stem Cell Infusion

Details regarding stem cell infusion procedures are best outlined in full in the Cedars-Sinai Medical Center SOPs authored by Dr. Stephen Lim and Dr. Michael Lill. ⁴⁸

4.7 Post-Transplant Follow-Up and Imaging

Evaluations should consist of interval history, complete physical exam, and laboratory studies including CBC and chemistry panel. Follow up does not need to take place at the transplant center.

Post transplant patients are at an increased risk for secondary malignancies and vigilant follow-up is paramount.

Symptoms of possible organ toxicity should be evaluated as clinically indicated.

Follow-up imaging will be completed as clinically indicated by the treating physician. Timelines provided in the Trial Procedures flowchart are a recommendation but may vary slightly per subject.

Once a subject progresses, he or she will be followed for survival status only.

4.7.1 Criteria for the Therapeutic Response/Outcome Assessment

MRI of the brain with and without contrast will be performed pre-transplant and post-transplant followed then by 3 month interval scans. This will be performed with the Standard Neuro-Oncology sequence guidelines if clinically indicated at the follow-up time points (refer to Section 4-Trial Procedures).

If there is a contra-indication towards MRI, then CT Scan with and without contrast is acceptable.

PET/CT will be performed at baseline, but will only be performed during follow-up visits if clinically indicated by the treating physician.

Radiographic response:

As assessed by MRI/CT. Tumor measurements must be recorded in centimeters and must be measured at the longest diameter and its perpendicular at the widest portion of the tumor. For tumors that are difficult to measure (ie. irregular shape), a visual interpretation of the magnitude of response is acceptable.

4.7.2 If tumor is present at the onset of Transplant

- Complete response (CR): disappearance of all enhancing tumor. Patients must be off steroid therapy and neurologically stable or improved. If CSF cytology was previously positive, it must be reassessed and negative. If ophthalmologic examination was previously positive, it must be reassessed and negative for cells.
- Partial response (PR): >50 % decrease in tumor size in comparison with baseline scan. Patients must be neurologically improved or stable on a stable or decreasing dose of corticosteroids.
- Progressive disease (PD): >25% increase in enhancing tumor or the appearance of new lesions. The patient may be neurologically stable or worse and on stable or increasing doses of steroids.
- Stable disease (SD): all other situations.⁴⁹

4.8 Neurocognitive Testing

- The importance of neuro-cognitive testing in primary CNS lymphoma has been well described and is a priority in brain tumor research from the NCI as well as the International Primary CNS Lymphoma Collaborative Group (IPCG). A standard neuropsychological test battery has been designed and validated which incorporates quality of life testing and takes under one hour (see table 1 below)

- Assessment intervals for neuro-psychological testing and QOL is recommended to be performed with the initial cognitive evaluation be carried out at the time of relapse pre-induction and preferably before the initiation of treatment. Follow-up assessments are recommended to be conducted in patients with 6-month intervals following treatment completion for the initial 2 years.⁵⁰⁻⁵¹
- Neurocognitive testing is not required for study participation; however, this data will be collected if this test is performed. Additionally, neurocognitive testing can be performed locally.

Table 1. Test battery for the assessment of neuropsychological functions and quality of life

Domain	Test	Description	Reference
Attention/Executive	(Digits Forward and Backward; WAIS-III)	Auditory attention	43
	Trail Making Test (Parts A and B)	Psychomotor speed (A); sequencing (B)—alternate form available (flexibility index = B–A)	44
	Brief Test of Attention	Auditory working memory	45
Verbal memory	Hopkins Verbal Learning Test—Revised	12-word list:	46
		Three learning/recall trials	
		Delayed recall	
		Recognition (discrimination index) Six alternate forms	
Motor	Grooved Pegboard Test	Motor speed and dexterity (dominant and nondominant hand)	47
Quality of life	EORTC-QLQ 30	30-item self-report scale (physical, social, emotional, cognitive status)	48
	BCM 20	20-item self-report scale (tumor and treatment-related symptoms)	49
Premorbid IQ Estimation	Barona Index	Weighted composite score on the basis of age, gender, race, residence, education, and occupation	50

EORTC-QLQ-C30, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30; BCM 20, Brain Cancer Module 20.

4.9

4.9 End of study

Subjects will be considered off study once all follow up has been completed or one year after enrollment of the last subject, whichever comes first.

As an aspect of this study is assessing the safety and toxicity of the therapy used, these issues are not likely areas that would lead to a patient withdrawing from a study. If at the point leading up to the transplant their condition deteriorates physically or mentally due to pre-transplant chemotherapy and/or radiation then we would withdraw them from the study, particularly if we feel they would not be able to tolerate undergoing an autologous stem cell transplant.

4.10 Removal of Subjects from Study

Patients may be removed from the study if any one or more of the events listed below occurs. The reason for removal and the date are to be recorded. An end of study treatment evaluation and study follow up should be performed whenever possible.

- 1) Patient voluntarily withdraws (follow-up permitted)
- 2) Patient withdraws consent (termination of treatment and follow-up)

- 3) Patient is unable to comply with protocol requirements
- 4) Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator)
- 5) Patient experiences toxicity that makes continuation in the protocol unsafe
- 6) Treating physician judges continuation on the study would not be in the patient's best interest
- 7) Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event)
- 8) Patient did not actually receive the study drug temozolomide in the context of stem cell transplantation (as part of the transplant conditioning regimen) or did not proceed to stem cell transplantation
- 9) Loss to follow-up
- 10) Death of the patient
- 11) Patients initially enrolled at relapse but who were not responsive to induction therapy will not be continued on the study.

If a patient is removed from the study for one of the above reasons, that patient's information will not count towards to accrual goal and a number will be added back to the number of patients set as the goal for the study (20).

5. RISKS AND ADVERSE EVENTS:

5.1 Potential Risks to Participants

The risks for this study are two-fold:

1. Risk associated with autologous stem cell transplantation which is part of standard clinical care. The most common side effects associated with autologous stem cell transplantation include:
 - a) Neutropenia and leucopenia: Grade 4 in 100% of patients
 - b) Thrombocytopenia: Grade 4 in 100% of patients
 - c) Anemia: may be Grade 3-4 in 100% of patients
 - d) Oral mucositis: almost always < Grade 4 in approximately 75% of patients
 - e) Abdominal pain due to mucositis: usually < Grade 3 in 65% of patients
 - f) Diarrhea: usually < Grade 3 in 82% of patients
 - g) Hemodynamically significant hematemesis, hematochezia, or melena: 7% of patients
 - h) Fever: usually Grade 3 in 98% of patients (with 42% having infection noted via blood culture)
 - i) Pneumonitis: in 17% of patients (no specific CTCAE grading)
 - j) Infections, not otherwise specified: not unexpected due to prolonged state of leucopenia
 - k) Nausea and/or vomiting: in 100% of patients
2. Risks associated with the dose-escalation portion of the study to determine the target dose of efficacy and safety incorporating temozolomide into the autologous transplant regimen instead of melphalan (DRBEAT regimen).

Potential risks to human subjects include drug related toxicity, pain and discomfort associated with phlebotomy, and possible psychological discomfort while obtaining MRI scans.

The side effects and potential toxicities of all chemotherapeutic agents will be listed. Death may occur as a result of treatment. All efforts will be made to avoid any complication by completely reviewing patients' symptoms and monitoring blood tests.

Periodic phlebotomy is necessary to monitor for the potential treatment related toxicities; trained phlebotomy technicians or nurses will perform all phlebotomy.

MRI scans are the accepted and best method for assessing central nervous system tumors and patients with substantial anxiety can be treated with an anxiolytic prior to the study. In those patients where an MRI is not possible for medical reasons (eg. pacemaker, ferromagnetic intracranial aneurysm clips) a CT scan will be obtained instead.⁵⁰

5.2 Therapy-Specific Toxicities

5.2.1 Side Effects and Risks from Chemotherapy

Possible Side Effects from Experimental Drug - Temozolomide

Temozolomide studies have not tested its use in combination with systemic Ara-C. There are studies incorporating temozolomide with intrathecal Ara-C and this was a well-tolerated combination.³⁵⁻³⁶ There is however data showing temozolomide's combined use with rituximab and also with BCNU and with oral etoposide (which also showed safe interaction with gemcitabine).³⁷⁻⁴¹ The manufacturer of temozolomide performed studies in combination with dexamethasone and there were no unusual interactions. Overall, temozolomide appears to have a good safety profile when combined with other chemotherapeutic agents and it would not be expected to be different in the context of a transplant setting. It should not be expected that temozolomide will have any expected interactions with the other agents in the DRBEAT regimen. Cytarabine is noted to have a half-life elimination IV of 7-20 minutes initially and 1-3 hours terminally and would thus be out of the body system by the time temozolomide is to be administered on the days they are both given (days -5 to -2). Etoposide, with a terminal half-life elimination of 4-11 hours and a time to peak concentration in the serum of 1-1.5 hours (orally), has a higher chance of being in the body at the time of temozolomide administration but there is data that the two medications have been used as part of a regimen together. As noted above, any possible adverse interactions with BCNU also should not be an issue as this medication will be given the day prior to any temozolomide administration and its half-life elimination should not be a factor (initial plasma half-life of 1.4 minutes). The half-life is longer for rituximab and it may be in the system even well after the transplant but as noted earlier, there does not appear to be any adverse interaction between rituximab and temozolomide and the combination of these two medications is being used more and more frequently as reinduction chemotherapy for relapsed CNS B-cell lymphoma

Information provided from approved label via FDA¹⁷

Adverse Reactions:

- 1) The most common adverse reactions ($\geq 10\%$ incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, coordination abnormal, viral infection, amnesia, and insomnia.
- 2) The most common Grade 3 to 4 hematologic laboratory abnormalities ($\geq 10\%$ incidence) that have developed during treatment with temozolomide are: lymphopenia, thrombocytopenia, neutropenia, and leukopenia.
- 3) Allergic reactions have also been reported.

Please also see Section 4.5.2.

Possible Side Effects from Standard of Care Transplant Therapy:

High dose chemotherapy employed in autologous transplantation is associated with significant risks of morbidity and mortality. Commonly, a transplant may impair the cardiovascular system (dysfunction due to fluid overload, hyperdynamic circulation, ischemia, or direct cardiotoxicity from chemotherapy), the respiratory system (pneumonitis, chemotherapy damage), renal function (hypotension, tumor lysis, nephrotoxicity of drugs), or hepatic function (venoocclusive disease, hepatitis, hepatotoxicity from drugs). In addition, pre-existing renal or hepatic dysfunction may impair the elimination of the chemotherapeutic drugs, causing accumulation and possibly exacerbation of adverse events. It is well established that pre-existing liver injury predisposes to hepatic venoocclusive disease. During and after transplant, patients are predisposed to various opportunistic or latent infections, such as CMV infections, tuberculosis, that may further stress various organs systems.

A. Dexamethasone

(Adverse events noted via Up To Date online medical information resource. No current labeling guidelines available via FDA or manufacturers.⁵²)

1. Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, cardiomyopathy, CHF, circulatory collapse, edema, hypertension, myocardial rupture (post-MI), syncope, thromboembolism, vasculitis
2. Central nervous system: Depression, emotional instability, euphoria, headache, intracranial pressure increased, insomnia, malaise, mood swings, neuritis, personality changes, pseudotumor cerebri (usually following discontinuation), psychic disorders, seizure, vertigo
3. Dermatologic: Acne, allergic dermatitis, alopecia, angioedema, bruising, dry skin, erythema, fragile skin, hirsutism, hyper-/hypopigmentation, hypertrichosis, perianal pruritus (following IV injection), petechiae, rash, skin atrophy, skin test reaction impaired, striae, urticaria, wound healing impaired
4. Endocrine & metabolic: Adrenal suppression, carbohydrate tolerance decreased, Cushing's syndrome, diabetes mellitus, glucose intolerance decreased, hyperglycemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, pituitary-adrenal axis suppression, protein catabolism, sodium retention
5. Gastrointestinal: Abdominal distention, appetite increased, gastrointestinal hemorrhage, gastrointestinal perforation, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, weight gain
6. Genitourinary: Altered (increased or decreased) spermatogenesis
7. Hepatic: Hepatomegaly, transaminases increased
8. Local: Postinjection flare (intra-articular use), thrombophlebitis
9. Neuromuscular & skeletal: Arthropathy, aseptic necrosis (femoral and humeral heads), fractures, muscle mass loss, myopathy (particularly in conjunction with neuromuscular disease or neuromuscular-blocking agents), neuropathy, osteoporosis, paresthesia, tendon rupture, vertebral compression fractures, weakness
10. Ocular: Cataracts, exophthalmos, glaucoma, intraocular pressure increased
11. Renal: Glucosuria
12. Respiratory: Pulmonary edema
13. Miscellaneous: Abnormal fat deposition, anaphylactoid reaction, anaphylaxis, avascular necrosis, diaphoresis, hiccups, hypersensitivity, impaired wound healing, infections, Kaposi's sarcoma, moon face, secondary malignancy

B. Rituximab

Warnings and Precautions/Major Side Effects from FDA Labeling⁵³

WARNINGS AND PRECAUTIONS

1) **Infusion Reactions:** Rituxan can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituxan-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, consider resumption of the infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq 25,000/\text{mm}^3$).

2) **Tumor Lysis Syndrome (TLS):** Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia, can occur within 12–24 hours after the first infusion. Fatal TLS cases have occurred after administration of Rituxan. A high number of circulating malignant cells ($\geq 25,000/\text{mm}^3$) or high tumor burden confers a greater risk of TLS after rituximab. Consider prophylaxis for TLS in patients at high risk. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

3) **Severe Mucocutaneous Reactions:** Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has varied from 1–13 weeks following Rituxan exposure. Discontinue Rituxan in patients who experience a severe mucocutaneous reaction. The safety of re-administration of Rituxan to patients with severe mucocutaneous reactions has not been determined.

4) **Progressive Multifocal Leukoencephalopathy (PML):** JC virus infection resulting in PML and death can occur in Rituxan-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of Rituxan.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue Rituxan and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5) **Hepatitis B Virus (HBV) Reactivation:** Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with Rituxan. The

median time to the diagnosis of hepatitis was approximately 4 months after the initiation of Rituxan and approximately one month after the last dose.

Screen patients at high risk of HBV infection before initiation of Rituxan. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months following Rituxan therapy. Discontinue Rituxan and any concomitant chemotherapy in patients who develop viral hepatitis, and institute appropriate treatment including antiviral therapy. Insufficient data exist regarding the safety of resuming Rituxan in patients who develop hepatitis subsequent to HBV reactivation.

6) Infections: Rituxan is not recommended for treatment of patients with severe active infections. The following additional serious viral infections, either new, reactivated, or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred as late as one year following discontinuation of Rituxan and have resulted in death.

7) Cardiovascular: Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of Rituxan for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

8) Renal: Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with hematologic malignancies. Renal toxicity has occurred in patients with high numbers of circulating malignant cells ($\geq 25,000/\text{mm}^3$) or high tumor burden who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituxan is not an approved treatment regimen. Use extreme caution if this non-approved combination is used in clinical trials and monitor closely for signs of renal failure. Consider discontinuation of Rituxan for patients with a rising serum creatinine or oliguria.

9) Bowel Obstruction and Perforation: Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving Rituxan in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 days (range 1–77days) in patients with NHL. Perform a thorough diagnostic evaluation and institute appropriate treatment for complaints of abdominal pain, especially early in the course of Rituxan therapy.

10) Immunization: The safety of immunization with live viral vaccines following Rituxan therapy has not been studied and vaccination with live virus vaccines is not recommended.

For RA patients, physicians should follow current immunization guidelines and administer non- live vaccines at least 4 weeks prior to a course of Rituxan.

The effect of Rituxan on immune responses was assessed in a randomized, controlled Phase I study in patients with RA treated with Rituxan and methotrexate (MTX) compared to patients treated with MTX alone.

A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with Rituxan plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of patients in the Rituxan plus MTX group

developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%).

A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with Rituxan plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on Rituxan plus MTX vs. 70% of patients on MTX alone).

Most patients in the Rituxan-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

C. BiCNU

(carmustine for injection)

Information is directly from Food and Drug Administration⁵⁴

ADVERSE REACTIONS

1) **Pulmonary Toxicity:** Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported to occur from 9 days to 43 months after treatment with BiCNU and related nitrosoureas. Most of these patients were receiving prolonged therapy with total doses of BiCNU greater than 1400 mg/m². However, there have been reports of pulmonary fibrosis in patients receiving lower total doses. Other risk factors include past history of lung disease and duration of treatment. Cases of fatal pulmonary toxicity with BiCNU have been reported. Additionally, delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in a long-term study with 17 patients who received BiCNU in childhood and early adolescence (1–16 years) in cumulative doses ranging from 770 to 1800 mg/m² combined with cranial radiotherapy for intracranial tumors. Chest x-rays demonstrated pulmonary hypoplasia with upper zone contraction. Gallium scans were normal in all cases. Thoracic CT scans have demonstrated an unusual pattern of upper zone fibrosis. There was some late reduction of pulmonary function in all long-term survivors. This form of lung fibrosis may be slowly progressive and has resulted in death in some cases. In this long-term study, 8 of 17 died of delayed pulmonary lung fibrosis, including all those initially treated (5 of 17) at less than 5 years of age.

2) **Hematologic Toxicity:** A frequent and serious toxicity of BiCNU is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks post administration and persists for 1 to 2 weeks. Leukopenia occurs at 5 to 6 weeks after a dose of BiCNU and persists for 1 to 2 weeks. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

BiCNU may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses. The occurrence of acute leukemia and bone marrow dysplasias have been reported in patients following long-term nitrosourea therapy. Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

3) **Gastrointestinal Toxicity:** Nausea and vomiting after IV administration of BiCNU are noted frequently. This toxicity appears within 2 hours of dosing, usually lasting 4 to 6 hours, and is dose related. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect.

4) Hepatotoxicity: A reversible type of hepatic toxicity, manifested by increased transaminase, alkaline phosphatase and bilirubin levels, has been reported in a small percentage of patients receiving BiCNU.

5) Nephrotoxicity: Renal abnormalities consisting of progressive azotemia, decrease in kidney size and renal failure have been reported in patients who received large cumulative doses after prolonged therapy with BiCNU and related nitrosoureas. Kidney damage has also been reported occasionally in patients receiving lower total doses.

6) Other Toxicities: Accidental contact of reconstituted BiCNU with skin has caused burning and hyperpigmentation of the affected areas.

Rapid IV infusion of BiCNU (carmustine for injection) may produce intensive flushing of the skin and suffusion of the conjunctiva within 2 hours, lasting about 4 hours. It is also associated with burning at the site of injection although true thrombosis is rare.

Neuroretinitis, chest pain, headache, allergic reaction, hypotension and tachycardia have been reported as part of ongoing surveillance.

D. Etoposide

Information obtained directly from Package Insert⁵⁵

Adverse Reactions

The following data on adverse reactions are based on both oral and intravenous administration of etoposide as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

1) Hematologic Toxicity: Myelosuppression is dose related and dose limiting, with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported.

The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents.

2) Gastrointestinal Toxicity: Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion.

3) Hypotension: Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that Etoposide Injection be administered by slow intravenous infusion over a 30 to 60 minute period. If hypotension occurs, it usually responds to cessation of the infusion and administration of fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

4) Allergic Reactions: Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension have been reported to occur in 0.7% to 2% of patients receiving intravenous etoposide and in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of etoposide.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely. Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

5) Alopecia: Reversible alopecia, sometimes progressing to total baldness was observed in up to 66% of patients.

6) Other Toxicities: The following adverse reactions have been infrequently reported: aftertaste, fever, pigmentation, abdominal pain, constipation, dysphagia, transient cortical blindness, optic neuritis, and a single report of radiation recall dermatitis. Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with etoposide. Metabolic acidosis also has been reported in patients receiving higher doses.

E. Cytarabine

Information Obtained from Lowsky et al, TLI/ATG Protocol⁵⁶

Adverse Reactions

1) Expected Reactions: Because Cytarabine is a bone marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis and reduced reticulocytes can be expected as a result of administration with Cytarabine. The severity of these reactions are dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

2) Following 5-day constant infusions or acute injections of 50 mg/m² to 600 mg/m², white cell depression follows a biphasic course. Regardless of initial count, dosage level, or schedule, there is an initial fall starting the first 24 hours with a nadir at days 7-9. This is followed by a brief rise which peaks around the twelfth day. A second and deeper fall reaches nadir at days 15-24. Then there is a rapid rise to above baseline in the next 10 days. Platelet depression is noticeable at 5 days with a peak depression occurring between days 12-15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

Infectious Complications: Infection: Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body may be associated with the use of Cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

3) The Cytarabine (Ara-C) Syndrome: A Cytarabine syndrome has been described by Castleberry. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated as well as continuation of therapy with Cytarabine Injection.

4) Most Frequent Adverse Reactions: Anorexia, hepatic dysfunction, nausea, fever, vomiting, rash, diarrhea, thrombophlebitis, oral and anal inflammation or ulceration, bleeding (all sites). Nausea and vomiting are most frequent following rapid intravenous injection.

5) Less Frequent Adverse Reactions: Sepsis, abdominal pain, pneumonia, freckling, cellulitis at injection site, jaundice, skin ulceration, conjunctivitis (may occur with rash), urinary retention, dizziness, renal dysfunction, alopecia, neuritis, anaphylaxis, neural toxicity, allergic edema, sore throat, pruritus, esophageal ulceration, shortness of breath, esophagitis, urticaria, chest pain, pericarditis, headache, bowel necrosis, pancreatitis.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of Cytarabine) has been reported following some experimental Cytarabine dose schedules. These reactions include reversible corneal toxicity, and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis; sepsis and liver abscess; pulmonary edema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis. Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with experimental high dose therapy than with standard Cytarabine treatment programs. If experimental high dose therapy is used, do not use a diluent containing benzyl alcohol.

5.2.2 Possible Side Effects from Stem Cell Mobilization:

A. G-CSF

Information Obtained from Lowsky et al, TLI/ATG Protocol⁵⁶

Recombinant human G-CSF is an 18.9 kD protein produced in *Escherichia coli* (*E coli*) bacteria. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E coli*. Because the drug is produced in *E coli*, the product is nonglycosylated and thus differs from G-CSF isolated from a human cell. G-CSF is a sterile, clear, colorless, preservative-free liquid for parenteral administration in vials containing 300 mcg/ml for subcutaneous administration.

Potential Toxicities:

1. Musculoskeletal: In clinical trials, medullary bone pain was the only consistently observed adverse event attributed to G-CSF and was reported in approximately 24% of patients across all indications. The bone pain was generally mild to moderate in severity and controllable in most patients with non-narcotic analgesia; infrequently, bone pain was severe enough to require narcotic analgesia.
2. Cardiovascular: Rarely fluid retention; transient hypotension; pericardial effusion.

3. Dermatologic: Local inflammation at the injection site; rarely cutaneous vasculitis.
4. Other: Transient, mild to moderate elevations of uric acid, LDH, alkaline phosphatase and leukocyte alkaline phosphatase when given with cytotoxic drugs.
5. Rarely, normal donors receiving G-CSF have experienced swelling of their spleen, and on occasion, internal bleeding from the spleen or rupture of the spleen. Bleeding from or rupture of the spleen can present as malaise, flank or abdominal pain, or loss of consciousness from low blood pressure. Rupture of the spleen can be very serious and is potentially life threatening. Management of this problem could require blood transfusions or surgery.

5.2.3 Possible Side Effects from Stem Cell Infusion:

- a. A cough/gag response: This is a common occurrence when DMSO preservative is initially excreted through the lungs.
- b. Nausea/emesis: Many patients experience nausea during the infusion.
- c. Chills and flushing:
- d. Hypotension: Occasional patients will experience a drop in blood pressure with each successive bag.
- e. Hypertension, tachycardia: Occasional patients will experience hypertension or tachycardia.
- f. Decreased oxygen saturation: Maybe secondary to volume overload, broncho constriction or white blood cell pulmonary infiltration.
- g. Clumping of Stem Cells: Due to presence of DNA.

It is expected that patients after autologous transplant may be at a higher risk of developing secondary malignancy including acute leukemia and/or solid tumors.⁴⁸

5.2.4 Infectious Disease Adverse Risks:

Bone marrow and stem cell transplant patients are at risk for viral infections caused by Herpes group viruses such as herpes simplex, CMV, EBV and varicella-zoster. Less commonly, viral infections caused by respiratory syncytial virus, influenzae virus, parainfluenzae virus, rhinovirus and adenovirus may occur.

5.2.5 Diagnosis, Management, and Complications of Neutropenic Fever:

Bacterial infections as well as other causes may lead to neutropenic fever A full description of diagnosis and of guidelines the institution tends to follow for managing neutropenic fever are outlined in the SOPs.⁴⁸

6.0 Adverse Event Reporting

(Modified from Lowsky et al protocol)⁵⁶

Only Grade 3 and Grade 4 adverse events will be collected and documented.

6.1 Definitions:

- 1. Adverse Event** - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, medical treatment or procedure and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, medical treatment or procedure whether or not considered related to the medicinal product or treatment.
- 2. Life-threatening Adverse Event** – Any adverse event that places the patient or subject, in view of the investigator, at immediate risk of death from the reaction.
- 3. Unexpected Adverse Event**-An adverse event, the nature or severity of which is not consistent with the applicable product information (Investigator’s Brochure, product insert). For studies that do not involve investigational products or devices, an unexpected adverse event is an adverse event that is not described in the medical literature or consent form.
- 4. Serious Adverse Event (SAE)**-Any adverse event occurring that results in any of the following outcomes: death, a life threatening adverse event, a persistent or significant disability/incapacity, a congenital anomaly, requires intervention to prevent permanent impairment or damage.

6.2 Distinction between Serious and Severe

The term **severe** is used to describe the intensity (severity) of a specific event, for example mild, moderate or severe. The event itself however, may be of relatively minor medical significance, for example a severe headache. This is not the same as **serious**, which is based on the patient/event outcome and is usually associated with events that pose a threat to the patient’s life or functioning. Seriousness, not severity, serves as a guide for defining regulatory obligations.

6.3 Reporting Unexpected Serious Adverse Events

As delineated in section 5.1 of the protocol, there are numerous potential toxicities and adverse events associated with chemotherapy, radiation, and HCT. In an effort to report to regulatory agencies the toxicities that are relevant and meaningful for the evaluation of risks and benefits to study participants, the following guidelines will serve to determine what is reported as SAEs on this study.

6.3.1 SAE Reporting

SAEs are required to be reported to the IRB as soon as possible but at most 10 calendar days from the day the investigator learns of the event.

All serious adverse that have a reasonable possibility of relationship to the study must be reported to the IRB, regardless if they are unanticipated or anticipated.

In accordance with FDA regulations, serious is defined as: “Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.” (21 CFR 312.32(a))

6.3.2 Adverse Events that do not Require a SAE Report

The following will generally **not** require reporting as SAEs:

1. Relapse of disease: Relapse unfortunately remains a significant problem following both autologous and allogeneic transplantation. The risk of relapse is influenced by both patient and disease variables. Relapse will be captured on the case report forms as it is a secondary objective in this study;
2. Secondary Malignancies.: The occurrence of secondary malignancies and associated mortality is a known risk of cancer therapies. Any malignancy possibly related to cancer treatment should be reported via the Follow-Up Case Report Forms, and **do not** require an additional SAE report.

7. STATISTICAL CONSIDERATIONS:

7.1 Plan of Analysis

7.1.1 Analysis of Drug Efficacy

Analysis of efficacy will be performed to compare disease-free survival, response rate, and overall survival of CNS lymphoma patients treated with temozolomide with historical clinical data from our hospital using Kaplan-Meier estimates. The dose of temozolomide will be used as a covariate in this analysis.

7.1.2 Dose Escalation Scheme

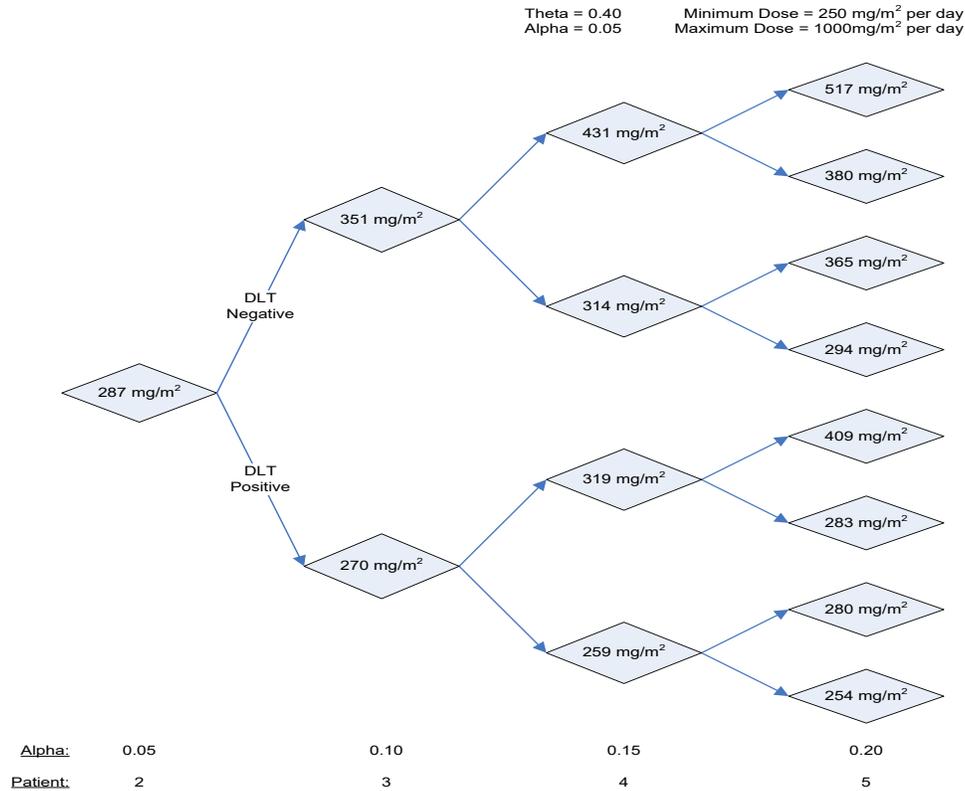
The target dose is defined to be the dose level of temozolomide that when administered to a patient results in a probability equal to $\theta = 0.40$ that a dose limiting toxicity will be observed within 3 weeks. The dose escalation will follow a Bayesian method permitting precise determination of the therapeutic working-dose while directly controlling the likelihood of an overdose. The method, known as EWOC (Escalation With Overdose Control), has been used to design clinical trials at the Fox Chase Cancer Center (PA), the Sylvester Comprehensive Cancer Center (FL), and the Winship Cancer Institute (GA). Babb et al. provided a comparison of EWOC with alternative design methods.⁵⁷ They showed that up-and-down designs treated only 35% of patients at optimal dose levels, versus 55% for EWOC, i.e., more patients are treated with doses outside the therapeutic window by up-and-down than by EWOC designs. Babb and Rogatko provide a summary of Bayesian design methods and Tighiouart et al. studied the performance of EWOC under a rich class of prior distributions for θ , where θ is defined as the probability of experiencing a DLT. EWOC was the first dose-finding procedure to directly incorporate the ethical constraint of minimizing the chance of treating patients at unacceptably high doses.⁵⁸⁻⁵⁹ Its defining property is that the expected proportion of patients treated at doses above the target dose is equal to a specified value α , the *feasibility bound*. This value is selected by the clinician and reflects his/her level of concern about overdosing. Zacks et al showed that among designs with this defining property, EWOC minimizes the average amount by which patients are underdosed.⁶¹ This means that EWOC approaches the target dose as rapidly as possible, while keeping the expected proportion of patients overdosed less than the value α . Zacks et al. also showed that, as a trial progresses, the dose sequence defined by EWOC approaches the target dose (i.e., the sequence of recommended doses converges in probability to the target dose).⁶⁰ Eventually, all patients beyond a certain time would be treated at doses sufficiently close to the target dose.

The dose for the first patient in the trial will be 250 mg/m² per day for 5 days as previous data indicates this to be a safe dose. Temozolomide comes in several dosing strengths: 5, 20, 100, 140, 180, 250mg. Doses will be rounded up or down to the nearest 20 mg to limit the amount of pills a patient has to swallow (thus limiting emetogenicity). If the dosing is exactly in between, the dose will be rounded up to the nearest 20 mg dose. For example, if a patient has a body surface area (BSA) of 2.25, the calculated dose would be 562.5 mg but the dose to be given will be 560 mg (i.e. two 250 mg tablets and three 20 mg tablets).

The dose for each subsequent patient will be determined so that, on the basis of all available data, the probability that it exceeds the target dose is equal to a pre-specified value α . In this trial, we will set $\alpha = 0.05$ (representing a 5% chance of overdosing) to start, this value being a compromise between the therapeutic aspect of the agent and its toxic side. At each dosing increase in the study design, α will increase by 5% until a maximum of 50% probability is achieved to control overdose. The dose selected for every patient in the trial will be between the minimum dose and the maximum allowable dose of 1000 mg/m² per day. For the EWOC modeling in this protocol, a uniform prior distribution will be used (see Babb et al.⁵⁸ for further details regarding the operating characteristics of the EWOC design). The Figure below shows all the possible dose

sequences that could be realized for the first 5 patients. Actual dose delivered daily will be rounded up to the nearest 5mg after adjusting for total body mass of the patient.

Example Decision Tree for Daily Dosing Schedule
Patients 1 to 5



Because it takes 3 weeks to resolve toxicity, a patient may be accrued to the trial before the responses of all previously treated patients have been determined. It will be at the PI's discretion whether to treat the newly accrued patient at the dose level determined on the basis of the currently available data or to wait until one or more toxicities are resolved. In this case, however, no more than 3 patients will be treated at the same dose level.

A maximum of 20 patients will be accrued to the trial. Procedures for determining the number of patients needed in a trial using a Bayesian framework depends on the investigators, goal and sets of criteria such as precision of the estimate of the target dose and frequency of DLTs. We have conducted extensive simulations under several scenarios of the true values of the target dose and probability of toxicity at the initial dose and posterior standard deviation and average length of credible interval of the target dose averaged across all possible trials for various sample sizes and target probability of DLT can be found at <http://sisyphus.emory.edu/Publications/output.htm>.

Upon completion of the trial, the target dose will be estimated as the median of the marginal posterior distribution of the target dose. The computation of the dose to be administered to each patient and the 95% highest posterior density credible interval estimate of the target dose will be carried out by Ms. Catherine Bresee of the Cedars-Sinai Medical Center's Samuel Oschin Comprehensive Cancer Institute with the computer program EWOC Version 2 (user-friendly, dialog-based, stand-alone application and the self-extracting file can be downloaded from <http://sisyphus.emory.edu/ewoc.html>).⁶¹

7.2 Interim Analysis and Stopping Rules

7.2.1 Interim Analyses Timelines

The CNS Lymphoma Study Group comprising the core group of principal investigators, statisticians, and data managers will plan on meeting at least as frequently as after every three patients enrolled, or between/in the setting of determining whether or not to dose escalate. Statistical considerations will necessitate meeting sooner as needed. At these meetings, the focus of the discussion will be two fold:

- a) Statistical considerations such as dose escalations
- b) Review of toxicities in enrolled subjects and reassessment of expected and unexpected toxicities and dose limiting toxicities. This meeting will occur independent of the Data and Safety Monitoring Board and will act as an adjunct to the DSMB.

7.2.2 Study Termination, Stopping Rules

The trial will be terminated after 20 patients are evaluated; or when the magnitude of change in the estimated mean target dose is smaller than 10% for 3 successive patients.

The trial will be terminated early if 5 dose related toxicities are observed for the first 7 patients or if at any time an interim mortality rate of >10% is observed.

8.0 STUDY MANAGEMENT

8.1 Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

8.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

8.3 Registration Procedures

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. Those subjects that do not pass the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause treatment delays after registration should be discussed with the Principal Investigator (PI). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Assignment of Subject ID: The study team will track all subjects who sign consent on a subject screening/enrollment log using a unique screening ID. Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered using a numeric ID (0001, 0002, etc.).

8.3.1 Eligibility Verification

Prior to registration, all subjects must undergo eligibility verification by the SOCCI Clinical Research Office (CRO). The following documents will be completed and provided for review:

- Copy of applicable source documents
- Eligibility checklist (signed by investigator)
- Signed patient consent form and Subject's Bill of Rights
- HIPAA authorization form

8.3.2 Registration

After eligibility is verified, registration is completed as follows:

- Assign a patient study number
- Assign the patient a dose as determined through communication with Biostatistics and the principal investigator
- Enter the patient in OnCore
- Notify the investigational pharmacy and treating physicians that a subject has gone on study and anticipated treatment start date

Oversight by the principal investigator is required throughout the entire registration process

8.4 Data Management and Quality Control and Reporting

The data will be entered into a HIPAA-compliant database. The Study Staff will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

8.5 Data and Safety Monitoring

8.5.1 Data Monitoring and Quality Assurance

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the PI during the course of the study through routine Disease Research Group (DRG) meetings or equivalent. In addition, the SOCCI CRO Quality Management Core (QMC) will conduct the following:

1. Audit preparations (AP) prior to audit conducted by any external auditing agency (i.e. NCI or FDA). The purpose an AP is to ensure adequate source documentation to support protocol compliance and data integrity are present and organized and to identify and correct any major findings prior to the external audit
2. A thorough review of selected subject cases, regulatory files, and IP accountability records (if applicable) within 2-3 months after the first subject is enrolled and annually thereafter while subjects are receiving investigational intervention.
3. Central eligibility verification for all subjects enrolled as described in protocol section 8.3.1.
4. Central review of all eligibility waiver requests by a SOCCI Medical Reviewer to assess appropriateness and risk to ensure quality data and ensure subject safety protections for investigator-initiated research

For any protocol, QMC has the authority to request more frequent reviews or closer safety monitoring if it is deemed appropriate for any reason.

8.5.2 Safety Monitoring

Oversight of the progress and safety of the study will be provided by the PI. The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. Adverse events and unanticipated problems are not expected, but if they occur they will be documented and reported according to CSMC IRB policies and procedures. If the PI becomes aware of any new safety information that may place subjects at increased risk than what was previously known the IRB will be promptly notified and if warranted, enrollment may be held until the PI determines whether a modification to the study is necessary and/or the informed consent documents are updated accordingly.

In addition, this protocol will utilize oversight by a Safety Committee On Early Phase Studies (SCOEPS). Committee membership includes experts in the field of oncology and early phase studies and biostatistics. SCOEPS' responsibilities are governed by the committee charter, or equivalent.

The SCOEPS will provide routine monitoring of safety and enrollment for all early phase investigator-initiated trials (IITs). The committee meets routinely and is responsible for reviewing and adjudicating all dose-limiting toxicities, dose escalations and appropriateness of the escalation, cohort expansion, subject replacements, select AEs, SAEs, and confirmation of attainment of maximum tolerated dose.

The SCOEPS findings and recommendations will be reported in writing to the Principal Investigator. A summary report will be forwarded by the Principal Investigator or his/her designee to the Cedars-Sinai Medical Center IRB.

8.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file per local guidelines.

8.7 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the SOCCI Medical Director and CSMC IRB, the study shall be conducted exactly as described in the approved protocol.

8.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 10 days from the investigator's awareness of the event.

8.7.2 Protocol Exceptions and Eligibility Waivers

An exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the IRB Policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement*.

A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

All exception requests must be reviewed by the SOCCI CRO Medical Director and the Institutional Review Board prior to implementation. The PI or her/his designee is responsible for submitting a protocol exception and its supporting documents to the SOCCI Medical Director for review. Planned exceptions to the protocol that are more than logistical and/or have the potential to affect the subject's safety and/or study integrity may not be implemented without prior approval from the SOCCI Medical Director and IRB.

8.7.3 Special considerations for Eligibility Waivers (EW)

In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be forwarded to the SOCCI CRO Medical Director for assessment **prior** to submission to the IRB for approval.

The CRO Medical Director will review the case and contact the investigator if additional information is needed or further discussion is warranted. The CRO Medical Director will provide a written assessment/recommended course of action. The CRO Medical Director's assessment must be uploaded into Webridge with the waiver request for IRB review and consideration. The CRO Medical Director may recommend future protocol changes.

Eligibility Waiver Submission Process

The PI and/or treating physician should provide written request for waiver which includes case history and justification for prospective deviation from the study design to the SOCCI CRO Medical Director.

8.7.4 Other Protocol Deviations

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety. Such planned deviations that do meet this definition and do not affect the subject's safety should be noted in the subject's research record or deviation log as described in the SOCCI Clinical Research Office's Working Instruction 11: Deviation and Noncompliance Reporting.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI Clinical Research Office's Working Instruction 11: *Deviation and Noncompliance Reporting*. In this case, a Protocol Deviation report must be submitted in Webridge, per IRB policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement*. All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

8.7.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

8.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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APPENDICES:

- A) Treatment of CNS Lymphoma
- B) Karnofsky Performance Status Scale
- C) IV administration of Temozolomide
- D) Summary of Changes

APPENDIX A

TREATMENT OF CNS LYMPHOMA

Timeline of Study Autologous HCT

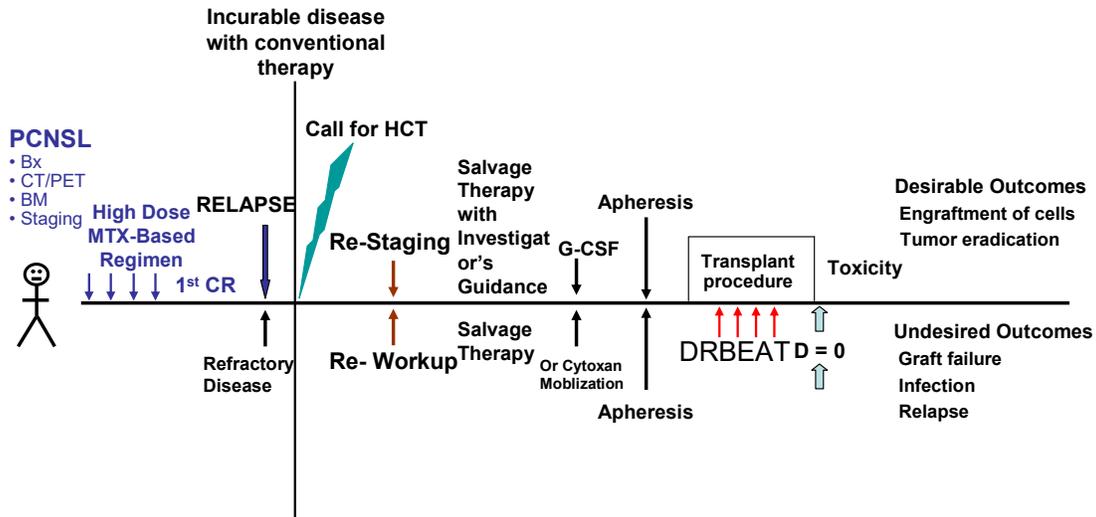


Figure modified from Lowsky presentation

Reinduction Chemotherapy

- Relapsed CNS Lymphoma is a heterogeneous disease and often reinduction chemotherapy is based upon prior treatments, responses and complications. The below are guidelines for the treating physician.
- Cranial irradiation should be reserved for non-responders to methotrexate or in cases of disease recurrence in chemotherapy non-responders. Whole brain radiation therapy is preferential in previously non-irradiated patients. Stereotactic radiotherapy may be an option for patients who have received whole brain radiation and considered for focal disease.⁶²⁻⁶³
- Retreatment with high dose methotrexate (ie, 3 to 8 g/m²) alone or in combination with a methotrexate-based combination chemotherapy if there has been a prior complete remission with this agent should be strongly considered. This selected group of patients has a high likelihood of achieving a second or even a third response to methotrexate. (examples of combinations regimens include methotrexate and cytarabine versus methotrexate and temozolomide)⁶⁴
- Alternative chemotherapy regimens (eg, topotecan, cytarabine, temozolomide, thiotepa, rituximab).⁶⁴⁻⁶⁹
- Intrathecal Chemotherapy/Intraocular Chemotherapy may be given in addition to the above treatments.

Please see the below table (5) for examples of salvage regimens in relapsed PCNSL.

Table 1
Salvage regimens for PCNSL

Treatment	Study	No.	mAge	Prior RT (%)	PS 0-1 (%)	CR + PR (%)	mPFS	mOS	1-year OS (%)	N (%)	PLT (%)	Other tox (%)
Topotecan [11]	Prospective	27	51	52	60	19 + 14	2.0	8.4	39	26	15	11
Temozolomide [9,10]	Prospective	36	60	86	28	25 + 6	2.8	4.0	31	6	3	3
Methotrexate [12]	Retrospective	22	58	14	–	73 + 19	26	26	70	5	5	36
Temozolomide + Rituximab [15]	Retrospective	15	69	13	67	40 + 13	2.2	10.5	58	7	27	7
VP16 + Ifosfamide + Ara-C [14]	Retrospective	16	54	100	37	37 + 0	4.5	6.0	41	69	50	37
i.a. Carboplatin ± VP16 ± CTX ± RT [13]	Retrospective	37	57	24	76	24 + 11	3.0	6.8	25	22	19	>30
Radiotherapy [17]	Retrospective	27	67	–	–	37 + 37	9.7	10.9	49	–	–	15 neuro
Radiotherapy [18]	Retrospective	20	–	–	–	60 + ?	–	19.0	–	–	–	58 neuro
HD-ara-C + VP16 → TTP + busulfan + CTX [23]	Prospective	43	52	33	–	50 + 0	–	18	–	–	–	TRM: 14
Intrathecal rituximab [24]	Phase I	10	56	80	–	0 + 60	–	5.2	30	–	–	–

mAge, median age; RT, radiotherapy; PS, performance status; CR, complete response; PR, partial response; mPFS, median progression-free survival; mOS, median overall survival; 1-year OS, 1-year overall survival; N, grade 3-4 neutropenia; PLT, grade 3-4 thrombocytopenia; tox, toxicity; i.a., intra-arterial; VP16, etoposide; HD-ara-C, high-dose cytarabine; TTP, thiotepea; CTX, cyclophosphamide.

Overall, the most likely, common toxicities related to autologous stem cell transplantation which one would expect after such high-dose therapy include:⁷

- 1) Neutropenia and leucopenia: Grade 4 in 100% of patients
- 2) Thrombocytopenia: Grade 4 in 100% of patients
- 3) Anemia: may be Grade 3-4 in 100% of patients
- 4) Oral mucositis: almost always <Grade 4 in approximately 75% of patients
- 5) Abdominal pain due to mucositis: usually < Grade 3 in 65% of patients
- 6) Diarrhea: usually < Grade 3 in 82% of patients
- 7) Hemodynamically significant hematemesis, hemochezia, or melena: 7% of patients
- 8) Fever: usually Grade 3 in 98% of patients (with 42% having infection noted via blood culture)
- 9) Pneumonitis: in 17% of patients (no specific CTCAE grading)
- 10) Infections, not otherwise specified: not unexpected due to prolonged state of leucopenia
- 11) Nausea and/or vomiting: in 100% of patients

APPENDIX B

KARNOFSKY PERFORMANCE STATUS SCALE

General

Index Specific criteria

Able to carry on normal activity; no special care needed.

100 Normal, no complaints, no evidence of disease.

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

80 Normal activity with effort, some signs or symptoms of disease.

Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.

70 Care for self, unable to carry on normal activity or to do work.

60 Requires occasional assistance from others but able to care for most needs.

50 Requires considerable assistance from others and frequent medical care.

Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.

40 Disabled, requires special care and assistance.

30 Severely disabled, hospitalization indicated, death not imminent.

20 Very sick, hospitalization necessary, active supportive treatment necessary.

10 Moribund

0 Dead

APPENDIX C

Addendum to: A Phase IIA Study of the Addition of Temozolomide to a Standard Conditioning Regimen for Autologous Stem Cell Transplantation in Relapsed and Refractory Central Nervous System (CNS) Lymphoma

This addendum is in relation to section 4.5 on Temozolomide Dosing. The purpose of this addendum is to incorporate more fully the concept of IV administration of temozolomide and our intent to use it as an option in our research protocol in patients with swallowing disorders whether mechanical or psychogenic.

On February 27th, 2009, the FDA granted approval for intravenous temozolomide. The IV form was noted to be bioequivalent to the oral form when administered over 90 minutes. The manufacturers performed randomized, multicenter studies confirming the bioavailability and bioequivalence of the PO and IV formulations which led to the IV formulation approval (Investigator brochure). Temozolomide oral and IV administered as a 90-minute infusion are bioequivalent for peak concentration (C_{max}) and overall exposure (AUC) for temozolomide. As per the brochure, because no data is available on the compatibility of temozolomide for injection with other intravenous substances or additives, other medications should not be infused simultaneously through the same intravenous line.

Work on the IV formulation was published in [Cancer Chemotherapy Pharmacology \(Diez BD, et al. 2010 Mar;65\(4\):727-34. Epub 2009 Jul 30\)](#). Based on the data obtained in the authors' study, "the exposure equivalence data obtained from this study allow for direct extrapolation across the range of therapeutically meaningful doses and administration schedules. In conclusion, this study demonstrated the exposure equivalence of a 90-min intravenous infusion with oral administration of temozolomide."

An earlier study also indicated that Temozolomide was rapidly absorbed, with maximum plasma concentrations being attained 0.7 h post dosing. Over the concentration range studied, temozolomide pharmacokinetics were not dose dependent and the relationship between dose and the area under the plasma concentration vs. time curve was linear ($r = 0.858$), (Newlands, et al Br J Cancer 1992, 65: 287-291). Thus based on the data available, temozolomide dosing is bioequivalent between oral and IV provided that it is given via a 90 minute IV infusion.

Local irritation is the main adverse event of the infusions. The investigator brochure mentioned that 10 out of 22 subjects reported a total of 11 injection-site adverse events and that all but one of these events was mild, and the only moderate event was not associated with any evidence of tissue damage or thrombosis on physical exam. The brochure also mentions that four subjects had a minor degree of local venous tenderness or irritation and that in three of these subjects, the irritation resolved within 4 hours and that in the fourth subject, the irritation resolved on the following day.

A major concern regarding not incorporating the IV formulation of Temozolomide in earnest in the initial protocol submission was that in order to maintain bioequivalence at very high doses, the volume necessary to be infused into patients could become quite burdensome since studies showed that the infusion would have to occur over 90 minutes. As an example provided by pharmacy:

IV Temozolomide is given as a straight drug as 2.5mg/ml

- For example, for BSA of 2m² at a dose of 150mg/m², a total volume of 120ml will need to be infused over 90min (80ml/hr)
- At higher dose, for example with the same BSA of 2m² at a dose of 1000mg/m², a total volume of 800ml will need to be infused over 90min (533ml/hr)

Thus if our study does reach for example the maximum dose for temozolomide of 1000 mg/m² per day for 5 days, then patients would be receiving 533 ml/hr (over 90 minutes). However, if a subject is unable to swallow the capsules, the IV modality would be the only way to administer the drug. The authors of the study feel that by monitoring fluid intake and output carefully, the volume status should not be a major issue should the need arise for the IV formulation of temozolomide at higher doses. Since all patients undergoing HSCT will have PICC lines placed, the two potential issues mentioned immediately above should not be a problem. Also, since temozolomide injection contains no inactive solvent such as propylene glycol, castor oil, or alcohol, infusion reaction would be minimal. However, we will still continue to reserve the IV formulation for those with swallowing disorders, whether mechanical or psychogenic.

APPENDIX D

Summary of Changes

This protocol is the amended version of the last IRB approved version (8/20/2012). Minor edits were made throughout the protocol. Substantive changes are outlined below.

1. Title Page:
 - A. Version control was added
 - B. Investigators and Study Staff were updated
2. List of Abbreviations updated
3. Section 2.5.1: Made reference to Appendix A as this was previously incorporated in the protocol with an earlier amendment
4. Section 3.0: Eligibility criteria clarified
5. Section 4.0: Procedures and time points updated
6. Sections 4.1, 4.2, and 4.3: Co-Investigators added as authors of SOPs to be used for study procedures
7. Section 4.5.2: Clarified that only AEs that are graded a 3 or a 4 will be collected
8. Section 4.7 and 4.7.1: Clarified that timelines for imaging may shift depending on treating physician's assessment. Follow-up after progression will be for survival status only.
9. Section 4.9: Deleted this section, since pharmacokinetic studies were never implemented
10. Section 4.10: Clarified reasons for subject removal
11. Section 6.0: Clarified that only AEs graded 3 or higher will be collected
12. Section 8: Added standard SOCCI study management language and deleted outdated text
13. Appendices: Added Appendix D Summary of Changes