

Pirtobrutinib in patients with Waldenström Macroglobulinemia previously treated with covalent BTK inhibitors: results from an Italian retrospective cohort treated within a compassionate use program

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Background. Pirtobrutinib, a non-covalent Bruton tyrosine kinase inhibitor (ncBTKi) developed to overcome resistance to covalent BTKi (cBTKi), has shown clinical efficacy with a favorable safety profile across different lymphoproliferative diseases, including Waldenström Macroglobulinemia (WM), in the prospective phase 1-2 BRUIN study. Real-world data on Pirtobrutinib in WM are extremely limited. The aim of this study was to evaluate efficacy and safety of Pirtobrutinib in relapsed/refractory WM patients treated within a compassionate use program (CUP) in Italy.

Methods. This retrospective study was approved by the IRB and conducted in accordance with principles stated in the Declaration of Helsinki. The primary endpoint was overall response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. Disease response was

assessed locally using modified IWWM-6 response criteria. PFS and OS were estimated using the Kaplan-Meier method from Pirtobrutinib initiation, with patients censored at last follow-up or death. Adverse events (AEs) were graded using CTCAE v5.0. All patients who had received at least 1 dose of Pirtobrutinib by data cut-off of July 15, 2026 were included in the analysis.

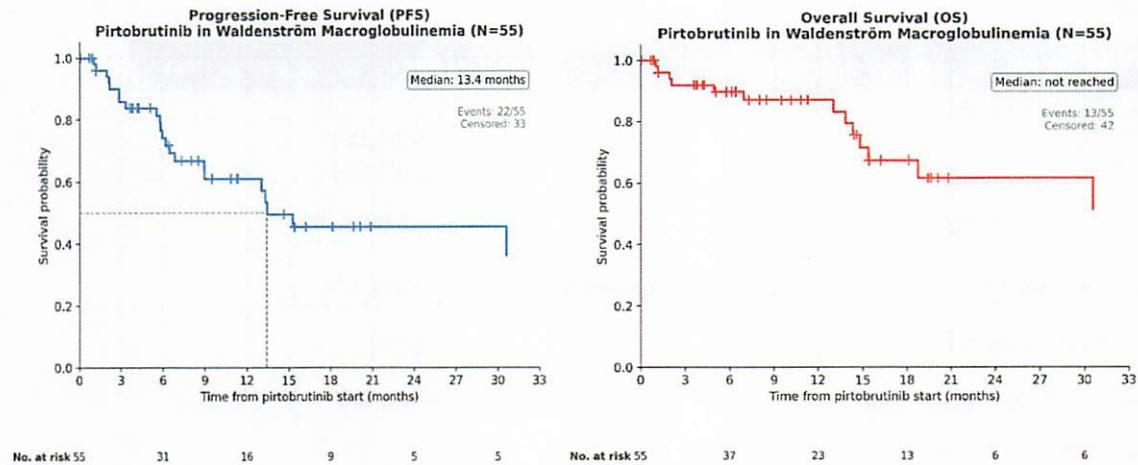
Results. From November 2022 to July 2026, 55 patients were treated across 26 Italian centers. Patients' characteristics at Pirtobrutinib initiation are reported in Table 1. The median age was 75.6 years (IQR 68.3–81.3), higher than the age of patients included in the BRUIN study (median 69 years, IQR 61-75). The median time from diagnosis to Pirtobrutinib start was 125 months (range: 27.9-344.6), and median number of prior lines of therapy was 3 (range: 1-9). All patients had been previously exposed to cBTKi, which had been discontinued for progression or toxicity in 44 (80%) and 11 (20%) cases, respectively. Prior lines of therapy included chemo-immunotherapy in 49 patients (89.1%), BCL-2 inhibitors in 8 (14.5%), rituximab+bortezomib in 6 (10.9%), nemtabrutinib in 3 (5.4%), autologous transplantation in 6 (10.9%). Fifty-one patients were evaluable for response. The ORR was 66.7%, including a VGPR+CR rate of 21.8%, similar to response observed in WM patients previously treated with cBTKi in the BRUIN study. Treatment modifications of Pirtobrutinib were reported in 13 patients (23.6%). Six patients (11.3%) reduced Pirtobrutinib dose, and 7 (12.7%) temporarily interrupted treatment for a median of 31 days due to AEs (infections n=7, grade 4 neutropenia n=3, bleeding n=1, orthopnea n=1, palpitations n=1). Five patients permanently discontinued Pirtobrutinib because of AEs, namely bleeding (n=2), severe infection (n=2), and heart failure (n=1). At the time of this report, 16 patients (29.1%) have progressed, and 10 of them have been subsequently treated with BTK degraders (n=4), chemotherapy±rituximab (n=4), or sonrotoclax (n=2). Overall, 13 patients (23.6%) have died. With a median follow-up of 10.2 months (IQR: 4.6-16.1), PFS and OS were 13.4 months and not reached, respectively (Figure 1).

Conclusion. In this real-world Italian cohort of WM patients previously treated with cBTKi, the efficacy of Pirtobrutinib was comparable to that observed in the BRUIN trial in terms of response and outcome. Pirtobrutinib confirmed a favorable safety profile, with no new safety signals reported, in this unselected elderly population.

Table 1. Patients characteristics

Characteristic	Result
Gender, n. of patients (%)	
Male	30 (54.5%)
Female	25 (45.5%)
Age (years), median (range)	75.6 (49.7–92)
Time from diagnosis to pirtobrutinib start (years), median (range)	10.4 (2.3–28.7)
Number of prior lines of therapy, median (range)	3 (1–9)
Prior covalent BTKi, n. of patients (%)	55 (100%)
Cause of cBTKi discontinuation, n. of patients (%)	
Progression	44 (80%)
Intolerance	11 (20%)
Response in 51 evaluable patients	
CR	1 (1.8%)
VGPR	11 (20%)
PR	21 (38.2%)
MR	1 (1.8%)
SD	13 (23.6%)
PD	4 (7.2%)
Overall response rate (CR+VGPR+PR+MR)	34/51 (66.7%)
Major response rate (CR+VGPR+PR)	33/51 (64.7%)

Figure 1. Progression-free Survival (PFS) and Overall Survival (OS) from Pirtobrutinib initiation



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