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REVIEW

Current and emerging treatment perspectives for adults with Waldenström macroglobulinemia

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ABSTRACT

Introduction: Waldenström Macroglobulinemia (WM) is distinguished from other indolent lymphomas by its unique molecular landscape and clinical behavior. With the emergence of new therapeutic options and improved survival rates, it has become increasingly important to balance the goal of prolonging survival with minimizing treatment-related toxicities.

Areas covered: This review focuses on the current therapeutic strategies for WM, emphasizing the clinical effectiveness of various agents and treatment groups and their associated toxicity profiles. Additionally, we discuss emerging therapies and combinations, which have shown encouraging preliminary results.

Expert opinion: WM remains an incurable disease, yet its indolent nature and the growing array of therapeutic options have significantly improved outcomes in first- and subsequent-line settings. Chemoimmunotherapy and BTK inhibitors have demonstrated high efficacy and durable responses, with the latter offering a stem-cell-sparing approach. However, unlike in CLL or multiple myeloma, evidence supporting the superiority of targeted agents over chemoimmunotherapy is not available. Consequently, treatment decisions depend on patient characteristics and shared decision-making to carefully balance risks, select appropriate regimens, and encourage clinical trial participation to advance in understanding this rare disease.

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1. Introduction

Waldenström Macroglobulinemia (WM) is an uncommon type of indolent lymphoma characterized by clonal lymphoplasmacytic cells in the bone marrow and evidence of a monoclonal IgM paraprotein [1,2].

WM stands apart from other indolent lymphomas due to its unique clinical behavior and molecular landscape. Key among these are MYD88 mutations, present in approximately 95% of patients [3–5], and CXCR4 mutations, found in 30–40% of patients [6,7]. These discoveries have led to widely used oral targeted agents that minimize chemotherapy-associated toxicities while offering prolonged disease control.

WM can cause symptoms not only from the direct infiltration of malignant cells into tissues, leading to anemia, splenomegaly, and lymphadenopathy, but also from complications related to the IgM monoclonal protein itself, such as neuropathy, cryoglobulinemia, cold agglutinin disease, amyloidosis, and hyperviscosity syndrome [8]. Some of these symptoms can be debilitating, significantly impacting quality of life. As new therapeutic options emerge, reaching a balance between controlling disease-related symptoms and minimizing treatment-related toxicities becomes increasingly critical [9,10].

2. Therapy selection

An essential step is carefully selecting which patients are appropriate candidates for treatment. The current consensus is to treat only symptomatic patients or those with critically deranged laboratory values (e.g. hemoglobin) [11]. Given that WM is incurable and no evidence supports a survival benefit from early intervention [12], starting treatment prematurely not only exposes the patient to unnecessary toxicities but also potentially exhausts a line of therapy, limiting future treatment options. For asymptomatic or smoldering WM, progression to symptomatic disease can take years to decades, making the 'watch and wait' strategy a suitable approach that may significantly delay treatment and reduce early exposure to risks [13,14]. The AWM risk score can help guide the frequency of monitoring in smoldering WM patients [14].

A wide range of therapeutic options has been evaluated and implemented in WM for symptomatic patients requiring treatment, expanding first-line treatments offering tailored and durable approaches while broadening the therapeutic arsenal for heavily treated populations. As survival rates improve and more patients require multiple lines of therapy throughout their lifetimes, the need for these expanded options continues to grow [15,16]. Figure 1 depicts standard and investigational agents in WM.

2.1. Chemoimmunotherapy

Chemoimmunotherapy regimens are among the oldest and most widely used approaches for treating WM, typically combining the anti-CD20 monoclonal antibody rituximab with a chemotherapy backbone [17–19]. Rituximab binds to the

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Article highlights

- WM is a rare indolent lymphoma with clonal lymphoplasmacytic cells and monoclonal IgM paraproteinemia. Despite advances in its molecular understanding and survival, it remains incurable.
- First-line treatments include chemoimmunotherapy and BTK inhibitors (BTKi). Chemoimmunotherapy provides deep, durable responses but is limited by myelotoxicity, while BTKi offers comparable effectiveness with a stem-cell-sparing approach but requires continuous administration.
- Proteasome inhibitor-based regimens, venetoclax, and newer non-covalent BTKi have demonstrated efficacy as therapeutic options, offering diverse mechanisms of action to address disease progression and specific clinical scenarios.
- Emerging treatments, such as BTKi combinations, novel BCL2 antagonists, BTK degraders, and immunotherapy, are under investigation in heavily pretreated patients to expand therapeutic options.
- Preliminary results of combination regimens have demonstrated promising deep responses, though long-term outcomes are still pending.
- Encouraging clinical trial participation is essential for advancing the understanding of this rare disease, while shared decision-making to balance the risks and benefits of therapies remains a priority.

CD20 transmembrane protein on B-cells, inducing cell death through antibody-dependent cytotoxicity and phagocytosis, complement activation, and direct apoptotic effects [20]. This mechanism synergistically sensitizes clonal lymphoma cells to the cytotoxic effects of chemotherapy [21].

Rituximab monotherapy in WM showed modest activity with response rates around 50% [22–24]. A significant limitation was the 'rituximab flare,' a transient IgM increase occurring in up to 50% of patients [25], which limits its use in monotherapy and initially in combinations when IgM exceeds 4000 mg/dL, as it can precipitate IgM-related symptoms such as hyperviscosity or worsening neuropathy. These risks can be managed by delaying rituximab when initiating chemotherapy or using plasmapheresis before.

Early chemoimmunotherapy regimens for WM included those based on nucleoside analogs, such as fludarabine and cladribine, which demonstrated significant efficacy [26,27]. However, their use has been mostly discontinued due to severe stem cell toxicity and an increased risk of myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and aggressive histological transformation [28,29].

Alkylator-based regimens, such as Dexamethasone, Rituximab, Cyclophosphamide (DRC) and Bendamustine, Rituximab (BR) are widely used to treat WM. DRC gained prominence after a phase II trial in 72 previously untreated WM patients demonstrated a high overall response rate (ORR) of 83%, with 74% achieving a major response (MR) and 7% achieving a complete response (CR) [30]. Long-term results from this study showed durable responses with a progression-free survival (PFS) of 35 months, though with a slow time to response (4 months to major response) [31].

A pivotal phase III trial randomized patients with indolent lymphomas to R-CHOP or BR. This trial revealed superior efficacy and tolerability of BR compared to R-CHOP, demonstrating lower rates of alopecia, hematological toxicity, infections,

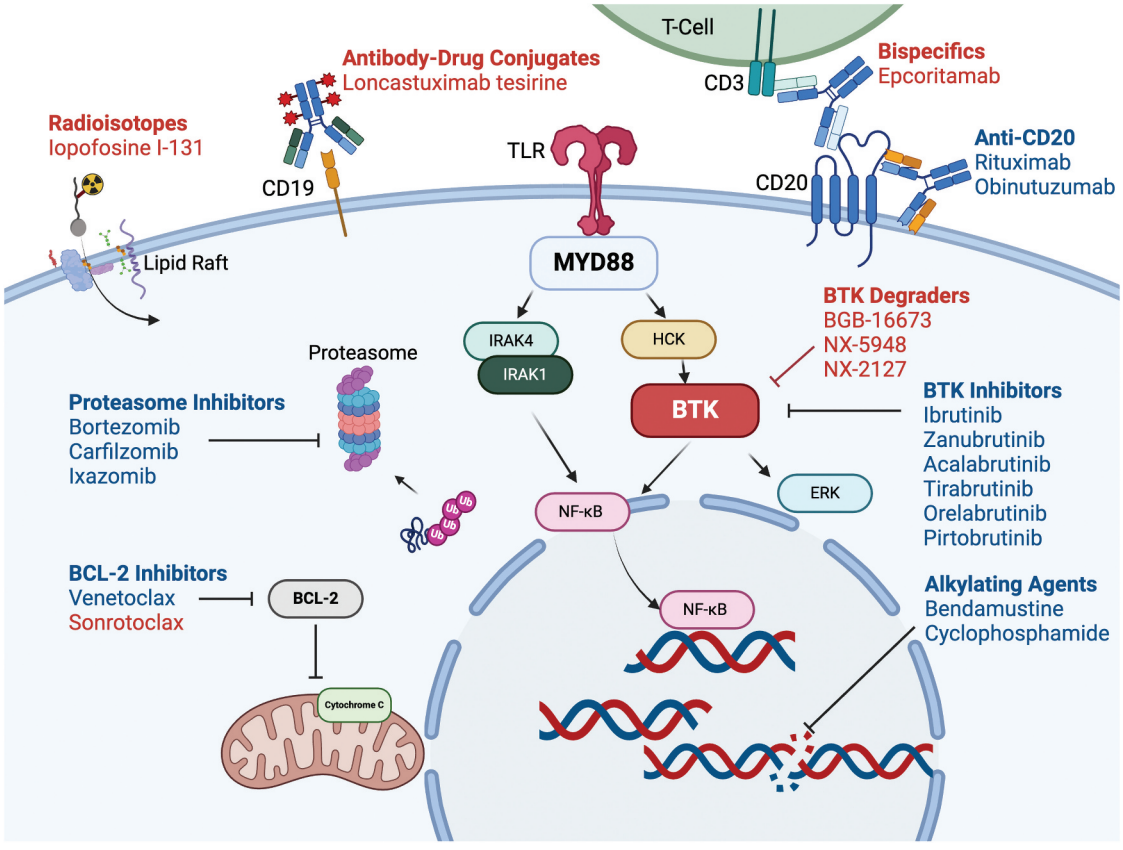

Figure 1. Overview of highlighted therapeutic strategies for Waldenström macroglobulinemia. Standard treatments are indicated in blue text, representing therapies currently in clinical use. Emerging treatments under investigation are shown in red text. Created in BioRender. Guijosa, A. (2025) https://BioRender.com/u10f992.

peripheral neuropathy, and stomatitis, albeit with a higher incidence of erythematous skin reactions. For the 49 WM patients included, BR offered a notably high median PFS of 69.5 months, more than doubling that of R-CHOP (28.1 months) [32]. A later randomized trial (MAINTAIN) reported no improvement in PFS or overall survival (OS) with 2-year rituximab maintenance following a major response to BR compared to observation [33]. However, this study has not yet been published.

Without prospective data directly comparing BR and DRC, both remain standard-of-care options in clinical practice. These regimens are valued for being time-limited therapies that provide deep and durable responses and extended treatment-free intervals. Nonetheless, they share limitations, including cytopenias and a risk of infections during and after therapy [34,35]. The potential long-term effects on stem cells are of particular concern, with follow-up studies reporting relatively high incidences of MDS/AML, and secondary malignancies [36–38].

BR and DRC have been compared using large retrospective cohorts [38–42]. These studies suggest that BR outperforms DRC regarding response rates, depth of response, PFS, time to next therapy, time to best response, and duration of response, though without a demonstrated OS benefit. However, the improved efficacy of BR is associated with increased toxicity, limiting its suitability for unfit patients. Additionally, bendamustine can cause prolonged T-cell depletion, which is particularly significant as novel therapies, such as bispecific antibodies and chimeric antigen receptor (CAR)-T cells under investigation in WM, rely on preserved T-cell function and may show reduced efficacy in patients previously treated with bendamustine [43,44].

2.2. BTK inhibitors

Identifying the *MYD88 L265P* mutation as the most common somatic alteration in WM [4] has led to adopting Bruton tyrosine kinase inhibitors (BTKi) as a standard treatment for WM [45]. MYD88, an adaptor protein in the toll-like receptor signaling pathway, activates BTK, a key component of B-cell receptor signaling that drives B-cell proliferation, maturation, and survival. The L265P mutation causes the spontaneous assembly of the signaling complex, leading to BTK and downstream nuclear factor κB (NF-κB) activation [46–48]. While the *L265P* mutation is the most common, rarer *MYD88* variants have been identified in 1–2% of cases [49–51].

Ibrutinib, a first-generation covalent BTKi, was the first approved therapy for WM, marking a significant shift in the treatment landscape by introducing an effective chemotherapy-free option in an oral formulation for managing the disease.

In the pivotal trial leading to its regulatory approval, 63 patients with previously treated WM were treated with ibrutinib monotherapy. An ORR of 91% and an MRR of 79% were achieved [45]. Notably, ibrutinib exhibited rapid activity, with a median time to minor and major responses of 4 and 8 weeks, respectively. Hemoglobin improvement was observed within 4 weeks of therapy and continued over subsequent cycles. Five-year follow-up data of this trial showed deepening responses over time, with a 54% PFS rate and 87% OS [52]. Its later evaluation in 30 untreated patients with WM showed similar results [53,54]. The study confirmed ibrutinib as an effective first-line option while avoiding the short- and long-term risks associated with alkylating agents. Though no direct randomized comparisons are available, a large retrospective multi-institutional study showed that PFS and OS were equivalent between BR and ibrutinib as first-line treatments [55].

The ibrutinib trials provided important insights into the prognostic significance of MYD88 and CXCR4 mutations in WM. The pivotal trial established the following prognostic hierarchy: MYD88 L265P/CXCR4 wild type (WT) patients had the most favorable responses (100% ORR, 91% MRR), followed by MYD88 L265P/CXCR4 mutated (86% ORR, 62% MRR), and MYD88 WT/CXCR4 WT (71% ORR, 0% MRR). Similarly, 5-year PFS rates were highest in MYD88 L265P/CXCR4 WT patients (70%), followed by MYD88 L265P/CXCR4 mutated (38%), with MYD88 WT/CXCR4 WT patients having a median PFS of only 0.4 months. In the treatment-naïve trial, which included only MYD88-mutated patients, response rates (VGPR: 14% vs. 44%) and PFS (4-year PFS rate: 59% vs. 92%) were lower in CXCR4-mutated patients compared to those without CXCR4 mutations [53,54].

More so, ibrutinib is not without relevant side effects. The most significant is atrial fibrillation, occurring in 10–20% of patients [45,56–58]. Other significant adverse effects include hypertension and bleeding, along with commonly reported issues such as neutropenia, diarrhea, fatigue, and muscle spasms. These side effects necessitate careful monitoring and management due to the indefinite nature of the therapy.

These limitations prompted the evaluation of zanubrutinib, a second-generation covalent BTKi with higher selectivity for BTK, in WM [59]. The phase III ASPEN trial compared zanubrutinib and ibrutinib as monotherapies. Cohort 1 included 201 WM patients, both treatment-naïve and previously treated, who were randomized to receive either treatment [60]. Zanubrutinib demonstrated numerically higher rates of VGPR+CR (36% vs. 25%), major response (81% vs. 80%), and ORR (95% vs. 94%), along with PFS rates at 42 months (78% vs. 70%), although these differences were not statistically significant. Notably, among patients with CXCR4 mutations, zanubrutinib elicited numerically deeper and more durable responses compared to ibrutinib. Additionally, while responses to ibrutinib were negatively impacted by TP53 mutational status, zanubrutinib response rates remained unaffected, although TP53 mutations adversely affected PFS in both treatment arms [61].

The ASPEN study underscored zanubrutinib's improved safety profile. Compared to ibrutinib, zanubrutinib was associated with a reduced incidence of any-grade adverse events (AEs) such as diarrhea (23% vs. 35%), muscle spasms (12% vs. 29%), hypertension (15% vs. 26%), atrial fibrillation/flutter (8% vs. 24%), and pneumonia (5% vs. 18%). However, zanubrutinib had a higher rate of neutropenia (35% vs. 20%) without an observed increase in infections. These differences contributed to a higher treatment discontinuation rate due to AEs among ibrutinib-treated patients [56], which aligns with frequent dose reductions and discontinuations noted in real-world studies [62,63].

Cohort 2 of the ASPEN study, comprising 28 MYD88 WT patients (previously treated and untreated) who received

zanubrutinib monotherapy, demonstrated greater efficacy than historical data for ibrutinib. The most recent update reported an ORR of 85%, a VGPR or better rate of 31%, and a median duration of response of 41 months [64].

These findings support zanubrutinib as the preferred BTKi, particularly for older patients or those with cardiac comorbidities, as well as for patients with CXCR4 mutations, TP53 mutations, and MYD88 WT. Other second-generation covalent BTK inhibitors, including acalabrutinib, orelabrutinib, and tirabrutinib, have also demonstrated efficacy with reduced cardiac toxicity. However, robust comparative evidence for these agents is limited, as available data are primarily derived from single-arm phase II trials evaluating each agent independently [65–70].

Patients receiving covalent BTKi therapy will eventually develop treatment resistance. Among those who develop resistance, a significant proportion acquires a BTK C481S mutation, which disrupts the binding of all covalent BTKi and leads to treatment failure [71].

Pirtobrutinib, a selective non-covalent BTKi that inhibits both WT and C481S-mutated BTK, has been developed in this context. The BRUIN phase 1/2 trial, which included patients with relapsed/refractory (R/R) WM, demonstrated its efficacy in this population, including those previously treated with covalent BTKi [72]. The latest IWWM12 update, among 80 WM R/R patients, reported an 80% ORR among patients with prior covalent BTKi therapy and an 88% ORR among covalent BTKi-naïve patients, with a median PFS of 22 months and a low rate of grade ≥ 3 treatment-emergent adverse events, consistent with the high selectivity profile of this medication [73]. The high selectivity and efficacy of pirtobrutinib in R/R WM, particularly after covalent BTKi failure, make it a promising option for sequencing after covalent BTKi.

2.3. Proteasome inhibitors

Proteasome inhibitors (PIs) are a cornerstone of treatment in multiple myeloma, where they target the malignant cells' reliance on efficient protein degradation due to the high burden of immunoglobulin production [74]. Their success has extended to WM, where similar IgM overproduction mechanisms are exploited, disrupting protein degradation and inducing cell death with proven clinical efficacy [75,76].

In WM, PI-based regimens provide an effective, time-limited alternative to BTKis and chemoimmunotherapy. These regimens avoid the continuous treatment required with BTKis and the significant myelotoxicity associated with chemoimmunotherapy, offering a favorable balance for certain patients. However, PIs are associated with adverse effects and show relatively lower efficacy than BR and continuous BTKis, as suggested by retrospective analyses [40–42].

The combination of bortezomib, dexamethasone, and rituximab (BDR) has been extensively studied in WM. In a phase II trial of previously untreated patients, BDR demonstrated rapid responses and high overall response rates. However, it was associated with significant neuropathic toxicity, including grade 2 or higher peripheral neuropathy (PN) in 69% of patients, leading to premature treatment discontinuation in over half of the cases. Additionally, herpes zoster reactivation was frequently observed in patients without antiviral prophylaxis, and rituximab flare was a common complication [77,78].

Subsequent trials, both in untreated and R/R disease, modified the BDR regimen by using subcutaneous bortezomib, weekly dosing (instead of twice weekly), and omitting maintenance therapy to reduce PN while holding rituximab in the first cycle to mitigate an IgM flare [79,80]. Although these adjustments improved both issues, dose reductions due to PN were still common. This increased risk of bortezomib-induced neuropathy in WM may perhaps be associated with concomitant paraprotein nerve damage and remains a significant limitation, especially for patients who present with WM-related neuropathy [81,82].

Carfilzomib, a second-generation proteasome inhibitor with low neurotoxicity, was evaluated with rituximab and dexamethasone (CaRD) in WM, demonstrating comparable effectiveness. Neuropathy was minimal, with only one patient (3%) experiencing grade 2 or higher events. However, the prolonged maintenance regimen in this trial resulted in decreased IgG and IgM levels and alterations in amylase, lipase, and bilirubin [83,84]. Most importantly, carfilzomib is associated with cardiovascular adverse events and should be avoided in patients at risk for cardiomyopathy [85].

To further improve the toxicity profile, ixazomib, an orally available PI, was evaluated in combination with dexamethasone and rituximab (IDR) in treatment-naïve WM patients [86]. The regimen demonstrated significant efficacy, with high response rates (ORR 96%, MRR 77%, VGPR 15%) and an excellent toxicity profile. Importantly, no grade 4 adverse events were observed, and only 4% of patients experienced grade 2 or higher neuropathy. Long-term results showed durable responses, with a median PFS of 40 months [87]. A more recent trial assessing ixazomib combined with subcutaneous rituximab and dexamethasone in R/R WM patients also achieved high response rates, with a 2-year PFS similar to that seen in the treatment-naïve setting [88].

Overall, PIs are effective in both first-line and relapsed/refractory WM. Unlike BTKi, PI efficacy and PFS are unaffected by CXCR4 mutations [89]. They are particularly beneficial for some WM-associated paraprotein complications such as amyloidosis, cold agglutinin disease, and cryoglobulinemia [90]. However, their use should be tailored to individual patient scenarios, carefully balancing their toxicity profiles.

2.4. BCL-2 inhibitors

BCL-2 is an antiapoptotic protein that inhibits mitochondrial permeabilization required for apoptosis initiation. The overexpression of BCL-2 has been identified in various cancers, playing a key role in oncogenic cell survival, including WM [91]. Venetoclax, a first-in-class oral BCL-2 inhibitor, has been utilized across hematological malignancies such as chronic lymphocytic leukemia (CLL) and AML [92].

A phase II trial of venetoclax monotherapy with dose escalation (200 to 800 mg) in 32 previously treated WM patients, of whom 38% had ≥ 3 prior lines of therapy and 50% had previously received a BTKi, demonstrated significant efficacy, with an ORR of 84%, an MRR of 80%, and a VGPR of 19%. The median PFS was 30 months. Efficacy

was reduced in refractory versus relapsed cases (ORR: 60% vs. 95%) and in patients with ≥ 3 prior lines of therapy compared to 1–2 lines (63% vs. 95%). Neutropenia was the most common grade ≥ 3 adverse event, affecting 45% of patients, while laboratory tumor lysis syndrome (TLS), frequently seen in CLL, occurred in only one patient. Venetoclax was well tolerated [93], making it an attractive option for WM following disease progression, including potential sequencing after BTKi therapy and ongoing exploration in BTKi combination regimens.

Building on this success, sonrotoclax, a next-generation BCL-2 inhibitor with greater potency and selectivity than venetoclax, is under evaluation in a large international trial as both monotherapy and combined with zanubrutinib [94].

2.5. Treatment combinations

Research into WM biology and the effects of drug combinations has highlighted the synergistic potential of concurrent therapies [91].

Early combination strategies in WM sought to improve outcomes by adding targeted agents to established regimens. These included two large randomized trials. The phase III iNNOVATE trial showed that adding ibrutinib to rituximab significantly improved PFS (30-month PFS: 82% vs. 28%), ORR (92% vs. 47%), and MRR (72% vs. 32%) with minimal added toxicity [58]. The findings demonstrated the efficacy of ibrutinib plus rituximab over rituximab monotherapy. However, it did not provide insights on the benefit of adding rituximab to ibrutinib. A patient-level pooled analysis suggested adding rituximab to ibrutinib might improve outcomes in WM patients with CXCR4 mutations [95]. On the other hand, the ECWM-1 trial evaluated bortezomib added to dexamethasone, rituximab, and cyclophosphamide (B-DRC vs. DRC). While B-DRC achieved higher MRR (81% vs. 70%) and faster response times, it did not significantly improve the 24-month PFS rates (81% vs. 73%; $p = 0.32$) [96]. The trial excluded patients with baseline grade ≥ 2 neuropathy and used DRC as a comparator instead of BR, limiting its generalizability [82].

More recently, the widespread success of BTKis in WM has driven efforts to develop combinations with these agents to deepen responses and enable time-limited regimens. Of special interest is a study comparing chemoimmunotherapy (cyclophosphamide, dexamethasone, and rituximab) versus a BTKi-containing regimen (ibrutinib plus rituximab) (RAINBOW; NCT04061512), the first study to formally compare these two commonly used approaches in WM. Accrual is almost complete, and results are eagerly awaited.

An ongoing phase II study compares 24 months of ibrutinib plus rituximab versus 24 months of venetoclax plus rituximab in previously untreated WM patients with the possibility of crossing over upon disease progression (NCT04840602). A noteworthy approach for time-limited therapy involves combining BTKis with BCL-2 inhibitors. A phase II trial exploring 2 years of ibrutinib and venetoclax in treatment-naive WM demonstrated high response rates, including an ORR of 100%, an MRR of 96%, and a VGPR rate of 53%, with a median time to major response of 1.8 months. Unfortunately, study therapy was terminated early due to ventricular arrhythmias in four of the 45 participants, two of them being lethal [97]. Despite this, long-term data showed durable responses, with a 36-month PFS rate of 51%, although the median treatment duration was 10 months, and no patient completed the planned 24 cycles [98]. Building on these findings, a phase II trial combining pirtobrutinib, a highly selective noncovalent BTKi, with venetoclax in previously treated WM has reported preliminary results similar to those in treatment-naive patients. Among 16 participants, 56% with prior exposure to covalent BTKis, the regimen achieved an ORR of 100%, an MRR of 87%, and a VGPR rate of 56%, with rapid responses (median time to VGPR: 1.9 months) and no reported arrhythmia events to date [99].

Another area of exploration is the addition of BTKis to PI-based regimens. The ECWM-2 trial, a multicenter European phase II study, evaluated a regimen combining bortezomib and rituximab with ibrutinib (6 cycles of the combination, followed by 24 months of rituximab and ibrutinib, and subsequent ibrutinib treatment until progression or intolerable toxicity). Recently presented results demonstrated a notably high MRR of 98% and an ORR of 100%, with a median time to major response of 3 months. The trial met its primary endpoint, reporting a 1-year PFS rate of 93% and no progression events to date, with a follow-up of 37 months [100]. However, the study reported eight deaths, five attributed to COVID-19 and three to other respiratory infections, highlighting potential safety considerations. Similarly, a phase II study investigating a combination of zanubrutinib, ixazomib, and dexamethasone (ZID: 6 induction cycles followed by 24 consolidation cycles) reported high efficacy, with an ORR of 100%, an MRR of 96%, a CR/VGPR rate of 46%, and a median time to response of 2 months [101]. However, this efficacy did not translate into longer PFS, with a reported median of 40 months. Meanwhile, the ongoing randomized CZAR-1 trial, which recently completed accrual, evaluates the addition of carfilzomib for 2 years to ibrutinib monotherapy until progressive disease or intolerable toxicity. The trial aims to determine whether this combination improves CR/VGPR rates at 12 and 24 months [102].

The combination of BTKis with chemoimmunotherapy represents a novel therapeutic strategy. The BRAWM study, a prospective phase II trial, combines a fixed-duration regimen of bendamustine-rituximab (6 cycles) with one year of acalabrutinib as first-line therapy. The trial recently completed accrual with 63 patients and reported promising preliminary results. Among 47 patients assessed at cycle 7, the depth of response exceeded that observed with other regimens: 2% achieved a CR, and 62% achieved VGPR [103]. Similarly, a separate phase II trial evaluated the combination of zanubrutinib with bendamustine-rituximab. In this trial, zanubrutinib was administered over one year, and BR was administered for six cycles. Among 20 patients who completed induction therapy, the outcomes were favorable, with a CR rate of 10%, a VGPR rate of 55%, an MRR of 95%, and an ORR of 100% [101]. Furthermore, the ongoing ZEBRA trial (NCT06561347) is investigating using 15 months of zanubrutinib and four cycles of BR.

2.6. Stem cell transplantation

No prospective and limited retrospective data exist on using stem cell transplantation (SCT) in WM. High-dose chemotherapy

followed by autologous SCT is a treatment option for a selected group of patients with WM [104]. A recent consensus panel recommended considering autologous SCT in fit patients and chemotherapy-sensitive disease who had received at least two lines of chemoimmunotherapy [105]. The role of autologous SCT in BTKi-sensitive disease is unknown. Allogeneic SCT is not routinely recommended in patients with WM because of the high rate of transplant-related mortality, acute and chronic GVHD, the high risk of infections, and not offering a curative option.

2.7. Special issues in WM

2.7.1. Hyperviscosity

Symptomatic hyperviscosity is seen in 10% of patients with WM and is characterized by recurrent nosebleeds, headaches, and retinal vessel changes such as engorgement, increased tortuosity, 'sausaging' and hemorrhage. Hyperviscosity is rare with serum IgM levels < 3,000 mg/dl and should be managed with the prompt use of plasmapheresis as a temporizing measure before initiating definitive WM-directed therapy [106]. These patients can be treated with any of the regimens mentioned above. However, postponing rituximab initiation is reasonable to prevent a symptomatic IgM flare.

2.7.2. Cryoglobulinemia and cold agglutinin syndrome

A small proportion of patients with WM will present with or develop symptomatic cryoglobulinemia or cold agglutinin syndrome (CAS). Cryoglobulinemia is characterized by cyanosis of the hands, feet, nose, and lips when patients are exposed to cold temperatures. Painful, non-healing ulcers can sometimes develop in the lower extremities. CAS secondary to an underlying infectious or malignant process should be differentiated from primary cold agglutinin disease [107]. CAS presents clinically with hemolysis and jaundice upon exposure to cold temperatures. Notably, the cold agglutinin titer is a poor marker of the hemolytic activity. In patients with mild symptoms, cold avoidance is recommended. Acute, severe cases of cryoglobulins and CAS can be managed with plasmapheresis followed by WM-directed therapy. These patients can be treated with any of the regimens mentioned above. Recent data showed clinical benefits to using BTKi in patients with CAS [108]. Postponing rituximab initiation is reasonable to prevent a symptomatic IgM flare. The role of anti-complement agents in CAS is unknown.

2.7.3. Peripheral neuropathy

Peripheral neuropathy is observed in 20–25% of patients with WM and is typically the presenting symptom in these patients. Serum IgM levels are usually below 1000 mg/dl. In most cases, nerve conduction studies detected demyelinating changes, and a minority can have axonal changes or have normal nerve conduction (small fiber neuropathy). Some patients with demyelinating features will have detectable titers of anti-myelin-associated glycoprotein. Postponing rituximab initiation is reasonable in these patients to prevent a symptomatic IgM flare. Also, one should avoid agents that could cause neuropathy, such as bortezomib or vincristine. A study evaluating acalabrutinib plus rituximab in anti-MAG neuropathy is ongoing [109].

2.7.4. Acquired von Willebrand disease (aVWD)

aVWD is defined as levels of VW factor, VW activity, and factor VIII of < 30% and is typically seen in patients with WM and high serum IgM levels [110]. The patients with aVWD report easy bruising and platelet-type bleeding. For patients with active bleeding, using desmopressin can help decrease the bleeding temporarily. Any therapy directed at decreasing the levels of serum IgM would translate into an improvement in the coagulopathy. Therefore, using BTK inhibitors is not contraindicated in this setting.

2.7.5. Amyloidosis

Systemic AL amyloidosis can develop in 5–10% of the patients with WM and can occur at any time during the disease course. The clinical manifestations include nephrotic syndrome, cardiomyopathy, and peripheral and autonomic neurologic dysfunction, among other manifestations. Tissue should be sent for mass spectrometry to evaluate for other unrelated types of amyloidosis (e.g. ATTR, AA). In these patients, chemoimmunotherapy and proteasome inhibitor-based regimens are appropriate. Current guidelines recommend against the use of BTK inhibitors in WM-related amyloidosis [111]. The data with BCL2 antagonists are limited. Consolidation with high-dose chemotherapy and autologous stem cell rescue should be considered if appropriate.

2.7.6. Bing-Neel syndrome (BNS)

BNS is the involvement of the central nervous system by LPL cells, causing various neurological deficits, including headache, cranial nerve paralysis, back and limb pain, and changes in mental status [112]. BNS can occur at any time during the disease course. The diagnosis is made using MRI and with the detection of LPL cells in the cerebrospinal fluid or via biopsy. Treatment options for patients with BNS are limited to agents that cross the blood-brain barrier. Mounting data support using BTK inhibitors in BNS [113,114]. Other treatment options include bendamustine, fludarabine, and methotrexate.

2.7.7. Aggressive transformation

Histological transformation to an aggressive lymphoma, typically diffuse large B-cell lymphoma (DLBCL), is rare, with a cumulative incidence rate of 1% every 5 years [115]. DLBCL is suspected in patients who develop constitutional symptoms or symptoms associated with a rapid size increase of a mass or lymph node. Transformation can occur at any time during the course of the disease. A PET/CT should be performed in these cases, and transformation should be suspected if the SUV is ≥ 15. An excisional biopsy should be performed to establish the diagnosis. The management of transformed DLBCL should mimic the management of *de novo* DLBCL, though recent studies suggest worse outcomes and a high incidence of CNS involvement [116,117].

2.7.8. Supportive therapy

Supportive therapy is an important aspect of the care of patients with WM. The risk of infections is increased in patients with WM because of the disease itself and the exposure to therapy. Shingles prophylaxis with acyclovir or valacyclovir

should be used in patients receiving proteasome inhibitors. Shingles prophylaxis and prophylaxis for Pneumocystis should be considered in patients receiving alkylating agents and strongly considered in patients receiving nucleoside analogs. In patient with serum IgG levels <400 mg/dl and recurrent respiratory infections requiring antibiotics, intravenous immunoglobulin can help reduce the rate of infections. Granulocyte colony-stimulating factor, erythropoietin stimulating agents and thrombopoietin agonists can be used to treat cytopenias caused by the disease or the therapy as recommended by current guidelines.

2.7.9. Response assessment and attainment in WM

It is important to note that responses can be delayed in WM, especially when treating with rituximab alone or rituximab-containing regimens with median times to response of 8–12-weeks. Faster responses have been observed with covalent BTKi, with a median of 4 weeks [53,54]. For this reason, therapy should not be abandoned prematurely in the absence of clear symptomatic disease progression. In approximately a third of patients with WM treated with rituximab-containing regimens, the deeper response is observed years after completing treatment [118].

Additionally, there could be discordance between the serum IgM response and the disease burden in the marrow. This is seen in paradoxical IgM flares with rituximab, in which the serum IgM increases after rituximab exposure but does not represent disease progression [25]. Small IgM flares can be observed in patients with WM with infections, inflammatory conditions, or after vaccinations. Also, this could be seen when temporarily holding BTK inhibitors, inducing an IgM rebound, which typically returns to baseline after restarting the BTK inhibitor. With BTKi, the depth of serum IgM response with concurrent improvement in symptoms and blood counts might not be reflected in the marrow disease burden.

Finally, the attainment of CR is rare in WM, estimated at < 5% with chemoimmunotherapy, and rarely seen with BTKi, probably one of the most significant unmet needs and a roadblock to more durable remissions and a cure. Given the limitations of nephelometry and electrophoresis in reliably quantifying low monoclonal IgM levels, other technologies might be helpful. Mass spectrometry or polyclonal antisera assays for light or heavy chains hold promise and should be evaluated prospectively.

The issues mentioned above represent challenges to response assessment in routine clinical care and clinical trials. Additional research is needed to refine response assessment in WM further.

3. Novel therapies

Despite effective treatments yielding excellent outcomes in both first-line and relapsed/refractory settings, the prolonged survival of WM patients has driven the need for an expanded therapeutic arsenal. Among emerging therapeutic strategies, novel regimens have shown promising results in heavily treated WM, though most remain under investigation in clinical trials and await broader implementation.

Following the elucidation of BTK as a therapeutic target in WM, BTKis have transformed treatment. Nevertheless, resistance mechanisms, including BTK mutations such as C481S, T474I, V416L, and L528W, have emerged with both covalent and non-covalent BTKis across lymphomas. To address this, BTK degraders have been developed, targeting BTK through a novel mechanism involving polyubiquitination and subsequent proteasomal degradation, effectively bypassing resistance mutations [119,120]. Preliminary results from early-phase trials are promising. A first-in-human phase 1/2 trial of the novel BTK degrader BGB-16673 in heavily pretreated B-cell malignancies, including WM, demonstrated an ORR of 90%, an MRR of 81%, and VGPR in 14% of 21 evaluable WM patients. All participants had prior exposure to covalent BTKis, with 14% also exposed to non-covalent BTKis. The median number of prior therapies was 3.5 (range 2–11). The most common adverse event was neutropenia (32%; grade ≥ 3 in 23%) [121].

Loncastuximab tesirine, a CD19-targeted antibody-drug conjugate (ADC), has shown efficacy in diffuse large B-cell lymphoma and is now being evaluated in WM [122]. Interim results from an ongoing phase II trial, including seven heavily pretreated WM patients (median of two prior therapies), reported an MRR of 86% and a partial response rate of 43%, with one patient experiencing progressive disease. Notably, 57% and 86% of patients harbored TP53 and CXCR4 mutations, respectively. Adverse events, consistent with prior studies, included grade ≥ 3 cytopenias in 86% of patients and skin toxicity in all patients [123].

In a study of 65 heavily pretreated WM patients with a median of four prior lines of therapy, including BTKi, iopofosine I-131, a phospholipid radio-conjugate targeting lipid rafts in tumor cells, was evaluated [124]. Preliminary results showed an ORR of 80%, an MRR of 56%, and a median PFS of 51 weeks. However, significant cytopenias were reported, with grade 3 or higher thrombocytopenia in 80% of cases, neutropenia in 69%, and anemia in 45%.

Other immunotherapies are being explored in WM. In a small cohort of three heavily pretreated WM patients, CAR-T cell therapy yielded responses with no grade ≥ 3 cytokine release syndrome [125]. Epcoritamab, the first anti-CD20 bispecific antibody evaluated in WM, is under investigation, offering another potential therapeutic avenue [126].

4. Conclusion

As described above, safe and effective therapeutic options in WM are numerous, including alkylating agents, monoclonal antibodies, PIs, BTKi, and BCL2 antagonists, and keep expanding with the current development of BTK degraders, second-generation BCL2 antagonists, ADCs, bispecific antibodies, radio-conjugates, and CAR T-cells. Future studies should focus on combination regimens that look for deeper and more durable responses while keeping the patient's QOL at the forefront of our clinical efforts.

5. Expert opinion

Unlike CLL or multiple myeloma, in which using targeted agents has shown superiority over chemoimmunotherapy,

such evidence does not exist for WM. Therefore, treatment decisions for WM depend on patient characteristics and shared decision-making to balance risks and benefits, choose an effective regimen, and encourage clinical trial participation to advance understanding of this rare disease.

Current guidelines recommend chemoimmunotherapy or covalent BTKi as first-line therapy for symptomatic WM. Figure 2 illustrates treatment recommendations from IWWM-11 (2023) and NCCN guidelines (2024). Chemoimmunotherapy, particularly BR, is preferred for patients with extramedullary disease requiring rapid tumor reduction. DRC is an option for less fit patients. Based on the MAINTAIN study, rituximab maintenance has become less preferred. However, the study has not yet been published. BTKi therapy is also effective in WM and could be favored for unfit patients or patients who would prefer to avoid the toxicity of chemotherapy. Zanubrutinib is often preferred over other covalent BTK inhibitors for its improved toxicity profile, particularly in older patients, those with cardiac comorbidities, and those with CXCR4 or TP53 mutations. PI-based regimens are typically reserved for specific scenarios, such as AL amyloidosis, given their toxicity and slightly reduced efficacy, or patients who would prefer to avoid indefinite-duration therapy or chemotherapy.

In the second-line setting, covalent BTKi would be the preferred choice for patients who received frontline chemoimmunotherapy. Conversely, chemoimmunotherapy would be a preferred option for patients progressing on frontline covalent BTKi. In patients who cannot tolerate covalent BTKi, dose reductions can be an easy method of managing toxicities if they are benefiting clinically. If unacceptable toxicity persists despite dose reduction, switching to another covalent BTK inhibitor could be considered. In the third-line setting and beyond, options include pirtobrutinib, venetoclax, or PI-based regimens.

BTKis have revolutionized WM treatment, offering highly effective and durable oral therapies that have transformed disease management. These agents provide significant benefits, including prolonged disease control, the feasibility of sequencing therapies in cases of intolerance or resistance, and high efficacy in specific scenarios such as Bing-Neel Syndrome [113], all achieved through a stem-cell-sparing approach. A key challenge is the need for prolonged treatment duration. While BTKis effectively suppress cellular activity, discontinuation often leads to rapid IgM rebound [62,127]. Furthermore, temporary treatment interruptions, such as those required for surgery, frequently result in withdrawal symptoms [128]. The requirement for daily administration also presents challenges, including higher healthcare costs [129] and the cumulative incidence of adverse events that may affect quality of life (QOL) [10].

It is essential to note that clinical trial participation should be considered at any time during the disease course as treatment options continue to evolve with forthcoming updates and promising data on novel combinations, BTK degraders, CAR-T, and bispecific antibodies, which may reshape WM treatment and expand the therapeutic arsenal.

Ongoing and future clinical trials can help address several unmet needs in treating WM, including but not limited to the indefinite duration of BTK inhibitor therapy, chemotherapy-induced stem cell toxicity, and low rate of CR with standard treatments.

In prospective studies, the current CR attainment rate in WM patients remains below 5%. Intuitively, achieving deeper

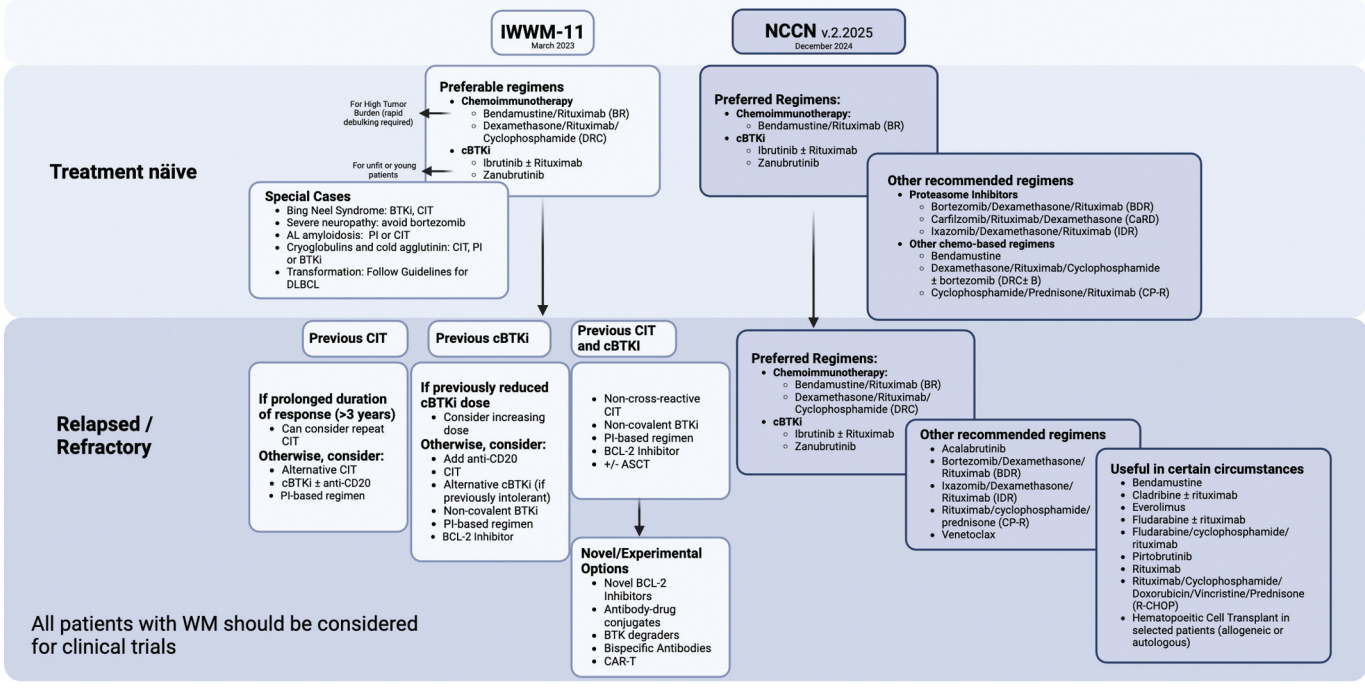

Figure 2. Adapted guideline comparison for the treatment of Waldenström Macroglobulinemia. This figure summarizes recommendations from the 11th international workshop on Waldenström's macroglobulinemia (IWWM-11) and the national comprehensive cancer network (NCCN). IWWM-11 guidelines are in light blue, while NCCN guidelines are in dark blue. The treatments are categorized for treatment-naïve and relapsed/refractory (R/R) patients. Abbreviations: cBtki, covalent BTK inhibitor; PI, proteasome inhibitor; CIT, chemoimmunotherapy; DLBCL, diffuse large B-cell lymphoma. Created in BioRender. Guijosa, A. (2025) https://BioRender.com/t64l173.

responses with combination regimens should lead to longer PFS, improved QOL, and extended treatment-free intervals. However, clinical trials are needed to confirm this. The depth of response observed with combination therapies has opened new areas of investigation in WM, including the potential use of minimal residual disease (MRD) as a prognostic marker. MRD assessment has been included as a secondary endpoint in several trials; however, these assessments have been conducted using heterogeneous methods, and a standardized approach to MRD measurement has yet to be established. Furthermore, its prognostic significance relative to conventional response criteria remains uncertain and requires further validation. Ultimately, using combination regimens and novel therapeutic strategies may increase CR rates, potentially leading to more prolonged remissions and, hopefully, a cure.

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AG and JJC designed the structure of the manuscript. AG drafted the initial version. All the authors critically reviewed the manuscript and approved the final version.

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