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#### Myeloablative Vs. Non-Myeloablative Consolidation for Primary Central Nervous System Lymphoma: Results of Alliance 51101

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#### Abstract:

While it is evident that standard dose whole brain radiotherapy as consolidation is associated with significant neurotoxicity, the optimal consolidative strategy for primary central nervous system lymphoma (PCNSL) is not defined. We performed a randomized phase 2 clinical trial via the U.S. Alliance cancer cooperative group to compare myeloablative consolidation supported by autologous stem cell transplantation with non-myeloablative consolidation after induction therapy for PCNSL. This is the first randomized trial to be initiated that eliminates whole brain radiotherapy as a consolidative approach in newly-diagnosed PCNSL. Patients, age 18-75 years, were randomly assigned in a 1:1 manner to induction therapy (methotrexate, temozolomide, rituximab and cytarabine) followed by consolidation with either thiotepa plus carmustine and autologous stem cell rescue versus induction followed by non-myeloablative, infusional etoposide plus cytarabine (EA) The primary endpoint was progression-free survival (PFS). 113 patients were randomized and 108 (54 in each arm) were evaluable. More patients in the non-myeloablative arm experienced progressive disease or death during induction (28% versus 11%, p = 0.05). Thirty-six patients received autologous stem cell transplant and 34 received non-myeloablative consolidation. The estimated 2year PFS was higher in the myeloablative versus non-myeloablative arm (73% versus 51%; p= 0.02). However, a planned secondary analysis, landmarked at start of consolidation, revealed that the estimated 2-year PFS in those who completed consolidation therapy was not significantly different between the arms (86% versus 71%; p = 0.21). Both consolidative strategies yielded encouraging efficacy and similar toxicity profiles. Clinicaltrials.gov (NCT01511562)

#### Conflict of interest: COI declared - see note

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Agreement to Share Publication-Related Data and Data Sharing Statement: De-identified patient data may be requested from Alliance for Clinical Trials in Oncology via concepts@alliancenctn.org if data are not publicly available. A formal review process includes verifying the availability of data, conducting a review of any existing agreements that may have implications for the project, and ensuring that any transfer is in compliance with the IRB. The investigator will be required to sign a data release form prior to transfer.

Clinical trial registration information (if any): Clinicaltrials.gov (NCT01511562)

# Myeloablative Versus Non-Myeloablative Consolidation for Primary Central Nervous System Lymphoma: Results of Alliance 51101

ASCT versus Non-Myeloablative Consolidation in PCNSL

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De-identified patient data may be requested from Alliance for Clinical Trials in Oncology via <u>concepts@alliancenctn.org</u> if data are not publicly available. A formal review process includes verifying the availability of data, conducting a review of any existing agreements that may have implications for the project, and ensuring that any transfer is in compliance with the IRB. The investigator will be required to sign a data release form prior to transfer.

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#### Abstract

While it is evident that standard dose whole brain radiotherapy as consolidation is associated with significant neurotoxicity, the optimal consolidative strategy for primary central nervous system lymphoma (PCNSL) is not defined. We performed a randomized phase 2 clinical trial via the U.S. Alliance cancer cooperative group to compare myeloablative consolidation supported by autologous stem cell transplantation with nonmyeloablative consolidation after induction therapy for PCNSL. This is the first randomized trial to be initiated that eliminates whole brain radiotherapy as a consolidative approach in newlydiagnosed PCNSL. Patients, age 18-75 years, were randomly assigned in a 1:1 manner to induction therapy (methotrexate, temozolomide, rituximab and cytarabine) followed by consolidation with either thiotepa plus carmustine and autologous stem cell rescue versus induction followed by non-myeloablative, infusional etoposide plus cytarabine (EA) The primary endpoint was progression-free survival (PFS). 113 patients were randomized and 108 (54 in each arm) were evaluable. More patients in the non-myeloablative arm experienced progressive disease or death during induction (28% versus 11%, p = 0.05). Thirty-six patients received autologous stem cell transplant and 34 received nonmyeloablative consolidation. The estimated 2-year PFS was higher in the myeloablative versus non-myeloablative arm (73% versus 51%; p=0.02). However, a planned secondary analysis, landmarked at start of consolidation, revealed that the estimated 2-year PFS in

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Clinicaltrials.gov (NCT01511562)

#### Funding

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#### Key Point

Both Myeloablative and Non-Myeloablative consolidation had encouraging efficacy and safety in PCNSL patients, age 18 to 75 years.

#### Introduction

Primary central nervous system lymphoma (PCNSL) is associated with outcomes inferior to systemic large B-cell lymphoma and is refractory to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).(1, 2) While the combination of methotrexate, temozolomide and rituximab (MTR) has been applied with significant efficacy as induction therapy in multicenter investigations in newly diagnosed PCNSL,(3, 4) it is highly unlikely that methotrexate-based induction strategies alone are curative for a significant fraction of patients.(5, 6) Standard dose (36-45 Gy) whole brain radiotherapy (WBRT) is associated with severe neurotoxicity, particularly in patients older than 60 years.(7, 8) While reduced- dose WBRT (23 Gy) has been studied as an alternative to standard

dose WBRT, long- term follow-up is lacking.(9) To date, no studies have compared nonradiation-based, dose-intensive chemotherapy consolidation strategies in PCNSL.

In the phase 2 Cancer and Leukemia Group B (CALGB) 50202 study, doseintensive chemotherapy consolidation after MTR induction consisted of nonmyeloablative, infusional etoposide plus high-dose cytarabine (EA).(4, 10) In this study, EA consolidation was evaluated only in patients who achieved a complete response to induction, was determined to be well tolerated in the multicenter setting, and resulted in a 2-year progression-free survival (PFS) of 57%, at least similar to that reported for reduced-dose WBRT.(4)

Several clinical trials have demonstrated the feasibility and efficacy of consolidation in PCNSL with myeloablative high-dose chemotherapy followed by autologous stem cell transplant (HDT/ASCT). Two randomized phase 2 trials demonstrated that HDT/ASCT is associated with promising 2-year progression-free survival, at least comparable to consolidative WBRT, but with a reduced frequency of clinical neurotoxicity.(11) In particular, the carmustine/thiotepa combination has been applied as a conditioning regimen with encouraging efficacy and safety in newly diagnosed PCNSL.(12, 13)

In this current trial, CALGB 51101 (NCT01511562), we compared the outcomes and toxicities of myeloablative consolidation and ASCT using the carmustine/thiotepa conditioning regimen versus those of non-myeloablative consolidation using doseintensive EA chemotherapy, and tested the hypothesis that myeloablative consolidation would be superior to the non-myeloablative regimen. Distinct from CALGB 50202, in CALGB 51101 these two consolidation approaches were evaluated in PCNSL patients who achieved stable disease or better with induction methotrexate, temozolomide, rituximab followed by single administration of high dose cytarabine (MTRA)(4).

#### Methods

#### Study Design

CALGB (Alliance) 51101 is a randomized, open-label, phase 2, multicenter trial. The study was conducted in the Alliance cooperative group in 27 hospitals in the United States. All participating hospitals received approval from their respective institutional review boards.

#### Patients

Patients with newly diagnosed PCNSL were the target population for this clinical trial. Key inclusion criteria included pathological diagnosis of diffuse large B cell lymphoma (DLBCL), no concurrent or prior systemic lymphoma, age 18-75 years, Karnofsky Performance Status (KPS)  $\geq$  30 in patients up to age 69 or  $\geq$  50 in patients ages 70-75, negative serology for human immunodeficiency virus, and no history of organ transplantation. Gender was self-reported by patients as male or female. All patients or legally authorized representatives signed informed consent approved by the institutional review board of each enrolling institution. The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice.

#### Randomization

Patients were randomized in a 1:1 allocation to receive induction chemotherapy followed by myeloablative chemotherapy versus induction therapy followed by nonmyeloablative chemotherapy. Patient randomization was performed at the time of registration through the Alliance Registration and Randomization Office.

Randomization was stratified by a composite of age and KPS (age < 51 years vs. age >51 years and KPS >70 vs. age >51 years and KPS < 70) using dynamic allocation.

#### Procedures

All patients received the same induction therapy consisting of intravenous (IV) methotrexate (8 g/m<sup>2</sup>, days 1 and 15 of cycles 1 and 2); temozolomide (150 mg/m<sup>2</sup>, days 7-11 of cycle 1 and 200 mg/m<sup>2</sup>, days 7-11 on cycle 2); rituximab 375 mg/m<sup>2</sup>, days 3, 10, 17, 24 of cycle 1 and days 3, 10 on cycle 2. This was followed by methotrexate (8 g/m<sup>2</sup>, days 1 and 15) and temozolomide (200 mg/m<sup>2</sup>, days 7-11) for cycles 3 and 4, followed by IV cytarabine (2 g/m<sup>2</sup> over two hours every 12 hours for 48 hours) for cycle 5. After these 5 cycles, patients in the myeloablative arm underwent stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) followed by stem cell collection. This was followed by IV carmustine 400 mg/m<sup>2</sup> on day -6, IV thiotepa 5 mg/kg every 12 hours on days -5 and -4, followed by stem cell infusion on day 0 with G-CSF 5 mcg/kg/day, days +4 and beyond until absolute neutrophil count was > 1500. Patients in the non-myeloablative arm received IV cytarabine 2 g/m<sup>2</sup> over 2 hours every 12 hours for eight doses (total dose, 16 g/m<sup>2</sup> and etoposide 5 mg/kg, administered IV over 96 hours (total dose, 40 mg/kg).<sup>4</sup> (Figure 1A)

#### Outcomes

The primary endpoint of the study was progression-free survival (PFS), defined as the time from randomization until disease progression or death from any cause, censoring patients alive and disease-free at the date of last disease assessment. Secondary endpoints included response to induction, event-free survival (EFS), overall survival (OS), assessment of adverse events (AEs) and tolerability, and neurocognition as measured by the Mini-Mental State Examination (MMSE). Response was evaluated using modified International PCNSL Collaborative Group criteria. EFS was defined from randomization until the first disease progression, start of alternative therapy, or death from any cause, censoring event-free patients at last disease assessment. OS was defined as the time from randomization until death from any cause, censoring patients alive at last follow-up.(14) AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.

#### **Statistical Analysis**

Initially, the study was designed to test for an improvement in PFS corresponding to an improvement in 2-year PFS from 50% to 70% for patients randomized to the myeloablative versus non-myeloablative arms. With 95 events in 160 patients, there was 90% power using a one-sided log-rank test and alpha=10%, assuming a median PFS of 3 months for patients who develop progression during induction therapy for each arm. Due to lower than expected accrual, the design was modified to provide 84% power with 64 events in 110 patients to detect an improvement in PFS corresponding to an improvement in the 2-year PFS rates from 50% vs. 73% in the non-myeloablative vs. myeloablative arms, respectively. Finally, with few events but mature follow-up, the protocol was amended to allow for the primary endpoint analysis after all patients had been followed for 3 years.

All randomized eligible patients who started induction therapy were included in the primary endpoint analysis (modified intent-to-treat population). Secondary analyses included the subset of patients who completed consolidation, with time-to-event analyses landmarked at the start of consolidation. PFS, EFS, and OS distributions were estimated using the Kaplan-Meier method. Per protocol, PFS distributions for the primary analysis were compared using a log-rank test; a stratified log-rank test was used for a sensitivity analysis and for other comparisons of time-to-event endpoints. Medians and 2-year estimates were calculated using Kaplan-Meier methods along with corresponding 95% confidence intervals. Response rates were estimated along with corresponding exact binomial 95% confidence intervals and compared between arms using Fisher's exact tests. Frequency tables of adverse events were summarized by maximum severity and types of adverse events, and differences in severe (grade 3+) adverse events were compared between arms using Fisher's exact tests. Similarly, the proportions of patients who required dose modifications, delays, or treatment holds were also summarized. The influence of factors (e.g., baseline neurocognitive impairment) on PFS, EFS, and OS were

evaluated using multivariable Cox regression models. Unless otherwise specified, all reported p-values are two-sided and statistical significance was declared for p<0.05. All data collection and analyses were performed by the Alliance Statistics and Data Management Center using SAS® version 9.4. Data quality was ensured by review of data by the Alliance Statistics and Data Management Center statistics and Data Management Center and by the study chairperson following Alliance policies. Data were locked as of January 20, 2021.

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The trial was registered with clinicaltrials.gov (NCT01511562).

#### Role of the funding source

This study was conducted through the Alliance cooperative group, which is funded by the National Cancer Institute (NCI). The NCI provided oversight for the design and implementation of this trial, but not in the data collection, analysis, interpretation of the results, or the writing of the report.

The study was approved by the IRB of each of the participating institutions.

#### Results

Of a total of 113 patients registered between November 17, 2012, and May 2, 2017; 57 were randomized to receive myeloablative treatment and 56 were randomized to receive non-myeloablative treatment across 27 centers. Five patients were ineligible or did not start protocol treatment. One hundred and eight (108) patients who were eligible and started treatment comprise the modified intent-to-treat population and are included in the primary endpoint analysis (54 in each arm) (Figure 1B).

Table 1 shows the distributions of baseline characteristics by treatment arm for 108 eligible patients who started induction therapy. There were no significant differences between the two arms with respect to the following prognostic variables: age, KPS, ophthalmologic involvement by lymphoma, involvement of cerebrospinal fluid (CSF) by lymphoma, or deep brain location.

There were six grade 5 adverse events (AEs) during induction, including four in the non-myeloablative arm (7.4%; sepsis, acute kidney injury, death NOS, and neoplasms benign/malignancy/other) and two in the myeloablative arm (3.7%; sudden death NOS

and other malignancy). There were no grade 5 AEs reported during consolidation therapy. One patient in the myeloablative arm experienced a grade 5 AE, a depression/suicide event that occurred 16 months after the end of treatment.

Notable grade 3 or higher adverse events during or after consolidation are presented by consolidation arm (Figure 2). Most patients experienced a grade 3 or higher hematologic AE, with a comparable proportion between myeloablative and non-myeloablative arms (92% versus 94%; p=0.99). Grade 3 or higher non-hematologic AEs were not significantly different between the two arms (79% in the myeloablative arm versus 68% in the non-myeloablative arm; p=0.30). All grade 3 or higher AEs reported during induction and after the start of consolidation are provided in the Supplemental Table 3.

Among the 38 patients receiving myeloablative consolidation therapy, 2 (5%) had dose modifications of thiotepa and 2 (5%) had dose delays; there were no omissions of drug. Two patients who began the myeloablative consolidation regimen did not complete it; one refused further treatment after stem cell mobilization, and another had unsuccessful stem cell collection. Among the 34 patients receiving non-myeloablative consolidation therapy, 1 (3%) required a dose modification to cytarabine and 2 (6%) had dose delays; there were no dose omissions. Overall, out of 72 patients who received consolidation, only two did not complete consolidation therapy and they were the two randomized to myeloablative therapy who discontinued treatment during stem cell collection, described above. Thus, the landmark analyses from start of consolidation focus on the 70 patients who started and completed the core component of the consolidation therapy.

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Among 108 eligible patients who started induction therapy, 85 (79%) completed all 5 cycles. At the conclusion of induction therapy, 54 (50%, 95% CI: 40-60%) achieved either a confirmed or unconfirmed complete response (CR + CR<sub>u</sub>), and 24 achieved a partial response (PR) for an overall radiographic response (ORR) rate of 72% (95% CI: 63-80%). By end of induction, 17 (15.7%) had progressive disease (PD), specifically 9% of those randomized to myeloablative versus 24% of those randomized to non-myeloablative arms. As shown in Table 2, although all patients received the same induction regimen, more patients randomized to the myeloablative arm responded (CR/CRu/PR) to MTR than patients randomized to the non-myeloablative consolidation therapy, 89% had a response or stable disease at the end of induction and were thus eligible to receive consolidation therapy (p=0.015).

Out of the 108 patients who started induction therapy, 23 did not complete induction treatment and an additional 13 patients completed induction but opted not to continue to consolidation therapy. Among the 54 evaluable patients randomized to the myeloablative arm, 9 (17%) did not complete induction (3 due to PD, 2 for AEs, 1 death, and 3 for other reasons) and 7 completed induction but did not receive consolidation (2 due to PD, 3 treatment refusals, 2 for other reasons, including insurance coverage). In the 54 evaluable patients randomized to the non-myeloablative arm, 14 (26%) did not complete induction but did not receive arm, 14 (26%) did not complete induction but did not receive consolidation (5 due to PD, 1 for treatment refusal).

Collectively, there was an imbalance between the myeloablative and non-

myeloablative arms in the proportion of patients who went off treatment due to progression or death (11% versus 28%, p = 0.049) prior to the start of consolidation, despite patients receiving the same induction therapy.

The median PFS from time of randomization was, respectively, 6 years (3.9 – not reached) versus 2.4 years (0.6 – not reached) in the myeloablative and the non-myeloablative arms (HR=0.51, 95% CI: 0.29 – 0.90; p=0.02, by log-rank and stratified log-rank tests). As shown in Figure 3A, there is early separation in the PFS curves before consolidation, highlighting the differences introduced between arms during the common induction treatment phase. Specifically, 6-month PFS estimates were 89% (95% CI: 77-95%) versus 71% (95% CI: 56-81%) in the myeloablative and non-myeloablative arms, respectively. By 2 years, the estimated PFS rates were 73% (95% CI: 58-83%) versus 51% (95% CI: 36-63%), respectively.

Per protocol, a secondary analysis was performed for the subset of patients who completed consolidation therapy. This secondary analysis was important given the imbalance in the number of patients with significant events precluding the start of consolidation therapy. Among 72 patients who went on to consolidation therapy in this study, 70 were able to complete that therapy. Clinical characteristics of these 70 patients who went on to consolidation were balanced between arms. (Supplemental Table 1). Of these 70 patients (36 completing myeloablative consolidation and 34 completing non-myeloablative consolidation), there was a nonsignificant trend for longer PFS in the myeloablative arm compared to the non- myeloablative arm (HR=0.58, 95% CI: 0.25 – 1.36; p=0.21) with estimated 2-year PFS rates after the start of consolidation of 86% (95% CI: 69-94%) versus 71% (95% CI: 52- 83%), respectively (Figure 3B). Across both

treatment arms, the overall median PFS was 4.9 years (95% CI: 2.5 to not reached) and the estimated 2-year PFS rate was 62% (95% CI: 52 – 71%).

Nine patients received non-protocol therapy prior to a PFS event (5 in the absence of a PFS event) and are included as events for EFS. In the subset of patients who completed consolidation, EFS estimates at 2 years after the start of consolidation were higher in the myeloablative arm versus the non-myeloablative arm, 86% (95% CI: 69- 94%) versus 68% (95% CI: 49-81%), but there was not a significant difference between the EFS curves (HR=0.61, 95% CI: 0.27 – 1.37; p=0.22).

With a median follow-up of 4.1 years, there have been 26 deaths in the 108 evaluable patients. Median OS was not reached in either arm, and there was no difference in OS in the myeloablative versus non-myeloablative arms (HR=0.60, 95% CI: 0.27 – 1.31; p = 0.19; Figure 3C). OS estimates at 2 years were 87% (95% CI: 74-93%) versus 78% (95% CI: 64-87%) in those randomized to the myeloablative and non-myeloablative arms. In the subset of patients who completed consolidation, there were only 8 deaths (5 in the myeloablative arm and 3 in the non-myeloablative arm). Few deaths occurred in the first 2 years after the start of consolidation, with 2-year OS estimates of 97% (95% CI: 81-100%) and 91% (95% CI: 75-97%) in the myeloablative and the non-myeloablative arms, respectively (Figure 3D). Additional planned correlative secondary endpoints per protocol will be presented in a future publication.

To identify individual clinical prognostic variables, we first evaluated candidates from the International Extranodal Lymphoma Study Group and Memorial Sloan-Kettering prognostic scoring systems for PCNSL.(15, 16) Outcome was not correlated with age, KPS, lactate dehydrogenase, deep brain involvement, or CSF involvement. We also considered baseline MMSE scores, available in 99 patients, of which 95 were evaluable for the primary endpoint. Unlike other clinical variables considered, baseline MMSE score was an independent prognostic variable for OS (but not PFS). Using data of van der Meulen *et al.*,(17) plus independent recursive partitioning analysis, we identified a cut point for the baseline MMSE score of 27 as a categorical variable, where scores less than 27 correlated with inferior OS (HR=3.25, 95% CI: 1.36 - 7.76; P=0.008, Figure 4A). Results were retained even after adjusting for treatment arm and age in the model. (HR=3.36, 95% CI: 1.39 - 8.12; P=0.006).

### Discussion

The results of CALGB 51101, the first randomized trial for PCNSL to be initiated in which neither arm involved WBRT, strongly support the feasibility, safety, and efficacy of intensive chemotherapy-based consolidation strategies, with both two dosemyeloablative and non-myeloablative arms achieving excellent PFS and OS without While comparisons between the two arms are limited by relatively small radiotherapy. sample size and confounded by significant differences in the frequency of disease progression and death as well as by response proportions between the two arms during identical induction therapy, the estimated 2-year PFS rates for the myeloablative arm, 73%, is encouraging and consistent with the outcomes in other phase 2 randomized trials that evaluated ASCT in newly diagnosed PCNSL.(11, 18) Notably, Kaplan-Meier analysis demonstrates that the non-myeloablative arm showed evidence for the emergence of a stable plateau in the PFS curve starting at four years, similar to previous studies using EA consolidation.(4)

Notably, Illerhaus and colleagues presented results of the IELSG43 trial in PCNSL

that compared a BCNU/thiotepa-based transplant-based consolidation to a distinct nonmyeloablative consolidation program, the DeVic regimen, based on ifosfamide, etoposide plus carboplatin. In this phase 3 study, PFS and OS results, currently available in abstract form (2022 annual meeting of the American Society of Hematology), significantly favored ASCT compared to the non-myeloablative regimen.

It is important to note that CALGB 51101 also supports the feasibility of autologous stem cell transplant as consolidation in older patients with PCNSL, consistent with the results of the MARITA trial, which demonstrated safety and efficacy of myeloablative consolidation in 14 older PCNSL patients, age 69-79.(19)

Notably, in CALGB 51101, the incidence of disease progression during the first year post-consolidation was markedly higher with non-myeloablative, EA-based consolidation. However, after year one post-consolidation, the frequency of CNS lymphoma progression was higher among patients who received the myeloablative therapy, likely reflecting the differential impact of dose intensity in chemotherapy-based consolidation on the timing of early versus delayed progression in PCNSL.

Both regimens were well tolerated in multicenter execution and there was limited severe clinical neurotoxicity; however, detailed formal neurocognitive testing has not yet been completed. Importantly, there was no treatment-related mortality (TRM) associated with either consolidative arm in this study. Notably, this is distinct from other prospective studies of similar size, in which ASCT, using a different consolidation regimen, thiotepa, busulfan and cyclophosphamide (TBC), has been reproducibly associated with TRM rates of ~11%. (11, 20) Our results therefore support the safety and efficacy of the carmustine/thiotepa combination as a transplant conditioning regimen in newly

diagnosed PCNSL, in patients ages 18-75 years.

Importantly, CALGB 51101 also highlights the limitations of current methotrexatebased induction approaches in PCNSL. While the MTRA combination was well tolerated and associated with an overall 50% rate of complete response, 19.4% of newly diagnosed PCNSL patients in this study exhibited disease progression or died during induction therapy, without receipt of consolidation, similar to the experience in previous studies.(4, 6, 10, 11) Identification of molecular biomarkers that identify the subpopulation of PCNSL patients destined to experience early disease progression during methotrexatebased induction therapy is a research priority, as is the incorporation of targeted agents with greater anti-lymphoma efficacy within induction strategies. Based on the CSF penetration and activity of lenalidomide in relapsed CNS lymphomas,(21, 22) as well as evidence for activity of checkpoint blockade in this setting,(23) a successor trial, Alliance A051901 (NCT04609046) has been developed to address the need for more effective induction strategies in PCNSL.

Our study confirms that baseline MMSE score in PCNSL has independent prognostic significance.(18) In our dataset inclusive of patients age up to 75 years, it was the most significant individual clinical prognostic variable. We conclude that baseline MMSE score needs to be considered a prognostic factor in PCNSL, used in patient counseling in practice, and in risk stratification within design of future trials.

Acknowledging the limitations of a randomized phase 2 trial, Alliance 51101 demonstrates for the first time that each dose-intensive consolidation strategy, myeloablative and non-myeloablative, provides excellent disease control after MTR induction therapy in PCNSL, with acceptable toxicity. While there is a non-significant trend towards improved PFS, but not OS, among patients treated in the myeloablative arm, we envision that further insights into PCNSL biology will identify the subset of patients who require ASCT for optimal outcome as well as the subset that can achieve long-term survival and potentially cure with non-myeloablative therapy alone.

#### Contributors

TTB wrote the first draft of the manuscript with input from SG, ASR, SMG, SES, NM, LJS, JWF, BSK, NLB, EDH, BDC, NWJ, LN, JPL, JLR.

SG, ASR, SMG performed the statistical analysis.

All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

SG, SMG directly accessed and verified the underlying data reported in this manuscript.

#### **Declaration of interests**

The following authors declare competing interests: Tracy T. Batchelor (ONO Pharmaceuticals) Sharmila Giri (none), Amy S. Ruppert (Eli/Lilly, Telios), Susan M. Geyer (none), Scott E. Smith (none), Nimish Mohile (Biogen), Lode J. Swinnen (Abbvie), Jonathan W. Friedberg (none), Brad S. Kahl (Genentech/Roche), Nancy L. Bartlett (ADC Therapeutics, Affimed, Autolous, BMS/Celgene, Forty Seven, Gilead/Kite Pharma, Immune Design, Janssen, Merck, Millennium, Pfizer, Pharmacyclics, Roche/Genentech, Seattle Genetics), Eric D. Hsi (Eli Lilly, Abbvie, Virtuoso

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### **Figure Legends**

### Figure 1. Study Design and Consort Diagram

**Figure 2.** Incidence of Grade 3 and Higher Adverse Events During Consolidation. Comparison of Myeloablative vs. Non-Myeloablative Therapy: Thrombocytopenia, 81% vs. 85%; Neutropenia, 79% vs. 82%; Febrile Neutropenia, 53% vs. 53%; Anemia,

53% vs. 76%; Lymphopenia, 54% vs. 38%; Oral Mucositis, 37% vs. 12%;

Hyperglycemia,

3% vs. 18%; Hypophosphatemia, 11% vs. 12%; Generalized Muscle Weakness, 16% vs.

0%; Fatigue 11% vs. 0%; Anorexia, 11% vs 0%; Hypertension, 11% vs. 9%; Cognitive

Disturbance 8% vs. 0%; Delirium, 8% vs. 0%.

While the incidence of grade 3 or higher cytopenias and febrile neutropenia were comparable between the consolidative arms, two patients on the myeloablative arm experienced grade 4 sepsis versus none in the non-myeloablative arm. Also, three patients in the myeloablative arm experienced grade 3 cognitive disturbances versus none in the non-myeloablative arm; one of these occurred in a patient within 3 months after ending treatment, but the other two patients had these events occur 16 and 24 months after the end of treatment.

Also, among 108 patients who received induction therapy, the numbers of patients with dose modifications, omissions, or delays due to any of the 4 drugs administered were 84 (78%), 38 (35%), and 73 (68%), respectively. The numbers of patients with dose

modifications during MTRA induction were 81 (75%), 30 (28%), 1 (<1%), and 6 (6%) for each agent respectively; the numbers of patients with dose omissions were 21 (19%), 24 (22%), 10 (9%), and 1 (<1%), for each agent respectively; and the numbers of patients

with dose delays were 57 (53%), 26 (24%), 18 (17%), and 6 (6%), for each agent respectively.

# Figure 3. Kaplan-Meier analysis of Progression-Free and Overall Survival in 51101

(A). Progression-free survival of the modified intent-to-treat population according to consolidation group. (B). Progression-free survival from the time of consolidation according to consolidation group. (C). Overall survival of the modified intent-to-treat according to consolidation group. (D) Overall survival from the time of consolidation according to consolidation group.

Figure 4. Prognostic Variables including Mini-Mental State Examination in CALGB 51101. (A). Analysis of baseline clinical characteristics, adjusting for treatment arm, demonstrated that baseline MMSE was the only variable that

correlated with overall survival. Mean baseline MMSE score for the myeloablative group was 25.7 (SD 5.92). Mean baseline MMSE score for the non-myeloablative group was 25.8 (SD 6.31). Median baseline MMSE scores were 28 in each group. MMSE scores were summarized as a continuous measure as well as categorically, both as any neurocognitive impairment (MMSE <27 versus not) as well as level of neurocognitive impairment (severe, 0-9 versus moderate, 10-20 versus, mild 21-26 versus, normal 27-30).

B). Kaplan-Meier analysis using a MMSE score of 27 as a categorical variable suggests a significant correlation between baseline neurocognitive impairment on survival in PCNSL in CALGB 51101, p<0.01. The MMSE score of 27 as a categorical variable significantly correlated with overall survival in patients that received myeloablative therapy (p<0.02) and non-myeloablative therapy (p<0.07).

We found that the negative impact of impaired neurocognition is heavily influenced by the significant impact of severe cognitive impairment (MMSE score of 0-9) on OS in relation to those with normal cognition at baseline (HR=19.8, 95% CI: 4.94 - 79.0, p<0.001), even after adjusting for age and treatment arm. In this same model, we found that the mild (MMSE 21-26) and moderate (MMSE 10-20) cognitive impairment corresponded to a tendency toward worse OS outcomes (mild: HR=2.85, 95% CI: 1.06 - 7.66, p=0.03; moderate: HR=2.42, 95% CI: 0.62 - 9.43, p=0.20). Further, although an MMSE <27 (vs. not) at baseline was not associated with worse PFS, we found that severe cognitive impairment at baseline was significantly associated with worse PFS (HR=7.32, 95% CI: 2.09 - 25.6, p=0.001) in relation to those with normal baseline cognition, even adjusting for age and treatment arm. Caveats with these findings are based on the fact that there were more limited numbers of patients with moderate (n=9) and severe (n=3) cognitive impairment at baseline. Also, those with MMSE scores at baseline of at least 27 (i.e., no cognitive impairment) tended to have better Karnofsky PS (KPS) than those with any cognitive impairment (medians: 80 vs. 70, p<0.001); based on the nonsignificant influence of KPS on OS (p=0.27), this does not appear to have any confounding effects on the influence of baseline MMSE on OS. No other baseline characteristics were significantly associated with baseline MMSE status. Baseline MMSE continuous scores as well as categorical status (e.g., <27 vs.  $\geq 27$ ) were also not significantly different between the treatment arms. (Figure 4A and Supplemental Table 2).

Table 1.	Patient	Characteristics
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Characteristic	All Patients	Myeloablative	Non-Myeloablative	
	(N = 108)	(N=54)	(N=54)	
Age, years				
Median (IQR)	61 (54, 67)	61 (52 <i>,</i> 67)	61 (55, 68)	
Range	33-75	34-74	33-75	
Karnofsky Performance Status				
Median (IQR)	80 (70, 90)	80 (70 <i>,</i> 90)	70 (60, 90)	
Range	30-100	30-100	30-100	
Age/KPS risk groups, n (%)				
Age <51 years, any KPS	20 (19)	10 (19)	10 (19)	
Age <u>&gt;</u> 51 years, KPS <u>&gt;</u> 70	65 (60)	33 (61)	32 (59)	
Age <u>&gt;</u> 51 years, KPS <70	23 (21)	11 (20)	12 (22)	
Female, n (%)	47 (44)	22 (41)	25 (46)	
Elevated LDH, n (%)	26 (25)	13 (25)	13 (24)	
Deep brain involvement, n (%)	46 (43)	24 (44)	22 (41)	
Slit lamp result, n (%)				
Normal	90 (87)	43 (83)	47 (90)	
Minor RPE abnormality	7 (7)	3 (6)	4 (8)	
Decrease in vitreous cells of	1 (1)	1 (2)	0 (0)	
retinal infiltrate				
Recurrent or new disease	6 (6)	5 (10)	1 (2)	
CSF Cytology, n (%)				
Negative	67 (76)	35 (80)	32 (73)	
Atypical or suspicious	13 (15)	6 (14)	7 (16)	
Positive	8 (9)	3 (7)	5 (11)	

Table 2. Resp	onses to	Induction	
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	All	Myeloablative	Non-	Р
	(N = 108)	(N=54)	Myeloablative	
			(N=54)	
Response, n (%)				0.047
Complete remission (CR)	29 (27)	12 (22)	17 (31)	
Complete remission, unconfirmed (CR <sub>u</sub> )	25 (23)	18 (33)	7 (13)	
Partial remission (PR)	24 (22)	14 (26)	10 (19)	
Stable disease (SD)	8 (7)	4 (7)	4 (7)	
Progressive disease (PD)	18 (17)	5 (9)	13 (24)	
Not Evaluated	4 (4)	1 (2)	3 (6)	
Complete response [CR/CR <sub>u</sub> ], n (%)	54 (50)	30 (56)	24 (44)	0.17
Overall objective response [CR/CR <sub>u</sub> /PR], n (%)	78 (72)	44 (81)	34 (63)	0.026
Clinical benefit rate [CR/CR <sub>u</sub> /PR/SD], n (%)	86 (80)	48 (89%)	38 (70%)	0.015

## Figure 1

## Figure 1. Study Design and Consort Diagram

#### Α.



G-CSF 5 mcg/kg/d, starting Day +4

В.

Figure 2. Grade 3 or Higher Adverse Events After Start of Consolidation

# Figure 3



Figure 3. Kaplan-Meier analysis of Progression-Free and Overall Survival in 51101

## Figure 4

## Figure 4. Prognostic Variables including Mini-Mental State Examination in 51101

Α.

	PFS			OS		
Number of Patients (N = 95)	Hazard Ratio	95% CI	Р	Hazard Ratio	95% CI	Р
Treatment Arm (Myeloablative vs Non-myeloablative)	0.54	0.3-0.99	0.04	0.63	0.27-1.48	0.28
Age, 10-year increase	0.90	0.69-1.17	0.43	1.48	0.93-2.37	0.09
KPS, 10-unit increase	0.92	0.75-1.12	0.38	0.84	0.65-1.1	0.20
Gender, Female vs Male	0.79	0.43-1.47	0.45	0.50	0.19-1.27	0.14
Elevated LDH, Yes vs No	0.88	0.43-1.78	0.71	0.84	0.31-2.28	0.73
Deep Brain Involvement, Yes vs No	0.82	0.45-1.5	0.51	1.15	0.5-2.66	0.74
Slitlamp Result, Normal vs Other	1.29	0.51-3.29	0.59	0.73	0.25-2.17	0.57
CSF Result, Normal vs Other	1.22	0.58-2.59	0.59	2.22	0.65-7.55	0.20
MMSE Score, <27 vs >=27	1.25	0.68-2.28	0.46	3.25	1.36-7.76	0.008

B.

