Journal of Hematology & Oncology

RESEARCH

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Phase IB part of LOC-R01, a LOC network non-comparative randomized phase IB/II study testing R-MPV in combination with escalating doses of lenalidomide or ibrutinib for newly diagnosed primary central nervous system lymphoma (PCNSL) patients

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Abstract

Background Results of conventional induction chemotherapies in primary central nervous system lymphoma (PCNSL) need to be improved. Ibrutinib, a BTK inhibitor, and lenalidomide, an immunomodulatory drug, have shown promising results at relapse, supporting to further assess their individual use in combination with high-dose methotrexate-based chemotherapy.

Methods Patients with newly diagnosed PCNSL were randomized to receive four 28-day cycles of ibrutinib or lenalidomide in combination with R-MPV (rituximab, methotrexate, procarbazine, vincristine and prednisone) in a 3 + 3 design. Responders then received a consolidation with R-Cytarabine and an intensive chemotherapy with autologous stem cell transplantation. The objective of the phase IB study was to define the recommended phase II dose (RP2D) based on the dose-limiting toxicity (DLT) occurring during the first induction cycle.

Results Twenty-six patients (median age 52) were randomized. Four DLTs were observed: one grade 5 aspergillosis and pneumocystosis, one grade 4 catheter-related infection and two grade 3 increased alanine aminotransferase levels. RP2D of ibrutinib and lenalidomide were 560 mg daily (D3-14 and D17-28) and 15 mg daily (D1-21) respectively, in combination with R-MPV. In both arms, the most frequent grade ≥3 treatment-related adverse events were hepatic cytolysis, neutropenia and infections. One grade 4 Lyell's syndrome was reported at cycle 2 in the lenalidomide arm. After 4 induction cycles, the overall response rates were 76.9% and 83.3% in the lenalidomide and ibrutinib arm, respectively.

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Conclusion Targeted induction therapies combining lenalidomide or ibrutinib with R-MPV are feasible for first-line PCNSL. The safety profile is consistent with the known safety profiles of R-MPV and both targeted therapies. The phase II part of the study is ongoing.

Trial registration NCT04446962.

Keywords Primary central nervous system lymphoma, Phase IB trial, Ibrutinib, Lenalidomide

Background

Primary central nervous system lymphomas (PCNSL) are large B-cell lymphomas (LBCL) of immune-privileged sites [1] with constitutive NF-κβ signaling through Toll-like receptor/B-cell receptor (BCR) pathway activation [2–4]. PCNSLs are confined to the central nervous system (CNS), i.e., the brain, the eye, the cerebrospinal fluid (CSF) and/or the spinal cord, with no systemic infiltration. PCNSLs are associated with an inferior prognosis as compared to nodal LBCL [5].

The standard first-line treatment in patients up to 60–65 years old relies on an induction treatment based on high-dose (HD) methotrexate (MTX) and HD cytarabine chemotherapy, followed by a consolidation phase with intensive chemotherapy and autologous stem cell transplantation (ASCT) or whole brain radiotherapy (WBRT). ASCT acts on minimal residual disease through the dose-effect of the intensive chemotherapy and showed a significantly lower risk of neurocognitive decline, and a very encouraging long-term disease control in the first-line setting, with a two-year overall survival (OS) of 70% [6–11]. Despite these recent improvements, up to 25% of the patients are primary refractory to high-dose methotrexate and are therefore not able to benefit from consolidation therapy [5–7, 12].

Both ibrutinib, the first-in-class Bruton's tyrosine kinase (BTK) inhibitor, and lenalidomide, an immunomodulatory agent, have shown promising results in the relapse setting. In a phase II trial, single agent ibrutinib was associated with a 70% disease control rate, some durable responses, and a favorable safety profile among 44 relapsed/refractory PCNSL and primary vitreoretinal lymphoma (PVRL) patients [13, 14]. Another phase II study reported 36% of overall response rate (ORR) following an induction of 8 cycles of rituximab plus lenalidomide and manageable toxicities within a cohort of 45 patients with relapsed/refractory PCNSL and PVRL [15]. Furthermore, both targeted therapies may have a beneficial "on-target, off-tumor" effect on the PCNSL tumor microenvironment [16].

Therefore, the LOC-R01 study aimed to evaluate the toxicity and efficacy of an induction treatment combining either ibrutinib or lenalidomide with standard HD-MTX-based immunochemotherapy for newly diagnosed PCNSL patients.

Patients and methods

Patients

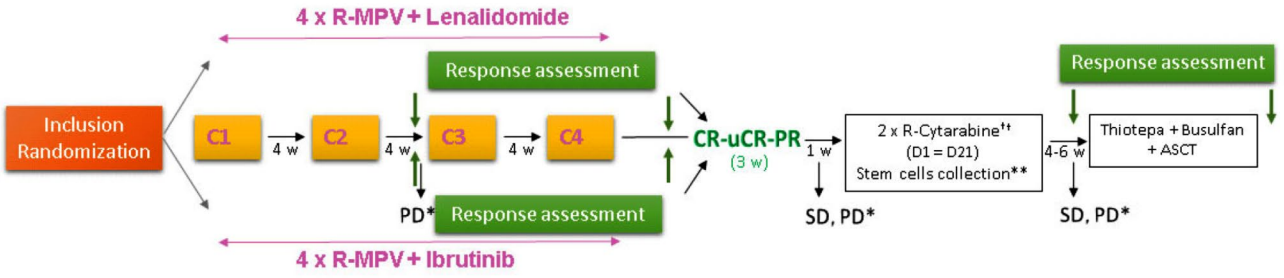
Eligible patients were aged between 18 and 60 years and had a newly diagnosis of pathologically confirmed large B-cell PCNSL or a measurable typical cerebral lesion on magnetic resonance imaging (MRI) with a diagnosis made by cytology and/or by flow cytometry on the vitreous or on the CSF, and at least one measurable lesion on MRI with gadolinium enhancement.

Patients were required to have the ability to swallow capsules and to fulfill the lenalidomide pregnancy prevention plan requirements, as well as adequate hematological, renal and hepatic functions. For the phase IB part of the study, a Karnofsky performance status (KPS) ≥ 40% was required. Main exclusion criteria included PVRL, an isolated CNS relapse of systemic non-Hodgkin lymphoma (NHL), a preexisting immunodeficiency and/or organ transplantation, other malignancies (except basocellular carcinoma and non-invasive cervix cancer), HIV or hepatitis B or C infection, major surgery within 4 weeks prior to the first dose of study drug (stereotactic biopsy and vitrectomy were not considered major surgery), history of stroke or intracranial hemorrhage (except minor post biopsy hemorrhage) within 6 months prior to inclusion, concomitant treatment with anticoagulation or strong CYP3A4 inhibitors, and clinically significant cardiovascular disease. Patients must not have received any prior treatment for PCNSL, with the exception of corticosteroids.

Study design and conduct

LOC-R01 (registered at www.clinicaltrials.gov as NCT04446962, synopsis of the trial provided in the supplemental Methods) is a non-comparative, randomized, open-label, multicenter phase IB/II study. The phase IB dose-escalation part of the trial, reported here, was based on a 3+3 design in order to determine the maximum tolerated dose (MTD) and evaluate the safety and tolerability of ibrutinib or lenalidomide in combination with standard HD-MTX-based induction immunochemotherapy for first-line PCNSL patients.

A maximum of one DLT for six patients was considered acceptable. Consequently, the minimum sample size was 18 evaluable patients (9 in each arm), and the maximum 36 (18 in each arm). An Independent Data Monitoring Committee (IDMC) was consulted to review the safety



* 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

Fig. 1 Schematic representation of the study treatment. R-MPV: rituximab 375 mg/m^2 D1, methotrexate 3.5 g/m^2 D1 and 15, procarbazine 100 mg/m^2 D1 to 7, vincristine 1.4 mg/m^2 D1 and D15 and prednisone 60 mg/day D1 to 5; R-Cytarabine: rituximab 375 mg/m^2, cytarabine 3 g/m^2/D D1 and D2; ASCT: autologous stem cell transplantation; CR: complete response; uCR: unconfirmed complete response; PR: partial response; SD: stable disease; PD: progressive disease; w: weeks

Table 1 Detailed dose levels and administration schedules of the study drugs

Study drug	Dose levels		
	K	K-1	K+1
Arm A: Lenalidomide	20 mg/D 14 days	15 mg/D 21 days	20 mg/D 21 days
Arm B: Ibrutinib*	420 mg (D3 to D14 and D17 to D28)	280 mg (D3 to D14 and D17 to D28)	560 mg (D3 to D14 and D17 to D28)

*Ibrutinib was suspended on the days of methotrexate infusion and the 2 days thereafter. However, if then next methotrexate was delayed for a cause that did not prevent the use of ibrutinib, ibrutinib was continued

profile of the treatments and validate the recommended phase II dose (RP2D) for both arms. The study was conducted in compliance with Good Clinical Practice, as defined by the International Conference on Harmonization and according to applicable regulatory requirements. The study protocol and all amendments were approved by the competent authority and independent ethics committee. All patients, or the persons on confidence in case the neurological status of the patient did not allow him to understand and/or to sign, provided written informed consent before enrollment.

Treatment and assessments

Patients were randomized (1:1) to receive four 28-day cycles of either ibrutinib or lenalidomide in combination with R-MPV (rituximab 375 mg/m^2 D1, methotrexate 3.5 g/m^2 D1 and 15, procarbazine 100 mg/m^2 D1 to 7, vincristine 1.4 mg/m^2 D1 and D15 and prednisone 60 mg/day D1 to 5), followed by a consolidation including two 21-day cycles of R-Cytarabine (rituximab 375 mg/m^2; cytarabine 3 g/m^2/D D1 and D2) and an intensive chemotherapy (thiotepa 250 mg/m^2/D D-7,-6,-5, busulfan 3.2 mg/kg/D D-4, -3 and 1.6 mg/kg at D-2) with autologous stem cell transplantation at D0 (Fig. 1).

During the dose-escalation, ibrutinib was given orally at 420/280/560 mg per day (D3 to D14 and D17 to D28) and lenalidomide was given orally, once daily, at 20 mg D1 to 14/15 mg D1 to 21/20 mg D1 to 21 (Table 1). Ibrutinib was suspended during 48 h from methotrexate infusion because of a suspected in vitro antagonism [17]. We decided to suspend ibrutinib for only two days in order to limit this possible antagonism when methotrexate is circulating in the patient's blood without reducing too much the exposure to ibrutinib.

The use of hematopoietic growth factors was allowed in both arms if required. Prophylaxis for pneumocystosis other than cotrimoxazole (such as aerosolized pentamidine or atovaquone) was recommended along with antiherpetic prophylaxis in both arms. Antithrombotic prophylaxis was mandatory in the lenalidomide arm. No fungal prophylaxis was recommended in the ibrutinib arm, in order to minimize drug interactions and facilitate dose escalation. At the time we designed the study, there were no clear recommendations regarding the use of fungal prophylaxis with ibrutinib or dose adjustment of ibrutinib with fungal prophylaxis. A lower risk of aspergillosis was also expected in newly-diagnosed PCNSL patients. Vincristine was tapered or stopped in case of peripheral neuropathy at the discretion of the investigator. A strong recommendation to rapidly taper any glucocorticoid therapy was made to reduce the risk of infection in both arms as well as to consider the risk of aspergillosis in the event of clinical sign of infection in the ibrutinib arm. The sponsor and investigators developed management strategies for specific adverse events (AEs) during the study conduct.

Response assessment was performed according to the International Primary CNS Lymphoma Collaborative Group (IPCG) criteria [18] before cycle 3 and after cycle 4 (before the first cycle of R-Cytarabine).

Outcomes

The primary endpoint of the phase IB was the incidence of a dose-limiting toxicity (DLT) during the first cycle for each treatment arm. The primary endpoint of the ongoing phase II was the complete response rate (complete response (CR) and unconfirmed completed response (uCR) as per IPCG criteria) after 4 cycles of induction therapy. The final analysis of the phase IB part of the trial is presented here.

DLTs were defined as the following events occurring within the DLT evaluation period (28 days after the start of cycle 1): grade≥3 non-hematological toxicity lasting more than 7 days (excluding fatigue, alopecia, nausea, vomiting and diarrheas corrected with adequate standard treatment; acute renal insufficiency due to high-dose methotrexate and delayed elimination of methotrexate; hepatic cytolysis associated to methotrexate and not clinically significant (was considered as DLT if hepatic cytolysis grade≥3 lasting>14 days and resulting in a delay of the next methotrexate≥7 days); toxicity of rituximab; grade 3 deep venous thrombosis responsive to anticoagulation; grade 3 rash with improvement to grade 1 within 10 days), grade 4 neutropenia lasting more than 7 days despite the use of G-CSF, life threatening febrile grade 3 or higher neutropenia, platelets count<25,000/mm3 or platelet transfusion dependency at day 28.

Patients who did not start lenalidomide or ibrutinib or who received less than 80% of the planned dose of lenalidomide or ibrutinib for a reason other than DLT were considered as not evaluable for the DLT assessment and were replaced.

Safety was assessed through physical examinations, vital sign measurements, laboratory tests, and AE reporting. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment-emergent AEs (TEAEs) were reported from treatment initiation through 3 months after induction. The investigators attributed causality for severe AEs.

Secondary endpoints for the phase IB included overall survival (OS), defined as the time from randomization to death of any cause, and progression-free survival (PFS) defined as the time from randomization to first progression or death of any cause; progression being defined per IPCG criteria. Patients still alive were censored at their date of last news.

Statistical analyses

All patients randomized to the ibrutinib or lenalidomide arms were included in the primary endpoint analysis, and those who received at least one treatment dose (ibrutinib or lenalidomide) were included in the analyses of secondary endpoints. Analyses were conducted separately for each treatment arm. Patients enrolled in the phase IB part of the trial will not be included in the efficacy analysis of the ongoing phase II. OS and PFS were estimated using the Kaplan-Meier method. Survival analyses were performed using R version 4.1.2 software.

Results

Patients

Between November 2020 and November 2021, 26 patients were enrolled in the phase IB part of the LOC-R01 study within 10 centers of the LOC network. Thirteen patients were randomized in each of the treatment arms (Fig. 2). One patient in the ibrutinib arm (dose K+1) was wrongly included as he presented with a major exclusion criterion (complete surgical resection). He did not receive the study treatment. Therefore, patients' characteristics are described for the whole population (N=26) whereas we report the secondary endpoints only for the patients who received at least one dose of treatment (N=13 in the lenalidomide arm and N=12 in the ibrutinib arm).

Main patient demographics and baseline clinical characteristics were well balanced between both arms, with some variations due to the small number of patients (Table 2). The median age was 52 years (32–60) and median KPS was 80 (40–100). Patients mostly presented with symptoms of motor/sensory deficit (34.6%) or cognitive impairment (30.8%).

All patients had cerebral MRI, showing contrast enhancement in all cases. In the lenalidomide arm, 23.1% and 69.2% of the patients had a unique or multiple lesions, respectively. In the ibrutinib arm, 53.8% and 46.2% of the patients had a unique or multiple lesions, respectively. Among the patients who had a lumbar puncture (84.6%) at inclusion, CSF infiltration by lymphoma cells was reported in 30% and 50% of the patients in the lenalidomide and ibrutinib arm, respectively. Among the patients who had an ophthalmologic examination (96.2%) at inclusion, ocular localization of the lymphoma was reported in 8.3% and 23.1% of the patients in the lenalidomide and ibrutinib arm, respectively. The diagnostic was made on a brain biopsy in 24/26 (92.3%) patients and CSF analysis or vitrectomy in 2/26 (7.7%) patients.

Eight and 11 patients completed the four cycles of R-MPV-based induction immunochemotherapy in the lenalidomide and ibrutinib arm, respectively (Fig. 2). Four patients (30.8%) discontinued lenalidomide early, because of toxicity (one post-cycle 2, one during cycle 2 and two during cycle 4, Fig. 2). Deaths were reported for 1 patient in the lenalidomide arm (progressive disease) and 1 patient in the ibrutinib arm (sepsis).

Safety

Lenalidomide arm

At dose K (20 mg/D during 14 days, N=7 patients), 2 patients experienced DLTs, including one grade 4

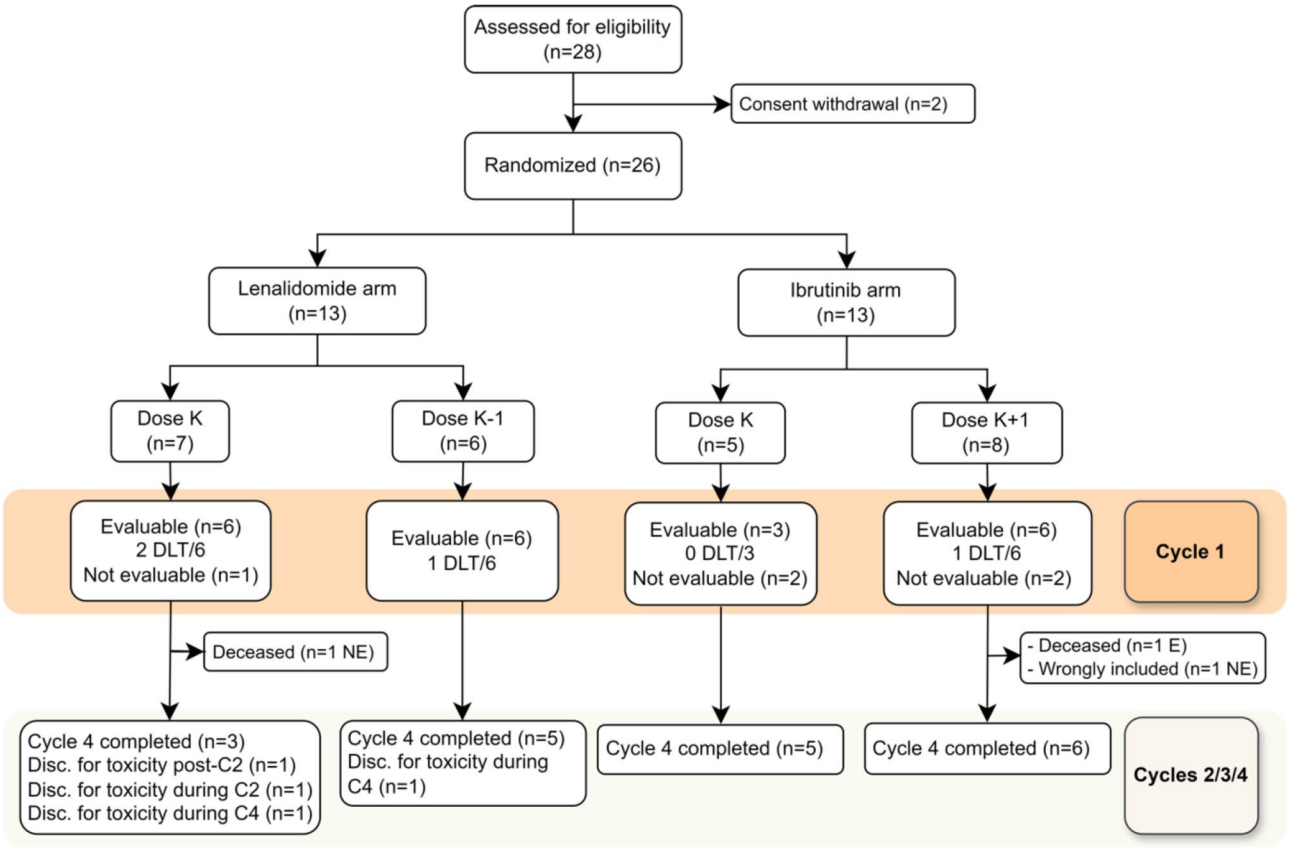


Fig. 2 LOC-R01 phase IB flow chart. Lenalidomide dose K: 20 mg per day D1 to 14; Lenalidomide dose K-1: 15 mg per day D1 to 21; Ibrutinib dose K: 420 mg per day (D3 to 14 and D17 to 28); Ibrutinib dose K + 1: 560 mg per day (D3 to 14 and D17 to 28); DLT: dose-limiting toxicity; E: evaluable; NE: not evaluable; Disc: discontinued

catheter-related infection lasting more than 7 days and one grade 3 increased alanine aminotransferase (ALT) levels lasting 16 days. These 2 DLTs required enrollment of a de-escalation cohort (dose K-1: 15 mg/D during 21 days, $N=6$ patients). Of note, one patient was considered as not evaluable among the DLT period at dose K because he died from tumor progression only 2 days after treatment initiation. One of 6 patients treated at dose K-1 experienced a DLT, namely a grade 3 increased ALT lasting more than 14 days and leading to a postponement of cycle 2 by more than 7 days. Therefore, dose K-1 (lenalidomide 15 mg daily from D1 to D21) was the maximum tolerated dose and defined as the RP2D by the IDMC, in combination with R-MPV.

During the whole induction phase, the most frequently ($N\geq3$ patients) reported TEAEs (all grade), across all dose levels, were hepatic cytolysis ($N=8$, 61.5%), peripheral sensory neuropathy ($N=7$, 53.8%), infections ($N=5$, 38.5%), anemia ($N=5$, 38.5%), constipation ($N=5$, 38.5%), neutropenia ($N=4$, 30.8%), maculopapular rash ($N=3$, 23.1%), thromboembolic event ($N=3$, 23.1%), dyspnea ($N=3$, 23.1%) and fatigue ($N=3$, 23.1%) (Table 3). Most patients ($N=10$, 76.9%) experienced a grade 3 or higher TEAE. The most frequent grade 3 or 4 TEAEs related to lenalidomide in combination with R-MPV were hepatic cytolysis ($N=5$, 38.5%), neutropenia ($N=3$, 23.1%) and infections ($N=3$, 23.1%). Of note, one patient had a grade 4 Lyell's syndrome during cycle 2, most likely related to lenalidomide. She was transferred to an intensive dermatology unit for specialized care, and her Lyell's syndrome gradually improved. The pharmacovigilance study concluded that the drugs to be preferentially incriminated were lenalidomide, followed by valaciclovir and atovaquone.

Treatment-related serious AEs were reported for 5 patients (38.5%), including infections (one bacteriemia of grade 2, one sepsis and one endocarditis of grade 3 and two catheter-related infections of grade 4), one grade 4 Lyell's syndrome and one grade 2 thromboembolic event.

Dose delays (≥7 days) because of an AE occurred in 3 (42.9%) and 3 (50%) patients at dose K and K-1, respectively (Table 4). Besides, across all dose levels, 5 (38.5%) patients had a dose reduction of lenalidomide because of an AE, while 4 (30.8%) and 8 (61.5%) patients received less methotrexate and vincristine, respectively (Table 4).

Table 2 Baseline demographic and clinical characteristics

Characteristic	Lenalidomide arm (*N* = 13)	Ibrutinib arm (*N* = 13)	Total (*N* = 26)
Age (years), median (range)	53 (36–60)	52 (32–60)	52 (32–60)
Sex ratio, M/F	1.2	2.25	1.6
KPS (%), median (range)	80 (50–100)	80 (40–100)	80 (40–100)
Symptoms at diagnosis	5 (38.5%)	4 (30.8%)	9 (34.6%)
Motor/sensory deficit, N(%)	5 (38.5%)	3 (23.1%)	8 (30.8%)
Cognitive impairment, N(%)	2 (15.4%)	2 (15.4%)	4 (15.4%)
Gait disorder, N(%)	2 (15.4%)	2 (15.4%)	4 (15.4%)
Headache/intracranial hypertension, N(%)			
Elevated serum LDH, N(%)	3 (23.1%)	8 (61.5%)	11 (42.3%)
Diagnostic method	13 (100%)	11 (84.6%)	24
Cerebral biopsy, N(%)	0 (0%)	1 (7.7%)	(92.3%)
CSF analysis, N(%)	0 (0%)	1 (7.7%)	1 (3.8%)
CSF analysis + vitrectomy, N(%)			1 (3.8%)
MRI	13 (100%)	13 (100%)	26
Contrast enhancement, N(%)	3 (23.1%)	7 (53.8%)	(100%)
Unique vs. multiple/diffuse lesions, N(%)	vs. 9 (69.2%)	vs. 6 (46.2%)	10 (38.5%)
Infratentorial involvement, N(%)	3 (23.1%)	1 (7.7%)	vs. 15 (57.7%)
			4 (15.4%)
CSF analysis	10 (76.9%)	12 (92.3%)	22
Done, N(%)	3 (30%)	6 (50%)	(84.6%)
Lymphomatous meningitis (positive cytology and/or flow cytometry), N(%)			9 (40.9%)
Ophthalmologic examination	12 (92.3%)	13 (100%)	25
Done, N(%)	1 (8.3%)	3 (23.1%)	(96.2%)
Ocular involvement, N(%)			4 (16%)

M/F: male/female; KPS: Karnofsky Performance Scale; LDH: Lactate dehydrogenase; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging

Ibrutinib arm

At dose K (420 mg, *N*=5 patients), 2 patients were not evaluable for the DLT since they received less than 80% of the planned ibrutinib dosage (39% and 54% respectively) because of a methotrexate-related hepatic cytolysis. No DLT was noted at dose K, which resulted in the enrollment of an escalation cohort (dose K+1: 560 mg, *N*=8 patients). Two patients were not evaluable for DLT at dose K+1 (one patient had delirium and mistook the treatment (71% of the planned dose) and the other was the previously mentioned wrongly enrolled patient). One of 6 evaluable patients treated at dose K+1 experienced a DLT, namely a grade 5 septic shock due to invasive pulmonary aspergillosis and pneumocystosis resulting in the patient's death. The clinical course of this patient was very unfortunate. He was treated with high dose corticosteroids after he underwent the stereotactic biopsy. His tumor was placed in the hypothalamic-pituitary region responsible for a difficult-to-treat insipidus diabetes resulting in large natremia variations and a subsequent central pontine myelinolysis followed by comatose state. At the same time, he presented with a severe bronchopulmonary infection for which he was transferred to intensive care unit (ICU). Pneumocystosis and aspergillosis were identified, but the ICU physicians, together with the patient's family decided to limit the healthcare and no specific treatment for pneumocystosis or aspergillosis was delivered. The patient had received one aerosolized pentamidine as pneumocystis prophylaxis.

Consequently, dose K+1 (ibrutinib 560 mg daily from D3 to D14 and D17 to D28) was the maximum tolerated dose and defined as the RP2D by the IDMC, in combination with R-MPV.

During the whole induction phase, the most frequently reported TEAEs (all grade), across all dose levels, were infections (*N*=6, 50%), peripheral sensory neuropathy (*N*=6, 50%), hepatic cytolysis (*N*=6, 50%), anemia (*N*=5, 41.7%), diarrhea (*N*=4, 33.3%), nausea (*N*=4, 33.3%), thrombocytopenia (*N*=4, 33.3%), fatigue (*N*=3, 25%), neutropenia (*N*=3, 25%), creatinine increased (*N*=3, 25%) and headache (*N*=3, 25%) (Table 3). Of note, only one patient experienced a grade 1 atrial fibrillation. Most patients (*N*=9, 75%) experienced a grade 3 or higher TEAE. The most frequent grade ≥ 3 TEAEs related to ibrutinib in combination with R-MPV were hepatic cytolysis (*N*=4, 33.3%), neutropenia (*N*=3, 25%) and infections (*N*=3, 25%), including one grade 5 septic shock previously described.

Treatment-related serious AEs were reported for 3 patients (25%), including infections (two sepsis and one urinary tract infection of grade 3 and one of grade 5), one grade 4 neutropenia and one grade 3 anemia.

Dose delays (≥7 days) because of an AE occurred in 1 (20%) and 3 (42.9%) patients at dose K and K+1, respectively (Table 4). Besides, across all dose levels, 6 (50%) patients had a dose reduction of ibrutinib because of an AE, while 3 (25%) patients received less vincristine (Table 4).

Treatment efficacy

In the lenalidomide arm (Fig. 3A), across all dose levels, ORR was 76.9% (10/13 patients), after 4 induction cycles, with 6/13 patients (46.1%) achieving CR/uCR and 4/13 patients (30.8%) achieving partial response (PR). Three patients were not evaluable for response. One patient died from tumor progression only 2 days after treatment initiation and two discontinued the treatment because of toxicity (Lyell's syndrome and infection).

In the ibrutinib arm (Fig. 3B), after 4 induction cycles, across all dose levels, ORR was 83.3% (10/12 patients), with 3/12 patients (25%) achieving CR/uCR and 7/12 patients (58.3%) achieving PR. One patient had stable disease. One patient was non evaluable for response because he died from grade 5 septic shock during cycle 1.

Table 3 Treatment-emergent adverse events

	Lenalidomide (*N* = 13) *N* (%)				Ibrutinib (*N* = 12) *N* (%)				Total (*N* = 25) *N* (%)			
Type of toxicity	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Highest toxicity	2 (15.4%)	5 (38.5%)	5 (38.5%)	-	3 (25%)	5 (41.7%)	3 (25%)	1 (8.3%)	5 (20%)	10 (40%)	8 (32%)	1 (4%)
Investigations (highest toxicity)	**2 (15.4%)**	**5 (38.5%)**	**1 (7.7%)**	**-**	**4 (33.3%)**	**3 (25%)**	**1 (8.3%)**	**-**	**6 (24%)**	**8 (32%)**	**2 (8%)**	**-**
Cholestasis	2 (15.4%)	-	-	-	2 (16.7%)	-	-	-	4 (16%)	-	-	-
Creatinine increased	-	1 (7.7%)	-	-	2 (16.7%)	1 (8.3%)	-	-	2 (8%)	2 (8%)	-	-
Hepatic cytolysis	3 (23.1%)	4 (30.8%)	1 (7.7%)	-	2 (16.7%)	3 (25%)	1 (8.3%)	-	5 (20%)	7 (28%)	2 (8%)	-
Gastrointestinal disorders (highest toxicity)	**5 (38.5%)**	**-**	**-**	**-**	**5 (41.7%)**	**1 (8.3%)**	**-**	**-**	**10 (40%)**	**1 (4%)**	**-**	**-**
Abdominal pain	1 (7.7%)	**-**	**-**	**-**	1 (8.3%)	1 (8.3%)	-	-	2 (8%)	1 (4%)	-	-
Colitis	-	**-**	**-**	**-**	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Constipation	5 (38.5%)	**-**	**-**	**-**	2 (16.7%)	-	-	-	7 (28%)	-	-	-
Diarrhea	2 (15.4%)	**-**	**-**	**-**	4 (33.3%)	-	-	-	6 (24%)	-	-	-
Nausea	1 (7.7%)	**-**	**-**	**-**	4 (33.3%)	-	-	-	5 (20%)	-	-	-
Vomiting	-	**-**	**-**	**-**	2 (16.7%)	-	-	-	2 (8%)	-	-	-
Metabolism and nutrition disorders (highest toxicity)	**3 (23.1%)**	**1 (7.7%)**	**-**	**-**	**2 (16.7%)**	**1 (8.3%)**	**-**	**-**	**5 (20%)**	**2 (8%)**	**-**	**-**
Anorexia	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Hyperkalemia	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Hypernatremia	1 (7.7%)	-	-	-	1 (8.3%)	1 (8.3%)	-	-	2 (8%)	1 (4%)	-	-
Hypokalemia	1 (7.7%)	1 (7.7%)	-	-	1 (8.3%)	-	-	-	2 (8%)	1 (4%)	-	-
Hypomagnesemia	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Hyponatremia	2 (15.4%)	-	-	-	-	1 (8.3%)	-	-	2 (8%)	1 (4%)	-	-
Hypophosphatemia	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Blood and lymphatic system disorders (highest toxicity)	**3 (23.1%)**	**3 (23.1%)**	**1 (7.7%)**	**-**	**2 (16.7%)**	**2 (16.7%)**	**2 (16.7%)**	**-**	**5 (20%)**	**5 (20%)**	**3 (12%)**	**-**
Anemia	5 (38.5%)	-	-	-	3 (25%)	2 (16.7%)	-	-	8 (32%)	2 (8%)	-	-
Lymphocyte count decreased	-	2 (15.4%)	-	-	-	-	-	-	-	2 (8%)	-	-
Neutrophil count decreased	1 (7.7%)	2 (15.4%)	1 (7.7%)	-	-	1 (8.3%)	2 (16.7%)	-	1 (4%)	3 (12%)	3 (12%)	-
Platelet count decreased	-	-	-	-	3 (25%)	1 (8.3%)	-	-	3 (12%)	1 (4%)	-	-
White blood cell decreased	-	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-
Nervous system disorders (highest toxicity)	**6 (46.2%)**	**1 (7.7%)**	**-**	**-**	**7 (58.3%)**	**1 (8.3%)**	**-**	**-**	**13 (52%)**	**2 (8%)**	**-**	**-**
Headache	2 (15.4%)	-	-	-	3 (25%)	-	-	-	5 (20%)	-	-	-
Peripheral sensory neuropathy	6 (46.2%)	1 (7.7%)	-	-	5 (41.7%)	1 (8.3%)	-	-	11 (44%)	2 (8%)	-	-
Post-lumbar puncture syndrome	1 (7.7%)	-	-	-	1 (8.3%)	-	-	-	2 (8%)	-	-	-
Infections and infestations (highest toxicity)	**2 (15.4%)**	**1 (7.7%)**	**2 (15.4%)**	**-**	**3 (25%)**	**2 (16.7%)**	**-**	**1 (8.3%)**	**5 (20%)**	**3 (12%)**	**2 (8%)**	**1 (4%)**
Aspergillosis infection	-	-	-	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)
Bacteremia	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-

Table 3 (continued)

	Lenalidomide (*N* = 13) *N* (%)				Ibrutinib (*N* = 12) *N* (%)				Total (*N* = 25) *N* (%)			
Type of toxicity	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Catheter related infection	-	-	2 (15.4%)	-	-	-	-	-	-	-	2 (8%)	-
COVID-19 Infection	1 (7.7%)	-	-	-	1 (8.3%)	-	-	-	2 (8%)	-	-	-
Endocarditis	-	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-
Lung infection	-	-	-	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)
Pharyngitis	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Sepsis	-	1 (7.7%)	-	-	-	2 (16.7%)	-	1 (8.3%)	-	3 (12%)	-	1 (4%)
Stye	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Tooth infection	2 (15.4%)	-	-	-	-	-	-	-	2 (8%)	-	-	-
Urinary tract infection	1 (7.7%)	-	-	-	1 (8.3%)	1 (8.3%)	-	-	2 (8%)	1 (4%)	-	-
General disorders and administration site conditions (highest toxicity)	**3 (23.1%)**	**-**	**-**	**-**	**4 (33.3%)**	**-**	**-**	**-**	**7 (28%)**	**-**	**-**	**-**
Edema limbs	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Fatigue	3 (23.1%)	-	-	-	3 (25%)	-	-	-	6 (24%)	-	-	-
Fever	1 (7.7%)	-	-	-	1 (8.3%)	-	-	-	2 (8%)	-	-	-
Malaise	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Odynophagia	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Skin and subcutaneous tissue disorders (highest toxicity)	**2 (15.4%)**	**1 (7.7%)**	**1 (7.7%)**	**-**	**4 (33.3%)**	**-**	**-**	**-**	**6 (24%)**	**1 (4%)**	**1 (4%)**	**-**
Dry skin	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Erythema multiforme	1 (7.7%)	-	-	-	1 (8.3%)	-	-	-	2 (8%)	-	-	-
Hyperhidrosis	1 (7.7%)	-	-	-	1 (8.3%)	-	-	-	2 (8%)	-	-	-
Lyell's syndrome	-	-	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-
PAC inflammation	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Pruritus	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Rash maculo-papular	2 (15.4%)	1 (7.7%)	-	-	1 (8.3%)	-	-	-	3 (12%)	1 (4%)	-	-
Respiratory, thoracic and mediastinal disorders (highest toxicity)	**3 (23.1%)**	**-**	**-**	**-**	**-**	**-**	-	-	**3 (12%)**	**-**	**-**	**-**
Cough	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Dyspnea	3 (23.1%)	-	-	-	-	-	-	-	3 (12%)	-	-	-
Oxygen desaturation	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Rhinorrhea	1 (7.7%)	-	-	-					1 (4%)	-	-	-
Cardiac disorders (highest toxicity)	**1 (7.7%)**	**-**	-	-	**1 (8.3%)**	**-**	**-**	**-**	**2 (8%)**	**-**	**-**	**-**
Atrial fibrillation	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Chest pain - cardiac	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Musculoskeletal and connective tissue disorders (highest toxicity)	**2 (15.4%)**	**-**	-	-	**-**	**-**	-	-	**2 (8%)**	**-**	**-**	**-**
Back pain	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Muscle cramp	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-
Vascular disorders (highest toxicity)	**3 (23.1%)**	**-**	-	-	**-**	**1 (8.3%)**	**-**	**-**	**3 (12%)**	**1 (4%)**	**-**	**-**

Table 3 (continued)

	Lenalidomide (*N* = 13) *N* (%)				Ibrutinib (*N* = 12) *N* (%)				Total (*N* = 25) *N* (%)			
Type of toxicity	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypertension	-	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-
Thromboembolic event	3 (23.1%)	-	-	-	-	-	-	-	3 (12%)	-	-	-
Ear and labyrinth disorders (highest toxicity)	**-**	**-**	-	-	**1 (8.3%)**	**-**	**-**	**-**	**1 (4%)**	**-**	**-**	**-**
Vertigo	-	-	-	-	1 (8.3%)	-	-	-	1 (4%)	-	-	-
Endocrine disorders (highest toxicity)	**1 (7.7%)**	**-**	**-**	**-**	**-**	**-**	-	-	**1 (4%)**	**-**	**-**	**-**
Hypopituitarism	1 (7.7%)	-	-	-	-	-	-	-	1 (4%)	-	-	-

TEAEs were defined as AEs occurring after the first dose of lenalidomide or ibrutinib, in combination with R-MPV, and through the whole induction phase; i.e. four evaluable cycles of lenalidomide or ibrutinib + R-MPV. TEAEs were classified according to the system organ class (SOC) of the common terminology criteria for adverse events (CTCAE) v5.0 and summarized by considering the highest grade achieved per patient. The term "highest toxicity" refers to the most severe grade observed within each SOC and overall

Survival

After a median follow-up of 20.2 months (range: 13.5–28.3), the median PFS and OS were not reached in any of the treatment arms. In the lenalidomide arm, 18-month PFS and OS were 59% (95% CI 36% – 95%) and 85% (95% CI 67% – 100%), respectively. In the ibrutinib arm, 18-month PFS and OS were both 92% (95% CI 77% – 100%) (Figure S1).

Discussion

We report here the results from a prospective dose-escalation trial which determined the RP2D of lenalidomide or ibrutinib in association with the conventional and widely used R-MPV for first-line treatment of PCNSL. This phase IB trial identified a RP2D of 15 mg daily (D1-21) lenalidomide or 560 mg daily (D3-14 and D17-28) ibrutinib, in combination with R-MPV.

R-MPV-like is a common regimen for PCNSL, with a favorable toxicity and a consistent efficacy profile [7, 19–23], which prompted us to select R-MPV as a backbone to combine with targeted therapies. Adding lenalidomide or ibrutinib to the intensive MATRix chemoimmunotherapy regimen (methotrexate, cytarabine, thiotepa and rituximab) was not feasible because of its high hematological toxicity, with 67%, 83% and 47% of grade ≥ 3 neutropenia, thrombocytopenia and anemia, respectively [24]. 16% of grade ≥ 3 febrile neutropenia were reported in the IELSG32 trial [24]. The toxicity of this association could even be higher in the real-world setting, with 65% of all-grade infections and 22% of admission to an intensive care unit described in a retrospective Canadian study [25] and 6% of treatment-related deaths recorded in a retrospective European study [26].

Lionakis et al. tested whether various chemotherapies could be synergistic or not with ibrutinib [17]. They showed that anti-folates (including methotrexate) had an antagonistic effect with ibrutinib in PCNSL in vitro, whereas DNA-damaging molecules were synergistic. Based on their findings, they conducted a phase IB study to evaluate ibrutinib in association with etoposide, cytarabine, a liposomal formulation of doxorubicin, temozolomide and rituximab (DA-TEDDi-R) [17]. Eighteen patients were enrolled, either at first-line ($N=5$) or in the relapsed/refractory setting. Despite a non-favorable toxicity profile, notably grade ≥ 3 pulmonary infections in 9/18 patients [17], no DLT were reported based on the protocol definition and the highest dose of 840 mg of ibrutinib was selected as the RP2D, in association with DA-TEDDi-R. Grommes et al. launched a phase IB trial to determine the MTD of ibrutinib combined with high-dose methotrexate and rituximab (4 cycles), followed by continuous ibrutinib until disease progression or toxicity [27]. No first-line PCNSL patients were enrolled. Three patients had newly diagnosed secondary CNS lymphoma

Table 4 Treatment exposure and dose modifications

	Lenalidomide			Ibrutinib		
	Dose K, *N* = 7	**Dose K-1, *N* = 6**	**Overall, *N* = 13**	**Dose K, *N* = 5**	**Dose K + 1, *N* = 7**	**Overall, *N* = 12**
Mean relative dose intensity, % (SD)	77.2 (33)	95.6 (12.3)	85.7 (26.4)	NA	NA	NA
Lenalidomide	NA	NA	NA	84.8 (7.1)	92 (7.5)	89 (7.9)
Ibrutinib	98.5 (3.2)	95.4 (6.1)	97.1 (4.8)	99.8 (1.2)	99.1 (2.1)	99.4 (1.8)
Rituximab	82.8 (17.9)	93.1 (6.5)	87.5 (14.4)	99.2 (0.9)	97.1 (6.5)	97.9 (4.9)
Methotrexate	83.8 (32.5)	94.1 (9.9)	88.5 (24.5)	98 (8.1)	104.4 (6.7)	101.7 (7.7)
Procarbazine	61.6 (19.2)	82.8 (27.5)	71.4 (24.9)	87.5 (28.0)	90.5 (20.1)	89.3 (22.5)
Vincristine						
Dose delay because of an AE, N (%)	3 (42.9)	4 (66.7)	7 (53.8)	2 (40)	5 (71.4)	7 (58.3)
≥ 3 days	3 (42.9)	3 (50)	6 (46.2)	1 (20)	3 (42.9)	4 (33.3)
≥ 7 days						
Dose reduction because of an AE, N (%)	3 (42.9)	2 (33.3)	5 (38.5)	NA	NA	NA
Lenalidomide	NA	NA	NA	3 (60)	3 (42.9)	6 (50)
Ibrutinib	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	1 (8.3)
Rituximab	4 (57.1)	0 (0)	4 (30.8)	0 (0)	1 (14.3)	1 (8.3)
Methotrexate	1 (14.43)	0 (0)	1 (7.7)	1 (20)	0 (0)	1 (8.3)
Procarbazine	6 (85.7)	2 (33.3)	8 (61.5)	1 (20)	2 (28.6)	3 (25)
Vincristine						

The mean relative dose intensity was calculated as the total received dose divided by the total expected dose, in average of the 4 cycles per patient. Dose delays and reductions were considered if occurring in at least one of the four induction cycles. For rituximab and procarbazine, doses were often rounded because of bottle/tablet management. SD: standard deviation; NA: not applicable; AE: adverse event

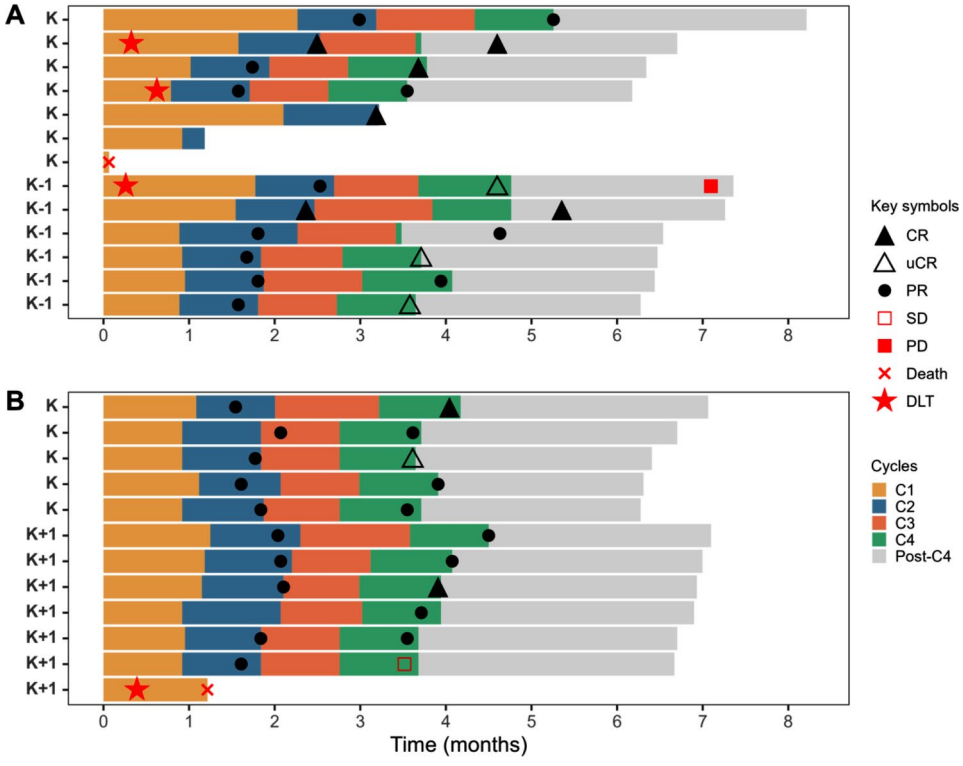


Fig. 3 Swimmer plots depicting patients' responses to lenalidomide (**A**) or ibrutinib (**B**), in combination with R-MPV, over time. *Lenalidomide dose K: 20 mg per day D1 to 14; Lenalidomide dose K-1: 15 mg per day D1 to 21; Ibrutinib dose K: 420 mg per day (D3 to 14 and D17 to 28); Ibrutinib dose K + 1: 560 mg per day (D3 to 14 and D17 to 28); CR: complete response; uCR: unconfirmed complete response; PR: partial response; SD: stable disease; PD: progressive disease; DLT: dose-limiting toxicity*

(SCNSL) and 12 presented with a relapsed/refractory PCNSL or SCNSL. As no DLT was observed during the DLT period, 840 mg was the RP2D of ibrutinib, in combination with methotrexate and rituximab. An ORR of 80% was reported in this trial. Similar results were reported in the real world setting for 11 newly diagnosed PCNSL patients who received a combination of ibrutinib (560 mg daily) with high-dose methotrexate followed by continuous ibrutinib until disease progression [28].

In this phase IB part of our study, we focused on the toxicity profile of the combination of R-MPV with either lenalidomide or ibrutinib in first-line treatment of a homogeneous group of PCNSL patients. The safety profile was consistent with the known safety profiles of R-MPV and both targeted therapies. Omuro et al. reported up to 51% grade ≥ 3 alanine aminotransferase and/or aspartate aminotransferase increased, 21% grade ≥ 3 neutropenia, 12% grade 3 infections, 9% grade ≥ 3 thromboembolism and 6% grade 3 peripheral neuropathy among 32 newly diagnosed PCNSL patients treated with R-MPV [21]. In our trial, we paid a specific attention to the risk of hepatic cytolysis. This AE could be related to lenalidomide or ibrutinib, but also to methotrexate or procarbazine, or to the drug combination. Notably, we used the chronological sequence for causality assessment. In the ibrutinib arm, hepatic cytolysis was considered as R-MPV-related when it occurred during the days when ibrutinib was suspended. Causality was more difficult to establish in the lenalidomide arm as both targeted therapy and immunochemotherapy were given at the same time. Thus, we assumed possible causality of lenalidomide in case of hepatic cytolysis occurring after this drug combination and we may have overestimated the hepatic toxicity of lenalidomide. We also report 24% grade ≥ 3 infectious events and 52% all-grade peripheral neuropathy with both regimens and two cases of grade ≥ 3 skin toxicity in the lenalidomide arm. We did not observe cumulative cardiac toxicity as ibrutinib was administered only during induction.

The AEs observed in our trial are close to those described for the ibrutinib/methotrexate combination [27, 28], except for peripheral neuropathy, which may be related to the vincristine included in the R-MPV regimen, and are different from treatment-associated toxicity observed with the DA-TEDDi-R regimen where pulmonary infections occurred in 9/18 patients, including 5 cases of aspergillosis and one pneumocystosis [17]. Notably, we observed only one case of grade 5 aspergillosis and pneumocystosis with ibrutinib at dose K+1 in a patient who had a complex clinical course. This may be due to the fact that our study was designed exclusively for fist-line treatment, thus reducing the patients' exposition to previous immunosuppressive chemotherapies and glucocorticoids.

We observed more treatment discontinuation because of toxicity in the lenalidomide than the ibrutinib arm. The ongoing randomized phase II part of the study will consolidate the results related to toxicity and provide data on the efficacy of the combination of R-MPV with either ibrutinib or lenalidomide in the context of consolidation with high-dose chemotherapy and ASCT. Of note, patients enrolled in the phase IB part of the trial will not be included in the efficacy analysis of the ongoing phase II.

We observed promising rates of overall response in both arms and only one case of progressive disease but these data should be interpreted with caution as response evaluation was not part of the objectives of the phase IB part of the study and was only assessed according to the local principal investigator. A central review of the MRI images is being performed in the phase II part of the study, which will allow for a better assessment of the efficacy of both induction treatments. Importantly, ancillary studies, including radiomic analyses as well as CSF and blood biomarkers assessment will complete the clinical trial.

Conclusions

Both induction regimens combining lenalidomide (15 mg daily, D1-21) or ibrutinib (560 mg daily, D3-14 and D17-28) with R-MPV are feasible and the safety profile is consistent with the known safety profiles of R-MPV and both targeted therapies. The benefit of adding lenalidomide or ibrutinib to the first-line treatment of PCNSL cannot be determined in this phase of the study. Efficacy data of targeted induction therapies will be provided by the ongoing phase II part of the study.

Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ASCT	Autologous Stem Cell Transplantation
BCR	B-cell Receptor
BTK	Bruton's Tyrosine Kinase
CNS	Central Nervous System
CR	Complete Response
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DA-TEDDi-R	Etoposide, Cytarabine, Liposomal Doxorubicin, Temozolomide, Rituximab, and Ibrutinib
DLT	Dose-Limiting Toxicity
G-CSF	Granulocyte Colony-Stimulating Factor
HD	High Dose
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IELSG	International Extranodal Lymphoma Study Group
IPCG	International Primary CNS Lymphoma Collaborative Group
KPS	Karnofsky Performance Status
LBCL	Large B-cell Lymphoma
MATRix	Methotrexate, Cytarabine, Thiotepa, and Rituximab
MTD	Maximum Tolerated Dose
MTX	Methotrexate
NHL	Non-Hodgkin Lymphoma
ORR	Overall Response Rate

OS	Overall Survival
PCNSL	Primary Central Nervous System Lymphoma
PFS	Progression-Free Survival
PR	Partial Response
PVRL	Primary Vitreoretinal Lymphoma
R-Cytarabine	Rituximab and Cytarabine
R-MPV	Rituximab, Methotrexate, Procarbazine, Vincristine, and Prednisone
RP2D	Recommended Phase II Dose
SCNSL	Secondary CNS Lymphoma
SD	Stable Disease
TEAEs	Treatment-Emergent Adverse Events
WBRT	Whole Brain Radiotherapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-024-01606-w.

Supplementary Material 1

Acknowledgements
We thank the patients and their families for their participation in the study, Rachida Bouzit for her contribution to database creation, data cleaning and management, Lynda Corvi for the project management and Marie-Laure Tanguy for the methodology. We also thank the hematologists, neurooncologists, ophthalmologists and the nurse staff of the participating centers.

Author contributions
Conception and design: SC, GH, HC, AM, CM. Provision of study material or patients: CM, JF, SA, HC, OL, CO, MF, PF, HR, CL, CE, GH and SC. Statistical analyses: CM. Collection and assembly of data: AM, CM, JF, SA, HC, OL, CO, MF, PF, HR, CL, CE, GH, SC. Administrative support: CLAM, CM and SC analyzed the data, made the figures and wrote the paper. All authors had access to all primary clinical study data, participated in data interpretation and agreed to the final version of the manuscript.

Funding
This study was supported by a Grant PHRC-K 18–070 from the French Government. Ibrutinib was provided by Janssen and lenalidomide was provided by BMS. The pharmaceutical partners did not provide with other fundings, and did not participate in the conception, conduct or analysis of the study nor in the writing of this report Sponsor of the study: Institut Curie. Clinical trial information: NCT04446962; EudraCT: 2019-003632-23.

Data availability
Deidentified individual participant data that underlie the reported results will be made available from 12 months to 48 months after the publication date at the Clinical Research Department of Institut Curie. Personal consent of all patients whose data will be transmitted and processed has been previously collected. Transmission and processing of patients' data will be done in compliance with the regulation on the protection of personal data. Data will be available after submission to the corresponding author of a proposal identifying the use of the data. The proposal will have to be approved by the corresponding author of the article and the Clinical Research Department of Institut Curie. The study synopsis is included as a data supplement available with the online version of this article.

Declarations

Ethics approval and consent to participate
The study was conducted in compliance with Good Clinical Practice, as defined by the International Conference on Harmonization and according to applicable regulatory requirements. The study protocol and all amendments were approved by the competent authority and independent ethics committee. All patients, or the persons on confidence in case the neurological status of the patient did not allow him to understand and/or to sign, provided written informed consent before enrollment.

Consent for publication
Not applicable.

Competing interests
AM performed scientific and medical consulting for Novartis, Janssen, Kite/Gilead and MSD and received research grants from Mnemo Therapeutics. OL has received honoraria and travel fundings from Roche, Kite/Gilead, BMS, Janssen and AstraZeneca. HR has received honoraria from Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda and Roche; and is a member on an entity's Board of Directors or advisory committees of Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, ADC Therapeutics, Incyte and Miltenyi. SC received a research grant from AstraZeneca.

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Received: 31 July 2024 / Accepted: 6 September 2024
Published online: 19 September 2024

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