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Efficacy of bendamustine and rituximab in splenic marginal zone lymphoma: results from the phase II BRISMA/IELSG36 study

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Summary

Splenectomy in addition to immunotherapy with rituximab can provide quick and sometimes durable disease control in patients with splenic marginal zone lymphoma (SMZL). However, systemic chemotherapy is ultimately required in many cases. The BRISMA (Bendamustine-rituximab as first-line treatment of splenic marginal zone lymphoma)/IELSG (International Extranodal Lymphoma Study Group)36 trial is an open-label, single arm phase II study designed by the IELSG in cooperation with the Fondazione Italiana Linfomi and the lymphoma Study Association according to Simon's two-stage method. The primary endpoint was complete response rate. Fifty-six patients with SMZL diagnosis confirmed on central revision were treated with bendamustine (90 mg/m^2 days 1, 2) and rituximab (375 mg/m^2 day 1) every 28 days for six cycles (B-R). The overall response and CR rates were 91% and 73%, respectively. Duration of response, progression-free survival and overall survival at 3 years were 93% (95% confidence interval [CI] 81–98), 90% (95% CI 77–96) and 96% (95% CI 84–98), respectively. Toxicity was mostly haematological. Neutropenia grade ≥3 was recorded in 43% of patients; infections and febrile neutropenia in 5·4% and 3·6%. Overall, 14 patients (25%) experienced serious adverse events. Five patients (9%) went off-study because of toxicity and one patient died from infection. In conclusion, B-R resulted in a very effective first-line regimen for SMZL. Based on the results achieved in the BRISMA trial, B-R should be considered when a chemotherapy combination with rituximab is deemed necessary for symptomatic SMZL patients.

Keywords: Splenic Marginal Zone Lymphoma, bendamustine, rituximab, first-line therapy, immunochemotherapy.

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Splenic marginal zone lymphoma (SMZL) (Piris *et al*, 2017) is a rare indolent B-cell lymphoma, involving the spleen, bone marrow (BM) and, frequently, the blood. The disease is often asymptomatic, indolent and a minority of patients never need treatment (Montalbán *et al*, 2012); however, approximately 70% of cases eventually requires treatment. Because of the rarity of the disease, no randomized trials are available for SMZL, and information on therapeutic options are mostly based on retrospective series (Iannitto *et al*, 2004; Else *et al*, 2012; Cervetti *et al*, 2013; Kalpadakis *et al*, 2013; Xing *et al*, 2015; Perrone *et al*, 2016). Splenectomy (Lenglet *et al*, 2014; Olszewski & Ali, 2014), as well as immunotherapy with rituximab (Else *et al*, 2012; Kalpadakis *et al*, 2013), can provide a quick and sometimes durable disease control in patients with SMZL allowing 5-year progression-free survival (PFS) and overall survival (OS) of 48–61% and 65–84%, respectively (Kalpadakis *et al*, 2017). Although both splenectomy and immunotherapy are effective in inducing responses in most patients, they are not curative, and approximately 25% of patients experience poor outcome and survive less than 5 years (Arcaini *et al*, 2006; Montalbán *et al*, 2012). Immunochemotherapy including anthracyclines or purine analogues provide promising results in terms of complete response rate (CRR) and PFS (Orciuolo *et al*, 2010; Cervetti *et al*, 2013; Iannitto *et al*, 2015) even if associated with substantial toxicity.

The combination of bendamustine and rituximab (B-R) has been shown to be highly effective for indolent B-cell lymphomas, including SMZL (Rummel *et al*, 2013; Flinn *et al*, 2014), with manageable toxicity profile (Laurenti *et al*, 2015; Castelli *et al*, 2017). Nevertheless, B-R has never been tested in a prospective trial specifically designed for SMZL. The BRISMA (Bendamustine-rituximab as first-line treatment of splenic marginal zone lymphoma)/IELSG (International Extranodal Lymphoma Study Group)36 phase II trial was launched to investigate the activity and safety of B-R as first-line systemic treatment of non-splenectomized SMZL patients or on those relapsing after splenectomy.

Patients and methods

Study design

The BRISMA/IELSG36 study, a single arm international phase II trial (EudraCT Number 2011-000880-28, NCT02853370) was conducted by the IELSG to investigate on the activity and safety of six courses of bendamustine in combination with rituximab as first-line treatment in patients with symptomatic, untreated SMZL.

Approval by local institutional review boards and/or ethics committees was required before study conductance to comply with the Good Clinical Practice requirements. All participants provided written informed consent before study entry.

Patient population

In previously splenectomized patients, diagnosis was based on spleen histology according to World Health Organization (WHO) criteria (Piris *et al*, 2017). The diagnosis of SMZL in non-splenectomized patients was based on the integration of peripheral blood lymphocyte morphology and immunophenotype (Matutes *et al*, 2008; Piris *et al*, 2017), and was confirmed by central pathology revision before starting protocol treatment. Flow cytometry analysis and biomolecular investigations at baseline and at all time points during treatment and follow-up were centralized in two laboratories, one in Italy and one in France.

Main inclusion criteria comprised: diagnosis of CD20+ SMZL confirmed by central review; active, symptomatic (as described in the next paragraph) and measurable disease; age ≥18 years; Eastern Cooperative Oncology Group performance status ≤2; life expectancy >6 months. Splenectomized patients were eligible if presenting with disease progression. Patients with active hepatitis B infection or active and untreated hepatitis C virus (HCV) infection were excluded.

Criteria for active symptomatic disease.

1 Symptomatic disease in non-splenectomized patients is defined by any of the following: (i) splenomegaly ≥6 cm below left costal margin or progressive painful splenomegaly, not eligible for or unwilling to undergo splenectomy; (ii) haemoglobin <100 g/l and/or platelet count $<80 \times 10^9$/l, and/or absolute neutrophil count (ANC) $<1{\cdot}0 \times 10^9$/l; (iii) enlarged lymphadenopathy or involvement of extranodal sites.
2 Development of lymphadenopathy or involvement of extranodal sites or rapidly rising lymphocyte count in splenectomized patients.
3 SMZL with concomitant hepatitis C infection not responding to or relapsing after interferon ± ribavirin.

Baseline and restaging evaluations and response criteria

At baseline, after three treatment cycles and at the end of treatment, each patient underwent: extensive clinical examination; complete serum biochemistry, including lactate dehydrogenase (LDH) and β2-microglobulin; peripheral blood and BM immunophenotyping; BM biopsy and computed tomography (CT) scans of the chest, abdomen and pelvis. Evaluation of response to therapy and subsequent treatment decisions were based on clinical response, as assessed by the treating physician according to Matutes *et al* (2008). A further centralized response assessment was performed by the study Principal Investigators. Results are presented based on centralized review. Specifically, complete response (CR) required the disappearance of all evidence of disease: (i) regression to normal size on CT-scan of organomegaly (splenomegaly, hepatomegaly and lymphadenopathies); (ii) normalization of the blood counts (Hb >120 g/l; platelet count $>100 \times 10^9$/l; ANC $>1{\cdot}5 \times 10^9$/l and no evidence of circulating clonal B cells); (iii) no evidence or minor (<5%) BM infiltration detected by immunohistochemistry. Partial response (PR) required regression of at least 50% in the measurable disease manifestations and no new sites of disease. This should include: resolution or decrease in spleen size, improvement on cytopenias and resolution or decrease in lymphadenopathy, if present. BM should show a decrease in the level of lymphoid infiltration and improvement of the haemopoietic reserve. At the end of treatment, patients with minimal residual splenomegaly (longitudinal diameter 14 cm) after over 80% shrinkage of initial massive splenomegaly, or small residual abdominal lymph nodes (<2 cm) were centrally reviewed by the Principal Investigators and classified as CR unconfirmed (CRu). Patients classified as CRu with residual abnormalities that remained stable or decreased on imaging studies after 6 months of follow-up were formally coded as CR. No response/stable disease (NR/SD) and progressive disease (PD) corresponded to less than 10% improvement on the disease manifestations, and to deterioration, by increase >50%, of measurable signs of the disease from nadir, respectively. Relapsed disease was defined as reappearance of any measurable sign of the disease after achievement of a CR.

Patients were defined as responders if they had achieved CR, CRu or PR at the end of treatment. Patients without response assessment (due to whatever reason) were considered as non-responders.

Treatment

The B-R regimen consisted of a 28-day cycle, including bendamustine 90 mg/m^2 (day 1–2), and rituximab 375 mg/m^2 (day 1). Bendamustine administration had to be delayed for 7 days if grade 4 haematological toxicity or clinically significant grade ≥2 non-haematological toxicity occurred, and in patients with baseline cytopenias if worsening was recorded. In any case of neutropenia (<1·0 × 10^9/l) at day +28, subsequent cycles were to be given with granulocyte colony-stimulating factor support (filgrastim, lenograstim or pegylated-filgrastim), according to European Organization for Research and Treatment of Cancer guidelines (Aapro *et al*, 2011). Prophylaxis with valaciclovir 500 mg once a day and trimethoprim/cotrimoxazole 800 mg twice a day, twice a week, was recommended for all patients during all treatment cycles.

Patients achieving a CR after three cycles received only one more cycle of B-R, while those achieving a PR received three additional cycles. Patients not achieving at least a PR after three courses were withdrawn from the study.

Follow-up

Follow-up visits were scheduled every 6 months for 5 years, and included extended physical examination, haemocytometer analysis, peripheral blood smear and flow cytometry, serum LDH and β2-microglobulin levels, minimal residual disease (MRD) assessment, serum protein electrophoresis and abdominal ultrasound (CT-scan was performed at discretion of the treating physician). Repeated BM biopsy was scheduled at the end of treatment, and annually for 5 years during follow-up.

Outcome measures

All analyses were made according to the intention to treat principle. The primary study endpoint was the complete response rate (CRR) evaluated after the third B-R cycle and at the end of treatment. Secondary end points were: overall response rate (ORR: CR + CRu + PR), progression-free survival (PFS), duration of response (DOR), event-free survival (EFS) overall survival (OS), toxicity (according to CTCAE v4.0; https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) and risk of histological transformation. Time-related endpoints were defined according to standard criteria (Cheson *et al*, 2007): PFS: measured from time of study entry until lymphoma relapse/progression, or death from any cause; DOR: measured from time of documentation of tumour response to disease progression; EFS, measured from time of study entry until any treatment failure, including disease progression/relapse, histological transformation or initiation of new anti-lymphoma therapy or death from any cause; OS: measured from date of protocol treatment start until date of death irrespective of cause.

Sample size calculation and statistical analysis

Sample size was calculated with a reference CRR of 60% (p0) and an alternative CRR of 80% (p1), an alpha error of 0·05 (two sided) and a power of 0·9. A sample size of 53 evaluable patients was needed. According to Simon's optimal two-stage design, the alternative hypothesis would have been considered not reached if ≤12 CR were observed in the first 19 cases (stage 1) or ≤37 CR were observed in the 53 evaluable cases (stage 2).

Continuous variables were reported as median value, and 2·5–97·5 percentiles, categorical variables as absolute and percentage frequencies, with Clopper–Pearson binomial 95% confidence intervals (95% CI). Median follow-up was estimated as potential follow-up based on the Kaplan–Meier for the censored times (Schemper & Smith, 1996).

The Kaplan–Meier method was used to estimate the survival functions with 95% CI, and survival curves we compared by means of the log-rank test.

Data were collected using the OpenClinica software (community edition ver 3.1.2; OpenClinica, LLC, Waltham, MA, USA) and analysed with Stata v14.0 (StataCorp LLC, College Station, TX, USA).

Results

Patient characteristics

Between December 2013 and October 2014, 78 patients were registered, of which 22 were considered ineligible: 16 for unconfirmed SMZL diagnosis and 6 for other reasons (Fig 1). Fifty-six patients were included in this final analysis; their demographics and baseline clinical features are reported in Table I. Median age at diagnosis was 66 years, and 59% were males. Two patients had prior splenectomy and experienced disease progression within 1 year prior to registration; BM was involved in all patients. No patient had received anti-hepatitis C virus therapy prior to the study entry.

Treatment outcome

Forty-five (80%) out of the 56 evaluable patients completed treatment: 7 (12%) received four cycles because they had achieved CR after three cycles, and 38 (68%) received six cycles. Protocol treatment discontinuation occurred in 11 (20%) patients (Fig 1). Overall, 284 cycles were administered during the study: of these, 241 (85%) were administered at full doses. Bendamustine dose reduction was needed in four patients during cycles 4–6; the relative dose intensity was 0·99 for bendamustine and 0·98 for rituximab.

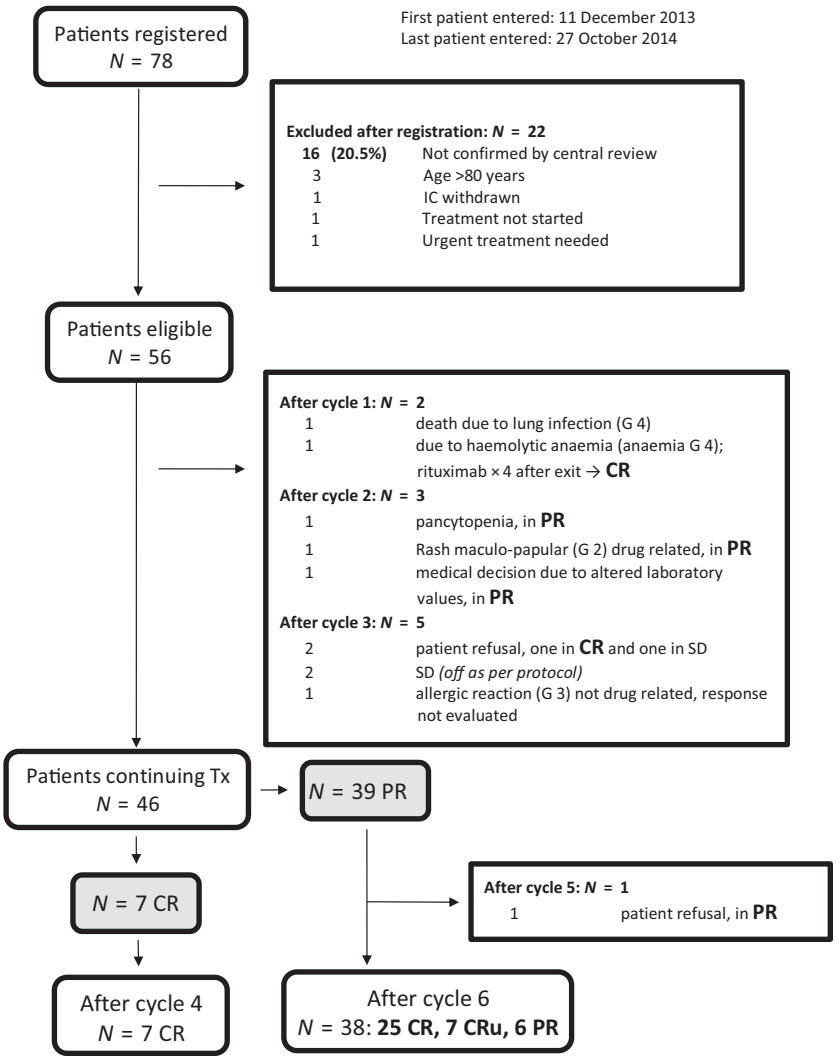

Fig 1. Study flow-chart. CR, complete response; CRu, complete response, unconfirmed; IC, informed consent; PR, partial response; SD, stable disease; Tx, therapy.

Clinical activity

Interim analysis. As per protocol, a centralized interim analysis on the first 19 evaluable patients was performed. CR was reported in 14 patients (74%; 95% CI: 49–91), 1 more than the predetermined activity threshold (13 CR). Further, the ORR was 94% (95% CI: 83–98) and no relevant safety issues were reported.

Final analysis. Response assessment was performed by local clinicians after 3 B-R cycles: at this time point, response was complete in 7 (13%, 95% CI: 5–24) and partial in 39 patients (70%, 95% CI: 56–81), with an overall response rate of 82% (95% CI: 72–92). Importantly, a centralized review of final response was performed, according to the intention to treat principle. Forty-one patients were classified as CRs (34 CR and 7 CRu) (73%, 95% CI: 60–84), with the low margin ≥ of 60% (p0); residual abnormalities of seven CRu patients remained stable or even decreased on imaging studies after 6 months of follow-up, so their response was reclassified as CR. PR and ORR were assessed in 10 patients (18%, 95% CI: 9–30) and 51 patients (91%, 95% CI: 80–97), respectively. Four patients were classified as stable disease (SD) (7%, 95% CI: 2–17) (Table II).

Time dependent outcomes

The median observation time was 32 months (range 2–52). At the time of the present analysis, three relapses have been reported, with a 3-year DOR rate of 93% (95% CI 81–98). PFS events included four disease progression/relapse and 1 death (lung infection).

The estimated 3-year PFS, EFS and OS rates were 90% (95% CI: 77–96), 80% (95% CI, 65–89) and 96% (95% CI: 84–98), respectively (Fig 2). The limited number of events did not enable conclusions to be drawn regarding

PFS stratified by risk group (Intergruppo Italiano Linfomi [IIL] score, $P = 0{\cdot}70$; Haemoglobin-Platelet-LDH-extra-hilar-Lymphadenopathy [HPLL] score, $P = 0{\cdot}11$; Arcaini *et al*, 2006; Montalbán *et al*, 2012). The estimated 3-year PFS and OS of the 10 patients who did not complete the scheduled protocol treatment cycles was 63% and 90%, respectively.

Table I. Characteristics of eligible patients at registration ($N = 56$)

Parameter	*N*	[2·5–97·5 percentile]
Median age, years	56	66 [37–78]
		N (%)
Age >60 years	56	41 (73)
Gender, male	56	33 (59)
ECOG-PS >1	53	2 (4)
Stage IV	56	56 (100)
LDH >ULN	55	22 (40)
B2M >ULN	50	46 (92)
Hb <120 g/l	56	26 (46)
Hb <100 g/l	56	10 (18)
Albumin <35 g/l	52	8 (15)
Platelet count $<150 \times 10^9$/l	56	42 (75)
Platelet count $<80 \times 10^9$/l	56	8 (14)
ALC $>5{\cdot}0 \times 10^9$/l	55	31 (56)
Splenomegaly >6 cm	53	40 (75)
Bone marrow Involvement	56	56 (100)
Thoracic and/or abdominal lymphadenopathy	56	34 (54)
Extranodal involvement	56	2 (5)
Prognostic scores		
IIL (Arcaini *et al*, 2006)	55	
Low (0)		22 (40)
Intermediate (1)		14 (25)
High (2–3)		19 (35)
HPLL (Montalbán *et al*, 2012)	55	
A (1)		28 (52)
B (2)		25 (46)
C (3)		1 (2)

ALC, absolute lymphocyte count; B2M, β2-microglobulin; ECOG-PS, Eastern Cooperative Oncology Group performance status; Hb, haemoglobin; HPLL, Haemoglobin-Platelet-LDH-extra-hilar-Lymphadenopathy; IIL, Intergruppo Italiano Linfomi; LDH, lactate dehydrogenase; SMZL, splenic marginal zone lymphoma; ULN, upper limit of normal.

Toxicity

Adverse events of any grade were reported in 50 (89%) patients, including treatment related grade ≥3 toxicity reported in 38 (68%) patients. Five patients discontinued treatment due to toxicity. The most frequent grade ≥3 adverse events were neutropenia (24, 42·8%), thrombocytopenia (9, 16·1%) and anaemia (5, 8·9%) (Table III; Fig 3).

Non-haematological toxicity was almost exclusively of grade 1–2, with nausea/vomiting, maculo-papular rash and infusion-related reactions being the most frequent adverse events; only five patients experienced grade ≥3 toxicities: infections in two (3·6%) and febrile neutropenia in three (5·3%) (Table IV). Serious adverse events occurred in 14 patients (25%) and lethal toxicity (lung infection) in one (1·8%). Two second solid tumours (one kidney cancer; one malignant peripheral nerve sheath tumour) and one secondary diffuse large B-cell lymphoma were diagnosed at 9,14 and 10 months respectively after entry into the trial. Diffuse large B-cell lymphoma showed BM, peripheral blood and pleural involvement and did not respond to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) treatment; this patient died from progressive disease 7 months later.

Discussion

This international multicentre trial showed that B-R is a safe and active first-line treatment for patients with symptomatic, progressive SMZL. Activity of B-R compares favourably with other previously reported rituximab-chemotherapy combinations in SMZL (Tsimberidou *et al*, 2006; Else *et al*, 2012; Cervetti *et al*, 2013; Rummel *et al*, 2013; Flinn *et al*, 2014; Iannitto *et al*, 2015). In particular, by comparing the results with those of the previous FIL trial investigating the R-COMP (ritiuximab, cyclophosphamide, vincristine, Myocet™ [non-pegylated liposomal doxorubicin, prednisone)

Table II. Treatment response.

Response	Restaging after 3 cycles	% (95% CI)	Final	% (95% CI)
CR	7	13 (5–24)	41	73 (60–84)
PR	39	70 (56–81)	10	18 (9–30)
ORR	46	82 (70–91)	51	91 (80–97)
SD	3	5 (1–15)	4	7 (2–17)
NA	6	11 (4–22)	1*	2 (0–10)
Early withdrawal	1†	2 (0–10)	–	–

95% CI, Clopper–Pearson binomial 95% confidence interval; CR, complete response; NA, not assessed. ORR overall response rate; PR, partial response; SD stable disease.

*1 patient discontinued due to allergic reaction, with no response assessment.

†1 patient in CR after three cycles refused to continue treatment: final response was coded as CR.

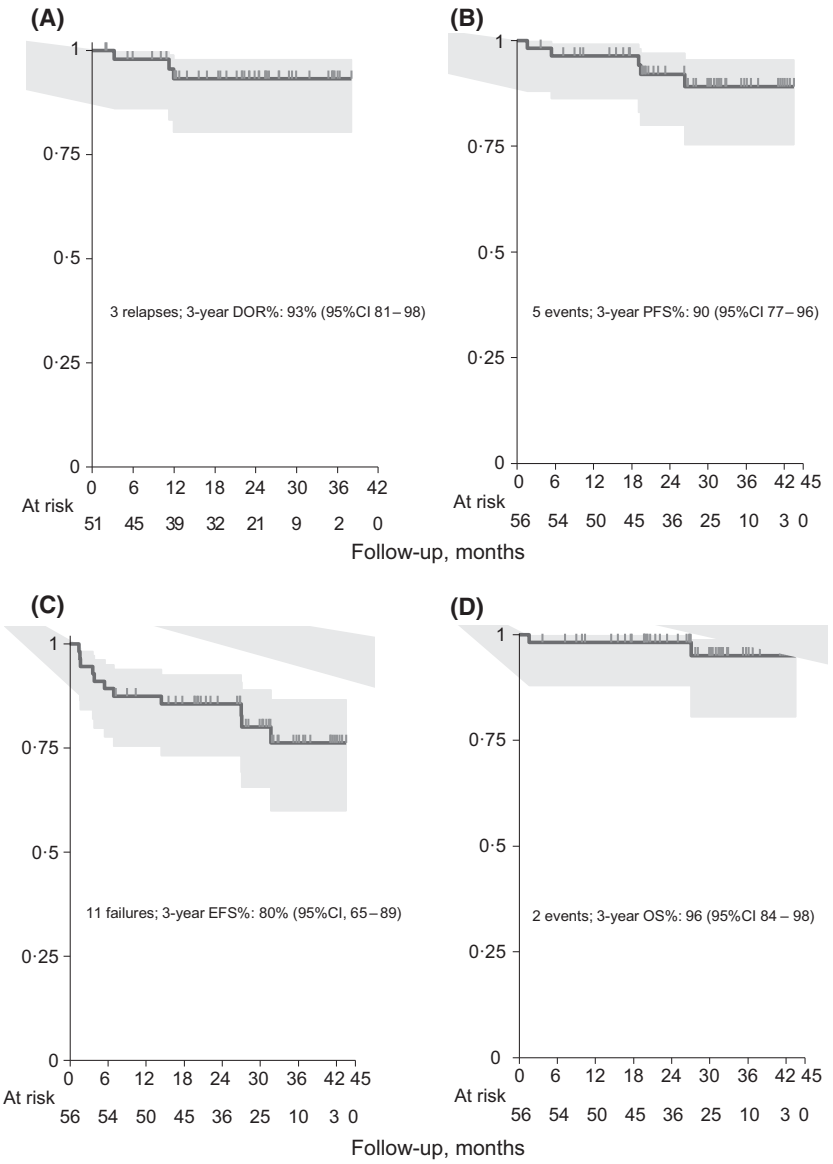

Fig 2. (A) Duration of response (DOR), (B) progression-free survival (PFS), (C) event-free survival (EFS) and (D) overall survival (OS). 95% CI, 95% confidence interval.

regimen (Iannitto *et al*, 2015), it emerged that B-R is associated with a better toxicity profile over R-COMP, with lower rates of severe infections (3·6% vs. 8%) and lethal toxicity (1·8% vs. 8%). Importantly, disease failures were uncommon, with only two deaths at a median follow-up of 32 months, which lead us to recommend this combination as first choice for unsplenectomized patients with symptomatic, progressive SMZL.

Centralization of the diagnostic process and the adoption of rigorous criteria for staging, response assessment and toxicity monitoring allowed the present study to advance the current state of knowledge.

Firstly, at the end of treatment, about half of the cases coded as PR by local investigators were centrally reclassified by the study coordinators as CRu and eventually as CR 6 months later (Cheson *et al*, 2007), in cases where the minimal residual splenomegaly, after over 80% shrinkage of an initial massive enlargement, or small residual abdominal lymph nodes remained unchanged. However, it is impossible to evaluate whether a "normal" spleen still harbours foci of neoplastic cells on the basis of CT or sonographic scans. Therefore, the Matutes criteria of "resolution of organomegaly" (Matutes *et al*, 2008) that was adopted for staging and clinical response evaluation, although satisfactory for routine palliative management of SMZL patients, does not seem to be adequate when comparing the effectiveness of different treatments. Data regarding the evaluation of fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in

Table III. Adverse events grade ≥3 during cycles 1–3, 4 and 5–6.

	Cycles 1–3%	Cycle 4%	Cycles 5–6%
Haematological			
Anaemia	7·1	–	2·5
Leucopenia	25·0	17·4	22·5
Neutropenia	28·6	17·4	27·5
Thrombocytopenia	14·3	2·2	5·0
Fever	1·8	–	–
Febrile neutropenia	1·8	4·3	–
Non-haematological			
Blood and lymphatic system disorders	–	–	–
Cardiac disorders	1·8	–	–
Endocrine disorders	–	–	–
Gastrointestinal disorders	3·6	2·2	–
General disorders and administration site conditions	3·6	–	–
Immune system disorders	1·8	–	–
Infections	3·6	–	–
Investigations	–	–	–
Metabolism and nutrition disorders	1·8	–	–
Musculoskeletal and connective tissue disorders	–	–	–
Nervous system disorders	–	–	–
Renal and urinary disorders	1·8	–	–
Reproductive system and breast disorders	–	–	–
Respiratory, thoracic and mediastinal disorders	3·6	–	–
Skin and subcutaneous tissue disorders	1·8	–	–
Surgical and medical procedures	–	–	–
Vascular disorders	1·8	–	–

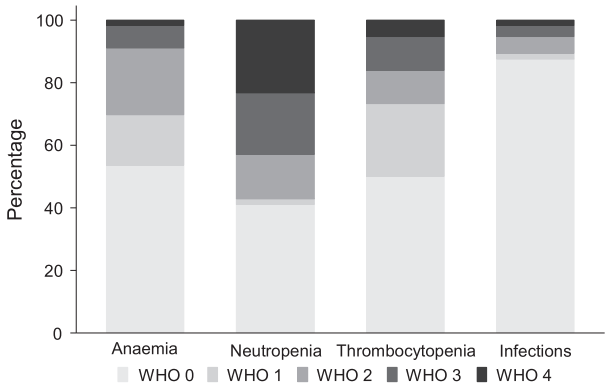

Fig 3. Overall haematological toxicities (World Health Organization [WHO] grades].

SMZL are scanty and may help to assess the response to treatment (Rutherford *et al*, 2008; Carrillo-Cruz *et al*, 2015). On this basis, properly designed trials exploring the sensitivity and accuracy of integration of functional imaging (i.e. FDG-PET or whole-body magnetic resonance imaging) with standard CT scan for SMZL staging and response assessment are warranted.

The second point concerns the reproducibility and concordance of SMZL diagnosis. The diagnosis of spleen tissue is considered the gold standard, but an indirect diagnosis based on BM histology and cytological and immunophenotypic data in peripheral blood is considered acceptable. However, the accuracy and reproducibility of this indirect approach has never been prospectively validated. Our study planned to centralize both flow-cytometry investigations and histological and cytological review as mandatory for study eligibility. After central review, 80% of initial diagnoses were confirmed. Those cases considered inaccurate were either indolent small non-marginal B-cell lymphomas or marginal nodal lymphomas, disseminated.

Lastly, we believe that the clinical results achieved by this study may be of value in clinical practice and pave the way for future prospective trials on SMZL. There are different effective treatment options for SMZL, varying from splenectomy to rituximab as monotherapy or in combination with chemotherapy, but the lack of randomized trials prevents any definite conclusion on which treatment could produce a better outcome.

In this scenario, monotherapy with rituximab, which provides a high ORR and quick symptom relief at the expense of mild toxicity, has cautiously been considered the best option (Dreyling *et al*, 2013). The interesting results with rituximab monotherapy (six weekly single doses) followed by maintenance for one or 2 years (single-dose rituximab every 2 months) in SMZL (Kalpadakis *et al*, 2013) have been recently confirmed in an extended series of 108 patients (Kalpadakis *et al*, 2018). The overall response rate after the end of induction was 92%, including 44% CR, 21% CRu and 27% PR. Maintenance therapy was associated with a significantly better freedom-from progression (FFP) rate: 9-year FFP rates were 76% for patients who received maintenance *versus* 42% for those who did not ($P = 0{\cdot}0006$). Despite the large difference in FFP rate, there was no difference in OS (10-year OS was 89% vs. 92%) for the maintenance *versus* no maintenance comparison, respectively. The high rate of sustained response and the minimal toxicity compares very favourably with the results of the B-R combination reported by Castelli *et al* (2017) and Rummel *et al* (2013), and recommend rituximab monotherapy as an active first line treatment for SMZL patients. However, these studies carry the inherent biases associated with retrospective analyses; moreover, the schedule of treatment with maintenance is currently not approved for SMZL.

Indeed, the use of immunochemotherapy as a first-line treatment for SMZL based on a few retrospective and dated studies (Tsimberidou *et al*, 2006; Orciuolo *et al*, 2010; Else *et al*, 2012; Xing *et al*, 2015) is debated.

However, two large phase III studies on indolent B-cell lymphomas have shed light on the efficacy and toxicity of

Table IV. Non-haematological toxicity. Maximum grade during/after therapy.

Non-haematological AE category	Adverse events Grade 1–2		Adverse events Grade 3–4	
	n (%)	Adverse event term	*n* (%)	Adverse event term
Blood and lymphatic system disorders	1 (1·8)	Disseminated intravascular coagulation	–	
Cardiac disorders	–		1 (1·8)	Angioplasty
Endocrine disorders	1 (1·8)	Diabetes imbalance	–	
Gastrointestinal disorders	22 (39·3)	Nausea/vomiting (14) Diarrhoea (6) Acute abdominal pain (splenic stroke) Constipation	3 (6·3)	Nausea/vomiting Constipation Mucositis oral
General disorders and administration site conditions	12 (21·4)	Infusion reaction (6) Fatigue (6)	2 (3·6)	Infusion reaction Fatigue
Immune system disorders	–		1 (1·8)	Allergic reaction*
Infections	4 (7·1)	Lung infection Vaginal infection Pharyngitis Abdominal infection	2 (3·6)	Lung infection Erysipelas
Investigations	4 (7·2)	Weight loss (2) Creatinine increased Blood bilirubin increased	–	
Metabolism and nutrition disorders	1 (1·8)	Anorexia	1 (1·8)	Tumour lysis syndrome
Musculoskeletal and connective tissue disorders	2 (3·6)	Chest wall pain Bone pain	–	
Nervous system disorders	3 (5·3)	Paresthesia (3)	–	
Renal and urinary disorders	–		1 (1·8)	Urinary tract obstruction
Reproductive system and breast disorders	1 (1·8)	Testicular pain	–	
Respiratory, thoracic and mediastinal disorders	2 (3·6)	Bronchospasm Cough	2 (3·6)	Pleural effusion Pneumonitis
Skin and subcutaneous tissue disorders	8 (14·3)	Rash maculo-papular (7) Pruritus	1 (1·8)	Rash maculo-papular
Surgical and medical procedures	1 (1·8)	Transurethral resection	–	
Vascular disorders	1 (1·8)	Oedema	1 (1·8)	Hypotension

*No relationship with study drugs suspected.

B-R on small subsets of MZL (Rummel *et al*, 2013; Flinn *et al*, 2014). More recently, a phase II study dedicated to non-splenic extranodal MZL at any site or stage, has been shown to be extremely effective, achieving a 100% CRR and excellent short- and long-term outcomes (Salar *et al*, 2017). Interestingly, the incidence of grade ≥3 adverse events during treatment, most commonly haematological toxicities, was similar to that found in the present trial. Finally, Castelli *et al* (2017) reported promising results from a retrospective evaluation of 70 symptomatic SMZL patients treated with B-R: sixty patients (86%) achieved CR and seven (10%) achieved PR. The median duration of remission was 18 months and side effects were generally mild.

The results presented here deal with a first attempt to investigate B-R combination in a prospective multicentre trial focusing on SMZL. In this experience, B-R induced a quick and durable control of the disease with a very high clinical response rate. Moreover, 13% of our patients achieved CR after only three cycles and therefore required a total of only four cycles. Although any direct comparison is not appropriate, the different time-dependent outcomes (DOR, PFS, EFS and OS) and safety profile of B-R combination addressed in this trial compare favourably with those reported using regimens including anthracycline or cladribine (Cervetti *et al*, 2013; Iannitto *et al*, 2015), which leads us to recommend B-R over other rituximab-chemotherapy combinations for patients with symptomatic SMZL. A prospective randomized multicentre trial comparing B-R *versus* R is warranted in order to confirm our results and determine which prognostic subgroup of SMZL benefits most from this immunochemotherapy.

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Authorship contributions

E.I. designed the study, performed research, enrolled patients, interpreted data, performed central diagnostic and clinical responses review, wrote the manuscript; M.B., interpreted

data, and wrote the manuscript; S.A., A.F., designed the study, performed research, enrolled patients, interpreted data, reviewed the manuscript; L.M., performed statistical analysis and wrote the manuscript; M.C. was responsible for patient recruitment and data collection and data checking; C.H., S.M., K.B, R.G, performed research, enrolled patients, interpreted data and reviewed the manuscript; C.T., A.T.G, L.B., performed pathological central review; S.Z., performed centrally flow cytometry and biomolecular analysis; C.S., B.C., C.P., I.A., A.M.L., M.M., G.G., M.G.C, J.D., B.T., A.P., F.R., F.P., enrolled patients, reviewed the manuscript; A.G., reviewed peripheral blood smears and participated in the central pathological review. E.Z., designed the study, interpreted data, reviewed the manuscript; M.F., designed the study, interpreted data, performed central clinical responses review, reviewed the manuscript; C.T., designed the study, performed research, enrolled patients, interpreted data, performed central diagnostic and clinical responses review. All authors approved the final version of the manuscript and submission of the manuscript.

Conflicts of interest

C.H., *Honoraria Amgen, Celgene, Gilead Sciences, Janssen, Novartis, Roche, Takeda; Consulting or Advisory Role, Amgen, Celgene, Janssen, Roche, Janssen. Travel, Accommodations, Expenses, Amgen, Celgene, Roche*. R.G., *Gilead:* Membership on an entity's Board of Directors or advisory committees. E.Z., Celgene, Mundipharma, Roche: Research Funding; Bayer, Celtrion Healthcare, Gilead, Janssen, Sandoz, Takeda: Consultancy; Bayer, Celtrion Healthcare, Gilead Healthcare, Janssen, Roche, Sandoz, Takeda; Celgene, Janssen, Roche: Honoraria, **M.F.,** *Takeda:* Honoraria, Research Funding, Mundipharma, Honoraria and Research funding. C.**T.,** *Janssen:* Consultancy; *Roche:* Consultancy, Honoraria, Research Funding; *Bayer:* Consultancy, Honoraria; *Celgene:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria. The remaining authors declare no competing financial interests.

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