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Bendamustine and rituximab in elderly patients with low-tumour burden follicular lymphoma. Results of the LYSA phase II BRIEF study

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Summary

The treatment of low-tumour burden follicular lymphoma (LTBFL) remains a challenge. Rituximab-based strategies may be improved by adding chemotherapy. This Lymphoma Study Association multicentre phase II study assessed rituximab and bendamustine in 63 patients with untreated LTBFL who were aged over 60 years old and had a follicular lymphoma International Prognostic Index (FLIPI) score ≥2. Induction comprised 4 weekly cycles of rituximab 375 mg/m^2 intravenously combined with 2 cycles of bendamustine 90 mg/m^2 days 1–2 with a 28-day interval, followed by twelve cycles of 375 mg/m^2 rituximab maintenance therapy every 8 weeks. The primary endpoint was complete response (CR)/unconfirmed CR (CRu), at 12 weeks. Median age was 67·4 years and median FLIPI was 3. Ultimately, 18 patients (29%) had high tumour burden according to Groupe d'Etude des Lymphomes Folliculaires criteria. The 12-week CR/CRu rate was 54·0% and the overall response rate was 93·7%. Surprisingly, 3 patients died during maintenance (2 sepsis, 1 neoplasm). Progression-free survival was 85·4% at 24 months. In LTBFL patients with FLIPI ≥2, two cycles of rituximab and bendamustine result in a CR rate of 54·0%. However, the treatment-related deaths observed do not allow this regimen to be recommended for LTBFL patients aged over 60 years.

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Keywords: follicular lymphoma, rituximab, bendamustine, tolerance, efficacy.

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Asymptomatic low-tumour burden follicular lymphoma (LTBFL) is a presentation of follicular lymphoma (FL) without high-tumour burden (HTB) criteria according to Groupe d'Etude des Lymphomes Folliculaires (GELF; Brice *et al*, 1997; Solal-Céligny *et al*, 1998) or British National Lymphoma Investigation (Ardeshna *et al*, 2003) criteria. A watch-and-wait (WW) strategy is acceptable in LTBFL (Horning & Rosenberg, 1984), as no overall survival (OS) benefit has been observed with immediate treatment in randomised studies (Brice *et al*, 1997; Ardeshna *et al*, 2003).

Four weekly courses of rituximab (4R) as monotherapy result in an overall response rate (ORR) of 80% with a complete response [CR: CR+unconfirmed CR (CRu)] rate (Cheson *et al*, 1999) of 52% and a median progression-free survival (PFS) of 23·4 months (Colombat *et al*, 2001, 2012). A longer time to next treatment has been observed with 4R compared to WW [hazard ratio (HR) = 0·21; $P < 0·0001$] without OS benefit (Ardeshna *et al*, 2014). In LTBFL, maintenance therapy with rituximab has also been associated with a longer time to start of new treatment (TTNT) (HR = 0·53; $P = 0·011$) (Ardeshna *et al*, 2014), without OS benefit. However, some patients with LTBFL may have unfavourable prognostic factors at diagnosis, such as a high FL International Prognostic Index (FLIPI) score (Solal-Céligny *et al*, 2004), and require a shorter time to treatment initiation (Solal-Céligny *et al*, 2012). In a study assessing LTBFL patients treated with 4R with a follow-up of more than 7 years, no patient with a high FLIPI score achieved a long-term remission (Colombat *et al*, 2006). In the RESORT study comparing maintenance therapy with rituximab to re-treatment with 4R in LTBFL, CR was only 11·8% after 4R induction, mostly because of missing bone marrow evaluation (Kahl *et al*, 2014). This study did not show an improvement in TTNT with planned maintenance compared with rituximab monotherapy at time of progression. However, an intermediate or high FLIPI score was associated with an increased risk of progression in multivariable analysis [HR = 1·71; 95% confidence interval, CI (1·01–2·87)] (Kahl *et al*, 2014). These LTBFL patients with a high FLIPI score might benefit from a more intensive approach.

Bendamustine has been assessed in FL in combination with rituximab. In a phase II study in patients with relapsed/refractory low-grade lymphomas, 4 cycles of bendamustine and rituximab (BR) resulted in a CR rate of 60% with a median PFS of 24 months (Rummel *et al*, 2005). Two prospective randomised studies comparing BR to R-chemotherapy (mostly R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) as first-line therapy have shown CR rates of 40% and 31%, and 93% and 97% in the StiL (Rummel *et al*, 2013) and BRIGHT (Flinn *et al*, 2014) studies, respectively. In the StiL study, FL patients showed a prolonged PFS compared to that achieved with R-CHOP (HR = 0·61, $P = 0·072$), while the toxicity of BR appeared lower. To our knowledge, BR has not yet been assessed in LTBFL.

The aim of the multicentric phase II BRIEF study was to assess the efficacy and toxicity of 2 cycles of BR followed by maintenance therapy in untreated LTBFL patients with a FLIPI score of 2 or above.

Patients and methods

Eligibility

Inclusion criteria were: histologically confirmed $CD20^+$ FL (grades 1, 2 and 3a), age ≥60 years, untreated FL, Eastern Cooperative Oncology Group (ECOG) performance score between 0 and 2, adequate haematological function (unless related to lymphoma), adequate renal, cardiac and hepatic functions, low tumour burden (GELF criteria) with intermediate or high FLIPI score; at least one measurable lesion. Low tumour burden was defined as: no mass >7 cm, less than three masses >3 cm, no systemic or B symptoms, no splenic enlargement, no compressive syndrome, no increased lactate dehydrogenase (LDH) or β_2-microglobulin levels, and no cytopenia (defined as platelet count $<100 \times 10^9$/l, haemoglobin <100 g/l or absolute neutrophil count $<1·5 \times 10^9$/l,). Patients were excluded if they were positive for human immunodeficiency virus, hepatitis B core (HBc) antigens or hepatitis C virus, or if they had any prior or concomitant malignancies.

Pathology review

Diagnostic biopsies were centrally reviewed by expert pathologists of the French Study Group of the Adult Lymphoma / Lymphoma Study Association for histological confirmation according to the World Health Organization classification (Swerdlow *et al*, 2008).

Baseline assessments

Baseline laboratory tests were performed within 28 days of registration to verify eligibility. Baseline imaging included ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) scan and computed tomography scans of the neck, chest, abdomen and pelvis. A baseline bone marrow (BM) biopsy was required.

Treatment protocol

The induction phase included 4 weekly doses of rituximab at 375 mg/m^2 intravenously (IV), combined with 2 courses of bendamustine (90 mg/m^2 days 1–2 and days 29–30). Patients achieving a partial remission (PR) or CR/CRu at week 12 received rituximab as a maintenance therapy at 375 mg/m^2 IV every 2 months for 2 years (Fig 1). Patients with stable or progressive disease at week 12 were withdrawn from the study. No specific guidelines were given concerning anti-infectious prophylaxis (i.e. *Pneumocystis jirovecii*, or *Herpes simplex*) or granulocytic growth factor use.

Efficacy assessments

Response was assessed using the 1999 (Cheson *et al*, 1999) and 2007 (Cheson *et al*, 2007) International Working Group (IWG) criteria after the induction phase, at week 12. Final assessment was made at week 108 (Fig 1).

Statistics

The primary endpoint was the CR rate according to 1999 IWG criteria (Cheson *et al*, 1999) after induction treatment. Secondary endpoints were the CR rate according to 2007 IWG criteria (Cheson *et al*, 2007) at week 12, ORR (according to 1999 and 2007 IWG criteria) at week 12 and 108, response duration, PFS, OS and safety. Assuming an alpha risk of 0·05 and beta risk of 0·10 in a one-tailed test, a CR rate of 40% for an ineffective treatment and 60% for an effective treatment, 56 assessable patients were needed with a cut-off at 28 CR. Comparison of proportions was performed with the Fisher's exact test.

Safety

Adverse events (AEs) and serious AEs (SAEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v. 4.0 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

Data analysis

Efficacy was assessed in all patients included in the study. Safety was assessed in patients who received at least one dose of experimental drug (i.e., rituximab or bendamustine). The per-protocol analysis was performed in patients who met all inclusion and exclusion criteria.

Ethics

The BRIEF protocol was approved by the ethics committee of Nancy, France, on December 23, 2010 and by the National Agency for Medicines and Health Products Safety (ANSM) on December 10, 2010. The study was conducted in accordance with the declaration of Helsinki. Patients were asked to provide written informed consent before registration.

Results

Patient distribution

Sixty-three patients were included in the study between 22 February 2011 and 20 June 2012. One patient did not receive

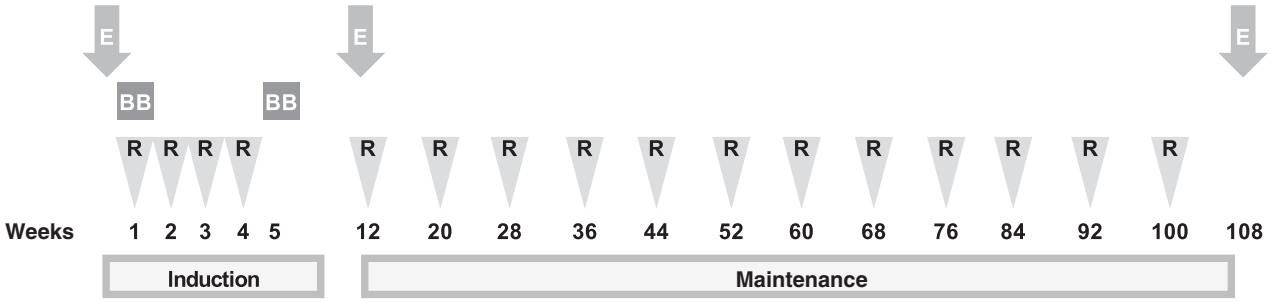

Fig 1. BRIEF study design. The BRIEF study is a single-arm phase II trial assessing the tolerance of 2 cycles of bendamustine + rituximab in induction therapy followed by rituximab maintenance therapy. BB, bendamustine 90 mg/m^2 days 1 and 2 with a 28-day interval. R, rituximab 375 mg/m^2 every week for 4 doses followed by rituximab maintenance therapy at 375 mg/m^2 every 8 weeks for 12 doses. E, tumour assessment with computed tomography and ^{18}fluorodeoxyglucose-positron emission tomography scans.

any study drug (inclusion criteria violation) and was excluded from the toxicity analysis. One patient experienced grade 1 diarrhoea and fever during the induction phase, precluding the administration of bendamustine at day 30, but was included in the toxicity and efficacy analyses (Fig 2).

Pathology review

After pathology review, all diagnoses of FL were confirmed, except for 1 patient whose tumour was classified as diffuse large B cell lymphoma (DLBCL) and 1 patient with grade 3B FL. Histological samples of six patients could not be reviewed because no additional material was available (Table I).

Patient characteristics

The 63 patients included 34 men and 29 women, with a median age of 67·4 years (range: 61–84). The median Cumulative Illness Rating Scale-Geriatric (CIRS-G) score was of 3 (range: 0–10) and most patients (76·2%) had an ECOG performance score equal to 0. All patients but one had a stage III-IV disease and most of them had a high FLIPI score (69·8%). Lymphoma involvement was nodal in all cases (100%), and 42 (66·7%) patients also had extranodal disease. Characteristics are detailed in Table I.

Compliance

Unexpectedly, deviations from the inclusion/exclusion criteria were observed in 25 patients (39·6%), with the presence of 1 or more GELF high tumour burden (HTB) criteria in 18 patients (tumour >7 cm: 8; B symptoms: 5; high LDH level: 4; high β_2-microglobulin level: 6; 3 sites larger than 3 cm: 5; symptomatic splenomegaly: 3; compressive symptoms: 5; serous effusion: 1), diagnosis made more than 6 months ago (2 patients), 1 DLBCL and 1 grade 3B FL (after pathology review). The median percentage of planned dose received during the induction phase was 99·1% (quartile [Q]1–Q3: 98–100) for bendamustine and 98·9% (Q1–Q3: 98–100) for rituximab. As soon as the decision to discontinue the maintenance therapy with rituximab was made by the Data and Safety monitoring committee (DSMC) due to three lethal therapy-related cases observed, all patients immediately discontinued treatment.

Response at the end of induction

According to 1999 IWG criteria (Cheson *et al*, 1999), 34 out of the 63 [54·0%; 95% CI (40·9–66·6)] patients achieved a CR/CRu at the end of the induction phase. The ORR was 93·7% [95% CI (85·8–99·9)]. According to 2007 IWG criteria (Cheson *et al*, 2007), the CR rate was 57·1% and the ORR was

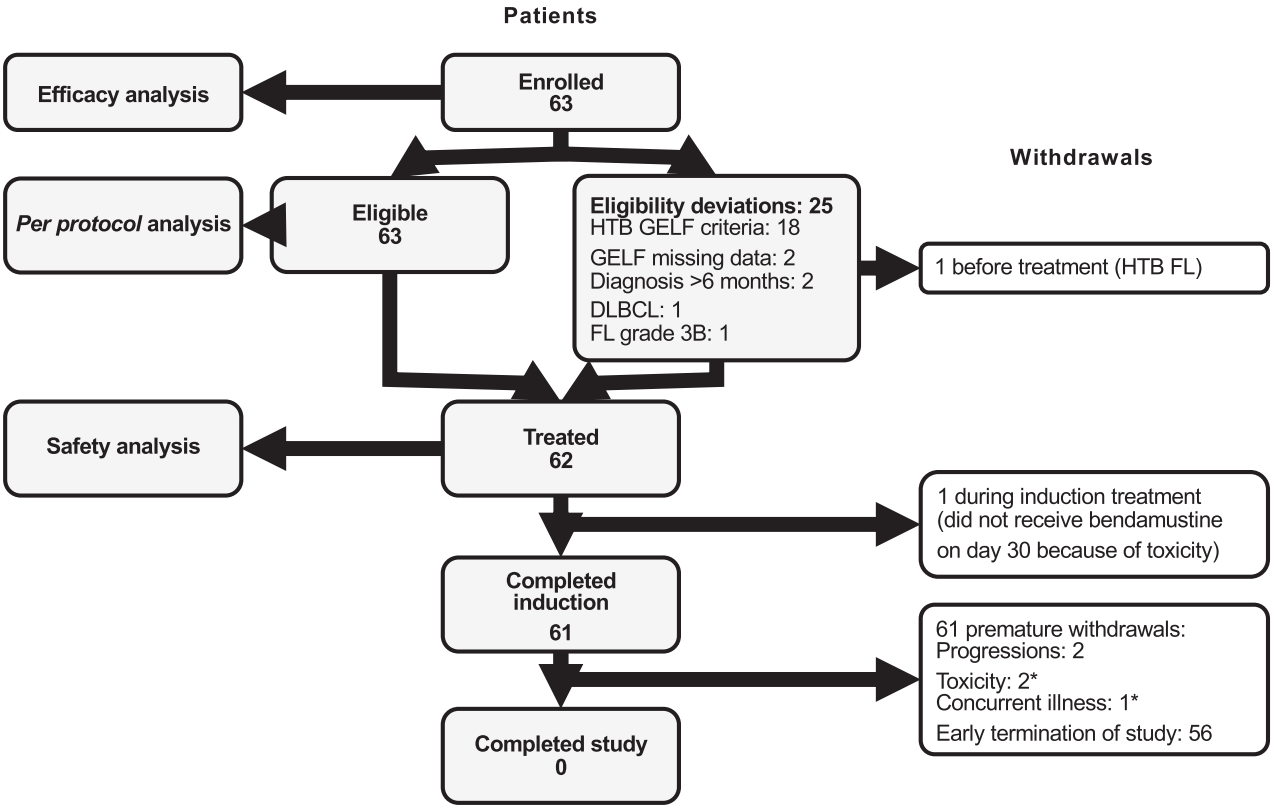

Fig 2. Study flowchart. Sixty-three patients were included in the study and efficacy analysis. One patient did not receive study treatment because of inclusion criteria violation and was excluded from the safety analysis. The other reasons for treatment discontinuation are indicated in the boxes on the right. B, bendamustine. Asterisks (*) indicate the deaths that occured during the study.

Table I. Patient characteristics ($N = 63$).

	N	(%)
Sex		
Female	29	(46·0)
Male	34	(54·0)
Age, years		
Median, [Q1–Q3]	67·4	[64–75]
CIRS-G score		
Median, [min–max]	3	[0–10]
Performance status		
0	48	(76·2)
1–2	5	(23·8)
3–4	0	(0)
Ann Arbor stage		
I-II	1	(1·6)
III-IV	62	(98·4)
B symptoms		
Yes	6	(9·5)
No	57	(90·5)
Histology		
Grade 1–2 FL	43	(68·2)
Grade 3A FL	7	(11·1)
Grade 3B FL	1	(1·6)
FL (other*)	5	(7·9)
DLBCL	1	(1·6)
Not reviewed†	6	(9·5)
Mass >6 cm		
Yes	12	(19·0)
No	51	(81·0)
Compressive syndrome		
Yes	5	(7·9)
No	58	(92·1)
Nodal involvement		
<4	18	(28·6)
≥4	45	(71·4)
Extranodal involvement		
Yes	30	(47·6)
No	33	(52·4)
Bone marrow involvement		
Yes	30	(47·6)
No	28	(44·4)
No biopsy available	5	(7·9)
LDH level		
Normal	58	(92·0)
Elevated	4	(6·3)
Missing	1	(1·6)
β_2-microglobulin level		
≤3 mg/l	55	(87·3)
>3 mg/l	6	(9·5)
Missing	2	(3·2)
FLIPI score		
0–1	0	(0)
2	19	(30·2)
3–5	44	(69·8)
FLIPI2 score		
0	0	(0)
1–2	34	(64·2)
3–5	19	(35·8)
Missing	10	(15·8)

FLIPI, follicular lymphoma international prognostic index; FL, follicular lymphoma; DLBCL, diffuse large B cell lymphoma; CIRS-G, Cumulative Illness Rating Scale-Geriatric.

*Other FL: undetermined grade (1), with diffuse areas (1), possible follicular lymphoma (2), bone marrow biopsy with possible involvement (1).

†6 considered FL per local site.

95·2%, respectively. Ten patients with a negative ^{18}FDG-PET-scan were considered in PR only because a BM assessment was missing (Fig 3). In the 37 patients of the *per protocol* population, the CR rate was 59·4% and the ORR was 91·9%. Among the 18 patients retrospectively assessed as HTB and the 43 LTB patients (2 missing data), CR was achieved in 9 (50·0%) and 23 (53·5%), respectively ($P = 1·0$), while ORR was achieved in 18 (100%) and 39 (90·7%), respectively. No pretherapeutic criteria were found to predict a CR.

At the end of treatment (including maintenance phase for responders), 48 (76·2%) and 57 (90·5%) patients achieved a CR/CRu and OR, respectively, according to 1999 IWG criteria, whereas 42 (66·7%) and 46 (73%) patients achieved a CR and OR according to 2007 IWG criteria, respectively.

Tolerance

Most AEs were haematological and leucopenia occurred in more than half of the patients (Table II). All observed toxicities are detailed in Fig 4. Thirteen patients experienced 37 SAEs during the study, one patient before and 2 patients during the induction phase, 10 during the maintenance phase and 2 during the follow-up. The first pre-planned DSMC met on 10 July 2012. During this meeting, two deaths were carefully examined and were considered as possibly related to study treatments (one infection and one adenocarcinoma). When a third death (infection), occurring 6 months after study entry, was reported to the pharmacovigilance department, the DSMC was contacted and immediately recommended (October 2012) to discontinue treatment with rituximab during the maintenance phase, which resulted in early study termination for 56 patients (Fig 2), and additional safety monitoring recommendations in which CD4/CD8, serum electrophoresis and IgA, IgG and IgM assessments were added to the follow-up. The characteristics of the 3 patients with a fatal outcome are presented in Table III.

Progression

Survival was studied until 1 July 2016, after a median follow-up of 52 months. A total of 13 (20·6%) patients experienced

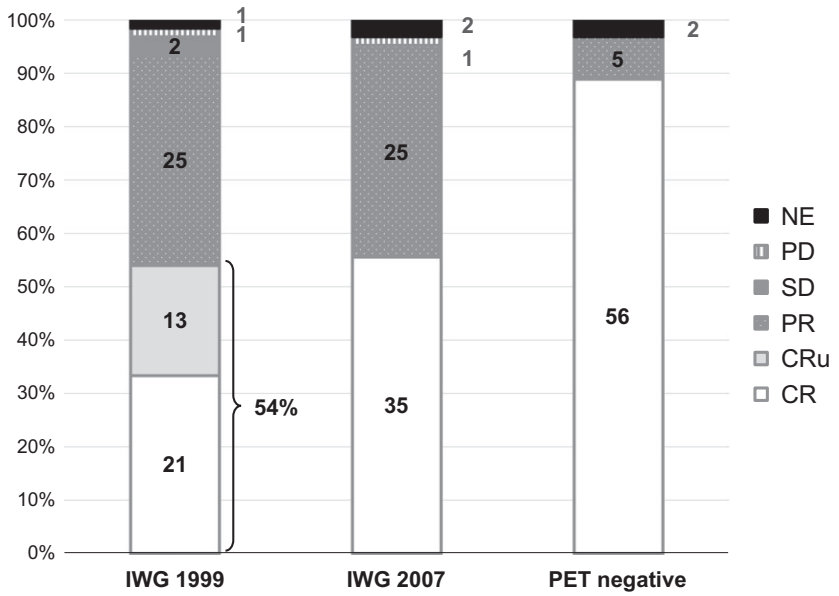

Fig 3. Response rate after the induction phase according to assessment criteria and bone marrow assessment availability. The histograms indicate the percentage of patients with the corresponding response at the week 12 assessment. NA, not assessable; PD, progressive disease; SD, stable disease; PR, partial response; CRu, unconfirmed complete response; CR, complete response.

Table II. Incidence of adverse events reported during induction, maintenance, and follow-up among the 62 patients of the safety analysis.

	Induction		Maintenance		Follow-up	
N (%)	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Anaemia	32 (51·6)		14 (22·6)		2 (3·2)	
Leucopenia	34 (54·8)	5 (8·1)	29 (46·8)	4 (6·5)	7 (11·3)	
Lymphopenia	3 (4·8)	17 (27·4)	15 (24·2)	7 (11·3)	6 (9·7)	3 (4·8)
Neutropenia	18 (29)	7 (11·3)	15 (24·2)	12 (19·4)	6 (9·7)	3 (4·8)
Febrile neutropenia				2 (3·2)		
Sepsis				1* (1·6)		
Thrombocytopenia	21 (33·9)		8 (12·9)		5 (8·1)	
Creatinine increase	6 (9·7)		6 (9·7)			
AST/ALT increase	14 (22·6)		7 (11·3)		1 (1·6)	
Fever (non-infectious)	4 (6·5)		3 (4·8)		2 (3·2)	
Other infections	2 (3·2)		12 (19·4)	1 (1·6)	10 (16·1)	1 (1·6)
Fatigue/asthenia	18 (29)		8 (12·9)	1 (1·6)	5 (8·1)	
Mucositis	2 (3·2)				1 (1·6)	
Nausea	15 (24·2)		2 (3·2)			
Vomiting	6 (9·7)		1 (1·6)			
Diarrhoea	7 (11·3)		5 (8·1)			
Other GI	16 (25·8)		11 (17·7)	2 (3·2)	3 (4·8)	
Atrial fibrillation	1 (1·6)		1 (1·6)			
Extrasystoles	1 (1·6)					
Peripheral neuropathy	2 (3·2)		1 (1·6)		1 (1·6)	
Lung infection			2 (3·2)	2* (3·2)		
Neoplasm	1 (1·6)	1	2 (3·2)	3* (4·8)	2 (3·2)	1 (1·6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastro-intestinal.
*Including 1 with a fatal outcome.

disease progression (Fig 5A), and 3 deaths unrelated to lymphoma occurred as detailed above. Progressions occurred in the sites initially involved in 11 patients, and in new sites in 5 patients and some patients had multiple lesions. The estimated PFS at 24 months was 85·4% [95% CI (73·8–92·1)] for all patients and it was 89·2% [95% CI (73·7–95·8)] in the *per*

protocol population. The estimated PFS at 24 months was 88·1% [95% CI (73·7–94·9)] in the LTB group vs. 77·8% [95% CI (51·1–91·1)] in the HTB group ($P = 0·69$). In the multivariate analysis, two factors influencing PFS were identified: the cumulative dose of rituximab per 100-mg increase [HR: 0·887, 95% CI (0·819–0·959); $P = 0·003$] and the presence of a mass >6 cm at baseline [HR: 4·849; 95% CI (1·064–22·10); $P = 0·041$].

Survival

Median OS was not reached with the 3 previously mentioned deaths unrelated to lymphoma, and 1 related to lymphoma progression lymphoma, Fig 5B). No further analysis could be performed due to the limited number of events.

Discussion

The results of the BRIEF study indicate that two cycles of BR result in a CR/CRu rate of 54·0% and an ORR of 95·2% according to 1999 IWG criteria (Cheson *et al*, 1999) in treatment-naïve LTBFL patients with a FLIPI score greater than or equal to 2.

One originality of our study is the definition of the population (i.e. low tumour burden with intermediate-to-high FLIPI score), which had not been evaluated in other studies. Median PFS and OS were not reached with the actual follow-up. Our observed PFS (85·4% at 24 months) is higher than that observed with 4 weekly courses of rituximab (4R) in most studies.

In the phase II study assessing 4R in treatment-naive LTBFL patients, the best CR rate (at any time during 1 year after treatment) was 52%, the ORR was 80%, and the median PFS was 23·5 months (Colombat *et al*, 2001, 2012), and these values are lower than in our study. Similarly, in a phase II study assessing 4R in asymptomatic newly diagnosed advanced FL patients from the North Central Cancer Treatment Group, the CR rate was 36%, the ORR 72% and the median time to progression (TTP) 2·2 years. Interestingly, patients with high LDH had a lower ORR (33%) and a shorter TTP (6 months) (Witzig *et al*, 2005). The RESORT study has also assessed 4R retreatment at the time of LTBFL progression in patients initially treated with 4R, compared to maintenance therapy with rituximab. The CR rate after the induction phase was 11·8%, the ORR was 70·8%, and the time to treatment failure was not different, at 61% and 64% at 3 years in the retreatment and maintenance arms, respectively (Kahl *et al*, 2014). However, the GELF criteria used in this study did not take into account high LDH or β_2-microglobulin levels, which were found in 13% and 42% of

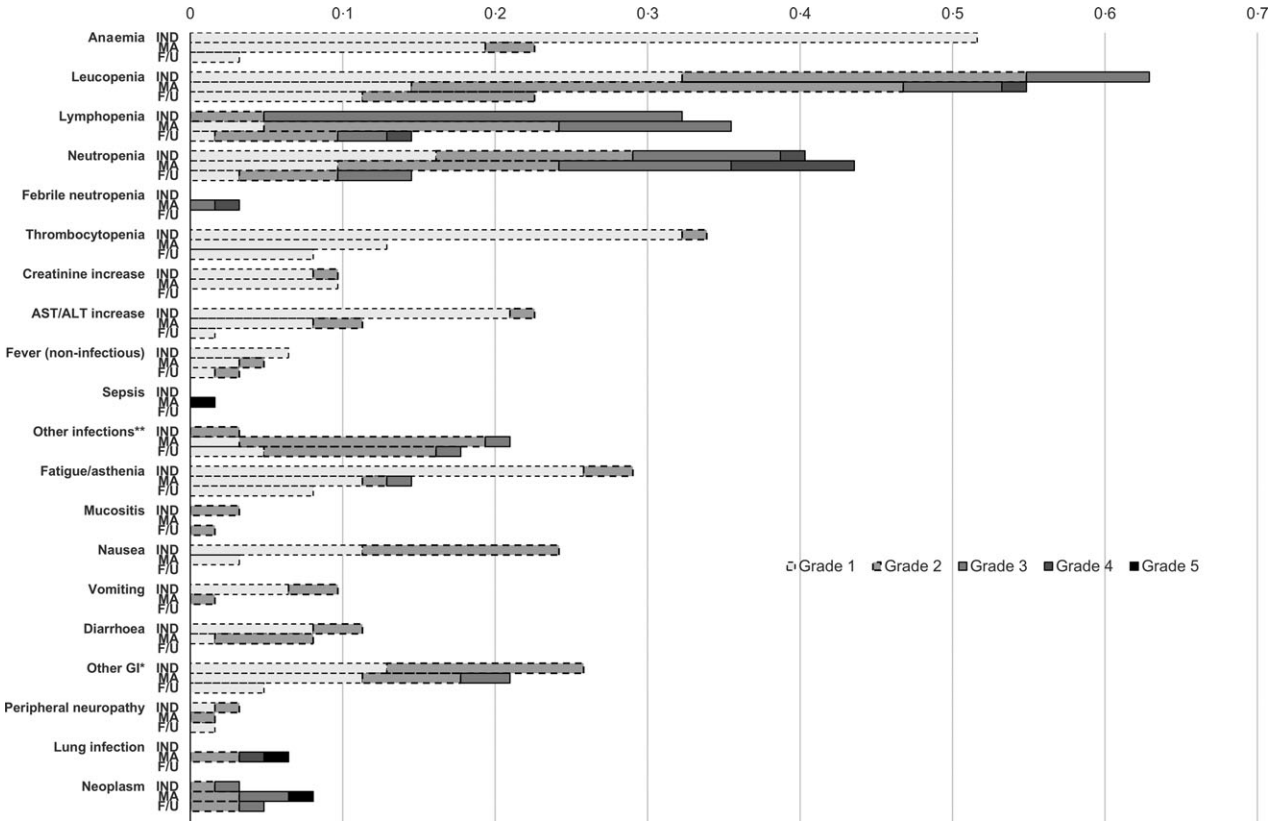

Fig 4. Toxicity. The horizontal bars represent the number of adverse events experienced per patient during the induction (IND), maintenance (MA) and follow-up (F/U) phases of the study in the safety population. Colour legends: Grade 1: Light grey with thin broken line border; Grade 2: medium grey with thick broken line border; Grade 3: medium grey with solid border; Grade 4: dark grey with solid border; Grade 5; black.

patients, respectively. In the 'rituximab *versus* watch-and-wait' (RWW) study, the CR rate at 7 months was 36%, the ORR was 77% and the median PFS was longer than 4 years in the 4R induction arm, and increased to 51%, 88% and not reached, respectively in the 4R + R maintenance arm (Ardeshna *et al*, 2014). Our efficacy results compare favourably with these studies.

Toxicities were mostly haematological and manageable for most patients, with no significant grade 3/4 toxicity. However, we unexpectedly observed 3 deaths related to treatment. Therefore, the DSMB decided to discontinue study treatment administration. Treatment-related deaths have not been reported in the two previously published rituximab and bendamustine studies (Rummel *et al*, 2013; Flinn *et al*, 2014). The reasons for these unanticipated toxicities are unclear. One patient who died from *Streptococcus pneumoniae* lung infection had profound hypogammaglobulinaemia (Table III), whereas the two others had no risk factors. In this context, the possibility that an intensive treatment with 4 doses of rituximab over the first month of the induction phase could increase immunosuppression cannot be completely ruled out. The fact that no mandatory antimicrobial prophylaxis or growth factor use was planned may have also contributed to some degree of vulnerability.

Of note, in the recently reported GALLIUM study, it appeared in preliminary results that a small excess of severe and eventually fatal toxicities occurred predominantly during the bi-monthly R maintenance period in patients receiving BR as compared to rituximab and CVP (cyclophosphamide, vincristine, and prednisone) or CHOP as induction therapy (although this was not a randomized comparison) (Marcus *et al*, 2016). On the other hand, the recent US phase 3 HTB FL study report of the comparison of BR to bortezomib+BR, and of evaluation of the addition of lenalidomide to R maintenance did not find treatment-related mortality to be an issue (Evens *et al*, 2017).

The ^{18}FDG-PET-scan, performed to monitor the response, also showed that the metabolic response was higher than in the 2007 IWG definition of the CR because some BM biopsies were missing, indicating that 2 cycles of BR could lead to 91·8% PET-scan negativity. The impact of missing BM biopsies on the calculation of the CR according to 1999 IWG criteria has not been assessed, to our knowledge, in other FL studies.

A concern of our study is that some patients with HTB characteristics were included in the trial. This could be due to the unusual inclusion criteria associating the FLIPI score and GELF criteria. However, regarding the *per protocol* population, the fact that most relapses occurred in sites initially involved suggests that 2 cycles of BR, even if followed by some rituximab maintenance cycles, could not reduce FL minimal residual disease enough to allow a prolonged remission.

Non-chemotherapeutic approaches, such as rituximab and lenalidomide combinations (Fowler *et al*, 2014), alternative anti-CD20 monoclonal antibodies (Negrea *et al*, 2011; Salles

Table III. Characteristics of the 3 patients with a fatal outcome unrelated to lymphoma.

Patient	Age at inclusion (years)	Time between inclusion and death (months)	Cause of death	Risk factors	Disease status at death	Last cycle received
1	74	7·5	Septic shock with *Pseudomonas aeruginosa* pneumopathy	None	Partial response	Week 28
2	64	9·4	Adenocarcinoma of unknown origin	None	Complete response	Week 28
3	64	4·5	*Streptococcus pneumoniae* pneumopathy	Alcohol and tobacco use. hypogamma-globulinaemia	Not assessed	Week 12

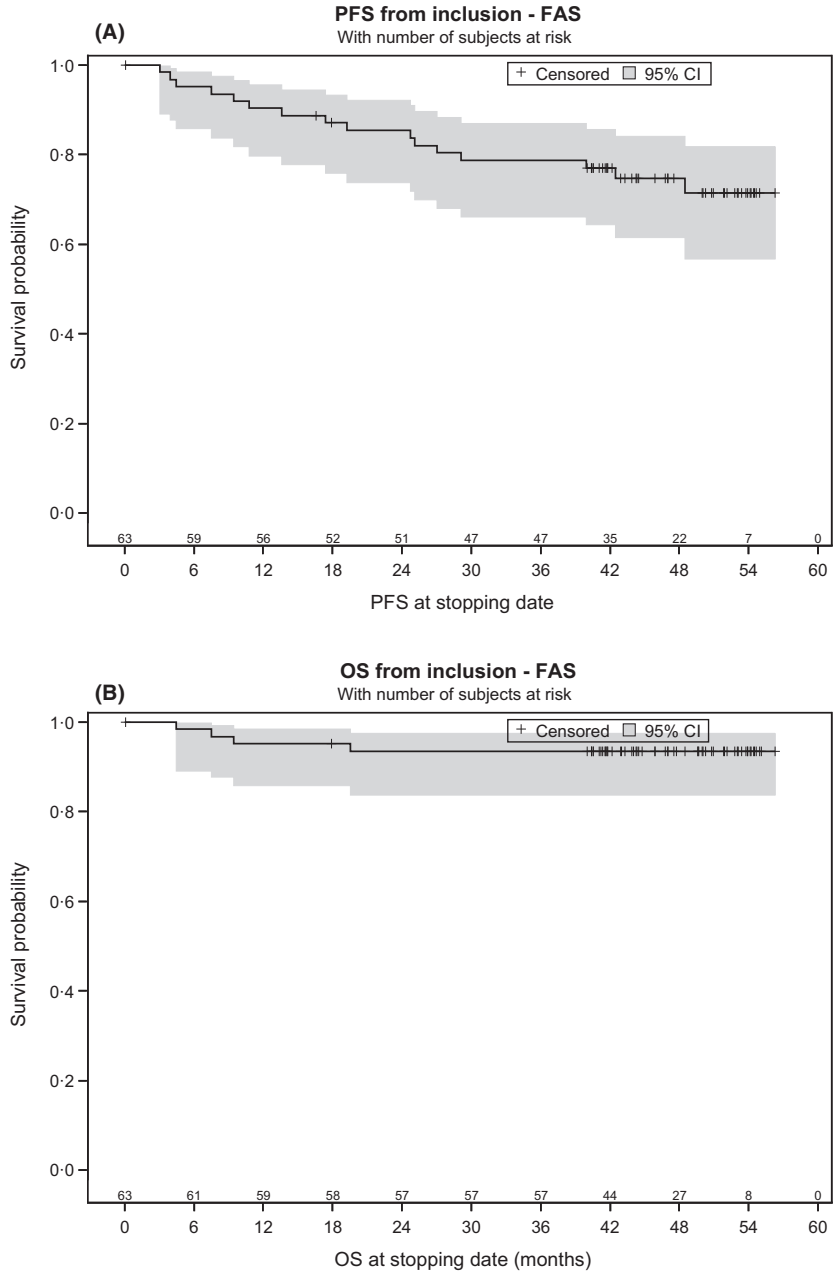

Fig 5. Outcome of the 63 patients included in the study. (A) progression-free survival (PFS) from study entry. (B) Overall survival (OS) from study entry. The number of patients at risk are shown above the relevant timepoint. 95% CI, 95% confidence interval.

et al, 2013), BCL2 inhibitors (Roberts *et al*, 2015), HDAC inhbitors (Chen *et al*, 2015), PI3 kinase inhibitors (Gopal *et al*, 2014), immunomodulatory drugs (Fowler *et al*, 2014; Leonard *et al*, 2015), immunotherapies (Westin *et al*, 2014), or proteasome inhibitors (Evens *et al*, 2014), with or without rituximab, are promising. The role of rituximab maintenance therapy in LTBFL is unclear, with evidence from the RESORT trial indicating that maintenance treatment might be dispensable (Kahl *et al*, 2014).

Based on our findings, we do not recommend the BRIEF schedule of rituximab and bendamustine followed by rituximab maintenance therapy for low-burden FL, even when the FLIPI score is greater than or equal to 2. The monitoring of patients for prolonged lymphopenia and/or low $CD4^+$ T cells, as well as the implementation of a mandatory antimicrobial prophylaxis, such as cotrimoxazole and valaciclovir, and appropriate immunoglobulin support should be considered for such a combination, which will need to be validated in a prospective randomized study. The wealth in novel non-chemotherapeutic agents may also provide attractive alternatives for the management of untreated low-tumour burden FL with unfavourable prognostic factors.

In conclusion, two cycles of bendamustine administered concomitantly with 4 weekly cycles of rituximab may result in a high response rate and PFS. Due to the observed toxicity-related deaths, this regimen may not be recommended in LTBFL. Further research to identify short-term treatments with low toxicity and prolonged PFS should be encouraged for these patients.

Authorship

E.G., A.S, and P.F. designed the study, wrote the protocol, recruited patients, collected data, analysed data and wrote the manuscript. P.B., B.A., K.L., C.F., H.T., C.A., P.S., H.G., N.M., E.N.-V., H.G., B.S., R.B., H.O., and J.F. approved the protocol, included patients, collected data and revised the manuscript. L.X. performed pathology review. O.C. performed the imaging review. All authors approved the final version of the manuscript.

Collaborators

The following collaborators, who do not meet the criteria for authorship, contributed to patient inclusion: Dr Laurence Sanhes, Maréchal Joffre Hospital, Perpignan, France; Dr Samami Kargar, Wallonie Picarde Hospital, Tournai, Belgium; Dr Henry Jardel, Atlantic Britain Hospital, Vannes, France; Prof. Guillaume Cartron, University Hospital, Montpellier, France; Prof. Gilles Salles, Lyon Sud University Hospital, Lyon, France; Prof. Dominique Bordessoule, Dupuytren University Hospital, Limoges, France; Dr Antoine Thyss, Antoine Lacassagne Centre, Nice, France; Dr Nicolas Albin, Mathilde Clinic, Rouen, France; Dr Isabelle Moullet, Clinique de la Sauvegarde, Lyon, France; Prof. Corinne Haioun, Henri Mondor University Hospital, Créteil, France; Dr Delarue, Necker University Hospital, Paris, France; Dr Christophe Fermé, Gustave Roussy Institute, Villejuif, France; Dr Joël Fleury, Public Health Pole, Clermont Ferrand, France.

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Conflict of interest

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