haematologica
Journal of the Ferrata Storti Foundation

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Received: February 24, 2026.
Accepted: June 4, 2026.

Citation: Ji Yun Lee, Sang-A Kim, Deok-Hwan Yang, Hyeon-Seok Eum, Myung-Won Lee, Hyun Jung Lee, Jae-Yong Kwak, Young Hoon Park, Young Rok Do and Jeong-Ok Lee. Phase II study of lenalidomide maintenance after rituximab-methotrexate-based induction therapy in primary central nervous system lymphoma.
Haematologica. 2026 June 18. doi: 10.3324/haematol.2026.300790 [Epub ahead of print]

Phase II study of lenalidomide maintenance after rituximab-methotrexate-based induction therapy in primary central nervous system lymphoma

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Running title: Lenalidomide Maintenance in Elderly PCNSL

Clinical Trial Registration: ClinicalTrials.gov identifier: NCT05260619. Study title: Lenalidomide Maintenance Treatment in Patients With Primary Central Nervous System Lymphoma (PCNSL-LEM). Study type: Interventional, open-label, prospective, multicenter, single-arm phase II trial. Protocol identifier: B-2107-699-001 (Seoul National University Bundang Hospital IRB). Sponsor: Consortium for Improving Survival of Lymphoma (CISL).

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Conflict of interest statement

The authors declare no competing financial interests.

Funding

This study was granted from Seoul National University Bundang Hospital Research Fund (grant no. 02-2021-00056).

Author Contributions

JYL and JOL conceptualized and designed the study, coordinated, and supervised the data collection. JYL and JOL analyzed the data, drafted, and revised the manuscript. SAK, DHY, HSE, MWL, HJL, JYK, YHP, and YRD contributed to the clinical trial. All authors agreed to be responsible for all aspects of the study. All authors read and approved of the final manuscript.

Data availability

The data may be obtained from the corresponding authors on reasonable request.

Acknowledgments

The Lymphoma Working Group of the Korean Society of Hematology and the Consortium for Improving Survival of Lymphoma conducted this study. We thank all patients and investigators involved in this study. Lenalidomide was kindly provided by Samyang Biopharm.

Abstract

Adults with primary central nervous system lymphoma (PCNSL) who are ineligible for consolidative whole-brain radiotherapy (WBRT) or autologous stem-cell transplantation (ASCT) due to advanced age, comorbidities, or impaired performance status have limited treatment options. Lenalidomide is active in relapsed PCNSL, but prospective data on its use as maintenance are limited. We conducted a multicenter phase II trial of lenalidomide maintenance in adults with PCNSL who achieved at least a partial response after 2–6 cycles of methotrexate- and rituximab-based chemoimmunotherapy and were not candidates for WBRT or ASCT. Lenalidomide 15 mg was given orally on days 1–21 of 28-day cycles for up to 12 cycles or until progression or toxicity. The primary endpoint was 2-year progression-free survival (PFS) from maintenance initiation. Thirty-one patients were enrolled (median age 72 years); 30 received lenalidomide with a median of 11 cycles, and 50% completed all 12. At a median follow-up of 20.7 months, the 2-year PFS was 58.8% (95% CI, 43.4–79.8%), exceeding the pre-specified alternative threshold of 55%, although the formal one-sample log-rank test did not reach statistical significance ($p = 0.084$). The 2-year overall survival was 83.9%. Grade 3–4 neutropenia occurred in 53.3%, whereas most non-hematologic adverse events were grade 1–2. Treatment was discontinued for toxicity in 13%; one grade 5 pneumonia occurred, and no thromboembolic events were observed. These findings suggest that lenalidomide maintenance is feasible and potentially beneficial in consolidation-ineligible PCNSL patients, though the hypothesis-generating nature of this single-arm study warrants confirmation in randomized comparative trials.

Keywords: Primary central nervous system lymphoma, Lenalidomide, Maintenance therapy, Chemoimmunotherapy

Introduction

Primary diffuse large B-cell lymphoma (DLBCL) of the central nervous system (CNS), termed primary CNS lymphoma (PCNSL), is an aggressive extranodal non-Hodgkin lymphoma confined to the brain, spine, cerebrospinal fluid (CSF), or vitreoretinal space [1, 2]. Methotrexate (MTX), the most effective agent against PCNSL, forms the backbone of induction chemoimmunotherapy. Commonly used HD–MTX–based regimens include MATRix (MTX, cytarabine, thiotepa, and rituximab) [3], R–MPV (rituximab, MTX, procarbazine, and vincristine) [4], R–MBVP (rituximab, MTX, carmustine, teniposide, and prednisolone) [5], and rituximab–MTX–temozolomide (R–MT) [6]. No single regimen has been established as a global standard; regimen selection is guided by patient factors including age, fitness and comorbidities, as well as regional or institutional preference [7, 8]. Consolidation with whole-brain radiotherapy (WBRT) or high-dose chemotherapy with autologous stem-cell transplantation (ASCT) improves progression-free survival (PFS) and overall survival (OS) in younger, fit patients [9-11]. However, PCNSL is a disease of older adults. Between 2000 and 2019, according to the Surveillance, Epidemiology, and End Results (SEER) database on PCNSL, 63% of patients were over 60 years old, indicating an increasing incidence of PCNSL in the elderly population [12, 13]. This trend underscores the growing impact of PCNSL on older adults and highlights the need for targeted treatment strategies for transplant-ineligible patients, in whom neurotoxicity and transplant-related morbidity substantially limit the use of intensive consolidation. In elderly or consolidation-ineligible PCNSL patients receiving MTX-based induction without intensive consolidation, outcomes remain suboptimal. The intergroup ANOCEF-GOELAMS randomized phase II trial, which compared two MTX-based regimens without rituximab in patients aged ≥60 years (median age 72 years), reported 2-year PFS rates of approximately 25–31% across treatment arms [14],

providing a key historical benchmark for this population.

When maintenance therapy was subsequently introduced in prospective elderly-focused studies — procarbazine in the PRIMAIN study (rituximab-based induction, ≥65 years; 2-year PFS 37.3%) [15] and temozolomide in the elderly subgroup of the Nordic Lymphoma Group phase II study (aged 66–75 years; 2-year PFS approximately 44%) [16] — outcomes improved, suggesting that maintenance strategies may compensate for the absence of intensive consolidation. Lenalidomide, a second-generation immunomodulatory drug, penetrates the blood-brain barrier at low doses and exhibits single-agent activity in relapsed PCNSL [17, 18] and in combination with rituximab (REVRI regimen), has demonstrated an overall response rate of 35.6% in relapsed/refractory PCNSL [19]. A retrospective study suggested that low-dose lenalidomide (5–10 mg/day) maintenance after induction therapy is a safe and effective treatment strategy in elderly patients with PCNSL [20]. Currently, no prospective clinical trials have been reported evaluating lenalidomide maintenance after induction therapy in PCNSL, so we initiated a multicenter single-arm phase II trial to test lenalidomide maintenance in patients who received chemoimmunotherapy induction and were ineligible for consolidative WBRT or ASCT.

Methods

Study Design and Patients

This was an open-label, prospective, multicenter, single-arm phase II trial (Consortium for Improving Survival of Lymphoma; CISL). The study was approved by the IRB (B-2107-699-001) of Seoul National University Bundang Hospital and registered at ClinicalTrials.gov

(NCT05260619). Written informed consent was obtained after induction completion per the Declaration of Helsinki. Eligible patients were ≥19 years old with histologically confirmed PCNSL (or radiologically/clinically diagnosed if biopsy was infeasible), had received 2–6 cycles of MTX- and rituximab-based induction with at least a partial response (PR), and were ineligible for consolidative WBRT or ASCT. Ineligibility for consolidation was assessed after induction completion based on age, performance status, organ function, comorbidities, and clinical judgment. Induction regimens included R-MPV, R-MA (rituximab, methotrexate, and cytarabine), and R-MTX. Full eligibility criteria are provided in the Supplementary Appendix. The lower age limit of ≥19 years was set to allow enrollment of younger patients deemed unfit for consolidation based on comorbidities, frailty, or impaired organ function rather than age alone. Baseline clinical and laboratory characteristics were collected, and prognostic risk was assessed using the International Extranodal Lymphoma Study Group (IELSG) scoring system [21].

Treatment

Lenalidomide (15 mg orally, days 1–21 every 28 days) was initiated 6 weeks (±7 days) after the last induction cycle and continued for 12 cycles or until progressive disease, unacceptable toxicity, or withdrawal. Dose adjustments were protocol-specified; the minimum permitted dose was 10 mg/day (Supplementary Appendix). Thromboprophylaxis with aspirin or low-dose heparin was recommended.

Study endpoints and assessments

The primary endpoint was 2-year PFS, calculated from study entry to disease progression or death. Secondary endpoints included response rates assessed according to the International PCNSL Collaborative Group (IPCG) criteria [22], OS, and safety. Tumor response was

assessed by brain MRI at cycles 3, 6, 9, and 12, every 3 months during the first year after maintenance, every 4 months during the second year, and every 6 months thereafter. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (version 5.0).

Sample size calculation

Sample size was calculated using a one-sample log-rank design assuming a 2-year PFS of 30% with induction chemotherapy alone without maintenance and 55% with lenalidomide maintenance, with a two-sided type I error of 5% and 80% power. 26 evaluable patients were required; allowing for 14% attrition, the target was 31 patients. This 30% null was informed by historical 2-year PFS rates (25–31%) in prospective studies of elderly/consolidation-ineligible PCNSL populations [14]; the lower bound was selected to reflect the least favorable historical outcome and to ensure a conservative design. Detailed rationale is provided in the Introduction.

Statistical Analysis

The primary analysis followed the intention-to-treat (ITT) principle. Response rates were summarized with 95% exact confidence intervals (CIs) using binomial distribution. Survival was estimated using the Kaplan–Meier method. Statistical significance was set at $p < 0.05$. Analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Between April 2022 and January 2025, 32 patients were screened, of whom one withdrew

consent prior to enrollment due to family objection; 31 patients were enrolled across 8 participating centers. All patients had a biopsy-proven diagnosis of PCNSL with DLBCL, except for one patient at risk of postoperative neurologic deficit. All enrolled patients had parenchymal brain involvement; no patient had leptomeningeal-only disease or primary vitreoretinal lymphoma. Table 1 summarizes the baseline characteristics of the 31 patients. The median age was 72 years (range, 61–83), with 74.2% aged ≥70 years, and 35.5% were male.

Among the 8 patients younger than 70 years, six were assessed as unfit for consolidation based on comorbidities, frailty, or post-induction functional decline — including poorly controlled diabetes mellitus (n=1), sensorineural hearing loss (n=1), hemiplegia with frailty (n=1), severely impaired functional status and small body habitus precluding ASCT as assessed by the treating investigator (ECOG PS 2–3; n=1), and post-induction functional decline without pre-existing comorbidity (n=2). Of the remaining two patients, one declined ASCT owing to overall clinical condition and comorbid disease, and one declined based on personal preference.

With the exception of one protocol-deviation case, all patients received rituximab–MTX–based induction, most commonly R-MPV (rituximab, methotrexate, procarbazine, and vincristine; 87.1%). The protocol-deviation patient received single-agent MTX (6 cycles) without rituximab due to financial constraints, as rituximab was not covered by national insurance for this indication. Induction treatment was administered for a median of 6 cycles (range 3–6) with a median methotrexate dose of 2.9 g/m² (range 1.5–4.0). Induction response was complete response (CR) in 83.9%, unconfirmed CR in 3.2%, and PR in 12.9%. High or intermediate IELSG risk was present in 90.3% of patients, and deep brain lesions were observed in 74.2%. Elevated LDH and CSF protein were noted in 33.3% and 60.0% of evaluable patients, respectively. Ocular involvement and positive CSF cytology were uncommon (10.0% and 16.0%, respectively).

Efficacy

Of 31 enrolled patients, 30 received lenalidomide maintenance therapy (Figure 1). One patient withdrew consent before treatment initiation. The median number of lenalidomide maintenance cycles was 11.0 (range, 1.0–12.0). During the 12-month treatment period, 15 patients (50%) discontinued therapy: 9 due to disease progression, 4 due to AEs, and 2 at patient request. The remaining 15 patients (50%) completed the planned 12 months of lenalidomide maintenance (Figure 1). Among the 30 patients who received lenalidomide maintenance, three were in PR after induction chemotherapy; of these, two subsequently converted to CR after three cycles of lenalidomide maintenance, suggesting active anti-lymphoma activity of lenalidomide in the CNS setting. Among the 15 patients who experienced disease progression, 9 progressed while actively receiving lenalidomide maintenance (leading to treatment discontinuation) and 6 progressed after lenalidomide had been discontinued, either following completion of the planned 12 cycles (n=3) or after early discontinuation for reasons other than progression (n=3). Subsequent treatment data were available for all 15 patients: 12 (80%) received salvage radiotherapy, one received salvage chemotherapy (cytarabine, ifosfamide, and etoposide), one received intrathecal methotrexate, and one declined further treatment. Of the 5 total deaths observed during the study period, 4 were attributable to disease progression and one to treatment-related pneumonia.

The median follow-up duration, estimated using the reverse Kaplan-Meier method, was 20.7 months (95% CI, 14.1–27.9 months). Figure 2A and 2B show Kaplan–Meier Estimates of PFS and OS up to 42 months. At 2 years, the estimated PFS rate was 58.8% (95% CI, 43.4%–79.8%), and the OS rate was 83.9% (95% CI, 70.0%–100.0%). From the start of induction therapy, the estimated 2-year PFS rate was 58.9% (95% CI, 43.4%–79.9%), and the 2-year OS rate was

84.0% (95% CI, 70.1%–100.0%). The reason why the 2-year PFS or OS measured from the initiation of lenalidomide maintenance and from the start of induction are almost identical is that the duration of induction was relatively short (median 4.1 months, range 3.1–5.5 months), so there is little time difference between the two measurement points. The formal two-sided one-sample log-rank test against the null hypothesis of a 2-year PFS of 30% yielded a chi-square statistic of 2.98 (1 degree of freedom; p = 0.084). The observed 2-year PFS of 58.8% exceeded the pre-specified alternative threshold of 55%. In an exploratory subgroup analysis stratified by age, the 2-year PFS was 52.5% (95% CI, 34.9%–79.1%) in patients aged ≥70 (n=22) and 75.0% (95% CI, 50.3%–100.0%) in those aged <70 (n=8), with no statistically significant difference between groups (log-rank p=0.27; Figure 2C). Two-year OS was 78.3% (95% CI, 60.8%–100.0%) in patients ≥70 and 100% in patients <70, in whom no deaths were observed (log-rank p=0.16; Figure 2D).

Safety

All 30 patients who received ≥1 dose of lenalidomide were evaluable for safety (Table 2). Hematologic toxicity was predominant, with neutropenia occurring in 76.7% (grade 1–2: 23.3%; grade 3: 26.7%; grade 4: 26.7%). Granulocyte colony-stimulating factor (G-CSF) was administered in 15 patients (50.0%) for neutropenia management. One patient permanently discontinued lenalidomide after cycle 4 due to recurrent grade 4 neutropenia despite G-CSF support. Grade 3–4 thrombocytopenia and anemia were infrequent (3.3% and 0%, respectively). Non-hematologic AEs were mostly grade 1–2; the most common were skin rash (43.3%), pruritus (23.3%), upper respiratory infection and decreased appetite (each 20.0%), and constipation (16.7%). Grade 3 events included rash and pruritus (each 6.7%), dizziness, urinary tract infection, biliary sepsis, pneumonia, and nausea (each 3.3%). One grade 5 pneumonia

occurred in an 81-year-old patient after cycle 5 of lenalidomide maintenance, representing the sole treatment-related death. Dose interruptions were required in 16 patients (53.3%) and dose reductions in 11 (36.7%), mainly for neutropenia. Two protocol deviations occurred regarding dose reduction, in which lenalidomide was reduced below the minimum permitted dose of 10 mg. One patient developed recurrent grade 2 skin rash; lenalidomide was reduced to 10 mg at cycle 3 and further to 5 mg from cycle 5 onward, and this patient completed 12 cycles of lenalidomide maintenance. The other patient experienced recurrent grade 3-4 neutropenia; lenalidomide was reduced to 10 mg at cycle 3 and to 5 mg from cycle 4 onward, but study treatment was discontinued after cycle 4 because of recurrent grade 4 neutropenia.

A total of five serious adverse events (SAEs) occurred in three patients. Pneumonia was the most frequent SAE (three events), including one case of Grade 5 pneumonia in an 81-year-old patient. The remaining SAEs were biliary sepsis and urinary tract infection (one event each). Three of the five SAEs were considered related to lenalidomide by investigator assessment. Lenalidomide was permanently discontinued in all three patients who experienced SAEs. Four SAEs resolved without sequelae, whereas the Grade 5 pneumonia resulted in death. Permanent discontinuation of study treatment due to AEs occurred in four patients (13.3%): the previously mentioned patient with recurrent grade 3–4 neutropenia and three patients who experienced SAEs.

Discussion

PCNSL remains a therapeutic challenge in elderly patients, particularly those ineligible for consolidative WBRT or ASCT because of age-related neurotoxicity concerns and limited

physiological reserve. This prospective, multicenter, single-arm phase II trial provides the first prospective evidence on lenalidomide maintenance therapy following methotrexate- and rituximab-based chemoimmunotherapy induction in this vulnerable population.

Our cohort comprised predominantly elderly patients (median age 72 years) who were not candidates for consolidative ASCT or WBRT because of advanced age, comorbidities, impaired performance status, and/or organ dysfunction. This profile reflects the epidemiologic reality that PCNSL disproportionately affects older adults with limited physiological reserve, in whom neurotoxicity and treatment-related morbidity are major concerns [13]. Our study demonstrated a 2-year PFS rate of 58.8% from the initiation of lenalidomide maintenance, exceeding the pre-specified alternative threshold of 55%, although the formal two-sided one-sample log-rank test did not reach statistical significance ($p = 0.084$). Although this result may appear modest given the 87.1% CR/CRu rate after induction, a high CR rate after MTX-based induction reflects chemosensitivity but does not reliably predict durable disease control without subsequent consolidation in this biologically aggressive tumor [23, 24]. The majority of patients entered maintenance already in CR or CRu; the small number entering in PR (n=3) precludes meaningful assessment of whether the benefit of lenalidomide maintenance differs according to response status at enrollment, a question that warrants prospective evaluation in future trials. To address whether the observed benefit applied specifically to elderly patients — the intended target of this regimen — we performed an exploratory age-stratified analysis of our cohort. Although patients aged ≥70 years achieved a 2-year PFS of 52.5%, which did not reach the 55% threshold pre-specified for the overall cohort, this threshold was not designed as a hypothesis-testing parameter for any subgroup, and the 95% CI in this subgroup (34.9%–79.1%) encompasses the threshold. Notably, patients in the <70 years subgroup (n=8) were also judged ineligible for intensive consolidation because of comorbidity or frailty, and the lack

of a significant between-group difference (p=0.27 for PFS) argues against the interpretation that the overall outcome was driven by younger, fitter patients; nonetheless, the small subgroup size limits the strength of any between-group inference. Importantly, the 2-year PFS in elderly patients still compares favorably with the historical 2-year PFS rates of approximately 37–44% reported in elderly cohorts receiving procarbazine or temozolomide maintenance [15, 16], and the 2-year OS of 78.3% represents a clinically meaningful survival outcome. These exploratory findings therefore support a clinical role for lenalidomide maintenance in elderly PCNSL patients aged ≥70 years, although confirmation in a larger, dedicated elderly cohort is required.

Prior prospective studies incorporating maintenance therapy reported 2-year PFS rates of 37.3% with procarbazine maintenance (PRIMAIN study) [15] and approximately 44% with temozolomide maintenance (Nordic Lymphoma Group study) [16] in elderly or consolidation-ineligible PCNSL patients, and our observed 2-year PFS of 58.8% is numerically higher than these figures. However, direct comparison is not appropriate, as our study enrolled only patients who had already achieved at least a PR to induction and remained fit to proceed to maintenance, whereas the PRIMAIN and Nordic studies measured PFS from induction initiation across the full intent-to-treat population. A landmark analysis at the time of maintenance initiation would be the methodologically ideal approach for comparison; however, individual patient-level data from the historical comparator studies are unavailable for such an analysis. In addition, differences in induction regimens, cycle duration, and timing of study entry across trials limit the ability to make direct head-to-head comparisons. The phase II study by Bairey et al. reported 2-year PFS and OS rates of 72.6% and 89%, respectively, with ibrutinib maintenance in 20 elderly PCNSL patients following induction response [25]. However, 14 of 20 patients (70%) in that study received post-induction consolidation prior to ibrutinib maintenance — 12 with cytarabine-based chemotherapy and 2 with ASCT — whereas all patients in our cohort

proceeded directly to lenalidomide maintenance without any consolidation. Although cytarabine-based consolidation is less intensive than ASCT and remains feasible in many transplant-ineligible patients, the receipt of any consolidation step in the majority of the Bairey cohort still represents an additional disease-directed intervention beyond maintenance alone, and the numerically higher PFS observed in that study may in part reflect this contribution rather than the activity of the maintenance agent per se. These comparisons collectively suggest that lenalidomide maintenance alone achieves meaningful disease control in a truly consolidation-ineligible population, though prospective randomized trials in this specific setting are warranted.

For patients with PCNSL who respond to induction chemotherapy, the choice of consolidation strategy significantly impacts outcomes. Available evidence supporting maintenance comes from a Thai retrospective study, which showed that consolidation or maintenance after induction significantly improved 2-year PFS (63.6% vs 39.5%; HR 0.41) [26], and the Nordic phase II study, which demonstrated that temozolomide maintenance after de-escalated induction reduced relapse rates and improved PFS in elderly patients [16]. Our lenalidomide maintenance data extends this concept. For patients fit enough to receive intensive consolidation, ASCT yields superior outcomes: the randomized phase III MATRix/IELSG43 trial established ASCT as the standard consolidation for fit PCNSL patients, demonstrating 3-year PFS of 79% and OS of 86% versus 53% and 71% with non-myeloablative chemoimmunotherapy [27]. The MARTA trial similarly confirmed feasibility of ASCT in older but fit patients (median age 71 years), with a 12-month PFS of 58.8%, though at the cost of 6% treatment-related mortality [28]. WBRT-based consolidation can achieve 2-year PFS rates of approximately 80%, but both WBRT and ASCT carry substantial risks of neurotoxicity and cognitive decline [3, 29, 30]. In contrast, no clinically apparent neurotoxicity attributable to

lenalidomide was observed in our study, and no patient discontinued therapy for neurologic reasons. Formal neurocognitive testing was not performed, however, and subtle cognitive effects cannot be excluded; our data should therefore be interpreted as reassuring with respect to overt neurologic safety rather than as evidence of preserved neurocognitive function. Together, these findings highlight that while ASCT and WBRT offer superior disease control in fit patients, lenalidomide maintenance provides a meaningful and less toxic alternative for those ineligible for intensive consolidation, and ASCT should still be considered for carefully selected older patients with adequate fitness.

The median of 11 cycles delivered, with 50% of patients completing all 12 planned cycles, suggests that lenalidomide maintenance is feasible even in an elderly population. Nonetheless, the toxicity profile warrants careful consideration. Grade 3–4 neutropenia occurred in 53.3% of patients—a rate approximately three- to fourfold higher than the 15% reported with temozolomide maintenance in the Nordic study [16] and substantially higher than the predominantly grade 1–2 adverse events observed with ibrutinib maintenance in the Bairey et al. study [25]. This high rate of neutropenia necessitated dose interruptions in 53.3% and dose reductions in 36.7% of patients, and 13% discontinued treatment due to toxicity. Furthermore, one patient (3.3%) died from grade 5 pneumonia during lenalidomide maintenance, underscoring the potential for serious infectious complications in this elderly, immunocompromised population. The overall hematologic toxicity burden of lenalidomide is meaningfully greater than that of alternative maintenance agents and should be weighed carefully against the clinical benefit when selecting maintenance therapy for individual patients. Close monitoring of complete blood counts, proactive dose adjustment, and vigilance for infectious complications are essential components of management in this population. Non-hematologic AEs were mostly grade 1–2; the most common were skin rash (43.3%) and

infections (e.g., upper respiratory in 20.0%), which were generally manageable, and no thromboembolic events were observed with recommended thromboprophylaxis. Two patients received doses below the protocol-defined minimum of 10 mg/day in response to recurrent toxicities, further highlighting the need for individualized dose management in frail elderly patients.

Several limitations warrant consideration. First, the single-arm design precludes direct statistical comparison to observation or alternative maintenance strategies. In addition, the formal one-sample log-rank test did not reach statistical significance ($p = 0.084$), although the observed 2-year PFS of 58.8% exceeded the pre-specified alternative hypothesis threshold of 55%. Second, this study enrolled only patients who achieved at least a PR to induction chemotherapy and remained clinically fit to proceed to maintenance, thereby structurally excluding those who progressed, experienced prohibitive toxicity, or deteriorated in performance status during induction. This introduces an inherent guarantee-time bias, as only patients with favorable tumor biology and preserved functional reserve entered the observation period. Data on the total number of patients who initiated induction at participating centers but were not subsequently enrolled are unavailable, precluding quantification of this selection effect. Accordingly, the reported outcomes should be interpreted as applicable to this selected, response-eligible subpopulation rather than to all patients initiating first-line therapy. Third, data maturity is a recognized constraint of the current analysis. The relatively short median follow-up of 20.7 months means that the 2-year PFS estimate relies substantially on Kaplan–Meier extrapolation and should therefore be interpreted with caution, as reflected by the wide 95% CI (43.4–79.8%). The decision to report at this time point reflects our judgment that timely dissemination of the first prospective evidence on lenalidomide maintenance in this rare disease setting would still provide clinically meaningful information; nevertheless, updated data with

longer follow-up will be required to confirm the durability of disease control and to assess the risk of late relapse. Fourth, the modest sample size (n = 31) limits the ability to detect rare toxicities or meaningful differences among prognostic subgroups. In particular, the small numbers of patients in the individual IELSG risk subgroups (low-risk, n = 1; high-risk, n = 7) precluded meaningful subgroup analyses. Fifth, although most patients received R-MPV induction, some heterogeneity in induction regimens was present, and one protocol-deviation case was included, which may modestly affect interpretability when comparing results across studies. Sixth, the fixed 12-month duration of lenalidomide maintenance represents only half of the current two-year follow-up period, limiting the ability to attribute late survival benefit solely to maintenance therapy. Moreover, the optimal duration of maintenance in PCNSL remains undefined, as the 12-month schedule was based on pragmatic considerations rather than dose- or duration-optimization studies. Longer follow-up or randomized comparison with observation will be required to isolate the specific contribution of lenalidomide. Finally, formal quality-of-life assessment was not incorporated into the study protocol, precluding evaluation of patient-reported outcomes, including fatigue, a recognized toxicity of lenalidomide and an important consideration in elderly patients.

In conclusion, lenalidomide maintenance at 15 mg for 12 cycles after methotrexate- and rituximab-based induction demonstrates promising activity and an acceptable, albeit notable, toxicity profile in elderly or consolidation-ineligible PCNSL patients. This trial provides the first prospective evidence that lenalidomide maintenance is feasible and potentially beneficial in this population and supports its further evaluation as a maintenance strategy. However, the single-arm design, modest sample size, and borderline formal test statistic preclude definitive efficacy conclusions, and these findings should be considered hypothesis-generating. Randomized trials comparing lenalidomide maintenance to observation or alternative agents

such as ibrutinib are needed to establish superiority, define the optimal maintenance strategy, and identify patients most likely to benefit.

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Table 1. Patients' baseline characteristics (n = 31).

	N	%
Age, median years (range)	72 (61–83)	
Age ≥ 70 years	23	74.2
Male sex	11	35.5
ECOG PS ≥ 2	8	25.8
Increased LDH*	10/30	33.3
Deep brain lesions†	23	74.2
Increased CSF protein*	15/25	60.0
IELSG risk group§		
Low	1	3.2
Intermediate	21	67.7
High	7	22.6
Unknown	2	6.5
Ocular involvement*	3/30	10.0
Positive CSF cytology*	4/25	16.0
Induction regimen		
MTX	1	3.2
R-MA	2	6.5
R-MPV	27	87.1
R-MTX	1	3.2
Median number of cycles	6 (3–6)	
Median MTX dose (g/m^2)	2.9 (1.5–4.0)	
MTX dose ≥ 3 g/m^2	13	41.9
Response of induction		
CR	26	83.9
CRu	1	3.2
PR‡	4	12.9

*Denominators are the number of assessed patients †deep regions of the brain were defined as the periventricular regions, basal ganglia, brainstem, and/or cerebellum. The cutoff values for normal CSF protein concentration were 45 mg/dL in patients ≤ 60 years old and 60 mg/dL in patients older than 60 years. Median (Min–Max) ‡One patient with partial response withdrew consent before treatment initiation and did not receive lenalidomide maintenance. §Among the 6 patients with missing CSF protein data, 4 could be classified unambiguously based on the remaining IELSG parameters; the remaining 2 patients spanned the boundary between risk groups and are listed as 'Unknown', yielding 29 evaluable patients for the IELSG risk analysis.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; CSF, cerebrospinal fluid; IELSG, international extranodal lymphoma study group; MTX, methotrexate; R-MA, rituximab, methotrexate, cytarabine; R-MPV, rituximab, methotrexate, procarbazine, vincristine; R-MTX, rituximab, methotrexate; CR, complete response; CRu, unconfirmed complete response; PR, partial response.

Table 2. Adverse events

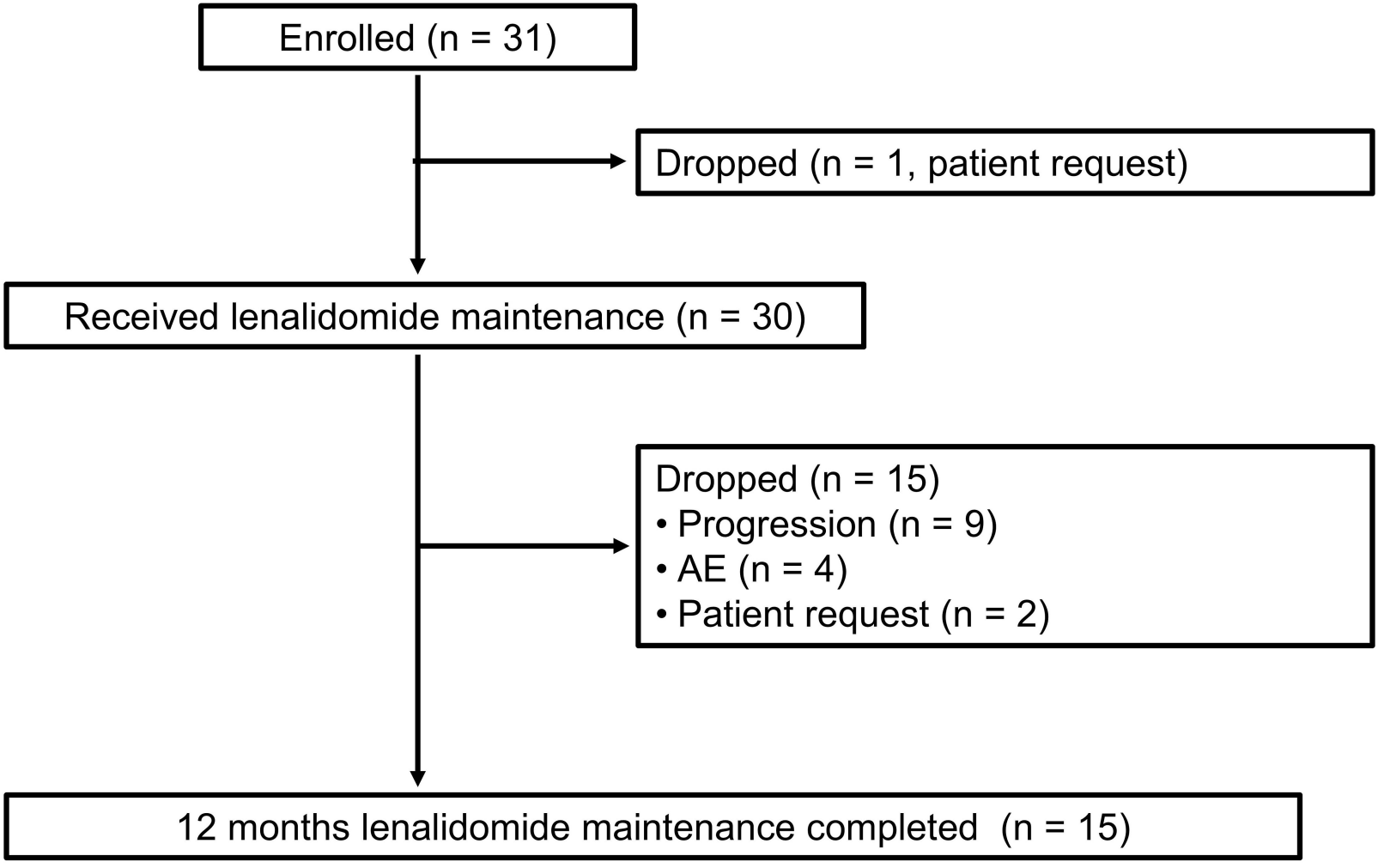
	Grade 1-2	Grade 3	Grade 4	Grade 5
Neutropenia	7 (23.3%)	8 (26.7%)	8 (26.7%)	0
Thrombocytopenia	5 (16.7%)	1 (3.3%)	0	0
Anemia	5 (16.7%)	0	0	0
Skin rash	11 (36.7%)	2 (6.7%)	0	0
Pruritus	5 (16.7%)	2 (6.7%)	0	0
Upper respiratory infection	6 (20.0%)	0	0	0
Constipation	5 (16.7%)	0	0	0
Decreased appetite	6 (20.0%)	0	0	0
Dizziness	4 (13.3%)	1 (3.3%)	0	0
Back pain	3 (10.0%)	0	0	0
Diarrhea	3 (10.0%)	0	0	0
Peripheral neuropathy	3 (10.0%)	0	0	0
Urinary tract infection	1 (3.3%)	1 (3.3%)	0	0
Biliary sepsis	0	1 (3.3%)	0	0
Pneumonia	0	1 (3.3%)	0	1 (3.3%)
Nausea	0	1 (3.3%)	0	0

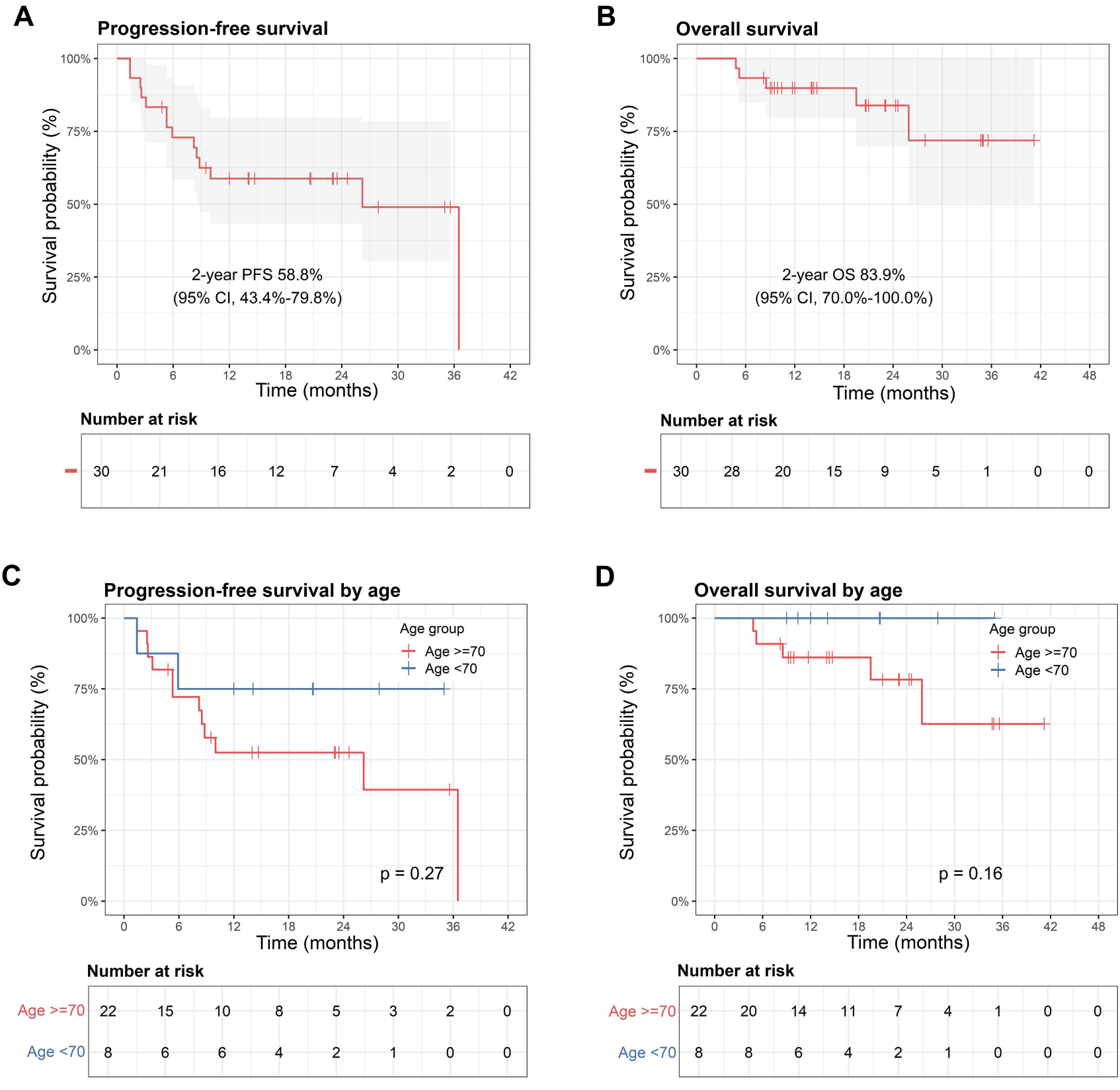
Adverse events in patients treated with lenalidomide maintenance therapy (n = 30). Data are n (%). The table includes grade 1 or 2 adverse events occurring in at least 10% of patients and all grade 3–5 events are reported.

Figure legends

Figure 1. Patient disposition and treatment completion

Figure 2. Kaplan–Meier survival curves. (A) Progression-free survival and (B) overall survival in the entire cohort (n=30). (C) Progression-free survival and (D) overall survival stratified by age (≥70 vs <70 years). P-values are from the log-rank test.


Enrolled (n = 31)
Dropped (n = 1, patient request)
Received lenalidomide maintenance (n = 30)
Dropped (n = 15)
• Progression (n = 9)
• AE (n = 4)
• Patient request (n = 2)
12 months lenalidomide maintenance completed (n = 15)


A
Progression-free survival
Survival probability (%)
100%
75%
50%
25%
0%
2-year PFS 58.8%
(95% CI, 43.4%-79.8%)
0 6 12 18 24 30 36 42
Time (months)
Number at risk
30 21 16 12 7 4 2 0
B
Overall survival
Survival probability (%)
100%
75%
50%
25%
0%
2-year OS 83.9%
(95% CI, 70.0%-100.0%)
0 6 12 18 24 30 36 42 48
Time (months)
Number at risk
30 28 20 15 9 5 1 0 0
C
Progression-free survival by age
Survival probability (%)
100%
75%
50%
25%
0%
Age group
Age >=70
Age <70
p = 0.27
0 6 12 18 24 30 36 42
Time (months)
Number at risk
Age >=70 22 15 10 8 5 3 2 0
Age <70 8 6 6 4 2 1 0 0
D
Overall survival by age
Survival probability (%)
100%
75%
50%
25%
0%
Age group
Age >=70
Age <70
p = 0.16
0 6 12 18 24 30 36 42 48
Time (months)
Number at risk
Age >=70 22 20 14 11 7 4 1 0 0
Age <70 8 8 6 4 2 1 0 0 0

Supplement Material

Phase II study of lenalidomide maintenance after rituximab-methotrexate-based induction therapy in primary central nervous system lymphoma

Contents

1. Study scheme

2. Inclusion and exclusion criteria

3. Endpoints in this clinical trial

4. Dose interruption and reduction procedures

5. Supplementary methods

1. Study scheme

This was a prospective, open-label, multicenter, single-arm phase II trial evaluating lenalidomide maintenance after induction chemoimmunotherapy consisted of MTX- and rituximab-based regimens in patients with primary central nervous system lymphoma (PCNSL).

Eligible patients were adults (≥19 years) with newly diagnosed PCNSL (primary diffuse large B-cell lymphoma of the central nervous system) who had received 2–6 cycles of induction chemoimmunotherapy consisted of MTX- and rituximab-based regimens and achieved at least a partial response on brain magnetic resonance imaging (MRI), but were not candidates for consolidative autologous stem cell transplantation (ASCT) or whole-brain radiotherapy (WBRT) due to age, comorbidities, or other clinical reasons.

Screening assessments were performed within 2 weeks prior to enrolment (medical history, physical examination, Eastern Cooperative Oncology Group [ECOG] performance status, vital signs, laboratory tests, and pregnancy testing for women of childbearing potential) and within 4 weeks for baseline brain MRI. Additional imaging with chest and abdominal computed tomography (CT) and whole-body 18F-FDG PET/CT could be performed at the investigator's discretion.

Lenalidomide maintenance started 6 weeks (±7 days) after the last cycle of induction chemoimmunotherapy consisted of MTX- and rituximab-based regimens. The starting dose was 15 mg orally once daily on days 1–21 of each 28-day cycle, for up to 12 cycles (1 year), with predefined dose interruptions and reductions permitted according to hematologic and non-hematologic toxicity.

Patients attended the clinic before each cycle for clinical assessment (history, physical examination, ECOG performance status, vital signs) and laboratory tests, including complete blood count with differential, serum chemistry, liver function tests, lactate dehydrogenase, and pregnancy testing for women of childbearing potential. Brain MRI for tumor assessment was performed after cycles 3, 6, 9, and 12, and earlier if there was clinical suspicion of progression. Tumor responses and progression were evaluated according to the Response Criteria for Primary Central Nervous System Lymphoma.

After completion or discontinuation of lenalidomide, patients entered protocol-defined follow-up. Clinical assessment and imaging were scheduled every 3 months during the first year, every 4 months during the second year, and every 6 months thereafter, for a total follow-up of up to 5 years or until disease progression or death.

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2. Inclusion and exclusion criteria

Inclusion criteria

- Histologically confirmed primary central nervous system lymphoma (primary diffuse large B-cell lymphoma of the central nervous system). If histologic confirmation was not feasible, patients with characteristic radiologic and clinical findings consistent with PCNSL were eligible.
- Age ≥19 years.
- Previously treated with at least 2 and up to 6 cycles of induction chemoimmunotherapy consisted of MTX- and rituximab-based regimens and achieved at least a partial response on response assessment.
- Not eligible for consolidative autologous stem cell transplantation or whole-brain radiotherapy (e.g., due to advanced age, comorbidities, or other clinical considerations).
- ECOG performance status ≤2.

- Adequate hematologic, renal, and hepatic function, defined as: absolute neutrophil count (ANC) ≥1.0 × 10^9/L; platelet count ≥75 × 10^9/L; calculated creatinine clearance ≥30 mL/min; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN); and total bilirubin ≤2.0 × ULN.
- For women: either postmenopausal for at least 2 years, surgically sterile, or of childbearing potential with two negative pregnancy tests (within 10–14 days and within 24 hours prior to the first lenalidomide dose) and agreement to adhere to the lenalidomide pregnancy prevention and risk management program, including the concurrent use of two reliable methods of contraception or complete abstinence from heterosexual intercourse from at least 28 days before starting lenalidomide, throughout the trial, during any treatment interruptions, and for at least 28 days after permanent discontinuation.
- For men (including those who are surgically sterilized): agreement to use an effective barrier method of contraception or to practice complete abstinence from heterosexual intercourse during lenalidomide treatment and for at least 28 days after the last dose, and to comply with the lenalidomide pregnancy prevention and risk management program.
- Ability to swallow capsules and willingness and ability to comply with all protocol-required procedures and evaluations.
- Provision of written informed consent and authorization for use of personal medical information in accordance with local regulations.

Exclusion criteria

- Planned consolidation with autologous stem cell transplantation or whole-brain radiotherapy after induction chemoimmunotherapy consisted of MTX- and rituximab-based regimens.
- Prior treatment with lenalidomide for any indication.
- History of other malignancies within the previous 5 years, except adequately treated non-melanoma skin cancer or in situ carcinoma of the cervix uteri. Patients with thyroid cancer who had completed active treatment (surgery and/or radioiodine therapy) and had no evidence of recurrence for ≥1 year were permitted.
- Pregnant or breastfeeding women, or women of childbearing potential not willing or unable to use adequate contraception as per protocol requirements.
- Clinically significant cardiovascular disease within 6 months before enrolment, including inadequately controlled congestive heart failure, symptomatic coronary artery disease, clinically relevant arrhythmias, or recent myocardial infarction.
- Active, severe infection requiring systemic therapy.
- Known active hepatitis B or C infection or human immunodeficiency virus (HIV) infection.
- Known hypersensitivity or intolerance to lenalidomide or any of its excipients.
- Any medical, psychiatric, or social condition that, in the opinion of the investigator, could interfere with protocol adherence or put the patient at undue risk.

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3. Endpoints in this clinical trial

The primary efficacy endpoint of this phase II trial was 2-year progression-free survival (PFS). PFS was defined as the time from the first dose of lenalidomide maintenance therapy to the date of documented disease progression, relapse, or death from any cause, whichever occurred first. Patients

who were alive and free from progression at the time of analysis, or who were lost to follow-up, were censored at the date of the last disease assessment.

Key secondary endpoints included:

- Overall response rate (ORR), defined as the proportion of patients achieving complete response (CR) or partial response (PR) during lenalidomide maintenance, as assessed by brain MRI using the Response Criteria for Primary Central Nervous System Lymphoma.
- Overall survival (OS), defined as the time from the first dose of lenalidomide to death from any cause, with surviving patients censored at the date of last follow-up.
- Safety and tolerability, evaluated by the incidence, severity, and type of adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.
- Subsequent treatments following disease progression.

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4. Dose interruption and reduction procedures

Lenalidomide was administered at a starting dose of 15 mg orally once daily on days 1–21 of each 28-day cycle for up to 12 cycles. Dose interruptions and reductions were implemented according to predefined criteria, primarily in response to hematologic and non-hematologic toxicities.

Hematologic toxicity – neutropenia

- At the first and second occurrences of absolute neutrophil count (ANC) $<1.0 \times 10^9$/L, lenalidomide was withheld. Granulocyte colony-stimulating factor (G-CSF) could be administered at the investigator's discretion, and complete blood counts were monitored at least weekly. Once ANC recovered to $\geq 1.0 \times 10^9$/L, lenalidomide was resumed at 15 mg daily.
- At the third occurrence of ANC $<1.0 \times 10^9$/L, lenalidomide was again withheld and G-CSF support and weekly monitoring were provided. Upon recovery of ANC to $\geq 1.0 \times 10^9$/L, treatment was resumed at a reduced dose of 10 mg daily.
- At the fourth occurrence of ANC $<1.0 \times 10^9$/L, lenalidomide was permanently discontinued.

Hematologic toxicity – thrombocytopenia

- At the first and second occurrences of platelet count $<50 \times 10^9$/L, lenalidomide was withheld and platelet counts were monitored weekly. When platelet counts recovered to $\geq 50 \times 10^9$/L, lenalidomide was restarted at 15 mg daily.
- At the third occurrence of platelet count $<50 \times 10^9$/L, lenalidomide was withheld and weekly monitoring continued. After recovery to $\geq 50 \times 10^9$/L, treatment was resumed at a reduced dose of 10 mg daily.
- At the fourth occurrence of platelet count $<50 \times 10^9$/L, lenalidomide was permanently discontinued.

Renal impairment

Patients were required to have a baseline creatinine clearance (CrCl) ≥30 mL/min to initiate lenalidomide. If, during treatment, CrCl decreased to <30 mL/min and this decline was considered related to lenalidomide, the drug was interrupted until renal function recovered to CrCl ≥30 mL/min. After recovery, lenalidomide could be restarted at the next lower dose level (i.e., a 5-mg dose reduction), at the investigator's discretion.

Non-hematologic toxicity

For lenalidomide-related non-hematologic adverse events of grade 3–4 (excluding alopecia), lenalidomide was withheld until the toxicity improved to grade ≤2. Thereafter, treatment could be resumed at a reduced dose level (typically a 5-mg reduction from the previous dose). If severe non-hematologic toxicity recurred despite appropriate dose reductions, permanent discontinuation of lenalidomide was recommended at the investigator's discretion.

5. Supplementary methods

Study design and patient selection

In practice, 30 of 31 enrolled patients had histologic confirmation of DLBCL, whereas one patient was enrolled based on characteristic radiologic and clinical findings due to a prohibitive risk of neurologic deficit from biopsy. Induction chemoimmunotherapy consisted of MTX- and rituximab-based regimens, including R-MPV (rituximab, methotrexate, procarbazine, and vincristine), R-MA (rituximab, methotrexate, and cytarabine), and R-MTX, administered according to institutional standards or published protocols. The number of induction cycles and MTX dose intensity were determined by the treating investigator based on regimen-specific recommendations and patient fitness.

Eligibility for consolidative therapies was determined based on age, performance status, and organ function. ASCT was generally reserved for younger and fit patients and was not routinely pursued in those aged ≥ 70 years, unless they were considered exceptionally fit at the treating physician's discretion. WBRT was frequently deferred or avoided because of concerns about delayed neurocognitive toxicity rather than strict contraindications, particularly in older patients or those with poor performance status.

Treatment details

Lenalidomide (15 mg orally, days 1–21 every 28 days) was initiated 6 weeks (± 7 days) after the last chemoimmunotherapy induction cycle and continued for 12 cycles (1 year) or until progressive disease (PD), unacceptable toxicity, or withdrawal. Dose adjustments for toxicity were protocol-specified (see section 4 above). For hematologic toxicity, lenalidomide was withheld when ANC < 1.0 $\times 10^9$/L or platelet count < 50 $\times 10^9$/L. Therapy was resumed at 15 mg/day upon recovery for the first and second occurrence, and at a reduced dose of 10 mg/day for the third occurrence. Lenalidomide was permanently discontinued at the fourth event. G-CSF support was provided for neutropenia as clinically indicated. For renal impairment, lenalidomide was withheld if creatinine clearance (CrCl) decreased to < 30 mL/min and resumed only after recovery to ≥ 30 mL/min, at a dose reduced by 5 mg based on physician judgment. For other Grade 3–4 non-hematologic toxicities considered related to lenalidomide, treatment was held until resolution to Grade ≤ 2 and then resumed at a 5 mg reduced dose (i.e., from 15 mg to 10 mg daily). Per protocol, 10 mg/day was the minimum permitted dose. Thromboprophylaxis with aspirin or low-dose heparin was recommended.

Study endpoints and assessment schedule

The primary endpoint of the trial was the rate of 2-year PFS. PFS for all patients was calculated from the time of entry onto the study until disease progression or death because of PCNSL. Secondary efficacy outcomes included response rates, OS, and safety.

Tumor response was assessed by brain magnetic resonance imaging (MRI) scans at cycles 3, 6, 9, and 12, and every 3 months during the first year after completion of maintenance therapy, every 4 months during the second year, and every 6 months thereafter until PD or death. Safety was evaluated at each cycle via physical examination, vital signs, ECOG, complete blood count, and biochemistry. Adverse

events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (version 5.0). All patients who received at least one dose of therapy were considered evaluable for safety. When reporting the overall incidence of AEs, each patient was counted once according to the highest grade experienced, even if recurring events occurred.

Sample size calculation

Sample size was calculated using a one-sample log-rank design comparing the observed PFS curve with a historical control. We assumed a 2-year PFS of 30% with standard therapy and 55% with the investigational lenalidomide maintenance, with a two-sided type I error rate of 5% and 80% power. Under these assumptions, a total of 26 evaluable patients were required. Allowing for an anticipated 14% attrition rate due to early withdrawal, ineligibility for maintenance, or loss to follow-up, we increased the target sample size to 31 patients. Accordingly, the regimen was considered promising if the observed 2-year PFS rate in the intention-to-treat cohort was compatible with the alternative hypothesis of approximately 55%, rather than with the 30% rate expected under historical standard therapy.

Statistical analysis

The primary analysis was performed according to the intention-to-treat (ITT) principle, including all enrolled patients. One patient who received methotrexate-only induction therapy without rituximab represented a protocol deviation but was retained in the ITT population. Descriptive statistics were employed to quantify medians and ranges for continuous variables and numbers and percentages for categorical variables. Response rates were summarized with point estimates and 95% exact confidence intervals (CIs) using binomial distribution. The median follow-up time was calculated using the reverse Kaplan–Meier (KM) method. Survival was estimated using the KM method. The Log-rank (Mantel–Cox) method was employed to assess the statistical significance of differences in survival curves. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using R statistical software version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Because lenalidomide is associated with an increased risk of venous thromboembolism, primary thromboprophylaxis with low-dose aspirin or low-molecular-weight heparin was recommended, according to the investigator's judgement and patient-specific risk factors.