

## POD24 is a Novel Determinant of Prognosis in Patients with Waldenström Macroglobulinemia

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### Abstract:

Waldenström macroglobulinemia (WM) is characterized by recurrent MYD88 and CXCR4 mutations, whose prognostic value in chemoimmunotherapy-treated patients remains unclear. Moreover, the typically prolonged progression-free survival (PFS) correlates inconsistently with overall survival (OS), underscoring the importance of examining other surrogates. Progression of disease within 24 months (POD24), an established early endpoint, delineates functionally high-risk patients in other indolent lymphomas. This international study evaluated 253 patients receiving frontline fixed-duration bendamustine-rituximab (BR), a common chemoimmunotherapy for WM. At median follow-up of 5.9 years, 5-year PFS and OS were 65% and 87%, respectively; 5-year PFS was similar between MYD88L265P (90%) and MYD88wild-type (WT) subcohorts (64% each,  $p=0.4$ ). Among 89 patients with known CXCR4 status, the subcohort with CXCR4mutation (28%) had shorter PFS (median, 3.3 versus 8.8 years; HR 2.8,  $p=0.0036$ ) and OS (HR 2.6,  $p=0.036$ ) compared to CXCR4WT. POD24 occurred in 11.5% of patients who demonstrated inferior subsequent OS (5-year OS: 71% versus 86%; HR 3.1,  $p=0.005$ ) and higher mortality (SMR 3.7), unlike the non-POD24 group, whose mortality was comparable to the matched general population (SMR 1.1). In conclusion, BR is effective, irrespective of the MYD88 status, but CXCR4 mutations and POD24 portend worse outcomes. Non-POD24 patients represent a cohort with distinctly favorable outcome.

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45 **Key words:** Lymphoplasmacytic lymphoma, POD24, MYD88, CXCR4,  
46 Chemoimmunotherapy

47 **Abstract**

48 Waldenström macroglobulinemia (WM) is characterized by recurrent *MYD88* and  
49 *CXCR4* mutations, whose prognostic value in chemoimmunotherapy-treated patients  
50 remains unclear. Moreover, the typically prolonged progression-free survival (PFS)  
51 correlates inconsistently with overall survival (OS), underscoring the importance of  
52 examining other surrogates. Progression of disease within 24 months (POD24), an  
53 established early endpoint, delineates functionally high-risk patients in other indolent  
54 lymphomas. This international study evaluated 253 patients receiving frontline fixed-  
55 duration bendamustine-rituximab (BR), a common chemoimmunotherapy for WM. At  
56 median follow-up of 5.9 years, 5-year PFS and OS were 65% and 87%, respectively; 5-  
57 year PFS was similar between *MYD88*<sup>L265P</sup> (90%) and *MYD88*<sup>wild-type (WT)</sup> subcohorts  
58 (64% each, p=0.4). Among 89 patients with known *CXCR4* status, the subcohort with  
59 *CXCR4*<sup>mutation</sup> (28%) had shorter PFS (median, 3.3 versus 8.8 years; HR 2.8, p=0.0036)  
60 and OS (HR 2.6, p=0.036) compared to *CXCR4*<sup>WT</sup>. POD24 occurred in 11.5% of  
61 patients who demonstrated inferior subsequent OS (5-year OS: 71% versus 86%; HR  
62 3.1, p=0.005) and higher mortality (SMR 3.7), unlike the non-POD24 group, whose  
63 mortality was comparable to the matched general population (SMR 1.1). In conclusion,  
64 BR is effective, irrespective of the *MYD88* status, but *CXCR4* mutations and POD24  
65 portend worse outcomes. Non-POD24 patients represent a cohort with distinctly  
66 favorable outcome.

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68

69 **Key Points**

70 **Key Point 1:** *CXCR4 mutations portend inferior outcome for patients with WM treated*  
71 *with frontline BR, whereas MYD88L265P does not impact survival.*

72 **Key Point 2:** POD24 serves as an early surrogate endpoint by reliably identifying  
73 patients with unfavorable subsequent survival.

74

75 **Introduction**

76 Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma, with distinct  
77 somatic alterations: clonal *MYD88*<sup>L265P</sup> mutation, detectable in most patients, and  
78 subclonal *CXCR4* mutation(s), present in 25–40% of patients.<sup>1</sup> Our approach to WM has  
79 steadily evolved, although anti-CD20 monoclonal antibody, rituximab, remains the  
80 linchpin, and frequently used in combination with limited-duration chemotherapy.<sup>1</sup>  
81 Bruton tyrosine kinase inhibitors (BTKi) are also highly effective, but their activity may  
82 be compromised in the absence of mutated *MYD88*.<sup>2</sup> Moreover, BTKi, in general, have  
83 reduced efficacy in the presence of mutated *CXCR4* (*CXCR4*<sup>MUT</sup>) and require  
84 continuous administration, potentially increasing not only the costs, but likelihood of  
85 cumulative toxicities and drug-drug interactions: factors that make finite-duration  
86 chemoimmunotherapy still considerably appealing.<sup>3,4</sup> Bendamustine–rituximab (BR)  
87 regimen gained popularity before ibrutinib’s approval, based on a subset analysis of the  
88 StiLNHL1-2003 trial that showed durable remission [median progression-free survival  
89 (PFS) of 69.5 months] in treatment-naïve WM patients.<sup>5</sup> Subsequent studies confirmed  
90 its efficacy, catapulting it to the preferred chemoimmunotherapeutic regimen, although  
91 how recurrent molecular alterations, *MYD88*<sup>L265P</sup> and *CXCR4*<sup>MUT</sup> impact its efficacy  
92 remains less clear.<sup>6,7</sup> Furthermore, the typically prolonged progression-free survival  
93 (PFS) attesting to the efficacy of many treatments correlates inconsistently with overall  
94 survival (OS) in patients with WM<sup>4,5,8,9</sup>, underscoring the importance of examining other  
95 surrogates such as the progression of disease within 24 months of treatment initiation

96 (POD24), an established early endpoint to delineate functionally high-risk patients in  
97 other indolent lymphomas.<sup>10-13</sup> We examined the implications of POD24, *MYD88*<sup>L265P</sup>  
98 and *CXCR4*<sup>MUT</sup> in patients treated with BR in the frontline setting.

## 99 **Methods**

### 100 **Participants**

101 Following Institutional Review Board approval, we included consecutively evaluated  
102 patients with active/symptomatic WM across medical centers in the United States and  
103 Europe, diagnosed between January 01, 2012, and July 31<sup>st</sup>, 2021, that were treated  
104 with upto 6 cycles of frontline fixed-duration BR. Consent and when applicable, a waiver  
105 of consent, was obtained per institutional IRB guidelines. The study was conducted per  
106 the Declaration of Helsinki. Patients on rituximab maintenance therapy post-BR were  
107 excluded to avoid biases, as this strategy is not universally embraced. Responses were  
108 categorized per the IWWM-11 Consensus criteria.<sup>14</sup>

### 109 **Statistics**

110 Non-parametric tests were used to compare continuous variables, while Chi-square or  
111 Fisher's exact test assessed nominal variables. The time-to-event outcomes were  
112 determined using the Kaplan-Meier method, with subgroup comparisons via the log-  
113 rank test. Reverse censoring was utilized for calculating the follow-up time. PFS was  
114 calculated from the time of initiation of BR until progression or death, whichever was  
115 earlier. OS was calculated from the initiation of treatment until last follow-up or death,

116 with patients censored if alive at last follow-up. To estimate the prognostic impact of  
117 POD24, we performed a landmark analysis in patients alive at 24 months, excluding  
118 those with a follow-up <24 months (n=201). Follow-up was then calculated from the 2-  
119 year mark for the 2 subcohorts: those who progressed (POD24 cohort) and those who  
120 did not progress within 24 months of initiation of BR therapy (the reference cohort).  
121 Additionally, we utilized POD24 as a time-dependent covariate to evaluate its  
122 association with subsequent OS. For assessment of POD24 as a time-dependent  
123 covariate (n=202), the endpoints were calculated from the time of progression for the  
124 POD24 group and from 2-years for the reference cohort.<sup>10,15</sup> Patients that did not  
125 progress but died due to non-WM causes within 2 years of treatment initiation were  
126 excluded from the time-dependent analysis.

127 To further examine the superior outcome of patients without progression within 24  
128 months, we compared their OS with a cohort of healthy age-, sex-, calendar-year-, and  
129 country of origin-matched population. Expected survival was calculated based on the  
130 death rate data obtained from the Human Mortality Database (HMD) for France, the  
131 United Kingdom, Greece, and the United States [available at [www.mortality.org](http://www.mortality.org), HMD,  
132 Max Planck Institute for Demographic Research (Germany), University of California,  
133 Berkeley (USA), and French Institute for Demographic Studies (France); data  
134 downloaded on 3/14/2025]. The observed and expected survival rates were analyzed by  
135 calculating the standardized mortality ratio (SMR) and corresponding 95% confidence  
136 interval.

## 137 Results

138 The baseline characteristics of the cohort (n=253) are outlined in **Table 1**. The median  
139 follow-up was 5.9 (95%CI: 5.3-6.5) years and the median number of administered  
140 cycles of BR was 6 (range: 1-6). Major response rate was high (94%), despite 25 (10%)  
141 patients discontinuing BR prematurely (Tables S1 and S2). Median PFS was 6.7 years  
142 [95%CI: 5.5-8.8; 5-year PFS, 65% (95%CI: 61-75%)]. Median OS was not reached (NR)  
143 [5-year OS, 87% (95%CI: 83-92%); Figures S1A-1B].

144 Among 172 patients with known *MYD88*<sup>L265P</sup> status, 154 (90%) harbored *MYD88*<sup>L265P</sup>.  
145 Both subcohorts, with *MYD88*<sup>L265P</sup> and *MYD88*<sup>WT</sup> genotypes, demonstrated comparable  
146 baseline characteristics (Table S3), response (Figure S2), PFS (5-year rate 64% in  
147 each group; p=0.4) and OS rates (5-year 89% vs. 74% p=0.44), respectively [**Figure**  
148 **1A-B**]. Among 89 patients with known *CXCR4* status, 25 (28%) exhibited *CXCR4*<sup>MUT</sup>  
149 genotype (Table S4). The response rates were lower for patients with *CXCR4*<sup>MUT</sup> versus  
150 *CXCR4*<sup>WT</sup> (Figure S2). Five-year PFS rate was 43% [median 3.3 (95%CI: 1.9-NR)  
151 years] and 78% [median 8.8 (95%CI 6.7- NR) years], respectively; p=0.0036, **Figure**  
152 **1C**), which translated to significantly inferior OS for the *CXCR4*<sup>MUT</sup> subcohort (**Figure**  
153 **1D**). The PFS and OS outcomes, respectively, were comparable between the cohorts  
154 with and without the *MYD88* and *CXCR4* mutation status related data available for  
155 analyses (Figure S3).

156 Among 201 patients included in the POD24 landmark analysis, 23 (11.5%) patients  
157 progressed within 24 months of initiating BR. This subgroup had a significantly shorter

158 OS from 2-year landmark [Figure 2A]. Most patients in the POD24 cohort harbored  
159 *CXCR4*<sup>MUT</sup> (70%) compared to the reference cohort [20%; p=0.003; (Table S5)].  
160 However, the POD24 status remained independently prognostic for the landmark  
161 analysis-calculated OS after adjusting for the *CXCR4*<sup>MUT</sup> status [HR 4.9 (95%CI: 1.2-  
162 21), p=0.03; Table S6]. Patients with POD24 had a higher SMR of 3.7 [(95%CI: 1.6-7.4,  
163 p=0.004) compared to an age, sex, calendar year and country of origin-matched cohort  
164 of healthy individuals (Figure 2B). However, OS of the non-POD24 cohort (n=178) was  
165 comparable [SMR of 1.1 (95% CI: 0.7-1.6), p=0.75; Figure 2C]. Of 202 patients  
166 included in the time-dependent covariate POD24 analysis, 24 (12%) patients  
167 progressed within 24 months of starting BR. Five-year OS subsequent to progression  
168 was 74% for early progressors (n=24) versus 86% in the reference cohort (POD ≥24  
169 months, n=178) despite the follow-up starting at 2-year timepoint for the latter [HR 2.4  
170 (95%CI: 1.1-5.1), p=0.024; Figure S4].

## 171 Discussion

172 This multiinstitutional study demonstrates robust outcomes with BR that are unaffected  
173 by the *MYD88*<sup>L265P</sup> status, in contrast to the observations with BTKi therapy.<sup>2</sup> However,  
174 similar to the findings with BTKi, the presence of *CXCR4*<sup>MUT</sup> was associated with inferior  
175 outcomes. The C-terminal domain alterations of *CXCR4* result in the loss of inhibitory  
176 serines, preventing CXCR4 receptor downregulation/internalization and in turn inducing  
177 drug-resistance through persistently activated downstream pro-survival signalling.<sup>16</sup>  
178 Previous studies involving BR were underpowered to detect *CXCR4*<sup>MUT</sup> associated

179 outcome disparity.<sup>6</sup> This largest report, to date, substantiates the preclinical data  
180 suggesting *CXCR4*<sup>MUT</sup> associated resistance to BR, akin to the ASPEN trial findings  
181 with BTKi<sup>17</sup>, wherein lower VGPR rates in the *CXCR4*<sup>MUT</sup> subcohort receiving  
182 zanubrutinib (45% versus 21% with *CXCR4*<sup>WT</sup>) or ibrutinib (31% versus 10%) translated  
183 to shorter PFS.<sup>4</sup>

184 Our study identified POD24 as an early surrogate endpoint for OS. Notably, *CXCR4*<sup>MUT</sup>,  
185 but not high-risk IPSS-WM enriched the POD24 cohort. By estimating survival  
186 probabilities from the 24-month landmark, we attempted to account for the biases  
187 arising from the time-dependent covariate POD24 based grouping. Leveling the field,  
188 the landmark analysis generated a more accurate report of the POD24-effect on  
189 mortality, eliminating the impact of early deaths. Patients with active WM are known to  
190 have a markedly inferior outcome compared to the corresponding survival of the  
191 matched general population (SMR 4.6-6.3).<sup>18</sup> Our study interestingly suggests that if  
192 patients are alive and progression-free 2 years post-BR therapy their subsequent OS is  
193 equivalent to that of the matched general population, underscoring the usefulness of  
194 POD24 endpoint in patient counseling.

195 Similar outcomes of the subcohorts, with and without the molecular data, suggest that  
196 the biases resulting from the missing, retrospectively gathered information are minimal.  
197 A small sample-size precluded the examination for specific *CXCR4* (nonsense *versus*  
198 frameshift) mutational impact. Additional limitations include the lack of centralized  
199 molecular marker assessment, absence of non-L265P *MYD88*<sup>MUT</sup> data, and sparse



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242 JJC provided the data for this analysis. JPA, SD, DRW, DRL, CLC, ED, EK, EU, OT, P.  
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245 authors approved the final version of the manuscript.

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Parameter	
Age (years) at treatment initiation, median (range)	66.5 (40-87)
Sex, n (%) Females	91 (36)
Serum IgM, mg/dL, median (interquartile range)	3000 (1315-5067)
Hemoglobin, g/dL, median (interquartile range)	9.9 (8.3-11.5)
Platelet count, x 10 <sup>9</sup> /L, median (interquartile range)	210 (119-311)
Bone marrow lymphoplasmacytic infiltrate, median, % (range)	54 (26-80)
Beta-2 microglobulin, mcg/mL, median (interquartile range)	3.6 (2.5-5.2)
<i>MYD88</i> <sup>L265P</sup> mutated, n (%)	154/172 (90)
<i>CXCR4</i> mutated, n (%)	25/89 (28)
Elevated serum lactate dehydrogenase, n (%)	21 (18)
<b>International Prognostic Scoring System for WM</b>	
Low Risk, n (%)	25/136 (19)
Intermediate Risk, n (%)	38/136 (28)
High Risk, n (%)	73/136 (54)
WM: Waldenström Macroglobulinemia	

302

303 **Figure Legends**

304 **Figure 1. Progression-free survival (PFS) and Overall Survival (OS) by genotype.**

305 **A)** Patients with a MYD88 mutated and wild type genotype had comparable PFS; the  
306 five-year PFS was 64% for both MYD88L265P and MYD88WT genotypes ( $p=0.4$ );  
307 median PFS was not reached in either cohort. **B)** The median OS was not reached in  
308 either MYD88L265P mutated and MYD88WT subcohorts, and 5-year OS rates were  
309 comparable [89% (95% CI: (83-94) vs 74% (95% CI: 55-100), respectively,  $p=0.44$ ). **C)**  
310 Patients with a CXCR4 mutated genotype demonstrated an inferior PFS [5-year PFS  
311 rates 43 % versus 78% for CXCR4WT genotype,  $p=0.0036$ ; HR: 2.8 (95% CI: 1.4-5.7)].  
312 **D)** The median OS was not reached for subcohorts with either CXCR4 genotype; 5-year  
313 OS was 75% (95% CI: 58-98) for CXCR4MUT versus 91% for CXCR4WT [95% CI: 83-  
314 99 ( $p=0.036$ ); HR 2.6 (95% CI: 1.02-6.9)] subcohort.

315 **Figure 2. Progression of disease within 24 months. A) 2-year Landmark Analysis**

316 **(n=201):** Patients with disease progression within 24 months had a higher risk of death  
317 compared to those without disease progression within 24 months [5-year OS of 71%  
318 and 86%, respectively; HR 3.1 (95% CI: 1.4-6.9),  $p=0.005$ . **B) Comparison of OS for**  
319 **POD24 cohort with general population:** When compared with an age, sex, calendar  
320 year and country of origin-matched cohort, the OS for patients that were alive and  
321 progressed within 24 months of initiation of BR was significantly inferior to that of the  
322 general population [Observed deaths: 8, expected deaths: 2.1; Standardized Mortality  
323 Ratio of 3.7 (95% CI: 1.6-7.4),  $p=0.004$ ]. **C) Comparable OS of non-POD24 cohort**  
324 **and the matched general population from the 2-year landmark:** When compared  
325 with an age, sex, calendar year and country of origin-matched cohort, the OS for  
326 patients that did not progress within 24 months of initiation of BR was comparable to  
327 that of the general population [Observed Deaths: 23; Expected Deaths: 21.2;  
328 Standardized Mortality Ratio of 1.1 (95% CI: 0.7-1.6),  $p=0.75$ ].



