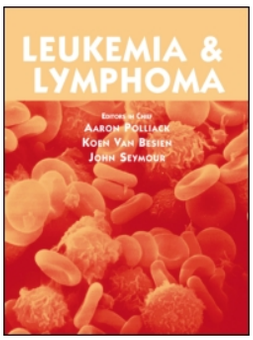

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: http://www.tandfonline.com/loi/ilal20

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To cite this article: Stefano Luminari, Maria Goldaniga, Marina Cesaretti, Lorella Orsucci, Alessandra Tucci, Alessandro Pulsoni, Flavia Salvi, Luca Arcaini, Angelo Michele Carella, Alessandra Tedeschi, Antonello Pinto, Caterina Stelitano & Luca Baldini (2015): A Phase II study of Bendamustine in Combination With Rituximab as Initial Treatment for Patients With Indolent non-follicular non-Hodgkin's Lymphoma., Leukemia & Lymphoma, DOI: 10.3109/10428194.2015.1091934

To link to this article: http://dx.doi.org/10.3109/10428194.2015.1091934

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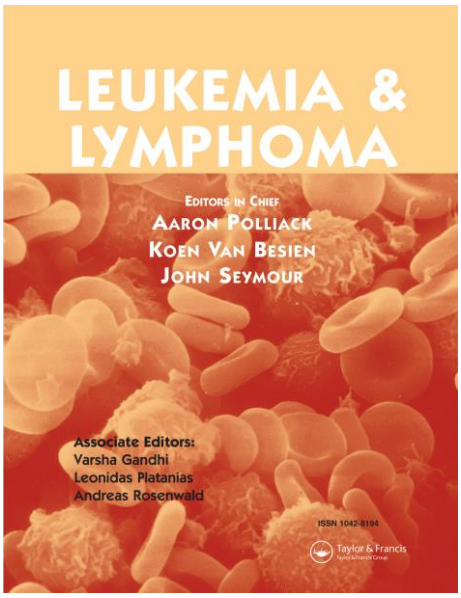
Just Accepted by *Leukemia & Lymphoma*



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doi: 10.3109/10428194.2015.1091934

Abstract

The purpose of this phase 2 study was to determine the activity and safety of 6 cycles of bendamustine and 8 rituximab (RB) as first-line treatment of adult patients with advanced stage non-follicular indolent non-Hodgkin lymphomas (INFL). The primary endpoint was the complete response rate (CRR) with expected CRR of 75%.

Sixty-nine patients were enrolled; median age was 65 years (45-75), 65% were male, 93% of patients had stage IV disease.

Complete and overall response rates were 48% (95% IC 35.6-60.2), and 86% (IC 75.0-92.8).

The most common grade 3/4 adverse events were neutropenia (43%), thrombocytopenia (7%), anemia (4%); whereas the rate of febrile neutropenia was very low (3%). At a median follow up of 22 months (1-43 months), 2-year progression free survival was 89% (IC: 79-95), and 2-year overall survival was 96% (IC: 87-99).

RB combination is active and well tolerated in patients with advanced stage previously untreated INFL.

A Phase II study of Bendamustine in Combination With Rituximab as Initial Treatment for Patients With Indolent non-follicular non-Hodgkin's Lymphoma.

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Abstract word count: 150

Text word count: 3786

Number of tables: 3

Number of Figures: 2

Number of references: 23

Running head: Bendamustine and rituximab for INFL.

Keywords: Indolent non-follicular lymphomas, chemotherapy, bendamustine, rituximab.

ABSTRACT

The purpose of this phase 2 study was to determine the activity and safety of 6 cycles of bendamustine and 8 rituximab (RB) as first-line treatment of adult patients with advanced stage non-follicular indolent non-Hodgkin lymphomas (INFL). The primary endpoint was the complete response rate (CRR) with expected CRR of 75%.

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RB combination is active and well tolerated in patients with advanced stage previously untreated INFL.

INTRODUCTION

Non-follicular indolent non-Hodgkin lymphomas (INFLs) are mature B-cell neoplasms that encompass a heterogeneous group of lymphoid malignancies, including small lymphocytic

(SLL), lymphoplasmacytic (LPL/IC), and marginal zone lymphomas (MZL) [1]. INFLs are slow-growing tumors that typically affect the older population and are characterized by a prolonged natural history with a median survival of up to 10 years [1]. Standard treatment does not differ among INFL subtypes and ranges from a “wait and see” approach for patients with low tumor burden to systemic chemotherapy for symptomatic patients [2-9]. As in follicular cell lymphomas or chronic lymphocytic leukemia (CLL), chemoimmunotherapy combining rituximab with alkylating agents or purine analogues represents the most widely accepted diffuse treatment option [10-12].

The Fondazione Italiana Linfomi (FIL, former “Intergruppo Italiano Linfomi”) conducted several studies on INFL to assess the role of anthracyclines in a randomized phase III trial [11] and the activity of fludarabine in combination with cyclophosphamide (FC) in a phase II study [13]. More recently, the activity of FC combined with rituximab (FCR) followed by rituximab maintenance was investigated in a further trial [12]. This study demonstrated that FCR was very active in INFL, with an overall response rate (ORR) of 89.1%, a complete remission rate (CRR) of 67.4% and a substantial 3-year progression-free survival (PFS) of 90.1%. Despite its impressive antitumor efficacy, the acute toxicity profile of the FCR combination as well as the risk of secondary malignancies associated with fludarabine-based regimens represent major concerns [12], stimulating the search for safer and equally active regimens.

Recently, bendamustine was shown to be a very active agent in B-cell tumors and when combined with rituximab (R) as a front line treatment of indolent lymphomas, was resulting at least as active but by far less toxic than R-CHOP [14,15]. In 2011 FIL, launched the INFL09

phase II trial, aimed at assessing activity and safety of rituximab and bendamustine (RB) combination as upfront therapy for patients with advanced INFLs.

DESIGN AND METHODS

Study design

We designed a prospective, multicenter, open-label, single-arm, phase II trial aimed to determine the activity and safety of a chemoimmunotherapy with 6 courses of bendamustine in combination with 8 doses of rituximab in patients with advanced untreated INFLs (INFL09, EudraCT number: 2010-019248-37, ClinicalTrials.gov Id: NCT01929265). The primary study endpoint was the CRR and the secondary endpoints were the partial response (PR) rate, ORR, safety, overall survival (OS) and PFS.

The study was conducted in 20 centers in Italy between February 2011 and March 2012. The study protocol was approved by the ethics committee of each institution. All patients gave written informed consent before treatment start. Data were collected using the Openclinica software (Community edition ver 3.1.2; Openclinica LLC, USA).

Eligibility criteria

Patients aged 18-75 years diagnosed with INFL (including SLL, LPL/IC, and MZL with the exclusion of splenic and primary extranodal MZL) according to the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissue [1], as demonstrated by lymph node~~s~~ and/or bone marrow biopsy, were included. Patient inclusion was based on local immunopathology assessment report as no upfront histology review was

planned. Patients with histologic features consistent with MZL with concomitant involvement of the marrow, and/or spleen, and/or lymph nodes and/or extranodal sites but lacking the diagnostic features of splenic, nodal or extranodal MZL sites were categorized as disseminated MZL.

Additional inclusion criteria were: no previous treatment for lymphoma, stage III-IV disease or stage II disease with more than three involved sites, presence of at least one criteria for the definition of active disease (including systemic symptoms, hemoglobin <10 g/dL, platelets <100 x 10^9/L, diffuse bone marrow infiltrate, lymphocyte doubling time <12 months in leukemic cases, bulky disease > 7 cm). Patients had to have adequate hepatic, renal, and cardiac function (left ventricular ejection fraction (LVEF)≥45% at bidimensional echocardiogram), absolute neutrophil count (ANC) ≥1 x 10^9/l and platelet count ≥75 x 10^9/l, unless due to bone marrow involvement by lymphoma; an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and a life expectancy >6 months.

Study treatment

Eligible patients were treated with 6 courses of RB combination, followed by 2 rituximab doses. Each cycle was administered every 28 days and consisted of rituximab 375 mg/m^2 i.v. on day 1 (cycle 1 to 8), and bendamustine 90 mg/m^2 i.v. on days 1-2 or 2-3 (cycle 1 to 6) according to institutional/patient/physician choice. During cycle 1 rituximab could be administered on day 8 to prevent tumor lysis syndrome. At the end of the fourth RB course, patients were evaluated for tumor response; patients with progressive disease (PD) were considered as treatment failure, study protocol had to be discontinued, and adequate salvage therapy was administered according to local practice. Patients without evidence of disease progression completed the planned treatment. One month after administration of

the last rituximab dose, patients had to be evaluated for tumor response. The delivered dose intensity (DI) was calculated according to Hryniuk, taking into account also rituximab [16].

During the follow-up phase, patients were evaluated for tumor response at months 6, 12, 18 and 24.

Concomitant medications for supportive care and for medical conditions other than lymphoma were permitted, as clinically indicated. Cotrimoxazole and antifungal prophylaxis was mandatory. Antiviral prophylaxis including acyclovir was allowed but not mandatory.. For HBcAb positive patients, prophylaxis for hepatitis B reactivation with lamivudine 100 mg/die was mandatory from the start of the treatment until one year after the end of the treatment.

Efficacy assessments

Tumor response was defined according to the 2007 revised version of Cheson's criteria [17]. In case of initial bone marrow involvement, the procedure had to be repeated at the end of treatment; if not done patients could not be defined as complete remission (CR). Response was assessed locally and centrally reviewed blinded of patients outcome.

Survival and toxicity

The OS was defined as the time from study entry to the last observation or death from any cause. Patients who have not died at the time of the final analysis were censored at the date of the last contact.

The PFS was defined as the time elapsed from study entry to the time of documented disease progression, relapse, or death from any cause. Responding patients, patients who are lost to follow up, those who withdraw the consent or drop-out due to adverse event were censored at the date of last available assessment. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 3.0, http://ctep.cancer.gov/reporting/ctc.html) and reported on a patient basis.

Statistical analysis

The safety analysis included all enrolled patients who received at least one dose of study agent and efficacy analysis was conducted on all eligible patients as per intention to treat principle.

The primary objective of the study was to demonstrate clinical activity of RB regimen in terms of CR rate. Initial study assumptions were based on response rates observed in indolent lymphomas in previous studies [13,12]. The median expected CR rate for advanced stage INFLs with the same characteristics treated with standard rituximab plus chemotherapy was estimated to be 60% (p0). The INFL09 study was designed with the hypothesis to increase CR rate to 75% (p1). Considering a two-tailed statistical test with an alpha error of 0.05 and a statistical power of 80%, 67 patients were required at the end of the study and at least 47 CRs observed to confirm the initial hypothesis. Considering a drop-out of 10%, the final accrual was planned at 69 cases. The study was initially designed with a Simon's 2 stage design requiring at least 18 CRs among the first 27 treated patients.

RESULTS

Patient characteristics

Between February 2011 and March 2012, 72 patients with INFLs were consecutively enrolled at 20 Italian institutions. Three patients were subsequently excluded due to major violation of inclusion criteria (one patient with mantle cell lymphoma and one with follicular lymphoma (FL) following local histology review) or to consent withdrawal (one patient). The main clinical and hematological characteristics of the 69 accrued patients are summarized in Table I. The main reasons for starting treatment were diffuse bone marrow involvement (38%), hemoglobin less than 10 g/dL (33%) and systemic symptoms or rapid disease progression (22%). According to local pathology assessment, patients had LPL/IC in 32 cases, SLL in 17 and MZL in 20 cases. Pathology reports were subsequently reviewed with available clinical data being accurate enough to confirm the initial diagnosis in 54 (78%) cases (26 LPL/IC, 12 SLL, 16 MZL); unconfirmed cases were reclassified as SLL (1 case), as MZL (2 cases) and as LPL/IC (4 cases) or reported as low grade B cell lymphoma not otherwise specified (LG NOS) (8 cases) being cases with inconclusive immunohistochemistry details. Among the 18 patients with MZL, 6 cases were classified as nodal MZL and the remaining cases had the features of disseminated MZL.

Overall no HCV positive cases were enrolled; one and 7 patients were included with baseline HBsAg and anti-HBcAb positivity, respectively, and were all being treated with lamivudine prophylaxis.

Fifty-three out of 69 patients received all 6 planned courses of RB followed by the 2 R doses (76.8%) and 59 at least 6 treatment cycles (85,5%). Treatment was prematurely interrupted in 3 patients due to progressive disease (one after cycle 2, one after cycle 4 and one after cycle 6), in 6 due to toxicity (one after cycle 1, one after cycle 2, one after cycle 3 and three

after cycle 4) and 2 due to the discovery of a second malignancy (one after cycle 1 and one after cycle 2) (Figure 1).

Overall, 487 RB cycles were administered during the study. All but 72 cycles were administered on time: median delay was 5 days (range 1 to 42). Rituximab was administered as planned in all but 9 cases for whom the antibody was started after the first cycle (3 patients) or prematurely discontinued due to adverse reaction (6 patients). Dose reductions were adopted in 5 patients and in 14 cycles (3%). Bendamustine was administered as planned in all cases; dose reductions of bendamustine were prompted in 9 patients and in 18 cycles (4%). Despite reported dose reductions, calculated DI was very high being 0.931 and 0.905 for bendamustine and rituximab respectively.

Response assessment

The study was initially designed with a Simon's 2 stage design. However due to the very fast accrual we were not able to stop accrual at the planned stage I. Then due to the absence of safety issues observed with RB combination it was decided to perform a unique assessment of study endpoints with completion of study accrual (69 patients).

Based on the intention to treat analysis and on the local assessment of response, 39 patients achieved CR at the end of therapy (CRR=57%; 95% IC 44-68), and 59 patients had an objective response (ORR=86%; 95% IC 75.0-92.8). After centralized review 6 CR patients were reclassified as PR due to persistence of serum monoclonal component. Revised CR and ORR rates according to Cheson 2007 criteria [17] were 48% (95% IC 35.6-60.2) and 86% (95% IC 75.0-92.8), respectively (Table II).

Analysis of survival

The median follow up at the time of current analysis was 22 months (range 1-43 months). Regarding the definition of PFS, 11 failures were recorded including 7 progressions, 3 relapses and 1 death for severe infection in a patient in CR.

As per OS, 3 patients died, two for progressive disease after 4 and 9 months from enrollment and one due to a severe infection after 3 months from enrollment.

On the basis of the ITT analysis, 2-years PFS was 89% (95% CI: 79-95), and OS was 96% (95% CI: 87-99) (Figure 2).

Toxicity

The safety analysis was available for all 69 patients and for 487 cycles. Overall, the combination of RB resulted manageable and well tolerated.

The recorded toxicity was mainly restricted to the hematopoietic system. Thirty patients (43%) experienced anemia that was graded as severe (Grade ≥ 3) in 3 of them (4%). Neutropenia was observed in 44 patients (63%), of whom 30 (43%) developed a grade 3/4 event. Grade 3/4 febrile neutropenia occurred in 2 patients (3%). Thrombocytopenia was observed in 21 patients (30%), and was graded as severe in 5 (7%); moreover in 5 patients thrombocytopenia was present before treatment start whereas only 1 patient developed severe thrombocytopenia during therapy (cycle 8).

Granulocyte stimulating factors (filgrastim or PEG filgrastim) were administered in 44 patients (64%) and in 152 cycles (31%). Use of G-CSF was described in 17%, 28%, 40%, 48%, 45% and 41% of patients from cycle 1 to 6 and dropped to 17% and 11% at cycle 7 and 8;

the median number of G-CSF doses calculated for filgrastim only was 4 (range 2 to 15). Erythropoietin was administered in 17 patients (25%) and 40 cycles (8%).

A detailed summary of hematological and non hematological events is reported in Table III.

One patient died during treatment due to a severe infection (fungal pneumonitis) after cycle 1. Three cases of secondary malignancy occurred: 1 Merkel skin tumor was diagnosed at cycle 1, 1 prostate cancer and 1 myofibroblastic tumor, both were diagnosed at cycle 2.

Subgroup analysis

Study results were also evaluated by patients subgroups as unplanned analysis. Comparable CR and ORR rates were observed among different histologic subtypes; CR was 56%, 43% and 62% in MZL, LPL/IC and SLL subtypes, respectively, without statistically significant differences (Table II); ORR was 72%, 96% and 92% in MZL, LPL/IC, SLL with lower rates observed for MZL cases (P=0,017). Two-year PFS was 82% (95% IC 55-94), 97% (95% IC 79-99) and 91% (95% IC 51-99) in MZL, LPL/IC and SLL subtypes, respectively, again with an inferior PFS observed for MZL cases (p=0.0061).

DISCUSSION

The results of the INFL09 phase II trial demonstrated that bendamustine in combination with rituximab is an active and well tolerated regimen for patients with advanced stage symptomatic and untreated INFLs. Unfortunately, with the observed CR rates of 48% we missed our ambitious primary aim to show a 75% CR rate; however, considering the 86% ORR and the 2-year PFS of 89%, our results are in line with those from other studies

investigating the RB combination or different fludarabine-based regimens [12,13]. In terms of safety, RB was associated with a 43% of grade 3/4 neutropenia with negligible rates of febrile neutropenia and infectious events, so confirming the favorable toxicity profile previously reported for this combination [18].

Since introduction of bendamustine, the RB combination has progressively been imposed as a standard approach for indolent non Hodgkin lymphoma and as an excellent alternative to other existing regimens. Differently from CLL and FL, randomized trials supporting this choice in INFL are missing and treatment decisions for this subset of patients mainly rely on results of phase II trials or are extrapolated from results achieved in phase III studies also including other indolent lymphomas.

Before availability of bendamustine, initial treatment of patients with INFL was mainly based on fludarabine- or alkylator-based regimens [3]. This approach changed after the introduction of rituximab that was added to chemotherapy to boost anti-lymphoma activity of the various chemotherapy platforms [12]. As observed for CLL [19], excellent results were achieved with the FCR immunochemotherapy that was also studied by our group in a phase II study on 46 patients with INFL. By taking into account previous treatment outcomes for INFL, introduction of the FCR combination allowed a CR rate increase to 67.4% as compared to 29.4% and 40.6%, usually achievable with alkylating agents or FC regimens, respectively [11,13].

Looking at the best results obtained with FCR combination and despite a formal comparison is not appropriate, current data from the INFL09 failed to suggest a superiority of RB but can be used to support that the RB regimen has a similar anti-lymphoma activity to FCR.

In addition, patients treated with fludarabine-based regimens displayed substantial rates of hematologic adverse events, mainly severe neutropenia and/or febrile neutropenia as well as infectious complications. These patients were also shown to be at significant risk of developing secondary malignancies, including myelodysplastic syndromes or acute leukemia, and solid tumors [20]. Furthermore, use of fludarabine has been acknowledged as a predictor for poor stem cell mobilization [21].

The INFL09 was specifically designed to study RB combination in INFL and results should be compared with those from other studies investigating the same combination in indolent lymphomas. In the StiL group trial [14], patients with previously untreated indolent and mantle cell lymphoma were randomized to RB versus R-CHOP. At median follow-up of 45 months median PFS was significantly longer in the RB group than in the R-CHOP group (69,5 months versus 31,2 months; p<0,0001) and RB was better tolerated than R-CHOP. The ORR did not differ between the treatment groups; however, the rate of CR was significantly increased in patients in the RB group (40% versus 30%; p=0,021). Although the most frequent histotype for the Stil trial was FL, other indolent lymphoma subtypes were enrolled, including MZL (13%), LPL/IC (8%) and SLL (4%). RB activity was similar across all histological subgroups with the only exception of MZL for which both RB and R-CHOP resulted in a similar median PFS. Toxicity of RB was mainly hematological with 29% rate of grade 3/4 neutropenic events.

In the BRIGHT phase 3 randomized study, RB was compared with R-CHOP or R-CVP [15] for the initial treatment of patients with indolent and MCL. In this study BR therapy was non inferior to the standard therapy in terms of CR rate (31% and 25% in the BR and in the standard-therapy treatment group, respectively) (p=0,0225). Similar to what observed in the

Stil study, toxicity of RB was mainly hematological with 39-49% of grade 3/4 neutropenic events.

Finally, a prospective phase II trial has been carried out by the GELTAMO group [22] in untreated patients with CD20 MALT lymphoma requiring systemic therapy. Patients were treated with RB regimen; at the end of treatment, ORR was 100% with a CR rate of 98%.

The rate of grade 3/4 neutropenic event was 20% with a 5% rate of febrile neutropenia.

With the exception of the outstanding results of the GELTAMO trial, in our study we were able to confirm that activity of RB combination in INFL is high and can be set at 30-40% and at 80-90 % when measured in terms of CR or of ORR, respectively. Differently from the other studies our series was characterized by the highest rates of severe neutropenia and by a high rate of G-CSF use increasing to a maximum rate of 48% at cycle 4.

These rates are closer to the ones observed in patients with CLL [23] but cannot be clearly explained by the characteristics of our patients. Looking at the very low rate of infectious complication observed in our study and confirmed by the main published series, however, hematologic toxicity with RB is confirmed as highly manageable.

Finally in order to put our results in the right context major limitations of the study should be acknowledged. The major problem with our study is with the initial assumptions of a 75% CR rate with RB that is 15% increase from a H0 of 60%. When the study was designed data on the activity of RB were not fully available and considering the superiority versus R-CHOP observed in the Still trial it was hypothesized that similar improvement could be observed if FC-R was used as a comparator. H0 of 60% was defined using our previous experience with FCR on the same patient population [12]. With additional data from the Still study and with

the Bright study results it was then clear that superiority of BR activity over the standards is not a realistic goal. If we had to design the INFL09 study today we would have been much more conservative modifying both H0 and H1 of the study.

Second, while, inclusion of different histological subtypes might be regarded as a shortcoming of the present study, it is to be underlined that such lymphoma entities, although different in terms of pathologic features, share a common clinical presentation, a similar overall prognosis and are currently managed with the same treatment approach. The relatively rare incidence of each distinctive INFL subtype and the lack of straightforward diagnostic criteria to define differential diagnosis makes it difficult to investigate each single lymphoma subtype separately also within large cooperative groups. Nonetheless some differences in terms of ORR and PFS were observed in our study, with relatively lower activity of RB in MZL compared with other subtypes, similar to what suggested by the Stil study (14); however, our data cannot be used to draw any conclusion on a different recommendation concerning the use of RB combination in INFL subtypes. Only studies specifically designed for specific INFL subtypes might clarify if a different activity of RB across INFL subtype is real.

In conclusion the INFL09 results provide new data on the good activity and the good safety profile of RB combination for the treatment of indolent lymphomas and prompt this combination as a valuable option in patients with advanced INFL requiring treatment.

Several first- and second-generation small molecule inhibitors targeting multiple signalling pathways relevant to tumour cell growth are being extensively tested in indolent NHL. These molecules, including PI3K/Akt/mTOR, HDAC, BTK, proteasome inhibitors and immunomodulatory drugs, have shown promising results across a wide range of indolent

lymphoma subtypes. However, these molecules usually display a moderate single-agent activity, as well as due to compensatory pathway activation and acquired resistance mechanisms, should be ideally combined with conventional anticancer drugs, to maximize their therapeutic potentials. Given its substantial anti-lymphoma activity and the absence of overlapping severe extra-haematological toxicities, the RB platform may represent a valuable candidate for combination with such newer target-based agents in non-follicular indolent lymphomas.

FUNDING SUPPORT

We gratefully acknowledge Mundipharma Pharmaceuticals srl Italia for providing a contribution consisting of drug supply (bendamustine) and a financial support to the study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Stefano Luminari has received personal fees from Pfizer and serves in an advisory role for Roche, Celgene and Teva outside the submitted work. Luca Arcaini has received personal fees from Mundipharma and serves in an advisory role for Roche, Celgene and Gilead outside the submitted work. Antonello Pinto has received personal fees from Roche, Celgene, Takeda and Mundipharma and has received non-financial support from Mundipharma, outside the submitted work.

All other author report no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

SL was the principal investigator and takes primary responsibility for the paper. SL and LB designed the study. MG, SL, LO, AT, AP, FS, LA, AMC, AT, AP, CT and LB recruited the patients. MC coordinated patient's recruitment and was in charge of data quality check. SL and LB co-ordinated the research. SL, MC and LB wrote the paper. All authors have critically reviewed and approved the final manuscript.

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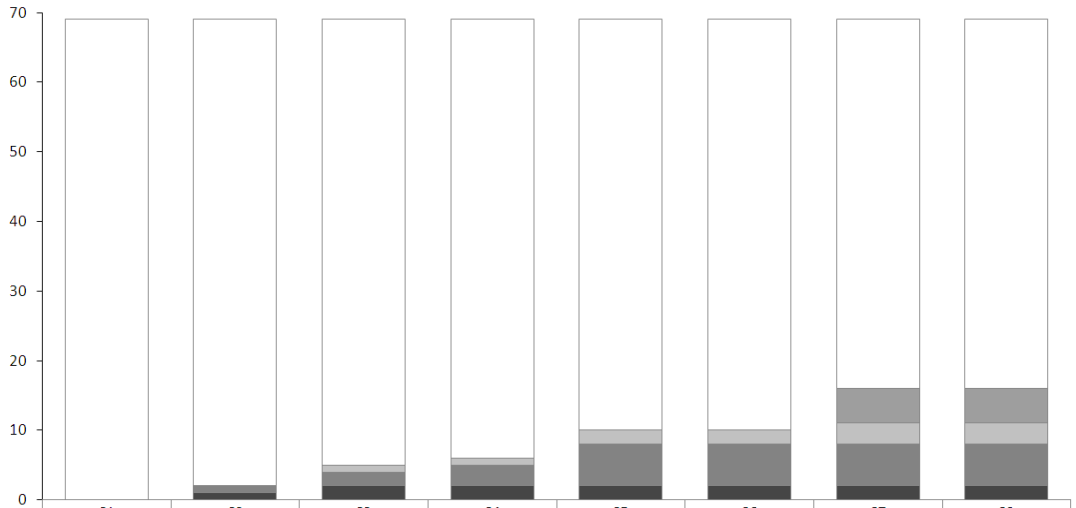
FIGURE LEGENDS

Figure 1. Reason for treatment interruption by cycle in patients who prematurely discontinued RB protocol.



	C1	C2	C3	C4	C5	C6	C7	C8
ongoing	69	67	64	63	59	59	53	53
medical decision	0	0	0	0	0	0	5	5
progression	0	0	1	1	2	2	3	3
toxicity	0	1	2	3	6	6	6	6
second tumour	0	1	2	2	2	2	2	2

Figure 1. Reason for treatment interruption by cycle in patients who prematurely discontinued RB protocol.

Figure 2. OS (a) and PFS (b) of 69 eligible patients

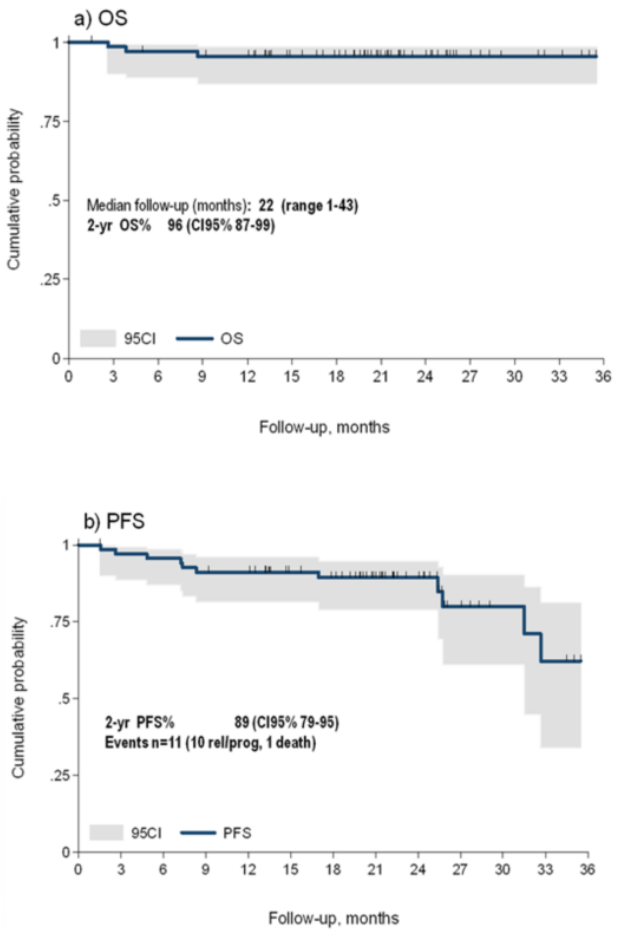


Figure 2. OS (a) and PFS (b) of 69 eligible patients

Table I. Patient characteristics (N=69)

Characteristics	N	%
M/F	45 (65%) /24 (35%)	
Median age	65 (45-75)	
LPL/IC	30	43
MZL	18	26
SLL	13	19
LG NOS	8	12
III-IV stage	68	99
B symptoms	11	16
ECOG PS		
0 - 1	64	93
2 - 3	5	7
LDH>UNL	10	14
B-2-micro>UNL	43	62
Median hb	11.60 (4.6-15.7)	
Median PLT	194 (36-499)	
Median lymphocyte	1.80 (0.3-71.2)	
BM +	64	93
Serum MC	45	66

FLIPI		
0-1	3	4
2	19	28
3-5	47	68

Abbreviations: LPL/IC denotes lymphoplasmacytic lymphomas, MZL denotes marginal zone lymphomas, SLL denotes small lymphocytic lymphoma, LG NOS denotes low grade not otherwise specified, ECOG denotes eastern cooperative oncology group, PS denotes performance status, LDH denotes Lactate dehydrogenase, UNL denotes upper normal limit, hb denotes hemoglobin, PLT denotes platelet, BM denotes bone marrow, MC denotes monoclonal antibody, FLIPI: follicular lymphoma international prognostic index.

Table II. Centrally reviewed response by INFL subtype*.

	ALL CASES (N=69)		MZL (N=18)		LPL/IC (N=30)		SLL (N=13)		LG NOS (N=8)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
CR	33	48	10	56	13	43	8	62	2	25
PR	26	38	3	17	16	53	4	31	3	38
SD	0	0	0	0	0	0	0	0	0	0
PD	6	9	2	11	1	3	1	8	2	25
NE	4	6	3	17	0	0	0	0	1	13
ORR	59	**86**	13	**72**	29	**96**	12	**92**	5	63

*INFL subtype was reclassified after review of pathology reports.

Abbreviations: CR denotes complete remission, PR denotes partial remission, SD denotes stable disease, PD denotes progressive disease, NE denotes not evaluable, ORR denotes overall response rate, LPL/IC denotes lymphoplasmacytic lymphomas, , SLL denotes small lymphocytic lymphoma, MZL denotes marginal zone lymphomas, LG NOS denotes low grade not otherwise specified.

Table III. Summary of grade 3/4 adverse events reported in the trial and of grade 1/2 events reported in more than one patient (*).

HEMATOLOGICAL TOXICITY (N=69)	1/2	%	3/4	%
Anemia	27	39	3	4
Leucopenia	13	19	21	30
Neutropenia	14	20	30	43
Thrombocytopenia	16	23	5**	7
Febrile Neutropenia	-	-	2	3

** In 5 patients thrombocytopenia was present before treatment start and only 1 patient developed severe thrombocytopenia during therapy

NON HEMATOLOGICAL TOXICITY (N=69)	1/2	%	3/4	%
NEUROLOGY				
Syncope	1	1	1	1
MUSCULOSKELETAL/SOFT TISSUE				
Bone pain / pain	5	7	-	-
Muscle weakness	6	9	1	1
CONSTITUTIONAL SYMPTOMS				
Chills	2	3	-	-
Weight loss	-	-	1	1
Fever	14	20	-	-
GASTROINTESTINAL				
Constipation	9	13	-	-

Anorexia	3	4	-	-
Diarrhea	4	6	-	-
Taste alteration (dysgeusia)	3	4	-	-
Heartburn/dyspepsia	2	3	-	-
Mucositis oral / Mucositis	3	4	-	-
Nausea	15	22	2	3
Vomiting	6	9	1	1
PULMONARY/UPPER RESPIRATORY				
Cough	2	3	-	-
Pneumonia/respiratory infection	-	-	1	1
INFECTION				
Infection	9	13	1	1
CARDIAC GENERAL				
Myocarditis	-	-	1	1
DERMATOLOGY/SKIN				
Rash	12	17	2	3
SECONDARY MALIGNANCY				
Secondary maglinancies	-	-	2	3
LYMPHATICS				
Edema: limb	2	3	-	-
VASCULAR				
Thrombosis/thrombus/embolism	1	1	1	1
ALLERGY/IMMUNOLOGY				
Allergic reaction/hypersensitivity	1	1	1	1

* Adverse event categories with only one grade 1-2 event and no grade 3-4 were not included in the table