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RESEARCH ARTICLE

Depth of Response From Fixed-Duration Treatment Is Associated With Superior Survival in Waldenstrom Macroglobulinemia

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ABSTRACT

As the treatment paradigm for Waldenström macroglobulinemia (WM) continues to evolve, the debate surrounding the prioritization of depth of response versus disease control as therapeutic goals gains significant relevance. However, the impact of depth of response from fixed-duration therapy on overall survival (OS) was unclear. This multicenter study evaluated the prognostic impact of depth of response using a landmark survival analysis. A total of 440 patients with WM treated with frontline fixed-duration regimens were included. Attaining a major response (MaR) was associated with superior outcomes, including significantly longer OS. The estimated 5-year PFS rates for patients with MaR at 6 months versus not were 50% versus 32%, respectively, $p < 0.001$, and the estimated 5-year OS rates for patients with MaR at 6 months versus not were 89% versus 70%, respectively, $p < 0.001$. In a multivariable analysis, MaR at 6 months was independently associated with superior PFS (HR 0.66, $p = 0.007$) and OS (HR 0.28, $p < 0.001$). Similar results were seen when considering deeper responses (CR + VGPR vs. PR). Depth of response at 6 months is an important prognostic marker in WM and an independent predictor of PFS and OS. These results support its utilization as a suitable endpoint in clinical studies in WM.

1 | Introduction

Several practice-altering advances over the last decade have transformed the treatment paradigm of Waldenström macroglobulinemia (WM), an indolent non-Hodgkin lymphoma characterized by the presence of an IgM monoclonal gammopathy in the serum and a lymphoplasmacytic lymphoma involving the bone marrow [1, 2]. At present, fixed-duration regimens, such as bendamustine plus rituximab (BR), dexamethasone, rituximab, cyclophosphamide (DRC), and bortezomib,

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dexamethasone, rituximab (BDR), or continuous therapy with BTK inhibitors, such as ibrutinib and zanubrutinib, represent the preferred frontline treatment options for WM [1, 3].

Given the growing number and diversity of treatment options currently available and on the horizon, the debate over prioritizing depth of response versus disease control as treatment goals in WM remains a crucial and relevant issue. Previous studies have shown that achieving a major response (MaR) at 6 months in patients undergoing continuous treatment with ibrutinib is linked to improved progression-free survival (PFS) [4]. Achieving a MaR to fixed-duration rituximab-based regimens has also been associated with clinical benefit and longer disease control. Deeper responses, such as very good partial response (VGPR) or better, were also associated with improved PFS in fixed-duration regimens [5–7] and incorporated as a primary endpoint in a recent phase 3 clinical trial comparing BTK inhibitors in WM [8].

While the depth of response has predictably been associated with superior PFS, its association with overall survival (OS) is not known, as the available studies are limited by smaller sample sizes, shorter follow-up, and mostly focused on single-treatment regimens. In this international, multicenter study of patients with WM treated with frontline fixed-duration regimens, we explore the impact of depth of response on time-to-event outcomes and demonstrate an association with superior OS in patients with WM.

2 | Methods

2.1 | Patient Selection

All consecutive patients with WM treated with a frontline fixed-duration regimen (DRC, BDR, or BR) over the past 10 years at Mayo Clinic Rochester (USA), Dana-Farber Cancer Institute (USA), Fondazione IRCCS Policlinico San Matteo (Italy), and Niguarda Cancer Center (Italy) were included in this study. All patients met clinicopathologic criteria for a WM diagnosis and required treatment initiation based on guidelines from the International Workshop on WM (IWWM-6) [6]. All patients provided informed consent to have their data collected for research. The study was approved by the Institutional Review Board and conducted following the Declaration of Helsinki.

2.2 | Data Collection

Pertinent clinicopathologic data were collected at the time of frontline therapy initiation. Categorical responses were assessed based on modified IWWM-6 criteria [9], Major response (MaR) was defined as achieving a response of PR or better (PR + VGPR+CR). Response to treatment was assessed at 6, 12, and 18 months after the initiation of therapy, in accordance with standard clinical practice. *MYD88*^{L265P} mutational status was assessed in peripheral blood (PB) and/or bone marrow (BM) samples using allele-specific polymerase chain reaction (AS-PCR) [10–12] or amplification-refractory mutation system (ARMS) [13, 14].

2.3 | Statistical Analysis

Patient characteristics and response rates are presented using descriptive statistics. *Chi*-square and Fisher's exact tests assessed differences between categorical variables, and Wilcoxon rank sum tests were used to compare continuous measures between groups. All time-to-event analyses were performed from the time of treatment initiation using the Kaplan–Meier method and compared using the log-rank test. Progression-free survival (PFS) was defined as the time from treatment initiation to progression and/or death, where those alive and progression-free at their last evaluation were censored at that time point. Time-to-next therapy (TTNT) was defined from treatment initiation until documented next therapy for WM; patients who had not required subsequent therapy at their last evaluation were censored at that time point. Deaths prior to initiating subsequent therapy were considered competing risk events. The OS was defined as the time from treatment initiation to death due to any cause. For disease-specific survival (DSS), deaths from WM or its directly associated complications (e.g., progressive WM, infection, transformation/AL amyloidosis, myelodysplastic syndrome) were treated as events of interest and non-WM-related deaths as competing events.

For landmark analyses, PFS, OS, DSS, and TTNT were estimated starting at the 6-, 12-, and 18-month marks, respectively; patients who were event-free and had non-zero follow-up were included in the time point-specific landmark analyses. Survival curves for PFS and OS were generated using the Kaplan–Meier method for incomplete observations and estimates for median and time point-specific survival rates. These time-to-event distributions were compared using the log-rank test. TTNT and DSS were evaluated using cumulative incidence analyses that accounted for competing risks, where data were assessed using the cumulative incidence function and distributions compared using the Fine Gray test. Univariable and multivariable Cox proportional hazards regression models were used to evaluate the influence of depth of response on these time-to-event survival outcomes with or without adjustment for other risk factors of interest; hazard ratios (HRs) were used to reflect the effects of the variables on these survival endpoints, along with corresponding 95% confidence intervals (CIs). In addition, cumulative incidence and competing risks regression were used to evaluate the incidence of subsequent therapy events as well. Using the Bonferroni correction, p values < 0.017 were considered statistically significant to account for multiple comparisons with three landmark analyses time points. Calculations were obtained using SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA).

3 | Results

3.1 | Patient Characteristics

The overall analysis cohort consisted of 440 patients who were treated with frontline fixed-duration therapy (see Table 1 for characteristics). Frontline therapy included: DRC ($n = 224$, 51.5%), BR ($n = 133$, 30.6%), BDR ($n = 78$, 17.9%), and not specified ($n = 5$). The median age at the time of diagnosis was

TABLE 1 | Baseline patient characteristics.

	Count (%) or median (range)
Age at diagnosis, years	65.7 (36–94.5)
Sex, male	261 (59.3%)
Hemoglobin at diagnosis, g/dL	10.5 (3.6–17.1)
Platelet count at diagnosis, 10^9/L	219 (5–580)
Serum ß2-microglobulin at diagnosis, mg/L	3.1 (0–30)
Serum IgM at diagnosis, mg/dL	3470 (80–13000)
Bone marrow involvement at diagnosis, %	50 (10–100)
IPSSWM	
Low risk	67 (21%)
Intermediate Risk	88 (27.6%)
High Risk	164 (51.4%)
Missing	121
$MYD88^{L265P}$ mutation status	
Positive	198 (88%)
Negative	25 (12%)
Missing	217
Treatment regimen	
DRC	224 (51.5%)
BR	133 (30.6%)
BDR	78 (17.9%)
Missing	5

Abbreviation: IPSSWM, International Prognostic Scoring System for Waldenström macroglobulinemia.

65.7 years (range: 36–94.5), and 59.3% were men. Risk based on the International Prognostic Scoring System (IPSS)-WM included: low ($n = 67$, 21%), intermediate ($n = 88$, 27.6%), and high risk ($n = 164$, 51.4%) or missing ($n = 121$) in the entire cohort. There was no difference in IPSS-WM among patients who received DRC, BR, or BDR. The median follow-up for the entire cohort was 72 months (95% CI: 65.4–75.7), and the median follow-up was comparable among the treatment cohorts. At the data cut-off, 83.0% of patients ($n = 365$) were alive, 50.0% of patients ($n = 222$) had progressed, and 22.5% of patients ($n = 99$) required salvage therapy.

3.2 | Response to Fixed-Duration Therapy

Categorical response rates at 6, 12, and 18 months are shown in Table 2. Evaluable responses at 6 months from frontline therapy were available in 417 (94.7%), at 12 months were available in 374 (85%) patients, and at 18 months were available in 336 (76.4%) patients, which were included in the 6-, 12-, and 18-month landmark analysis.

TABLE 2 | Categorical response rates to fixed-duration chemoimmunotherapy at 6, 12, and 18 months from treatment initiation.

	At 6 months	At 12 months	At 18 months
MaR			
CR	22 (5.0%)	29 (6.6%)	34 (7.7%)
VGPR	61 (13.9%)	64 (14.5%)	58 (13.2%)
PR	218 (49.5%)	210 (47.7%)	187 (42.5%)
Less than MaR			
MR	79 (18.0%)	49 (11.1%)	28 (6.4%)
SD	31 (7.0%)	13 (3.0%)	9 (2.1%)
PD	6 (1.4%)	9 (2.1%)	20 (4.5%)
Missing	23 (5.2%)	66 (15.0%)	104 (23.6%)

Abbreviations: CR, complete response; MaR, major response; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

When considering the entire cohort, the median PFS was 5.0 years (95% CI: 4.5–5.6); the 5-year PFS was 51% (95% CI: 46%–56%). The median TTNT was 10.1 years (95% CI: 8.1-NA); the 5-year cumulative incidence rate of a new treatment (NT) was 21% (95% CI: 17%–27%) when accounting for competing risks. The median OS was not reached; the 5-year OS was 87% (95% CI: 83%–90%).

We next explored the landmark analysis at 6, 12, and 18 months from the initiation of therapy. The 6-month assessment is thought to represent the most clinically relevant time point, at the completion of the fixed-duration treatment regimens and prior to the initiation of maintenance therapy, when applicable. It also provides prognostic information earlier in the disease course. The 12- and 18-month landmark results are reported in the Supporting Information.

3.3 | Landmark Analyses at 6 Months

For the LM6 cohort, the median PFS was 4.5 years (95% CI 4.0–5.1), and the estimated 5-year PFS rate starting from the 6-month mark was 45% (95% CI: 40%–51%). The 5-year PFS for patients who attained MaR at 6 months versus those who did not was 50% (95% CI: 44%–57%) versus 32% (95% CI: 24%–42%, $p < 0.001$), respectively (Figure 1A). The median TTNT was 9.5 years (95% CI 7.6-NA), and the estimated 5-year cumulative incidence rate of a NT was 21.7% (95% CI: 17%–27%) for the entire LM6 cohort with death as a competing risk. The 5-year cumulative incidence of NT for patients who attained MaR at 6 months versus those who did not was 14% (95% CI: 10%–20%) versus 47% (95% CI: 36%–61%, $p < 0.001$), respectively (Figure 1B).

For the entire LM6 cohort, the estimated 5-year OS rate starting from the 6-month mark was 84% (95% CI: 80%–88%). Patients who attained MaR at 6 months had a significantly higher 5-year OS rate (89%, 95% CI: 85%–94%) than those who did not (70%, 95% CI: 62%–80%; $p < 0.001$; Figure 1C). For the entire LM6 cohort, the estimated 5-year cumulative incidence of disease-specific death (DSD) starting from the 6-month mark was 7%

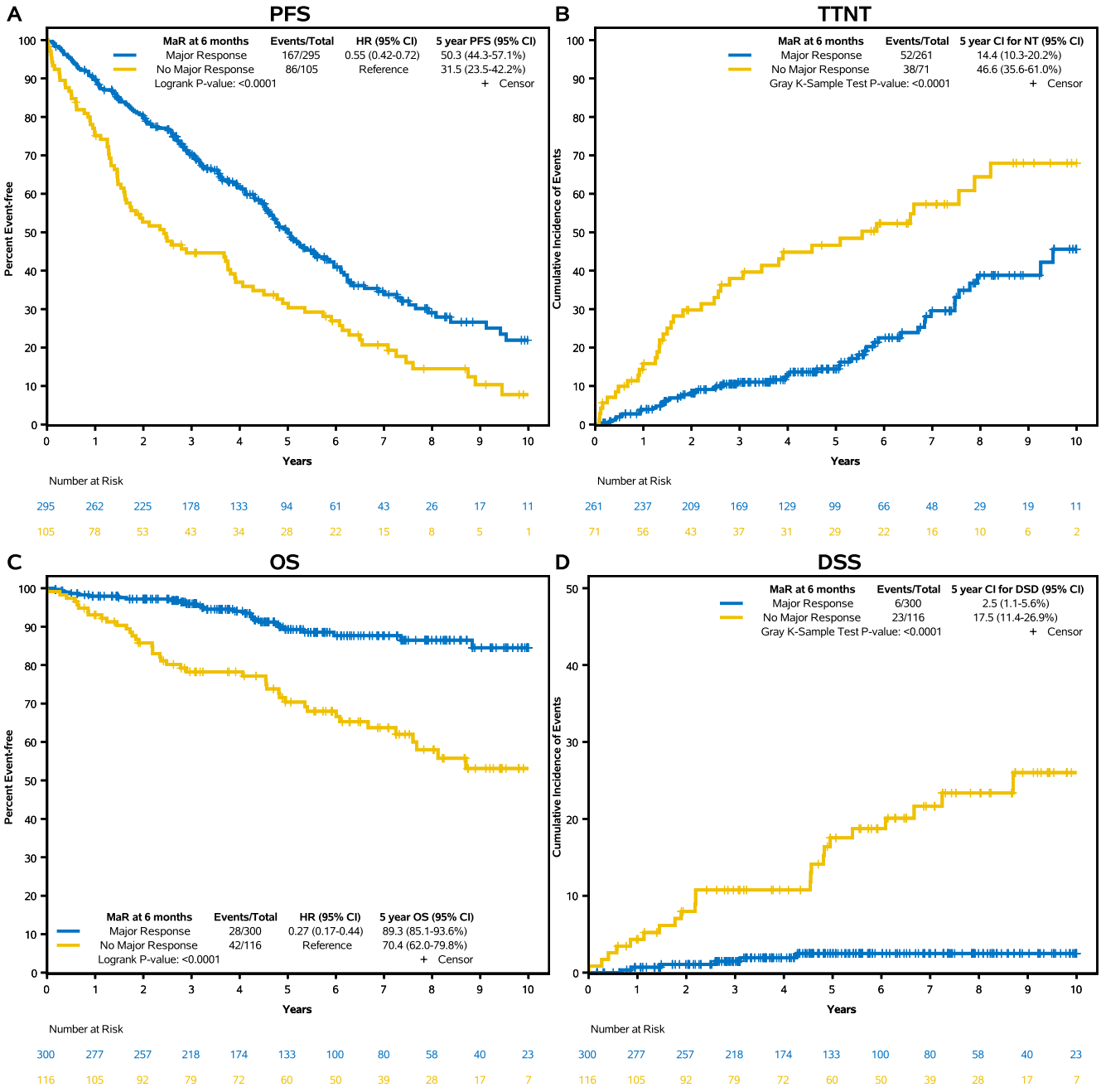

FIGURE 1 | Landmark analysis of time to event outcomes by depth of response at 6 months. (A) Kaplan–Meier analysis of progression free survival (PFS) curve according to attaining partial response (PR) or better at 6 months or not; (B) CI analysis of Time-to-next-treatment (TTNT) according to attaining PR or better at 6 months or not; (C) Kaplan–Meier analysis of Overall Survival (OS) according to attaining PR or better at 6 months or not; (D) CI analysis of Disease Specific Survival (DSS) according to attaining PR or better at 6 months or not. All x-axes represent time since 6-month landmark. CI, Cumulative Incidence; NT, New Treatment; DSD, Disease-specific death. [Color figure can be viewed at wileyonlinelibrary.com]

(95% CI: 5%–11%). Similar to the effects observed for OS, patients who attained MaR at 6 months had a significantly lower 5-year cumulative incidence of DSD (3%, 95% CI: 1%–6%) than those who did not (18%, 95% CI: 11%–27%; $p < 0.001$; Figure 1D).

Given the superior time-to-event outcomes associated with attaining a MaR at LM6, we next analyzed the outcomes of patients within the MaR cohort by comparing patients who achieved a CR + VGPR versus those achieving a PR. We found that patients who attained CR + VGPR at 6 months did not have significantly different PFS (52%, 95% CI 41%–66%) versus those who only achieved a PR (50%, 95% CI 43%–58%; $p = 0.26$). However, when focusing on the need for NT, patients who attained CR + VGPR at 6 months had a significantly lower 5-year cumulative incidence of NT (3%, 95% CI 1–12) versus those who only achieved a PR (19%, 95% CI 13%–26%; $p = 0.011$). The 5-year OS for patients who attained CR + VGPR at 6 months versus those who achieved a PR was similar at 89% (95% CI 80%–98%) versus 89% (95% CI 85%–95%, $p = 0.97$), respectively. Similarly, the 5-year cumulative incidence of DSD for patients who attained CR + VGPR at 6 months versus those who achieved a PR was 3.4% (95% CI 1%–14%) versus 2% (95% CI 1%–6%, $p = 0.66$), respectively.

3.4 | Univariable Analyses for PFS and OS

We fitted univariable models to evaluate the prognostic utility of risk factors for PFS and OS (Table S1) based on the landmark analyses (complete results on Table S1). Attaining a MaR at 6, 12, or 18 months was associated with better PFS (6-month landmark HR 0.55 [95% CI: 0.43–0.71; $p < 0.001$], 12-month landmark HR 0.41 [95% CI: 0.30–0.56; $p < 0.001$], 18-month HR 0.37 [95% CI: 0.25–0.55; $p < 0.001$]), while age > 65 and high IPSSWM at the time of treatment initiation were associated with worse PFS (age > 65 HR 1.48, 95% CI: 1.17–1.88; $p = 0.001$ and high IPSSWM HR 1.45, 95% CI: 1.11–1.89; $p = 0.007$). No other variables were statistically associated with either a better or worse PFS in the univariate setting. A similar trend was noted when MaR was further broken down into CR + VGPR versus PR (Table S2).

Similarly, attaining a MaR at 6, 12, or 18 months was associated with better OS (6-month landmark HR 0.27 [95% CI: 0.17–0.44; $p < 0.001$], 12-month landmark HR 0.33 [95% CI: 0.2–0.55; $p < 0.001$], 18-month landmark HR 0.23 [95% CI: 0.13–0.41; $p < 0.001$]), while age > 65 years and high IPSSWM at the time of treatment initiation were associated with worse OS (age > 65 HR 3.86, 95% CI: 2.24–6.66; $p < 0.001$ and high IPSSWM HR 2.53, 95% CI: 1.36–4.71; $p = 0.003$). No other variables were statistically associated with either a better or worse OS in the univariate setting. A similar trend was found when MaR was further broken down into CR + VGPR versus PR (Table S2).

When further analyzing the MaR cohort into patients that achieved a CR + VGPR or a PR, the univariable analysis showed that CR + VGPR or PR were both independently associated with superior PFS and OS at the 6-, 12-, and 18-month time points (Table S2).

3.5 | Multivariable Analyses for PFS and OS

Similar to the univariate analyses, landmark models were also used to assess the influence of MaR status at the time point of interest while adjusting for known WM prognostic factors. For the LM6 cohort analysis, attaining a MaR at 6 months was an independent prognostic factor for superior PFS (HR 0.66, 95% CI: 0.49–0.89; $p = 0.007$) and OS (HR 0.28, 95% CI: 0.15–0.51; $p < 0.001$) as shown in Table 3. Similarly, in the LM12 analysis, attaining a MaR at 12 months was an independent prognostic factor for superior PFS (HR 0.37, 95% CI: 0.26–0.53; $p < 0.001$) and OS (HR 0.35, 95% CI: 0.18–0.68; $p = 0.002$; Table 3) as was attaining a MaR at 18 months in the LM18 analyses (Table S3). Age > 65 was associated with inferior OS but not PFS in each landmark analysis (Table 3).

4 | Discussion

In this international, multicenter study, we demonstrate that achieving a deeper response with fixed-duration frontline chemoimmunotherapy is an independent predictor of superior PFS and OS for patients with WM. A lower incidence of DSD is also correlated with the depth of response. Achieving a MaR and younger age (< 65 years at diagnosis) were the only factors independently associated with longer OS in multivariable analyses. The large sample size and longer patient follow-up in our study, compared to previously published work on the depth of response in WM [3–5, 12], are fundamental strengths that empower the recognition of the depth of response as an important prognostic marker for OS and support its utilization as a suitable endpoint in clinical studies in WM.

Our landmark analysis at the different milestone time points revealed that attainment of MaR at 6, 12, and 18 months was a prognostic factor for PFS and OS. The prominent separations in PFS found in our cohort of fixed-duration frontline chemoimmunotherapy (DRC, BR, BDR) parallel previous findings related to BTK inhibitor therapy as the depth of response is important and prognostic in WM [15]. When exploring even deeper responses, achieving a CR + VGPR did not appear to significantly differentiate survival-based outcomes such as PFS, OS, and cumulative incidence of disease-specific death when specifically compared to those who achieved a PR. However, achieving a deeper response of CR + VGPR did correspond to a significantly lower risk of requiring subsequent treatment in the landmark analyses at 6, 12, and 18 months. We do note that when looking at the response as a multilevel factor (CR + VGPR vs. PR vs. no MaR), both deep response

TABLE 3 | Multivariate Cox proportional-hazard regression model for PFS at 6 months.

	PFS		OS	
Characteristic	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
6 months				
Age > 65 years at treatment	1.30 (0.91–1.85)	0.14	7.52 (2.78–20.35)	**< 0.001**
High IPSSWM	1.23 (0.87–1.74)	0.23	0.78 (0.38–1.64)	0.52
MaR at 6 months	0.66 (0.49–0.89)	**0.007**	0.28 (0.15–0.51)	**< 0.001**
12 months				
Age > 65 years at treatment	1.30 (0.89–1.91)	0.18	7.68 (2.77–21.30)	**< 0.001**
High IPSSWM	1.43 (0.98–2.09)	0.06	0.69 (0.32–1.49)	0.34
MaR at 12 months	0.37 (0.26–0.53)	**< 0.001**	0.35 (0.18–0.68)	**0.002**

Note: Bold numbers represent statistically significant values ($p < 0.05$).

groups were associated with significantly better outcomes compared to those who did not achieve a MaR at the various landmark time points. Overall, these findings demonstrate the potential role of incorporating depth of response, including CR + VGPR rates, as an effective endpoint in clinical studies of patients with WM.

The demographic and disease characteristics of patients included in our study are consistent with those previously reported for patients with WM [4, 5, 14–24]. Accordingly, the distribution of patients as low, intermediate, and high risk per IPSSWM was similar to that of the original study through which the IPSSWM was developed [25].

To further understand the independent impact of attaining a MaR at 6, 12, and 18 months on PFS and OS, we assessed univariable and multivariable Cox proportional-hazard regression models containing clinically relevant factors, including age, hemoglobin value, platelet count, Serum β2-microglobulin level, serum IgM level, *MYD88*^{L265P}, and bone marrow involvement ≥ 50%. In these models, attaining a MaR at 6, 12, and 18 months emerged as an independent favorable prognostic factor for PFS and OS, even when adjusting for other factors, and was associated with a lowering of risk by 33%–76% of progression and/or all-cause death compared to patients who did not attain a MaR at 6, 12, and 18 months.

Approximately 29% of patients in our study received rituximab maintenance therapy. The distribution of rituximab maintenance use was similar among the MaR versus no-MaR groups at the 6-month time points (30% vs. 22% at LM6, $p = 0.12$) therefore, we do not expect a biased influence of rituximab maintenance in the conclusions of our study. To further explore the influence of rituximab maintenance therapy in our results, we excluded all patients receiving rituximab maintenance therapy and reanalyzed all time-to-event outcomes for the landmark analysis at 6 months. Again, a superior PFS, rate of NT, rate of DSD, and OS were associated with depth of response after excluding all patients who received rituximab maintenance (Table S4). We also explored the impact of missing data for IPSSWM score and found no differences in the study conclusions in patients where this data point was missing (Figure S1).

This study aimed to explore the impact of the depth of response on the outcomes of patients with WM, regardless of which fixed-duration regimen was used in the frontline. The comparative efficacy of the three fixed-duration frontline regimens included in this study (DRC, BR, BDR) in a similar patient population has been addressed in previous studies [26, 27].

Among the three time points evaluated (6, 12, and 18 months) for response assessment, the 6-month time point is the most clinically relevant and useful for future studies and clinical practice. The 6-month time point marks the end of fixed-duration therapy (and prior to initiation of rituximab maintenance therapy); it is available earlier in the disease course and, therefore, more convenient and helpful in clinical practice and is associated with a prominent separation in time-to-event outcomes by response categorization in our study. The importance of the 6-month time point is echoed in other studies looking at the response to ibrutinib in WM [4].

Our study is not without limitations. *MYD88*^{L265P} mutational status is missing for 217 patients (49.3%). However, previous studies have shown that *MYD88*^{L265P} mutational status may not have a prognostic impact on patients with WM who were treated with fixed-duration chemoimmunotherapy [14, 27]. *CXCR4* mutational status was not available in our cohort of patients, which has emerged as a significant, potentially adverse prognostic factor in patients treated with BTK inhibitors in some prior studies [22, 28–31]. Missing values in treatment response data also reflect the inevitable limitations of a retrospective study design such as ours. Landmark analyses also only include those who have not had the event of interest prior to and have any follow-up after that landmark time point. Notwithstanding these limitations, our study is the largest reporting a multicenter, international cohort in WM patients on fixed-duration chemoimmunotherapy in the frontline setting, with significantly longer follow-up than prior studies of depth of response in WM.

In summary, the depth of response at 6 months following fixed-duration frontline therapy in WM was associated with a longer PFS and TTNT, but most importantly, it was also associated with superior OS. The categorical response attained at the 6-month time point after initiating therapy showed a prominent separation of outcomes and likely represents the most useful time point for future research and clinical practice. Additionally, deeper response (CR + VGPR) rates were independently associated with a decreased incidence of requiring the next line of therapy, supporting the incorporation of CR + VGPR rates as an endpoint in future studies of patients with WM, which remains an incurable disease.

Author Contributions

J.P. and J.P.A. designed the study. J.P.A., N.D.P., S.S.Z., J.J.C., A.R.G., J.G., C.C., and A.M.F. collected and categorized patient data. J.P., N.D.P., J.P.A., L.D.P., and S.M.G. performed the analysis. J.P., N.D.P., and J.P.A. drafted the initial manuscript. J.J.C., S.S., M.V., A.T., P.K., T.M.H., T.E.W., R.A.K., M.A.G., S.P.T., and S.M.A. critically revised the manuscript. All authors approved the final manuscript.

Ethics Statement

The study was approved by the Institutional Review Board and conducted following the Declaration of Helsinki.

Conflicts of Interest

J.P.: research funding to institution from Biofourmis, Karyopharm, and advisory board compensation from Abbvie. J.J.C.: research funds and/or consulting fees from Abbvie, AstraZeneca, Beigene, Cellectar, Janssen, Kite, Loxo, Mustang Bio, and Pharmacyclics. A.M.F.: advisory boards and sponsorship for conferences from Janssen, Abbvie, Beigene, and AstraZeneca.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.