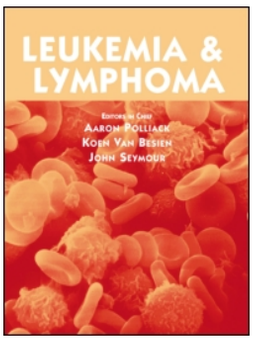


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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

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**To cite this article:** Andrew R. Branagan, Mathew Lei, Steven P. Treon & Jorge J. Castillo (2021): Clinical application of genomics in Waldenström macroglobulinemia, Leukemia & Lymphoma, DOI: 10.1080/10428194.2021.1881514

**To link to this article:** https://doi.org/10.1080/10428194.2021.1881514

Published online: 11 Feb 2021.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2021.1881514

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REVIEW



# Clinical application of genomics in Waldenström macroglobulinemia

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**ABSTRACT**

Waldenström Macroglobulinemia (WM) is an incurable hematologic malignancy characterized by lymphoplasmacytic infiltration of the bone marrow and the presence of monoclonal immunoglobulin (IgM). Although a portion of WM patients may experience a relatively indolent course, patients may experience IgM-related morbidity and/or disease-related mortality. This underscores the need for novel approaches to improve response and survival rates. Significant progress had been made in our understanding of the genomics and biology of WM. The discovery of the highly recurrent somatic mutations in the *MYD88* gene detected in 90–95% and the *CXCR4* gene detected in 30–40% of WM patients has provided an opportunity to develop novel targeted approaches. Mutational status has important implications in predicting response to therapies such as BTK inhibitors. Treatment of WM should be guided by many factors including performance status, comorbidities, goals of therapy, and toxicities. In this review, we describe how current genomics may be utilized to optimize WM treatment selection. As the therapeutic landscape of WM continues to expand with more targeted approaches, the genomics in WM will likely play a greater role in individualizing treatment.

**ARTICLE HISTORY**
Received 4 December 2020
Revised 16 January 2021
Accepted 21 January 2021

**KEYWORDS**
Genomics; Waldenström macroglobulinemia; treatment

## Introduction

Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by the presence of monoclonal IgM protein, irrespective of serum level [1]. WM represents a rare disease that accounts for approximately 1–2% of diagnoses of non-Hodgkin lymphoma with approximately 1000 to 1500 new diagnoses each year in the United States (US). In the US, the reported age-adjusted incidence rate for WM for males and females is 9.2 and 3.0 per million, respectively [2]. WM is more prevalent in Caucasians and is rare in African Americans [3]. WM is a disease of the elderly, with a median age of diagnosis of 72 years [2]. There is a strong familial predisposition with WM that may be driven by a underlying genetic predisposition [4].

The discovery of the recurrent somatic mutations, which were identified *via* whole genome sequencing, in *MYD88* and *CXCR4* in patients with WM marked an important advance in the understanding of the genomic basis of WM. Despite the high response rates and depth of responses with the advent of novel treatment options, WM currently remains incurable, but relative survival rates have improved given the advances allowing for new targeted therapies. Patients with WM will present with various symptoms that are characteristic of elevated IgM and lymphoplasmacytic infiltration in the bone marrow or other organs, however, a quarter of patients or more may be asymptomatic on presentation [5]. End organ damage may include cytopenias, predominantly anemia, and paraprotein-related complications such as peripheral neuropathy, AL amyloidosis, cryoglobulins, and cold agglutinins. Patients with high serum IgM levels can present with hyperviscosity syndrome. Symptoms from hyperviscosity include skin and mucosal bleeding, retinopathy, neurological disorders, and, in rare instances, cardiovascular complications. Additionally, patients may present with constitutional B-symptoms, lymphadenopathy, or splenomegaly. Bing-Neel syndrome, which is defined by lymphoplasmacytic infiltration of the central nervous system (CNS), is a rare complication of WM. Another rare manifestation of WM is the autoinflammatory disorder characterized by neutrophilic urticarial dermatoses, Schnitzler syndrome.

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## Genomics of Waldenström macroglobulinemia

The somatic *MYD88 L265P* mutation is detectable in 90–95% of WM patients while non-*L265P MYD88* mutations have been identified in 1% to 2% of WM patients [6]. Although the somatic *MYD88* mutation was initially identified by whole genome sequencing, it has been confirmed by Sanger sequencing and allele-specific polymerase chain reaction (AS-PCR) assays have been developed as well [7]. Furthermore, the *MYD88 L265P* mutation can also be identified by peripheral blood with AS-PCR and next-generation sequencing methods [8,9]. *MYD88* encodes for an adaptor protein for toll-like receptor that triggers the interleukin-1 receptor-associated kinases (IRAK) 1 and 4 molecules and Bruton tyrosine kinase (BTK), which mediates nuclear factor kappa B (NFKB) activation. *MYD88* mutations occur in the TIR domain, which is important for the dimerization of the *MYD88* protein. Additionally, *MYD88* mutations promote the expression of hematopoietic cell kinase (HCK), an SRC kinase that is normally downregulated during B-cell maturation, promoting pro-survival signaling. Chromosomal abnormalities, such as those affecting chromosome 3p, can increase the allele frequency of mutant *MYD88*. Although copy neutral loss of heterozygosity is the most common process for homozygosity of mutant *MYD88*, amplification of the mutant *MYD88* or deletions of the wild type *MYD88* have both been observed [10]. Although the majority of WM patients have *MYD88* mutations, approximately 5–10% of WM patients are *MYD88* wild type. Patients without *MYD88* mutations, despite having similar disease histologically to patients with *MYD88* mutations, typically present with less BM infiltration and lower serum IgM levels [11]. Even with the differences observed in disease presentation between these patients, those without *MYD88* mutations have inferior outcomes compared to those with *MYD88* mutations, specifically a shorter overall survival (OS) and an increased risk of transformation to an aggressive lymphoma [11–13]. A study by others did not detect a survival difference between WM patients with and without *MYD88* mutations [14]. However, a less sensitive test was used for *MYD88* mutation detection, which could explain this discrepancy.

Somatic *CXCR4* mutations are present in 30–40% of WM patients and occur in the C-terminal domain, at the same site as the mutations characteristic of the congenital warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome. The acquired *CXCR4* mutations are primarily subclonal and highly associated with *MYD88* mutations. CXCR4 is a receptor for stromal-derived factor 1 (SDF-1) that is produced by the bone marrow stroma. Upon ligand binding to CXCR4, β-arrestins bind to the C-terminal domain and trigger ERK and AKT signaling promoting cell survival. Normally, GRK2/3 would act as negative regulators of CXCR4, however, *CXCR4* mutations result in truncation of the C-terminal domain which prevents GRK2/3-mediated phosphorylation that would otherwise abrogate the prosurvival and proinflammatory signaling. Clinical presentation of patients with *CXCR4* mutations is less likely to include adenopathy, and more likely to include greater bone marrow infiltration, higher serum IgM levels, symptomatic hyperviscosity and acquired von Willebrand disease [11,15–17]. *CXCR4* mutations were initially identified by whole genome sequencing and subsequently confirmed by AS-PCR and Sanger sequencing [18]. Additionally, the use of peripheral blood cell-free DNA to detect *CXCR4* mutations by AS-PCR presents a potential minimally invasive method [19]. Numerous nonsense and frameshift *CXCR4* mutations have been characterized thus far, however the clinical significance of frameshift mutations is still unclear [20]. Testing for CXCR4 mutations is not standardized. At DFCI, we use PCR probes for nonsense mutations and Sanger sequencing for frameshift mutations in CD19-selected bone marrow samples. However, most commercially available CXCR4 mutation detection platforms are based on next-generation sequencing techniques run on unselected samples, which could impact the sensitivity of CXCR4 mutation detection.

Other mutations observed in WM patients include those affecting *ARID1A*, *CD79A/B*, *TP53*, *TNFAIP3*, *HIVEP2*, and *BTH1*. Also, nearly half of WM patients have deletions in chromosome 6q, particularly on locus q21 to q25, affecting *BTK*, *BCL2*, and *NFKB*. Interestingly, chromosomal deletions in 6q appear to be mutually exclusive of *CXCR4* mutations [21]. While other mutations such as *CD79A/B* and *TP53* may be present in approximately 10% of WM patients, somatic mutations of *ARID1A* are found in 17% of WM patients [22–24]. *TP53* is a tumor suppressor gene located at chromosome 17p13 whose gene product, P53, functions as a transcription factor regulating cellular proliferation and cell-cycle arrest [25]. The incidence of somatic *TP53* mutations has been reported in a cohort of WM patients as 7%, with 58% of cases associated with *TP53* deletions suggesting that biallelic inactivation of *TP53* is not uncommon [24]. A lack of association was noted between TP53 mutations and MYD88, CD79A/B, or CXCR4. WM patients with a TP53 mutation experience shorter TTP and OS and is a high-risk

group. Gene mutation analysis using PCR and next-generation sequencing (NGS) methods can be used to detect *TP53* alterations [24].

*ARID1A*, along with its frequently co-mutated homolog *ARID1B*, is a member of the SWItch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex and acts as a tumor suppressor gene [26]. Inactivating mutations of *ARID1A*, predominantly nonsense or frameshift, are observed in a variety of cancers and results in changes in gene expression through defective chromatin remodeling. In comparison to those who only have *MYD88* mutations, patients with both *ARID1A* and *MYD88 L265P* mutations have greater bone marrow infiltration and more marked cytopenias, specifically anemia and thrombocytopenia [7].

CD79, a transmembrane bound molecule, is a heterodimer composed of CD79A and CD79B, which are stabilized by a disulfide bond. The B-cell receptor (BCR) is composed of a transmembrane immunoglobulin molecule coupled to a CD79A/B heterodimer. As members of the immunoglobulin (Ig) gene superfamily, CD79A/B functions in the B-cell receptor pathway (BCR) and facilitates signal transduction. The extracellular portion of the CD79A/B molecule interacts with transmembrane Ig molecules while the cytoplasmic portions of the CD79/B molecule serves as the link to transduce the extracellular signal. Activating mutations in the immunoreceptor tyrosine-based activation motif (ITAM) of CD79A and CD79B have been observed in activated B-cell-like (ABC) diffuse large B-cell lymphoma (DLBCL), which promotes BCR and prosurvival signaling [27]. Resistance to ibrutinib is conferred MYD88 mutations alone are present in ABC DLBCL, while response to ibrutinib is observed for tumors with *CD79A* or *CD79B* mutations and *MYD88* mutations [28]. While *CD79A/B* mutations are primarily observed in WM patients with *MYD88* mutations, one report has described a *CD79B* mutation in a patient with MYD88 wild type WM. Furthermore, one study described that *CXCR4* mutations appeared to be mutually exclusive to *CD79A/B* mutations in patients with WM and *MYD88 L265P* mutations [15]. In another series of patients with WM, *CD79B* mutations and *MYD88 L265P* were observed in more transformed WM patients than in non-transformed WM patients [29]. The significance of *CD79A* and *CD79B* mutations on clinical outcomes is still unclear for WM.

It is unclear if any of the mutations described previously are acquired due to the recurrent exposure to therapy. *MYD88* and *CXCR4* mutations have been described at similar rates in treatment naïve and previously untreated WM patients. Furthermore, *MYD88* and *CXCR4* mutations have been detected in individuals with a diagnosis of IgM monoclonal gammopathy of undetermined significance, at a rate of 50–60% and 10–20%, respectively [18,22,30,31]. The detection of these mutations in patients with pre-malignant processes and prior to therapy initiation argues against acquisition as a result of treatment exposure.

## Effect of genomic profile on waldenström macroglobulinemia therapies

If patients are asymptomatic, observation should be considered given the absence of OS benefit in treating asymptomatic patients [32,33]. Furthermore, patients who are asymptomatic may not progress to symptomatic disease. Treatment should be initiated for those with symptomatic disease, which may include symptoms related to hyperviscosity, peripheral neuropathy, lymphadenopathy, cold agglutinin disease, amyloidosis, cryoglobulinemia, and/or cytopenias. Although elevated levels of IgM is not an indication for treatment, an IgM level of $>$6,000 mg/dL is associated with a high risk of developing symptomatic hyperviscosity and treatment initiation should be considered on an individual basis [34]. Furthermore, the need for prompt disease control should be tailored based on disease presentation, for example, as with hyperviscosity. Plasmapheresis is generally indicated in the setting of symptomatic hyperviscosity with considerations made for the severity of symptoms associate as in the case with neuropathy, cryoglobulinemia, and cold agglutinemia [35]. For patients with WM initiating therapy, the classes of available agents include alkylators, nucleoside analogues, monoclonal antibodies, proteasome inhibitors, and BTK inhibitors. Consensus recommendations are available from the International Workshops on WM (IWWM) and additional practice guidelines are available [34,36–38]. Treatment strategies should be individualized and take into account a patient's age, performance status, and comorbidities. Goal of therapy, speed and quality of response, and the toxicities of treatment should also be considered. In this context, mutational analysis is emerging as a potential tool to tailor treatment options for patients with WM. Table 1 shows response and survival outcomes of WM patients to selected treatment regimens.

### Single-agent rituximab

Rituximab is an anti-CD20 monoclonal antibody widely used in the treatment of patients with B-cell non-Hodgkin lymphoma. As initial therapy with rituximab

in WM patients, it may result in transient elevations in IgM levels in approximately half of patients, plasmapheresis should be considered prior to rituximab administration, or if rituximab is administered as part of a combination regimen, it may be delayed until the second cycle. Of note, with the combination of ibrutinib and rituximab there is a negligible incidence of transient elevations of IgM [39]. Single-agent rituximab has a reported ORR of 25–40% from a single cycle and 65% from an extended course of two cycles, with a median progression-free survival (PFS) ranging from 12–24 months [40–43]. Of note, the median time to best response with an extended course of rituximab is 17 months [41]. Initial management with single-agent rituximab should be considered for frail patients with WM not candidates for chemoimmunotherapy due to concerns for tolerability or those with immunologic disorders secondary to WM [44]. For patients not tolerating rituximab, treatment with ofatumumab, a fully human anti-CD20 monoclonal antibody, may be considered and has a reported ORR of 60% and a rate of IgM flare of 10% [45].

In the INNOVATE study, 75 patients with WM were treated with rituximab and placebo [39]. ORR and major response rates for patients with MYD88 mutations but without *CXCR4* mutations were 46% and 29%, respectively; for patients with *MYD88* and *CXCR4* mutations, response rates were 52% and 48%; and for patients without *MYD88* or *CXCR4* mutations, response rates were 55% and 22%, respectively. The 30-month PFS rates in all genomic groups were similar at approximately 30%. Based on these limited data, *MYD88* and *CXCR4* mutational status do not seem to impact outcomes to single-agent rituximab.

### *Rituximab-containing combinations*

Rituximab-based combinations are highly active across all lines of therapy with response rates greater than 80%, but with low rates of complete response [44]. Furthermore, fixed duration chemoimmunotherapy provides a treatment-free interval for patients. Standard chemoimmunotherapy regimes have combined rituximab with nucleoside analogies (i.e. fludarabine, cladribine), alkylating agents (i.e. cyclophosphamide, bendamustine) and proteasome inhibitors (i.e. bortezomib, carfilzomib, ixazomib) [35,46–52]. Purine analogues and anthracyclines should be avoided in the frontline setting given the risk for myelosuppression and secondary malignancies. Bendamustine-rituximab is a preferred treatment option for patients presenting with bulky disease. For patients presenting with AL amyloidosis, a proteasome inhibitor-based regimen or bendamustine-rituximab may be considered. For patients presenting with neuropathy, bortezomib-based regimens should be avoided.

Mounting data suggest that *MYD88* mutational status might not affect outcomes in WM patients treated with chemoimmunotherapy. In one study on 160 WM patients treated with rituximab combined with bendamustine or cyclophosphamide, 48 had available *MYD88* mutational status, and 10 were deemed *MYD88* wild type [53]. Overall response rates were similar between *MYD88* mutated and *MYD88* wild type patients. Median PFS (34 vs. 45 months, respectively) and time to next treatment (36 vs. 56 months, respectively) were shorter in *MYD88* wild-type patients but this difference was not statistically significant. A prospective study in WM patients treated with carfilzomib, dexamethasone and rituximab reported no impact of *MYD88* mutational status in patient outcomes [52].

The impact of *CXCR4* mutational status on proteasome inhibitor-containing regimens have been evaluated in prospective and retrospective studies. A prospective study suggested a lack of effect of *CXCR4* mutations in response to carfilzomib, dexamethasone and rituximab [52]. One retrospective study reported no differences in PFS between *CXCR4* mutated and *CXCR4* wild-type WM patients treated with bortezomib and rituximab [54]. Finally, a pooled analysis of 3 prospective studies in WM patients treated with rituximab, dexamethasone and bortezomib, carfilzomib or ixazomib showed no differences between *CXCR4* mutated and *CXCR4* wild-type WM patients with regards to depth of response and PFS [55]. No studies have formally evaluated the effect of *CXCR4* mutational status in WM patients treated with chemotherapy-containing regimens.

### *Bruton tyrosine kinase inhibitors*

Ibrutinib was FDA approved for the treatment of patients with symptomatic WM, based on the results of a prospective trial of 63 patients with previously treated WM with an associated ORR of 90% and a median PFS not yet reached at 5-years of follow-up [56,57]. Ibrutinib therapy in the frontline setting offers advantages and disadvantages compared with fixed duration rituximab-based combination regimens. Although ibrutinib therapy provides an oral option for patients with a unique side effect profile compared to chemotherapy, ibrutinib therapy is continuous and its toxicities such as bleeding and atrial fibrillation may limit its use in select patients.

An impact on the depth and duration of response was observed based on the genomic profile of WM patients, specifically, patients with *MYD88 L265P* as their sole genomic abnormality had deeper and more sustained responses compared to patients with concurrent *MYD88* and *CXCR4* mutations. Specifically, patients with *CXCR4* mutations exhibit a delay by four to five months to attaining a major response to ibrutinib and also had shorter PFS versus patients without *CXCR4* mutations [58]. Similar results based on the genomic profile of WM patients were observed in prospective clinical trials for those who were treatment naïve and those who were refractory to rituximab [59,60]. A retrospective study evaluated the impact of frameshift and nonsense *CXCR4* mutations on outcomes of WM patients treated with ibrutinib, and worse major response and PFS was reported in patients with nonsense *CXCR4* mutations [61]. Furthermore, clonality of $CXCR4^{S338X}$, a common nonsense *CXCR4* mutation, has been reported as an important determinate for response to ibrutinib. High $CXCR4^{S338X}$ clonality was associated with a shorter median PFS. Tumors with $CXCR4^{S338X}$ may have an intrinsic resistance to ibrutinib, with those exhibiting a high $CXCR4^{S338X}$ clonality having a higher degree of drug resistance [62].

In a randomized phase III study (INNOVATE), 150 patients with WM, of which 90 were previously untreated, were randomized 1:1 to ibrutinib and rituximab versus placebo and rituximab. The combination of rituximab and ibrutinib compared with placebo and rituximab demonstrated a higher ORR (92% and 47%, respectively), major response rate (72% and 32%, respectively), and very good partial response (VGPR) rate (23% vs 4%, respectively) [39]. Twenty patients were *MYD88* wildtype and 49 patients had *CXCR4* mutations. In *MYD88* wild type patients treated with ibrutinib-rituximab, ORR was 81% and VGPR rate was 27%, while, in *CXCR4* mutated patients, ORR was 100% with VGPR rate of 19%. These findings suggest that the addition of rituximab to ibrutinib might be beneficial in *MYD88* wildtype patients. Although the 30-month PFS rate was similar between patients with and without *CXCR4* mutations, the 36-month PFS rates for patients with and without *CXCR4* mutations were 64% and 84%, respectively [63]. Longer follow-up is needed to better understand the effect of *MYD88* and *CXCR4* mutations in WM patients treated with ibrutinib and rituximab.

## WM treatment selection based on mutational status

### Myd88 mutated and CXCR4 wildtype

The vast majority of WM patients harbor the *MYD88 L265P* mutation. For those patients who are *MYD88* mutated and *CXCR4* wild-type, BTK inhibitors should always be considered. BTK inhibitors may be used frontline or in any subsequent line of therapy in BTK inhibitor naïve patients. Currently, ibrutinib is the only FDA approved BTK inhibitor for WM. Ibrutinib may be prescribed with or without rituximab. Since ibrutinib monotherapy has not been prospectively compared to ibrutinib plus rituximab in clinical trials, any additional benefit from rituximab is currently unclear. However, because rituximab may deplete normal B-cells, we would omit rituximab in patients with significant hypogammaglobulinemia or severe recurrent infections.

### Myd88 and CXCR4 mutated

For WM patients who harbor both *MYD88* mutations and *CXCR4* nonsense mutations, BTK inhibitors are an option, however implications of the *CXCR4* mutational status should be considered. As previously mentioned, time to best response is longer and PFS shorter in WM patients with concurrent *MYD88* and *CXCR4* mutations. If we were to use a BTK inhibitor, we would more consider the combination with rituximab, although whether the addition of rituximab improves responses in *CXCR4* mutated patients remain to be determined. Alternate strategies with chemoimmunotherapy with rituximab-based regimen combining alkylator or proteasome inhibitor are preferred. Importantly, *CXCR4* mutated patients tend to have higher IgM levels and hyperviscosity is more common. As such, care should be taken to avoid rituximab-mediated IgM flare and rituximab may be added in the second cycle or following plasmapheresis, particularly in patients at greatest risk with serum IgM level $>$4,000 mg/dL. CXCR4 targeted agents are actively being studied to help overcome this unmet need of improving BTK inhibitor responses in this population.

### Myd88 wildtype

In WM patients who are *MYD88* wild type, several considerations are crucial. First, care should be taken to best ensure the diagnosis of WM as opposed to other similar entities such as marginal zone lymphoma or IgM multiple myeloma. Secondly, a false negative is always a possibility based on the sensitivity of available standard testing. In particular, with a low burden of disease, the mutational burden may be lower than the threshold for detection by PCR in an unsorted bone marrow sample. We have found discordance in detecting *MYD88* mutation after sorting bone marrow and testing CD19-selected cells versus unsorted bone marrow [64]. Single-agent BTK inhibitors should be avoided in *MYD88* wildtype patients, based on significantly shorter PFS compared to *MYD88* mutated

patients [58]. One could consider adding rituximab to ibrutinib in *MYD88* wildtype patients. Chemoimmunotherapy with rituximab-based regimens are preferred options, although there are limited data to recommend one regimen over another.

### Other mutations

*TP53* mutations are emerging as potential markers of adverse outcomes in WM patients [23,24]. This mutation may be *de novo* or acquired in a more advanced disease. Clinical trial participation would be preferred in this population whenever possible.

## Emerging targeted therapies

Acalabrutinib, zanubrutinib and tirabrutinib are novel BTK inhibitors currently undergoing clinical development in WM. The results of a phase II study on 106 WM patients (92 previously treated and 14 treatment naïve) treated with acalabrutinib monotherapy at 100 mg PO QD until disease progression or unacceptable toxicity was recently published [65]. With a median follow-up of 27 months, the ORR was 93% and the major response rate was 80%. The distribution of responses was similar between previously treated and treatment naïve patients. VGPRs were only attained in 9% of previously treated patients. Of 50 patients who were genotyped for MYD88, 14 patients (27%) were classified as *MYD88* wild type, with ORR of 79% and a major response of 64%. Patients were not tested for *CXCR4* mutations. The 2-year OS rates for previously treated and treatment naïve patients were 82% and 90% respectively. Most common grade $\geq$3 adverse events included neutropenia (16%), lower respiratory tract infection (12%) and liver enzyme elevation (7%). The rate of atrial fibrillation was 5%.

Zanubrutinib is also an oral BTK inhibitor administered at 160 mg PO BID and is being evaluated in a phase III study against ibrutinib 420 mg PO QD (ASPEN; NCT03053440). Results from a phase I/II study on 73 WM patients (49 previously treated and 24 treatment naïve) have shown an ORR of 92%, a major response rate of 82% and VGPR rate of 42%, with a median follow-up time of 24 months [66]. Estimated 24-month PFS rate was 81%. Most common grade $\geq$3 adverse events included neutropenia (10%), anemia (8%) and hypertension (5%). Arm C of the ASPEN study, which included 26 (21 previously treated and 5 treatment naïve) WM patients classified as *MYD88* wild type, reported ORR of 81%, major response of 54% and VGPR of 23%, with a median follow-up time of 12 months [67].

Data on a phase II study on 27 WM patients (9 previously treated and 18 treatment naïve) exposed to tirabrutinib 480 mg PO QD with a median follow-up time of 6 months showed ORR of 94% and a major response of 80% [68]. Neutropenia, atypical mycobacterial infection and rash were the most common grade $\geq$3 adverse events.

Akin to CLL patients, WM patients on BTK inhibitor therapy can develop mutations in *BTK* and/or *PCLG2*, which can render current BTK inhibitors ineffective [69]. A number of non-covalent, second-generation BTK inhibitors that could overcome the resistance associated with *BTK* and/or *PCLG2* mutations are underway. ARQ531 (NCT03162536) and LOXO-305 (NCT03740529) are currently being actively investigated in WM patients with BTK mutations progressing on ibrutinib.

The BCL2 inhibitor venetoclax has shown to be safe and effective in WM. An ongoing multicenter phase II study is evaluating venetoclax monotherapy in 30 previously treated WM patients, of which 15 were previously exposed to BTK inhibitors [70]. Venetoclax was escalated weekly to a maximum dose of 800 mg PO QD, which was then continued for 24 months. With a median follow-up of 18 months, ORR was 87%, major response rate was 81% and VGPR rate was 19%. The 2-year PFS rate was estimated at 76%. Time to and depth of response and PFS appeared to be adversely affected by prior BTK inhibitor exposure. *CXCR4* mutations were associated with lower rates of VGPR, but PFS did not appear to be affected. Most common grade $\geq$3 adverse events were neutropenia, anemia and diarrhea. No clinical laboratory tumor lysis syndrome occurred. Furthermore, with the synergy observed with dual BTK and BCL2 inhibition, the combination of ibrutinib and venetoclax are being investigated in an ongoing phase II study in untreated patients with WM (NCT04273139).

As *CXCR4* mutations can be detected in 30-40% of WM patients, the clinical development of CXCR4 targeted agents are of active interest. The anti-CXCR4 monoclonal antibody ulocuplumab in combination with ibrutinib is being investigated in a phase I/II study in previously treated and treatment naïve WM patients harboring *CXCR4* mutations (NCT03225716). The CXCR4 targeting small molecule mavorixafor in combination with ibrutinib is also undergoing clinical development in a multicenter phase 1B study (NCT04274738).

## Conclusions

WM is a highly heterogenous disease and therapy selection is based on a number of unique patient characteristics. Factors such as age, comorbidities,

**Table 1.** Response rates, median progression free survival, and median time to next treatment by mutational status in trials evaluating chemoimmunotherapy, ibrutinib, zanubrutinib, and venetoclax in patients with Waldenström macroglobulinemia.

| Study | Regimen | Treatment status | Design | Mutational status | N | ORR (%) | MRR (%) | VGPR (%) | Median PFS (mo. [95% CI]) | Median TTNT (mo. [95% CI]) |
|---|---|---|---|---|---|---|---|---|---|---|
| Paludo et al. 2017. [71] | DRC | TN and PT | Retrospective | $MYD88^{L265P}$ | 25 | 92 | – | – | 41 (16-59) | 56 (38-NR) |
| | | | | $MYD88^{WT}$ | 4 | 100 | – | – | 34 (15-34) | 37 (20-37) |
| Paludo et al. 2018. [53] | BR or DRC[a] | TN and PT | Retrospective | $MYD88^{L265P}$ | 38 | 92 | – | – | 45 (21-59) | 56 (41-NR) |
| | | | | $MYD88^{WT}$ | 10 | 100 | – | – | 34 (9-NR) | 36 (9-37) |
| Sklavenitis-Pistofidis et al. 2018. [54] | Bortezomib-rituximab[b] | PT | Retrospective | $MYD88^{L265P}$ $CXCR4^{MUT}$ | 17 | – | – | – | -[c] | – |
| | | | | $CXCR4^{WT}$ | 26 | – | – | – | -[c] | – |
| Dimopoulos et al. 2018. [39]; Buske et al. 2020. [72] | Ibrutinib-rituximab | TN and PT | Prospective | $MYD88^{L265P}$ $CXCR4^{WT}$ | 32 | 94 | 78 | 28 | -[c] | – |
| | | | | $MYD88^{L265P}$ $CXCR4^{MUT}$ | 26 | 100 | 73 | 19 | -[d] | |
| | | | | $MYD88^{WT}$ $CXCR4^{WT}$ | 11 | 82 | 63 | 27 | | |
| Gustine et al. 2019. [62] | Ibrutinib | TN and PT | Retrospective | $CXCR4^{S338X}$ | 37 | 92 | 62 | 10.8 | 44.1 | – |
| | | | | $CXCR4^{S338X\ clonality\ high}$ | 23 | 96 | 65 | 4 | 39.9 | – |
| | | | | $CXCR4^{S338X\ clonality\ low}$ | 14 | 86 | 57 | 21 | NR | – |
| | | | | $CXCR4^{Non\text{-}S338X}$ | 33 | 85 | 64 | 15 | NR | – |
| | | | | $CXCR4^{WT}$ | 110 | 96 | 85 | 35 | NR | – |
| Castillo et al. 2020. [73] | IDR[b] | TN | Prospective | $MYD88^{L265P}$ | 26 | 96 | 77 | 19 | 40 (22-NR) | 40 (24-NR) |
| | | | | $MYD88^{L265P}$ $CXCR4^{MUT}$ | 15 | 94 | 74 | 7 | 40 (22-53) | 40 (18-NR) |
| | | | | $MYD88^{L265P}$ $CXCR4^{WT}$ | 11 | 99 | 81 | 36 | 36 (17-NR) | NR |
| Treon et al. 2020. [57] | Ibrutinib[b] | PT | Prospective | $MYD88^{MUT}$ $CXCR4^{WT}$ | 36 | 100 | 97.2 | 47.2 | NR | – |
| | | | | $MYD88^{MUT}$ $CXCR4^{MUT}$ | 22 | 86.4 | 68.2 | 9.1 | 54 | – |
| | | | | $MYD88^{WT}$ $CXCR4^{WT}$ | 4 | 50 | 0 | 0 | 4.8 (1.2-NR) | – |
| Castillo et al. 2020. [74] | Ibrutinib[e] | PT | Retrospective | $MYD88^{MUT}$ | 129 | - | 74 | – | -[f] | – |
| | | | | $MYD88^{WT}$ | 3 | - | 33 | – | -[f] | – |
| | | | | $CXCR4^{MUT}$ | 47 | - | 62 | – | 4-yr PFS rate: 47% (25-67%) | – |
| | | | | $CXCR4^{WT}$ | 74 | - | 80 | – | 4-yr PFS rate: 67% (43-83%) | – |
| Owen et al. 2020. [65] | Acalabrutinib | TN and PT | Prospective | $MYD88^{L265P}$ | 36 | 94 | 81 | 11 | – | – |
| | | | | $MYD88^{WT}$ | 14 | 79 | 64 | 0 | – | – |
| Tam et al. 2020. [75] | Zanubrutinib | TN and PT | Prospective | $MYD88^{L265P}$ $CXCR4^{WT}$ | 65 | – | 82 | 34 | – | – |
| Garcia-Sanz et al. 2020. [76] | | | | $MYD88^{L265P}$ $CXCR4^{MUT}$ | 33 | – | 70 | 18 | – | – |
| | | | | $MYD88^{WT}$ | 26 | 80.8 | 50 | 26.9 | 12-mo. PFS rate: 72.4% | – |
| Trotman et al. 2020. [77] | Zanubrutinib | TN and PT | Prospective | $MYD88^{L265P}$ $CXCR4^{WT}$ | 39 | 97.5 | 87.2 | 59 | – | – |
| | | | | $MYD88^{L265P}$ $CXCR4^{MUT}$ | 11 | 100 | 90.9 | 27.3 | – | – |
| | | | | $MYD88^{WT}$ $CXCR4^{WT}$ | 8 | 100 | 62.5 | 12.5 | – | – |
| Castillo et al. 2019. [70] | Venetoclax | PT | Prospective | $MYD88^{L265P}$ $CXCR4^{WT}$ | 14 | 87 | 81 | 19 | 2-yr PFS rate: 76% (52-89%) | – |
| | | | | $MYD88^{L265P}$ $CXCR4^{MUT}$ | 17 | | | | | – |

Abbreviations: BR: bendamustine-rituximab; DRC: dexamethasone-rituximab-cyclophosphamide; IDR: ixazomib-dexamethasone-rituximab; MRR: major response rate; MUT: mutant; NR: not reached; ORR: overall response rate; PFS: progression-free survival; PT: previously treated; TN: treatment naïve; TTNT: time to next treatment; VGPR: very good partial response; WT: wild type.

[a]For patients who received BR, 14 and 5 were $MYD88^{L265P}$ and $MYD88^{WT}$, respectively; for patients who received DRC, 24 and 5 were $MYD88^{L265P}$ and $MYD88^{WT}$, respectively.

[b]All patients who had a CXCR4 mutation also were $MYD88^{MUT}$.

[c]$p = 0.994$.

[d]At median follow-up of 50 months (range, 0.5+ to 63) for the ibrutinib-rituximab arm ($n = 75$), median PFS was not reached (NR; 95% CI, 57.7-NR) and median TTNT was not reached.

[e]OFF trial group ($N = 157$) is reported.

[f]Inferior PFS observed in $MYD88^{WT}$ compared with $MYD88^{MUT}$ patients in the OFF trial group ($p = 0.03$).

functional status, disease-related complications, prior therapies, and goals of care are all important when selecting an individual WM treatment strategy. In academic centers, genomic testing for routine cytogenetics, *MYD88*, and *CXCR4* testing should be undertaken in all WM patients. In the community, MYD88 testing should be pursued in all WM patients and *CXCR4* testing in patients eligible for BTK inhibitors. WM patients with *MYD88* mutations should be considered for treatment with BTK inhibitors. Because WM patients with coexisting *MYD88* and nonsense *CXCR4* mutations may take longer to reach the best response and may have shorter PFS when treated with BTK inhibitor monotherapy, combination therapy or alternate agents may be better suited for certain patients.

Although generally indolent, WM is incurable, and some patients ultimately develop progressive disease and die from complications of their disease. Fortunately, OS has improved in the last couple of decades with the development of the latest treatment strategies. With a better understanding of the genetic pathogenesis of WM, more effective treatment strategies are being developed, such as CXCR4 blocking antibodies and small molecules overcome resistance to BTK inhibitors and exploit new molecular pathways. Deeper understanding may also allow opportunities to halt progression for premalignant or asymptomatic states. Additionally, more innovative and genomic therapies will likely continue to lead to deeper remissions, improved PFS and OS and closer to the possibility of a cure.

## Disclosure statement

ARB received honoraria from Pharmacyclics. SPT received research funding and/or honoraria from Abbvie, Beigene, BMS, Pharmacyclics and X4. JJC received research funding and/or honoraria from Abbvie, Beigene, Janssen, Pharmacyclics, Roche and TG Therapeutics. ML has no conflicts of interest to disclose.

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