

Partial response or better at six months is prognostic of superior progression-free survival in Waldenström macroglobulinaemia patients treated with ibrutinib

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Introduction

The oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib is approved in Europe and the United States (USA) for the treatment of patients with symptomatic Waldenström macroglobulinaemia (WM). The approval was based on the

Summary

Ibrutinib is associated with durable responses in patients with Waldenström macroglobulinaemia (WM). We hypothesized that response depth is predictive of progression-free survival (PFS) in WM patients treated with ibrutinib. Using landmark analyses, we evaluated response depth in two cohorts of WM patients treated with ibrutinib monotherapy. The learning cohort was composed of 93 participants from two clinical trials, and the validation cohort of 190 consecutive patients treated off clinical trial. Rates of partial response (PR) or better at six months in learning and validation cohorts were 64% and 71% respectively ($P = 0.29$). In the learning cohort, three-year PFS rates for patients who attained PR or better at six months *versus* not were 81% and 57% respectively ($P = 0.009$). In the validation cohort, three-year PFS rates for patients who attained PR or better at six months *versus* not were 83% and 54% respectively ($P = 0.008$). In multivariate analyses, attaining PR or better at six months was associated with superior PFS in the learning [hazard ratio (HR) 0.38; $P = 0.01$] and validation cohorts (HR 0.18; $P = 0.004$). Attaining PR at six months on ibrutinib emerges as an intermediate outcome of interest and should be validated as surrogate for PFS in clinical trials evaluating Bruton tyrosine kinase inhibitors in WM.

Keywords: Waldenström macroglobulinaemia, Ibrutinib, response.

results of a prospective phase II study in which 63 previously treated patients with WM were treated with ibrutinib monotherapy, with an overall response rate (ORR) of 91%, a major response [partial response (PR) or better] rate of 73% and a five-year progression-free survival (PFS) of 54%.¹ In two other prospective studies in previously untreated patients

or those refractory to rituximab therapy similar response rates were seen, with an 18-month PFS rate in previously untreated *versus* rituximab-refractory of 92% vs. 86% respectively.^{2,3} WM is an indolent malignancy, and with the use of effective therapies, PFS can be substantially prolonged, thereby requiring protracted patient follow-up in randomized controlled clinical trials.

Prior studies have suggested that depth of response correlates with PFS in WM patients treated with chemoimmunotherapy.⁴⁻⁶ However, it is unclear if depth of response can be used as a surrogate for PFS in patients with WM treated with ibrutinib monotherapy. This analysis is timely, as the recently published open-label, randomized phase III ASPEN study comparing zanubrutinib and ibrutinib, has the proportion of patients achieving very good partial response (VGPR) or better as the primary end-point.⁷

We hypothesized that the depth of response at a specific time point following treatment initiation is predictive of PFS in patients with WM treated with ibrutinib. We tested our hypothesis by evaluating two separate cohorts (learning and validation) of WM patients treated with ibrutinib monotherapy using a landmark analysis.

Patient and methods

Patient selection

The patients who participated in two prospective clinical trials (NCT01614821 and NCT02604511) at Dana-Farber Cancer Institute (DFCI), Memorial Sloan Kettering Cancer Center and Stanford Cancer Center composed the learning cohort. The validation cohort was composed of consecutive WM patients treated with ibrutinib monotherapy off clinical trial at DFCI and Mayo Clinic. All patients provided consent to having their data collected for research, and met clinicopathological criteria for a diagnosis of WM requiring treatment based on guidelines from the 2nd International Workshop on WM (IWW-2).^{8,9} Patients with central nervous system involvement by WM were excluded from the study.

Data collection

Pertinent clinicopathological data were collected at the time of ibrutinib therapy initiation. Categorical responses were assessed based on modified IWW-6 criteria,¹⁰ in which assessment of extramedullary disease was not required for attainment of a minor response (MR, 25–50% decrease in serum IgM from baseline), PR (50–90% decrease in serum IgM from baseline), VGPR (>90% decrease in serum IgM from baseline, or normalization of serum IgM levels with persistence of a detectable IgM monoclonal paraprotein in serum protein electrophoresis) but was mandated for attainment of complete response (CR; normalization of serum IgM level and serum protein electrophoresis and complete resolution of extramedullary disease as well as bone marrow involvement).

This modification to IWW-6 response criteria is widely used for clinical trial design. We evaluated two depths of response: attainment of PR or better, and VGPR or better. As the depth of response to ibrutinib monotherapy is time-dependent, with rates of response increasing over time, we chose two response assessment time points, at six (± 1 month, in the validation cohort) and 12 months (± 2 months, in the validation cohort) from treatment initiation. At DFCI and for patients from clinical trials, *MYD88* and *CXCR4* mutational status was assessed in CD19-selected bone marrow samples using allele-specific polymerase chain reaction (AS-PCR) for *MYD88* L265P and nonsense *CXCR4* mutations. Frameshift *CXCR4* mutations were assessed by Sanger sequencing. *MYD88* and *CXCR4* mutational detection techniques have been previously reported.¹¹⁻¹⁴ At Mayo Clinic, *MYD88* mutational status was assessed by the amplification-refractory mutation system (ARMS), a variant of AS-PCR. DNA is extracted using the Qiagen DNeasy kit (Qiagen, Valencia, CA, USA) from archived unsorted bone marrow aspirate sample pellets fixed in methanol + acetic acid. A single-tube multiplex ARMS is performed using primers situated in exon 5 of *MYD88* (NM_002468.4), including one primer specifically targeting the L265P alteration. Reaction products are analyzed using capillary electrophoresis (QIAxcel, Qiagen). *MYD88* wild-type control amplification yields a PCR product of 141 base pairs (bp), and if present, an additional specific 72-bp product denotes the L265P mutation. *CXCR4* mutational testing was not performed in Mayo Clinic patients.

Statistical analysis

Patients' characteristics and response rates are presented using descriptive statistics. Differences between categorical variables were assessed using the chi-squared test or the Fisher exact test, based on the number of observations. Depending on the time of the landmark analyses, PFS was estimated starting at the six-month mark (for patients with response assessment at six months) and starting at the 12-month mark (for patients with response assessment at 12 months). Survival curves were generated using the Kaplan–Meier method for incomplete observations and compared using the log-rank test. Since we performed four separate landmark analyses evaluating two depths of response (PR or better, and VGPR or better) at two difference time points (six and 12 months), $P < 0.0125$ was considered statistically significant ($P < 0.05$ divided by 4, to adjust for multiplicity). We then fitted univariate and multivariate Cox proportional-hazard regression models for PFS at each landmark. Outcomes are reported using hazard ratio (HR) with 95% confidence interval (CI). Differences in overall survival or survival after first treatment initiation were not assessed due to a small number of deaths in this cohort ($n = 37$; 13%) at the time of this report. Calculations were obtained using STATA 15 (StataCorp, College Station, TX, USA).

Results

Patients' characteristics

Ninety-three and 190 patients comprised the learning and validation cohorts respectively. The distribution of patients' characteristics as well as differences between groups are shown in Table I. In the validation *versus* learning cohort, there was a statistically lower proportion of male patients (62% vs. 74%, $P = 0.04$), and bone marrow involvement $\geq 50\%$ (48% vs. 68%; $P = 0.003$) and a trend towards a higher proportion of previously untreated patients (78% vs. 68%; $P = 0.07$) respectively. There were no statistical differences between cohorts in the proportion of patients age > 65 years, haemoglobin level ≤ 115 g/l, platelet count ≤ 100 K/ μ l, serum $\beta 2$ -microglobulin ≤ 3 mg/l, serum IgM level > 7000 mg/dl, IPPSWM distribution, MYD88 and CXCR4 mutational status. CXCR4 mutational status data were not available in one patient from the learning and 83 patients from the validation cohorts.

Response to ibrutinib therapy

Categorical response rates at six and 12 months in patients from the learning and validation cohorts are shown in Table II.

At six months, data on response were available in 86 patients (92%) from the learning cohort and in 150 patients (79%) from the validation cohort. In the learning cohort, seven patients were not evaluable for response as the follow-up time was shorter than six months, and therefore there were no missing data. In the validation cohort, 26 were not evaluable for response due to follow-up shorter than six months, leaving 14 patients (7%) with missing data. The rates of PR or better at six months in the learning and validation cohorts were 64% (55/86) and 71% (106/150),

respectively ($P = 0.29$), and the rates of VGPR or better were 9% (8/86) and 19% (28/150) respectively ($P = 0.06$).

At 12 months, data on response were available in 76 patients (82%) from the learning cohort and in 126 patients (66%) from the validation cohort. In the learning cohort, 16 patients were not evaluable for response as follow-up time was shorter than 12 months, leaving one patient (1%) with missing data. In the validation cohort, 54 patients were not evaluable for response due to follow-up time shorter than 12 months, leaving 10 patients (8%) with missing data. The rates of PR or better at 12 months in the learning and validation cohorts were 74% (56/76) and 81% (102/126), respectively ($P = 0.23$), and the rates of VGPR or better were 20% (15/76) and 25% (31/126) respectively ($P = 0.42$). There was one patient in the validation cohort who attained CR.

Landmark analyses at six months

The median follow-up times for the learning cohort was 40 months (95% CI 38–49 months) while it was 31 months (95% CI 28–34 months) for the validation cohort ($P < 0.001$).

In the learning cohort, the three-year PFS rate starting at the six-month mark was 72% (95% CI 60–81%; Fig 1A). For patients who attained PR or better at six months *versus* not, the three-year PFS rate starting at the six-month mark was 81% (95% CI 67–89%) vs. 57% (95% CI 35–74%) respectively ($P = 0.009$, Fig 1B). For patients who attained VGPR or better *versus* not at six months, the three-year PFS rate was 88% (95% CI 39–98%) vs. 70% (95% CI 58–80%) respectively ($P = 0.25$, Fig 1C).

In the validation cohort, the three-year PFS rate starting at the six-month mark was 76% (95% CI 66–84%; Fig 1D). For patients who attained PR or better at six months *versus* not, the three-year PFS rate starting at the six-month mark was 83% (95% CI 71–90%) vs. 54% (95% CI 32–71%)

Table I. Baseline characteristics of Waldenström macroglobulinaemia patients treated with ibrutinib from the learning and validation cohorts.

Characteristic	Learning cohort ($n = 93$)	Validation cohort ($n = 190$)	P value
Age > 65 years	50 (54%)	116 (61%)	0.24
Male sex	69 (74%)	118 (62%)	0.04
Haemoglobin level ≤ 11.5 g/dl	66 (71%)	131/179 (73%)	0.70
Platelet count ≤ 100 K/ μ l	9 (10%)	23/176 (13%)	0.41
Serum $\beta 2$ -microglobulin > 3 mg/l	65/91 (71%)	77/124 (62%)	0.15
Serum IgM level > 7000 mg/dl	6 (5%)	10/189 (5%)	0.98
Bone marrow involvement $\geq 50\%$	63 (68%)	78/161 (48%)	0.003
IPSSWM			
Low risk	20/91 (22%)	30/134 (22%)	0.54
Intermediate risk	34/91 (38%)	41/134 (31%)	
High risk	37/91 (41%)	63/134 (47%)	
MYD88 L265P mutation present	89 (96%)	137/146 (94%)	0.54
CXCR4 mutation present	36/92 (39%)	42/107 (39%)	0.99
Previously treated	63 (68%)	148 (78%)	0.07

IPSSWM, International Prognostic Scoring System for Waldenström macroglobulinaemia.

Table II. Categorical response rates to ibrutinib at six and 12 months in Waldenström macroglobulinaemia patients from the learning and validation cohorts.

At 6 months	Learning cohort (<i>n</i> = 86)	Validation cohort (<i>n</i> = 150)	<i>P</i> value
VGPR	8 (9%)	28 (19%)	0.18
PR	47 (55%)	78 (52%)	
MR	18 (21%)	30 (20%)	
NR	13 (15%)	14 (9%)	
At 12 months	Learning cohort (<i>n</i> = 76)	Validation cohort (<i>n</i> = 126)	<i>P</i> value
VGPR	15 (20%)	31 (25%)	0.41
PR	41 (54%)	71 (56%)	
MR	12 (16%)	18 (14%)	
NR	8 (11%)	6 (5%)	

VGPR, very good partial response; PR, partial response; MR, minor response; NR, no response.

respectively ($P = 0.008$, Fig 1E). For patients who attained VGPR or better *versus* not at six months, the three-year PFS rate starting at the six-month mark was 84% (95% CI 43–97 vs. 73% (95% CI 61–82%)) respectively ($P = 0.88$, Fig 1F).

Landmark analyses at 12 months

In the learning cohort, the three-year PFS rate starting at the 12-month mark was 71% (95% CI 57–81%; Fig 2A). For patients who attained PR or better at 12 months *versus* not, the three-year PFS rate starting at the 12-month mark was 75% (95% CI 58–86%) vs. 62% (95% CI 35–80%) respectively ($P = 0.08$, Fig 2B). For patients who attained VGPR or better *versus* not at 12 months, the three-year PFS rate starting at the 12-month mark was 69% (95% CI 26–91%) vs. 72% (95% CI 57–82%) respectively ($P = 0.99$, Fig 2C).

In the validation cohort, the three-year PFS rate starting at the 12-month mark was 71% (95% CI 57–81%; Fig 2D). For patients who attained PR or better at 12 months vs. not, the three-year PFS was 76% (95% CI 58–86%) vs. 56% (95% CI 27–77%), respectively ($P = 0.02$, Fig 2E), and therefore did not meet the pre-defined study criteria for statistical significance. For patients who attained VGPR or better at 12 months vs. not, the three-year PFS rate starting at the 12-month mark was 56% (95% CI 27–77%) vs. 75% (95% CI 62–84%) respectively ($P = 0.42$, Fig 2F).

Univariate and multivariate analysis

We fitted univariate models to identify predictive factors for PFS starting at the six-month mark in the learning and validation cohorts separately. These models are shown in Table III.

In the learning cohort, attaining a major response at six months was associated with better PFS (HR 0.37, 95% CI 0.17–0.80; $P = 0.01$), while serum IgM ≥ 7000 mg/dl (HR 4.65, 95% CI 1.36–16.0; $P = 0.01$) and *CXCR4* mutations (HR 2.47, 95% CI 1.13–5.39; $P = 0.02$) were associated with

worse PFS. No other variables were associated with either a better or worse PFS. In a multivariate model including attaining PR or better at six months and *CXCR4* mutations, attaining a major response at six months was an independent prognostic factor of adverse PFS (HR 0.38, 95% CI 0.15–0.84; $P = 0.01$). None of these variables violated the proportionality assumption ($P = 0.85$ and $P = 0.78$ respectively). The interaction term between PR or better at six months and *CXCR4* mutations was not significant ($P = 0.38$).

In the validation cohort, attaining PR or better at six months was associated with better PFS (HR 0.38, 95% CI 0.18–0.80; $P = 0.01$), while platelet count ≤ 100 K/ μ l (HR 4.73, 95% CI 1.94–11.5; $P = 0.001$) and *CXCR4* mutations (HR 3.01, 95% CI 1.09–8.30; $P = 0.03$) were associated with worse PFS. No other variables were associated with either a better or worse PFS. In a multivariate model including attaining PR or better at six months, platelet count ≤ 100 K/ μ l and *CXCR4* mutations, attaining PR or better at six months was an independent prognostic factor for better PFS (HR 0.18, 95% CI 0.05–0.58; $P = 0.004$). None of these variables violated the proportionality assumption ($P = 0.55$, $P = 0.71$ and $P = 0.39$ respectively). The interaction term between PR or better at six months and *CXCR4* mutations was not significant ($P = 0.97$).

Discussion

Ibrutinib is the only drug formally approved for the treatment of patients with symptomatic WM in the USA and Europe, and a number of prospective and retrospective studies have shown ibrutinib monotherapy to be safe, effective and able to induce durable responses in treatment-naïve as well previously treated patients with WM.^{1–3,15,16} Data, however, are limited regarding prognostic factors for PFS on ibrutinib therapy. Furthermore, the association between depth of response to and PFS on ibrutinib has not been previously evaluated.

To the best of our knowledge, this is the first study evaluating the prognostic value of depth of response on PFS in

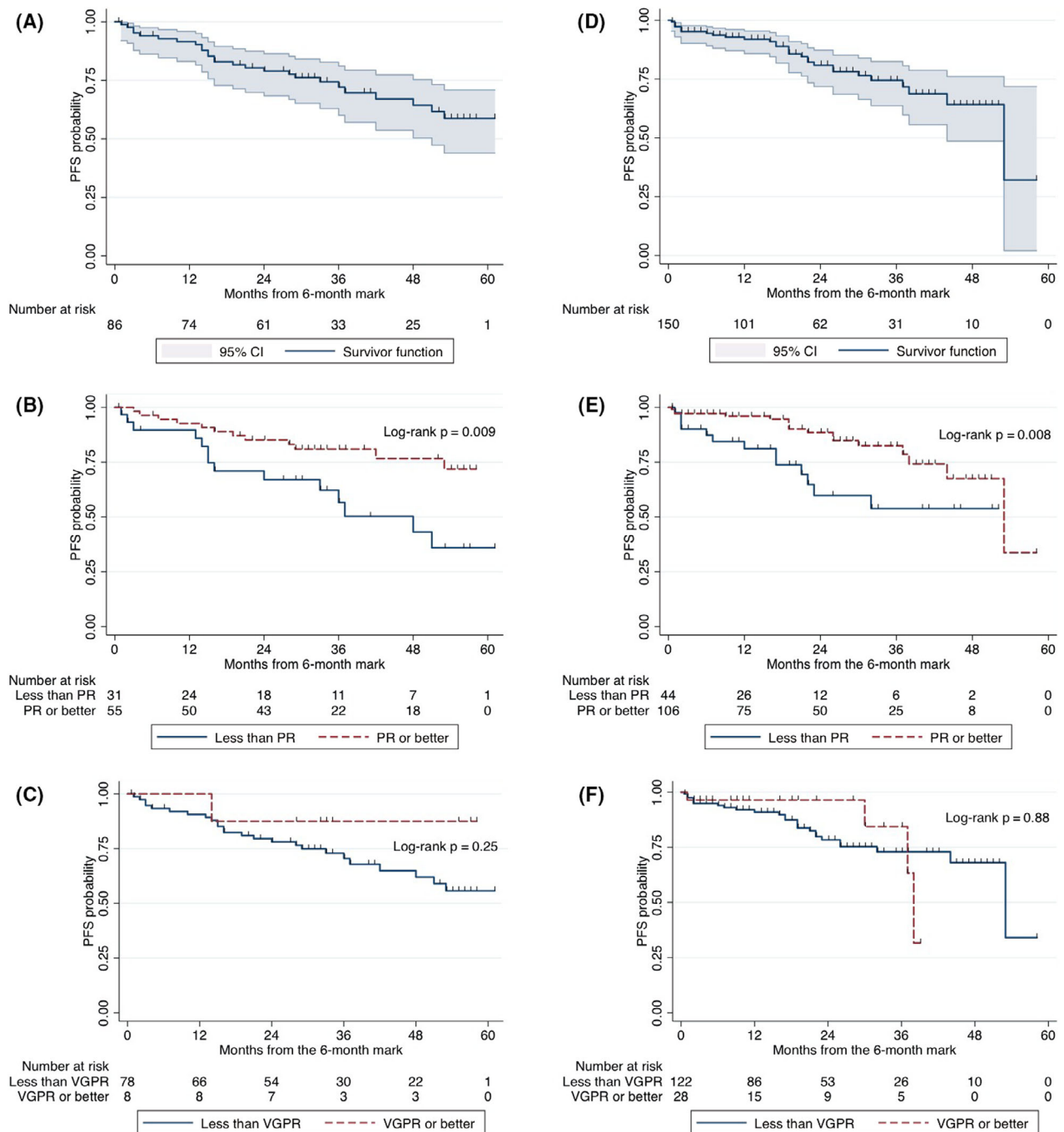


Fig 1. Kaplan–Meier progression-free survival (PFS) curves starting at the six-month mark in Waldenström macroglobulinaemia patients. Learning cohort: (A) PFS, (B) PFS according to attaining partial response (PR) at six months or not, and (C) PFS according to attaining very good partial response (VGPR) at six months or not. Validation cohort: (D) PFS, (E) PFS according to attaining PR at six months or not, and (F) PFS according to attaining VGPR at six months or not. CI, confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]

patients with WM treated with ibrutinib monotherapy. All the patients in the validation cohort were treated at academic institutions with experience in WM. Using a landmark analysis, we evaluated two depths of response, PR or better and VGPR or better, at two different time points, six and 12 months. The only combination of depth and timing of

response that met our predetermined criteria, and therefore the only factor prognostic of a superior PFS in both the learning and the validation cohorts, was attaining PR or better at six months. As the median follow-up time for the learning cohort was 40 months and for the validation cohort was 31 months, we presented PFS rates at three years. The

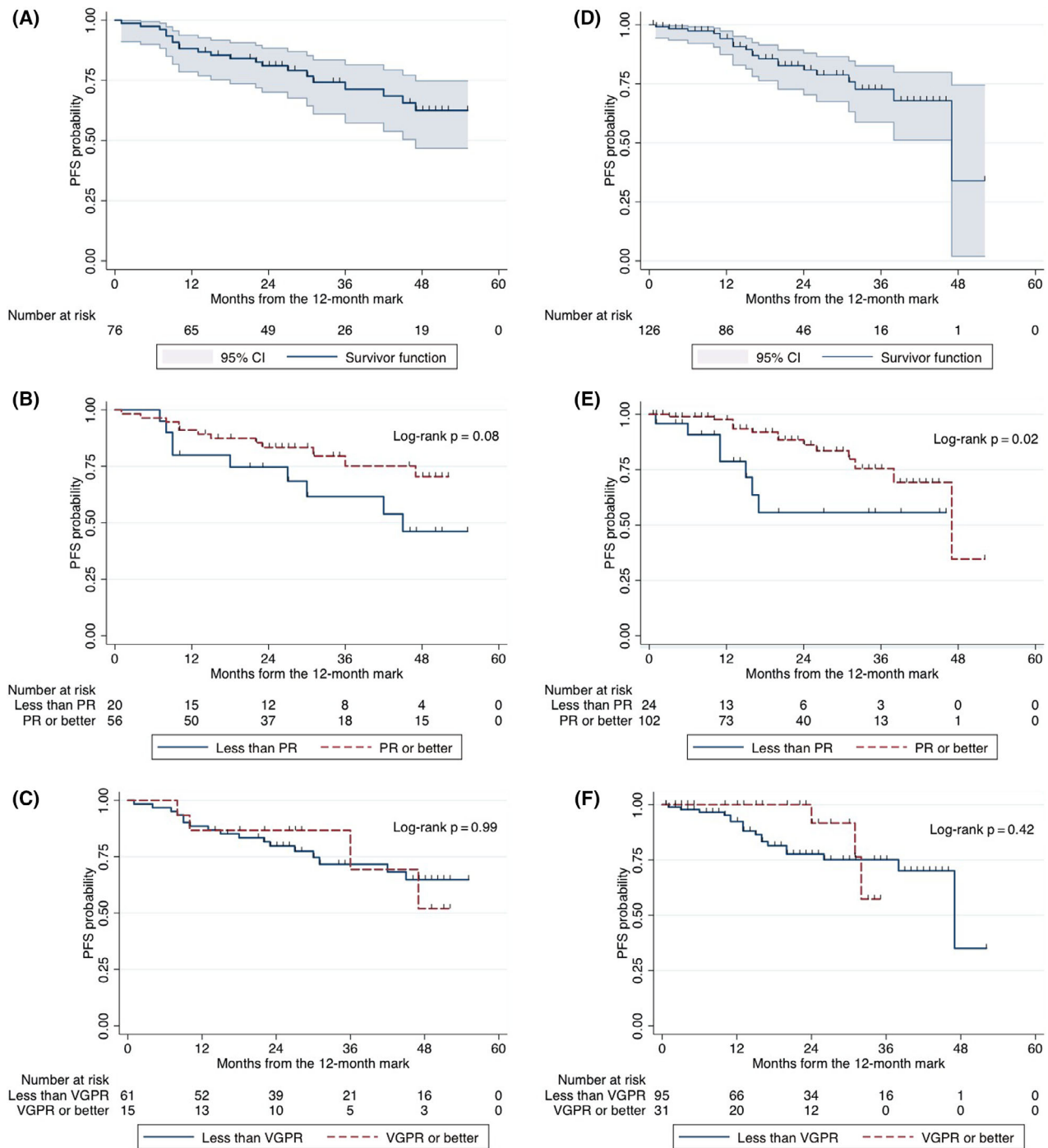


Fig 2. Kaplan–Meier progression-free survival (PFS) curves starting at the 12-month mark in Waldenström macroglobulinaemia patients. Learning cohort: (A) PFS, (B) PFS according to attaining partial response (PR) at 12 months or not, and (C) PFS according to attaining very good partial response (VGPR) at 12 months or not. Validation cohort: (D) PFS, (E) PFS according to attaining PR at 12 months or not, (F) PFS according to attaining VGPR at 12 months or not. CI, confidence interval. [Colour figure can be viewed at wileyonlinelibrary.com]

three-year PFS rates for attaining PR or better *versus* not in the learning cohort were 81% and 57%, respectively, while in the validation cohort the three-year PFS rates for attaining PR or better *versus* not were 83% and 54% respectively.

The baseline characteristics between our learning and validation cohorts were relatively similar, with higher proportion of men and bone marrow involvement $\geq 50\%$ in the validation cohort with no other differences. The patients included had a

Table III. Univariate Cox proportional-hazard regression models for progression-free survival in the learning and validation cohorts.

	Learning cohort		Validation cohort	
	HR (95% CI)	P value	HR (95% CI)	P value
Age >65 years	1.36 (0.63–2.96)	0.43	1.28 (0.60–2.77)	0.52
Male sex	1.02 (0.41–2.56)	0.96	1.80 (0.77–4.22)	0.18
Haemoglobin level ≤ 115 g/l	1.03 (0.45–2.38)	0.94	1.54 (0.58–4.09)	0.39
Platelet count ≤ 100 K/ μ l	2.76 (0.82–9.26)	0.10	4.73 (1.94–11.5)	0.001
Serum $\beta 2$ -microglobulin > 3 mg/l	0.53 (0.24–1.20)	0.13	1.39 (0.54–3.60)	0.49
Serum IgM level > 7000 mg/dl	4.65 (1.36–16.0)	0.01	1.23 (0.29–5.23)	0.78
Bone marrow involvement $\geq 50\%$	0.49 (0.23–1.06)	0.07	1.02 (0.47–2.24)	0.95
High <i>versus</i> low IPSSWM	1.45 (0.52–4.02)	0.47	3.77 (0.85–16.8)	0.08
Intermediate <i>versus</i> low IPSSWM	0.87 (0.30–2.51)	0.80	3.00 (0.61–14.7)	0.18
<i>MYD88</i> L265P mutation present	0.20 (0.03–1.58)	0.13	UTC	
<i>CXCR4</i> mutation present	2.47 (1.13–5.39)	0.02	3.01 (1.09–8.30)	0.03
Previously treated	1.65 (0.60–4.52)	0.33	1.69 (0.51–5.63)	0.39
PR or better at 6 months	0.37 (0.17–0.80)	0.01	0.38 (0.18–0.80)	0.01

IPSSWM, International Prognostic Scoring System for Waldenström macroglobulinaemia; PR, partial response; HR, hazard ratio; CI, confidence interval; UTC, unable to calculate.

Bold values denote statistically significant.

similar distribution to WM patients in the general population, with more than half of the patients being older than 65 years and an approximate 2-to-1 male predominance.^{17–19} The laboratory values for serum haemoglobin, $\beta 2$ -microglobulin and IgM levels as well as platelet counts were consistent with previous retrospective and prospective studies.^{4,5,15} Consistently, the proportion of patients deemed to be of low, intermediate and high risk based on the International Prognostic Scoring System for Waldenström macroglobulinaemia (IPSSWM) was similar to the seminal report by Morel and colleagues.²⁰ Finally, the distribution of the genomic alterations in *MYD88* and *CXCR4* are consistent with prior reports from our research group and others.^{11,16,21–23} Overall, we believe the characteristics of the patients reported in the present study are representative of the WM population, which would make our results generalizable.

We also assessed univariate and multivariate Cox proportional-hazard regression models to better understand the independent impact of attaining PR or better at six months on PFS. As data on prognostic factors in WM patients on ibrutinib therapy are limited, we constructed the statistical models by evaluating clinically relevant factors such as age, serum IgM levels and haemoglobin levels, among others. Attaining PR or better at six months was an independent favourable prognostic factor for PFS in both the learning and validation cohorts, associated with a 60–80% lower risk of progression and/or death than in patients who did not attain PR or better at six months.

We believe our findings of impact of attaining PR or better at six months are of clinical relevance and could help practitioners counselling patients and family members, and more importantly, serve as a surrogate for PFS in clinical trial design evaluating BTK inhibitors. The covalent,

irreversible BTK inhibitors acalabrutinib, zanubrutinib and tirabrutinib are undergoing clinical development in WM, and have shown encouraging safety and efficacy data.^{24–26} The results of the randomized ASPEN study have been recently published.⁷ In this open-label study, 201 WM patients were randomized to receive zanubrutinib or ibrutinib. The main objective of the study was to show superiority in VGPR rates of zanubrutinib over ibrutinib. In this regard, the study did not meet its end-point, as zanubrutinib and ibrutinib were associated with VGPR rates of 28% and 19%, respectively, and were not statistically different. Rates of PR or better were comparable at 77% and 78%, and with a median follow-up of 18 months, the 18-month PFS rates were also similar at 85% and 84% respectively.

The presence of *CXCR4* mutations emerged as an adverse prognostic factor for PFS in WM patients treated with ibrutinib monotherapy. We had previously reported an adverse impact of *CXCR4* mutations in depth of response and PFS in WM patients treated with ibrutinib monotherapy.^{1,3,16,27} However, not all *CXCR4* mutations appear to weigh equally on outcome, as there is mounting evidence that nonsense *CXCR4* mutations, especially with a clonality higher than 25%, might have a more adverse impact on outcomes to ibrutinib than frameshift *CXCR4* mutations.^{16,28} These findings support the development of therapeutic strategies targeting *CXCR4*, as one avenue for clinical research in patients with WM. Prospective clinical trials evaluating the combination of ibrutinib and the anti-*CXCR4* monoclonal antibody ulocuplumab (NCT03225716) and ibrutinib and the *CXCR4*-targeting small molecule mavorixafor (NCT04274738) are under way in WM patients who harbour a *CXCR4* mutation. Akin to chronic lymphocytic leukaemia, *BTK* *C481S* mutations have shown to confer resistance to irreversible, covalent

BTK inhibitors in patients with WM.^{29,30} A new generation of reversible, non-covalent BTK inhibitors that do not interact with the *C481* loci, such as vecabrutinib (NCT03037645), LOXO-305 (NCT03740529) and ARQ513 (NCT03162536), are also being evaluated in clinical trials.

Our study has limitations. First, the total sample size of 283 patients could be considered small, when compared to other malignancies. However, WM is a rare disease with an incidence of 1500 new cases per year in the USA. Taking this aspect into account, our cohort is the largest reporting clinical experience in WM patients on ibrutinib. Second, there were missing data on response in the validation and in the learning cohort. Yet, the rates of missing data were low, at 1% in the learning cohort and less than 10% in the validation cohort. Despite the difference in missing response data, the rates of response at six and 12 months were not statistically different between the learning and validation cohorts. Data on *CXCR4* mutational status were missing in 30% of patients, and the results of the subgroup analyses with regard to *CXCR4* mutational status should be taken with caution. Nevertheless, the clinical features of the patients in our cohorts (e.g. age and sex distribution as well as median serum IgM levels) were consistent with and representative of the general population of patients with WM.

We should note that the purpose of our study was to identify a predictive marker of PFS in WM patients that could be later validated as a surrogate marker in clinical trials. Our purpose was not to identify a timepoint in which ibrutinib therapy should be modified, and therefore not attaining PR or better at six months on ibrutinib monotherapy should not be factored into the decision of discontinuing or changing ibrutinib therapy in patients with WM. We conclude that attaining PR or better at six months on ibrutinib monotherapy was associated with better PFS and should be validated as a surrogate end-point for PFS in clinical trials evaluating BTK inhibitors in WM patients.

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Author contributions

JJC designed the study and performed the analysis. JJC, JPA, JNG, SZ and KM collected patients' data. MD, MLG, AK, CJ, XL, MM, NT, RK, LX, GY and ZRH performed molecular testing in patients' samples. JJC, JA, SZ, CAF, RHA, MLP, SMA, MAG, PK and SPT took care of patients. JJC and PK drafted the initial manuscript. All the authors critically reviewed and approved the final manuscript.

Conflicts of interests

JJC received honoraria and/or research funding from Abbvie, Beigene, Janssen, Kymera, Millennium, Pharmacyclics and TG Therapeutics. RHA received research funding from Janssen and Pharmacyclics. MLP received honoraria and/or research funding from Celgene, Kite, Merck, Novartis and Pharmacyclics. SMA received research funding from Affimed, AI Therapeutics, Bristol Myers Squibb, Pfizer, Regeneron, Seattle Genetics and Trillium. MAG received honoraria and/or research funds from Abbvie, Alnylam, Amgen, Annexon, Appellis, Celgene, Ionis/Akcea, Janssen, Johnson & Johnson, Pharmacyclics, Prothena, Teva and Spectrum. PK received research funding from Amgen, Celgene and Takeda Pharmaceuticals. SPT received research funding and/or consulting fees from Bristol Myers Squibb, Janssen and Pharmacyclics. All the other authors have no conflict of interests to disclose.

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