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RESEARCH ARTICLE

Assessment of fixed-duration therapies for treatment-naïve Waldenström macroglobulinemia

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Abstract

Comparative data guiding initial therapy for Waldenström macroglobulinemia (WM), an infrequently encountered non-Hodgkin lymphoma, are sparse. We evaluated three commonly used rituximab-based frontline regimens: rituximab-bendamustine (R-Benda); dexamethasone, rituximab, cyclophosphamide (DRC); and bortezomib, dexamethasone, rituximab (BDR) in 220 treatment-naïve patients with WM, seen at Mayo Clinic between November 1, 2000 and October 31, 2019. The median follow-up was 4.5 (95%CI: 4–5) years. The R-Benda cohort (n = 83) demonstrated superior overall response rate (ORR: 98%), in comparison to DRC (n = 92, ORR: 78%) or BDR (n = 45, ORR: 84%) cohorts, $p = 0.003$. Similarly, longer progression-free survival (PFS) was evident with R-Benda use [median 5.2 vs. 4.3 (DRC) and 1.8 years (BDR), $p < 0.001$]. The time-to-next therapy (TTNT) favored R-Benda [median, not-reached, 4.4 (DRC) and 2.6 years (BDR), $p < 0.001$). These endpoints were comparable between the DRC and BDR cohorts. Overall survival (OS) was similar across the three cohorts, $p = 0.77$. In a subset analysis of 142 patients genotyped for *MYD88*^{L265P} mutation, the ORR, PFS and TTNT were unaffected by the patients' *MYD88* signature within each cohort. In conclusion, ORR, PFS and TTNT with R-Benda are superior compared to DRC or BDR in treatment-naïve patients with active WM. The patient outcomes with any one of these three regimens are unaffected by the *MYD88*^{L265P} mutation status.

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1 | INTRODUCTION

Waldenström macroglobulinemia (WM) is an indolent, B-cell non-Hodgkin lymphoma associated with monoclonal IgM circulating protein and lymphoplasmacytic marrow infiltration.[1,2] As this infrequently encountered malignancy remains incurable, the current treatment approaches largely focus on disease control. The anti-CD20 monoclonal antibody, rituximab is the cornerstone of frontline therapy of WM, and used frequently as monotherapy or in combination with alkylating agents, proteasome inhibitors (PI) or ibrutinib.[3,4] Rituximab monotherapy has been found to be inferior to combination therapy.[3,5,6] However, there are scant comparative data to guide therapy for patients with treatment-naïve active WM in the absence of randomized controlled trials addressing this important issue. Oral fludarabine has demonstrated superiority to chlorambucil in the frontline setting in a phase 3 trial, but neither agent is considered suitable as primary therapy today, due to the expansion of our therapeutic options with more effective and safer regimens.[7,8] Several noteworthy recent clinical trials in this rare malignancy have combined both previously untreated and relapsed and/or refractory WM patient populations and are not necessarily adequately powered to discern the impact of initial therapies in different clinical settings. Therefore, we attempted to compare the efficacy of the most frequently used rituximab-based fixed-duration anti-WM regimens in routine practice [rituximab plus bendamustine (R-Benda); dexamethasone, rituximab, cyclophosphamide (DRC); and bortezomib, dexamethasone, rituximab (BDR)] to inform clinicians about the benefits and limitations of choosing one regimen over the other.

2 | METHODS

Patients with active WM seen consecutively at Mayo Clinic, Minnesota, Florida, and Arizona campuses who received any one of the three regimens: R-Benda, DRC, or BDR as primary therapy between October 1, 2000 and October 31, 2019 were included in this study. Patients with smoldering WM or with a concomitant diagnosis of AL-amyloidosis were excluded. Our research was conducted in accordance with the Declaration of Helsinki following the approval of the Mayo Clinic institutional review board. The response rates were assessed by the modified Sixth International Workshop on WM Criteria.[9] The overall response rate (ORR) was calculated by measuring the proportion of patients achieving at least a minor response, while major response rate (MRR) was defined as the proportion achieving a partial response or better.[9] Bendamustine in R-Benda was given at 90 mg/m^2 intravenously (IV) on days 1 and 2 (with dose reduction to 70 mg/m^2 for the elderly population) and rituximab at 375 mg/m^2 intravenously on day 1 of the 28-day cycle. The DRC regimen consisted of 21-day courses of dexamethasone IV 20 mg, rituximab IV 375 mg/m^2 on day 1 and oral cyclophosphamide 100 mg/m^2 twice daily on days 1 to 5. Typically, the patients received up-to six cycles of R-Benda or DRC as initial therapy. In the BDR regimen, given for upto 23 weeks, the duration of Cycle 1 was 21 days, while Cycles 2 to 5 were built for 35 days per cycle. Bortezomib was given at 1.3 mg/m^2 IV or subcutaneously (SQ) on day 1, 4, 8, and 11 of Cycle 1, and at 1.6 mg/m^2 in subsequent cycles with dexamethasone at 40 mg on days 1, 8, 15, 22 of the second cycle and beyond, and rituximab 375 mg/m^2 IV was given on day 1, 8, 15, 22 of the second and fifth cycle. The adverse events (AEs) were graded using the National Cancer Institute Common Toxicity Criteria v4.03. The *MYD88*^{L265P} mutation status was assessed using the previously-described allele-specific polymerase chain reaction,[10] with an analytical sensitivity of approximately 1% mutation detection in a wild-type (WT) background.[11] Patients who lacked *MYD88*^{L265P} alteration were categorized as *MYD88*^{WT}. When calculating the event-free survival (EFS), the discontinuation of treatment owing to therapy-related AEs, progression, or death was considered as an event. Progression free survival (PFS), time-to-next therapy (TTNT) and overall survival (OS) were calculated as per the published criteria, using the Kaplan-Meier method with JMP 14.0 software (SAS Institute, Cary, NC).[12,13] The difference between the survival curves was estimated using the log-rank test and a p value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient population

A total of 220 patients with symptomatic previously untreated WM received one of the three regimens as frontline therapy between October 1, 2000 and October 31, 2019. Of these 220 patients, 83 (38%) patients were treated with R-Benda, 92 (42%) patients were treated with DRC while 45 (20%) patients had BDR in the frontline setting. The proportional change in the use of these three regimens, reflecting a gradual change in practice over the duration of the study, is outlined in Figure S1. One hundred and forty-two (65%) patients were evaluated for *MYD88*^{L265P} mutation status (R-Benda, n = 67; DRC, n = 51; BDR, n = 24), and of those, 106 (75%) were noted to harbor this mutation; n = 59 (88%), n = 33 (65%), and n = 14 (58%) patients who were treated with R-Benda, DRC and BDR, respectively, $p = 0.002$. The median time from the diagnosis of symptomatic WM to frontline therapy was 0.6 months (95%CI: 0.5–1.0), 0.6 months (95%CI: 0.2–0.7) and 0.4 months (95%CI: 0.1–0.6) for patients who were treated with R-Benda, DRC and BDR, respectively, $p = 0.74$. The baseline characteristics of the patients are summarized in Table 1. Of 220 patients, a small subset of 23 patients [10%; R-Benda, n = 6 (7%), DRC, n = 12 (13%), BDR, n = 5 (11%), $p = 0.43$] received rituximab maintenance therapy following completion of the induction treatment; the median frequency of rituximab infusion was once in every 2 months (range: 1–3) and median duration of therapy was 1 year (range: 0.2–2).

3.2 | Treatment cycles and dose modifications

The median number of cycles was six (range: 1–6) for R-Benda, six for DRC regimen (range: 1–12) and six for BDR (range: 1–12). The range

TABLE 1 Baseline characteristics and laboratory parameters

Parameter	R-Benda	DRC	BDR	*p* value
Age, median, (range), year	66 (44–87)	65 (36–94)	60 (38–82)	0.14
Sex, Male, n (%)	53 (67)	57 (62)	27 (60)	0.63
Hemoglobin, median (range), g/dL	9.8 (4.6–14.8)	9.5 (5.9–15)	9 (3.6–14)	0.08
Platelets, median, (range), $\times 10^9$/dL	196 (30–580)	181 (12–481)	169 (34–460)	0.37
Involved/uninvolved free light-chain ratio	7.2 (0.7–509)	19 (1–973)	42 (2–411)	0.05
IgA, median (interquartile range), mg/dL	51.5 (2–214)	51 (6–781)	52 (5–205)	0.85
IgG, median (interquartile range), mg/dL	609 (44–3290)	589.5 (5–2630)	452 (232–1960)	0.51
IgM, median (interquartile range), mg/dL	3061 (90–10 000)	3770 (172–10 500)	4280 (927–63 321)	**0.01**
M-spike (g/dL)	2.2 (0.2–7.1)	2.5 (0.2–9)	2.9 (0.4–5.9)	0.13
MYD88^{L265P} mutation, n (%)	59 (88)	33 (65)	14 (58)	**0.001**
IPSS-WM score (n = 97)	N = 49	N = 42	N = 6	0.52
Low risk (%)	18	14	0	
Intermediate risk (%)	39	45	67	
High risk (%)	43	40	33	
LDH (U/L) median, (range)	134.5 (85–338)	154.5 (77–501)	134 (100–180)	0.26
LDH upper limit of normal, >222 U/L, (%)	12.5	20	15	0.19
Beta 2 microglobulin (μg/mL), median, (range)	3.9 (0.8–11.95)	3.2 (1.8–9.09)	3.4 (2.4–13.6)	0.37
Marrow LPL cells, median, % (range)	72.5 (10–100)	65 (10–95)	60 (10–95)	0.93

Note: All bold *p* values are <0.05, i.e. they are statistically significant.
Abbreviations: BDR, bortezomib, dexamethasone and rituximab; DRC, dexamethasone, rituximab and cyclophosphamide; LDH, lactate dehydrogenase; LPL, Lymphoplasmacytic lymphoma; R-Benda, rituximab and bendamustine.

exceeded the traditionally administered (and recommended) six cycles, with two patients in the DRC group and a single patient in the BDR group receiving a total of 12 cycles. The proportion of patients requiring dose modifications was similar in the three cohorts and was 11%, 7% and 7% in R-Benda, DRC and BDR cohorts, respectively, $p = 0.58$. In patients who received R-Benda, nine (11%) patients required modifications to the regimen (reasons for modification included grade three neutropenia in five patients, renal dysfunction in one, grade three fatigue in one and rituximab was permanently discontinued due to hypersensitivity in two patients). In the DRC cohort, six (7%) patients required treatment regimen modifications (grade three neutropenia in three patients, delayed initiation of rituximab in two patients due to markedly elevated baseline IgM, rituximab infusion reaction in one patient, and cyclophosphamide was held for transient hematuria in one patient). The BDR regimen was modified in three (7%) patients (rituximab was omitted due to rituximab-induced allergic reaction in one patient and bortezomib was omitted due to peripheral neuropathy in two patients).

3.3 | Treatment efficacy and endpoints

The median follow-up for the entire cohort was 4.5 years (95%CI: 4.0–5.0); 2.3 years (95%CI: 2.1–3.2) for the patients treated with R-Benda, 6.3 years (95%CI: 5.5–6.5) for the patients treated with DRC and 5.2 years (95%CI: 5.5–6.5) for patients treated with BDR, $p < 0.001$. The patients who received R-Benda achieved an ORR of 98%, with a median IgM reduction of 2585 (122–7030) mg/dL at the time of best response. The ORR was 78% in patients who received DRC, with a median IgM reduction of 2597 (302-9662) mg/dL and it was 84%, with a median IgM reduction of 2590 (517-8051) mg/dL at the time of best response for patients who had received BDR, (Figure 1).

The patients who received R-Benda had a MRR of 96% while the MRR was 53% and 68%, respectively, for patients who received DRC or BDR, $p < 0.001$. The estimated median PFS for the R-Benda cohort was 5.2 years [95%CI: 4.5-not-reached (NR)] and for the DRC cohort and BDR cohort, it was 4.3 years (95%CI: 3–5.9) and 1.8 years (95% CI: 0.8–6.8) respectively, $p = 0.001$, (Tables 2 and S1 and Figure 2(A)). The duration of response (DOR) was NR (95%CI: 4.5-NR) in the R-Benda cohort, but the DRC and BDR cohorts had a DOR of 3.9 years (95%CI: 1.8–6.3) and 3.6 years (95%CI: 1.0-NR), respectively, $p = 0.001$, (Tables 2 and S1). The patients who received R-Benda as primary therapy had a longer TTNT compared to those who received DRC or BDR; the median TTNT was NR (95%CI: 4.5-NR) for R-Benda cohort compared to 4.4 years (95%CI: 3–5.9) for DRC cohort and 2.6 (95%CI: 0.9–6.9) for BDR cohort, $p = 0.002$, (Tables 2 and S1 and Figure 2(B)). The median OS for the entire cohort was NR (95%CI: NR-NR), and the OS did not differ across the three cohorts, $p = 0.77$, (Tables 2 and S1 and Figure 2(C)). At 3 years, 94% of patients were alive in the R-Benda cohort, vs 90% in the DRC cohort as well as in the BDR cohorts. Although the proportion of patients receiving rituximab as maintenance was low and similar across the cohorts (R-Benda: 7%, DRC: 13%, BDR: 11%, $p = 0.43$), in order to assess the impact of induction therapy alone, we performed a subset analysis

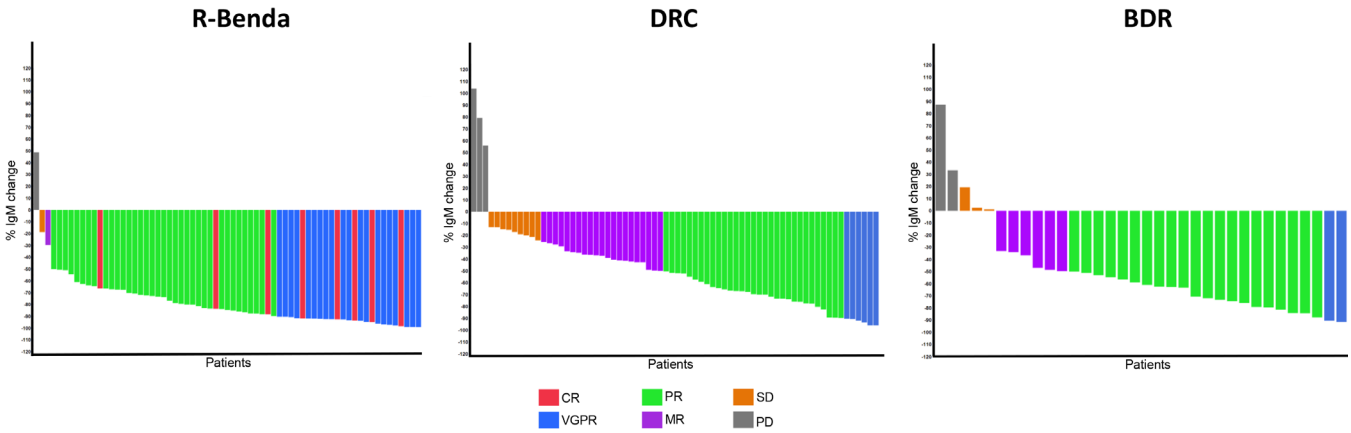

FIGURE 1 Change in serum IgM at the time of best response. Waterfall plot depicting the percent change of serum IgM at the time of best response as compared to the time of treatment initiation. CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease, R-Benda, rituximab and bendamustine; DRC, dexamethasone, rituximab and cyclophosphamide; BDR, bortezomib, dexamethasone and rituximab [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Clinically relevant endpoints based on treatment regimen

Parameters	R-Benda	DRC	BDR	*p* value
Overall response rate, (%)	98	78	84	**0.003**
Major response rate, (%)	96	53	68	**<0.001**
Event free survival, range; years (95%CI)	NR (4.4-NR)	4.3 (2.4–5.8)	1.6 (0.6–5.6)	**<0.001**
Progression free survival, range; years (95%CI)	5.2 (4.5-NR)	4.3 (3.0–5.9)	1.8 (0.8–6.8)	**0.001**
Time-to-next therapy, range; years (95%CI)	NR (4.5-NR)	4.4 (3.0–5.9)	2.6 (0.9–6.9)	**0.001**
Time to best response, range; months (95%CI)	4.5 (3.8–5.1)	5.9 (4.8–7.6)	6.7 (5.1–9.0)	**0.005**
Duration of response, range; years (95%CI)	NR (4.5-NR)	3.9 (1.8–6.3)	3.6 (1.0-NR)	**0.001**
Four-year overall survival, (%)	90	87	87	0.8

Note: All bold *p* values are <0.05, i.e. they are statistically significant; Please refer to Table S1 for expanded statistical analysis of the treatment related outcomes between the sub-cohorts.
Abbreviations: BDR, bortezomib, dexamethasone and rituximab; CI, confidence interval; DRC, dexamethasone, rituximab and cyclophosphamide; NR, not-reached; R-Benda, rituximab and bendamustine.

after excluding the patients who received rituximab maintenance therapy (n = 23) following the initial induction therapy. The treatment outcomes in this subset of patients are outlined in Table S1. Outcomes remained superior for the cohort of patients receiving R-Benda compared to the cohorts that received DRC or BDR regimens.

3.4 | Treatment response based on *MYD88*^{L265P} mutation status

Overall, 142 patients were genotyped for *MYD88* mutation. Of 67 patients who received R-Benda and had *MYD88*^{L265P} genotype data available, the ORR was 98% in the *MYD88*^{L265P} cohort vs. 100% in the *MYD88*^{WT} cohort, $p = 0.6$. In the DRC cohort with known *MYD88* mutation status (n = 51), the ORR was 77% for patients with *MYD88*^{L265P} vs. 84% with *MYD88*^{WT}genotype, $p = 0.6$. Of the 24 patients who received BDR and had undergone *MYD88*^{L265P} mutational assessment, the ORR was 75% in patients with *MYD88*^{L265P} as compared to 67% who had *MYD88*^{WT} genotype, $p = 0.7$. Importantly, the PFS, MRR, TTNT and DOR were not different within treatment groups based on the *MYD88*^{L265P} mutation status, (Table 3).

3.5 | Treatment related toxicities, and drug discontinuation

The AEs profiles were comparable across the treatment groups, barring neuropathy and neutropenia which were encountered more frequently in the BDR (17.5%) cohort and R-Benda (13%) cohort, respectively. The treatment related toxicities are summarized in Table 4 and details about treatment discontinuation could be found in the Supplementary Material S1.

3.6 | Salvage therapy

Eighty-three (38%) patients received salvage therapy during the follow-up; 10 (12%) in R-Benda cohort, 46 (50%) in DRC cohort and

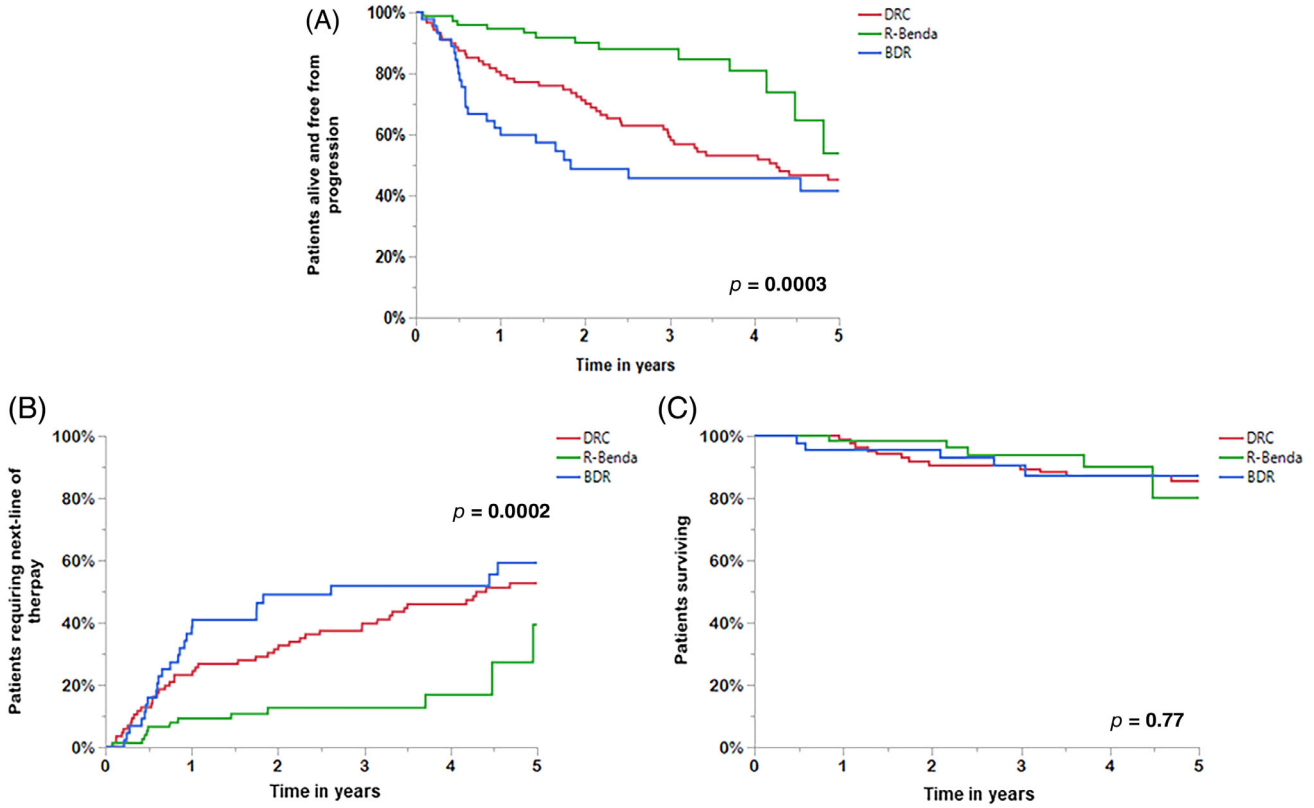

FIGURE 2 Treatment outcomes of R-Benda, DRC and BDR regimens when used in the frontline setting in patients with Waldenström macroglobulinemia. Kaplan Meier curves depicting (A) progression free survival (B) time-to-next therapy and (C) overall survival in patients with Waldenström macroglobulinemia who were treated with respective regimens in the frontline setting. R-Benda, rituximab and bendamustine; DRC, dexamethasone, rituximab and cyclophosphamide; BDR, bortezomib, dexamethasone and rituximab [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Clinically relevant endpoints based on *MYD88*^{L265P} mutation status

Parameter	Treatment	*MYD88*^{L265P}	*MYD88*^{WT}	*p* value
Overall response rate, n (%)	R-Benda	58 (98)	8 (100)	0.6
	DRC	25 (77)	15 (84)	0.6
	BDR	10 (75)	7 (67)	0.7
Major response rate, (%)	R-Benda	57 (96)	8 (100)	0.5
	DRC	16 (48)	7 (38)	0.5
	BDR	7 (50)	5 (55)	0.8
Time-to-next therapy, range; years (95%CI)	R-Benda	NR (4.9-NR)	NR (NR-NR)	0.3
	DRC	3.3 (2.1–4.3)	2.3 (0.5–5.7)	0.9
	BDR	1.8 (0.6–5.6)	1.4 (0.2-NR)	0.8
Time to best response, range; months (95%CI)	R-Benda	4.1 (3.3–5.0)	5 (2.7–10)	0.3
	DRC	7.4 (4.2–13.5)	5 (3.7–6.9)	**0.04**
	BDR	5.7 (3.7–6.7)	8.5 (2.6–11.8)	0.06

Note: All bold *p* values are <0.05, i.e. they are statistically significant.
Abbreviations: BDR, bortezomib, dexamethasone and rituximab; CI, confidence interval; DRC, dexamethasone, rituximab and cyclophosphamide; NR, not-reached; R-Benda, rituximab and bendamustine.

27 (60%) in the BDR cohort. One patient (1%) in the R-Benda cohort and 12 (13%) patients in the DRC cohort received a proteasome inhibitor-based salvage therapy. Alkylating agent-based salvage regimens were administered to 14 (31%) patients who had previously received BDR. Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor was used in five (6%) of the patients in the R-Benda cohort, four (4%) in the DRC cohort and six (13%) in the BDR cohort who received salvage therapy. Two patients (2.4%) in the R-Benda cohort required more than three lines of therapy compared to 13 (14%) and five (11%), in the DRC and BDR cohorts, respectively, during their disease course

TABLE 4 Adverse effects

Adverse effects	R-Benda patients, (%)	DRC patients, (%)	BDR patients, (%)	*p* value
Hematologic toxicities				
Anemia	5	9	2.5	0.34
% patients in grade < 3	3	3	2.5	
% patients in grade ≥ 3	1	6	0	
Thrombocytopenia	10	1	5	0.06
% patients in grade < 3	7	1	5	
% patients in grade ≥ 3	3	0	0	
Neutropenia	13	1	2.5	**0.009**
% patients in grade < 3	9	1	0	
% patients in grade ≥ 3	4	0	2.5	
Non-hematologic toxicities				
Fatigue	4	4	2.5	0.8
% patients in grade < 3	1.5	4	0	
% patients in grade ≥ 3	3	0	2.5	
Infections	4	6	2.5	0.7
Neuropathy	0	3	17.5	**0.001**
% patients in grade < 3	0	1.5	7	
% patients in grade ≥ 3	0	1.5	10.5	
Nausea	1.5	4	0	0.2
Diarrhea	3	0	0	0.4

Note: All bold *p* values are <0.05, i.e. they are statistically significant.
Abbreviations: BDR, bortezomib, dexamethasone and rituximab; DRC, dexamethasone, rituximab and cyclophosphamide; R-Benda, rituximab and bendamustine.

$p = 0.01$. Secondary myeloid neoplasms were not detected in any of the patients on alkylator-rituximab combinations (R-Benda or DRC) so far during the follow-up (median 4.3 years).

4 | DISCUSSION

Despite rapid expansion of therapies against WM in the past decade, including incorporation of BTK inhibitors and anti-CD20 antibody-based combination therapies, partnering alkylating agents or proteasome inhibitors with rituximab continues to be a viable therapeutic option for the patients with treatment-naïve WM.[1,14] Three of the most well-studied fixed-duration non-BTK inhibitor based regimens in the frontline setting in WM are R-Benda, DRC and BDR, all with proven efficacy and safety track record.[1,15] However, being a rare hematologic malignancy, representing approximately 2% of non-Hodgkin lymphoma cases, data from large randomized clinical trials are sparse in WM.[16] The void created by the absence of high-level evidence from randomized trials is filled with numerous cross-trial comparisons, fraught with limitations. The recently presented results of the randomized phase 2 ECWM1 trial failed to demonstrate any clinical benefit of adding bortezomib to the DRC backbone compared to DRC alone.[17] Moreover, similar to the findings of our study, the response to DRC or bortezomib plus DRC were not impacted by the *MYD88* mutation status. Peripheral neuropathy was observed in 18% of patients who received bortezomib plus DRC similar to the rate (17.5%) observed in our study with BDR albeit the follow-up of our study was longer (median 5.2 years for BDR vs 2.3 years for bortezomib + DRC in the ECWM1 trial).[17]

In our study, only two patients were treated prior to 2007 [BDR (n = 1) and DRC (n = 1)] while the remaining 218 patients received initial therapy between 2007–2019. As demonstrated in Figure S1, the changes in the treatment pattern highlight the use of DRC as one of the most preferred regimens between 2007 to 2013 that was overtaken by R-Benda as the predominantly used initial therapy in 2014, coinciding with the release of the promising results of the Greek trial with DRC in 2007 and the Study Group Indolent Lymphomas (STiL) trial with R-Benda in 2013.[21] The baseline characteristics of the three cohorts in our study were similar, with the exception of a higher proportion of patients with $MYD88^{WT}$ genotype in the BDR cohort. The proportion of patients receiving rituximab maintenance therapy was small (<15%) and alike across the three cohorts. Similarly, the time interval from the diagnosis to the initiation of treatment was comparable. Since R-Benda became the frontline regimen of choice more recently at our institution as per the Mayo mSMART Consensus criteria compared to the previously recommended DRC regimen, the follow-up period is shorter for the R-Benda cohort.[1,19] Despite the differences in the follow-up interval in our study, the median follow-up of 4.5 years for the entire cohort was sufficient to show the superiority of R-Benda over the other two regimens in terms of response

rates, PFS, EFS, DOR and TTNT. Moreover, as illustrated in Figure 2, a substantial proportion of events for PFS and TTNT occurred within 24 months of the commencement of DRC and BDR regimens. Therefore, our study conclusions are less likely to be impacted by the shorter follow-up (median 2.3 years) for the R-Benda cohort. The OS data are still immature across the three cohorts. The ORR for the R-Benda cohort was impressive at 98%. The complete response (CR) rates were low (12%), but matched the CR rates (12.2%) of retrospectively collated WM data with frontline R-Benda from 17 centers across four countries.[20] Our results, although involving patients outside of a clinical trial setting, are consistent with those observed in the phase 3 StiL NHL1-2003 trial, in which R-Benda was used as frontline therapy in a subset of 22 patients with WM, generating an ORR of 93%, and a median PFS of 69.5 months (5.8 years; interquartile range: 36.6–73 months).[18] Similar results were observed with R-Benda in the recently reported MAINTAIN trial showing an ORR of 91.4% and a median PFS of 5.4 years after a 5.9 year follow-up period. Our findings are also supported by the recent data from a global WM registry reporting on superior TTNT with R-Benda as compared to DRC, rituximab monotherapy or a BTK inhibitor in the frontline setting.[3]

The ORR of 80% and the 2-year PFS rate of 70%, with a median PFS of 3.4 years in our study for patients in the DRC cohort also are in line with the findings (ORR of 83%, 2-year PFS 71%) of the Greek study of 72 patients that examined this combination as primary therapy.[21] Furthermore, the updated analysis of that study also reported a median PFS of 3 years.[22]

Notably, the response rates in patients who received BDR were similar to the rates observed with DRC but inferior to that observed with R-Benda. With the follow-up of 5.2 years, we reported an 84% ORR with an MRR of 68% for the BDR cohort. The median PFS with BDR in our study was remarkably shorter at 1.8 years. In one study, an ORR of 96% (MRR 83%), with a 2-year PFS of 78% after 22.8 months of follow-up, was noted among 23 patients with WM who were treated with bortezomib-rituximab in the frontline setting.[23] However, another larger prospective study of 60 patients that received BDR as primary treatment reported a lower ORR (85%), albeit a longer median PFS of 3.5 years (vs. only 1.8 years with our study).[24] Importantly, treatment-emergent neuropathy rate of 20% in that study was similar to that observed in our study.

Another retrospective study that compared the efficacy of the three combination treatment regimens as primary therapy for patients with WM reported similar response rates across the three regimens.[25] However, in that study, the majority of patients (64%) received maintenance therapy with rituximab, which is an uncommon practice in WM, with equivocal benefit.[26,27] By contrast, in our study, fewer than 15% of patients in each arm received rituximab maintenance therapy. In an effort to avoid the biases resulting from deepening of the response with maintenance rituximab,[28] we also conducted a subset analysis after excluding the patients who had received rituximab maintenance. In this focused subset analysis, the patients treated with R-Benda had superior outcomes than those treated with DRC or BDR regimens.

With a few notable exceptions such as a higher incidence of peripheral neuropathy and neutropenia in patients who were treated with BDR and R-Benda, respectively, the toxicities associated with these regimens in our study appeared to be similar, including the hematologic toxicities. The proportion of patients across the three cohorts requiring dose modifications was similar as well.

To our knowledge, the current study is the largest study to date showing the lack of any impact of *MYD88*^{L265P} mutation on the outcomes of patients receiving these three regimens. Unlike the inferior response rate and prognosis observed with ibrutinib monotherapy in *MYD88*^{WT} WM cohort,[12] the *MYD88* status did not impact the outcomes of patients treated with R-Benda, DRC or BDR regimen. We had initially observed a hint of efficacy of chemoimmunotherapies, R-Benda and DRC, irrespective of the *MYD88* mutational profile in a previous small Mayo Clinic study.[29] A subsequent study by the French Innovative Leukemia Organization also showed that *MYD88*^{L265P} mutation did not influence the disease response or survival outcome of WM patients treated with R-Benda.[30] In addition to highlighting the efficacy of BDR regimen in both *MYD88* mutated and wild-type cohorts, our current larger study reinforced the finding of equivalent activity of R-Benda and DRC regimens in the respective cohorts stratified by their *MYD88* mutational profile. To what extent, the integration of rituximab, the common anti-CD20 backbone across all these regimens [as well as in the ibrutinib and rituximab (IR) regimen used in the iNNOVATE trial[5] showing efficacy in both wild-type and mutant cohorts] is instrumental in overcoming the negative impact of *MYD88*^{WT} observed with single-agent ibrutinib treated patients, is unclear at this time. However, the high efficacy of R-Benda in both wild-type and mutant cohorts (Table 3) is noteworthy, and offers a fixed-duration alternative to the continuous approach with IR.[5] Zanubrutinib, a novel potent BTK inhibitor with lesser off-target activity than ibrutinib has recently demonstrated high quality response in the *MYD88*^{WT} patient-population or those with an unknown *MYD88* mutation status.[31–33]

One study, with a median follow-up of nearly 9 years, reported 0.5%/person/year, and a cumulative incidence of 6.2% of developing myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) following bendamustine therapy in patients with non-Hodgkin lymphoma.[34] Bortezomib based treatments have not shown to be associated with second primary malignancies in patients with plasma cell dyscrasias.[35] After a median follow-up of 4.3 years, we did not find any evidence of MDS AML in patients treated with chemo-immunotherpies, R-Benda, DRC, or BDR.

The retrospective design makes our study vulnerable to unavoidable limitations. The absence of quality-of-life and patient reported outcome data as well as lack of information regarding the *CXCR4* mutation status are additional limitations of our study. Further, given that R-Benda has recently gained ground as a frontline regimen for patients with WM as compared to DRC and BDR regimens,[36,37] the follow-up in our study for patients who received R-Benda is shorter than that for patients treated with DRC or BDR. Notwithstanding these limitations, at comparable time points, R-Benda emerged superior to the other two regimens. Given the retrospective nature of our study, the AEs and rate of treatment modifications are likely underestimated in comparison to the single arm prospective studies for the respective regimens.[18,21,23]

In summary, this study represents a comparison of some of the most commonly used fixed-duration non-BTK inhibitor therapies for frontline treatment of WM and provides evidence in an area where a prospective study is unlikely to be conducted in the foreseeable future. Although the three regimens that were studied are effective, irrespective of the *MYD88*^{L265P} mutation status, our data support the use of R-Benda as primary therapy, taking into account the superior outcomes (MRR, superior PFS, TTNT and EFS) observed with this regimen in comparison to frontline DRC or BDR in patients with WM. Although the quality-of-life data were unavailable, we speculate that the longer duration of response with R-Benda is likely to be associated with improved quality of life following completion of therapy. Notably, the clinically relevant endpoints were not significantly different in patients who received DRC compared to BDR in the frontline setting and the toxicity profiles across the three groups were comparable, barring a higher incidence of neutropenia and neuropathy in patients who received R-Benda and BDR regimens, respectively. Given the indolent course and incurability of WM with the current regimens, it is not surprising to observe similar OS rates among the three cohorts with the current follow-up. Protracted follow-up, an important aspect, particularly for an indolent malignancy with a relapsing–remitting clinical course such as WM, will help shed more light on the impact of these three regimens on OS. However, as WM occurs typically in the elderly patient population, with high rates of competing risks of death from comorbidities, our data favor the use of fixed-duration R-Benda primary therapy that is associated with more durable disease control.

CONFLICT OF INTEREST

Dr. Gertz reports personal fees from Ionis/Akcea, personal fees from Alnylam, personal fees from Prothena, personal fees from Sanofi, personal fees from Janssen, grants and personal fees from Spectrum, personal fees from Annexon, personal fees from Appellis, personal fees from Amgen, personal fees from Medscape, personal fees from Physicians Education Resource, personal fees for Data Safety Monitoring board from Abbvie, and Celgene personal fees from Research to Practice, Speaker fees from Johnson and Johnson; Speaker fees from Medscape, Speaker fees DAVA oncology; Advisory Board for Pharmacyclics Advisory Board for Proclara outside the submitted work; Development of educational materials for i3Health. Educational Program development i3Health. Royalties from Springer Publishing. Grant Funding Amyloidosis Foundation; International Waldenstrom Foundation, NCI SPORE MM SPORE 5P50 CA186781-04. Dr. Ansell reports Research funding from BMS, Seattle Genetics, Takeda, ADC Therapeutics, Affimed, Trillium, Regeneron, AI Therapeutics. Dr. Kapoor reports the following COIs; Sanofi: Consultancy, Research Funding; Celgene: Honoraria; Cellectar: Consultancy; Janssen: Research Funding, Honoraria; Amgen: Research Funding; GlaxoSmithKline: Research Funding; Takeda: Honoraria, Research Funding, Karyopharm Honoraria, Beigene Honoraria; AbbVie, Research Funding, Honoraria. The rest of the authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Jithma P. Abeykoon, Saurabh Zanwar and Prashant Kapoor designed the study, collected and analyzed the data and drafted the manuscript. Stephen M. Ansell, Rong He, Patricia T. Greipp, Rebecca L. King, Sikander Ailawadhi, Jonas Paludo, Jeremy T. Larsen, Thomas M. Habermann, David Inwards, Ronald S. Go, Gita Thanarajasingam, Francis Buadi, Angela Dispenzieri, Carrie A. Thompson, Thomas E. Witzig, Martha Lacy, Wilson Gonsalves, Grzegorz S. Nowakowski, David Dingli, S. Vincent Rajkumar, Robert A. Kyle, Taimur Sher, Vivek Roy, Allison Rosenthal, Asher A. Chanan-Khan, Craig Reeder, Shaji Kumar, Morie A. Gertz critically appraised the data and reviewed the final draft. Shaji Kumar and Prashant Kapoor supervised the study. All authors have approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Email: kapoor.prashant@mayo.edu.

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SUPPORTING INFORMATION

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

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