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

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Ibrutinib Monotherapy for Relapse or Refractory Primary CNS Lymphoma (PCNSL) and Primary Vitreoretinal Lymphoma (PVRL): 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.

Running title: Ibrutinib single agent in relapse or refractory Primary CNS lymphoma

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Highlights:

Ibrutinib (560 mg/day) showed a significant clinical activity in R/R PCNSL and PVRL.

The ITT-ORR was 52 % after two 28-day cycles with activity in brain, eyes and CSF.

Responses were observed even in the absence of *CD79B* and *MYD88* mutation. The median PFS was 4.8 months (CI 95%; 2.8-12.7). Pulmonary aspergillosis occurred in 2 patients (4%). No fatal hemorrhage occurred.

ABSTRACT

Background

Primary central nervous system lymphomas (PCNSLs) are mainly diffuse large B-cell lymphomas (DLBCLs) of the non-germinal center 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, multicenter, phase-II study involved patients with refractory or relapsing (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 (CI 95%; 2.8-12.7) and 19.2 months (CI 95%; 7.2-NR) respectively. Thirteen patients received ibrutinib for more than 12 months. Two patients experienced pulmonary aspergillosis with a favorable (n = 1) or fatal outcome (n = 1). Ibrutinib was detectable in the 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 cerebrospinal fluid 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.

INTRODUCTION

Primary central nervous system lymphomas (PCNSLs) are mainly diffuse large B-cell lymphoma (DLBCL) of non-germinal center (nonGC) 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 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 signaling[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 tumor-bearing and non-tumor-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.

METHODS

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 (ECOG) performance status (PS) <2. (Supplemental Table 1 for detailed inclusion and exclusion criteria).

Study design

This was an open-label, prospective, multicenter, 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).

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 edema, but had to be tapered off and stopped as soon as possible. Antifungal prophylaxis was not planned.

Assessment of therapeutic response and toxicity

The therapeutic responses were assessed according to the International PCNSL Collaborative Group Response Criteria (IPCG)[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 intra-ocular (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 ≥ 2 AEs were reported for cardiac, renal, neuropathic and hemorrhagic toxicities, and only grade ≥ 3 AEs were reported for the toxicity on the other organs.

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).

Exploratory analyses

The cerebrospinal fluid 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 (FFPE) tumor samples of the initial diagnostic brain biopsies for determination on the *MYD88, CD79b* and *CARD11* somatic mutations (Supplemental material).

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% 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.

RESULTS

Patient characteristics

Fifty-two patients were recruited between September 2015 and July 2016 from 10 centers (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 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.

Therapeutic response

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 figure 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 tumoral mass greater than 90% but a residual lesion with gadolinium uptake over 3 mm. The intraocular 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).

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 localizations 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).

Duration of responses and survival

With a median FU of 25.7 months, the median PFS was 4.8 months (CI 95%; 2.8-12.7) (figure 1A) and the median OS was 19.2 months (CI 95%; 7.2-NR), (figure 1B). In the ITT analysis, median PFS and OS were 3.3 months (CI 95%; 2-6.4) and14.4 months (CI 95%; 4.2-21.2) (figures 1C and 1D), respectively. The median PFS was shorter in patients who presented a brain or spinal cord parenchyma lesion at time of inclusion in the study (2 months, CI 95%; 2-3) compared to that of the patients who entered the study for a PVRL with or without CSF involvement (22.7 months, CI 95%; 5-not reached; p =<0.0001) (figure 1E), which also translated into a shorter median OS (4.3 months, CI 95%; 3:9 in patients with brain involvement and Not reached in patients without brain involvement, p < 0.0001) (figure 1F). Age and disease status at the time of inclusion (relapse vs refractory) did not impact the PFS (Supplemental figure 2A, 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, 40 patients had ceased treatment after a median time of 4 months from inclusion (CI 95%: range 2-25) because of 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 (figure 2A, 2B).

Tolerance and toxicity

The dose of ibrutinib was reduced in two patients to 280 mg/day and 420 mg/day. Thirty adverse events (AE) affecting 26 patients were reported (Table 4). The SAE of special interest included two ventricular hemorrhages, one in a patient with CR with a favorable outcome and the other in a patient with progressive disease; two hemorrhages in the anterior chamber of the eye with a favorable outcome; two atrial fibrillations; and two proven pulmonary aspergillosis: after one month of ibrutinib with a favorable 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.

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).

Correlation with the cell of origin, mutational profiles and the response to ibrutinib (Table 5)

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), 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 harbored 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-κB pathways were identified in both GC and non-GC tumors.

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 favorable 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 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, 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 [22 23].

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 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 is pending[27]. The compilation of these results sketches an optimistic landscape with new therapeutic combinations to be tested in PCNLS patients.

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/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.

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Author disclosures of potential conflicts of interest:

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Disclosure

Hervé Ghesquières

Consulting or advisory role: Celgene, Gilead

Travel, accommodations, expenses: Gilead, Amgen

Sylvain Choquet

Consulting or advisory role: Celgene, Roche

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Figure 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)

Figure 2. Swimmer plots representing the durations of treatment in patients with (A) or without brain/spinal cord parenchymal involvement (B) at the time of inclusion in the study.

The median duration of the responses was 6.3 months (CI 95%; 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; CI 95%: 1.2-15) compared to that in the patients who entered the study for a PVRL with or without CSF involvement (median = 21 months; CI 95%: 3.5-NA; p = 0.017)

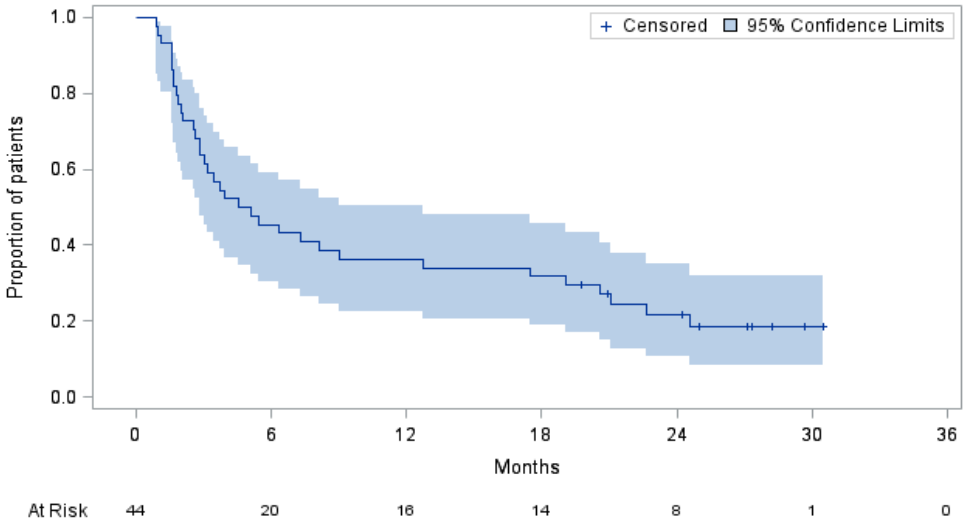
The two concurrent illnesses that lead to death were: a misdiagnosis of aortic aneurysm on a CT scan performed because of a thoracic pain. The patient underwent surgery. No aneurysm, no hemorrhage, no pathologic vessel walls were found. The patient died from multi-organ failure related to post-surgery 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.

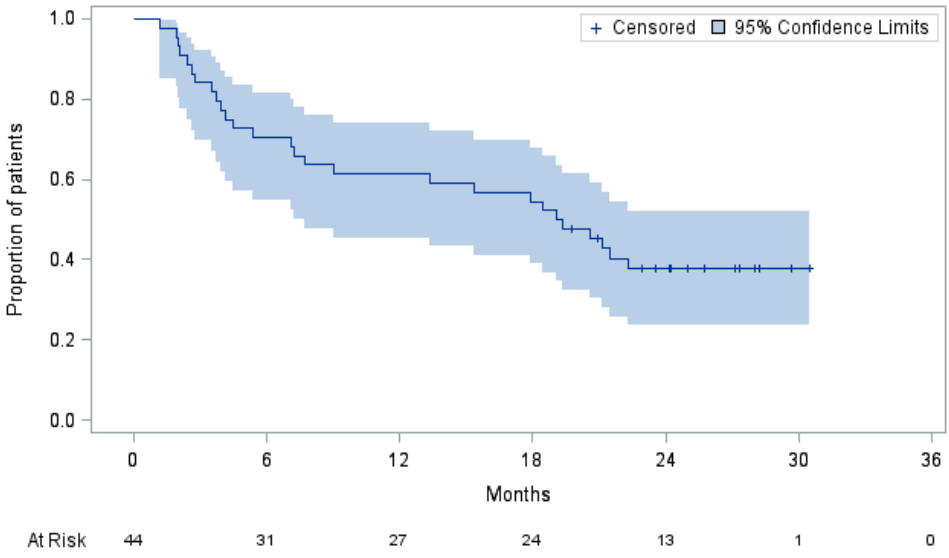
Figure 1.

A.



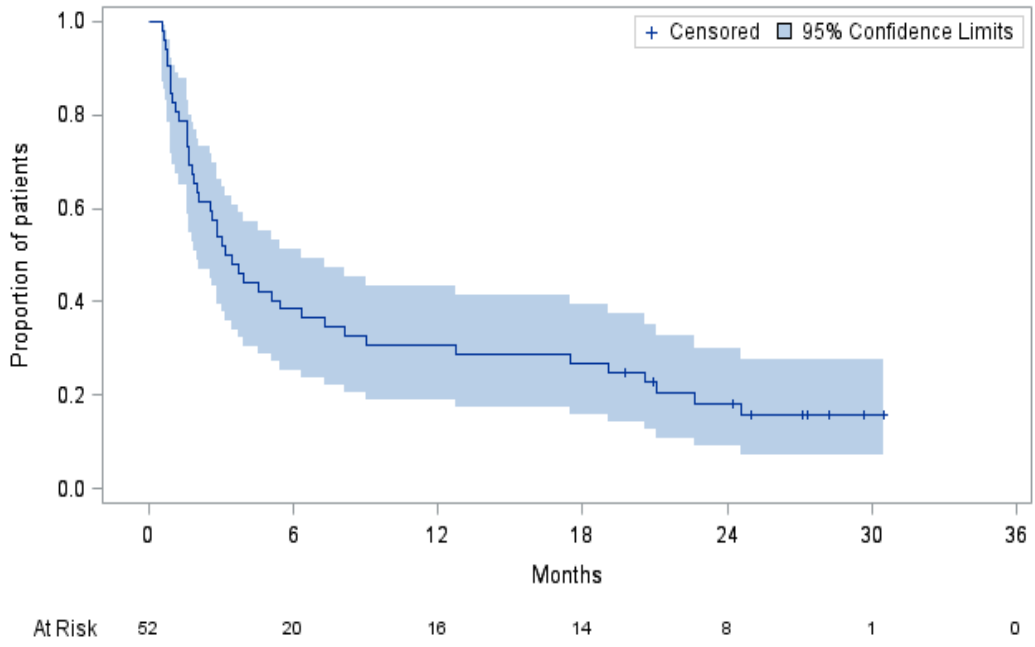
No. of Subjects	Event	Censored	Median Survival (95%CL)
44	79.5 % (35)	20.5 % (9)	4.8 (2.8 ; 12.7)

B.



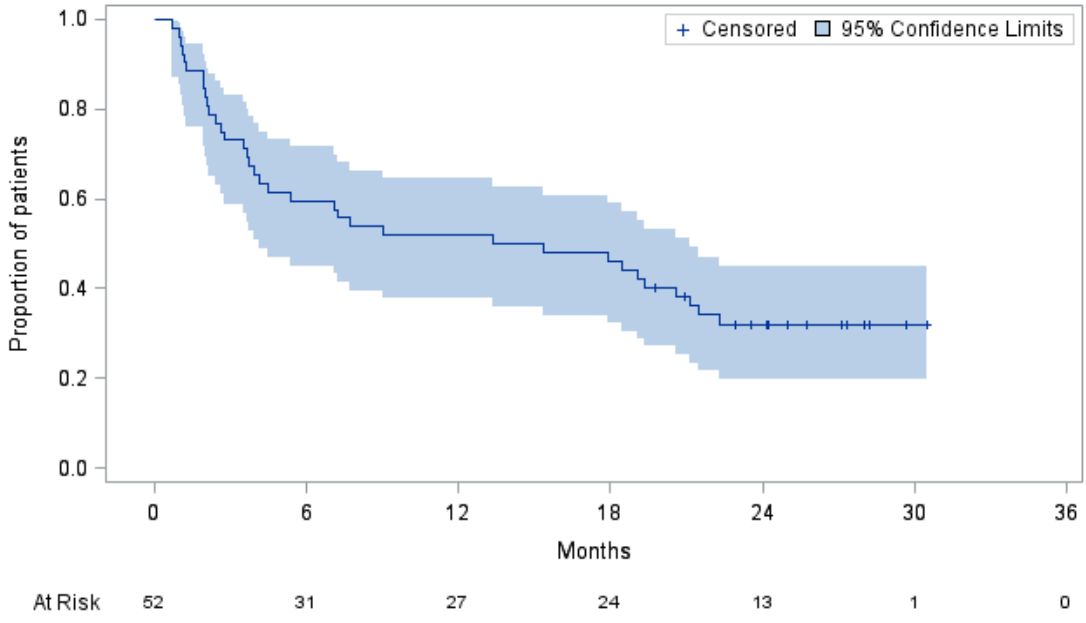
No. of Subjects	Event	Censored	Median Survival (95%CL)
44	61.4 % (27)	38.6 % (17)	19.2 (7.2 ; NA)

C.



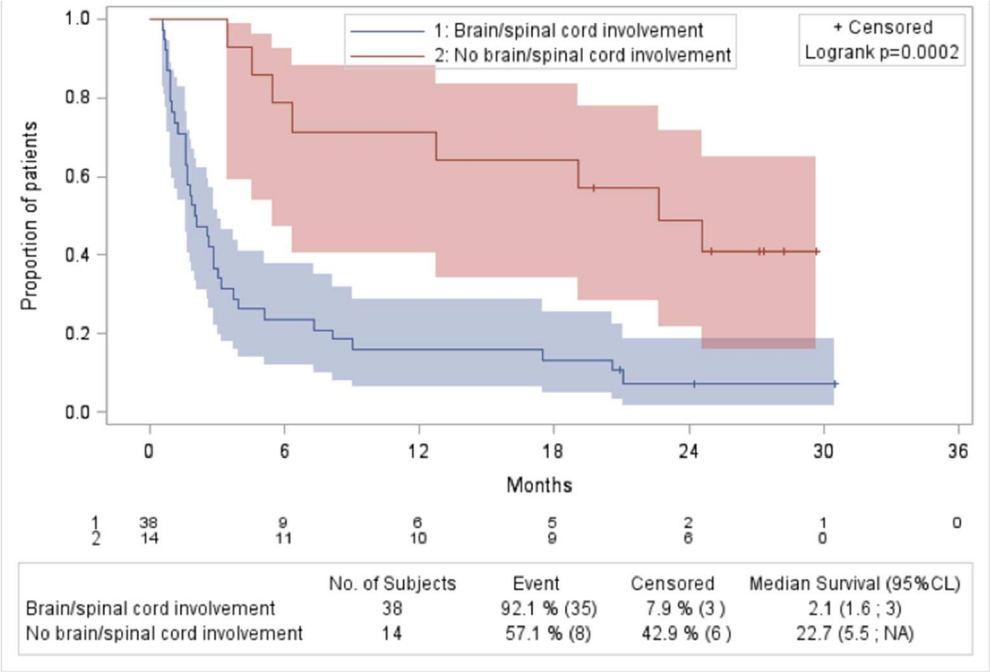
No. of Subjects	Event	Censored	Median Survival (95%CL)
52	82.7 % (43)	17.3 % (9)	3.3 (2 ; 6.4)

D.



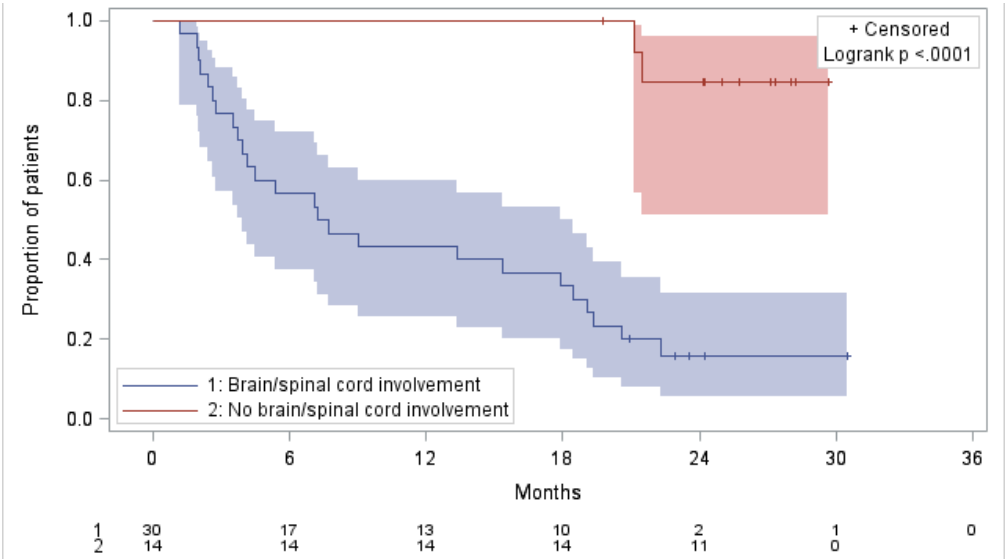
No. of Subjects	Event	Censored	Median Survival (95%CL)
52	67.3 % (35)	32.7 % (17)	14.4 (4.2 ; 21.2)

E.



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Brain/spinal cord involvement	38	92.1 % (35)	7.9 % (3)	2.1 (1.6 ; 3)
No brain/spinal cord involvement	14	57.1 % (8)	42.9 % (6)	22.7 (5.5 ; NA)

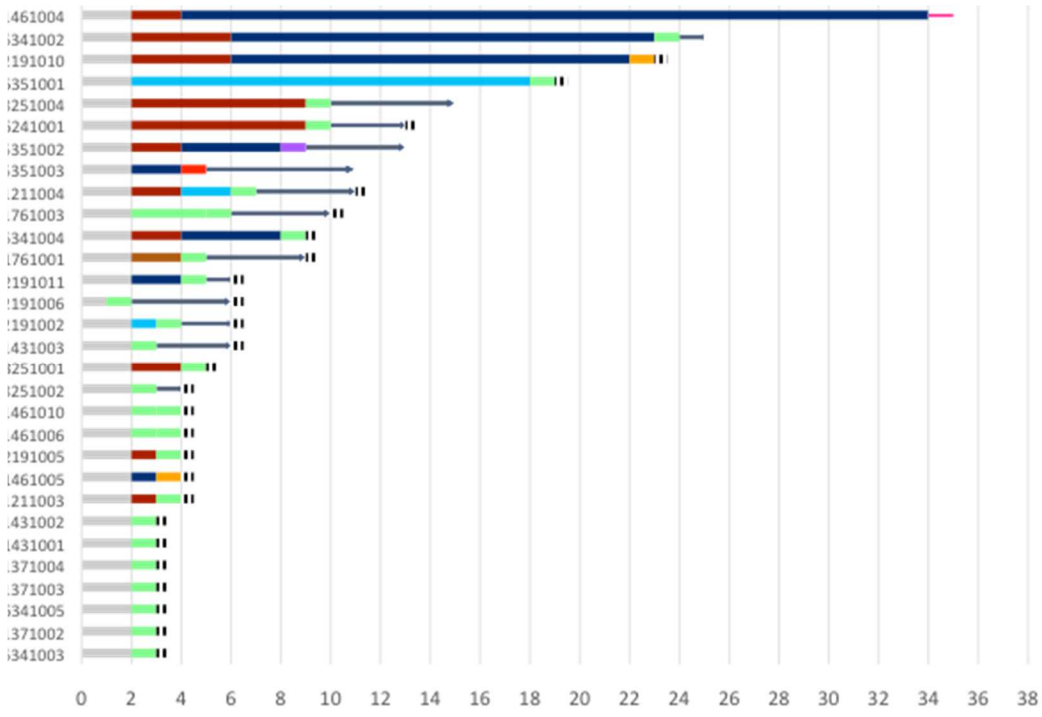
F.



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Brain/spinal cord involvement	30	83.3 % (25)	16.7 % (5)	7.5 (3.9 ; 18.4)
No brain/spinal cord involvement	14	14.3 % (2)	85.7 % (12)	Not reached

Re-ordered Figure 2.

A.



B.

Cycle of treatment

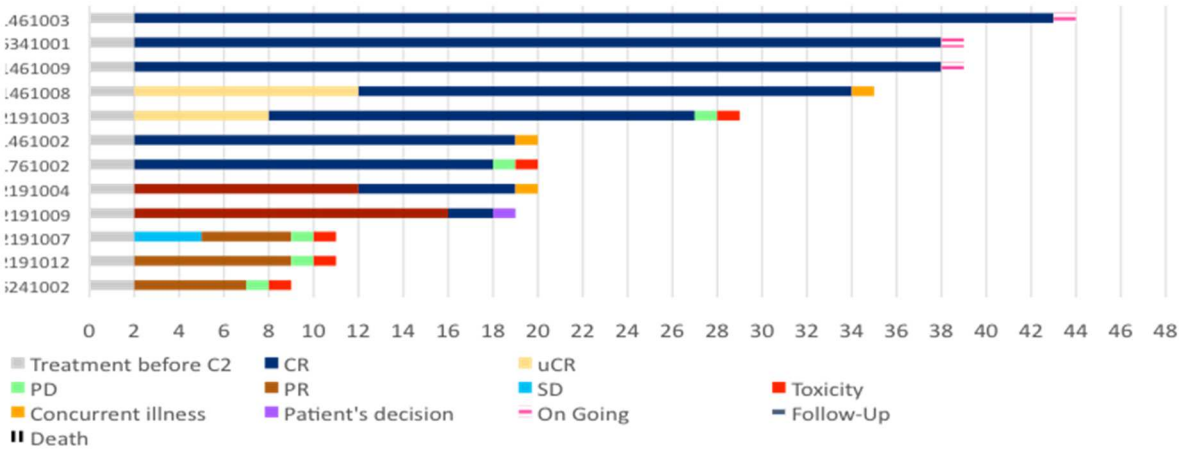


Table 1. Characteristics of the 52 patients included in the study (ITT population) and of the 44 patients evaluable for response (i.e who received 90% of the planned dose of ibrutinib during the first month of treatment)

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
Intra-ocular	**14**	**14**
With CSF	2	2
Corticosteroids during cycle 1	**19**	**14**

PS: ECOG Performance status; IO: Intraocular; CSF: cerebrospinal fluid; ASCT: autologous stem cell transplantation; WBRT: whole brain radiotherapy

Table 2. Therapeutic response after 2 cycles of ibrutinib.

	No brain lesion at inclusion N = 14	Brain lesion at inclusion N = 30	~~Whole~~ 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%)

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

	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

Table 4. Adverse events

Maximum Grade Per Patient Per Event (excluding unrelated)

Number of Evaluable Patients: 52

Grade of Adverse Event – n (%)

Rules for reporting AE are detailed in the protocol**.** Were reported:
- all AEs of grade ≥ 3 (hematological or non- hematological toxicities).
- All Serious adverse events, regardless of their grade
- All AEs of grade ≥ 2 for cardiac, renal, neuropathic and hemorrhagic toxicities
- All AEs of special interest

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	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

Re-ordered **Table 5:** Molecular characteristics and response to ibrutinib

COO: cell of origin determined by immunohistochemistry according to the Han algorithm; GC: Germinal Center; CR: complete response; PR: partial response; PD: progressive disease; na: not available; neg: negatif; WT: wild type

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

Figure 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)

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