review articles

Genomic Landscape of Waldenström Macroglobulinemia and Its Impact on Treatment Strategies

Steven P. Treon, MD, PhD[1,2]; Lian Xu, MS[1]; Maria Luisa Guerrera, MD[1,2]; Cristina Jimenez, PhD[1,2]; Zachary R. Hunter, PhD[1,2]; Xia Liu, MD[1,2]; Maria Demos, BS[1]; Joshua Gustine, MPH[1]; Gloria Chan, MS[1]; Manit Munshi, MS[1]; Nicholas Tsakmaklis, BA[1]; Jiaji G. Chen, BS[1]; Amanda Kofides, BS[1]; Romanos Sklavenitis-Pistofidis, MD[2,3,4]; Mark Bustoros, MD[2,3]; Andrew Keezer, BS[1]; Kirsten Meid, MPH[1]; Christopher J. Patterson, MAcc, MPH[1]; Antonio Sacco, RN[3,4]; Aldo Roccaro, MD, PhD[4]; Andrew R. Branagan, MD[5]; Guang Yang, PhD[1,2]; Irene M. Ghobrial, MD[2,3]; and Jorge J. Castillo, MD[1,2]

abstract

Next-generation sequencing has revealed recurring somatic mutations in Waldenström macroglobulinemia (WM), including *MYD88* (95%-97%), *CXCR4* (30%-40%), *ARID1A* (17%), and *CD79B* (8%-15%). Deletions involving chromosome 6q are common in patients with mutated *MYD88* and include genes that modulate NFKB, BCL2, Bruton tyrosine kinase (BTK), and apoptosis. Patients with wild-type *MYD88* WM show an increased risk of transformation and death and exhibit many mutations found in diffuse large B-cell lymphoma. The discovery of *MYD88* and *CXCR4* mutations in WM has facilitated rational drug development, including the development of BTK and CXCR4 inhibitors. Responses to many agents commonly used to treat WM, including the BTK inhibitor ibrutinib, are affected by *MYD88* and/or *CXCR4* mutation status. The mutation status of both *MYD88* and *CXCR4* can be used for a precision-guided treatment approach to WM.

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INTRODUCTION

Waldenström macroglobulinemia (WM) is a B-cell malignancy characterized as an immunoglobulin M (IgM)–secreting lymphoplasmacytic lymphoma using WHO criteria.[1] Patients can present with morbidity related to excess malignant lymphoplasmacytic cells (LPCs) in the bone marrow (BM), lymph nodes, and spleen, as well as IgM production that can produce symptomatic hyperviscosity, cryoglobulinemia, and autoimmune-related complications.[2] Despite advances in therapy, WM remains incurable. Treatment options for WM have largely represented therapeutics studied in other diseases, with more recent advances facilitated by next-generation sequencing (NGS).

Using NGS, recurring somatic mutations in *MYD88*, *CXCR4*, *ARID1A*, and *CD79* were identified in WM LPC. Copy number alterations, including those in chromosome 6q that affect regulatory genes for NFKB, Bruton tyrosine kinase (BTK), BCL2, and apoptotic signaling, were also identified.[3] Although most patients with WM (95%-97%) carry a point mutation in *MYD88* that switches leucine to proline at amino acid position 265, those that are wild type for *MYD88* show a more aggressive disease course and possess somatic mutations that overlap with those found in diffuse large B-cell lymphoma (DLBCL).[4,5] Herein, we discuss the genomic landscape of WM and the impact of underlying genomics on disease presentation, transcriptional changes, treatment outcome, and overall survival. The use of *MYD88* and *CXCR4* mutation status to guide treatment in treatment-naïve and previously treated patients with WM is also discussed.

Author affiliations and support information (if applicable) appear at the end of this article.

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MUTATIONS IN *MYD88*

A recurring somatic mutation in *MYD88* (L265P) was identified in 91% of patients with WM by paired tumor and normal whole-genome sequencing and subsequently confirmed by Sanger sequencing and allele-specific polymerase chain reaction (AS-PCR) assays by multiple investigators.[6] Using sensitive AS-PCR testing, *MYD88* L265P was found to be expressed in 93%-97% of patients with WM and was identified in both sorted B cells and plasma cells that make up the malignant clone in WM.[7-11] Non-L265P *MYD88* mutations have also been identified, although expression estimates for these variants are 1%-2% in WM.[12,13] Mutated *MYD88* was also detectable in patients with IgM but not immunoglobulin G or immunoglobulin A monoclonal gammopathy of unknown significance (MGUS), suggesting an early oncogenic role for *MYD88* in WM pathogenesis.[7,8,10] Patients with IgM MGUS with detectable mutated *MYD88* and patients with a higher mutated allele burden are at greater risk of progression to WM.[10,14]

The *MYD88* L265P mutation can also be detected by AS-PCR in peripheral-blood (PB) samples, particularly in treatment-naïve patients with WM.[15] Prior therapy with B-cell–depleting agents can greatly decrease detection of *MYD88* L265P in PB samples. *MYD88* L265P can also be found in skin lesions, CSF, and pleural effusions in patients with WM, providing a means of demonstrating extramedullary disease involvement.[16-18] Cell-free DNA has also been used to detect *MYD88* L265P from PB samples of patients with WM and may represent a novel means for establishing *MYD88* mutation status.[19,20]

Structural alterations on chromosome 3p can increase the allele burden of mutated *MYD88*.[6,21] Up to 15% of untreated and 25% of previously treated patients may be homozygous for *MYD88* as a result of deletions of the wild-type *MYD88* allele, amplifications of the mutant *MYD88* allele, and, more commonly, acquired uniparental disomy (aUPD) events.[22] aUPD events resulting in homozygous *MYD88* expression are associated with concurrent *CXCR4* mutations, the significance of which remains to be clarified but may be related to disease length and prior ibrutinib exposure.[6,23]

Patients with wild-type *MYD88* show similar histologic findings and transcription profile as patients with *MYD88*-mutated WM.[4,5] However, patients with wild-type *MYD88* with asymptomatic WM have a higher risk of symptomatic progression,[24] and those presenting with symptomatic disease have a greater risk of disease transformation[8,25] and decreased overall survival.[8] Patients with wild-type *MYD88* also show poor response to ibrutinib (discussed later). It is important to distinguish patients with suspected WM with wild-type *MYD88* disease from patients with other IgM-secreting malignancies. In one series, 30% of patients with suspected wild-type *MYD88* WM had an alternative diagnosis, including IgM multiple myeloma (MM). The presence of very high serum IgM levels, lytic lesions, and/or renal dysfunction may help identify IgM MM.[8,26,27] Use of cytogenetics to evaluate for t(11;14) and cyclin D1 staining can be helpful in distinguishing IgM MM from wild-type *MYD88* WM.[8,27,28]

MYD88 is an adaptor protein that interacts with the Toll-like and interleukin (IL)-1 receptors and dimerizes upon receptor activation. Dimerization of MYD88 provides a scaffold for recruitment of other proteins to a Myddosome complex that triggers downstream signaling, leading to nuclear factor-κB (NFKB) activation (Fig 1).[29] Both IRAK1/IRAK4 and BTK are Myddosome components and trigger NFKB.[30,31] Recruitment and activation of the IRAK and BTK molecules can be blocked by either knockdown or inhibition of MYD88 that leads to apoptosis of mutated *MYD88* WM cells. Mutated MYD88 can also upregulate transcription of the SRC family member HCK that normally is downregulated in late stages of B-cell ontogeny and can transactivate HCK via IL-6.[32] Activated HCK triggers prosurvival signaling of mutated *MYD88* WM cells through BTK, PI3K/AKT, and MAPK/ERK1/2. Both BTK and HCK are targets of ibrutinib, which has shown remarkable activity in patients with mutated *MYD88* WM.[32,33]

More recently, a role for mutated MYD88 as a trigger for B-cell receptor (BCR) pathway cross talk has been proposed. Phelan et al[34] described the existence of a MYD88-TLR9-BCR(IgM) (MY-T-BCR) supercomplex in mutated MYD88 tumor cells. Evidence for chronic activated BCR signaling exists in WM.[35,36] SYK, a component of the BCR pathway, is present in its active form in the Myddosome, and its activation is triggered by mutated MYD88.[37] Importantly, mutated MYD88–directed SYK activation triggers STAT3 and AKT prosurvival signaling. In preclinical studies, the addition of an SYK inhibitor triggered synthetic lethality when combined with ibrutinib.[37] Taken together, these studies show that mutated MYD88 can direct multiple prosurvival cascades that lead to NFKB, AKT, ERK, and STAT3 activation in WM cells (Fig 1). WM cells also export mutated MYD88 via extracellular vesicles, which may produce a growth-supportive proinflammatory microenvironment (Fig 1).[38]

MUTATIONS IN *CXCR4*

Somatic mutations involving the C-terminal domain of CXCR4 are present in up to 40% of patients with WM, and although they almost always occur in those with *MYD88* mutations, some patients with wild-type *MYD88* can also express *CXCR4* mutations.[21,39] *CXCR4* mutations are essentially unique to WM, with only a few cases of marginal zone lymphoma and activated B-cell (ABC) subtype of DLBCL reported so far. Germline mutations in the C-terminal domain of *CXCR4* are present in patients with WHIM (autosomal dominant warts, hypogammaglobulinemia, infection, and myelokathexis) syndrome.[40] In patients with WHIM syndrome, activation of CXCR4 by its ligand CXCL12 induces extended chemotactic signaling and neutrophil sequestration in the BM (myelokathexis) and impairment of lymphocyte development. In WM, > 40 nonsense and frameshift mutations in the C-terminal domain of *CXCR4* have been described.[41,42] Mutations in the C-terminal domain of *CXCR4* lead to loss of regulatory serines and promote sustained CXCL12-mediated activation of the AKT and ERK pathways and in vivo WM disease progression and dissemination in mice.[43-45] Despite the autonomous prosurvival signaling associated with CXCR4 mutations, inhibition of MYD88 triggers apoptosis in both wild-type and mutated CXCR4–expressing WM cells, consistent with a primary role for mutated MYD88 survival signaling in WM.[45]

Unlike *MYD88*, mutated *CXCR4* is subclonal, with highly variable clonality averaging approximately 35%. Multiple *CXCR4* mutations can also exist within individual patients that can occur in separate clones or as compound heterozygous events.[39] The subclonal nature of *CXCR4* mutations relative to *MYD88* and their paucity in IgM MGUS relative to WM suggest that *CXCR4* mutations are acquired after *MYD88*.[39] Clonal 6q deletions (del 6q21-25), which are found in 40%-50% of patients with WM, appear exclusive of *CXCR4* in treatment-naïve patients.[46] The increasing frequency of 6q deletions from IgM MGUS

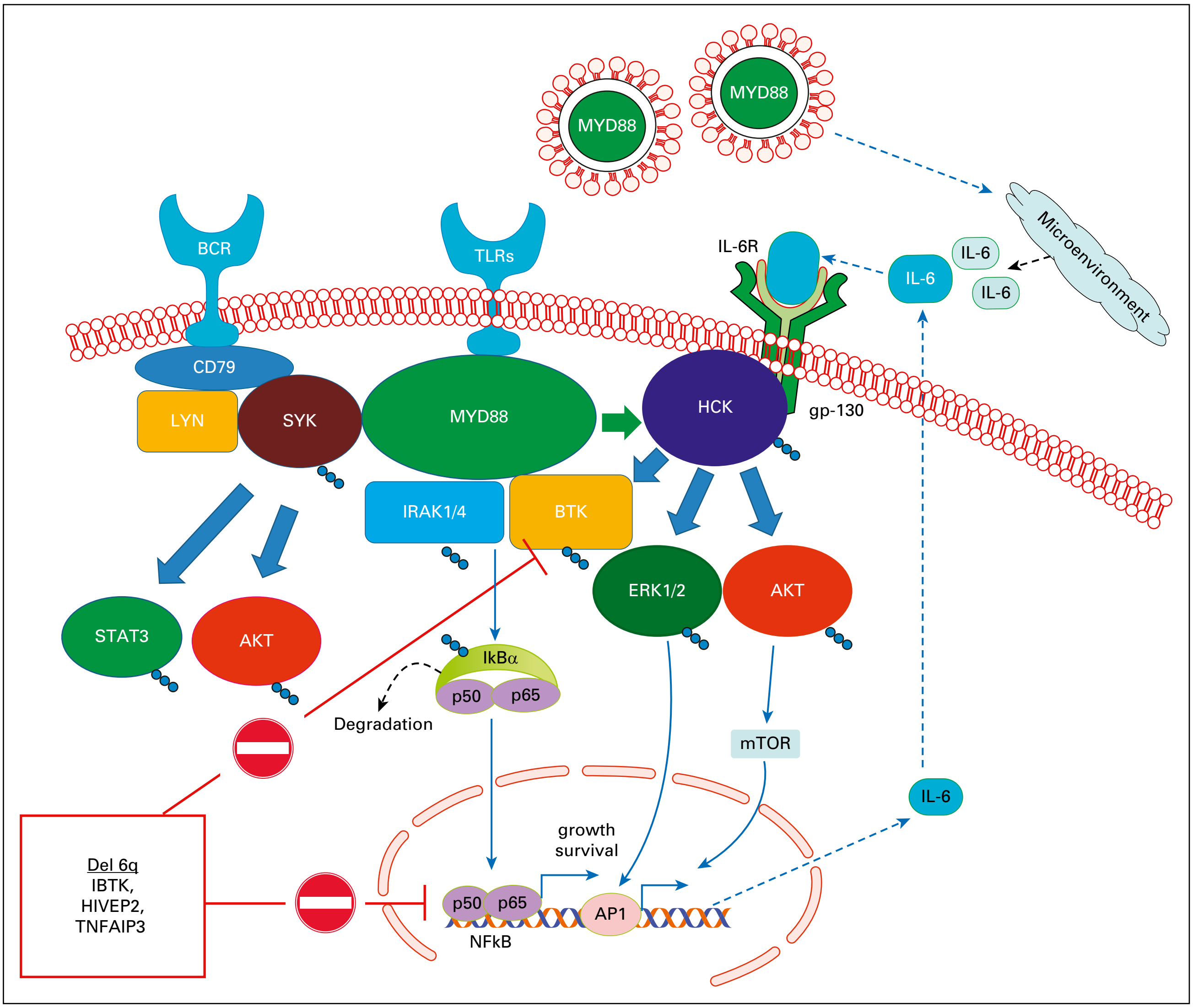

FIG 1. Prosurvival signaling mediated by mutated *MYD88*. Mutated *MYD88* triggers assembly of the Myddosome, which includes activated BTK and IRAK4/IRAK1 that transactivate NFKB. Mutated *MYD88* also transcriptionally upregulates and transactivates through interleukin (IL)-6 the SRC family member HCK, which triggers activation of BTK itself, as well as AKT and ERK. Mutated *MYD88* also mediates cross talk through LYN-activated SYK, which activates STAT3 and AKT prosurvival signaling. Deletions in chromosome 6q result in the loss of important regulators of MYD88 signaling, including inhibitor of BTK (IBTK) and the NFKB regulators HIVEP2 and TNFAIP3. Waldenström macroglobulinemia cells also export mutated MYD88 via extracellular vesicles to induce signaling cascades in mast cells and macrophages that provide a supportive proinflammatory microenvironment. BCR, B-cell receptor; mTOR, mammalian target of rapamycin; TLRs, Toll-like receptors.

through asymptomatic and symptomatic WM suggests that loss of genes within this region (discussed later) facilitates disease progression.[13,35,46] Taken together, these findings suggest that at least 2 distinct pathways mediated by either mutated *CXCR4* or del 6q21-25 promote IgM MGUS progression to symptomatic WM.

Like *MYD88*, *CXCR4* somatic mutations can affect WM disease presentation. Patients with mutated *CXCR4* present with less adenopathy, and those with nonsense *CXCR4* mutations have increased BM disease, serum IgM levels, and/or symptomatic hyperviscosity at presentation.[41] Nonsense *CXCR4* mutations are also associated with acquired von Willebrand factor deficiency.[41,47] Despite differences in clinical presentation, *CXCR4* mutations do not adversely affect overall survival but do seem to affect time to treatment.[8,13,41]

In vitro modeling of WM cells transduced with mutated CXCR4 reveals increased drug resistance in the presence of its ligand CXCL12 to multiple therapeutics including bendamustine, fludarabine, bortezomib, idelalisib, and ibrutinib.[43-45] These studies also showed that resistance mediated by mutated CXCR4 could be reversed by use of CXCR4-blocking agents in both in vitro and in vivo studies.[43-45]

OTHER RECURRING MUTATIONS

Somatic mutations in *ARID1A* are present in 17% of patients with WM, including nonsense and frameshift variants.[21] Patients with *ARID1A* and *MYD88* L265P mutations have greater WM disease involvement and lower hemoglobin and platelet counts. *ARID1A* and its frequently deleted homolog *ARID1B* (see later discussion) are on chromosome 6q.[46] Both are switch/sucrose nonfermentable (SWI/SNF) family members and serve as chromatin remodeling genes, thereby modulating gene regulation. Although still poorly understood, ARID1A can modulate TP53 and is thought to act as an epigenetic tumor suppressor in ovarian cancer.[3]

Mutations in *CD79A* and *CD79B* can be found in 8%-12% of patients with WM.[13,21,42] Both are components of the BCR pathway and can form heterodimers with each other.[3] The CD79A/B heterodimer associates with the immunoglobulin heavy chain required for cell surface expression of BCR and BCR-induced signaling. Activating mutations in the immunotyrosine-based activation motif of CD79A and CD79B occur in the ABC subtype of DLBCL and trigger SYK, PLCγ2, and BTK.[48] Mutated MYD88 cross talk through SYK may also explain chronic BCR signaling observed in WM cells.[37] Deletions of *LYN*, which are found in 70% of patients with WM, may contribute to hyperresponsive BCR signaling, as informed by lyn$^{-/-}$ transgenic mice.[21,49] Although mutations in both *CD79A* and *CD79B* are mainly found in patients with mutated *MYD88* including those with WM, a *CD79B* mutation was observed in a patient with wild-type *MYD88* WM.[21] In one study, mutations in *CD79A* and *CD79B* were nearly exclusive of *CXCR4* mutations, suggesting that *CD79A/B* mutations may also have an independent role in facilitating mutated *MYD88*–directed progression in WM.[42] In a small series of patients with WM, the coexpression of *CD79B* and *MYD88* mutations was associated with disease transformation.[50] Mutations in *TP53* are more rarely observed (2%-3%) in WM[13,21] and are associated with poor survival.[51,52]

MUTATIONS IN WILD-TYPE *MYD88* WM

A small number of patients with WM (3%-7%) lack mutations in *MYD88*, including non-L265P mutations.[5,21] Their disease course is marked by an increased risk of disease transformation[5,25] and shorter overall survival.[5] Moreover, patients with wild-type *MYD88* show little response to ibrutinib (discussed further later). These findings point to fundamental differences in underlying genomics. NGS identified somatic mutations in patients with wild-type *MYD88* WM that are predicted to trigger NFKB (*TBL1XR1*, *PTPN13*, *MALT1*, *BCL10*, *NFKB1*, *NFKB2*, *NFKBIB*, *NFKBIZ*, and *UDRL1F*), impart epigenomic dysregulation (*KMT2D*, *KMT2C*, and *KDM6A*), or impair DNA damage repair (*TP53*, *ATM*, and *TRRAP*).[5] Predicted NFKB activating mutations were downstream of BTK, and many overlapped with somatic mutations found in DLBCL.[5] Transcriptome studies revealed a distinctive transcriptional profile in patients with wild-type *MYD88* WM, although the most differentially expressed genes overlapped with those found in mutated *MYD88* WM.[5] These findings may help explain many of the uniform characteristics shared among patients with WM, regardless of their underlying *MYD88* mutation status.

COPY NUMBER ALTERATIONS

Copy number alterations are common in patients with *MYD88*-mutated WM and involve both chromosome 6q and non–chromosome 6q regions.[13,21,35] In chromosome 6q, loss of genes that modulate NFKB activity (*TNFAIP3* and *HIVEP2*), BCL2 (*BCLAF1*), apoptosis (*FOXO3*), BTK (*IBTK*), plasma cell differentiation (*PRDM1*), and *ARID1B* occur.[21,46] Non–chromosome 6q genes that are commonly deleted include *ETV6*, a transcription repressor; *BTG1*, which is often deleted in DLBCL and associated with glucocorticoid resistance in acute lymphocytic leukemia; and *LYN*, a kinase that regulates BCR signaling.[21,48,49] *PRDM2* and *TOP1*, which participate in TP53-related signaling, are also deleted in many patients with WM. In contrast to *MYD88*-mutated WM, recurring copy number alterations are rare in *MYD88* wild-type WM, including loss of chromosome 6q.[5,13,21]

IMPACT OF GENOMIC ALTERATIONS ON WM TREATMENT OUTCOME

The impact of *MYD88* and *CXCR4* mutations on treatment outcome has been evaluated in several clinical trials (Table 1). Patients with *MYD88* mutations who are wild type for *CXCR4* have better outcomes associated with ibrutinib monotherapy, including time to major response, depth of response, and progression-free survival.[33,53,54] Indeed, patients with both *MYD88* and *CXCR4* mutations exhibit a delay by 4-5 months in attaining a major response to ibrutinib monotherapy. No major responses were observed in previously treated patients with WM with wild-type *MYD88* treated with ibrutinib alone.[12,55] Patients with *MYD88* wild-type status also had much short progression-free survival on ibrutinib alone compared with *MYD88*-mutated patients, regardless of their *CXCR4* mutation status.[53]

Earlier disease progression has also been observed in *MYD88*- and *CXCR4*-mutated patients treated with ibrutinib alone or with ibrutinib and rituximab when compared with patients with mutated *MYD88* alone.[53,56] Somatic mutations at the site of ibrutinib-BTK binding (Cys481) have been observed in patients with WM who experienced progression on ibrutinib.[57] Multiple *BTK* mutations were observed in this study within individual patients with WM, particularly those with *CXCR4* mutations. Although the findings highlight the importance of BTK as a treatment target in *MYD88*-mutated WM, they also raise questions as to why *CXCR4*-mutated patients are particularly at risk for the acquisition of *BTK* Cys481 mutations.

TABLE 1. Summary of the Impact of *MYD88* and CXCR4 Mutation Status on Treatment Outcomes in Patients With Waldenström Macroglobulinemia

Agent	*MYD88*	*CXCR4*
BTK inhibitors		
Ibrutinib monotherapy	No major responses and short PFS in *MYD88* wild-type patients in prospective study	Fewer major responses and VGPRs, increased time to response, and shorter PFS in *CXCR4*-mutated patients in prospective studies
Ibrutinib plus rituximab		Fewer major responses and VGPRs and shorter PFS in *CXCR4*-mutated patients in prospective study
Zanubrutinib		Fewer major responses and VGPRs in *CXCR4*-mutated patients in prospective study (preliminary)
Proteasome inhibitors		
Bortezomib-based therapy		No impact of *CXCR4* mutation status on response rates, PFS, and OS in retrospective study
Carfilzomib, dexamethasone, rituximab		No impact of *CXCR4* mutation status on response rates, PFS, and OS in prospective study
Ixazomib, dexamethasone, rituximab		Longer median time to response in *CXCR4*-mutated patients in prospective study; response rates and PFS not affected by *CXCR4* mutation status
Alkylators		
Bendamustine-based therapy	Shorter PFS in *MYD88* wild-type patients in prospective study of bendamustine plus rituximab; no impact of *MYD88* status on overall response attainment, but PFS and TTNT were shorter in *MYD88* wild-type patients in a retrospective study	No impact of *CXCR4* mutation status on PFS with bendamustine plus rituximab in retrospective study
Cyclophosphamide, dexamethasone, rituximab	No impact of *MYD88* status on overall response attainment, but PFS and TTNT were shorter in MYD88 wild-type patients in a retrospective study	
mTOR inhibitor		
Everolimus	Nonresponse in *MYD88* wild-type patients in a prospective study	Lower overall and major response rates in *CXCR4*-mutated patients in a prospective study
BCL2 inhibitor		
Venetoclax		Lower major response and VGPR rates in *CXCR4*-mutated patients in a prospective study (preliminary)

NOTE. Overall response rate includes minor responses or better. Major response rate includes partial responses or better. Data adapted from Owen et al.[87]
Abbreviations: BTK, Bruton tyrosine kinase; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment; VGPR, very good partial response.

The presence of *CXCR4* mutations has also affected clinical outcomes with other agents. Fewer major responses were preliminarily reported with the BTK inhibitor zanubrutinib, as well as with the BCL2 inhibitor venetoclax, in prospective studies in patients with WM.[58,59] Time to response was also reported to be longer in patients with WM with *CXCR4* mutations receiving ixazomib-based therapy, a proteasome inhibitor (PI), in a prospective phase II study.[60] Conversely, a prospective study of patients with *CXCR4*-mutated WM treated with carfilzomib-based therapy showed no effect on clinical outcome.[61] In a retrospective study, Sklavenitis-Pistofidis et al[62] showed that bortezomib-based therapy could overcome the negative impact of *CXCR4* mutations on progression-free and overall survival.

Among treatment-naïve patients with WM receiving everolimus as a single agent in a prospective phase II study, nonresponders included patients who were *CXCR4* mutated, as well as those who were wild type for *MYD88*.[63] In a retrospective study by the French Innovative Leukemia Organization group, the use of bendamustine plus rituximab resulted in similar progression-free survival among *MYD88*-mutated patients with and without *CXCR4* mutations. Conversely, those with wild-type *MYD88* showed earlier progression.[64] In a retrospective study, Paludo et al[65] also observed a trend for shorter progression-free survival and time to next treatment among genotyped patients with *MYD88* wild-type WM who received alkylator-based (bendamustine or cyclophosphamide) therapy. There were no differences in overall response rates between genotyped patients who were *MYD88* mutated or wild type, and no data on major responses were reported.

Although the previously discussed studies indicate that *CXCR4* represents an important target in WM, differences in response outcome could be modulated by the type of

CXCR4 mutation as well as its clonal presence. In a study by Castillo et al,[66] patients on ibrutinib with nonsense mutations showed fewer major responses and shorter progression-free survival compared with those with frameshift *CXCR4* mutations or those wild-type for *CXCR4*. The clonality of CXCR4 may also be an important determinant of ibrutinib response. Gustine et al[67] investigated the impact of the *CXCR4* S338X nonsense variant on ibrutinib response outcome in patients with WM. Patients with a *CXCR4* S338X clonality of > 25% showed greater BM disease involvement and serum IgM levels, fewer very good partial responses, and shorter progression-free survival.

Given the importance of *CXCR4* mutation status in WM, a clinical trial assessing the impact of the CXCR4 inhibitor ulocuplumab with ibrutinib in patients with *CXCR4*-mutated WM was initiated (ClinicalTrials.gov identifier: NCT03225716). Mavorixafor, an orally administered CXCR4 antagonist, is also in clinical development for *CXCR4*-mutated WM. Although the use of antagonists to counter CXCR4 signaling in *CXCR4*-mutated patients represents a rational approach for advancing treatment in this population with WM, a targeted approach for those with *MYD88* wild-type WM remains elusive and represents an urgent priority.

GENOMIC-BASED TREATMENT APPROACH TO WM

MYD88 and *CXCR4* mutation status may be useful in treatment selection for symptomatic patients. Treatment algorithms recommended by the authors for the use of *MYD88* and *CXCR4* mutation status in the treatment approach of symptomatic untreated and previously treated patients are presented in Figures 2 and 3, respectively. In treatment-naïve patients, as well as those with previously treated WM, plasmapheresis should be considered as the first step in patients presenting with symptomatic hyperviscosity, rapidly progressing peripheral neuropathy attributed to demyelinating IgM disease, severe cryoglobulinemia, and cold agglutinemia.[68,69] To minimize risks of short- and long-term treatment-related adverse effects associated with chemoimmunotherapy, including neuropathy, immunosuppression, and stem-cell damage, as well as secondary myelodysplasia and malignancies, the use of ibrutinib can be considered for treatment-naïve patients with WM who carry

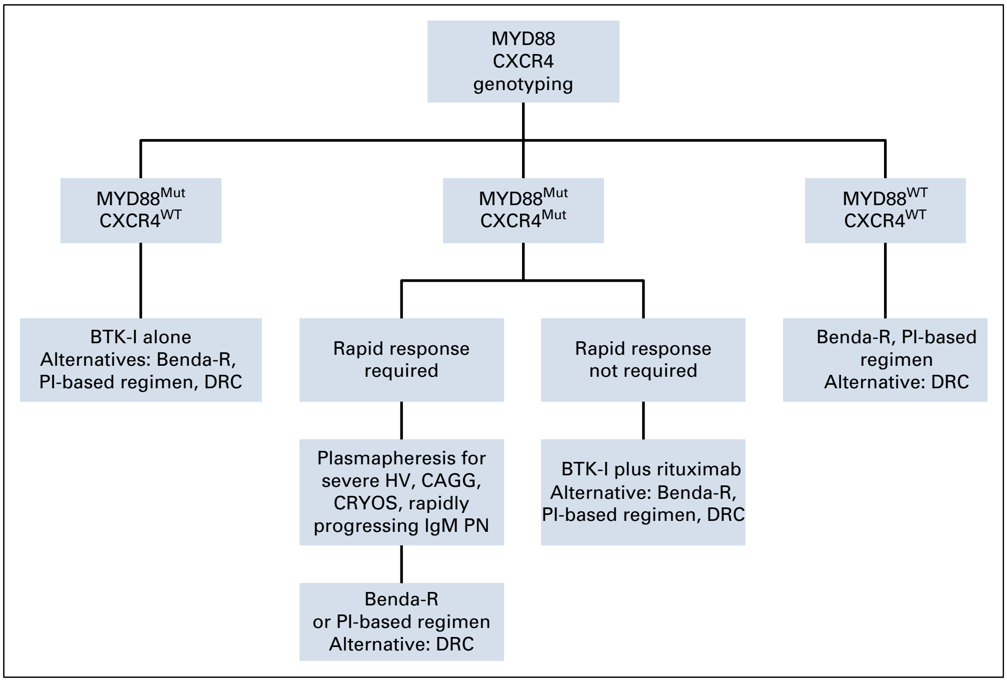

FIG 2. Genomic-based treatment algorithm for symptomatic, treatment-naïve patients with Waldenström macroglobulinemia. Rituximab should be held for serum immunoglobulin M (IgM) ≥ 4,000 mg/dL to prevent symptomatic IgM flare. Bendamustine and rituximab (Benda-R) should be considered as primary choice in patients with bulky adenopathy or extramedullary disease. Proteasome inhibitor (PI)–based regimens should be considered in patients with symptomatic amyloidosis, with autologous stem-cell transplantation as possible consolidation. Rituximab alone or with ibrutinib if *MYD88* is mutated or bendamustine may be considered in patients with IgM peripheral neuropathy (PN) depending on severity and pace of progression. Cyclophosphamide-based therapy such as dexamethasone, cyclophosphamide, and rituximab (DRC) represents an alternative to Benda-R but may be less effective. Maintenance rituximab may be considered in patients responding to rituximab-based regimens. BTK-I, Bruton tyrosine kinase inhibitor; CAGG, cold agglutinemia; CRYOS, cryoglobulinemia; HV, hyperviscosity; Mut, mutated; WT, wild type (not mutated).

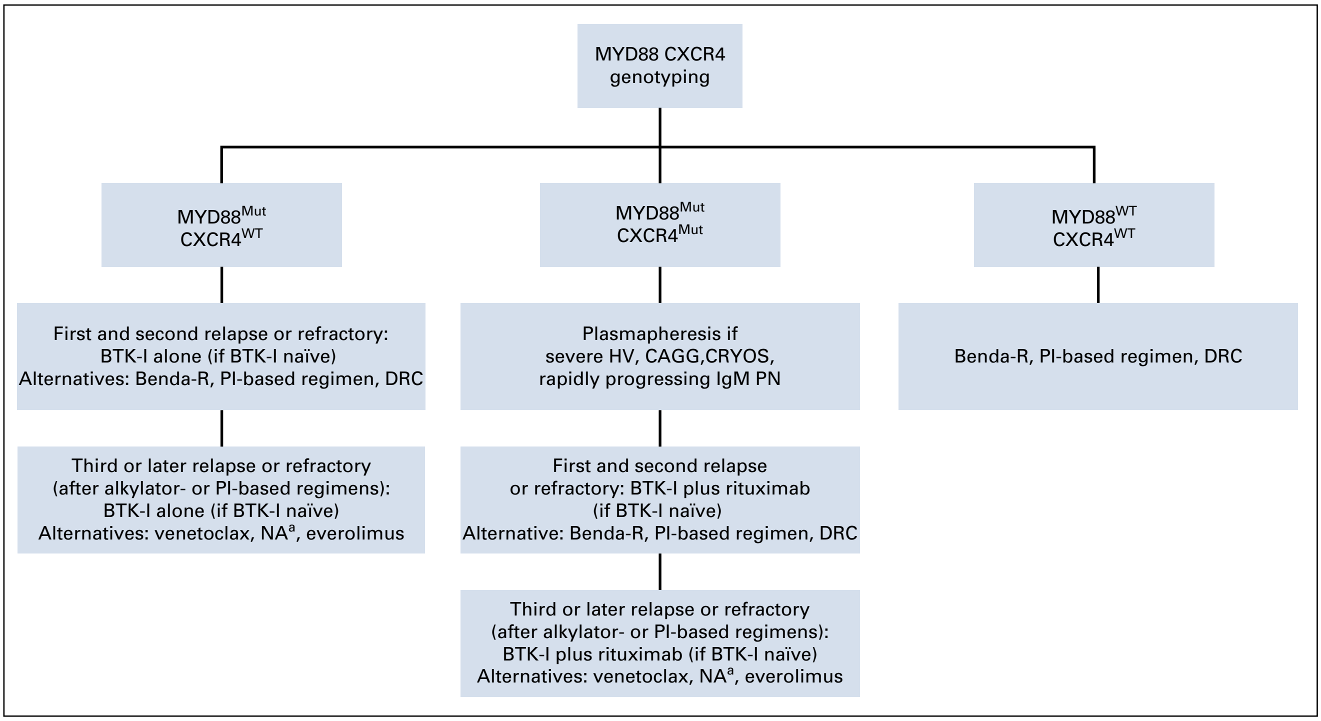

FIG 3. Genomic-based treatment algorithm for symptomatic, previously treated or refractory patients with Waldenström macroglobulinemia. Rituximab should be held for serum immunoglobulin M (IgM) ≥ 4,000 mg/dL to prevent symptomatic IgM flare. Bendamustine and rituximab (Benda-R) should be considered as primary choice in patients with bulky adenopathy or extramedullary disease. Proteasome inhibitor (PI)–based regimens should be considered in patients with symptomatic amyloidosis, with autologous stem-cell transplantation (ASCT) as possible consolidation. Rituximab alone or with ibrutinib if *MYD88* is mutated or bendamustine may be considered in patients with IgM peripheral neuropathy (PN) depending on severity and pace of progression. Rituximab combined with cyclophosphamide and dexamethasone (DRC) represents an alternative to Benda-R, although it may be a potentially less effective option. Maintenance rituximab may be considered in patients responding to rituximab-based regimen. ([a]) Nucleoside analogues (NA) should be avoided in younger patients and candidates for ASCT. ASCT may be considered in patients with multiple relapses and chemotherapy-sensitive disease. BTK-I, Bruton tyrosine kinase inhibitor; CAGG, cold agglutinemia; CRYOS, cryoglobulinemia; HV, hyperviscosity; Mut, mutated; WT, wild-type (not mutated).

only the *MYD88* mutation. Current nonrandomized comparisons of data from ibrutinib monotherapy and combined ibrutinib and rituximab studies show little difference in patients only have *MYD88* mutation; hence, ibrutinib alone can be considered for patients without bulky disease and symptomatic amyloidosis and for whom no contraindication to ibrutinib exists.[53-56]

Alternatives to ibrutinib that can be considered include bendamustine and rituximab (Benda-R) or PI-based therapy such as bortezomib, dexamethasone, and rituximab (BDR); carfilzomib, rituximab, and dexamethasone (CaRD); or ixazomib, dexamethasone, and rituximab (IDR). Randomized and nonrandomized studies suggest that cyclophosphamide-based therapy, although active in WM, may not be as effective as Benda-R or PI-based therapy.[65,70-72]

Because the role of ibrutinib is not well established in patients with WM with bulky disease and has been lackluster in symptomatic patients with light chain (LC) amyloidosis, alternatives should be sought for these patients.[33,73] Benda-R is a reasonable choice for those with bulky disease, ideally limited to 4 cycles to minimize prolonged cytopenias and long-term adverse events.[64,65,71] Dexamethasone, rituximab, and cyclophosphamide remains an alternative if Benda-R is not available.[72] A PI-based treatment such as weekly BDR to minimize treatment-related neuropathy or use of neuropathy-sparing PI regimens such as CaRD or IDR may be considered for those with symptomatic LC amyloidosis.[60,61,68,69,74] In these patients, consolidation with autologous stem-cell transplantation (SCT) may be considered.[75] Finally, patients with WM with IgM demyelinating neuropathy require deep and sustained responses to minimize myelin-directed monoclonal IgM deposition. For such patients, rituximab alone can be considered if the neuropathy is mild, but for more moderate to severe cases or patients with more rapid progression, the use of ibrutinib alone or with rituximab, Benda-R, or a regimen using a neuropathy-sparing PI such as CaRD or IDR may be considered.[33,60,61,68,69,76]

For patients with both *MYD88* and *CXCR4* mutations, the necessity to achieve a rapid response must be considered. Nonsense *CXCR4*-mutated patients in particular are at risk for presenting with symptomatic hyperviscosity requiring immediate disease control.[41] Rituximab should be avoided in patients with WM with high IgM levels or symptomatic hyperviscosity until such time as the IgM has decreased to

< 4,000 mg/dL to avoid a symptomatic rituximab flare.[68,69] For patients requiring more emergent responses, either bendamustine or a PI-based regimen may be considered. For patients without symptomatic hyperviscosity and emergent need for disease control, ibrutinib plus rituximab may be preferred versus ibrutinib alone because the median time to achieve a major response appears to be shorter with the combination (3 *v* 6-7 months, respectively).[53,54,56]

For patients presenting with wild-type *MYD88* WM determined by AS-PCR, Sanger sequencing or NGS that examines the TIR exon coding region of the *MYD88* gene should be done to exclude non-L265P *MYD88* mutations because patients with non-L265P *MYD88* mutations show responses to ibrutinib.[12] For patients with true *MYD88* wild-type WM, either bendamustine or PI-based therapy with rituximab can be considered because responses have been observed with these regimens in patients with both *MYD88* wild-type and mutated WM.[60,64,65] In all patients with WM showing a response to a fixed-duration rituximab-containing regimen, maintenance rituximab may be considered.[68,69] In patients who develop rituximab intolerance, ofatumumab may represent an option.[77,78] There are no data at this time on the use of obinotuzumab in WM.

In previously treated patients with WM (Fig 3), the reuse of a front-line regimen may be considered for patients with long responses (> 2-3 years), although alternatives to alkylators or nucleoside analogs should be considered if previously used to minimize stem-cell damage. Nucleoside analogs should also be avoided in younger patients who may be candidates for autologous SCT and to minimize risk of disease transformation.[69] The use of ibrutinib can be considered in symptomatic, previously treated patients with mutated *MYD88* WM following the algorithm described earlier for symptomatic treatment-naïve patients with WM (Fig 2). For patients who have been exposed to ibrutinib, either Benda-R or a PI-based regimen may be considered. Alternatively, off-label use of acalabrutinib may be considered for patients not tolerating ibrutinib given findings in patients with chronic lymphocytic leukemia showing a successful switchover from ibrutinib for intolerant patients.[79] The findings of a prospective randomized trial of zanubrutinib versus ibrutinib (ClinicalTrials.gov identifier NCT03053440) may also provide important guidance on the use of zanubrutinib in patients not tolerating ibrutinib.

For patients who have experienced multiple relapses and have been previously exposed to alkylators, PIs, and ibrutinib, the off-label use of venetoclax may be considered. High overall response rates and durable responses were observed in patients with WM on venetoclax, including those who were *CXCR4* mutated and previously exposed to a BTK inhibitor, although response depth was affected by these factors.[59,80] Everolimus, alone or in combination with bortezomib and rituximab, can also be considered in patients previously exposed to alkylators, PIs, and ibrutinib, although hematologic toxicities and autoimmune pneumonitis are noteworthy.[63,81,82] Diminished activity in patients with wild-type *MYD88* or mutated *CXCR4* has also been reported with everolimus and should be considered in context with other available treatments.[63] The use of cyclophosphamide, bortezomib, and dexamethasone, alone or with rituximab, is also an active regimen in previously treated patients with WM.[82]

The use of autologous SCT can be considered in patients with multiple relapses and who remain chemotherapy sensitive.[69,83] As mentioned earlier, autologous SCT may also be considered as a consolidative measure in patients with symptomatic amyloidosis.[75] Data on the efficacy and safety of allogenic SCT or cellular therapies are limited and should ideally be considered in the context of a clinical trial. Finally, both treatment-naïve and previously treated patients should actively be considered for clinical trials. A listing of clinical trials for WM can be found at ClinicalTrials.gov.

MOLECULAR DIAGNOSTIC APPROACHES AND LIMITATIONS

In patients with suspected WM, the use of AS-PCR on BM aspirates represents the most optimal initial assay for detection of *MYD88* L265P mutations. If the patient is determined to have wild-type *MYD88* by AS-PCR, Sanger sequencing or targeted NGS that examines the TIR exon coding region of *MYD88* can be performed to evaluate for non-L265P *MYD88* mutations.[10] Targeted NGS can also be used to identify *MYD88* L265P mutations, although false-negative results were observed in 30% of patients in one study when compared with AS-PCR, particularly in patients with low BM disease involvement.[84] The use of CD19-selected cells can improve chances of detection of mutated *MYD88*, although tumor selection is not routinely performed in clinical laboratories. CD19-selected PB mononuclear cells may also be used for AS-PCR testing of mutated *MYD88*, although diagnostic yield is greatly reduced with prior therapy, particularly rituximab, and use of unselected PB mononuclear cells.[15]

Targeted NGS or Sanger sequencing represents the best approach for evaluation of C-terminal mutations in *CXCR4* because > 40 nonsense and frameshift variants have been reported in WM.[8,13,39,42] Because *CXCR4* mutations are subclonal with a median clonal distribution of 35%, false-negative results can occur in patients with low BM disease burden and with use of unselected mononuclear cells for *CXCR4* mutation testing.[39] Ultra-deep NGS (> 1,000×) may improve detection of *CXCR4* mutations over Sanger sequencing in patients with low tumor burden and clonality.[85] However, although large insertions or deletions in CXCR4 are uncommon in WM, these may be missed with NGS but identified by Sanger sequencing.

SUMMARY

In summary, NGS has revealed recurring somatic mutations in WM that include *MYD88* and *CXCR4.* The genomic findings have contributed to ongoing targeted drug development and the recognition of a precision-guided treatment approach to WM. *MYD88* and *CXCR4* mutation status can be used to guide treatment decisions in WM.

AFFILIATIONS

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA
[2]Department of Medicine, Harvard Medical School, Boston, MA
[3]Center for Prevention of Progression of Blood Cancers, Dana-Farber Cancer Institute, Boston, MA
[4]Clinical Research Development and Phase I Unit, CREA Laboratory, Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia, Brescia, Italy
[5]Division of Hematology and Oncology, Massachusetts General Hospital, Boston, MA

CORRESPONDING AUTHOR

Steven P. Treon, MD, PhD, Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, M547, 450 Brookline Ave, Boston, MA 02215; e-mail: steven_treon@dfci.harvard.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Steven P. Treon, Mark Bustoros, Antonio Sacco, Aldo Roccaro, Irene M. Ghobrial
Administrative support: Christopher J. Patterson
Collection and assembly of data: Steven P. Treon, Lian Xu, Xia Liu, Maria Demos, Joshua Gustine, Manit Munshi, Nicholas Tsakmaklis, Jiaji G. Chen, Amanda Kofides, Andrew Keezer, Kirsten Meid, Christopher J. Patterson, Guang Yang, Irene M. Ghobrial
Data analysis and interpretation: Steven P. Treon, Maria Luisa Guerrera, Cristina Jimenez, Zachary R. Hunter, Gloria Chan, Romanos Sklavenitis-Pistofidis, Andrew R. Branagan, Irene M. Ghobrial, Jorge J. Castillo
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Genomic Landscape of Waldenström Macroglobulinemia and Its Impact on Treatment Strategies

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Steven P. Treon
Consulting or Advisory Role: Janssen, Pharmacyclics, BeiGene
Research Funding: Janssen, Pharmacyclics, Bristol-Myers Squibb
Travel, Accommodations, Expenses: Janssen Oncology
Other Relationship: Janssen, Pharmacyclics

Zachary R. Hunter
Honoraria: Janssen

Mark Bustoros
Honoraria: Takeda, DAVAOncology
Consulting or Advisory Role: Takeda

Antonio Sacco
Consulting or Advisory Role: Celgene (I), Janssen-Cilag (I)
Research Funding: AstraZeneca (I)
Patents, Royalties, Other Intellectual Property: Pending patent: Treatment of C1013G/CXCR4-Associated Waldenström's Macroglobulinemia With an Anti-CXCR4 Antibody; application No.: 16/271569-BMS Ref. 12242-US-PCD
Travel, Accommodations, Expenses: Janssen-Cilag (I)

Aldo Roccaro
Consulting or Advisory Role: Celgene, Janssen-Cilag
Research Funding: AstraZeneca
Patents, Royalties, Other Intellectual Property: Pending patent: Treatment of C1013G/CXCR4-Associated Waldenström's Macroglobulinemia With an Anti-CXCR4 Antibody; application No.: 16/271569-BMS Ref. 12242-US-PCD
Travel, Accommodations, Expenses: Janssen-Cilag

Andrew R. Branagan
Consulting or Advisory Role: Surface Oncology, Pharmacyclics/Janssen

Guang Yang
Employment: AbbVie (I)
Honoraria: Janssen

Irene M. Ghobrial
Honoraria: Celgene, Bristol-Myers Squibb, Takeda, Amgen, Janssen, Karyopharm Therapeutics, Cellectar, Adaptive Biotechnologies, Sanofi, Medscape
Consulting or Advisory Role: Bristol-Myers Squibb, Novartis, Amgen, Takeda, Noxxon Pharma, Celgene, Sanofi, Genentech, GlaxoSmithKline, GNS Healthcare, Karyopharm Therapeutics, Adaptive Biotechnologies, Janssen, Medscape, AbbVie
Travel, Accommodations, Expenses: Bristol-Myers Squibb, Novartis, Onyx, Millennium, Celgene, Takeda, Janssen Oncology

Jorge J. Castillo
Consulting or Advisory Role: Pharmacyclics, Janssen, Vical, Genentech
Research Funding: Pharmacyclics (Inst), AbbVie (Inst), Janssen (Inst), BeiGene (Inst), TG Therapeutics (Inst)

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