PROTOCOL SYNOPSIS

SPONSOR	International Extranodal Lymphoma Study Group (IELSG)
STUDY TITLE	Randomized Phase II Trial on Fitness- and Comorbidity- Tailored Treatment in Elderly Patients with Newly Diagnosed Primary CNS Lymphoma (FIORELLA Trial)
SHORT TITLE / STUDY ID	FIORELLA Trial / IELSG45
PROTOCOL VERSION	V1.0, 01.09.2017
TRIAL REGISTRATION	EudraCT: 2016-003116-12
CLINICAL PHASE	Phase II
INDICATION	Newly diagnosed primary central nervous system lymphoma in patients ≥70 years old
BACKGROUND AND RATIONALE	Primary central nervous system lymphomas (PCNSL) are rare aggressive malignancies, mostly of B-cell origin, representing 4% of intracranial neoplasms and 4-6% of extranodal non-Hodgkin's lymphomas (NHL). Despite improvements in treatment, PCNSL is associated with an aggressive course and unsatisfactory outcome. The median age at diagnosis is 61 years and age over 60 years has been reported to be an independent factor for a poorer outcome. The modern treatment of PCNSL includes two phases: induction and consolidation. The induction phase usually consists of a polychemotherapy combination, including high-dose methotrexate as a critical drug, while there are at least four different strategies that can be used as consolidation: whole-brain irradiation, myeloblative chemotherapy supported by autologous stem-cell transplantation, non-myeloblative chemotherapy, observation (only in patients who achieve complete remission after induction). The feasibility of this overall strategy is limited, for several reasons, in elderly patients with newly diagnosed PCNSL. High-doses of antimetabolite-based chemotherapy, the standard induction for patients younger than 70 years, is often not feasible in elderly patients. Among maintenance strategies, simple observation results in unacceptably high relapse rate and associated mortality while whole-brain irradiation and aggressive chemotherapies are associated with unacceptable toxicity and poor outcome. Thus, new strategies aimed at obtaining durable responses with an acceptable tolerability and reduced risk of neurocognitive decline are needed and these strategies should be tailored not only based on the patients' age but also on their specific co-morbidities and general health conditions. For the present trial, all patients aged ≥70 years taken into care at the participating sites will be invited to participate and after informed consent signature their baseline data will be collected in the trial database, including data of patients resulting in screening failure. This will allow to verify any potential screening bias by comparing the characteristics of included and excluded patients. Patients fulfilling the eligibility criteria are then screened for their suitability to receive a more or less aggressive anticancer treatment and assigned to two different treatment strategies accordingly.

	The more fit patients are assigned to the trial Part A and will receive the standard combination of high-dose methotrexate, procarbazine and rituximab as induction. Responding patients will subsequently be randomized to receive either procarbazine or lenalidomide as maintenance therapy. The more fragile patients are assigned to the trial Part B and will receive a less aggressive therapy consisting of concomitant whole-brain radiotherapy, temozolomide and rituximab as induction therapy, followed by temozolomide single-agent as maintenance treatment. **Rationale for trial Part A** Procarbazine is a lipophilic oral alkylating agent, easily crossing the blood brain barrier (up to 100% of plasma levels). There is no known cumulative toxicity for procarbazine and it is therefore currently in use as a viable maintenance treatment option aimed at eliminating residual lymphoma cells in the CNS and reduce the risk of relapse. Lenalidomide is an oral immunomodulatory agent, active against diffuse large B cell lymphoma, the most common category in PCNSL, which can be taken for years, showing an excellent safety profile. On this background, the Part A of the present trial consists of a randomized phase II trial conducted in elderly patients with newly diagnosed PCNSL responsive to high-dose methotrexate-based chemotherapy, comparing two different maintenance strategies: the oral chemotherapeutic drug procarbazine and the oral immunomodulatory agent lenalidomide. **Rationale for trial Part B** Whole-brain radiotherapy is the main therapeutic choice for patients with contraindications to chemotherapy and in particular for elderly patients. Brain irradiation is usually associated with transient disruption of the blood-tumor barrier, occurring from 1 week after the initiation of radiotherapy to 1 month after its completion, during which pharmaceutical agents have maximum access to tumor tissue. Concomitant delivery of active cytostatics, therefore, could result in increased tumor uptake. Concomitant delivery of radiotherapy and temozolomide is currently used as standard approach for the treatment of high-grade gliomas, with acceptable toxicity despite the use of a larger irradiation dose. Based on the above, in the Part B of the present trial, temozolomide and rituximab, two agents active against PCNSL, are delivered concomitantly to whole-brain radiotherapy to obtain a synergistic effect of radiation damage, antineoplastic effect of rituximab and cytostatic and radiomimetic effects of temozolomide. Finally, temozolomide maintenance has shown to be beneficial regarding sustained remission after initial response to induction therapy and its suitability to improve disease control in responding patients not fit for more aggressive therapies will therefore be tested in the Part B of this trial.
OBJECTIVES AND ENDPOINTS	**Part A** The <u>primary objective</u> of this prospective, randomized phase II trial is to compare the efficacy of a new maintenance treatment consisting of oral lenalidomide with the oral procarbazine maintenance currently in use, in elderly (≥70 years) patients with newly diagnosed PCNSL eligible to receive HD-MTX-based induction chemo-immunotherapy. The <u>primary efficacy endpoint</u> is the 2-year progression-free survival rate. Progression-free survival will be calculated from maintenance treatment start to relapse/progression or death due to any cause, whichever occurs earlier. The <u>secondary efficacy objectives</u> are to compare the effect of lenalidomide and procarbazine maintenance treatment in terms of: 1. Duration of response (Partial remission [PR] and Complete Remission [CR])

	2. Overall survival 3. Relapse rates and patterns 4. Safety profile 5. Early and late neurotoxicity The secondary efficacy endpoints are: 1. Difference between the two arms in time from first assessment of PR or CR to relapse/progression 2. Difference between the two arms in time from randomization to death due to any cause 3. Difference between the two arms in the following relapse rates and patterns: primary site vs. secondary CNS sites vs. extra-CNS sites; CNS sites: brain, meninges, cranial nerves, and/or eyes 4. Difference between the two arms in adverse events and adverse reactions incidence and severity 5. Difference between the two arms in incidence and severity of early and late neurotoxicity assessed by specific neuropsychological and Quality of Life tests The secondary safety objective is to compare the overall and neurological tolerability of lenalidomide and procarbazine. The secondary safety endpoints are: 1. Incidence and severity of adverse events and adverse reactions 2. Incidence and severity of early and late neurotoxicity assessed by neuropsychological and quality of life tests **Part B** The primary efficacy objective of this trial is to evaluate the efficacy of concomitant chemo-immuno-radiotherapy administered as induction treatment, followed by temozolomide maintenance in elderly (≥70 years) patients with newly diagnosed PCNSL ineligible to receive HD-MTX-based induction chemo-immunotherapy. The primary efficacy endpoint is the 2-year progression-free survival. Progression-free survival will be calculated from maintenance treatment start to relapse/progression or death sue to any cause, whichever occurs earlier. The secondary efficacy objectives are to evaluate: 1. The ability of the induction and maintenance treatment to induce objective tumor responses 2. Duration of response 3. Relapse rates and patterns 4. Overall survival The secondary efficacy endpoints are: 1. Proportion of patients showing CR, PR, SD, PD as best response to treatment 2. Time from first assessment of CR/PR to disease progression 3. Primary site vs. secondary CNS sites vs. extra-CNS sites; CNS sites: brain, meninges, cranial nerves, and/or eyes 4. Time from maintenance treatment start to death or last follow-up visit The secondary safety objectives are to evaluate the general and more specifically neurological tolerability of the induction and maintenance treatment. The secondary safety endpoints are: 1. Incidence and severity of adverse events and adverse reactions 2. Incidence and severity of early and late neurotoxicity assessed by neuropsychological and quality of life tests

	CORRELATIVE STUDY The objective of the correlative study is to identify biomarkers associated with lenalidomide and temozolomide antitumor activity. The following biomarkers will be assessed in tumor samples by central pathology review: 1. Cereblon (substrate receptor of the cullin-4 really interesting new gene [RING] E3 ligase complex) in patients receiving lenalidomide treatment (Part A) 2. Diffuse large B cell lymphomas cell of origin subtypes (germinal center B-cell [GCB] or activated B- cell [ABC]) in patients receiving lenalidomide treatment (Part A) 3. O^6-methylguanin-DNA-methyltransferase (MGMT) in patients receiving temozolomide (Part B)
STUDY DESIGN:	This is a multicenter open label phase II trial for patients aged 70 years or more, with newly diagnosed PCNSL. We expect to enroll 208 patients, who will be stratified according to their suitability to tolerate an induction chemo-immunotherapy regimen containing high-dose methotrexate. **Part A** Patients eligible for high-dose methotrexate-based induction chemotherapy will enter the run-in phase of Part A of the study and receive two courses of the HD-MTX-procarbazine-rituximab (or rituximab-biosimilar) combination every 43 days. Those in SD or better response after the two courses will be randomly assigned to procarbazine or lenalidomide maintenance monotherapy. Both drugs will be administered orally in 4 weeks cycles. The maximum number of maintenance courses will be 24 and 6 for lenalidomide and procarbazine, respectively. Forty assessable patients per treatment arm are required. **Part B** Patients ineligible for HD-MTX-based induction chemotherapy will be treated with concomitant whole-brain radiotherapy, temozolomide and rituximab in the single-arm phase II part of the trial. Patients showing SD or better response will receive temozolomide as maintenance therapy for 6 months. According to the Simon's two-stage minimax design, 46 patients will be treated in the first stage. If ≤ 16 patients will be progression-free at 2 years from maintenance treatment start, the study will be stopped. Otherwise, 19 additional patients will be treated for a total of 65.
ELIGIBILITY CRITERIA:	The following are the main eligibility criteria. **Inclusion criteria** - Histologically or cytologically assessed diagnosis of CD20+ diffuse large B-cell lymphoma. - Diagnostic sample obtained by stereotactic or surgical biopsy, CSF cytology examination or vitrectomy. - Lymphoma exclusively localized in the central nervous system (brain parenchyma and/or meningeal/CSF dissemination and/or eyes and/or cranial nerves). - Previously untreated patients (previous or ongoing steroid therapy admitted). - Age ≥70 years - Patients not eligible for high-dose chemotherapy supported by autologous stem cell transplant - ECOG PS ≤3. - Adequate bone marrow, cardiac, renal, and hepatic function - No previous or concurrent malignancies with the exception of

	surgically cured carcinoma in-situ of the cervix, carcinoma of the skin or other cancers without evidence of disease at least for 3 years (patients with a previous lymphoma at any time are NOT eligible). - Absence of any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule. - No concurrent treatment with other experimental drugs. - Patients receiving oral lenalidomide or procarbazine must agree to avoid sharing the study medication with another person and to return all unused study drug to the investigator. - Male patients must agree to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide, during dose interruptions and for up to 7 days after treatment discontinuation, even if they have undergone a successful vasectomy. - Informed consent from the patient, or legal representative, obtained before registration. **Exclusion criteria** - Lymphoma entity other than diffuse large B-cell lymphoma. - Extra-CNS disease. - Lymphoma exclusively localized in the eyes - Lymphoma infiltration of the cranial nerves as exclusive site of disease - Previous antineoplastic treatment for the PCNSL. - Patients eligible for ASCT. - HBsAg- and HCV-positive patients; HBsAg- and HCV-positive patients. HBcAb+ is not exclusion criteria in the absence of detectable levels HBVDNA. - HIV disease or immunodeficiency. - Severe concomitant illnesses/medical conditions (e.g. impaired respiratory and/or cardiac function, uncontrolled diabetes mellitus despite optimal medical management). - Active infectious disease. - Hypersensitivity to any active principle and/or any excipient according to the contraindications reported in the Summary of Product Characteristics (SmPCs) of the anticancer drugs used in the study
MEASUREMENTS AND PROCEDURES:	All patients entering the trial will undergo the following screening assessments during the two weeks preceding study treatment start: medical history, clinical visit, neurological signs and symptoms, neuropsychological tests, performance status, haematology and biochemistry, cerebrospinal fluid cytological examination, ophthalmologic examination (including slit lamp), echocardiography, respiratory volumes assessment, testicular ultrasonography, brain MRI for target lesions assessment, bone marrow aspirate and biopsy. CT scan and 18FDG-PET are optional before treatment, to be performed according to local standard policy to exclude extracranial lymphoma dissemination. In addition, central pathology reading will be performed on the existing tumor samples of patients assigned to the lenalidomide arm of Part A and of all patients assigned to Part B for tumor biomarkers analysis. **Part A** After screening, patients will receive 2 courses of <u>induction</u> chemo-immunotherapy administered as follows: Rituximab 375 mg/m^2 → standard infusion on days -6*, 1, 15 & 29

	Methotrexate 3 g/m^2 → 0.5 g/m^2 in 15 min. + 2.5 g/m^2 in 3-hr inf. on days 2,16,30 Procarbazine 60 mg/m^2/d → oral on days 2 to 11 The duration of each treatment course is 43 days (PRIMAIN regimen). *Rituximab on day -6 will be delivered only during the first course. Before starting each induction cycle patients will undergo a clinical visit with Performance Status and neurological signs and symptoms assessment, haematology and biochemistry tests. Brain MRI will be performed at the end of each cycle and the neuropsychological tests at the end of therapy. After induction treatment completion, patients showing complete/partial remission or disease stabilization will be randomized to receive lenalidomide or procarbazine as maintenance therapy as follows: Procarbazine → 100 mg/d per os, days 1 to 5 every 4 weeks for 6 courses Lenalidomide → 25 mg/d per os, days 1 to 21 every 4 weeks for 24 courses The clinical visit, including performance status, neurological signs and symptoms assessment, blood tests, and brain MRI, will be repeated before starting each maintenance course. In addition, during the follow-up phase lasting up to 24 months from randomization, the clinical visit, neurological signs and symptoms assessment, neuropsychological tests and brain MRI, will be carried-out every 3 months. Cerebrospinal fluid cytology and the ophthalmologic assessment are to be repeated at the end of the induction therapy and every 3 months during follow-up only if positive at baseline, while patients showing lymphoma presence in the spine at baseline will repeat the assessment only at the end of the follow-up period. **Part B** After screening patients will receive - whole-brain radiotherapy (a total dose of 23.40 Gy in 1.8 Gy daily fractions x 13 (5 days a week) - temozolomide 75 mg/m^2/d during radiotherapy - 4 weekly doses of rituximab 375 mg/m^2, starting on day 2 of the whole-brain radiotherapy. Patients achieving CR, PR or SD after induction will receive maintenance therapy with 12 courses of temozolomide administered on days 1-5, every 4 weeks at a dose of 150 mg/m^2/d at the first course, and of 200 mg/m^2/d at the subsequent courses, provided that during the first course no significant toxicity occurred. The clinical visit with neurological signs and symptoms and performance status assessment, the neuropsychological tests, haematology and biochemistry tests, and brain MRI for target lesions evaluation will be repeated at the end of the induction therapy and every 3 months during maintenance therapy and follow, while cerebrospinal fluid cytology and slit lamp examination are to be repeated only if positive at baseline. **Part A and Part B** All Adverse Events (AEs) regardless of causality emerging during induction and maintenance treatment will be recorded, while during the follow-up period only AEs with a suspected relationship to the study treatments (e.g., delayed neurological toxicities) and any new primary

	malignancies will be recorded.
STUDY PRODUCTS:	**Part A** Induction therapy: Rituximab, Methotrexate, Procarbazine Maintenance therapy: Procarbazine or Lenalidomide **Part B** Induction therapy: Whole-brain radiotherapy, Temozolomide, Rituximab Maintenance therapy: Temozolomide
NUMBER OF PARTICIPANTS WITH RATIONALE:	**Part A** Patients eligible for HD-MTX will be registered in a randomized phase II trial. The reported 2-year PFS rate for elderly patients with PCNSL eligible for HD-MTX is 40%. In order to detect a relative reduction of hazard by 50%, 51 events in total are required (one-sided test, type I error 5% and power 80%; log-rank test), with an accrual duration of 3 years and a follow-up of 2 years from randomization, 40 patients per arm need to be randomized. Considering an expected drop-out of 40% at the end of the run-in phase of induction therapy (due to toxicity or progressive disease), 134 patients (67 per arm) should be registered (accrual will be stopped when 40 assessable patients per arm are randomized). **Part B** For patients ineligible for HD-MTX, a Simon's two-stage minimax design will be applied. The null hypothesis that the true PFS rate at 2 years (calculated from maintenance treatment start) is 30% (P0) will be tested against a one-sided alternative hypothesis (P1) that the true 2-year PFS is 45%. In the first stage, 46 patients will be accrued. If 16 or fewer of these 46 patients will be progression-free at 2 years from maintenance treatment start, the study will be stopped. Otherwise, 19 additional patients will be accrued for a total of 65. Considering a dropout rate of 15%, 74 patients will be needed.
PARTECIPATING SITES	The list of participating sites will be provided in a separate document.
PLANNED STUDY DURATION AND SCHEDULE	Patient enrolment is expected to last 3 years. **PART A** - Induction therapy (run-in phase): about 10.5 weeks - Maintenance therapy: 24 months (lenalidomide arm) - Follow-up phase: 24 months from randomization - Patients will remain on study about 2.5 years. **PART B** - Induction therapy: 5 weeks - Maintenance therapy: 12 months - Follow-up phase: up to 24 months from maintenance treatment start - Patients will remain on study about 2.5 years.
STATISTICAL CONSIDERATIONS	The primary efficacy analysis will be on an intent-to-treat basis. Progression-free/overall survival and duration of response curves will be estimated using the Kaplan-Meier method. **PART A** The Log rank test will be used to compare the Kaplan-Meier curves of the two different treatment arms. Differences in response rate will be tested using the chi-square test.

	Independent association between studied variables and survival will be tested using the Cox proportional hazard model. An interim safety analysis will be performed after treatment of the first 10 patients randomly allocated to the experimental arm of lenalidomide maintenance in order to address feasibility and introduce timely treatment changes if necessary. **PART B** The null hypothesis will be rejected if 26 or more of the 65 assessable patients will be progression-free at 2 years. This design yields a type I error rate of 5% and power of 80% when the true 2-year PFS is 45% (alternative hypothesis).
GCP STATEMENT	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.