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RESEARCH ARTICLE

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Bendamustine plus rituximab for the treatment of Waldenström Macroglobulinemia: Patient outcomes and impact of bendamustine dosing

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Abstract

Bendamustine and rituximab (BR) therapy is commonly used in the treatment of Waldenström Macroglobulinemia (WM). The impact dose of Bendamustine dose on response and survival outcomes is not well-established, and the impact of its use in different treatment settings is not clear. We aimed to report response rates and survival outcomes following BR, and clarify the impact of depth of response and bendamustine dose on survival. A total of 250 WM patients treated with BR in the frontline

or relapsed settings were included in this multicenter, retrospective cohort analysis. Rates of partial response (PR) or better differed significantly between the frontline and relapsed cohorts (91.4% vs 73.9%, respectively; $p < 0.001$). Depth of response impacted survival outcomes: two-year predicted PFS rates after achieving CR/VGPR vs PR were 96% versus 82%, respectively ($p = 0.002$). Total bendamustine dose was predictive of PFS: in the frontline setting, PFS was superior in the group receiving ≥1000 mg/m^2 compared with those receiving 800–999 mg/m^2 ($p = 0.04$). In the relapsed cohort, those who received doses of <600 mg/m^2 had poorer PFS outcomes compared with those who received ≥600 mg/m^2 ($p = 0.02$). Attaining CR/VGPR following BR results in superior survival, and total bendamustine dose significantly impacts response and survival outcomes, in both frontline and relapsed settings.

1 | INTRODUCTION

Waldenström macroglobulinemia (WM) is an indolent lymphoma characterized by the infiltration of tissues (bone marrow, lymph nodes, and/or spleen) with clonal lymphoplasmacytic cells and consequent monoclonal IgM paraprotein production.[1] With a median age at diagnosis in the seventh decade, patients' comorbidities and performance status become key considerations in treatment choices.

Bendamustine is a cytotoxic agent with structural similarities to both alkylating agents and purine analogues and displays non-cross-resistance with other alkylators.[2] In combination with rituximab, it is a common choice in the treatment of WM. International guidelines recommend its use in both frontline and relapsed settings,[3,4] due to its efficacy and relatively favorable toxicity profile.[5] Response and survival outcomes of bendamustine/rituximab (BR) appear superior compared with rituximab monotherapy,[6] R-CHOP[7] (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and DRC (dexamethasone, rituximab, and cyclophosphamide),[8–10] although definitive randomized data are limited for comparisons with regimens other than R-CHOP. BR is considered to be especially useful (among the chemoimmunotherapeutic options) in patients in need of rapid disease control, or with bulky nodal or extranodal disease.[11,12] As per international consensus recommendations, the recommended dose of bendamustine (in combination with rituximab) in indolent non-Hodgkin lymphoma is 90 mg/m^2 on days 1 and 2 every 4 weeks for 6 cycles in the frontline setting, and 70–90 mg/m^2 on days 1 and 2 every 4 weeks for 4–6 cycles in the relapsed/refractory setting.[13]

Despite its frequent use in WM, questions remain regarding the best use of the BR regimen, including the benefit of achieving deeper responses for improved survival outcome, the optimal bendamustine dose to maximize survival outcome while minimizing toxicity, and its use in the elderly population. Herein, we report the response and survival outcomes of the largest published real-world experience of WM patients following BR therapy, and identify the implications of dose for maximizing favorable outcomes.

2 | METHODS

2.1 | Study design and participants

This analysis included unselected, consecutively treated patients with a confirmed diagnosis of WM according to the Second International Workshop on Waldenström's Macroglobulinemia (IWWM) criteria[14] who received bendamustine with rituximab between September 2010 and May 2020 in frontline or relapsed settings. Data were collected from 17 sites across four countries (Table S1).

The following baseline clinical and biological parameters[15] were retrospectively collected from the time of treatment commencement: blood counts, cross-sectional imaging (for the presence of adenopathy, splenomegaly, and extranodal disease), bone marrow histology, serum protein electrophoresis, total immunoglobulin levels, and Eastern Cooperative Oncology Group performance score (ECOG score). Treatment data collected were: number and types of prior therapies for previously treated patients, year of treatment commencement, center of treatment, number of bendamustine cycles, total bendamustine dose received (in mg/m^2), number of rituximab doses, dose and cycle reductions due to toxicity, and use of granulocyte colony stimulating factor (GCSF). The impact of the following prior therapies on depth of response were assessed: rituximab, purine analogues, Bruton tyrosine kinase inhibitors (BTKi), and autologous stem cell transplant (ASCT) (Table S2).

2.2 | Outcome measures

The primary outcomes were best response, progression free survival (PFS), and overall survival (OS). Depth of response was graded using the modified IWWM-6 response criteria,[16] with response in IgM level measured at 4–6 months following final chemotherapy dose. Major response rate (MRR) included patients who had achieved partial response (PR), very good partial response (VGPR), or complete response (CR). Overall response rate (ORR) also included those who achieved minor response (MR). PFS was defined as the time from commencement of cycle 1 of BR treatment to the earliest event of disease progression (by IWWM criteria[16]), or commencement of next treatment, or death

TABLE 1 Baseline patient characteristics.

Parameter	All patients ($n = 250$)	Frontline ($n = 139$)	Relapsed ($n = 111$)	p
Median age at start of BR (IQR), years	69.0 (62.1–76.0)	69.3 (60.4–76.0)	69.0 (65.2–76.2)	0.25
Male, No. (%)	167 (66.8)	95 (68.3)	72 (64.9)	0.56
ECOG performance score:				0.13
0, No. (%)	80 (32.0)	48 (34.5)	32 (28.8)	
1, No. (%)	123 (49.2)	70 (50.4)	53 (47.7)	
≥2, No. (%)	47 (18.8)	21 (15.1)	26 (23.4)	
Median time, diagnosis to BR start, months	15.6	2.1	76.1	<0.001*
Year of BR commencement:				<0.001*
2010–2015, No. (%)	85 (34.0)	32 (23)	53 (47.8)	
2016–2017, No. (%)	89 (35.6)	53 (38.1)	36 (32.4)	
2018–2019, No. (%)	76 (30.4)	54 (38.9)	22 (19.8)	
Hemoglobin ≤110 g/L, No. (%)	171 (68.4%)	98 (70.5%)	73 (65.8)	0.47
Platelet count ≥100 × 10^9/L, No. (%)	41 (16.4%)	18 (12.9%)	23 (20.7%)	0.09
Median bone marrow infiltration with LPL, %	60	60	60	0.26
Median paraprotein, g/L	23.2	26.5	21	0.049*
Adenopathy present, No. (%)	103 (41.2)	56 (40.3)	47 (42.3)	0.70
Splenomegaly present, No. (%)	54 (21.6)	36 (25.9)	18 (16.4)	0.09*
Extranodal disease present, No. (%)	36 (14.4)	18 (12.9)	18 (16.4)	0.47
Total bendamustine dose, median (range), mg/m^2	900 (70–1200)	1080 (1040–1080)	720 (70–1200)	<0.001*
Total bendamustine dose:				<0.001*
≥1000 mg/m^2, No. (%)	119 (47.6)	81 (58.3)	38 (34.2)	
800–999 mg/m^2, No. (%)	47 (18.8)	33 (23.7)	14 (12.6)	
600–799 mg/m^2, No. (%)	32 (12.8)	13 (9.4)	19 (17.1)	
<600 mg/m^2, No. (%)	52 (20.8)	12 (8.6)	40 (36.0)	
Rituximab doses received:				0.002*
0–3, No. (%)	57 (22.8)	20 (14.4)	37 (33.3)	
4–5, No. (%)	61 (24.4)	39 (28.0)	22 (19.8)	
6 or more, No. (%)	132 (52.8)	80 (57.6)	52 (46.9)	

Note: p values reflect differences between frontline and relapsed cohorts.
Abbreviations: BR, bendamustine/rituximab; IQR, interquartile range.
*Statistical significance reached.

due to disease or treatment. Patients who did not have documented disease progression at the time of data collection were censored on the date of their last recorded hospital contact. OS was defined as the time from commencement of cycle 1 of BR to death from any cause, with living patients censored at the time of last recorded hospital contact.

The primary outcomes were also assessed based on total bendamustine dose and number of rituximab doses received. As per recommendations for bendamustine dose of 70–90 mg/m^2 on days 1 and 2 for 4–6 cycles[13] (i.e., total bendamustine doses of 560 mg/m^2, 720 mg/m^2, 840 mg/m^2, and 1080 mg/m^2, respectively), total bendamustine dose was categorized, for more direct clinical application, into the following dose categories: <600 mg/m^2, 600–799 mg/m^2, 800–999 mg/m^2, and ≥ 1000 mg/m^2. Rates of toxicity related bendamustine (dose/cycle) reduction and GCSF use were assessed. Bendamustine starting dose was at the discretion of the treating physician.

2.3 | Statistical analysis

Survival analysis was undertaken using the Kaplan–Meier method,[17] with survival distributions compared using log-rank testing. Associations between baseline independent and outcome variables were assessed with the Chi-square and Fisher's exact tests for categorical variables, and Wilcoxon–Mann–Whitney test and Kruskal–Wallis ANOVA for numerical variables, as appropriate. Univariable and multivariable binary logistic regressions were performed for attainment of CR/VGPR and for toxicity related bendamustine reduction. Predictors of progression were identified with univariable and multivariable Cox proportional hazard models, stratified according to treatment setting (frontline vs relapsed). Statistical analyses were performed using IBM SPSS Statistics software, version 27.

TABLE 2 Response rates for patients with Waldenström Macroglobulinemia treated with Bendamustine/Rituximab.

Response	Total ($n = 250$)	Frontline ($n = 139$)	Relapsed ($n = 111$)	p value
Major response rate, No. (%)	209 (83.6)	127 (91.4)	82 (73.9)	<0.001
Objective response rate, No. (%)	229 (91.6)	136 (97.8)	93 (83.8)	<0.001
Categorical response, No. (%)				
Complete	22 (8.8)	17 (12.2)	5 (4.5)	0.027
Very good partial	71 (28.4)	49 (35.3)	22 (19.8)	0.007
Partial	116 (46.4)	61 (43.9)	55 (49.5)	0.372
Minor	20 (8.0)	9 (6.5)	11 (9.9)	0.322
Stable disease, No. (%)	17 (6.8)	2 (1.4)	15 (13.5)	
Progressive disease, No. (%)	1 (0.4)	0	1 (0.9)	
Died before assessment, No. (%)	3 (1.2)	1 (0.7)	2 (1.8)	

3 | RESULTS

3.1 | Patient and disease characteristics

A total of 250 patients with WM were treated with BR; 139 patients (55.6%) were treated in the frontline setting, and 111 patients (44.4%) had received one or more prior therapies for WM before receiving BR for relapsed disease (none of this cohort were treated for refractory disease). Baseline characteristics are shown in Table 1. Seven patients with non-IgM-secreting lymphoplasmacytic lymphoma were included in the analysis: five patients had an IgG paraprotein (two treated in the frontline setting and three treated in relapsed setting), and two patients had an IgA paraprotein (one patient treated in each of frontline and relapsed settings). Frontline and relapsed cohorts were similar in terms of sex, age at the commencement of BR, ECOG score, and the following baseline parameters: hemoglobin, bone marrow infiltration with LPL, and presence of adenopathy, splenomegaly and extranodal disease.

3.2 | Depth of response

Overall, 209 patients (83.6%) achieved a major response and 229 patients (91.6%) achieved an objective response. Three patients (1.2%) died of progressive disease during treatment, before response assessment could be undertaken.

Depth of response was significantly superior in frontline versus relapsed cohorts (Table 2): CR/VGPR was achieved in 66 patients (47.4%) versus 27 patients (24.3%), respectively ($p < 0.001$); major responses were seen in 127 patients (91.4%) versus 82 patients (73.9%), respectively ($p < 0.001$); overall responses were obtained by 136 patients (97.8%) versus 93 patients (83.8%) respectively ($p < 0.001$).

Depth of response did not differ within the relapsed cohort based on number of prior lines of therapy (Figure S1A): major responses were seen in: 73.6% of patients (39/53) who had received one prior line, 71.4% (20/28) who had received two prior lines, and 76.7% (23/30) who had received ≥3 prior lines ($p = 0.9$), with CR/VGPR achieved in 26.4% (14/53), 28.6% (8/28), and 16.6% (5/30) respectively ($p = 0.5$). The type of prior therapy also did not impact rates of CR/VGPR, major response or objective response (Figure S1B). Depth of response was unaffected by year of treatment commencement and center of treatment.

On univariable analysis, age, sex, total bendamustine dose, and number of Rituximab doses significantly impacted upon depth of response. Of 203 patients with a baseline ECOG score of 0 or 1, 176 (86.7%) achieved a major response, compared with 33 (70.2%) of the 47 patients with a baseline ECOG score of ≥2 ($p = 0.006$). In the frontline cohort, patients aged <70 years achieved higher rates of CR/VGPR (45/75, 60%) than subjects aged ≥70 years (21/64, 32.8%; $p = 0.001$). Multivariable binary logistic regression – adjusted for sex, ECOG score, bendamustine and rituximab doses, hemoglobin, platelet count, bone marrow infiltration, and extranodal disease – demonstrated older age, treatment in the relapsed setting, and higher baseline paraprotein to be the only significant predictors of non-attainment of CR/VGPR (Table S3).

3.3 | Survival

At a median follow-up of 37 months, disease progression had occurred in 25 patients (18.0%) treated in the frontline setting and 48 patients (43.2%) in the relapsed cohort ($p = 0.008$). Death due to all causes had occurred in 16 frontline patients (11.5%) and 40 relapsed patients (36.0%; $p < 0.001$).

In the frontline cohort, the median OS and PFS were not reached; 2-year and 5-year predicted OS/PFS rates were 94%/89% and 77%/60% respectively (Figure 1A,D). In the relapsed cohort, median OS was 58 months and median PFS was 50 months, with 2-year and 5-year predicted OS/PFS rates of 80%/67% and 43%/42% respectively (frontline vs. relapsed OS: HR 2.8, $p = 0.001$; frontline vs. relapsed PFS: HR 2.43, $p < 0.001$).

The type of prior therapy did not impact on PFS or OS, although there was a trend toward shorter PFS in those who had prior rituximab therapy compared with rituximab naïve patients ($p = 0.087$).

Depth of response was an important predictor of both OS and PFS. As there was no significant survival difference between the CR

and VGPR groups, these groups were analyzed together. Likewise, there was no significant survival difference between the groups who did not achieve an overall response (stable disease [SD], progressive disease [PD], and subjects who died before response was assessable); these groups were therefore analyzed together. Two-year predicted PFS rates were 96% in those achieving CR/VGPR, 82% in those achieving PR, and 49% in those achieving MR (CR/VGPR vs PR, $p = 0.002$); 5-year predicted PFS rates were 71%, 48%, and 31% in the CR/VGPR-, PR-, and MR-attaining cohorts respectively. Median PFS was 53 months in the PR cohort and was not reached in the CR/VGPR cohort. Median OS was 83 months after achieving CR/VGPR, 65 months after PR/MR and 28 months after SD/PD ($p < 0.001$). These differences were maintained when frontline and relapsed cohorts were analyzed separately (Figure 1B,E,F). An ECOG score of ≥2 was associated with worse OS (Figure 1C) and PFS (Figure 1G), with similar differences observed when frontline and relapsed cohorts were analyzed separately. There was no PFS or OS difference between ECOG scores of 0 and 1.

Cox proportional hazards regression models for PFS are shown in Table 3. Univariable analysis demonstrated no impact on PFS of age, sex, hemoglobin, platelet count, paraprotein level, bone marrow infiltration level, or presence of extranodal disease. Factors that significantly impacted on PFS on univariable analysis – ECOG score, depth of response, total bendamustine dose, and number of rituximab doses – as well as age (due to its potential impact on bendamustine dose), were included in a multivariable model. When these variables were adjusted for, ECOG score of ≥2, achievement of PR or less, and total Bendamustine dose of <1000 mg/m^2 (see below) were all independently associated with poorer PFS in the frontline setting, but number of Rituximab doses was not. In the relapsed setting, ECOG score of ≥2, achievement of PR or less, and receiving ≤3 doses of rituximab were all independently associated with poorer PFS.

3.4 | Impact of bendamustine dose on outcomes

Starting bendamustine doses were similar between frontline and relapsed cohorts, with 78.4% and 75.7% of patients, respectively, commencing treatment at a dose of ≥90 mg/m^2 on days 1 and 2 ($p = 0.6$). There was significant variation in bendamustine starting dose choice between centers noted in the frontline cohort; starting dose was independently affected by age and ECOG score. Patients in the frontline cohort received higher total bendamustine doses than those in the relapsed setting, due to higher rates of cycle truncation and dose reduction in the relapsed setting (median total bendamustine dose 1080 mg/m^2 vs. 720 mg/m^2, $p < 0.001$; Table 1).

Total bendamustine dose received, stratified into dose categories (see Section 2), significantly impacted on MRR as well as PFS. In the frontline setting, MRR was highest in the top dose category: 80/81 patients (98.8%) who received ≥1000 mg/m^2 achieved a major response, compared with 27/33 patients (81.8%) who received 800–999 mg/m^2, and 20/25 patients (80%) who received <800 mg/m^2 ($p = 0.001$). CR/VGPR rates in the aforementioned three dose categories were 53.1% (43/81), 45.5% (15/33), and 32% (8/25) respectively ($p = 0.17$). PFS was significantly longer in patients who received ≥1000 mg/m^2 compared with those receiving smaller doses (Figure 1H), including when adjusted for age, ECOG score, and depth of response (Table 3). In the relapsed cohort, there were no significant differences in response (MRR, ORR, or CR/VGPR rates) between the largest three dose categories. Similarly, there was no appreciable PFS difference based on total bendamustine dose if ≥600 mg/m^2 was received (Figure 1I). Those who received total doses of <600 mg/m^2 (i.e., 70 mg/m^2 on days 1 and 2 for 4 cycles, or less) had significantly poorer PFS compared with those who received ≥600 mg/m^2, with 2-year predicted PFS rates of 46% and 78% respectively ($p = 0.004$).

3.5 | Toxicity

Twenty-four frontline patients (17.3%) had toxicity related bendamustine reduction (both dose reductions and cycle truncation) compared with 39 relapsed patients (35.1%; $p < 0.001$); myelosuppression accounted for most of the toxicity related reductions in treatment. Of the 109 frontline patients who commenced treatment at a dose of ≥90 mg/m^2, 20 (18.3%) subsequently underwent bendamustine reduction due to toxicity, compared with 26/84 relapsed patients (31%; $p = 0.04$). Multivariable binary logistic regression analyses for toxicity-related bendamustine dose reduction were performed in both frontline and relapsed settings, and included age, ECOG score, and bendamustine starting dose (≥90 or <90 mg/m^2). The rate of toxicity related dose reduction was affected only by ECOG score in the frontline setting (ECOG score 0–1 vs. ECOG score ≥2: OR 3.63, 95% CI 1.37–9.65, $p = 0.01$), and not by age or starting dose. None of the variables affected rates of bendamustine reduction in the relapsed setting. Rates of GCSF use did not differ between frontline versus relapsed cohorts (30.9% vs. 36.9%; $p = 0.34$); rates of GCSF use also did not differ based on starting doses (32.3% for ≥90 mg/m^2 vs. 38.6% for <90 mg/m^2, $p = 0.43$).

Older subjects received lower total bendamustine doses. In the frontline cohort, median total bendamustine dose was 1080 mg/m^2 among subjects <70 years of age ($n = 75$) and 990 mg/m^2 in the ≥70-year group ($n = 64$) ($p = 0.051$). Of the 17 frontline patients aged ≥80 years, 13 (76.5%) received total bendamustine doses of ≥720 mg/m^2 and 10 (58.5%) received total doses of 1080 mg/m^2. In the relapsed cohort, median bendamustine dose received by subjects aged <70 years ($n = 59$) was 840 mg/m^2 compared with 585 mg/m^2 for those aged ≥70 years ($n = 52$; $p = 0.024$).

Rates of secondary malignancies were assessed. Two patients (0.8%) developed therapy-related myeloid neoplasms (t-MN), diagnosed at three and six years, respectively, after receiving BR; both had also received Fludarabine prior to being diagnosed with T-MN (and, in one case, prior to receiving BR). Rates of new solid tumor diagnoses were comparable pre- and post-BR (4.8% vs 3.6%).

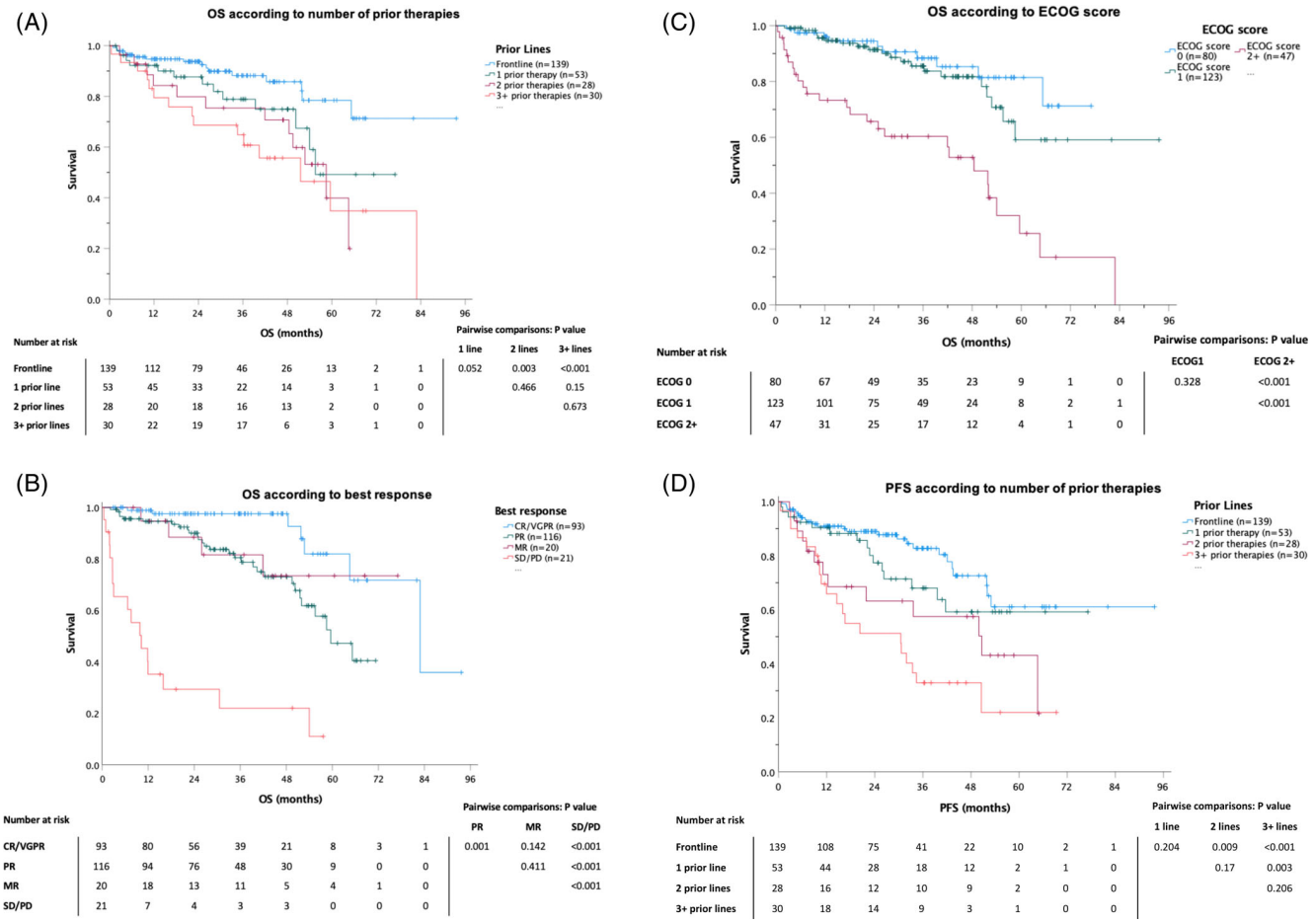

FIGURE 1 Kaplan–Meier estimates following BR therapy. (A) Overall survival (OS) according to number of prior therapies. (B) OS according to best response. (C) OS according to ECOG score pre-treatment. (D) Progression free survival (PFS) according to number of prior therapies. (E) PFS according to best response – frontline cohort. (F) PFS according to best response – relapsed cohort. (G) PFS according to ECOG score pre-treatment. (H) PFS according to total Bendamustine dose received – frontline cohort. (I) PFS according to total Bendamustine dose received – relapsed cohort. CR, complete remission; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response. [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

Herein, we report real-world experience of BR in the treatment of WM in both frontline and relapsed settings, in the largest such series published to date. This analysis reflects the experience of academic institutions as well as secondary care hospitals (Table S1). Prior to this analysis, evidence for the use of BR in WM had been largely obtained from small retrospective series (Table S4). We demonstrate excellent outcomes in unselected patients with WM treated with BR and address outstanding questions regarding the best use of this regimen. Our cohort included elderly patients as well as heavily pre-treated patients (12% of the total cohort received BR after three or more prior lines of therapy). A slightly larger number of patients were treated with BR in the frontline setting (55.6% of total cohort), and this cohort demonstrated superior response rates, longer PFS, and improved tolerability of BR compared with patients treated in the relapsed setting. PFS was found to be dependent on both depth of response achieved and total bendamustine dose received.

The benefit of achieving deeper responses has not always been clear,[18] with a previous retrospective series showing PFS benefit in achieving CR/VGPR following rituximab-based therapy[19] and another series showing no PFS benefit in achieving CR/VGPR following BR.[20] This analysis demonstrated a clear survival benefit with deeper responses, with the achievement of CR/VGPR being associated with longer PFS and OS in both frontline and relapsed settings. While the CR- and VGPR-attaining groups were analyzed together in the survival analyses (as there was no significant survival difference between these groups), it is possible that differences in survival outcome between the groups could emerge with longer follow-up. With attainment of deeper responses with BR, the resulting extension of the treatment free interval could minimize the cumulative burden of treatment toxicity for an individual. We therefore conclude that depth of response is an important treatment goal with BR therapy.

A previous evaluation of frontline patients showed that prospective dose reduction of bendamustine did not adversely affect the attainment of major response.[21] Within the limitations of its

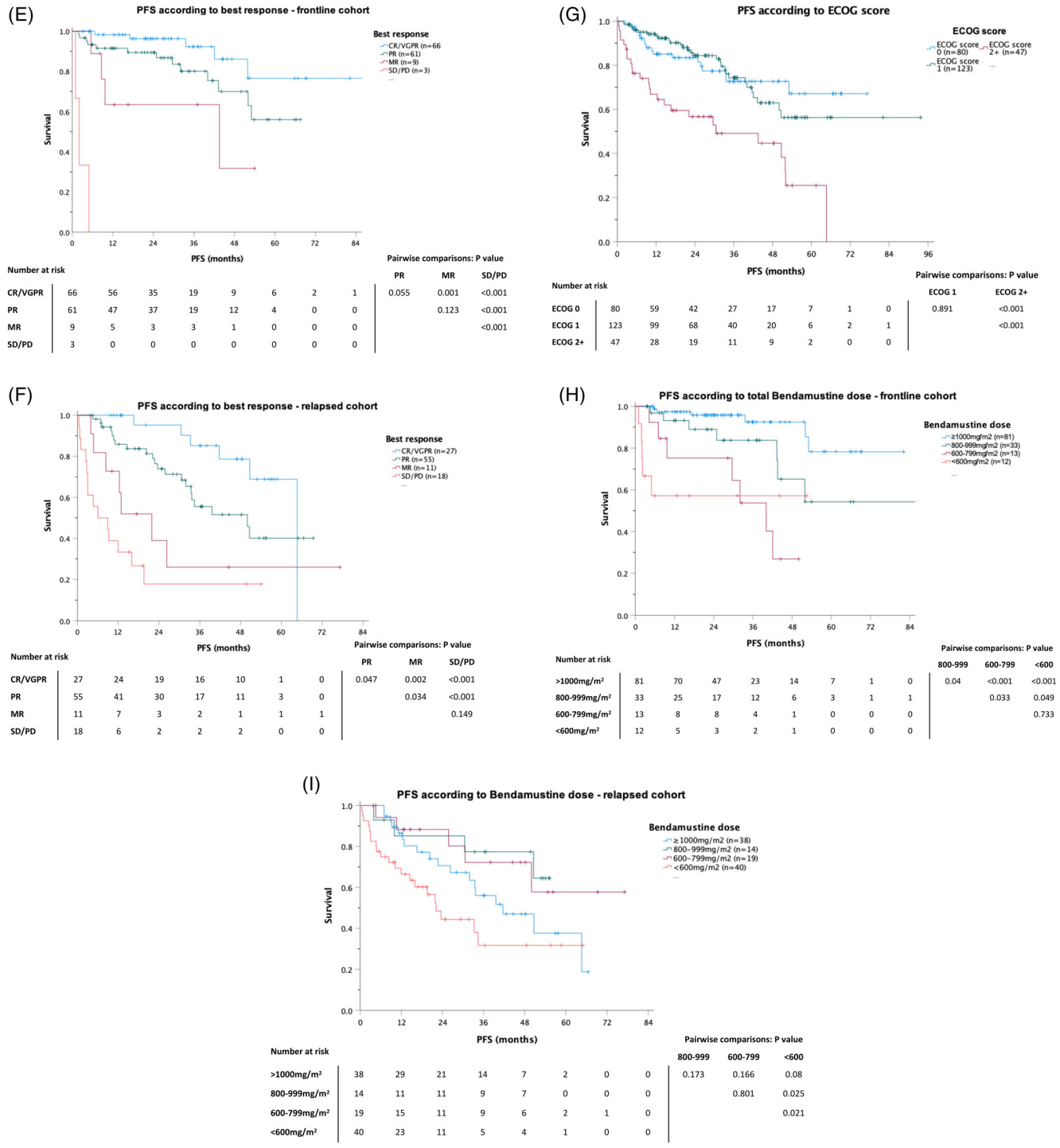

FIGURE 1 (Continued)

retrospective non-randomized context, this study more clearly delineates the bendamustine doses associated with superior response and PFS outcomes. In the frontline cohort, treatment with six cycles of 90 mg/m^2 on days 1 and 2 (i.e., total bendamustine dose of ≥1000 mg/m^2) appeared to produce superior PFS than lower bendamustine doses, even when adjusted for patient age and fitness (i.e., ECOG score); this finding therefore supports a starting dose of 90 mg/m^2 on days 1 and 2 for all frontline patients where possible, aiming to administer a total of six cycles. Conversely, in the relapsed cohort, no additional benefit is gained either in response rates or in PFS when a total dose of >600 mg/m^2 was used, suggesting that 4 cycles of 90 mg/m2 of bendamustine on days 1 and 2 may be sufficient in the relapsed cohort; in cases where this starting dose is not expected to be tolerated, a starting dose of 70 mg/m^2 on days 1 and 2 may be sufficient provided 5–6 cycles are administered. It is important to note that Bendamustine start dose and dose reductions were

TABLE 3 Cox proportional hazard regression models exploring factors associated with higher risk of progression following bendamustine/rituximab.

Frontline cohort					
		Univariable		Multivariable	
Variable	Category	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Sex	Female	Reference		-	-
	Male	2.03 (0.69–5.94)	0.19		
Age (years)[a]		1.03 (0.98–1.08)	0.16	1.01 (0.96–1.05)	0.77
ECOG score	0–1	Reference		Reference	
	2	3.55 (1.56–8.06)	0.03	2.73 (1.16–6.4)	0.02
Depth of response	CR/VGPR	Reference		Reference	
	Partial response or less	3.66 (1.37–9.78)	0.009	4.16 (1.45–11.95)	0.008
Bendamustine dose (mg/m^2)	Total dose[a]	0.997 (0.996–0.998)	<0.001	-	-
	≥1000	Reference	0.053	Reference	0.04
	800–999	2.93 (0.98–8.75)	<0.001	3.26 (1.05–10.17)	0.005
	600–799	9.36 (3.05–28.72)	<0.001	6.79 (1.78–25.94)	0.03
	<600	10.44 (3.13–34.81)		8.54 (1.2–60.49)	
Rituximab doses (No.)	≥6	Reference		Reference	
	4–5	2.24 (0.89–5.66)	0.09	1.04 (0.36–3.01)	0.94
	0–3	5.85 (2.13–16.03)	<0.001	1.34 (0.26–6.98)	0.73
Hemoglobin (g/dL)[a]		0.87 (0.72–1.06)	0.18	-	-
Platelet count ($\times 10^8$/L)[a]		0.996 (0.98–1.013)	0.65		
Paraprotein (g/dL)[a]		1.01 (0.84–1.22)	0.88	-	-
LPL % in bone marrow[a]		0.999 (0.98–1.01)	0.86	-	-
Extranodal disease	No	Reference	0.58	-	-
	Yes	1.347 (0.46–3.93)			
Relapsed cohort					
		Univariable		Multivariable	
Variable	Category	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Sex	Female	Reference		-	-
	Male	1.25 (0.676–2.294)	0.48		
Age[a]		1.01 (0.977–1.037)	0.69	0.998 (0.97–1.03)	0.91
ECOG score	0–1	Reference		Reference	
	2	2.52 (1.391–4.556)	0.002	3.28 (1.67–6.44)	<0.001
Depth of response	CR/VGPR	Reference		Reference	
	Partial response or less	3.44 (1.458–8.141)	0.005	3.83 (1.58–9.26)	0.003
Bendamustine dose (mg/m^2)	Total dose[a]	0.999 (0.998–1.00)	0.004	-	-
	≥1000	Reference		Reference	
	800–999	0.47 (0.159–1.409)	0.18	0.31 (0.1–0.97)	0.04
	600–799	0.52 (0.193–1.404)	0.12	0.45 (0.15–1.34)	0.15
	<600	1.75 (0.926–3.304)	0.08	0.77 (0.29–2.05)	0.61
Rituximab doses (No.)	≥6	Reference		Reference	
	4–5	1.06 (0.46–2.43)	0.89	1.36 (0.56–3.27)	0.5
	0–3	2.05 (1.1–3.82)	0.02	2.82 (1.14–6.97)	0.02
Hemoglobin (g/dL)[a]		0.75 (0.64–0.88)	<0.001	-	-
Platelet count ($\times 10^8$/L)[a]		1.007 (0.984–1.032)	0.55		
Paraprotein (g/dL)[a]		0.96 (0.8–1.15)	0.65	-	-

(Continues)

TABLE 3 (Continued)

Relapsed cohort					
		Univariable		Multivariable	
Variable	Category	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
LPL % in bone marrow[a]		1.004 (0.99–1.01)	0.43	-	-
Extranodal disease	No			-	-
	Yes	1.58 (0.78–3.17)	0.2		

Abbreviation: CI, confidence interval.
[a]Hazards to survival are relative to a unit increase in continuous variable.

at the discretion of individual clinicians, with dose choices being made in accordance with available international consensus guidelines.

Prior studies report that between 34 and 53% of patients were not able to receive the intended six cycles of treatment, with myelosuppression/hematologic toxicity being the most common reason for treatment truncation.[9,20,22,23] In this study, only 25% of patients overall required reductions in bendamustine due to toxicity, with treatment in the relapsed setting and a baseline ECOG score of ≥2 in the frontline setting predicting for higher rates of bendamustine reduction. Although the starting dose (≥90 mg/m^2 vs <90 mg/m^2 on days 1 and 2 of each cycle) was at the clinician's discretion, it had no appreciable effect on the rates of toxicity related bendamustine dose reduction in both treatment settings. Within the median follow-up time of approximately 3 years in this study, rates of secondary malignancy were low following BR therapy, although longer follow-up may reveal higher rates of t-MN.

This study did not evaluate time to best response as the BR regimen is already known to induce later responses: progressive decline in IgM is seen for some months following treatment completion,[20] and the cumulative incidence of objective response increases for up to 18 months after treatment initiation.[22,24] The impacts of MYD88 and CCXCR4 mutations were not assessed in this study specifically; the presence of these mutations has previously been shown to have no impact upon depth of response or progression-free survival following BR.[9,22] This study also did not assess the impact of ISSWM due to lack of available biological data.

In current clinical practice, the choice of bendamustine therapy and dose needs to be considered in conjunction with potential risks of the SARS-CoV-2 pandemic: studies have associated a total bendamustine dose of ≥1080 mg/m^2 with delayed CD4 recovery and prolonged CD4 lymphopenia identified as a risk factor for serious infection complications during follow-up after treatment.[25]

This study presents robust retrospective evidence that the BR combination, with its excellent response rates, long PFS intervals and favorable toxicity profile particularly in the frontline setting, retains an important role in the treatment of WM. Additionally, BR continues to be useful in the treatment of relapsed disease, with evidence from the current study that good responses are achievable even in the extensively pre-treated cohort and irrespective of type of prior therapy. Regarding the use of BR in the present era of increasing availability of Bruton tyrosine kinase inhibitors (BTKi), the BR combination reserves an important role for patients for whom limited treatment duration would be preferred over indefinite therapy, or for patients for whom BTKi are contraindicated; the PFS in frontline patients in this study is indeed comparable to the PFS seen in treatment-naïve patients on Ibrutinib monotherapy.[26] In both frontline and relapsed settings, attaining CR/VGPR results in superior PFS and OS. Total bendamustine dose significantly impacts response and survival outcomes in both frontline and relapsed settings.

AUTHOR CONTRIBUTIONS

Suzanne O. Arulogun designed the research study, collected data, performed statistical analysis, and drafted the paper; Duncan Brian, Harshita Goradia, Aaron Cooney, Tobias Menne, RayMun Koo, Aideen T. O'Neill, Josephine M.I. Vos, Guy Pratt, Deborah Turner, Kirsty Marshall, Kate Manos, Claire Anderson, Maria Gavriatopoulou, Charalampia Kyriakou, Monique C. Minnema, Marie J. Kersten, Kim Linton, and George Follows collected the data; Dima El-Sharkawi, Dipti Talaulikar, Helen McCarthy, and Shirley P. D'Sa reviewed the manuscript; Eirini Koutoumanou performed statistical analysis; Mark Bishton contributed to analysis of design and critically revised the manuscript; Ashutosh Wechalekar designed the research study and critically revised the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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