American Journal of Hematology

WILEY

AJH

RESEARCH ARTICLE

Final Report of a Phase II Study of Ibrutinib and Venetoclax in Previously Untreated Waldenström Macroglobulinemia

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Received: 10 November 2025 | **Revised:** 11 February 2026 | **Accepted:** 9 March 2026

ABSTRACT

The BTK inhibitor ibrutinib and the BCL-2 antagonist venetoclax are active therapies as single agents in Waldenström macroglobulinemia (WM). In this phase 2 study, we sought to investigate the combination of ibrutinib and venetoclax as a 2-year fixed-duration, oral-based, chemotherapy-free regimen in symptomatic, treatment-naive WM patients. All patients had *MYD88* mutations, 17 (38%) had *CXCR4* mutations, and 4 (9%) had *TP53* alterations. Following enrollment of 45 patients, treatment and enrollment were stopped due to the occurrence of ventricular arrhythmias in 4 (9%), which included two grade 5 events. The median treatment time was 10 cycles, each lasting 28 days. Follow-up continued after protocol treatment was terminated. The very good partial response/complete response (VGPR/CR) rate was 42%, and it was lower in patients with *CXCR4* (29% vs. 50%) or *TP53* (25% vs. 44%) mutations. With a median follow-up of 49 months, the median progression-free survival (PFS) was 36 months (range 28–42). The median treatment-free survival (TFS) and overall survival (OS) were not reached, and the 4-year TFS and OS rates were 73% and 91%, respectively. The median PFS after end of therapy (PFS-EOT) was 29 months. *TP53* mutations were associated with inferior PFS, TFS, and PFS-EOT, while *CXCR4* mutations did not adversely impact these outcomes. Given the deep and durable responses seen in this study, concurrent BTK and BCL-2 inhibition warrants further development in WM. *TP53* mutations emerged as an adverse factor in WM in this combination study.

1 | Introduction

Bruton tyrosine kinase (BTK) inhibitors and B-cell leukemia/lymphoma 2 (BCL-2) antagonists, administered as monotherapy, are highly active and well-tolerated in Waldenström macroglobulinemia (WM) [1–4]. Ibrutinib and zanubrutinib are approved by the US Food & Drug Administration, and venetoclax is endorsed by the National Comprehensive Cancer Network for the treatment of WM. Preclinical data demonstrated a synergistic effect when combining ibrutinib and venetoclax in WM [5], and clinical data have shown the combination to be safe and effective in chronic lymphocytic leukemia (CLL) [6]. The European Medicines Agency (EMA) has approved this combination for the treatment of CLL.

Based on this experience, we initiated a prospective study of the combination of the covalent BTK inhibitor ibrutinib and the BCL-2 antagonist venetoclax in patients with treatment-naïve WM. This was the first chemotherapy-free, fixed-duration, all-oral regimen to be evaluated in a clinical trial in WM. As

initially designed, the accrual goal was 50 patients. However, study enrollment and therapy were stopped on March 31, 2022, after enrollment of 45 patients because of ventricular arrhythmia events in 4 (9%) patients, including two grade 5 events, as previously reported [7].

After enrollment and protocol therapy were terminated, follow-up continued, and we present the final report of this study here. We aim to report on the durability of the response and to provide insights into predictive factors for survival, with a special interest in the impact of *CXCR4* and *TP53* mutations, as these mutations can affect treatment outcomes in WM patients receiving BTK inhibitors [1, 2, 8].

2 | Materials and Methods

This was an investigator-initiated, multicenter, prospective Phase 2 study in symptomatic patients with treatment-naïve WM (NCT04273139). The study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board (DFCI 19-651). All patients were at least 18 years old, had a clinicopathological diagnosis of WM, and met the treatment criteria established by the 2nd International Workshop for WM (IWWM-2) [9, 10]. All patients provided written consent before the commencement of research activities. Enrollment started on July 1, 2020, and stopped on February 10, 2022. Study therapy was stopped on March 31, 2022. The data cutoff for this report was March 31, 2025.

Intended therapy consisted of ibrutinib 420 mg once daily during cycle 1. Venetoclax was added in cycle 2 at 100 mg once daily for 1 week, followed by 200 mg once daily for 1 week, and then 400 mg once daily for 2 weeks. Ibrutinib 420 mg and venetoclax 400 mg were then administered concurrently, once daily, for cycles 3 to 24. Study therapy was given in 4-week cycles and was planned to stop after completing 24 cycles. No additional therapy was provided to participants after study therapy was stopped. The participants were monitored for disease progression and offered standard therapies or another clinical trial upon symptomatic progression. All patients received allopurinol 300 mg orally once daily, starting 3 days before and during cycle 2, and underwent tumor lysis syndrome monitoring with serum potassium, calcium, phosphorus, and uric acid measurements at 0, 8, and 24 h after the first 100 mg, 200 mg, and 400 mg doses of venetoclax. No antiviral, antibacterial, or antifungal prophylaxis was provided as part of the study.

All patients underwent baseline laboratory studies, a bone marrow biopsy with genotyping for *MYD88* using polymerase chain reaction, as well as next-generation sequencing assays for *CXCR4* and *TP53*. Additionally, computed tomography (CT) scans of the chest, abdomen, and pelvis with intravenous contrast were used to evaluate extramedullary disease. Bone marrow biopsies were performed after 6, 12, and 24 months of study therapy. CT scans were performed every 6 months only in patients who had extramedullary disease at baseline, defined as any lymph node ≥ 1.5 cm in maximum diameter or spleen size ≥ 15 cm, and continued until resolution of extramedullary disease.

The primary outcome was the attainment of a very good partial response (VGPR), defined as a 90% decrease in serum IgM level from baseline or normalization of serum IgM levels with persistence of an IgM monoclonal paraprotein detectable by serum protein electrophoresis and immunofixation. Based on an assumed null hypothesis of a VGPR rate of 25% or lower and an alternative hypothesis of 45% or higher, with a double-sided alpha of 0.03 and a power of 80%, a sample size of 50 participants was required. The study would have met its endpoint with at least 20 patients attaining VGPR.

The baseline patient characteristics were categorized and are presented descriptively using numbers and percentages. Differences between groups were assessed using the exact Fisher's test. Categorical responses were evaluated using the modified IWWM-6 criteria [11], where no extramedullary involvement resolution is needed to attain VGPR. Key events of interest included progression-free survival (PFS), treatment-free survival (TFS), overall survival (OS), and PFS after the end of treatment (PFS-EOT). PFS was defined as the time between treatment initiation and disease progression or death from any cause, TFS as the time from treatment initiation to the subsequent treatment, OS as the time from treatment initiation to the time of death from any cause, and PFS-EOT as the time from the end of treatment to disease progression or death from any cause. Times to events were estimated using the Kaplan–Meier method, and groups were compared using the log-rank test. *P*-values < 0.05 were considered statistically significant.

Univariate and multivariate Cox proportional-hazard regression models were fitted to identify predictors of PFS and TFS. The variables included in the Cox models were age (> 65, ≤ 65), sex (male, female), hemoglobin level (≤ 11.5 g/dL, > 11.5 g/dL), platelet count (≤ 100 k/μL, > 100 k/μL), serum IgM level (≥ 4000 mg/dL, < 4000 mg/dL), albumin level (< 4 g/dL, ≥ 4 g/dL), beta-2-microglobulin level (≥ 3 mg/L, < 3 mg/L), serum lactate dehydrogenase (LDH) level (normal, elevated), bone marrow involvement (≥ 60%, < 60%), lymphadenopathy (any lymph node ≥ 1.5 cm in maximum diameter, < 1.5 cm), splenomegaly (spleen size ≥ 15 cm, < 15 cm), *CXCR4* mutational status (mutated, wildtype), and *TP53* mutational status (mutated, wildtype). Variables with *p*-values < 0.05 in the univariate models were included in the multivariate models. Variables with *p*-values < 0.05 in the multivariate models were considered independent predictors of the event of interest. Estimates and graphs were obtained using Stata version 19 (StataCorp, College Station, TX, USA).

3 | Results

The baseline characteristics of the 45 enrolled patients are shown in Table 1. *MYD88* mutations were detected in all patients. Seventeen patients (38%) carried *CXCR4* mutations, and 4 (9%) *TP53* mutations. Of the four patients with *TP53* mutations, three had *CXCR4* mutations. Thrombocytopenia (platelet count ≤ 100 K/μL) was more prevalent at baseline in patients with *CXCR4* mutations compared to those with wild-type *CXCR4* (28% vs. 0%; $p = 0.048$). There were no other differences in baseline characteristics between patients with and without

TABLE 1 | Baseline characteristics of 45 previously untreated patients with Waldenström macroglobulinemia treated with ibrutinib and venetoclax.

Characteristic	*N* (%)
Age ≥ 65 years	24 (53%)
Male sex	30 (67%)
Hemoglobin level ≤ 11.5 g/dL	33 (73%)
Platelet count ≤ 100 k/μL	3 (7%)
Serum IgM level ≥ 4000 mg/dL	26 (58%)
Albumin level < 4 g/dL	31 (69%)
Beta-2-microglobulin level ≥ 3 mg/L	28 (64%)
Elevated serum LDH level	2 (4%)
Any lymph node ≥ 1.5 cm	24 (53%)
Spleen size ≥ 15 cm	12 (27%)
Bone marrow involvement ≥ 60%	26 (58%)
CXCR4 mutations	17 (38%)
Nonsense mutations	10 (59%)
Frameshift mutations	7 (41%)
TP53 mutations	4 (9%)

Abbreviation: LDH, lactate dehydrogenase.

CXCR4 mutations. There was a numerically higher proportion of women (75% vs. 29%; $p = 0.10$) and a lower proportion of serum beta-2-microglobulin levels < 3 mg/L (25% vs. 68%; $p = 0.12$) in those with *TP53* mutations. There were no other differences in baseline characteristics between patients with and without *TP53* mutations.

The median treatment duration was 10 cycles (range, 2–21 cycles), and no patient completed the planned study therapy. One patient (2%) achieved a complete response (CR), 18 (40%) a very good partial response (VGPR), 24 (53%) a partial response (PR), and 2 (4%) a minor response. One patient who had attained VGPR at the time of the previous report had normal blood counts, serum IgM levels, serum electrophoresis, and bone marrow results, and a residual lymph node greater than 1.5 cm [7]. This patient achieved CR 1 year after stopping study therapy, at which point the lymphadenopathy resolved. The VGPR/CR rate was numerically lower in patients with mutated (29%) versus wild-type (50%) *CXCR4* ($p = 0.15$), and in those with mutated (25%) versus wild-type (44%) *TP53* ($p = 0.43$). All patients harboring a *TP53* mutation achieved PR or better with study therapy.

With a median follow-up from treatment initiation of 49 months (95% CI, 47–53), 31 patients (69%) experienced disease progression, 11 patients (24%) started a new treatment, and four patients (9%) died. The criteria for disease progression were met because of increasing serum IgM levels in 23 patients (74%), death in four (9%), as detailed below, and symptomatic cytopenias, progressive lymphadenopathy, progressive neuropathy, and aggressive transformation in one patient (2%) each. The patient who experienced progressive neuropathy had non-demyelinating neuropathy with negative anti-myelin-associated glycoprotein titers and constitutional symptoms at baseline. The progressive neuropathic symptoms were observed in the absence of increasing serum IgM levels.

The median PFS was 36 months (95% CI, 28–42), and the 4-year PFS rate was 36% (95% CI, 22%–49%; Figure 1A). In univariate Cox models, platelet count ≤ 100 k/μL (HR 5.45; 95% CI 1.47–20.2; $p = 0.01$), high baseline serum LDH level (HR 7.98; 95% CI 1.68–37.9; $p = 0.009$), and *TP53* mutations (HR 8.26; 95% CI 2.28–29.9; $p = 0.001$) were associated with an inferior PFS. In a multivariate Cox model including these three factors, baseline platelet count ≤ 100 K/μL (HR 9.06; 95% CI 2.14–30.4; $p = 0.003$), and *TP53* mutations (HR 9.24; 95% CI 1.68–50.9; $p = 0.01$) were independently associated with an inferior PFS. All Cox models for PFS are shown in Table 2. The median PFS was 22 months (95% CI 10-not reached) in patients with platelet counts ≤ 100 k/μL and 39 months (95% CI 31–48) in patients with platelet counts > 100 k/μL (log-rank $p = 0.004$; Figure 1B). The median PFS was 12.5 months (95% CI 12.4-not reached) for patients with *TP53* mutations and 40.5 months (95% CI 31–50) for patients without *TP53* mutations (log-rank $p < 0.001$; Figure 1C). All the patients harboring a *TP53* mutation have progressed. *CXCR4* mutations did not impact PFS (log-rank $p = 0.93$; Figure 1D).

The median TFS was not reached, and the 4-year TFS rate was 73% (95% CI, 57%–84%; Figure 2A). In univariate Cox models, a high baseline serum LDH level (HR 12.8; 95% CI 1.3–123.3; $p = 0.03$) and *TP53* mutations (HR 8.06; 95% CI 2.06–31.6; $p = 0.003$) were associated with inferior TFS. In a multivariate Cox model including these two variables, only *TP53* mutations were independently associated with an inferior TFS (HR 6.16; 95% CI 1.28–29.6; $p = 0.02$). All Cox models for TFS are shown in Table 3. The median TFS for patients with *TP53* mutations was 16 months (95% CI, 13-not reached), compared to not reached for patients without *TP53* mutations (log-rank $p < 0.001$; Figure 2B). *CXCR4* mutations did not impact TFS (log-rank $p = 0.83$; Figure 2C).

The median OS was not reached. The 4-year OS rate was 91% (95% CI, 77%–96%; Figure 2D). No Cox models were evaluated due to the small number of events ($n = 4$). Besides the transformation to DLCBL reported previously, no other secondary cancers were observed during follow-up.

Excluding the two patients who died while on study therapy and the patient who transformed to an aggressive lymphoma, who continued study therapy until new treatment was started, there were 28 events of disease progression after EOT. The median follow-up from EOT was 39 months (95% CI 38–39; Figure 3A), and the median PFS-EOT was 29 months (95% CI, 21–37). *TP53* mutations were associated with an inferior PFS-EOT (HR 13.9, 95% CI 3.32–58.2; $p < 0.001$). The median PFS-EOT for patients with *TP53* mutations was 6.8 months (9% CI 3.2-not reached), versus 32 months (9% CI 22-not reached) for patients without *TP53* mutations (log-rank $p < 0.001$; Figure 3B). *CXCR4* mutation status, VGPR attainment at EOT (versus less than VGPR), or < 12 months of treatment (versus ≥ 12 months) did not affect PFS-EOT (Figure 3C–E).

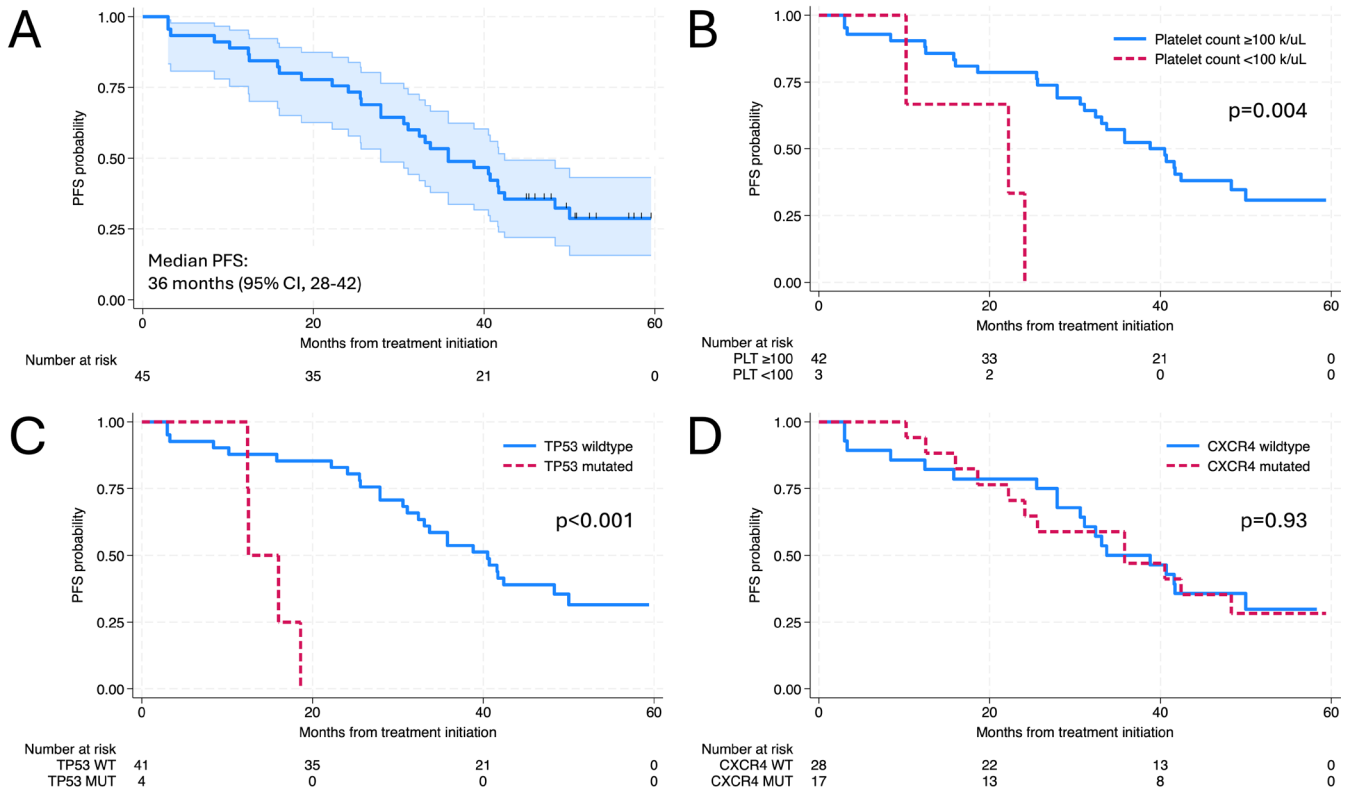

FIGURE 1 | Kaplan–Meier curves for progression-free survival (PFS) in all patients (A) and stratified by platelet count (B), *TP53* mutational status (C), and *CXCR4* mutational status (D) in 45 previously untreated patients with Waldenström macroglobulinemia treated with ibrutinib and venetoclax.

TABLE 2 | Univariate and multivariate proportional-hazards Cox regression analysis for progression-free survival in 45 previously untreated patients with Waldenström macroglobulinemia treated with ibrutinib and venetoclax.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age ≥ 65 years	1.28 (0.63–2.60)	0.50		
Male sex	1.09 (0.51–2.31)	0.83		
Hemoglobin level ≤ 11.5 g/dL	1.23 (0.53–2.85)	0.63		
Platelet count ≤ 100 k/μL	5.45 (1.47–20.2)	0.01	9.06 (2.14–38.4)	0.003
Serum IgM level ≥ 4000 mg/dL	1.12 (0.54–2.31)	0.76		
Albumin level < 4 g/dL	1.25 (0.58–2.73)	0.57		
Beta-2-microglobulin level ≥ 3 mg/L	1.53 (0.70–3.53)	0.28		
Elevated serum LDH level	7.98 (1.68–37.9)	0.009	1.94 (0.27–13.8)	0.51
Any lymph node ≥ 1.5 cm	1.79 (0.86–3.70)	0.12		
Spleen size ≥ 15 cm	1.11 (0.51–2.42)	0.80		
Bone marrow involvement ≥ 60%	1.88 (0.88–4.00)	0.10		
CXCR4 mutations	1.03 (0.50–2.13)	0.93		
TP53 mutations	8.26 (2.28–29.9)	0.001	9.24 (1.68–50.9)	0.01

Abbreviations: CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase.

Of 11 patients who initiated a new treatment, four started zanubrutinib monotherapy, one started venetoclax monotherapy, one started bendamustine and rituximab, one started R-CHOP (DLCBL transformation), and four started a clinical trial. Of the four patients with *TP53* mutations who had progressed, three initiated a new treatment: two

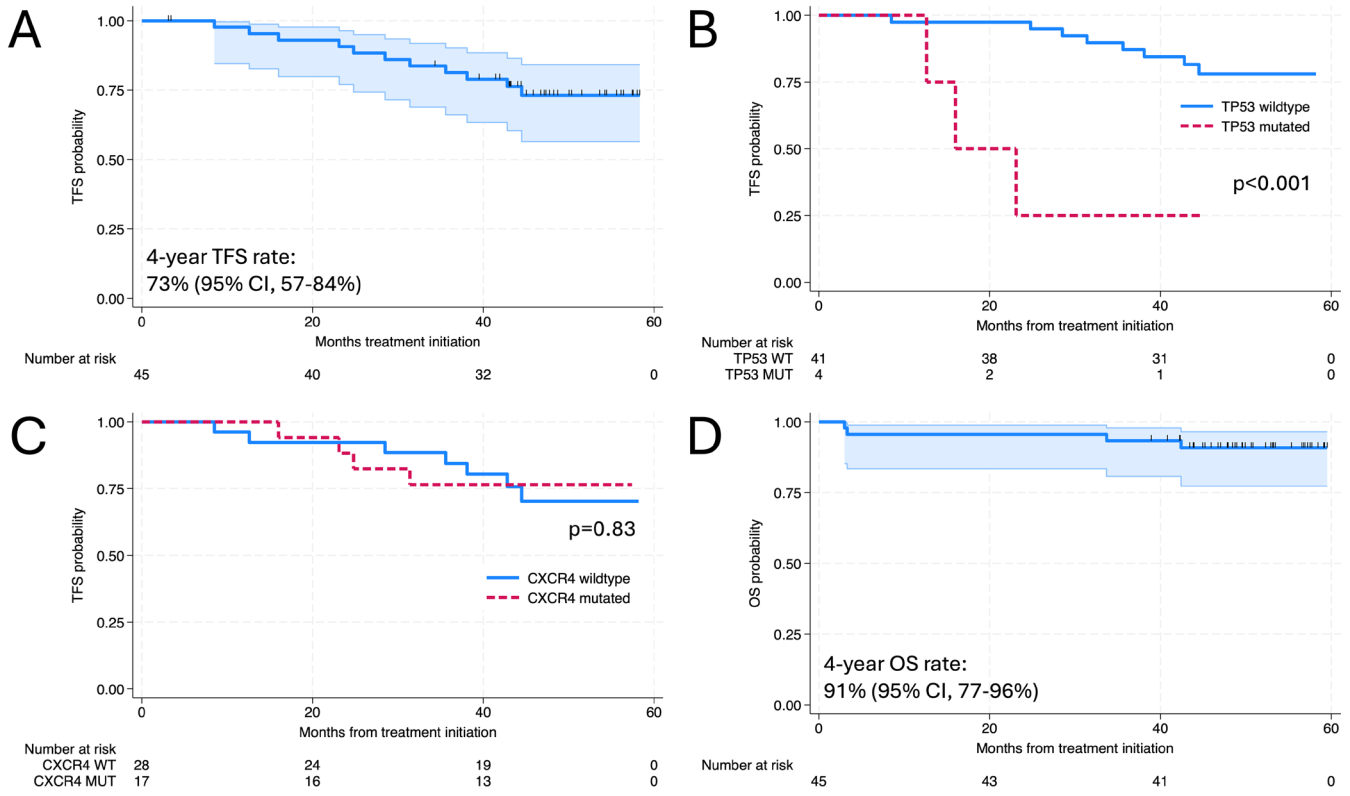

FIGURE 2 | Kaplan–Meier curves for treatment-free survival (TFS) in all patients (A), stratified by *TP53* mutational status (B), *CXCR4* mutational status (C), and overall survival (OS) in all patients (D), in 45 previously untreated patients with Waldenström macroglobulinemia treated with ibrutinib and venetoclax.

TABLE 3 | Univariate and multivariate proportional-hazards Cox regression analysis for treatment-free survival in 45 previously untreated patients with Waldenström macroglobulinemia treated with ibrutinib and venetoclax.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age ≥ 65 years	1.08 (0.33–3.54)	0.90		
Male sex	0.37 (0.11–1.21)	0.10		
Hemoglobin level ≤ 11.5 g/dL	0.97 (0.26–3.64)	0.96		
Platelet count ≤ 100 k/μL	1.39 (0.18–10.9)	0.75		
Serum IgM level ≥ 4000 mg/dL	1.20 (0.35–4.10)	0.77		
Albumin level < 4 g/dL	1.21 (0.32–4.58)	0.78		
Beta-2-microglobulin level ≥ 3 mg/L	0.93 (0.27–3.21)	0.92		
Elevated serum LDH level	12.8 (133–123.3)	0.03	2.69 (0.21–34.2)	0.45
Any lymph node ≥ 1.5 cm	1.08 (0.33–3.54)	0.90		
Spleen size ≥ 15 cm	0.62 (0.13–2.86)	0.54		
Bone marrow involvement ≥ 60%	1.39 (0.41–4.74)	0.60		
CXCR4 mutations	0.88 (0.26–2.99)	0.83		
TP53 mutations	8.06 (2.06–31.6)	0.003	6.16 (1.28–29.6)	0.02

Abbreviations: CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase.

were treated with zanubrutinib and one with bendamustine and rituximab. All patients responded to the subsequent line of treatment. Of the four patients who died, two died of ventricular arrhythmia while on and responding to therapy, as previously reported; one of amyotrophic lateral sclerosis 32 months after EOT; and one of an unknown cause

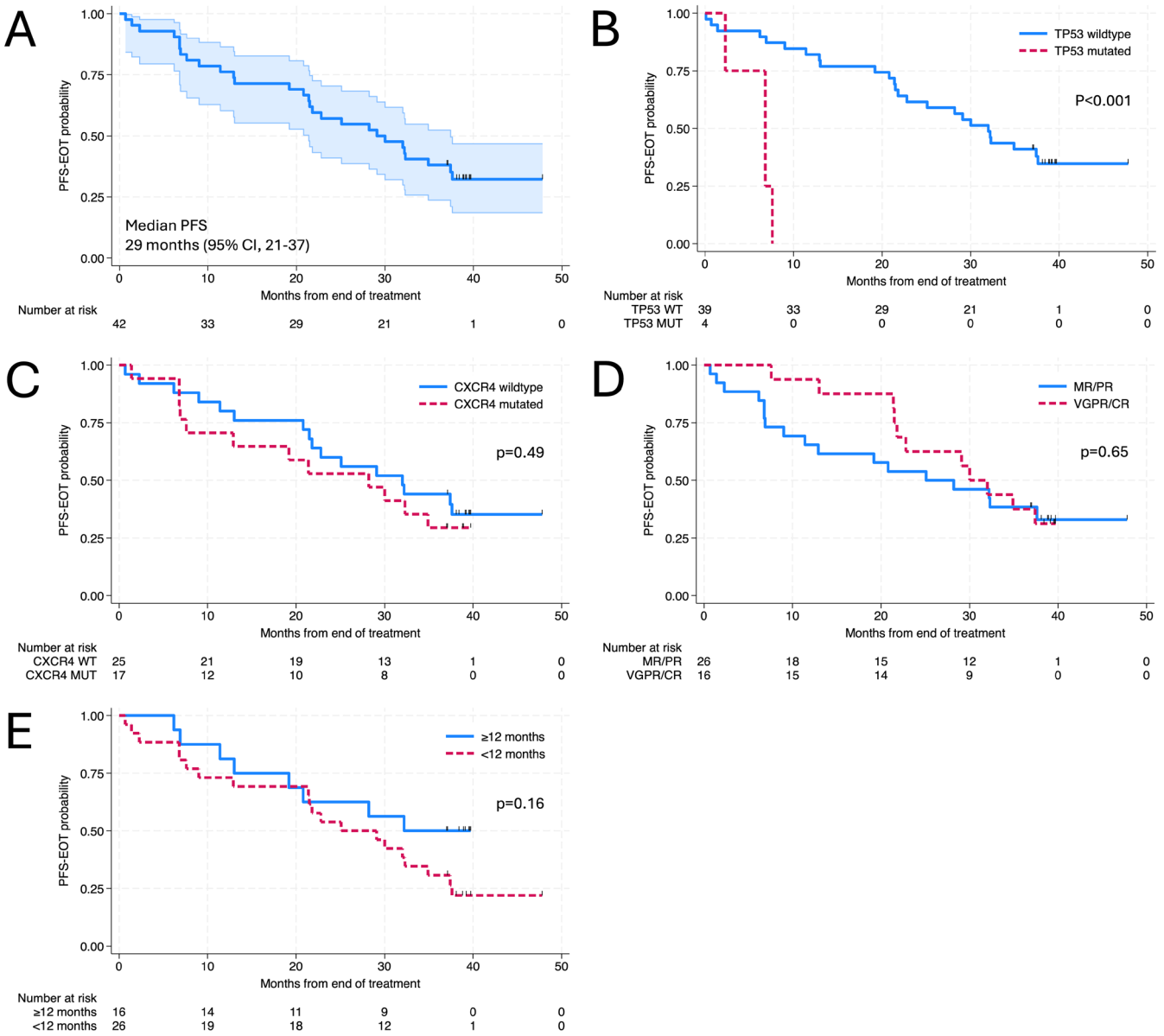

FIGURE 3 | Kaplan–Meier curves for progression-free survival after end of treatment (PFS-EOT) for all patients (A), according to *TP53* mutational status (B), *CXCR4* mutational status (C), depth of response at EOT (D), and time on study therapy (E) in 42 previously untreated patients with Waldenström macroglobulinemia treated with ibrutinib and venetoclax. Three patients (two who died and one who transformed to an aggressive lymphoma) were excluded from this analysis because study treatment was stopped at the time of the event.

25 months after EOT. All deaths occurred in the absence of WM progression.

4 | Discussion

BTK inhibitors are arguably the most effective single-agent therapies in WM, associated with fast, deep, and durable responses. However, the indefinite duration of the regimen, along with the potential cumulative incidence of side effects over time, and the cost associated with chronic therapy, poses specific clinical challenges. The combination of BTK inhibitors with a BCL2 inhibitor demonstrated synergy in preclinical studies using WM models, as well as safety and efficacy in clinical trials involving CLL patients. This prompted us to investigate the combination of ibrutinib and venetoclax as a 2-year fixed-duration treatment in symptomatic, treatment-naïve WM. Although our study was terminated early due to an unexpected high incidence of ventricular arrhythmias, including grade 5 events, important lessons applicable to the future development of combined BTK and BCL2 inhibition in WM were identified through continued patient follow-up. With a median duration of therapy of 10 months, we observed a VGPR/CR rate of 42% at best response and a median PFS of 36 months with combined ibrutinib and venetoclax in symptomatic, treatment-naïve patients with WM. Furthermore, the combination did not appear to affect the response to subsequent lines of therapy, which included covalent and non-covalent BTK inhibitors and BCL-2 antagonists.

The median PFS of 36 months with the combination of ibrutinib and venetoclax appears inferior, despite a similar, if not

higher, VGPR/CR rate compared with ibrutinib monotherapy as frontline treatment in patients with WM, for whom the 4-year PFS rate was 76% [2]. The observed inferior PFS could support the notion that sustained BTK inhibition is required for more effective suppression of the malignant WM clone. However, recent data in CLL showed that fixed-duration regimens combining BTK and BCL-2 inhibitors were not inferior to continuous ibrutinib monotherapy [12]. A longer time on combination therapy before stopping might have led to a longer time to disease progression, a hypothesis that should be tested in the future with a safer combination, ideally in a randomized controlled study.

The durability of the response to the combination was longer than expected in patients with WM who stopped BTK inhibitors, for whom the median time to an IgM rebound has been reported as 4 weeks [13], more in line with the previous experience with venetoclax in WM, where the median PFS in patients with WM treated with a dose of 800 mg once daily for 2 years was 36 months [14]. Notably, the median TFS with venetoclax monotherapy was 43 months, whereas the median TFS in this study had not yet been reached after 49 months of follow-up. The observed difference in TFS could have been a direct effect of using the combination of ibrutinib and venetoclax, or it could have been due to a difference in the populations studied, previously treated in the venetoclax study versus untreated in the present study.

CXCR4 mutations significantly affected the depth and durability of response in patients with WM treated with ibrutinib monotherapy [15]. In the frontline setting, the 4-year PFS rate was 59% in patients with WM [2]. Although *CXCR4* mutational status significantly impacted the depth of response to venetoclax monotherapy, the median PFS was unaffected [14]. In the present study, *CXCR4* mutations were associated with numerically lower rates of VGPR. Still, *CXCR4* mutational status had no detectable impact on PFS, TFS, or PFS-EOT, suggesting a synergistic effect between ibrutinib and venetoclax that may have blunted the adverse impact of *CXCR4* mutations in patients with WM who receive the combination. The short and heterogeneous duration of study therapy does not permit reliable estimates and therefore makes our observation hypothesis-generating.

Of particular interest was the inferior PFS, TFS, and PFS-EOT observed in patients with *TP53* mutations who received ibrutinib and venetoclax, acknowledging the small number of patients with these mutations in this study. The precise incidence and prevalence of *TP53* mutations in WM are still to be determined. However, initial data originating from small case series suggested that patients with *TP53*-mutated WM have poorer outcomes [16, 17]. A *post hoc* analysis of the randomized ASPEN study reported a prevalence of 25% and confirmed that *TP53* mutations confer a higher risk of disease progression in patients with WM treated with single-agent covalent BTK inhibitors [8]. More recently, we reported poor survival associated with *TP53* alterations and an increased incidence of these alterations in patients with WM who had previously received chemotherapy [18]. Future efforts should focus on standardizing *TP53* mutation detection techniques, as current next-generation sequencing platforms do not clearly distinguish *TP53*-mutated cells within the WM clone from those in the myeloid compartment. Additional research is needed to understand the incidence and prevalence of *TP53* mutations as well as their impact on response depth and duration in patients with WM.

The events in this study allowed us to investigate the depth of response and the duration of study therapy as predictors of PFS-EOT. One could assume that deeper responses or longer study therapy would be associated with longer median PFS-EOT. However, our subset analysis did not show such an association, which is inconsistent with recent data in CLL, where the depth of response to the combination was predictive of PFS [12]. An explanation is that the sample size was small and not powered to detect differences between groups. It is possible that other emerging biological markers, such as *TP53* mutations, supersede response depth or treatment duration in WM.

Because of the high incidence of ventricular arrhythmias observed in this study, we cannot recommend treating patients with WM with the combination of ibrutinib and venetoclax. However, based on the ease of oral administration, the absence of secondary myeloid neoplasms, and the long-term benefits many patients in this study have experienced with a fixed-duration regimen that permitted effective re-treatment with BTK- or BCL-2-targeting agents upon disease progression, the combination of BTK inhibitors and BCL-2 antagonists warrants further exploration.

An important question is whether fixed-duration combinations or oral targeted agents are superior to fixed-duration chemoimmunotherapy (CIT) regimens. CIT regimens such as cyclophosphamide, dexamethasone, and rituximab, or bendamustine and rituximab are highly effective in WM [19, 20]. In the absence of direct comparisons, the combination of ibrutinib and venetoclax appeared to induce a comparable depth of response to CIT. However, the PFS durability was shorter, providing additional avenues for research to investigate longer therapy durations or more potent oral combinations.

As a follow-up to this study, we initiated a Phase 2 clinical trial evaluating the combination of the non-covalent BTK inhibitor pirtobrutinib with venetoclax in previously treated, symptomatic WM patients (NCT05734495). Pirtobrutinib monotherapy is highly active in previously treated WM and has a low risk of cardiac arrhythmias. However, the median PFS was short in patients whose disease was resistant to covalent BTK inhibitors [21]. The combination of pirtobrutinib and venetoclax induced a VGPR/CR rate of 56% ($n = 15$), including three patients who achieved CR, among the first 27 patients who completed 6 months on study [22]. Another study is evaluating the combination of pirtobrutinib, venetoclax, and rituximab in previously untreated WM (NCT07231952), which is run by the WM-NET, a United States-based consortium of 25 academic centers focused on developing clinical trials in WM (wm-net.org).

In summary, the combination of ibrutinib and venetoclax induced a high rate of deep and durable responses in patients with WM. The concurrent inhibition of BTK and BCL-2 is a feasible treatment strategy for WM, enabling the implementation of fixed-duration, oral, targeted regimens that can minimize toxicity, disease resistance, and the costs associated with indefinite duration therapy.

Author Contributions

J.J.C., S.P.T., and S.S. designed the study. J.J.C., A.R.B., A.G., A.R.-G., H.C., M.K., and S.S. provided care to the participants. N.B., J.N., A.E., C.B., K.M., and C.J.P. provided regulatory support. M.L.G., A.K., S.L., X.L., N.T., and Z.R.H. performed genomic analysis. J.J.C., A.R.B., G.K., A.G., S.P.T., and S.S. analyzed the data. J.J.C. drafted the initial manuscript. All the authors critically reviewed the initial manuscript and approved the final version.

Acknowledgments

Portions of this research were presented at the 11th International Workshop on Waldenström Macroglobulinemia in Prague, Czech Republic, in October 2024, at the 66th American Society of Hematology Annual Meeting in San Diego, CA, in December 2024, and at the 67th American Society of Hematology Annual Meeting in Orlando, FL, in December 2025.

The authors thank the WMR Fund, the Kaplan Family Fund for Waldenström Macroglobulinemia, the Bayer Family Research Fund, the Fred and Michele Brettschneider Family Research Fund, the Deborah Cummins Waldenström Memorial Fund, and the Vanier Family WM Research Fund for their support.

Funding

This work was supported by AbbVie and Pharmacyclics.

Disclosure

J.J.C. received research funds or honoraria from AbbVie, BeOne, Cellectar, Johnson & Johnson, Loxo, Mustang Bio, Nurix, Pharmacyclics, and Schrodinger. A.R.B. received research funds and/or honoraria from Adaptive, BeOne, CSL Behring, Genzyme, Karyopharm, Pharmacyclics, and Sanofi. G.v.K. received research funds or honoraria from AbbVie, Eli Lilly, Genmab, and Pharmacyclics. S.P.T. received research funding or consulting fees from AbbVie/Pharmacyclics, Janssen, BeOne, Eli Lilly, Bristol Myers Squibb, and Ono Pharmaceuticals; and is a named inventor of MYD88 and CXCR4 testing for Waldenström macroglobulinemia and has assigned all interests to their institution. S.S. received research funds or honoraria from ADC Therapeutics, AstraZeneca, BeOne, Cellectar, and Sobi. The remaining authors declare no competing financial interests.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Reasonable data requests should be made to the corresponding author, Jorge J. Castillo (jorgej_castillo@dfci.harvard.edu). Deidentified data will be available immediately after print publication.

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