Synopsis

SPONSOR	International Extranodal Lymphoma Study Group (IELSG)	
NAME PRODUCT / INTERVENTION	Methotrexate, Procarbazine, Rituximab, Lenalidomide, and Temozolomide	
NAME OF ACTIVE PRINCIPLE *(if the product is a medicinal product)*	Methotrexate, Procarbazine, Rituximab, Lenalidomide, and Temozolomide	
PROTOCOL CODE	IELSG45	
PROTOCOL TITLE	Randomized Phase II Trial on Fitness- and Comorbidity-Tailored Treatment in Elderly Patients with Newly Diagnosed Primary CNS Lymphoma (FIORELLA Trial)	
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STUDY SITES	Four countries involved: Italy, Switzerland, Denmark, and Finland. Twenty-five enrolling sites	
STUDY PERIOD	First Patient Enrolled 18 Jun 2019 Last Patient Enrolled 12 Sep 2022	
DEVELOPMENT PHASE	Phase II	
OBJECTIVES	**Part A. Patients eligible for high-dose methotrexate-based (HD-MTX) induction chemotherapy** <u>Primary Objective</u> To assess whether maintenance therapy with lenalidomide, initiated following disease stabilization or a better response achieved through standard HD-MTX-based induction treatment, in elderly patients (≥70 years) with newly diagnosed primary central nervous system lymphoma (PCNSL), led to an improved 2-year PFS rate compared to maintenance therapy with procarbazine (PCZ). <u>Secondary Objectives</u> The secondary objectives included: • Comparison between the two treatment arms in the time from initial assessment of partial response (PR) or complete response (CR) to disease relapse or progression • Comparison in overall survival (OS), defined as the time from randomization to death from any cause • Comparison of relapse rates and patterns between the two arms, including primary versus secondary CNS sites versus extra-CNS sites; CNS sites: brain, meninges, cranial nerves, and/or eyes • Comparison of the incidence and severity of adverse events (AEs) and adverse drug reactions between the two arms • Comparison of the incidence and severity of early and late neurotoxicity, evaluated through standardized neuropsychological	

	evaluations and quality of life (QoL) instruments up to two years from randomization • Evaluation of the prognostic significance of geriatric assessment tools: CIRS, IADL, IAL, and G8 **Part B. Patients ineligible for HD-MTX-based induction chemotherapy** Primary Objective To assess the efficacy of concomitant chemo-immuno-radiotherapy administered as induction treatment, followed by maintenance therapy with temozolomide (TMZ), in elderly patients (≥70 years) with newly diagnosed PCNSL who were not eligible to receive HD-MTX-based induction chemo-immunotherapy Secondary Objectives The secondary objectives were: • Proportion of patients achieving CR, PR, stable disease (SD), or progressive disease (PD) as their best response to treatment • Time from initial assessment of CR or PR to disease relapse or progression • Time from initiation of maintenance therapy to death due to any cause • Distribution of relapse rates and patterns: primary versus secondary CNS sites versus extra-CNS sites; CNS sites: brain, meninges, cranial nerves, and/or eyes • Incidence and severity of AEs and adverse drug reactions • Incidence and severity of early and late neurotoxicity, assessed through standardized neuropsychological evaluations and QoL instruments up to two years from maintenance treatment start • Prognostic role of geriatric assessments: CIRS, IADL, ADL and G8
STUDY DESIGN AND METHODOLOGY	Multicenter, open-label, phase II clinical trial designed for patients aged ≥70 years with newly diagnosed PCNSL. Participants were stratified based on their clinical eligibility to undergo induction chemoimmunotherapy incorporating HD-MTX. Patients suitable for HD-MTX-based induction therapy entered the run-in phase of **Part A** (induction phase) and received two cycles of a combination regimen comprising HD-MTX, procarbazine, and rituximab (or a rituximab biosimilar), administered every 43 days. Patients achieving SD or better response following induction were randomized to receive maintenance monotherapy with either procarbazine or lenalidomide. Both agents were administered orally in 4-week cycles for up to 24 cycles (lenalidomide) or 6 cycles (procarbazine). Patients considered ineligible for HD-MTX-based induction therapy were enrolled in the single-arm **part B** cohort and treated with a combination of whole-brain radiotherapy (WBRT), temozolomide, and rituximab (induction phase). Those demonstrating SD or better response proceeded to maintenance therapy with temozolomide for a duration of 12 months. In this trial conducted in elderly patients, the lenalidomide dose and maintenance duration were to be re-evaluated to account for the potential impact of toxicity and non-compliance, based on a safety analysis on the first 10 patients randomly assigned to this treatment arm and treated.for at least 6 cycles.

<table>
<tr><td rowspan="6">SUBJECT POPULATION</td><td>Number of Subjects Planned</td><td>208</td></tr>
<tr><td>Number of Subjects Enrolled and Treated</td><td>55 (Part A)
17 (Part B)</td></tr>
<tr><td>Number of Subjects Randomized</td><td>23 (14 lenalidomide arm + 9 procarbazine arm)</td></tr>
<tr><td>Number of Subjects for Efficacy Analysis</td><td>22 (Part A)
11 (Part B)</td></tr>
<tr><td>Number of Subjects for Safety Analysis</td><td>22 (Part A)
11 (Part B)</td></tr>
<tr><td colspan="2"><u>Brief description of demographic and baseline characteristics</u>
Among the 72 enrolled and treated patients, 34 were male and 38 were female. The mean age was 75 years (range 70 – 87). The IELSG score, calculated on 55 patients with available data included 4 patients (7%) with a low IELSG score, 38 patients (69%) with an intermediate score, and 13 patients (24%) with a high score. Regarding lesion distribution, among the 62 patients considered in this analysis, 37 patients (60%) presented with a single lesion, while 25 patients (40%) had multiple lesions.
Specific disease involvement was also documented. Ocular involvement was identified in four patients (6%), and meningeal involvement was reported in five patients (7%) among the 67 patients analyzed.
Of the 55 patients enrolled in Part A of the study, 26 were male and 29 were female. The mean age of this group was 75.4 years, ranging from 70 to 86 years. In Part B, 17 patients were enrolled, including 8 males and 9 females. The mean age in this group was slightly higher, at 78.1 years, ranging from 71 to 87 years.

<u>Brief description of subjects excluded from the primary analysis population</u>
Twenty-three patients were randomized into Part A of the study: 14 to the lenalidomide arm and 9 to the procarbazine arm. Of the 23 randomized patients, 22 received treatment. One patient in the lenalidomide arm was randomized but did not initiate treatment due to disease progression and was excluded from the primary analysis population.</td></tr>
<tr><td>ELIGIBILITY CRITERIA</td><td colspan="2">Inclusion criteria
Inclusion criteria for trial registration
• Confirmed diagnosis of CD20-positive diffuse large B-cell lymphoma (DLBCL) based on a histological or cytological evaluation.
• Diagnostic samples obtained through stereotactic or surgical biopsy, cerebrospinal fluid (CSF) cytology, or vitrectomy.
• Lymphoma exclusively localized in the CNS (brain parenchyma and/or meningeal/CSF dissemination and/or eyes and/or cranial nerves).
• Previously untreated lymphoma. Prior or ongoing corticosteroid therapy is permitted.</td></tr>
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	• Patient aged ≥70 years. ***Inclusion criteria for treatment (both Part A and B)*** • Lymphoma exclusively localized in the CNS, involving the brain parenchyma and/or meningeal/CSF dissemination. Note: Patients with disease exclusively localized in the eyes or solely infiltrating the cranial nerves are excluded (refer to Exclusion Criteria). • Patients deemed ineligible for high-dose chemotherapy supported by autologous stem cell transplantation. • Eastern Cooperative Oncology Group (ECOG) Performance Status ≤3. • Adequate organ function, defined as: o Bone marrow: Platelet count ≥70,000/mm³ (70×10e9/L), Hemoglobin ≥8 g/dL (80 g/L), Absolute Neutrophil Count (ANC) ≥1,000/mm³ (1×10e9/L) o Renal: Creatinine clearance ≥30 mL/min o Cardiac: Left Ventricular Ejection Fraction (LVEF) ≥30% o Hepatic: Total serum bilirubin <2.5 mg/dL; Aspartate Aminotransferase (AST)/Alanine Aminotransferase (ALT) <2.5× upper limit of normal • No history of previous or concurrent malignancies, except for: o Surgically cured in situ carcinoma of the cervix o Carcinoma of the skin o Other cancers with no evidence of disease for at least 3 years. Note: Patients with a history of lymphoma at any time are not eligible. • No familial, social, or geographic conditions that could interfere with adherence to the study protocol or follow-up schedule. • No concurrent treatment with other investigational drugs. • Patients receiving oral lenalidomide, procarbazine, or temozolomide must agree: o Not to share the study medication with others o To return all unused study medication to the investigator • Male patients must commit to using a latex or synthetic condom during any sexual contact with females of reproductive potential: o While taking lenalidomide o During any treatment interruptions o For up to 7 days after discontinuing treatment. This applies even if the patient has undergone a successful vasectomy. • Written informed consent must be obtained from the patient or their legal representative prior to registration. **Exclusion criteria** • Diagnosis of a lymphoma subtype other than DLBCL. • Evidence of disease outside the CNS (extra-CNS involvement). • Lymphoma confined exclusively to the eyes. • Lymphoma involving only the cranial nerves as the sole site of disease. • Prior antineoplastic treatment for the PCNSL. • Eligibility for high-dose chemotherapy with autologous stem cell transplantation (ASCT). • Positive serology for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV). Note: hepatitis B core antibody (HBcAb) positivity is not exclusionary if hepatitis B virus (HBV) deoxyribonucleic acid (DNA) is undetectable. • Diagnosis of human immunodeficiency virus (HIV) infection or any form of immunodeficiency. • Presence of severe comorbid conditions, including but not limited

	to significant respiratory or cardiac impairment, and uncontrolled diabetes mellitus despite optimal medical therapy • Active infectious disease • Any contraindication listed in the Summary of Product Characteristics (SmPC) for the commercial anticancer drugs used in this study.
STUDY PRODUCTS / DOSE AND MODE OF ADMINISTRATION/ INTERVENTIONS	**Part A** Induction *Treatment* Two cycles, every 43 days. • Rituximab 375 mg/m^2, intravenously on days -6 (cycle 1 only), 1, 15, 29. • Methotrexate (MTX) 3 g/m^2/day, intravenously on days 2, 16, and 30. • Procarbazine 60 mg/m^2/day, orally from day 2 to 11. *Assessments* • *At different time points during each cycle*: clinical examination, performance status assessment, hematological and biochemical analyses, and evaluation of neurological signs and symptoms. • *Day 1 of each cycle*: whole brain magnetic resonance imaging (MRI). • *End of induction*: neuropsychological tests and QoL panel, CSF cytology and ophthalmologic assessment in patients positive at baseline or if relapse/progression was suspected, whole brain MRI. Maintenance (in patients achieving CR, PR, or SD) *Treatment (after randomization)* • Procarbazine 100 mg/day, orally from day 1 to 5, every 4 weeks for 6 cycles. • Lenalidomide 25 mg/day, orally from day 1 to 21, every 4 weeks for 24 cycles. *Assessments* • *Day 1 of each cycle, every 3 months during follow-up (i.e., up to 2 years from randomization or relapse/progression) and at the end of follow-up*: clinical examination, performance status assessment, hematological and biochemical analyses, evaluation of neurological signs and symptoms. • *Every 3 months during treatment and follow-up: and at the end of follow-up*: neuropsychological tests and QoL panel, CSF cytology and ophthalmologic assessment in patients positive at baseline or if relapse/progression was suspected, whole brain MRI. In addition, at the end of follow-up: spine MRI in case of dissemination at that level and Flourine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT) scan of neck-thorax-abdomen if there was a suspicion of systemic dissemination.
	Part B Induction *Treatment* • WBRT 1.8 Gray (Gy)/day, daily fractions x 13 days (5 days a week) - total dose of 23.40 Gy, • Temozolomide 75 mg/m²/day, orally every day for the whole duration of radiotherapy (7 days a week).

	• Rituximab at a dose of 375 mg/m², intravenously once weekly for four consecutive weeks, beginning on day 2 of WBRT (days 2, 9, 16 and 23). *Assessments* • *Days 1, 15 and 29 and end of induction*: clinical examination, performance status assessment, hematological and biochemical analyses, and evaluation of neurological signs and symptoms. • *End of induction*: neuropsychological tests and QoL panel, CSF cytology and ophthalmologic assessment in patients positive at baseline or if relapse/progression was suspected, whole brain MRI. Maintenance *Treatment* (in patients achieving CR, PR, or SD) • Temozolomide 150 mg/m^2/day (to be escalated to 200 mg/m^2/day, if no serious treatment-related AEs or grade 4 toxicity occurred during the first cycle) orally from day 1 to 5, every 4 weeks for 12 cycles. *Assessments* • *Day 1 of each cycle, every 3 months during follow-up (i.e., up to 2 years from randomization or relapse/progression) and at the end of follow-up*: clinical examination, performance status assessment, hematological and biochemical analyses, evaluation of neurological signs and symptoms. • *Every 3 months during treatment and follow-up: and at the end of follow-up*: neuropsychological tests and QoL panel, CSF cytology and ophthalmologic assessment in patients positive at baseline or if relapse/progression was suspected, whole brain MRI. In addition, at the end of follow-up: spine MRI in case of dissemination at that level and 18F-FDG PET/CT scan of neck-thorax-abdomen if there was a suspicion of systemic dissemination.
DURATION OF TREATMENT	**Part A** Induction: 10.5 weeks Maintenance: 24 months (lenalidomide arm), 6 months (procarbazine arm) **Part B** Induction: 5 weeks Maintenance: 12 months Patients remained on study for 2.5 years at maximum.
STUDY ENDPOINTS	**Part A** Primary endpoint The difference in 2-year progression-free survival (PFS) between the two treatment arms, measured from the time of randomization to the occurrence of disease relapse, progression, or death from any cause. Secondary endpoints To compare the two treatment arms with respect to the following parameters: • Duration of response, including PR and CR • OS • Rates and patterns of relapse • Safety profile

	• Incidence of early and late neurotoxicity
	Part B Primary endpoint The assessment of 2-year PFS, defined as the time from the initiation of maintenance therapy to the occurrence of disease relapse, progression, or death from any cause. Secondary endpoints The secondary endpoints included: • Response rates (RR) • Duration of response • OS • Rates and patterns of relapse • Safety profile • Incidence of early and late neurotoxicity • Role of geriatric assessments: CIRS, IADL, ADL and G8
STATISTICAL METHODS	Primary Efficacy Analysis: The primary efficacy analysis was conducted on an intent-to-treat (ITT) basis. PFS, OS, and duration of response were estimated using the Kaplan–Meier method. **Part A** Comparative Analysis Kaplan–Meier survival curves for the two treatment arms were to be compared using the log-rank test. Differences in RRs between treatment groups were to be assessed using the chi-square test. Independent associations between clinical and demographic variables and survival outcomes were to be evaluated using the Cox proportional hazards model. **Part B** Hypothesis Testing A Simon's two-stage minimax design was applied. The null hypothesis had to be rejected if at least 26 of the 65 evaluable patients remained progression-free at 2 years. This design provides a type I error rate of 5% and a statistical power of 80%, assuming a true 2-year PFS rate of 45% under the alternative hypothesis. **Interim analysis** In the initial protocol, an interim safety analysis was planned once the first ten patients randomized to the lenalidomide maintenance experimental arm had completed at least six treatment cycles. This analysis aimed to evaluate the feasibility of the treatment strategy and introduce timely modifications if necessary. In protocol version 3.0 an assessment of the dropout rate in Part A of the study was introduced, to be conducted at the same time of the safety analysis. Preliminary data indicated that the dropout rate at the end of the run-in phase of primary chemo-immunotherapy was higher than the one on which the sample-size calculation was based and corresponding to a drop-out rate of 40%. This evaluation was to be performed on approximately 50 patients, representing the number expected to be enrolled to achieve 10 patients randomized to the lenalidomide arm. As outlined in the protocol, if the dropout rate exceeded 50%, the IELSG45 study would be closed.

SUMMARY OF RESULTS	**Efficacy Results** The IELSG45 study was closed early due to insufficient enrollment, and efficacy analyses were limited to progression-free survival (PFS) and overall survival (OS), with 3-year outcomes reported for greater data maturity. Following patients for a longer period facilitated the detection of later events, providing more meaningful and interpretable outcomes. Overall, 3-year PFS and OS were 21% and 25%, respectively, with most events occurring in the first year and stabilization thereafter. In Part A, the lenalidomide arm achieved 3-year PFS of 46% and OS of 54%, while the procarbazine arm had 3-year PFS of 33% and OS of 44%; Kaplan–Meier trends were broadly similar. In Part B, which included patients ineligible for HD-MTX regimens, outcomes were poorer (3-year PFS 18%, OS 24%). These results highlight the challenges of treating less fit elderly patients with newly diagnosed PCNSL and emphasize the need for careful patient selection and stratification. **Safety Results** The IELSG45 study confirmed the expected safety profile of the tested regimens, with no unexpected toxicities observed. Overall, non-hematologic adverse events (AEs) were generally mild or moderate, while severe toxicity was primarily hematologic, especially neutropenia. In Part A, the lenalidomide arm reported 134 AEs, with about 25% drug-related and 22% Grade ≥3; 13 SAEs were documented, 3 of which were treatment-related. The procarbazine arm recorded 90 AEs, mostly non-drug-related, with 16–18% Grade ≥3 and 7 SAEs, including 1 treatment-related event. In Part B, the temozolomide arm had 36 AEs, one third Grade ≥3, and 14 SAEs, of which 5 were considered treatment related. Fatal events occurred in both Parts A and B, predominantly due to disease progression, underscoring the need for careful patient selection and pre-treatment assessment in this less fit PCNSL population.
CONCLUSIONS	The IELSG45 FIORELLA trial highlights the challenges involved in tailoring treatment to fitness levels and comorbidities in elderly patients with newly diagnosed PCNSL. While no unexpected toxicities were observed, a dropout rate of 60% revealed the vulnerability of the study population and led to early trial termination. Despite the anticipated closure, the trial provided important insights into treatment outcomes in elderly patients with newly diagnosed PCNSL. The high dropout rate underscores the need for careful patient selection, refined eligibility criteria incorporating comorbidity assessments, and stratified treatment strategies. Future studies should integrate more precise screening tools and interim analyses to better align treatment intensity with patient resilience and improve trial feasibility.
VERSION AND DATE OF THE REPORT	Version 1.0 – 19 December 2025