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REVIEW ARTICLE

# Waldenström Macroglobulinemia: Targeted Agents Taking Center Stage

**Shayna Sarosiek**[1,2] · **Jorge J. Castillo**[1,2]

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## Abstract

With the worldwide approval of the oral covalent Bruton tyrosine kinase (BTK) inhibitors ibrutinib and zanubrutinib for treating patients with Waldenström macroglobulinemia (WM), targeted agents have certainly taken center stage in the therapeutic landscape of WM. This review discusses the biological and clinical data supporting current and up-and-coming targeted agents in WM. Bruton tyrosine kinase inhibitors induce fast, deep, and durable responses in patients with WM, comparable to chemoimmunotherapy; however, there is a glaring absence of comparative studies between these regimens. The high response and progression-free survival rate and the ease of administration of BTK inhibitors must be balanced against their specific adverse-event profile with unique toxicity (e.g., bleeding and cardiac arrhythmia) and the indefinite duration of the therapy. Novel targeted agents of interest include BCL2 antagonists (e.g., venetoclax and sonrotoclax) and non-covalent BTK inhibitors (e.g., pirtobrutinib and nemtabrutinib), among others. The therapeutic landscape of patients with WM will benefit from the robust participation of patients in clinical trials.

**Key Points**

Covalent Bruton tyrosine kinase inhibitors, such as ibrutinib and zanubrutinib, have become a standard for treating patients with Waldenström macroglobulinemia.

The therapeutic options recently increased with safety and efficacy data on the BCL2 inhibitor venetoclax and the non-covalent BTK inhibitor pirtobrutinib.

Several novel targeted agents are in clinical development, making clinical trial participation paramount to improving patients' outcomes.

✉ Shayna Sarosiek
shayna_sarosiek@dfci.harvard.edu

[1] Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, 450 Brookline Ave, Mayer 221, Boston, MA 02215, USA

[2] Department of Medicine, Harvard Medical School, Boston, MA, USA

## 1 Introduction

Waldenström macroglobulinemia (WM) is a rare indolent lymphoma defined by a malignant lymphoplasmacytic clone that resides in the bone marrow and produces a monoclonal IgM paraprotein. Waldenström macroglobulinemia is characterized by the presence of a recurrent somatic mutation in *MYD88 L265P*, which is found in the majority of patients with WM (>95%); 30–40% of patients will also have somatic mutations in the C-terminal of *CXCR4*, similar to those observed in patients with WHIM syndrome [1, 2]. Mutations in *TP53* have also been described in 5–20% of WM patients [3–6].

Mutated MYD88 homodimerizes at the cellular membrane level, recruiting several intracellular molecules and forming the MYDdosome. BTK, HCK, and IRAK1/4 are essential members of the MYDdosome [7]. Downstream effects of the inherently activated MYD88 include overactivation of nuclear factor-*kappa* B (NF-kB), providing the malignant lymphoplasmacytic cells, which are important mechanisms of protection against apoptosis. Mutated CXCR4 activates upon binding with its ligand CXCL12 and, in contrast to unmutated CXCR4, it does not undergo intracellular inactivation [8]. CXCR4 persistence induces

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an overactivation of PI3K, AKT, and ERK, supplying an additional activation pathway supplementary to MYD88. *CXCR4*-mutated cell lines showed resistance to BTK inhibitors, which was abrogated by adding BCL2 antagonists. Clinically, *CXCR4* mutations have been associated with lower response rates and shorter progression-free survival (PFS) in WM patients treated with BTK inhibitors [9].

## 2 Current Management of Waldenström Macroglobulinemia (WM)

Although 20% of patients with WM may not require therapy for over a decade, most patients will require treatment with multiple lines of therapy throughout their disease course due to the development of WM-related symptoms such as symptomatic cytopenias, hyper-viscosity, or other IgM-related complications [10–12]. In those patients meeting treatment criteria, various options are currently available for treating WM, including chemoimmunotherapy, proteasome inhibitor-based therapy, Bruton tyrosine kinase (BTK) inhibitors, and the BCL2 inhibitor venetoclax.

Chemoimmunotherapy, including bendamustine-rituximab and dexamethasone-rituximab-cyclophosphamide, has been standard therapy in WM for many years based on high response rates and long PFS [13–16]. Side effects of these alkylating agents include cytopenias, infections, gastrointestinal symptoms, and a possibility of stem cell toxicity and myeloid neoplasms. Rituximab, an anti-CD20 monoclonal antibody, has also been combined with the more targeted proteasome inhibitors, most commonly bortezomib, as an effective treatment option in WM [17–20]. However, the broad application of bortezomib-based therapy is limited in WM due to neurotoxicity, especially peripheral neuropathy, present in many patients with WM at baseline. Rituximab monotherapy is a commonly used regimen worldwide, although it is not typically recommended due to low response rates and short PFS [21, 22]. Additionally, it is associated with immunosuppression, rituximab intolerance, and paradoxical serum IgM flares, which could be symptomatic. More recently, therapeutic options have transitioned to a more targeted approach with the addition of the BTK inhibitors ibrutinib, acalabrutinib, and zanubrutinib, and the BCL2 antagonist venetoclax as standard therapies for WM [23–26].

## 3 Covalent BTK Inhibitors

The covalent BTK inhibitor ibrutinib set the stage for using and developing BTK inhibitors in WM when it received FDA approval in 2015. Ibrutinib, a first-generation BTK inhibitor, has proven efficacy in treatment-naïve and relapsed or refractory WM with overall response rates of 100% and 91%, major response rates of 79% and 87%, and very good partial response (VGPR) rates of 30% and 30%, respectively [23, 26]. The 5-year PFS rate for previously treated patients was 54%, and the 4-year PFS rate for treatment-naïve patients was 76%. *CXCR4* mutations were associated with lower VGPR and inferior PFS rates in treatment-naïve and previously treated patients. *MYD88* wild-type disease (using a detection technique with a sensitivity of 0.1%) was associated with the shortest PFS to ibrutinib monotherapy in previously treated patients [26]. The side effect profile of ibrutinib was unique. It included hematologic adverse effects, such as neutropenia and thrombocytopenia, and non-hematologic adverse effects, including bleeding, arthralgia, infection, and atrial fibrillation.

The INNOVATE study compared the combination of ibrutinib and rituximab against placebo and rituximab and showed a superiority of the former in major response (76% vs 31%) and VGPR or better (30% vs 5%) and 54-month PFS rates (68% vs 25%) [27]. *CXCR4* mutations affected the VGPR or better rates to ibrutinib and rituximab (23% vs 44%), but it did not affect 54-month PFS rates (63% vs 72%). Similarly, in patients without *MYD88* mutations, the VGPR rate was lower at 27%, but the 54-month PFS rate was not affected at 70%. However, the study used a detection technique with a sensitivity of 2% to assess for mutations. The adverse-event profile of ibrutinib was similar to that observed with monotherapy. Given the lack of an ibrutinib plus placebo arm, the benefit of adding rituximab to ibrutinib is unclear.

Second-generation covalent BTK inhibitors have now been developed, including acalabrutinib and zanubrutinib. Acalabrutinib was demonstrated to have efficacy in WM in a Phase 2 single-arm clinical trial with an overall response rate of 93% in both treatment-naïve and relapsed or refractory patients [24]. The median PFS was 68 months in previously treated patients [28]. Although responses were reported in patients without *MYD88* mutations, the study assessed *MYD88* mutational status in less than half of the cohort using low-sensitivity testing with a high false positive rate. Furthermore, the study did not evaluate the presence of *CXCR4* mutations. The side effect profile was similar to ibrutinib and included neutropenia, infection, and atrial fibrillation, although no direct comparison was made to ibrutinib in WM patients. A recent Phase 3 study reported lower rates of atrial fibrillation with acalabrutinib versus ibrutinib in patients with previously treated chronic lymphocytic leukemia (CLL) [29].

Subsequently, the results of the Phase 3 open-label ASPEN trial randomizing 199 eligible patients with relapsed or refractory WM to zanubrutinib or ibrutinib were reported. In this trial, the overall response rates were 94% for zanubrutinib and 93% for ibrutinib. Numerically,

more patients achieved a VGPR with zanubrutinib (28% vs 19%), although this difference was not statistically significant. The 42-month PFS rates for zanubrutinib and ibrutinib were 78% and 70%, respectively [30]. Zanubrutinib induced higher VGPR (21% vs 10%) and 42-month PFS rates (73% vs 49%) than ibrutinib. Zanubrutinib induced responses in WM patients with *MYD88* wildtype disease using a detection technique with a 0.5% sensitivity [31]. Again, the side-effect profile was similar between these agents, although there were lower rates of atrial fibrillation, diarrhea, hemorrhage, and hypertension with zanubrutinib. Neutropenia rates were higher with zanubrutinib than with ibrutinib without an increased risk of infection.

Two additional covalent BTK inhibitors, tirabrutinib and orelabrutinib, have shown similar efficacy and side-effect profiles compared to earlier BTK inhibitors [32, 33]. Although these treatments are not routinely used in the USA for WM, they are commonly used in Asia. The outcomes reported in selected clinical trials evaluating targeted agents in patients with WM are shown in Table1.

It is essential to note that BTK inhibitor therapy does not induce complete responses (CRs). However, the clinical benefit of attaining a CR in an indolent disease with long survival is unclear and not the main objective of therapy in WM. Another important aspect is the high cost of these agents and the indefinite therapy duration, making these treatments potentially less accessible outside of the USA.

Given the increasing use of BTK inhibitors to treat WM, the number of covalent BTK inhibitors available, and the indefinite duration nature of the treatment, managing adverse events is a topic of robust research. There are three potential courses of action for patients experiencing adverse events affecting their safety, activities of daily living, or quality of life (Fig. 1, Table 1).

One option is to manage adverse events with symptomatic management, temporary drug hold, or dose reductions. Temporary ibrutinib discontinuation can be associated with withdrawal symptoms in 20% of patients and can be managed with low doses of steroids [34]. Common withdrawal symptoms include fevers, night sweats, and fatigue. The onset of symptoms is within 24 hours from ibrutinib hold, with resolution within 12 hours of restarting the drug in most patients. Dose reduction in BTK inhibitors is a reasonable approach in patients with adverse events to these agents, especially those who benefit clinically from therapy. In a recent study of 353 WM patients treated with standard doses of ibrutinib, a dose reduction was needed in 27% of the patients due to adverse events [35]. Female sex and age ≥65 years were independent risk factors for a dose reduction. An improvement in adverse events was observed in 65% of the patients whose dose of ibrutinib was reduced. Rheumatologic and gastrointestinal adverse events improved in 80% of the patients, while bleeding improved only in 30%. The hematologic response was sustained or deepened on the lower doses in 79% of patients.

A second approach is to switch to another covalent BTK inhibitor. Recent studies have shown that patients who experience adverse events can switch from ibrutinib to acalabrutinib or zanubrutinib. In a prospective study of 33 patients with CLL and intolerance to ibrutinib who were switched to acalabrutinib, 64% did not experience a recurrence of the symptoms that led to ibrutinib intolerance [36]. Another prospective study of 60 CLL patients showed similar results, with 60% not experiencing a recurrence of intolerance [37]. A third study evaluated zanubrutinib in 67 patients with

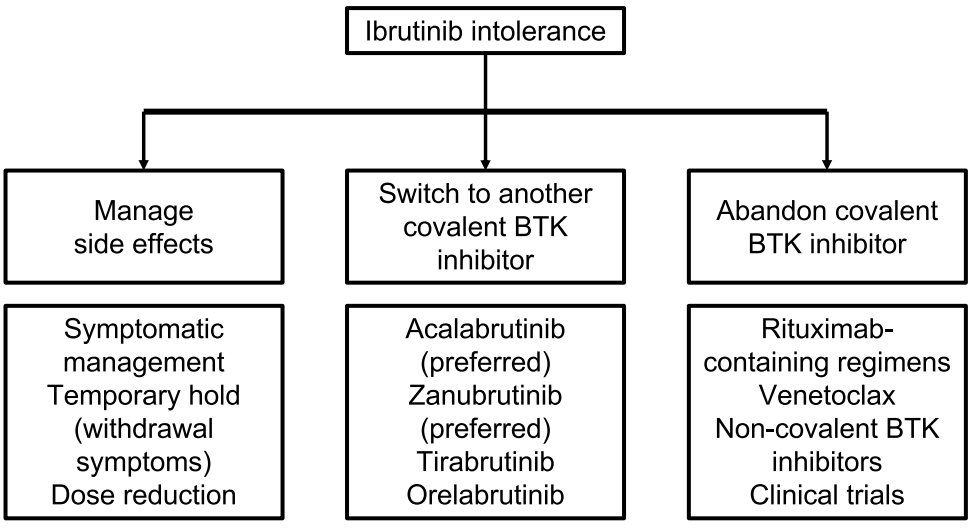


**Fig. 1** A proposed approach to managing ibrutinib intolerance

Adapted from: Munoz J, Sarosiek S, Castillo JJ. Managing ibrutinib-intolerant patients with B-cell malignancies. Oncologist; 28(4): 309-318.

**Table 1** Outcomes from selected clinical trials evaluating targeted agents in patients with Waldenström macroglobulinemia

| Agent/regimen | *N* | Setting | Mutations | Major | VGPR | PFS |
|---|---|---|---|---|---|---|
| Ibrutinib | 36 | RR | MYD88+ CXCR4− | 97% | 47% | 5-year: 70% |
| | 22 | RR | MYD88+ CXCR4+ | 68% | 9% | 5-year: 38% |
| | 4 | RR | MYD88− CXCR4− | 0% | 0% | Median: 0.4 years |
| Ibrutinib[a] | 16 | TN | MYD88+ CXCR4− | 94% | 44% | 4-year: 92% |
| | 14 | TN | MYD88+ CXCR4+ | 78% | 14% | 4-year: 59% |
| Ibrutinib + rituximab | 32 | TN/RR | MYD88+ CXCR4− | 81% | 44% | 54-month: 72% |
| | 26 | TN/RR | MYD88+ CXCR4+ | 77% | 23% | 54-month: 63% |
| | 11 | TN/RR | MYD88− CXCR4− | 73% | 27% | 54-month: 70% |
| Acalabrutinib[b] | 36 | TN/RR | MYD88+ | 78% | 28% | NR |
| | 14 | TN/RR | MYD88− | 57% | 0% | NR |
| Zanubrutinib | 65 | TN/RR | MYD88+ CXCR4− | 83% | 45% | 42-month: 81% |
| | 33 | TN/RR | MYD88+ CXCR4+ | 79% | 21% | 42-month: 73% |
| | 28 | TN/RR | MYD88− CXCR4− | 65% | 31% | 42-month: 54% |
| Venetoclax[a] | 15 | RR | MYD88+ CXCR4− | 86% | 29% | Median: 28 months |
| | 17 | RR | MYD88+ CXCR4+ | 76% | 12% | Median: 30 months |

*N* number, *NR* not reported, *PFS* progression-free survival, *RR* relapsed/refractory, *TN* treatment naïve, *VGPR* very good partial response

[a] *MYD88* wildtype patients were not included

[b] *CXCR4* mutations were not assessed

B-cell malignancies who were intolerant to acalabrutinib or ibrutinib [38]. Seventy percent of the adverse events experienced with ibrutinib and 83% of those with acalabrutinib did not recur on zanubrutinib. However, the median follow-up was short at 12 months. Data are lacking on switching to tirabrutinib or orelabrutinib. Switching to another covalent BTK inhibitor is not recommended if there is disease progression while on covalent BTK inhibitor therapy.

Finally, a third option is to switch therapies. Potential treatment options include chemoimmunotherapy, proteasome inhibitors, or BCL2 inhibitors if not used previously or consider a clinical trial. We recommend trying dose reductions first and switching to another covalent BTK inhibitor as a second option, especially in patients with good disease control, while reserving abandoning BTK inhibitor therapy as a last resource. Cessation of BTK inhibitors without initiating additional definitive therapy is not typically recommended due to the high risk of IgM rebound and disease progression [39].

## 4 Non-covalent BTK Inhibitors

With a BTK inhibitor, many patients with WM achieve prolonged hematologic responses, although some patients develop treatment intolerance requiring dose reductions or medication cessation. Other patients develop resistance to covalent BTK inhibitors through multiple mechanisms, including *PLCγ2* and *BTK C481S* mutations [40, 41]. For those with disease resistance or treatment intolerance, novel BTK inhibitors are being developed. Non-covalent BTK inhibitors do not interact with *C481* to exert their function and, therefore, are effective in patients who may have developed *BTK C481S*. Pirtobrutinib, a non-covalent BTK inhibitor that inhibits both wild-type and mutated *BTK*, is the most advanced in clinical development. In an initial Phase 1/2 trial, 78 patients with WM were treated [42]. All patients had relapsed or had refractory disease, and 61 had prior covalent BTK inhibitor therapy. Forty of these patients had discontinued their prior covalent BTK inhibitor therapy

due to disease progression. Of the 72 evaluable patients, the major response rate was 68%, with 17 very good partial responses (VGPRs) (24%) and 32 partial responses (PRs) (44%). The median PFS was 19 months, but the median follow-up was short at 16 months. The adverse-effect profile for the entire B-cell malignancy cohort was similar to prior BTK inhibitors, with the most frequent adverse events being contusion, diarrhea, and fatigue. However, the Grade ≥3 adverse effect rates were low, with only 3% hypertension, 1% hemorrhage, and 1% atrial fibrillation. Nemtabrutinib, another non-covalent BTK inhibitor with activity in both wild-type and mutated *BTK*, has been explored in a Phase 1/2 clinical trial that enrolled 112 patients, including six patients with WM [43].

Although the individual responses of the patients with WM are unknown, the overall response rate in the 36 patients with CLL and a *C481* mutation was 58%. The side-effect profile for this therapy was similar to other BTK inhibitors. It included neutropenia, fatigue, nausea, thrombocytopenia, diarrhea, and hypertension, in addition to the unique side effect of dysgeusia in 21% of patients. The initial clinical trials with non-covalent BTK inhibitors have included patients with relapsed/refractory disease or those intolerant to covalent BTK inhibitors, so their role in BTK inhibitor-naïve patients is not yet known.

## 5 BCL2 Antagonists

Another therapy recently explored in hematologic malignancies is the BCL2 antagonist venetoclax. BCL2 is an important anti-apoptotic protein, and venetoclax has been proven to improve outcomes in CLL and acute leukemia [44–46]. An initial Phase 2 trial using venetoclax in WM included 32 evaluable patients, including 16 patients with prior BTK inhibitor exposure [47]. In this trial, venetoclax was ramped up to a final dose of 800 mg orally once daily for two years. The overall response rate was 84%, with major and very good partial response rates of 81% and 19%, respectively. Time to minor and major responses were 1.9 and 5.1 months, respectively. The median PFS was 30 months, with several progression events shortly after stopping therapy. Treatment response and PFS were not affected by *CXCR4* mutational status. Treatment-related neutropenia was the only recurrent grade ≥3 adverse event in 45% of patients. Based on these data, venetoclax was added to the National Comprehensive Cancer Network (NCCN) guidelines as a potential treatment for relapsed WM.

Due to the efficacy of venetoclax shown in this original WM trial, in addition to the safety of venetoclax in combination with ibrutinib in mantle-cell lymphoma and CLL [48, 49], a Phase 2 trial using venetoclax in combination with ibrutinib was initiated [50]. The preliminary data from this trial reported enrollment of 45 patients with an overall response rate of 100%, a very good partial response rate of 40% ($n = 18$), a partial response rate of 53% ($n = 24$), and a minor response rate of 7% ($n = 3$). The median time to response was 1.9 months. Time to response was 2.8 months in those with a *CXCR4* mutation compared with 1.8 months in those without the mutation ($p = 0.048$). The VGPR rate was also lower in those patients with a *CXCR4* mutation (24% vs 50%, $p = 0.08$). Grade ≥3 adverse events that occurred in at least one patient included neutropenia (29%), mucositis (4%), tumor lysis syndrome (4%), and cardiac arrest/ventricular arrhythmia (7%). Four patients (9%) had a ventricular arrhythmia, two of whom died of cardiac arrest. Due to this complication, trial enrollment was halted, and treatment was stopped in all patients before the planned 2 years of therapy were completed. Although this was an effective regimen, the safety concerns have prohibited the continued development of this regimen in WM. The safety and efficacy of venetoclax combined with pirtobrutinib, a novel non-covalent BTK inhibitor thought to have less cardiac toxicity, is being explored in a Phase 2 clinical trial (NCT05734495). Additional clinical trials explore other BCL2 antagonists, such as sonrotoclax, in patients with previously treated WM (NCT05952037).

## 6 Bruton Tyrosine Kinase Degraders

Bruton tyrosine kinase inhibition has been highly effective in treating WM, but other therapies will be required in patients with intolerance or resistance. In these cases, BTK degradation may be a potentially effective therapy. Early data demonstrating the potential of BTK degradation were proven with the proteolysis targeting chimeras (PROTACs) MT-802 and P13I, which reduced active phosphorylated BTK in lymphoma cells with wild-type and C481 mutated BTK [51]. Further success of BTK degradation and the antiproliferative effects of BTK degradation was also demonstrated with the BTK degrader DD-03-171 [52]. This compound was initially studied in the laboratory and demonstrated suppression of signaling and proliferation of cancer cells, even in those cells with *BTK C481S* mutations.

Additionally, DD-03-171 was used in patient-derived xenografts and showed improved survival and decreased tumor burden in these murine models. Clinical development of additional BTK degraders followed closely with the orally bioavailable BTK and IKZF3 degrader NX-2127. Early results from a Phase 1 clinical trial that enrolled patients with relapsed B-cell malignancies were reported after the enrollment of 28 patients (NCT04830137) [53]. All patients had been previously treated with a BTK inhibitor, and of the 14 CLL patients tested, BTK mutations were found in C481 (29%), L528 (29%), T474 (14%), and V416 (7%). Of the 12 evaluable CLL

patients, the overall response rate was 33%, with an increased response rate over time (17% at two months and 50% at six months). Enrollment in this trial continues in patients with CLL and other B-cell malignancies. The selective BTK degrader NX-5948 is also being further developed in a clinical trial after initial preclinical data demonstrated effective BTK degradation in vivo and in vitro (NCT05131022). This agent also penetrates the central nervous system and demonstrates activity in brain malignancies. Therefore, continued development and exploration of this agent in Bing-Neel syndrome is warranted. Multiple additional BTK degraders are currently being explored in B-cell malignancies in clinical trials, including BGB-16673 (NCT05294731 and NCT05006716), ABBV-101 (NCT05753501), and AC676 (NCT05780034). These therapies may play a role in the future standard therapy of B-cell malignancies.

## 7 CXCR4 Antagonists

*CXCR4* mutations are known to affect the clinical presentation of the disease, as well as the therapeutic outcomes with BTK inhibitors [1, 54–56]. Due to the longer time to response, lower level of deep hematologic responses, and shorter PFS demonstrated in prior trials [23, 26, 57], the possibility of CXCR4 antagonism has been explored. An initial clinical trial using ulocuplumab in combination with ibrutinib was conducted and demonstrated major and VGPR response rates of 100% and 33%, respectively [58]. The median time to minor response was 0.9 months and 1.2 months to major response. The 2-year PFS rate was 90%. The most frequent recurrent grade ≥2 adverse effects were thrombocytopenia, rash, and skin infections. The response rates and time to response observed in this study compared favorably to historical controls and demonstrated the safety and efficacy of CXCR4 antagonism. Subsequently, mavorixafor, an oral small-molecule antagonist of CXCR4 was studied in a Phase 1b clinical trial in combination with ibrutinib patients with WM (NCT04274738). Ten patients had enrolled at the time of preliminary data presentation, and an overall response rate of 100% was reported in the eight evaluable patients [58]. Four patients achieved a major response, and one a VGPR. This clinical trial has been completed, and final data are expected soon. Although neither of these products is currently being developed for patients with WM, CXCR4 remains a potential therapeutic target for patients with WM.

## 8 Mucosa-associated Lymphoid Tissue Lymphoma Translocation Protein 1 (MALT1) Inhibitors

Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) is a para-caspase that plays a crucial role in regulating NF-kB signaling. It has been implicated in lymphomagenesis in activated B-cell (ABC) diffuse large B-cell lymphoma and other lymphomas such as WM with wild-type and mutated *MYD88* [59, 60]. In vivo and in vitro activity of MALT1 inhibitors was demonstrated, and therefore clinical trials are being pursued [61]. JNJ-67856633, an oral MALT1 inhibitor, is currently being evaluated in a Phase 1b dose-escalation trial in combination with ibrutinib in patients with relapsed or refractory B-cell lymphomas (NCT04876092). This compound is also being studied in another Phase 1 clinical trial combining JNJ-67856633 with a novel BTK inhibitor JNJ-64264681 to evaluate the safety of these agents and determine a recommended Phase 2 dosing strategy (NCT04657224). Two additional MALT1 inhibitors SGR-1505 and ONO-7018 are being used in Phase 1 clinical trials for patients with B-cell malignancies to evaluate safety, explore pharmacologic characteristics, and determine the maximum tolerated dose of each compound (NCT05544019 and NCT05515406).

## 9 Interleukin-1 Receptor-Associated Kinase (IRAK) Inhibitors

*MYD88 L265P* activates many downstream pathways, including BTK and IRAK1/IRAK4. Dysregulation of these pathways occurs in many cancers, including WM [62]. Prior preclinical research demonstrated antiproliferative effects of IRAK1 and IRAK4 inhibition, as well as synergistic activity of BTK and IRAK inhibition leading to increased blocking of NF-kB signaling and death of WM cells [62–64]. Hence, the development of a Phase 1 study of emavusertib (CA-4948), an oral inhibitor of IRAK4, in patients with relapsed or refractory hematologic malignancies including WM (NCT03328078) [65]. This study was designed to evaluate the pharmacokinetics and pharmacodynamics, safety, and tolerance of CA-4948, including exploration of the efficacy of single-agent emavusertib and the combination of emavusertib with ibrutinib. Of the initial 30 patients enrolled with various hematologic malignancies, three had WM. The most common non-hematologic adverse effects included diarrhea, vomiting, fatigue, dyspnea, and myalgias. Most hematologic adverse events were mild to moderate, including thrombocytopenia,

anemia, and neutropenia. Three patients discontinued treatment due to rash, fatigue, and lipase or amylase elevation. Eight of 28 patients had at least a 20% decrease in tumor burden, with two WM patients achieving a partial response. The recommended Phase 2 dosing from this trial was 300 mg twice daily. Continued recruitment in this trial will provide additional data on the efficacy of this therapy, and future studies with other IRAK inhibitors are being planned.

## 10 Role of Genomic Profiling with Targeted Agents

Genomic profiling plays an important role in confirming the diagnosis of WM and determining optimal therapeutic regimens based on the expected cadence of disease response and the depth and durability of hematologic response associated with specific therapies. It is well known that the presence or absence of mutations in *MYD88* and *CXCR4* affect responses to BTK inhibitors, with the most rapid and deep hematologic responses, as well as the longest PFS, occurring in patients with *MYD88* mutations and wild-type *CXCR4*. Based on the available data on covalent BTK inhibitors, zanubrutinib would be the preferred agent as it is associated with lower rates of bleeding, infection, and arrhythmia, as well as numerically higher rates of VGPR and 42-month PFS, especially in patients with *CXCR4*-mutated disease. Data on the efficacy of BTK inhibitors in patients without *MYD88* mutations are scant, and although acalabrutinib and zanubrutinib claim to be effective in this group of patients, the detection techniques used in these studies had lower detection rates than in the studies evaluating ibrutinib monotherapy. The effects of other mutations on disease outcomes and treatment responses are not yet well understood. For example, early data regarding *TP53* alterations, which are present in up to 20% of WM patients and may appear de novo during the disease course, suggest a shorter PFS and decreased overall survival, but not enough is known regarding perturbations in *TP53* to guide treatment choices [3, 5]. The same is true for multiple other recurrent mutations that occur with a lower frequency in WM, such as *KMT2D*, *ARID1A*, *CD79B*, *NOTCH2*, and *PRDM1* [6, 66]. All efforts should be made to better understand the genetic landscape of WM, especially in the structured setting of clinical trials, to determine the prevalence of specific genetic mutations and better understand the effect these mutations have on response to targeted therapies.

## 11 Future Pathways to Explore

In addition to genomic alterations in WM, a better understanding of the pro-survival signaling within the malignant cells of WM will likely lead to more targeted therapies. For example, the role of HCK, IRAK1, and IRAK4 in the MYDdosome is being explored. Inhibition of these factors, independently or combined with BTK inhibition, may be essential in preventing downstream NF-kB activation. Further downstream, the overactivation of AKT and ERK contributes to the growth and proliferation of malignant cells and may be potential targets for future WM therapies. Much remains to be understood about the intracellular pathways of the malignant cells in WM and the role of the bone marrow niche.

## 12 Future of WM Care

Treatment options for patients with WM have significantly improved in the last decade with the availability of oral targeted agents that allow for treatment of even those who are frail or have significant comorbidities, as well as those with refractory and multiply relapsed disease. Despite these significant advances, much work remains in this field. Current laboratory and clinical research focus on discovering new therapeutic targets and developing novel, more effective agents with improved side-effect profiles. In parallel with the development of new therapies, ongoing research focuses on understanding the role of deeper hematologic responses, such as complete hematologic responses and minimal residual disease negativity, in achieving prolonged PFS or improved overall survival in WM. A better understanding of our treatment goals will allow current and future targeted therapies to be developed to their maximum potential.

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## References


1. Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014;123(11):1637–46.
2. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med. 2012;367(9):826–33.
3. Gustine JN, Tsakmaklis N, Demos MG, et al. TP53 mutations are associated with mutated MYD88 and CXCR4, and confer an adverse outcome in Waldenstrom macroglobulinaemia. Br J Haematol. 2019;184(2):242–5.
4. Krzisch D, Guedes N, Boccon-Gibod C, et al. Cytogenetic and molecular abnormalities in Waldenstrom's macroglobulinemia patients: correlations and prognostic impact. Am J Hematol. 2021;96(12):1569–79.
5. Poulain S, Roumier C, Bertrand E, et al. TP53 mutation and its prognostic significance in Waldenstrom's macroglobulinemia. Clin Cancer Res. 2017;23(20):6325–35.
6. Varettoni M, Zibellini S, Defrancesco I, et al. Pattern of somatic mutations in patients with Waldenstrom macroglobulinemia or IgM monoclonal gammopathy of undetermined significance. Haematologica. 2017;102(12):2077–85.
7. Munshi M, Liu X, Kofides A, et al. A new role for the SRC family kinase HCK as a driver of SYK activation in MYD88 mutated lymphomas. Blood Adv. 2022;6(11):3332–8.
8. Cao Y, Hunter ZR, Liu X, et al. The WHIM-like CXCR4(S338X) somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenstrom's Macroglobulinemia. Leukemia. 2015;29(1):169–76.
9. Castillo JJ, Xu L, Gustine JN, et al. CXCR4 mutation subtypes impact response and survival outcomes in patients with Waldenstrom macroglobulinaemia treated with ibrutinib. Br J Haematol. 2019;187(3):356–63.
10. Bustoros M, Sklavenitis-Pistofidis R, Kapoor P, et al. Progression risk stratification of asymptomatic Waldenstrom macroglobulinemia. J Clin Oncol. 2019;37(16):1403–11.
11. Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol. 2003;30(2):116–20.
12. Zanwar S, Abeykoon JP, Ansell SM, et al. Disease outcomes and biomarkers of progression in smouldering Waldenström macroglobulinaemia. Br J Haematol. 2021;195(2):210–6.
13. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203–10.
14. Paludo J, Abeykoon JP, Shreders A, et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenstrom macroglobulinemia. Ann Hematol. 2018;97(8):1417–25.
15. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenstrom macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol. 2007;25(22):3344–9.
16. Kastritis E, Gavriatopoulou M, Kyrtsonis MC, et al. Dexamethasone, rituximab, and cyclophosphamide as primary treatment of Waldenstrom macroglobulinemia: final analysis of a phase 2 study. Blood. 2015;126(11):1392–4.
17. Auer RL, Owen RG, D'Sa S, et al. Subcutaneous bortezomib, cyclophosphamide and rituximab (BCR) versus fludarabine, cyclophosphamide and rituximab (FCR) for Initial Therapy of Waldenström's macroglobulinemia: a randomised phase II study. Blood. 2016;128(22):618.
18. Dimopoulos MA, Garcia-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). Blood. 2013;122(19):3276–82.
19. Ghobrial IM, Hong F, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrom macroglobulinemia. J Clin Oncol. 2010;28(8):1422–8.
20. Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenstrom macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05–180. J Clin Oncol. 2009;27(23):3830–5.
21. Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenstrom's macroglobulinemia with rituximab. J Clin Oncol. 2002;20(9):2327–33.
22. Treon SP, Emmanouilides C, Kimby E, et al. Extended rituximab therapy in Waldenstrom's macroglobulinemia. Ann Oncol. 2005;16(1):132–8.
23. Treon SP, Gustine J, Meid K, et al. Ibrutinib monotherapy in symptomatic, treatment-naive patients with Waldenstrom macroglobulinemia. J Clin Oncol. 2018;36(27):2755–61.
24. Owen RG, McCarthy H, Rule S, et al. Acalabrutinib monotherapy in patients with Waldenstrom macroglobulinemia: a single-arm, multicentre, phase 2 study. Lancet Haematol. 2020;7(2):e112–21.
25. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib versus ibrutinib in symptomatic waldenstrom macroglobulinemia: the aspen study. Blood. 2020;136(18):2038–50.
26. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 2015;372(15):1430–40.
27. Buske C, Tedeschi A, Trotman J, et al. Ibrutinib plus rituximab versus placebo plus rituximab for Waldenstrom's macroglobulinemia: final analysis from the randomized phase III innovate study. J Clin Oncol. 2022;40(1):52–62.
28. Owen R, McCarthy H, Rule S, et al. P1130: acalabrutinib in treatment-naive or relapsed/refractory Waldenström macroglobulinemia: 5-year follow-up of a phase 2. Single-arm study. HemaSphere. 2022;6:1020–1.
29. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. J Clin Oncol. 2021;39(31):3441–52.
30. Dimopoulos MA, Opat S, D'Sa S, et al. Zanubrutinib Versus Ibrutinib in Symptomatic Waldenstrom Macroglobulinemia: Final Analysis From the Randomized Phase III ASPEN Study. J Clin Oncol. 2023:JCO2202830.
31. Dimopoulos M, Sanz RG, Lee HP, et al. Zanubrutinib for the treatment of MYD88 wild-type Waldenstrom macroglobulinemia: a substudy of the phase 3 ASPEN trial. Blood Adv. 2020;4(23):6009–18.
32. Cao XX, Jin J, Fu CC, et al. Evaluation of orelabrutinib monotherapy in patients with relapsed or refractory Waldenstrom's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study. EClinicalMedicine. 2022;52: 101682.

33. Sekiguchi N, Rai S, Munakata W, et al. A multicenter, open-label, phase II study of tirabrutinib (ONO/GS-4059) in patients with Waldenstrom's macroglobulinemia. Cancer Sci. 2020;111(9):3327–37.
34. Castillo JJ, Gustine JN, Meid K, Dubeau T, Severns P, Treon SP. Ibrutinib withdrawal symptoms in patients with Waldenstrom macroglobulinemia. Haematologica. 2018;103(7):e307–10.
35. Sarosiek S, Gustine JN, Flynn CA, et al. Dose reductions in patients with Waldenstrom macroglobulinaemia treated with ibrutinib. Br J Haematol. 2023;201(5):897–904.
36. Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. Blood Adv. 2019;3(9):1553–62.
37. Rogers KA, Thompson PA, Allan JN, et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. Haematologica. 2021;106(9):2364–73.
38. Shadman M, Flinn IW, Levy MY, et al. Zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous Bruton tyrosine kinase inhibitors in the USA: a phase 2, open-label, single-arm study. Lancet Haematol. 2023;10(1):e35–45.
39. Gustine JN, Meid K, Dubeau T, et al. Ibrutinib discontinuation in Waldenstrom macroglobulinemia: etiologies, outcomes, and IgM rebound. Am J Hematol. 2018;93(4):511–7.
40. Xu L, Tsakmaklis N, Yang G, et al. Acquired mutations associated with ibrutinib resistance in Waldenstrom macroglobulinemia. Blood. 2017;129(18):2519–25.
41. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. N Engl J Med. 2014;370(24):2286–94.
42. Palomba ML, Patel MR, Eyre TA, et al. Efficacy of pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in relapsed/refractory Waldenström macroglobulinemia: results from the phase 1/2 bruin study. Blood. 2022;140(Supplement 1):557–60.
43. Woyach JA, Flinn IW, Awan FT, et al. Efficacy and safety of nemtabrutinib, a wild-type and C481S-mutated bruton tyrosine kinase inhibitor for B-cell malignancies: updated analysis of the open-label phase 1/2 dose-expansion bellwave-001 study. Blood. 2022;140.
44. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617–29.
45. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374(4):311–22.
46. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016;17(6):768–78.
47. Castillo JJ, Allan JN, Siddiqi T, et al. Venetoclax in previously treated Waldenstrom macroglobulinemia. J Clin Oncol. 2022;40(1):63–71.
48. Jain N, Keating M, Thompson P, et al. Ibrutinib and venetoclax for first-line treatment of CLL. N Engl J Med. 2019;380(22):2095–103.
49. Tam CS, Anderson MA, Pott C, et al. Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. N Engl J Med. 2018;378(13):1211–23.
50. Castillo JJ, Sarosiek S, Branagan AR, et al. Ibrutinib and venetoclax in previously untreated Waldenström macroglobulinemia. Blood. 2022;140:564–5.
51. Buhimschi AD, Armstrong HA, Toure M, et al. Targeting the C481S ibrutinib-resistance mutation in bruton's tyrosine kinase using PROTAC-mediated degradation. Biochemistry. 2018;57(26):3564–75.
52. Dobrovolsky D, Wang ES, Morrow S, et al. Bruton tyrosine kinase degradation as a therapeutic strategy for cancer. Blood. 2019;133(9):952–61.
53. Mato AR, Wierda WG, Ai WZ, et al. NX-2127-001, a first-in-human trial of NX-2127, a Bruton's tyrosine kinase-targeted protein degrader, in patients with relapsed or refractory chronic lymphocytic leukemia and B-cell malignancies. Blood. 2022;140(2329-2332).
54. Castillo JJ, Moreno DF, Arbelaez MI, Hunter ZR, Treon SP. CXCR4 mutations affect presentation and outcomes in patients with Waldenstrom macroglobulinemia: a systematic review. Expert Rev Hematol. 2019;12(10):873–81.
55. Roccaro AM, Sacco A, Jimenez C, et al. C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. Blood. 2014;123(26):4120–31.
56. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood. 2014;123(18):2791–6.
57. Castillo JJ, Meid K, Gustine JN, et al. Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia. Leukemia. 2022;36(2):532–9.
58. Treon SP, Meid K, Hunter ZR, et al. Phase 1 study of ibrutinib and the CXCR4 antagonist ulocuplumab in CXCR4-mutated Waldenstrom macroglobulinemia. Blood. 2021;138(17):1535–9.
59. Hailfinger S, Lenz G, Ngo V, et al. Essential role of MALT1 protease activity in activated B cell-like diffuse large B-cell lymphoma. Proc Natl Acad Sci USA. 2009;106(47):19946–51.
60. Hunter ZR, Xu L, Tsakmaklis N, et al. Insights into the genomic landscape of MYD88 wild-type Waldenstrom macroglobulinemia. Blood Adv. 2018;2(21):2937–46.
61. Fontan L, Yang C, Kabaleeswaran V, et al. MALT1 small molecule inhibitors specifically suppress ABC-DLBCL in vitro and in vivo. Cancer Cell. 2012;22(6):812–24.
62. Yang G, Liu X, Chen J, et al. Targeting IRAK1/IRAK4 Signaling in Waldenstrom's Macroglobulinemia. Blood. 2015;126(23):4004.
63. Ni H, Shirazi F, Baladandayuthapani V, et al. Targeting myddosome signaling in Waldenstrom's macroglobulinemia with the interleukin-1 receptor-associated kinase 1/4 inhibitor R191. Clin Cancer Res. 2018;24(24):6408–20.
64. Hatcher JM, Yang G, Wang L, et al. Discovery of a selective, covalent IRAK1 inhibitor with antiproliferative activity in MYD88 mutated B-cell lymphoma. ACS Med Chem Lett. 2020;11(11):2238–43.
65. Nowakowski GS, Leslie LA, Younes A, et al. Safety, pharmacokinetics and activity of CA-4948, an irak4 inhibitor, for treatment of patients with relapsed or refractory hematologic malignancies: results from the phase 1 study. Blood. 2020;136:44–5.
66. Kuiatse I, Baladandayuthapani V, Lin HY, et al. Targeting the spleen tyrosine kinase with fostamatinib as a strategy against Waldenstrom macroglobulinemia. Clin Cancer Res. 2015;21(11):2538–45.


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