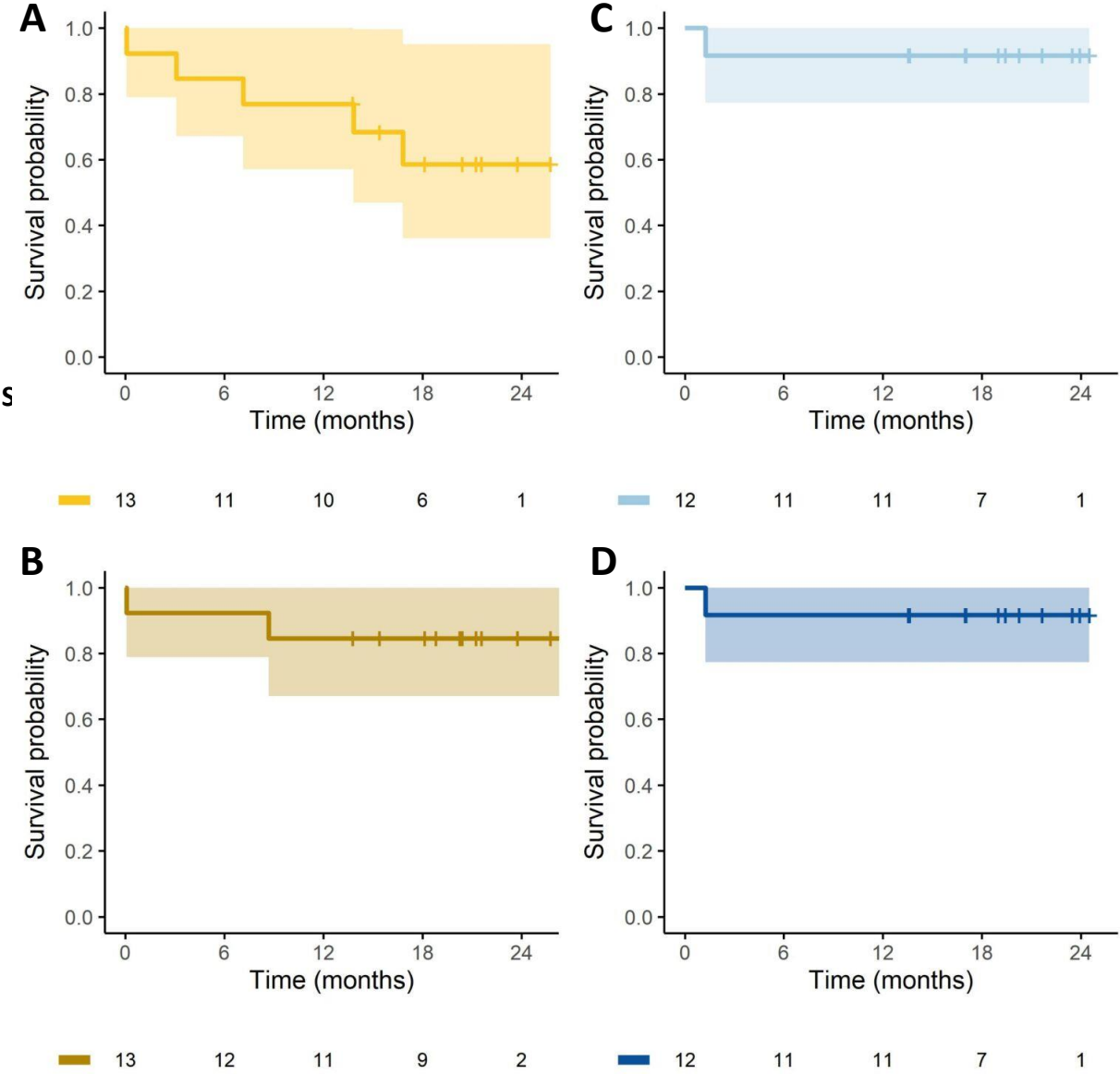


Supplemental data

Supplemental figure 1

Figure S1. Survivals of patients enrolled in the phase IB LOC-R01 trial. PFS (A) and OS (B) in the lenalidomide arm, in combination with R-MPV. PFS (C) and OS (D) in the ibrutinib arm, in combination with R-MPV.



Supplemental methods

SYNOPSIS – PROTOCOL N° 2019-02

A) CLINICAL TRIAL IDENTIFICATION	
<p>Protocol number: IC 2019-02 EudraCT number: 2019-003632-23 Version and date: Version 6.0 – 2023/06/15</p>	
<p>Title of the trial: LOC-R01: Randomized Phase IB/II Study of escalating doses of Lenalidomide and Ibrutinib in association with R-MPV as a targeted induction treatment for patients aged 18 to 60 (extended to 65 for phase II) with a newly diagnosed Primary Central Nervous System Lymphoma.</p>	
<p>Running title: LOC-R01: Lenalidomide and Ibrutinib in association with R-MPV first-line treatment of PCNSL.</p>	
<p>Coordinator: Dr Carole SOUSSAIN Institut Curie – Site Saint-Cloud - Service d'Hématologie Clinique 35 rue Dailly – 92210 SAINT-CLOUD - FRANCE Phone: + 33 (0)1 47 11 15 36 - Email: carole.soussain@curie.fr</p>	
<p>Estimated number of centers: 10 for the phase IB; 25 for the phase II</p>	<p>Number of patients: Phase I part: 26 patients Phase II part: 92 patients Total: 118 patients</p>
B) PROMOTOR IDENTIFICATION	
<p>INSTITUT CURIE 26 rue d'Ulm – 75248 PARIS Cedex 05</p>	
<p>Legal representative of the sponsor: Professor Steven LE GOUILL General Director of the Hospital Group INSTITUT CURIE 26 rue d'Ulm – 75248 Paris Cedex 05 - FRANCE Phone: +33 (0)1 56 24 56 30 – Fax: +33 (0)1 53 10 40 29 – Email: dr.ci.promotion@curie.fr</p>	
C) GENERAL TRIAL INFORMATION	
<p>Indication: Primary Central Nervous System Lymphoma (PCNSL) in patients aged 18 to 65 (18 to 60 in phase IB), in first-line treatment</p>	
<p>Methodology: Open label, prospective multicenter phase IB/II study</p>	
<p>Primary objective of the study: Phase IB: To determine the Maximal Tolerated Dose (MTD) and/or RP2D (Recommended Phase II Dose) of Lenalinomide and Ibrutinib when each is administered in association with R-MPV.</p>	

Phase II: To assess the complete response rates after the 4 cycles of each targeted induction chemotherapy in first-line treatment of PCNSL patients.

Secondary objectives of the phase Ib part:

To assess the 18-month Overall Survival and the 18-month Progression-Free Survival (progression according to IPCG criteria).

Secondary objectives of the phase II part:

To assess:

1. Complete response rate (CR + uCR) after 2 cycles of induction treatment.
2. Overall response rate (CR + uCR + PR), Stable Disease (SD) and primary refractory patients (PD) during induction treatment, before and after the Autologous Stem Cells Transplantation (ASCT).
3. 2-year Overall Survival (2-y OS) and 2-year Progression-Free Survival (2-y PFS)
4. Safety of the targeted induction chemotherapy.
5. Correlation between induction response and overall survival and progression free survival.
6. Percentage of patients who will receive ASCT.
7. Efficacy of stem cell collection and tolerance of ASCT after targeted induction chemotherapy.
8. Effectiveness of salvage chemotherapies after failure of the targeted induction chemotherapy.
9. Long-term survivals (OS and PFS).
10. Correlation of the IL10 & IL6 levels in CSF at diagnosis and at the end of each induction treatment with response and survivals.
11. Correlation between the lymphoid subpopulations at baseline and the treatment outcomes, and variations of the lymphoid subpopulations during targeted induction treatments.
12. Collection of biological samples for further ancillary studies.

Objectives of the further ancillary studies:

1. Assessment of the ctDNA levels before and at the end of each induction treatment (or at relapse or progression during induction treatment) and correlation with response and survivals.
2. Correlation between the molecular characteristics of the disease at diagnosis and correlation with the treatment outcomes results.
3. Influence of genetic polymorphisms on the outcome of PCNSL patients treated with targeted immunochemotherapies.

Primary endpoint of the study:

Phase IB: The primary endpoint is the occurrence of a Dose Limiting Toxicity (DLT) during the first cycle of treatment for each treatment arm. The phase IB is a 3+3 dose escalation design.

Phase II: The primary endpoint for the phase II part of the study is the Complete Response (CR) rate including unconfirmed CR (CR+uCR) at the end of the 4 cycles of induction therapy. Assessment of response will be based on the International Primary CNS Lymphoma Collaborative Group (IPCG)²⁷.

Secondary endpoints of the phase Ib part:

1. Overall Survival (OS) is defined as the time from randomization to death of any cause. Patients still alive at the date of last contact will be censored at this date.
2. Progression-Free Survival (PFS) is defined as the time from randomization to first progression or death of any cause (if the patient does not progress); progression being defined per IPCG criteria. Patients still alive without progression at the date of last contact will be censored at this date.

Secondary endpoints of the phase II part:

1. Response rates (CR + uCR) after 2 cycles of induction treatment as well as overall response (CR + uCR + PR), stable disease (SD), and primary refractory patients (PD) after 2 and 4 cycles of induction treatment, after the 2 cycles of R-Cytarabine and after the ASCT will be evaluated according to the International Primary CNS Lymphoma Collaborative Group (IPCG).
2. Overall Survival (OS) will be calculated from the date of randomization to the date of death, whatever the cause. Patients alive at the date of last contact will be censored at this date.
3. Progression-Free Survival (PFS) will be calculated from the date of randomization to the date of progression or death (if the patient does not progress). Patients alive without progression at the date of last contact will be censored at this date.
4. The severity of the toxicity of treatment induction or ASCT will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE 5.0) whenever possible and described by system organ class, preferred term. (A patient having the same event more than once will be counted only once).
5. The percentage of patients who will receive ASCT will be presented.
6. Failure of hematopoietic stem cells collection is defined as a number of collected CD34 below $3 \times 10^6/\text{kg}$.
7. Response to salvage chemotherapies after failure of the induction chemotherapy will be evaluated according to the International Primary CNS Lymphoma Collaborative Group (IPCG).
8. Incidence of second malignancies will be calculated.

Inclusion criteria:

1. Newly diagnosed Primary Central Nervous System Lymphoma (PCNSL).
2. a) Aged between 18 and 60 (≥ 18 and ≤ 60) – phase IB
b) Aged between 18 and 65 (≥ 18 and ≤ 65) – phase II.
3. Histological confirmed diagnosis of Primary central nervous system lymphoma of Diffuse Large B-Cell Lymphomas (DLBCL) type **OR** patients with a measurable typical cerebral lesion on MRI with a diagnosis made by cytology and/or by flow cytometry on the vitreous or on the cerebral spinal fluid.
4. Measurable lesion on MRI with gadolinium enhancement.
5. Adequate hematological, renal and hepatic function (Laboratory Parameters realized within 14 days before inclusion):
 - a. Absolute neutrophil count (ANC) $\geq 1000/\text{mm}^3$
 - b. Platelets $\geq 100,000/\text{mm}^3$ independent of transfusion support
 - c. Alanine aminotransferase and aspartate aminotransferase $\leq 3 \times$ Upper Limit of Normal (ULN)
 - d. Total bilirubin $\leq 1.5 \times$ ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

e. Estimated Glomerular Filtration Rate ≥ 60 mL/min/1.73m².

6. Able to swallow capsules.
7. Karnofsky performance status: 40-100% for the phase IB and no restriction on the KPS for the phase II.
8. Able to understand teratogenic risks of the Lenalidomide and Ibrutinib. Patient must be able to understand and fulfill the Lenalidomide Pregnancy Prevention Plan requirements. This plan may be accepted by the person of confidence in case of impaired cognitive status of the patient.
9. Women of childbearing potential (WCBP)* and men who are sexually active must be practicing a highly effective method** of birth control. Women should avoid a pregnancy while taking treatment by Lenalidomide or Ibrutinib and for up to 1 month after ending treatment. Men must agree to not to father a child or donate sperm during treatment by Lenalidomide or Ibrutinib and up to 3 months after the last dose of study drug.
10. Women of childbearing potential (WCBP)* must have a negative serum (beta-human chorionic gonadotropin [β -hCG]) or urine pregnancy test at inclusion.
11. Signed informed consent, which could be signed by a person on confidence in case the neurologic status of the patient does not allow him to understand and/or to sign.

**A woman is considered of childbearing potential (WCBP) if she:*

1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

***Women of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence. All male patients should use condoms throughout treatment duration, during dose interruption and for 3 months after cessation of Lenalidomide or Ibrutinib, if their partner is pregnant or of childbearing potential who is not using effective contraception and even if the male patient has undergone vasectomy*

Non-inclusion criteria:

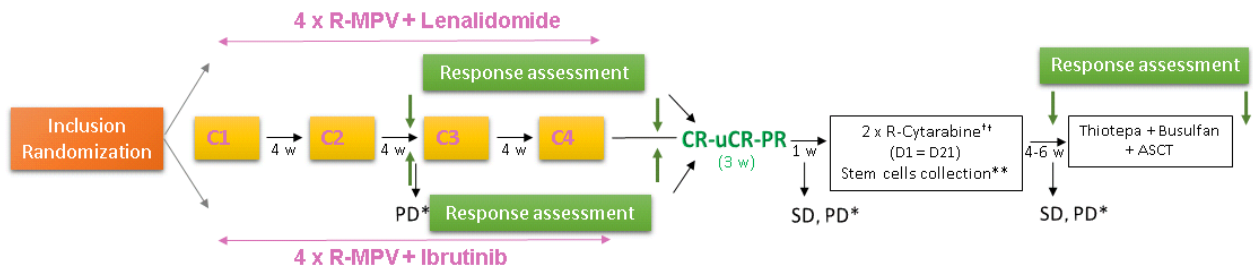
1. Histology other than DLBCL.
2. Positive HIV serology.
3. Active viral infection with Hepatitis B or C virus.
4. Preexisting immunodeficiency and/or organ transplant recipient.
5. Isolated CNS relapse of systemic NHL.
6. Prior treatment for PCNSL (except corticosteroids).
7. Isolated primary vitreo-retinal lymphoma.
8. Major surgery, within 4 weeks prior to the first dose of study drug. Stereotactic biopsy and vitrectomy are not considered major surgery.
9. History of stroke or intracranial hemorrhage (except minor post biopsy hemorrhage) within 6 months prior to inclusion.
10. Requires anticoagulation with warfarin or equivalent vitamin K antagonists.
11. Requires treatment with strong CYP3A4 inhibitors.
12. Pregnancy or lactation.
13. Clinically significant cardiovascular disease.
14. Any other active malignancy, except basocellular carcinoma and non-invasive cervix cancer.
15. Inclusion in another experimental anti-cancer drug therapy*.
16. No social security affiliation.
17. Persons under legal protection.

**For ethical reasons, the exclusion period within which the patient cannot be included in another trial will not be defined but discussed on a case to case basis*

D) DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCTS**Drugs:** Cycles of 28 days

Drug name	Pharmaceutical Form	Administration Route	Posology
R-MPV + study drug			
RITUXIMAB	Solution to be diluted for intravenous infusion	IV	375 mg/m ² D1
METHOTREXATE*	Solution for injection	IV	3.5 g/m ² D1 and 15
PROCARBAZINE	Capsule	PO	100 mg/m ² D1 to 7
VINCRIStINE	Solution for injection	IV	1.4 mg/m ² D1 and D15 (capped at 2 mg)
PREDNISONE	Tablet	PO	60 mg/day D1 to 5
LENALIDOMIDE or IBRUTINIB	Hard capsule	PO	MTD according to results of phase IB*
	Hard gelatin capsule	PO	
Study Drug	*Dose levels		
	K-1	K	K+1
Arm A: Lenalidomide	15 mg/D D1 to D21	20 mg/D D1 to D14	20 mg/D D1 to D21
Arm B: Ibrutinib	280 mg (D3 to D14 and D17 to D28)	420 mg (D3 to D14 and D17 to D28)	560 mg (D3 to D14 and D17 to D28)
* MTX can be administered for logistical purpose on D2. Ibrutinib will be started 48 h after MTX.			
Recommended standard consolidation: the induction phase will be followed by two 21-day cycles of R-Cytarabine (Rituximab 375 mg/m ² ; Cytarabine 3g/m ² /D D1 and D2) and followed 4-6 weeks after by an intensive chemotherapy with hematopoietic stem cell rescue (Thiotepa 250 mg/m ² /D D-7, D-6, D-5; Busulfan 3.2 mg/kg/D D-4, D-3 and 1.6 mg/kg on D-2; peripheral stem cells on D0).			

Therapeutic scheme:



* Patients in PD after 2 cycles of induction; patients SD or PD after 4 cycles of induction or after R-Cytarabine will be considered as treatment failure

** The first R-Cytarabine cycle will start 4 weeks after D1 of C4.

**Stem cells will be collected after the first R-Cytarabine cycle, and if necessary after the second cycle

Treatment duration:

Duration of the study induction treatment: 4 months

Recommended standard consolidation: 3 months for phase IB and phase II patients

E) STATISTICAL ANALYSIS

Total number of patients

Phase I: The phase IB is a 3+3 dose escalation design. The Maximum Tolerated Dose (MTD) is determined by the highest dose that will cause, at most, one Dose-Limiting Toxicity (DLT) on 6 patients. Depending on the observed number of DLT, a minimum of 18 patients (9 in each arm) and a maximum of 36 patients (18 in each arm) might be required to establish the MTD.

Phase II: The patient number calculation is based on a single-stage A'Hern design. We set: $P_0 = 45\%$ and $P_1 = 65\%$. With $\alpha = 0.08$ and $\beta = 0.09$, 44 evaluable patients (who received at least one dose of treatment) are needed in each arm. With an estimated rate of patients included but not treated of 5%, a total of 46 patients should be enrolled in each arm of the phase II (total = 92 patients).

Analyses of the primary endpoints

All analyses will be performed separately for each treatment arm.

Phase IB:

Descriptive statistics of safety will be presented using National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 by treatment group.

Phase II: According to the A'Hern design, if at least 25 of 44 evaluable patients are in CR/uCR at the end of the 4 cycles of induction therapy, we will conclude that the treatment is efficient. Patients without response assessment at the end of the 4 cycles of induction therapy (whatever the reason) will be considered as non-responders. The response rate will be presented with its two-sided exact 95% confidence interval using the Clopper-Pearson method and calculated on all evaluable patients.

F) ESTIMATED TRIAL DURATION

Inclusion period: 42 months (phase IB : 12 months estimated; phase II : 30 months estimated)

To determine RP2D after last inclusion in phase IB, inclusion period was necessary closed during 4 months to carry out all tasks required before opening the phase II part of the study (toxicity monitoring, data analysis, SRC and IDMC meetings, dose for phase II determination of each experimental product, initiation visits for phase II, logistics and experimental products supply).

Induction treatment: 4 months

Patient follow-up period since inclusion:

10 years follow-up for the last included patient

Estimated Total study duration: 14 years

- First analysis (primary end-point) at the end of the induction treatment (46 months)
- Second analysis (secondary end-points) 18 months after randomization of the last patient included in the phase II
- Long-term events at 5 and 10 years of the last patient included in the phase II.