



## RESEARCH ARTICLE

# Venetoclax or Pirtobrutinib in Relapsed/Refractory Waldenström Macroglobulinemia: Clinical and Molecular Predictors and Sequencing Implications

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## ABSTRACT

Venetoclax and pirtobrutinib have emerged as two chemotherapy-free options for relapsed or refractory Waldenström macroglobulinemia (WM). However, evidence to guide treatment sequencing or identify molecular subsets most likely to benefit from each agent remains limited. We retrospectively evaluated consecutive WM patients treated with venetoclax or pirtobrutinib. Major response rate (MRR) and progression-free survival (PFS) were assessed for each agent, with predictors of response and PFS analyzed using logistic and Cox regression. Comparative efficacy was examined in unmatched analyses and in a 1:1 matched cohort. Among 91 treatment exposures (64 venetoclax and 27 pirtobrutinib) across 80 unique patients, treatment discontinuation due to adverse effects occurred in 12 of 64 patients (19%) treated with venetoclax and in none treated with pirtobrutinib. In the venetoclax cohort, *TP53* alterations were associated with shorter PFS (10.0 vs. 35.6 months;  $p < 0.001$ ). In the pirtobrutinib cohort, *CXCR4* mutations predicted lower MRR (40% vs. 91%;  $p = 0.01$ ) and shorter PFS (8.3 months vs. not reached;  $p = 0.02$ ). When transitioning from a cBTKi, IgM rebound occurred in 62% (8/13) of patients initiating venetoclax without overlap, whereas no rebound was observed with cBTKi-venetoclax overlap (0/5) or with pirtobrutinib initiation (0/15). In the matched cohort ( $n = 42$ ), venetoclax and pirtobrutinib demonstrated comparable outcomes for MRR ( $p = 0.91$ ) and PFS ( $p = 0.83$ ). Despite the retrospective design and limited sample size, these findings indicate comparable efficacy between venetoclax and pirtobrutinib with distinct molecular vulnerabilities and support consideration of pirtobrutinib sequencing when transitioning from a cBTKi, as well as further exploration of combination strategies that may exploit complementary vulnerabilities.

## 1 | Introduction

Covalent BTK inhibitors and chemoimmunotherapy regimens are used as standard frontline treatment approaches for Waldenström macroglobulinemia (WM), providing durable disease control; however, as a still incurable disease, virtually all patients eventually experience disease progression [1–5]. In recent years, the treatment arsenal for WM has expanded

considerably, providing additional options for patients whose disease progresses after or becomes resistant to multiple lines of therapy [6–8]. This progress is critical in a still-incurable disease, where survival gains rely on the incremental benefit of each treatment and on the ability to sequence multiple effective options. Together, these advances have driven the steady extension of overall survival observed over recent decades [9, 10].

With broader therapeutic experience and longer follow-up, the long-term effects of chemotherapy, including alkylating agents and nucleoside analogues, have become better defined. These treatments have been linked to higher rates of secondary malignancies [11, 12] and may contribute to the emergence of high-risk genomic features such as *TP53* alterations [13, 14]. These observations have supported the growing interest in chemotherapy-free approaches.

Two novel chemotherapy-free agents are now included in major treatment guidelines and have become key components of therapy for relapsed or refractory WM: the BCL2 inhibitor venetoclax and the non-covalent BTK inhibitor pirtobrutinib [7, 8]. Both agents have demonstrated meaningful activity in phase II studies, with median progression-free survival (PFS) of 36 months for venetoclax in the recently published long-term analysis [15] and 36 months for pirtobrutinib according to the most recent trial update [16]. While encouraging in the relapsed/refractory setting, the duration of benefit observed is shorter than that typically reported in the frontline setting, where covalent BTK inhibitors and chemoimmunotherapy in treatment-naïve patients achieve median PFS of 69 to 80 months [1–5].

Importantly, no direct comparisons between venetoclax and pirtobrutinib exist, and interpretation across trials is limited by important differences in their design and study populations. The venetoclax trial included fewer patients who had been previously treated with cBTKis [15, 17], while the pirtobrutinib trial enrolled a more heavily pretreated cohort [16]. Neither study evaluated the impact of *TP53* alterations (*TP53* mutations and 17p deletions), which have been proven to be a key determinant of response across multiple treatment classes in WM [13, 18–21].

As a result, although both agents are effective treatment options for previously treated WM, no data guide how they should be sequenced or whether specific subgroups may benefit more from one therapy over the other. This is particularly relevant for patients previously exposed to cBTKis, who make up the most common group in whom these therapies are used.

To address these knowledge gaps, we conducted the first off-trial study directly examining real-world outcomes with venetoclax and pirtobrutinib in relapsed or refractory WM. Our objective was to identify predictors of response and clinical outcomes for each therapy and to explore their comparative effectiveness and implications for sequencing.

## 2 | Methods

We conducted a retrospective cohort study of all consecutive patients with WM who received venetoclax or pirtobrutinib and were evaluated at the Bing Center for Waldenström Macroglobulinemia at Dana-Farber Cancer Institute (DFCI), regardless of whether treatment was initiated at our institution or elsewhere. Patients were identified through the institutional pharmacy informatics database and the Electronic Medical Record Search Engine (EMERSE) [22], and eligibility

was confirmed by manual review of the electronic medical records.

Eligible patients had a confirmed diagnosis of WM according to IWWM-2 criteria [23] and received venetoclax or pirtobrutinib monotherapy, excluding those treated for Bing-Neel syndrome. Genetic testing for *MYD88*, *CXCR4*, and *TP53* was performed on bone marrow samples. *MYD88* and *CXCR4* mutations were analyzed by allele-specific PCR (AS-PCR) and Sanger sequencing on CD19-selected bone marrow or by AS-PCR for *MYD88* and next-generation sequencing (NGS) for *CXCR4* when CD19 selection was unavailable. *TP53* status was assessed in unselected bone marrow samples using targeted amplicon-based NGS, enabling detection of pathogenic *TP53* point mutations and *TP53* copy number loss by read-depth analysis (variant allele frequency cutoff >0.1%) [24]. In a subset of patients ( $n=16$ ), fluorescence in situ hybridization (FISH) was performed to detect del (17p). Patients with either a pathogenic *TP53* point mutation or del (17p) were considered to have *TP53*-altered disease.

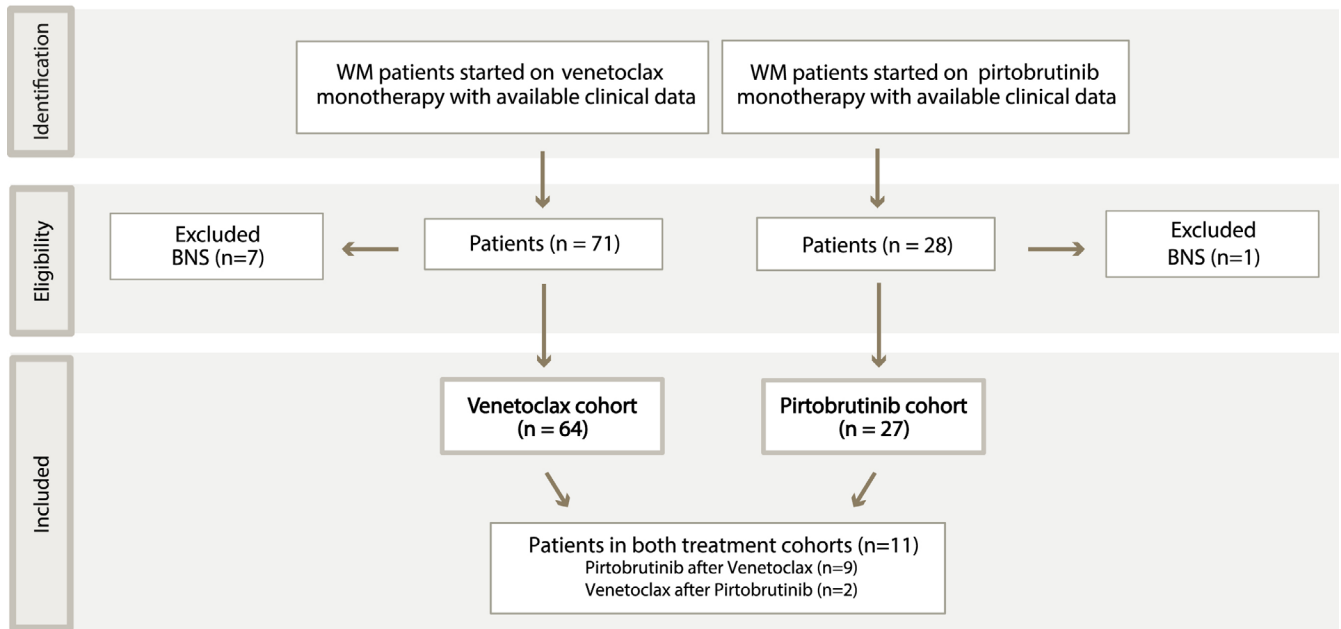
Patients were divided into two treatment cohorts: cohort 1 (venetoclax monotherapy) and cohort 2 (pirtobrutinib monotherapy). Patients who received both agents sequentially at different time points in their disease course were included in both cohorts. In these cases, each treatment period was considered a distinct clinical exposure, and baseline clinical and molecular characteristics were assessed at the time of each treatment initiation to evaluate factors associated with the major response rate (MRR; partial response or better) and PFS.

MRR was defined as  $\geq 50\%$  reduction in serum IgM levels from baseline, and PFS was defined as the time from treatment initiation to disease progression, last follow-up, or death from any cause. Additionally, patients who transitioned from a cBTKi to either venetoclax or pirtobrutinib within 1 month were evaluated for IgM rebound ( $> 25\%$  increase from the baseline serum IgM level) [25].

Ultimately, the two cohorts were compared to evaluate the comparative efficacy of pirtobrutinib and venetoclax in both unmatched and 1:1-matched analyses, with matching based on prior progression on a cBTKi and the number of prior lines of therapy. These variables were selected based on earlier data indicating prognostic relevance and differential distribution between treatment groups in the original clinical trials [15, 17, 26, 27]; moreover, they had complete data, allowing for exact matching.

### 2.1 | Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Categorical variables were reported as counts and percentages and compared using Chi-squared tests or Fisher's exact tests as appropriate. Continuous variables were expressed as medians with ranges and compared using the Wilcoxon rank-sum test. PFS was estimated using the Kaplan–Meier method and compared with the log-rank test. Predictors of MRR were evaluated using logistic regression, and predictors of PFS were assessed with Cox proportional-hazards regression models. The outcome measure for logistic regression was the odds ratio (OR) with 95% confidence



**FIGURE 1** | Patient selection and cohort assembly. Flow diagram of patients with Waldenström macroglobulinemia treated with venetoclax or pirtobrutinib monotherapy with available clinical data at Dana-Farber Cancer Institute. Patients with Bing-Neel syndrome were excluded. One patient in the venetoclax cohort had prior pirtobrutinib exposure but lacked available clinical data at the pirtobrutinib time point and was therefore not included in the pirtobrutinib cohort.

interval (CI), and for Cox regression, the hazard ratio (HR) with 95% CI. All multivariable models were adjusted for age and sex, as well as significant variables ( $p < 0.05$ ) in univariate analyses.

The matched cohorts were constructed using exact 1:1 matching between venetoclax and pirtobrutinib. Matching criteria included progression on a covalent BTK inhibitor (yes vs. no) and number of prior treatment lines ( $> 3$  vs. 1–3). Exact matching was performed within these strata, and a 1:1 balance was achieved by random sampling within each stratum when multiple patients were available. Patients who received both treatments sequentially were included in the matched cohort only once. Median follow-up was calculated using the reverse Kaplan–Meier method. Statistical analyses were conducted using Stata version 18.0 (College Station, TX, USA), and figures were generated using Stata and RStudio (version 2025.09.2).

### 3 | Results

A total of 91 treatment exposures were analyzed (64 venetoclax and 27 pirtobrutinib) among 80 unique patients who initiated either treatment between June 2016 and April 2025. Eleven patients received both agents sequentially: 9 (82%) received venetoclax followed by pirtobrutinib, and 2 (18%) received pirtobrutinib followed by venetoclax (Figure 1).

The median age was 69 years (range 39–88) for venetoclax and 72 years (56–85) for pirtobrutinib ( $p = 0.39$ ). Female sex (30% [19/64] vs. 26% [7/27];  $p = 0.72$ ) and *CXCR4* mutational status (46% [26/57] vs. 48% [11/23];  $p = 0.86$ ) were evenly distributed. Prior progression on cBTKi was less common for venetoclax (38% [24/64] vs. 81% [22/27];  $p < 0.001$ ), and patients on venetoclax had fewer prior treatments (median 3 [range 1–13] vs. 4 [1–7];  $p = 0.22$ ). A

total of 18/64 (28%) for venetoclax and 5/27 (19%) for pirtobrutinib received therapy within a clinical trial ( $p = 0.34$ ). *TP53* alterations were less frequently observed at baseline for those treated with venetoclax (25% [11/44]) vs. pirtobrutinib (50% [9/18];  $p = 0.06$ ). Among patients with *TP53* alterations, 17 of 20 (85%) harbored a *TP53* mutation, while 3 of 20 (15%) had del (17p), including two in the pirtobrutinib cohort and one in the venetoclax cohort. No patients harbored both alterations.

Treatment discontinuation due to adverse effects occurred in 12 of 64 patients (19%) treated with venetoclax, compared with 0 of 27 patients (0%) treated with pirtobrutinib ( $p = 0.016$ ). Discontinuations occurred predominantly in the off-trial setting (11 of 46; 24%), with only one observed in the clinical trial setting (1 of 18; 6%). Among patients discontinuing venetoclax, the most common causes were cytopenias (8 of 12; 67%), followed by gastrointestinal adverse events, including diarrhea, abdominal pain, and dysgeusia (4 of 12; 33%). The median time on treatment was 16.16 months (IQR, 5.3–25.5) for venetoclax and 12.35 months (IQR, 5.4–17.7) for pirtobrutinib.

Best response was assessed among evaluable exposures for response (venetoclax,  $n = 62$ ; pirtobrutinib,  $n = 25$ ). With a data cut-off for follow-up in July 2025, the median follow-up was 36 (95% CI 25–56) months for venetoclax and 18 months (95% CI 12–25) for pirtobrutinib. Patient characteristics are summarized in Table 1.

#### 3.1 | Venetoclax Cohort

In the venetoclax cohort ( $n = 64$ ), the MRR was lower among patients with *TP53* alterations compared to those without (45% vs. 82%;  $p = 0.02$ ), as well as among those treated outside a clinical trial (59% vs. 94%;  $p < 0.01$ ) (Table 2). A numerically lower MRR

**TABLE 1** | Baseline characteristics of patients treated with venetoclax or pirtobrutinib.

Factor	Level	Venetoclax	Pirtobrutinib	<i>p</i>
<i>N</i>		64	27	
Age, median (range)		69 (39–88)	72 (56–85)	0.39
Sex	Female	19 (30%)	7 (26%)	0.72
	Male	45 (70%)	20 (74%)	
Hemoglobin (g/dL), median (range)		10.3 (6.0–16.8)	9.5 (7.0–16.6)	0.28
Platelets ( $\times 10^9/L$ ), median (range)		194 (2–445)	127 (23–303)	<b>0.02</b>
IgM (mg/dL), median (range)		2648 (205–8342)	2678 (126–9460)	0.50
Bone marrow involvement (%), median (range) ( <i>n</i> = 34 <sup>a</sup> /18 <sup>a</sup> )		40 (5–95)	42 (7–95)	0.76
MYD88 ( <i>n</i> = 61 <sup>a</sup> /27)	WT	1 (2%)	1 (4%)	0.55
	MUT	60 (98%)	26 (96%)	
CXCR4 ( <i>n</i> = 57 <sup>a</sup> /23 <sup>a</sup> )	WT	31 (54%)	12 (52%)	0.86
	MUT	26 (46%)	11 (48%)	
TP53 ( <i>n</i> = 44 <sup>a</sup> /18 <sup>a</sup> )	WT	33 (75%)	9 (50%)	0.06
	ALT	11 (25%)	9 (50%)	
BTK ( <i>n</i> = 43 <sup>a</sup> /17 <sup>a</sup> )	WT	39 (91%)	13 (76%)	0.14
	MUT	4 (9%)	4 (24%)	
Prior lines of therapy, median (range)		3 (1–13)	4 (1–7)	0.22
Prior lines of therapy	1–3	39 (61%)	13 (48%)	0.26
	> 3	25 (39%)	14 (52%)	
Prior cBTKi exposure	None	21 (33%)	0 (0%)	<b>&lt; 0.001</b>
	Exposed	43 (67%)	27 (100%)	
Previously progressed on cBTKi	No	40 (62%)	5 (19%)	<b>&lt; 0.001</b>
	Yes	24 (38%)	22 (81%)	
Prior ncBTKi exposure	None	61 (95%)	—	—
	Exposed	3 (5%)	—	
Prior exposure to BCL2i	None	—	18 (67%)	—
	Exposed	—	9 (33%)	
Treatment on a clinical trial	No	46 (72%)	22 (81%)	0.34
	Yes	18 (28%)	5 (19%)	

Note: Bold *p*-values indicate statistical significance ( $p < 0.05$ ).

Abbreviations: ALT, altered; BCL2i, BCL2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; MUT, mutated; ncBTKi, non-covalent Bruton tyrosine kinase inhibitor; WT, wild-type.

<sup>a</sup>*n* = number of patients with available data (missing values excluded).

was also observed in patients with *CXCR4* mutations (58% vs. 80%;  $p = 0.07$ ). In the multivariable analysis, adjusting for age, sex, and significant factors from the univariable analysis, no variables were independently associated with MRR (all  $p > 0.05$ ; Table S1).

The median time to first response among patients treated with venetoclax was 1.87 months (95% CI, 1.4–2.2). Time to first response was longer in patients who had previously progressed on a cBTKi (3.5 months; 95% CI, 1.5–4.2) compared with those without prior cBTKi progression (1.6 months; 95% CI, 1.1–1.9) ( $p = 0.07$ ). Time to first response did not vary by *CXCR4* or *TP53* status.

Survival analysis demonstrated a shorter PFS among patients with prior progression on a cBTKi (11.8 months [95% CI, 5.4–40.2] vs. 35.6 months [95% CI, 28.1–56.0];  $p = 0.003$ ), those harboring *TP53* alterations (10.0 months [95% CI, 3.1–15.0] vs. 35.6 months [95% CI, 27.9–47.6];  $p < 0.001$ ), patients who had received > 3 prior lines of therapy (16.6 months [95% CI, 7.0–33.0] vs. 41.5 months [95% CI, 28.1–66.1];  $p = 0.002$ ), and those not enrolled in a clinical trial (29.0 months [95% CI, 10.0–NA] vs. 40.2 months [95% CI, 28.1–56.0];  $p = 0.03$ ) (Figure 2A–F). In the multivariable analysis adjusting for age, sex, and significant factors identified in the univariable model, only *TP53* alterations

**TABLE 2** | Response rates in the venetoclax and pirtobrutinib cohorts stratified by clinical and molecular characteristics.

<b>Venetoclax</b>								
<b>Subgroup</b>	<b>Category</b>	<b>Total (n)</b>	<b>NR n (%)</b>	<b>mR n (%)</b>	<b>PR n (%)</b>	<b>VGPR n (%)</b>	<b>MRR (PR + VGPR)</b>	<b>p</b>
Prior cBTKi	Prior progression	24	8 (33.3%)	2 (8.3%)	12 (50.0%)	2 (8.3%)	14 (58.3%)	0.14
	No prior progression	38	3 (7.9%)	6 (15.8%)	19 (50.0%)	10 (26.3%)	29 (76.3%)	
CXCR4 status	Mutated	26	5 (19.2%)	6 (23.1%)	11 (42.3%)	4 (15.4%)	15 (57.7%)	0.07
	Wild type	30	5 (16.7%)	1 (3.3%)	16 (53.3%)	8 (26.7%)	24 (80.0%)	
TP53 status	Altered	11	3 (27.3%)	3 (27.3%)	3 (27.3%)	2 (18.2%)	5 (45.5%)	<b>0.02</b>
	Wild type	33	4 (12.1%)	2 (6.1%)	18 (54.5%)	9 (27.3%)	27 (81.8%)	
Prior lines	1–3 lines	37	5 (13.5%)	4 (10.8%)	21 (56.8%)	7 (18.9%)	28 (75.7%)	0.19
	> 3 lines	25	6 (24.0%)	4 (16.0%)	10 (40.0%)	5 (20.0%)	15 (60%)	
Setting	Off-trial	44	11 (25.0%)	7 (15.9%)	20 (45.5%)	6 (13.6%)	26 (59.1%)	<b>0.006</b>
	Clinical trial	18	0 (0.0%)	1 (5.6%)	11 (61.1%)	6 (33.3%)	17 (94.4%)	
Dose	< 400mg	6	2 (33.3%)	0 (0.0%)	4 (66.7%)	0 (0.0%)	4 (66.7%)	0.88
	≥ 400mg	56	9 (16.1%)	8 (14.3%)	27 (48.2%)	12 (21.4%)	39 (69.6%)	

<b>Pirtobrutinib</b>								
<b>Subgroup</b>	<b>Category</b>	<b>Total (n)</b>	<b>NR n (%)</b>	<b>mR n (%)</b>	<b>PR n (%)</b>	<b>VGPR n (%)</b>	<b>MRR (PR + VGPR)</b>	<b>p</b>
Prior cBTKi	Prior progression	20	4 (20.0%)	4 (20.0%)	8 (40.0%)	4 (20.0%)	12 (60.0%)	0.40
	No prior progression	5	1 (20.0%)	0 (0.0%)	1 (20.0%)	3 (60.0%)	4 (80.0%)	
CXCR4 status	Mutated	10	5 (50.0%)	1 (10.0%)	3 (30.0%)	1 (10.0%)	<b>4 (40.0%)</b>	<b>0.013</b>
	Wild type	11	0 (0.0%)	1 (9.1%)	5 (45.5%)	5 (45.5%)	10 (90.9%)	
TP53 status	Altered	9	3 (33.3%)	0 (0.0%)	4 (44.4%)	2 (22.2%)	6 (66.7%)	0.71
	Wild type	8	0 (0.0%)	2 (25.0%)	3 (37.5%)	3 (37.5%)	6 (75.0%)	
Prior lines	1–3 lines	11	4 (36.4%)	1 (9.1%)	3 (27.3%)	3 (27.3%)	6 (54.5%)	0.38
	> 3 lines	14	1 (7.1%)	3 (21.4%)	6 (42.9%)	4 (28.6%)	10 (71.4%)	
Setting	Off-trial	20	4 (20.0%)	3 (15.0%)	7 (35.0%)	6 (30.0%)	13 (65.0%)	0.84
	Clinical trial	5	1 (20.0%)	1 (20.0%)	2 (40.0%)	1 (20.0%)	3 (60.0%)	
Prior BCL2i	Yes	9	1 (11.1%)	2 (22.2%)	3 (33.3%)	3 (33.3%)	6 (66.7%)	0.84
	No	16	4 (25.0%)	2 (12.5%)	6 (37.5%)	4 (25.0%)	10 (62.5%)	

Note: Best overall response is reported according to the 11th International Workshop on Waldenström's Macroglobulinemia (IWWM-11) criteria. Response categories are defined as follows: VGPR (very good partial response), PR (partial response), mR (minor response), and NR (no response or stable disease). The major Response Rate (MRR) is defined as the proportion of patients achieving at least a partial response (VGPR + PR). *p*-values represent the statistical comparison of the major response rate (MRR) between the analyzed subgroups, cBTKi: covalent Bruton tyrosine kinase inhibitor. Bold *p*-values indicate statistical significance ( $p < 0.05$ ).

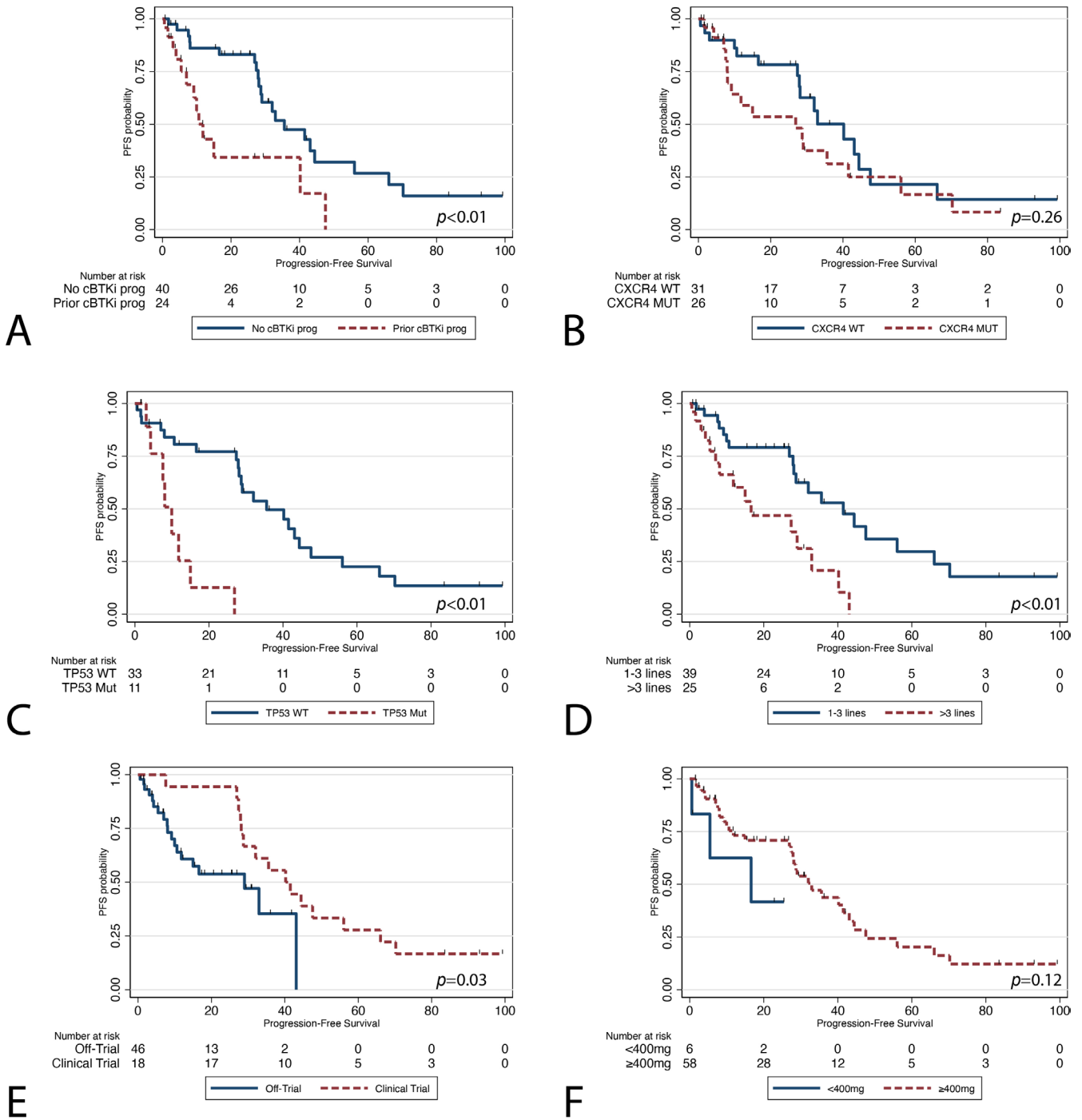
remained independently associated with inferior PFS (HR 4.71; 95% CI, 1.46–15.23;  $p = 0.01$ ) (Table S2).

### 3.2 | Pirtobrutinib Cohort

In the pirtobrutinib cohort ( $n = 27$ ), the MRR was lower among patients with *CXCR4* mutations (40% vs. 91%;  $p = 0.013$ ). No significant differences in MRR were observed by age, sex, *TP53* status, prior cBTKi exposure, or the number of previous therapy lines (all  $p > 0.05$ ; Table 2). In the multivariable analysis, *CXCR4* mutations remained associated with lower MRR (OR 0.05; 95% CI, 0.003–0.74;  $p = 0.03$ ) (Table S3).

The median time to first response among patients treated with pirtobrutinib was 0.92 months (95% CI, 0.66–1.84). Time to first response was longer in patients with a *CXCR4* mutation (1.83 months; 95% CI, 1.9–NR) than in those without (0.78 months; 95% CI, 0.36–NR) ( $p = 0.06$ ). No differences were seen in patients who had progressed to cBTKi or had *TP53* alterations.

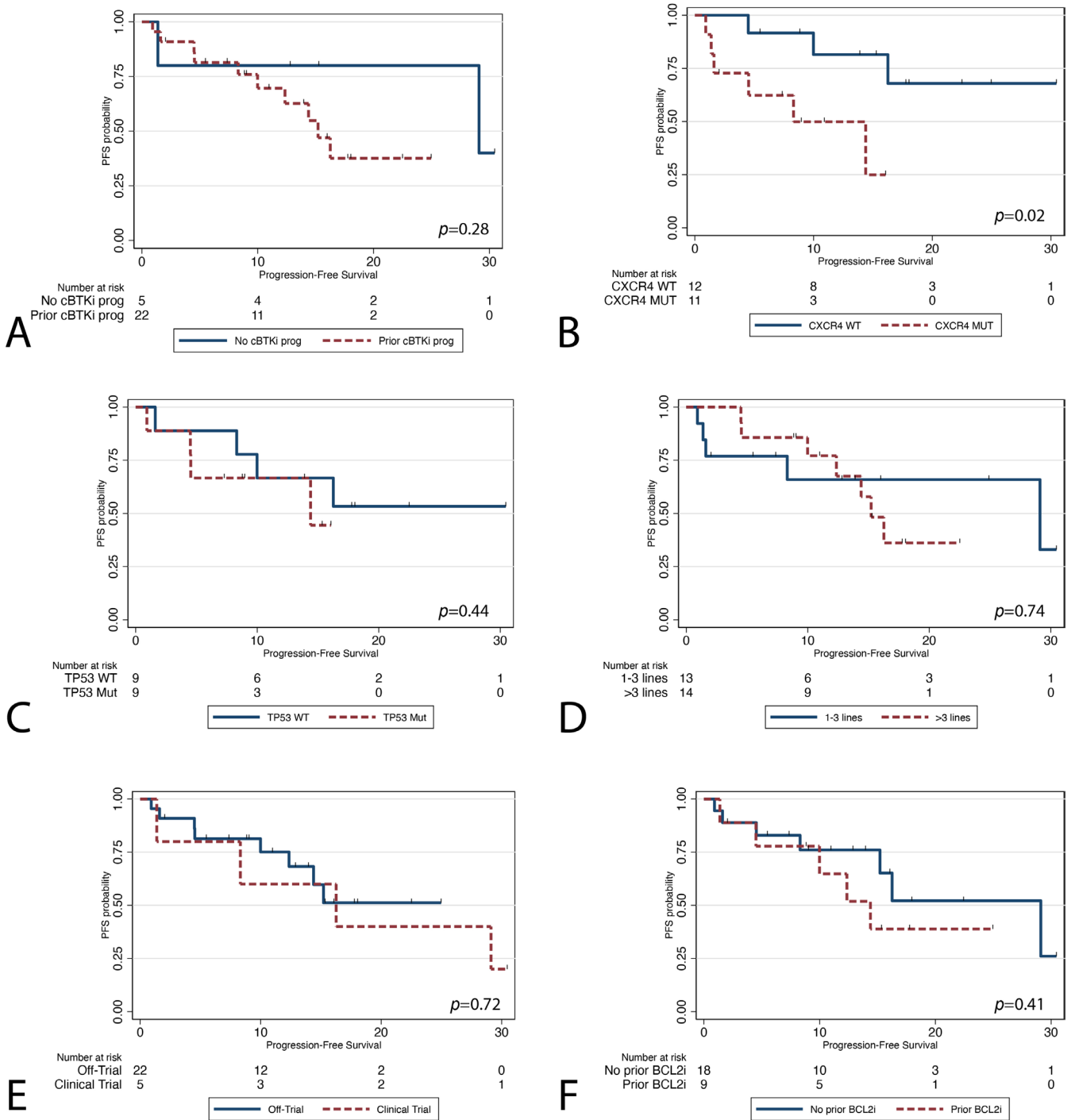
Similarly, *CXCR4* mutations were associated with shorter PFS (8.3 months [95% CI, 1.4–not reached] vs. not reached [95% CI, 10.0–not reached];  $p = 0.02$ ) (Figure 3B). Although progression on a prior cBTKi was numerically associated with shorter PFS (15.2 months [95% CI, 9.99–not reached] vs. 29.1 months [95% CI, 1.38–not reached]), this difference did not reach statistical



**FIGURE 2** | Progression-free survival (PFS) with venetoclax according to clinical and molecular subgroups. (A) Prior covalent BTK inhibitor (cBTKi) progression, (B) *CXCR4* mutation, (C) *TP53* status, (D) number of prior therapy lines (1–3 vs. >3), (E) treatment setting (off-trial vs. clinical trial), and (F) Venetoclax dose (<400 mg vs. ≥400 mg). Kaplan–Meier curves display PFS probability over time; *p*-values correspond to log-rank tests.

significance ( $p = 0.28$ ), noting that the latter subgroup was small ( $n = 5$ ) (Figure 3A). Importantly, *TP53* status did not impact PFS in patients treated with pirtobrutinib ( $p = 0.44$ ), among the 18 patients with *TP53* testing available (9 wild-type and 9 altered) (Figure 3C). Other variables, including number of prior lines of therapy, clinical trial enrollment, and prior BCL2 inhibitor exposure, were not significantly associated with PFS (Figure 3D–F). In the multivariable analysis, *CXCR4* mutations remained associated with shorter PFS (HR 5.06; 95% CI, 0.97–26.3;  $p = 0.05$ ) (Table S4).

Of note, among patients with *TP53*-altered disease who received both agents sequentially, four were treated with venetoclax followed by pirtobrutinib: three did not respond to venetoclax but responded to pirtobrutinib, while one achieved a partial response with venetoclax and a VGPR with pirtobrutinib. One additional *TP53*-altered patient received pirtobrutinib first without response and subsequently venetoclax, which was discontinued shortly thereafter due to adverse effects.



**FIGURE 3** | Progression-free survival (PFS) with pirtobrutinib according to clinical and molecular subgroups. (A) Prior covalent BTK inhibitor (cBTKi) progression, (B) *CXCR4* mutation, (C) *TP53* status, (D) number of prior therapy lines (1–3 vs. > 3), (E) treatment setting (off-trial vs. clinical trial), and (F) prior BCL2 inhibitor exposure. Kaplan–Meier curves display PFS probability over time with corresponding log-rank  $p$  values.

### 3.3 | Sequencing From cBTKi to Venetoclax or Pirtobrutinib

Among 33 patients who transitioned from a cBTKi to venetoclax or pirtobrutinib within 1 month, three transition strategies were observed. Thirteen patients received venetoclax without overlap, of whom 8 (62%) experienced IgM rebound. Five patients received venetoclax with continued cBTKi overlap (median overlap duration, 2.0 months; IQR, 1.17–12.60), and none experienced IgM rebound. In contrast, 15 patients transitioned from

a cBTKi to pirtobrutinib without overlap, and no IgM rebound events were observed (Figure 4).

### 3.4 | Venetoclax and Pirtobrutinib Efficacy Comparison

Venetoclax and pirtobrutinib demonstrated comparable MRR (69% vs. 64%;  $p=0.63$ ). The median PFS was 32.0 months (95% CI, 27.4–43.1) for venetoclax and 16.3 months (95% CI, 10.0–not

reached) for pirtobrutinib, with no statistically significant difference between the two ( $p=0.16$ ). These results should be considered in the context of clear baseline imbalances between cohorts.

Consequently, in the 1:1 matched cohort based on prior progression to a cBTKi and the number of prior therapy lines, we obtained a 42-patient cohort, with 21 patients per treatment group (Table S5). In this matched cohort, MRR remained equivalent (OR 0.92; 95% CI, 0.2–3.4;  $p=0.91$ ), and no difference in PFS was observed (HR 1.1; 95% CI, 0.4–2.7;  $p=0.83$ ) (Figure 5).

## 4 | Discussion

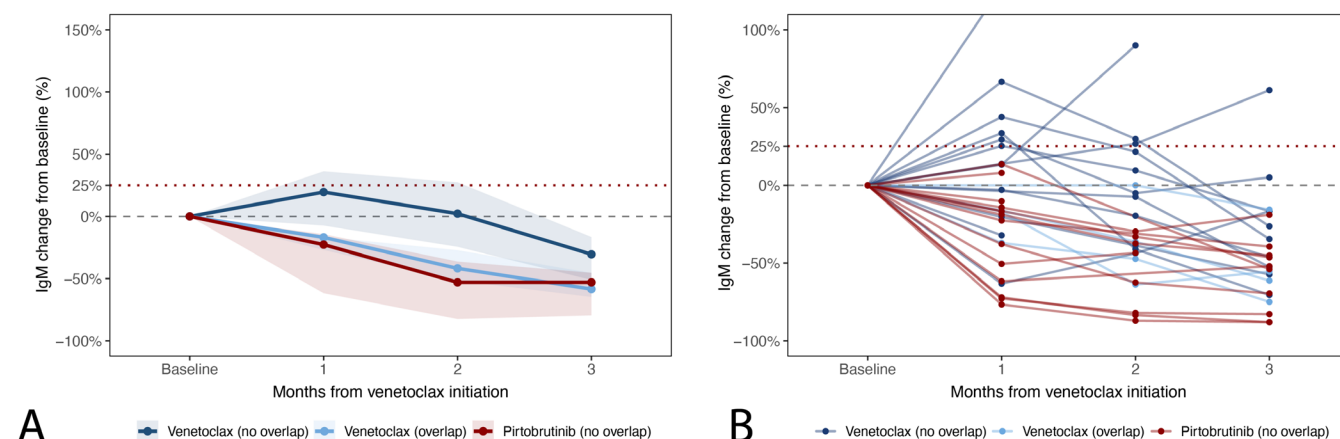
This study, to the best of our knowledge, provides the first comparison of venetoclax and pirtobrutinib in relapsed or refractory WM, outlining their distinct molecular vulnerabilities and sequencing implications, particularly after cBTKi exposure.

Our findings highlight important distinctions in molecular predictors of outcome. Most notably, *TP53* alterations had a pronounced

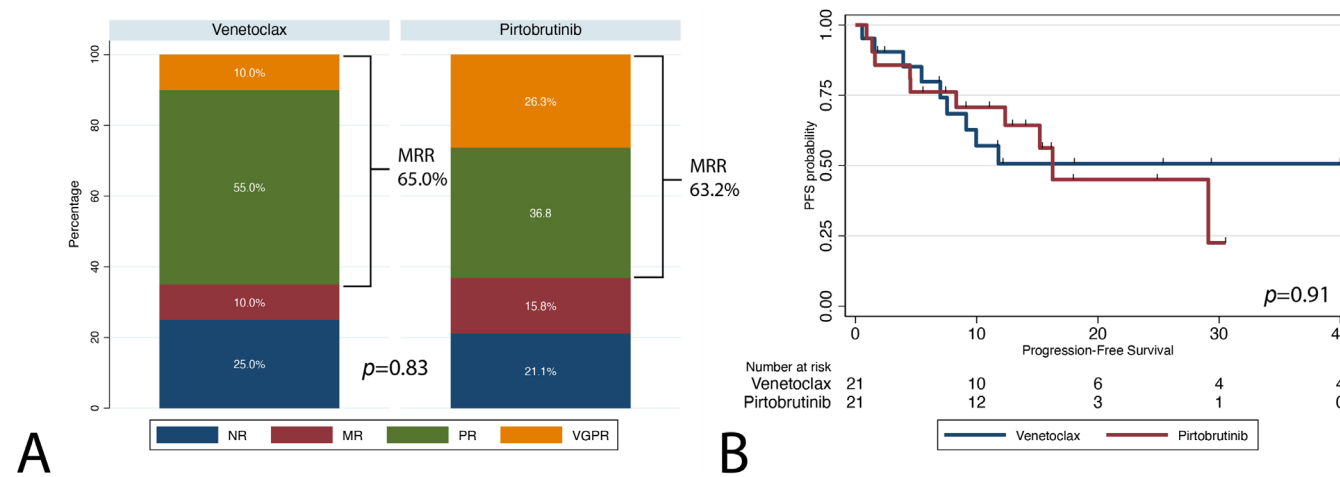
adverse effect in the venetoclax cohort, mirroring the results from a recent multicenter retrospective study of patients with lymphoplasmacytic lymphoma treated with venetoclax, in which *TP53*-altered disease was also associated with inferior outcomes. However, this association did not persist after multivariable adjustment [21]. Pre-clinical findings in leukemia and lymphoma show that *TP53*-deficient cells can survive and even expand despite BCL2 inhibition because of an increased apoptotic threshold, making inherent resistance to venetoclax biologically plausible [28].

In contrast, *TP53* alterations did not appear to influence outcomes in the pirtobrutinib cohort. This may reflect an effect similar to, or potentially more favorable than, that observed with zanubrutinib, for which the impact of *TP53* alterations is considerably smaller than with ibrutinib [13]. While no other data on the impact of *TP53* alterations in WM have been reported, evidence from chronic lymphocytic leukemia suggests that pirtobrutinib retains efficacy irrespective of *TP53* status [29].

These findings are encouraging, as few, if any, therapies in WM appear to be agnostic to *TP53* status. However, the observed



**FIGURE 4** | IgM rebound during transition from covalent BTK inhibitor (cBTKi) discontinuation toward subsequent therapy with venetoclax or pirtobrutinib. (A) Percent change from baseline IgM around the time of transition among patients treated with venetoclax (with or without overlap) and those receiving pirtobrutinib without overlap. (B) Individual trajectories of IgM levels during the rebound period, stratified by overlap status.



**FIGURE 5** | Comparative analysis of venetoclax and pirtobrutinib in 1:1 matched cohorts. (A) Distribution of best response according to IWWM-11 criteria, including NR = no response, MR = minor response, PR = partial response, and VGPR = very good partial response. (B) Kaplan–Meier curves illustrating progression-free survival (PFS) for patients treated with venetoclax or pirtobrutinib.  $p$  values correspond to the major response rate (MRR) and PFS comparisons between cohorts.

activity of pirtobrutinib in *TP53*-altered patients should be interpreted with caution, given the small sample size. *TP53* alterations were primarily assessed by NGS, whereas FISH for del (17p) was performed in a limited subset of patients. This limited our ability to identify del (17p), including both single- and double-hit *TP53* alterations. A very recent study showed that double-hit *TP53* alterations are strongly associated with inferior outcomes in WM [14], although their impact across different therapies remains incompletely defined. Future studies should incorporate systematic *TP53* testing to better understand the prognostic and therapeutic implications of single- versus double-hit *TP53* alterations.

Conversely, *CXCR4* mutations were associated with lower MRR and shorter PFS with pirtobrutinib, while their effect in the venetoclax cohort was minimal. A similar pattern has been described with ibrutinib [1–4], with this effect appearing to be mitigated by the addition of rituximab [30–32]. The adverse impact of *CXCR4* mutations on treatment response appears less pronounced with zanubrutinib [13, 33] and has not been studied for acalabrutinib [34].

In the completed but unpublished phase II pirtobrutinib trial in previously treated WM, *CXCR4* status was available in 54 patients [35]; although no formal efficacy analysis by *CXCR4* status was reported, lower MRR was observed in *CXCR4*-mutated versus wild-type disease (50% vs. 76%) [36]. Combined with our findings, these data suggest that *CXCR4* mutations may impact response to pirtobrutinib.

Differences in baseline characteristics across pirtobrutinib and venetoclax clinical trials [15, 17, 35] and within our study preclude direct or unadjusted comparisons between the two agents. After accounting for these imbalances, including through the matched cohort, our results do not point to a clear efficacy advantage that would justify selecting one agent over the other. Additionally, outcomes were comparable regardless of whether patients received pirtobrutinib before venetoclax or vice versa, suggesting that either approach is feasible and that other factors, such as molecular predictors or patient preference, may be more informative in guiding treatment selection.

From a treatment-sequencing perspective, transitioning from a cBTKi to venetoclax was associated with frequent and clinically relevant IgM rebound, reflecting the high rate of IgM rebound most commonly shortly after cBTKi discontinuation [37] and the delayed time to response with venetoclax, particularly in cBTKi-exposed patients [17]. Our data suggest that BTKi-venetoclax overlap may mitigate IgM rebound. Still, caution should be taken when transitioning from ibrutinib to venetoclax, as high-grade ventricular arrhythmias have been reported with this combination in WM [38], a finding not studied with other cBTKis and not observed in other lymphomas [39–42]. In this context, sequencing the highly selective non-covalent BTKi pirtobrutinib first may represent a reasonable option when transitioning from cBTKis [26], supported by its shorter time to response and its recently demonstrated safety when combined with venetoclax in WM [43].

It is important to note the notably high discontinuation rate due to treatment-related toxicity in the venetoclax cohort, particularly in the off-trial setting, which may have contributed

to lower response rates compared with patients treated within clinical trials, together with other factors observed in the trial setting, including higher venetoclax dosing (800 mg daily) [17]. Although not explicitly evaluated in this study, this observation is consistent with prior reports indicating higher toxicity with venetoclax compared with pirtobrutinib, particularly notable with respect to cytopenias [17, 27].

Moreover, our findings provide a strong rationale for combining pirtobrutinib and venetoclax. Early clinical data from a phase II study in previously treated WM have shown very deep responses with this time-limited combination, supporting the hypothesis of synergy [43], and a separate frontline study incorporating pirtobrutinib, venetoclax, and rituximab is currently underway (PRoVen; NCT07231952).

Important limitations should be considered when interpreting our findings. The retrospective design and relatively small sample size, particularly in the pirtobrutinib cohort, have limited statistical power and the ability to identify predictors of outcome. The retrospective nature of this study limited the assessment of adverse events because of inconsistent electronic medical record documentation. It resulted in substantial missing data, including a lack of genetic testing in a large proportion of patients, limiting the generalizability of our findings. Additionally, inherent limitations of retrospective analyses may bias time-to-event outcomes, as heterogeneous IgM testing intervals can influence estimates of PFS and time to response. Moreover, inclusion of patients who received both therapies in both cohorts may have further confounded our findings.

In addition, although matching was performed to minimize bias across key variables, the matched analysis remained relatively small, as only a limited number of patients could be paired across treatment groups. Furthermore, matching could only be performed on variables without missing values, which precluded matching by *CXCR4* and *TP53* status and limited our ability to assess balance for these variables in the resulting cohort, despite apparently similar distributions. Of note, there is minor patient overlap in our study with a previously published multicenter retrospective study of venetoclax-treated lymphoplasmacytic lymphoma patients [21].

Despite these constraints, the study includes a large, well-characterized cohort with genotyping, all of which are systematically followed by dedicated clinical and laboratory teams. To our knowledge, this remains the only study to directly compare and provide sequencing insights for these two increasingly utilized novel agents. The cohort also reflects a mix of patients primarily managed at our institution, and others followed mainly in external practices who initiated therapy both within and outside our center, offering a broader view across various care settings. Altogether, these strengths provide meaningful insights into previously unexplored aspects of two of the most innovative therapies in WM.

## 5 | Conclusion

Venetoclax and pirtobrutinib demonstrate comparable activity in relapsed or refractory WM, each with distinct limitations.

*TP53* and *CXCR4* mutations were associated with inferior outcomes with venetoclax and pirtobrutinib, respectively, suggesting potential non-overlapping molecular vulnerabilities. Venetoclax administered after covalent BTK inhibition was frequently complicated by IgM rebound. In contrast, pirtobrutinib was associated with a more favorable transition profile, including lower rates of treatment discontinuation due to toxicity and a faster time to response. Despite the retrospective design and limited sample size, these observations support further exploration of pirtobrutinib-first sequencing in this setting, as well as combination strategies that may exploit complementary vulnerabilities.

### Author Contributions

A.G. and J.J.C. designed the study. A.G., N.T., and M.K. collected the data. J.J.C. and S.S. provided patient data. M.K., N.B., J.N., A.E., and K.M. contributed to clinical coordination. N.T., A.K., M.L.G., Z.R.H., and S.P.T. performed the laboratory studies. A.G. and J.J.C. performed the statistical analyses. J.J.C., S.S., S.P.T., and Z.R.H. provided overall supervision. A.G. and J.J.C. drafted the initial version of the manuscript. All authors critically reviewed and approved the final manuscript.

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The authors have nothing to report.

### Ethics Statement

This study was approved by the Institutional Review Board of the participating institution, which waived the requirement for informed consent due to the retrospective nature of the study.

### Conflicts of Interest

J.J.C. received research funds or consulting fees from AbbVie, AstraZeneca, BeOne, Collectar, Johnson & Johnson, Loxo, Nurix, Pharmacylics, and Schrodinger. S.S. received research funding or consulting fees from ADC Therapeutics, AstraZeneca, BeOne, Collectar, and Sobi. S.P.T. received research funding and/or consulting fees from AbbVie/Pharmacylics Inc., Janssen Oncology Inc., BeOne Inc., Eli Lilly Pharmaceuticals, Bristol Myers Squibb, and Ono Pharmaceuticals.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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### Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Variables associated with the major response rate (MRR) in venetoclax-treated patients, according to univariate and multivariate logistic regression analyses. **Table S2:** Variables associated with progression-free survival (PFS) in venetoclax-treated patients, according to univariate and multivariate Cox regression analyses. **Table S3:** Variables associated with the major response rate (MRR) in pirtobrutinib-treated patients, according to univariate and multivariate logistic regression analyses. **Table S4:** Variables associated with progression-free survival (PFS) in pirtobrutinib-treated patients, according to univariate and multivariate Cox regression analyses. **Table S5:** Baseline clinical and molecular characteristics of patients included in the 1:1 matched cohort by the treatment group. Patients were matched on prior lines of therapy and prior progression on covalent BTK inhibitors (cBTKi). For variables with missing data, the total number of evaluable patients is indicated by a number following the variable name, denoted by an asterisk.