European Journal of Cancer 117 (2019) 121–130

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Clinical Trial

Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' *i*LOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network☆

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☆ The results of the interim analysis were presented as an oral presentation at the 58th annual meeting of the American Society of Hematology, San Diego, California, December 2016 (abstract #782), and part of the final analysis was presented as an oral presentation at the 14th International Conference on Malignant Lymphoma, Lugano, June 2017 (abstract # 60).

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https://doi.org/10.1016/j.ejca.2019.05.024

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Received 10 April 2019; received in revised form 23 May 2019; accepted 28 May 2019
Available online 3 July 2019

KEYWORDS
Primary CNS lymphoma;
Primary vitreoretinal lymphoma;
Relapse;
Ibrutinib

Abstract ***Background:*** Primary central nervous system lymphomas (PCNSLs) are mainly diffuse large B-cell lymphomas (DLBCLs) of the non-germinal centre B-cell subtype, with unmet medical needs. This study aimed to evaluate the efficacy and toxicity of ibrutinib in DLBCL-PCNSL

Patients and methods: This prospective, multicentre, phase II study involved patients with relapse or refractory(R/R) DLBCL-PCNSL or primary vitreoretinal lymphoma. The treatment consisted of ibrutinib (560 mg/day) until disease progression or unacceptable toxicity occurred. The primary outcome was the disease control (DC) rate after two months of treatment (P0 < 10%; P1 > 30%).

Results: Fifty-two patients were recruited. Forty-four patients were evaluable for response. After 2 months of treatment, the DC was 70% in evaluable patients and 62% in the intent-to-treat analysis, including 10 complete responses (19%), 17 partial responses (33%) and 5 stable diseases (10%). With a median follow-up of 25.7 months (range, 0.7–30.5), the median progression-free and overall survivals were 4.8 months (95% confidence interval [CI]; 2.8–12.7) and 19.2 months (95% CI; 7.2-NR), respectively. Thirteen patients received ibrutinib for more than 12 months. Two patients experienced pulmonary aspergillosis with a favourable (n = 1) or fatal outcome (n = 1). Ibrutinib was detectable in the cerebrospinal fluid (CSF). The clinical response to ibrutinib seemed independent of the gene mutations in the BCR pathway.

Conclusion: Ibrutinib showed clinical activity in the brain, the CSF and the intraocular compartment and was tolerated in R/R PCNSL. The addition of ibrutinib to standard methotrexate-base induction chemotherapy will be further evaluated in the first-line treatment.

Clinical trial number: NCT02542514.

1. Introduction

Primary central nervous system lymphomas (PCNSLs) are mainly diffuse large B-cell lymphoma (DLBCL) of non-germinal centre (non-GC) subtype with activation of the NF-kappa B pathway [1,2], recurrent somatic mutations in the CD79B (Y196) and MYD88 (L265P) and a restricted repertoire of IGHV genes [3–8]. PCNSLs require specific treatments able to reach the brain parenchyma, cerebrospinal fluid (CSF) and intraocular (IO) compartment. Ibrutinib is an irreversible selective inhibitor of Bruton tyrosine kinase (BTK). It induces in vitro cell growth arrest and apoptosis in DLBCL driven by active chronic BCR signalling [9] and has shown clinical activity in DLBCL [10,11]. In murine CNS lymphoma models, ibrutinib achieved a therapeutic concentration in the CSF, diffused in both tumour-bearing and non–tumour-bearing brain hemispheres and prolonged the survival of CNS lymphoma-bearing mice [12]. Activity of ibrutinib in PCNSL has been suggested in a retrospective study [13] and in phase IB studies [14,15]. This 'proof-of-concept' prospective study aimed to assess the tolerance and efficacy of ibrutinib in relapse or refractory (R/R) PCNSL, the drug concentration in the CSF and explore the correlation between molecular profiles and treatment outcome.

2. Methods

2.1. Patients

Immunocompetent adult patients with R/R PCNSL or primary vitreoretinal lymphoma (PVRL) were eligible if they had received prior high-dose methotrexate and had an Eastern Cooperative Oncology Group performance status < 2 (Supplemental Table 1 for detailed inclusion and exclusion criteria).

2.2. Study design

This was an open-label, prospective, multicentre, phase II study approved by the Committee for the Protection of Persons of Ile de France, and the French Agency for the Safety of Health Products, and conducted according to the Declaration of Helsinki and Good Clinical Practice. All patients or guardians provided written informed consent (NCT02542514).

2.3. Treatment

The treatment consisted of 560 mg ibrutinib orally once daily (28-day cycles) until disease progression or unacceptable toxicity occurred. Additional corticosteroid treatments were allowed during the first 4 weeks of treatment in the presence of life-threatening cerebral oedema but had to be tapered off and stopped as soon as possible. Antifungal prophylaxis was not planned.

2.4. Assessment of therapeutic response and toxicity

The therapeutic responses were assessed according to the International PCNSL Collaborative Group Response Criteria [16]. The therapeutic response assessment was planned after 2, 4, 6, 9 and 12 cycles of treatment. The follow-up assessments were planned 3 months after the last treatment administration and then every 3 months during the first 2 years, then every 6 months. The patients' MRIs were centrally reviewed by clinicians blinded to the local MRI report. Ophthalmological examinations were performed by ophthalmologists with experience in PVRL. Dosage of interleukin-10 (IL-10) in the anterior chamber was performed whenever possible, as a marker of the IO disease [17,18]. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (AE) version 4. Any AEs meeting seriousness criteria were reported. Otherwise, only grade >II AEs were reported for cardiac, renal, neuropathic and haemorrhagic toxicities, and only grade >III AEs were reported for the toxicity of the other organs.

2.5. Outcomes

The primary end-point was the disease control (DC) rate, including complete and unconfirmed complete response (CR + uCR), partial response (PR) and stable disease (SD) after 2 cycles of treatment. The secondary end-points were the toxicity of ibrutinib, CR rate after 4, 6, 9 and 12 cycles of treatment, overall survival (OS) and progression-free survival (PFS).

2.6. Exploratory analyses

The CSF samples were collected through lumbar puncture before the first dose on day 1 cycle 1 and immediately before ibrutinib intake on day 29. The ibrutinib concentration was determined by ultra-performance liquid chromatography–tandem mass spectrometry (precision < 15% of the coefficient of variation and accuracy within 15% of the actual value) [19].

DNA was extracted from formalin-fixed, paraffin-embedded tumour samples of the initial diagnostic brain biopsies for determination on the *MYD88, CD79b* and *CARD11* somatic mutations (Supplemental material).

2.7. Statistical analysis

The analysis of the primary criterion was based on a two-stage Simon's phase II design with the following hypotheses: 10% (null hypothesis), 30% (alternative hypothesis), risk 1-sided $\alpha = 0.05$; power = 80%. The patients who received 90% of the planned dose during the first month of treatment were evaluable for response. In the first stage (n = 18 evaluable patients), at least 3 patients should have achieved a DC after 2 months of treatment to proceed to the second stage. The second stage analysis could be performed with at least 35 evaluable patients. With 44 evaluable patients, the treatment could be considered effective if at least 8 patients achieved a DC. Survivals were calculated from the date of registration, to the date of disease progression or death for the PFS, and to the date of death for the OS. The PFS and OS were estimated using the Kaplan–Meier method with 95% confidence intervals [CIs]. All analyses were performed with data monitored until April 30, 2018, using SAS version 9.3 or higher and AdClin version 3.3.3 or higher.

An additional intention-to-treat (ITT) analysis was performed, including an analysis of the survivals according to the presence or absence of a brain parenchyma/spinal cord involvement at inclusion in the study.

3. Results

3.1. Patient characteristics

Fifty-two patients were recruited between September 2015 and July 2016 from 10 centres (Supplemental Table 2). Most patients (N = 38, 73%) were included for a relapse and 14 patients (27%) for a refractory disease. Eight patients prematurely stopped the treatment before day 25 because of disease progression (n = 7) or toxicity (n = 1). These patients were considered in the ITT analysis. Forty-four patients were evaluable for the primary end-point. Patients' characteristics are provided in Table 1. The median age was 70 years (range, 52–81 years).

Thirty patients presented with brain (n = 28) or spinal cord (n = 2) lymphoma associated with IO and/or CSF involvement (n = 6). Fourteen patients had

Table 1
Characteristics of the 52 patients included in the study (ITT population) and of the 44 patients evaluable for response (i.e who received 90% of the planned dose of ibrutinib during the first month of treatment).

N	52	44
Sex ratio M:F	**6:7**	**5:6**
Median age	**67.5 (range, 47–82)**	**70 (range, 52–81)**
≥ 60	**35 (67%)**	**33 (75%)**
PS		
0–1	**35 (67%)**	**33 (77%)**
2	**17 (33%)**	**11 (23%)**
Number of previous lines of treatment		
1	**19 (36.5%)**	**18 (41%)**
2	**19 (36.5%)**	**15 (34%)**
3	**9 (17%)**	**6 (14%)**
4	**5 (10%)**	**5 (11%)**
Previous ASCT	7	4
Previous WBRT	11	1
Status from previous treatment		
Relapse	**38 (73%)**	**31 (70%)**
Refractory	**14 (27%)**	**13 (30%)**
Disease assessment at the time of inclusion in the study		
Brain parenchyma/spinal cord	**38**	**30**
With IO	4	4
With CSF	2	1
With IO + CSF	1	1
Intraocular	**14**	**14**
With CSF	2	2
Corticosteroids during cycle 1	**19**	**14**

ITT population, intention-to-treat population; PS, performance status; IO, intraocular; CSF, cerebrospinal fluid; ASCT, autologous stem cell transplantation; WBRT, whole-brain radiotherapy.

isolated IO lymphoma associated with CSF involvement (n = 2). Among these 14 patients, 8 patients had PVRL at the time of the initial diagnosis and 6 patients had PCNSL at initial diagnosis but an isolated IO relapse at inclusion in this study. These patients are referred to as the PVRL group. Fourteen patients received concomitant corticosteroids during the first month of treatment.

3.2. Therapeutic response

3.2.1. Primary end-point

After 2 months of treatment, 31 patients achieved a DC (70%) including CR + uCR (n = 10, 23%), PR (n = 16, 36%) and SD (n = 5, 11%), resulting in an overall response rate (CR + uCR + PR) of 59%. The treatment failed in 13 patients (29%) (Table 2 and Supplemental Fig. 1). In the ITT analysis (n = 52), the DC and the ORR rates after 2 months of treatment were 62%, and 52%, respectively, (CR: n = 10, 19%; PR: n = 17, 33%; SD: n = 5, 10%). The treatment failed in 20 patients (38%). Responses were observed in all CNS compartments. The parenchyma lesions completely regressed in 4 cases and partially regressed in 10 (17%) cases, including 5 nearly CR with a regression of the tumoural mass greater than 90% but a residual lesion with gadolinium uptake over 3 mm. The IO involvement completely or partially cleared in 10 (71%) and 4 (29%) cases, respectively. Among the 4 patients with CSF involvement at baseline, 3 CSF completely cleared and one was not checked after 2 cycles of treatment.

Most patients who entered CR or PR at 2 months had not received corticosteroids during the first month of treatment (22 CR+PR/29 vs 4 PR/14 patients who received steroids) (Supplemental Table 3).

3.2.2. Secondary end-points

The DC and ORR rates after 4, 6, 9 and 12 cycles of treatment were 39% and 39%, 32% and 27%, 32% and 29% and 27% and 25%, respectively, (Table 3).

Among the 16 patients in PR after 2 cycles, 7 patients achieved complete remission at subsequent cycles (C4: n = 3; C6: n = 2 and C9: n = 2).

The IL10 levels in the anterior chamber of the eye before and during treatment were available for 15 patients who presented with IO involvement at the time of inclusion in the study. Clinical CRs of IO localisations were associated with undetectable or nearly undetectable levels of IL10, while PDs were associated or preceded by an increasing level of IL10 (Supplemental Table 4).

3.2.3. Duration of responses and survival

With a median follow-up of 25.7 months, the median PFS was 4.8 months (95% CI; 2.8–12.7) (Fig. 1A) and the median OS was 19.2 months (95% CI; 7.2-NR) (Fig. 1B). In the ITT analysis, median PFS and OS were 3.3 months (95% CI; 2–6.4) and 14.4 months (95% CI; 4.2–21.2) (Fig. 1C and D), respectively. The

Table 2
Therapeutic response after 2 cycles of ibrutinib.

Therapeutic response	No brain lesion at inclusion, N = 14	Brain lesion at inclusion, N = 30	Evaluable population for response, N = 44	Intent-to-treat population, N = 52
CR + uCR	7 (50%)	3 (10%)	10 (23%)	10 (19%)
PR	5 (36%)	11 (37%)	16 (36%)	17 (33%)
ORR	12 (86%)	14 (47%)	26 (59%)	27 (52%)
SD	**2 (14%)**	**3 (10%)**	**5 (11%)**	**5 (10%)**
DC	**14 (100%)**	**17 (57%)**	**31 (70%)**	**32 (62%)**
PD	0	13 (43%)	13 (30%)	20 (38%)

CR, complete response; uCR, unconfirmed complete response; PR, partial response; SD, stable disease; DC, disease control; PD, progressive disease.

Table 3
Therapeutic responses after 4, 6, 9 and 12 cycles in the 44 evaluable patients.

Therapeutic response	Cycle 4	Cycle 6	Cycle 9	Cycle 12
CR + uCR	9	11	13	11
PR	8	1	0	0
ORR	**39%**	**27%**	**29%**	**25%**
SD	0	2	1	1
DC	**39%**	**32%**	**32%**	**27%**
PD	8	2	3	0
Not reaching the time point	19	28	27	32

CR, complete response; uCR, unconfirmed complete response; PR, partial response; SD, stable disease; DC, disease control; PD, progressive disease

median PFS was shorter in patients who presented a brain or spinal cord parenchyma lesion at time of inclusion in the study (2 months, 95% CI; 2–3) compared to that of the patients who entered the study for a PVRL with or without CSF involvement (22.7 months, 95% CI; 5-not reached; p =<0.0001) (Fig. 1E), which also translated into a shorter median OS (4.3 months, 95% CI; 3:9 in patients with brain involvement and not reached in patients without brain involvement, $p < 0.0001$) (Fig. 1F). Age and disease status at the time of inclusion (relapse vs refractory) did not impact the PFS (Supplemental Fig. 2A and 2B). The response lasted more than 12 months in 15 patients, including 6 patients with cerebral involvement at the time of inclusion in the study. One subsequent brain relapse was observed in the PVRL patients. At the time of analysis,

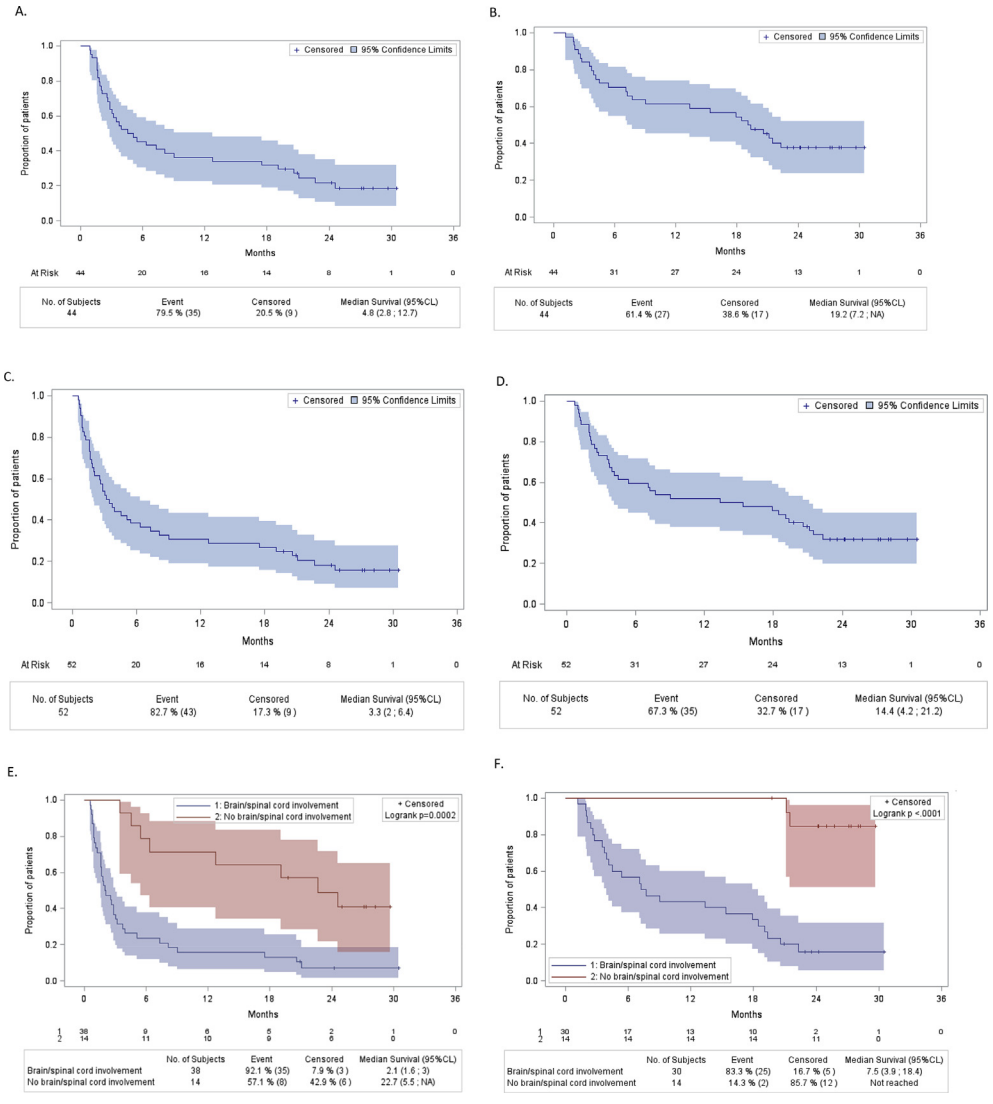

Fig. 1. Survivals. (A) Progression-free survival in the 44 evaluable patients. (B) Overall survival in the 44 evaluable patients. (C) Progression-free survival in the 52 patients included in the study according to the intention-to-treat analysis. (D) Overall survival in the 52 patients included in the study according to an intention-to-treat analysis. (E) Progression-free survival in patients with and without brain involvement at the time of inclusion in the study (intent-to-treat population). (F) Overall survival in patients with and without brain involvement at the time of inclusion in the study (intent-to-treat population).

40 patients had ceased treatment after a median time of 4 months from inclusion (95% CI: range 2–25) because of progressive disease (PD) (n = 31), toxicity (n = 5), concurrent illness (n = 3, fatal in 2 patients) unrelated to PCNSL or ibrutinib and a patient's decision while in CR (n = 1). Four patients were still on treatment at time of the analysis. The outcomes are displayed in a swimmer plot (Fig. 2A and B).

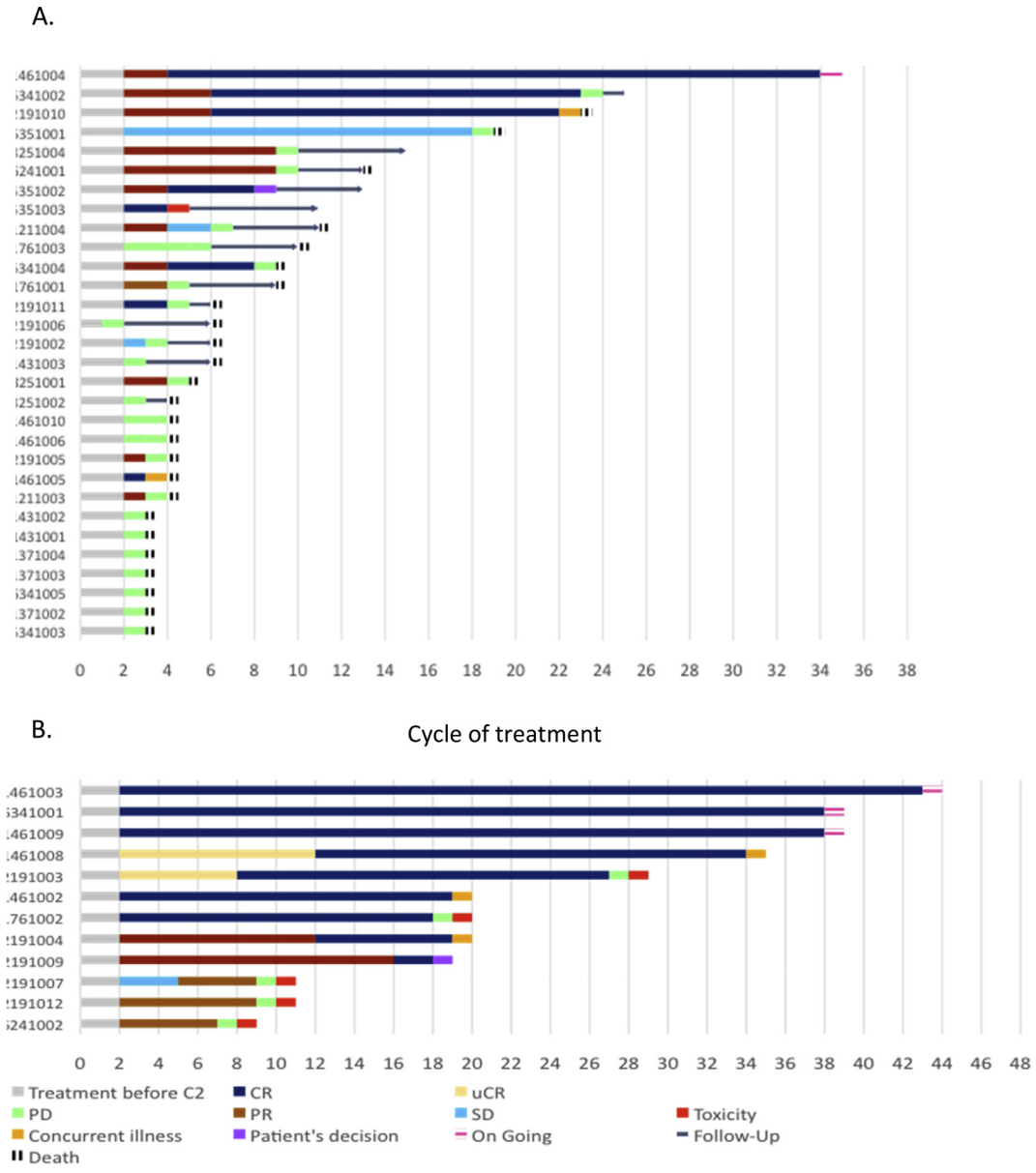

Fig. 2. Swimmer plots representing the durations of treatment in patients with (A) or without brain/spinal chord parenchymal involvement (B) at the time of inclusion in the study. The median duration of the responses was 6.3 months (95% CI; 3.1–19.3) and was shorter in the patients who presented a brain/spinal chord parenchyma lesion at the time of inclusion in the study (median = 3.3 months; 95% CI: 1.2–15) compared to that in the patients who entered the study for a PVRL with or without CSF involvement (median = 21 months; 95% CI: 3.5-NA; p = 0.017). The two concurrent illnesses that lead to death were a misdiagnosis of aortic aneurysm on a CT scan performed because of a thoracic pain. The patient underwent surgery. No aneurysm, no haemorrhage and no pathologic vessel walls were found. The patient died from multi-organ failure related to postsurgery complications. The other patient was a frail elderly woman, with medical history of asthma and Parkinson disease, who died from a general state alteration. Among the patients who ceased the study treatment for a reason other than progressive disease, the response durations after the end of the study protocol were 3, 8, 11, 12, 16, 16 and 18 months or not evaluable in the patients who died from a treatment-related toxicity or a concurrent illness while taking ibrutinib. The four patients still on treatment at time of the analysis were included in the study for a PCNSL relapse (n = 1), an IO relapse of a PCNSL (n = 2) or a PVRL relapse (n = 1) and experienced long lasting CR of 36, 36, 32 and 32 months respectively. CI, confidence interval; PVRL, primary vitreoretinal lymphoma; CSF, cerebrospinal fluid; PCNSL, primary central nervous system lymphoma; CR, complete response; IO, intraocular; PD, progressive disease; PR, partial response; uCR, unconfirmed complete response; SD, stable disease.

3.2.4. Tolerance and toxicity

The dose of ibrutinib was reduced in two patients to 280 mg/day and 420 mg/day. Thirty AEs affecting 26 patients were reported (Table 4). The serious adverse events of special interest included two ventricular haemorrhages, one in a patient with CR with a favourable outcome and the other in a patient with PD; two haemorrhages in the anterior chamber of the eye with a favourable outcome; two atrial fibrillations and two proven pulmonary aspergillosis: after one month of ibrutinib with a favourable outcome in one patient and after 21 days of ibrutinib in a patient suffering from severe flu with interstitial pneumonia leading to a fatal respiratory distress. Both patients were not neutropenic at the time of infection and received corticosteroids along with ibrutinib.

3.2.5. Ibrutinib concentration in CSF

The baseline and steady-state CSF ibrutinib concentrations were measured in 23 patients. Ibrutinib was detectable (>0.15 ng/ml) in all samples tested at a steady state. The mean CSF ibrutinib concentration was 0.23 ng/ml (0.52 nM) (range, 0.2–0.84 ng/ml).

3.2.6. Correlation with the cell of origin, mutational profiles and the response to ibrutinib

The cell of origin determined by immunohistochemistry according to the Hans algorithm [20] was available for 18 patients and was non-GC (n = 13), GC (n = 3) and unknown (n = 2). The mutations in the BCR pathway were determined for 18 patients. No mutation in *CARD 11* was observed. No concurrent mutations in *MYD88* and *CD79B* were observed. Seven patients harboured wild-type *CARD 11, CD79b* and *MYD88*, of which the best therapeutic responses were CR (n = 2), PR (n = 2) and PD (n = 3). A mutation in *MYD88* was observed in 9 patients and was associated with either PR (n = 2) or PD (n = 7). One patient had a mutation in *CD79b* and achieved PR. Mutations in the BCR–NF-

Table 4
Adverse events.

Therapeutic response	Grade I		Grade II		Grade III		Grade IV		Grade V	
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events
Infections and infestations										
Bronchopulmonary aspergillosis	0	0	1 (2%)	1	0	0	0	0	1 (2%)	1
Erysipelas	0	0	1 (2%)	1	1 (2%)	0	0	0	0	0
Pneumonia	0	0	0	0	1	1	0	0	0	0
Nervous system disorders										
Cerebral haemorrhage	1 (2%)	1	1 (2%)	1	0	0	0	0	0	0
Cardiac disorders										
Atrial fibrillation	0	0	1 (2%)	2	1 (2%)	1	0	0	0	0
Gastrointestinal disorders										
Diarrhoea	1 (2%)	2	1 (2%)	2	0	0	0	0	0	0
Mouth ulceration	1 (2%)	1	0	0	0	0	0	0	0	0
General disorders and administration site conditions										
Asthenia	0	0	1 (2%)	1	0	0	0	0	0	0
Pyrexia	0	0	0	0	1 (2%)	1	0	0	0	0
Vascular disorders										
Blue toe syndrome	0	0	1 (2%)	1	0	0	0	0	0	0
Haematoma	1 (2%)	1	0	0	0	0	0	0	0	0
Blood and lymphatic system disorders										
Neutropenia	0	0	0	0	0	0	2 (4%)	2	0	0
Febrile neutropenia	0	0	0	0	1 (2%)	1	0	0	0	0
Leukopenia	0	0	0	0	1 (2%)	1	0	0	0	0
Eye disorders										
Hyphaema	0	0	1 (2%)	1	1 (2%)	1	0	0	0	0
Musculoskeletal and connective tissue disorders										
Muscle spasms	0	0	2 (4%)	2	0	0	0	0	0	0
Investigations										
Alanine aminotransferase increased	0	0	0	0	1 (2%)	1	1 (2%)	1	0	0
Gamma-glutamyltransferase increased	0	0	0	0	1 (2%)	1	1 (2%)	1	0	0

AEs, adverse events.
Maximum Grade Per Patient Per Event (excluding unrelated).
Number of evaluable patients: 52.
Grade of adverse event – n (%).
Rules for reporting AEs are detailed in the protocol and were reported as follows.
All AEs of grade ≥III (haematological or non-haematological toxicities).
All serious AEs, regardless of their grade.
All AEs of grade ≥II for cardiac, renal, neuropathic and haemorrhagic toxicities.
All AEs of special interest.

κB pathways were identified in both GC and non-GC tumours (Table 5).

4. Discussion

This study is the first phase II studies of ibrutinib in a large series of R/R oculocerebral lymphomas, excluding secondary CNS lymphomas, thus providing robust data on both the antilymphoma activity of ibrutinib in PCNSL and PVRL and on quantitative information regarding the risk of aspergillosis. In the ITT analysis, ibrutinib (560 mg/day) resulted in an ORR rate after two 28-day cycles of 52% with a favourable toxicity profile. These results are consistent with two phase-I studies [14,15] involving 13 and 18 R/R PCNSL patients treated with escalated doses of ibrutinib up to 840 mg. Responses were observed in all compartments of the CNS with an ibrutinib concentration in the CSF above the efficacy threshold level at a steady state. The duration of the responses of the brain lesions was short as previously reported [13–15]. However, fifteen (29%) patients experienced long-lasting CR > 12 months.

The role of MYD88/CD79B mutations in DLBCL responses to ibrutinib is still in debate, and a clear correlation between mutational profiles in PCNSL and response to ibrutinib remains difficult to establish in a limited number of patients. Our genomic findings differ from the results reported by Grommes *et al.* [14]. We observed resistance to ibrutinib in the absence of *CARD11* mutation and with a mutation in the BCR pathway. In a series of systemic lymphomas [11], the patients with *MYD88* mutations but *wt CD79B* were unresponsive to ibrutinib. We observed therapeutic responses in patients with *wt CD79*, and *wt MYD 88* and in patients with *MYD88* mutations but *wt CD79B*. The risk of aspergillosis during treatment with ibrutinib has been estimated as 2% in a cohort of 566 patients with non-CNS B-cell malignancies [21] and 4% and 11% in early-phase studies for R/R PCNSL patients treated with ibrutinib single agent [14,15]. An inhibition of both BTK and ITK, involved in innate and adaptive immunity, were suggested mechanisms underlying the risk of fungal infection, which could be enhanced by the frequent exposure to corticosteroids in PCNSL patients, especially patients experiencing relapse [2223].

Table 5
Molecular characteristics and response to ibrutinib.

Patient	CARD11	CD79B	MYD88	COO	Best response
1461003	WT	WT	WT	Na	CR
1461005	WT	WT	WT	Non-GC	CR
1211004	WT	WT	WT	Non-GC	PR
1371001	WT	WT	WT	Non-GC	PR
1431001	WT	WT	WT	Non-GC	PD
1371003	WT	WT	WT	Non-GC	PD
1211001	WT	WT	WT	Non-GC	PD
1211003	WT	WT	L265P	Non-GC	PR
8251001	WT	WT	L265P	GC	PR
1211002	WT	WT	L265P	Na	PD
1461001	WT	WT	L265P	Non-GC	PD
2191008	WT	WT	L265P	GC	PD
1371002	WT	WT	L265P	Non-GC	PD
1371004	WT	WT	L265P	Non-GC	PD
1461010	WT	WT	L265P	Non-GC	PD
6341003	WT	WT	L265P	Na	PD
6241001	WT	Y196D	WT	Non-GC	PR
1761004	WT	NA	WT	Non-GC	PD
1461004	NA	NA	NA	GC	CR
5351002	NA	NA	NA	CD10 neg	CR
5351002	NA	NA	NA	CD10 neg	CR

COO, cell of origin determined by immunohistochemistry according to the Han algorithm; GC, germinal centre; CR, complete response; PR, partial response; PD, progressive disease; Na, not available; neg, negative; WT, wild type.

Immunomodulatory agents have been tested in R/R PCNSL patients. The combination of pomalidomide with dexamethasone resulted in an ORR of 48% and a median PFS of 5.3 months [24]. The combination of lenalidomide and rituximab resulted in the best ORR of 67% and a median PFS of 7.8 months [25]. Immune checkpoint inhibition by the anti-PD1 monoclonal antibody has shown promising therapeutic activity in an immunocompetent preclinical CNS lymphoma model [26], and results of a clinical trial investigating nivolumab are pending [27]. The compilation of these results sketches an optimistic landscape with new therapeutic combinations to be tested in PCNLS patients.

5. Conclusion

In conclusion, this prospective 'proof-of-concept' phase II study showed a clinical, radiological and biological activity of ibrutinib in the brain, the IO compartment, the CSF and the spinal cord of patients with relapse or refractory PVRL and PCNSL. Although ibrutinib can be considered a treatment alternative in selected patients not eligible for a more intensive treatment at relapse, these results call for further assessment of the benefit of ibrutinib in combination with chemo/immunotherapies at relapse and in first-line treatment for PCNSL. If a longer follow-up confirms the long-lasting CR rate with rare brain relapse in R/R PVRL, ibrutinib should then be evaluated in the first-line treatment for PVRL.

Author contributions

Carole Soussain and the LYSA group helped in the conception and design. Sylvain Choquet, Caroline Houillier, Hervé Ghesquières, Cécile Moluçon-Chabrot, Maryline Barrié, Marie Blonski, Remy Gressin, Eileen Boyle, Fontanet Bijou, Aline Clavert, Khê Hoang-Xuan, Emmanuelle Nicolas-Virelizier, Abderrazak El Yamani, Roch Houot, Marjan Ertault de la Bretonnière and Carole Soussain helped in provision of study materials or patients. Carole Soussain, Sylvain Choquet, Caroline Houillier, Hervé Ghesquières, Cécile Moluçon-Chabrot, Maryline Barrié, Marie Blonski,

Remy Gressin, Eileen Boyle, Fontanet bijou, Khê Hoang-Xuan, Emmanuelle Nicolas-Virelizier, Roch Houot, Cécile Moluçon-Chabrot, Remy Gressin, Khê Hoang-Xuan helped in collection and assembly of data. Carole Soussain, Keyvan Rezai and LYSARC statisticians helped in data analysis and interpretation. Carole Soussain, Sylvain Choquet, Hervé Ghesquières, Khê Hoang-Xuan, Caroline Houillier and Keyvan Rezai helped in manuscript writing. Delphine Leclercq and Marie Blonski helped in MRI review. All authors helped in the final approval of the manuscript. All authors were accounted for all aspects of the work.

Funding

This investigator-initiated study was funded by Janssen and sponsored by the LYSARC (The Lymphoma Academic Research Organization). Janssen did not participate in the conception, conduction or analysis of the trial or the writing of this report.

Conflicts of interest statement

Hervé Ghesquières is a consultor or advisor for Celgene and Gilead. He received travel and accommodation expenses from Gilead and Amgen. Sylvain Choquet is a consultor or advisor for Celgene and Roche. Carole Soussain received research funding from Pharmacyclics. All remaining authors have declared no conflicts of interest.

Acknowledgements

The authors thank all the patients and their families for having granted them their trust. They thank all the investigators, the investigator centres, the pathologists and radiologist who have been involved in this study. This study was funded by Janssen and sponsored by the LYSARC.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.05.024.

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