Blood Reviews xxx (xxxx) xxx

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Current approach to Waldenström macroglobulinemia

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ARTICLE INFO

Keywords:
Lymphoplasmacytic lymphoma
IgM monoclonal gammopathy
MYD88
CXCR4
BTK inhibitor
Chemoimmunotherapy

ABSTRACT

Waldenström macroglobulinemia (WM) is a unique CD20+, B-cell non-Hodgkin lymphoma, characterized by lymphoplasmacytic infiltration of the bone marrow and circulating monoclonal immunoglobulin M. The clinical manifestations and outcomes of patients are highly variable. High-level evidence supports integration of monoclonal anti-CD20 antibody, rituximab, to the chemotherapy backbone to treat WM. However, its contemporary management has become more nuanced, with deeper understanding of the pathophysiology and incorporation of Bruton's tyrosine kinase (BTK) inhibitors to the treatment paradigm. Prior knowledge of the patients' *MYD88*^{L265P} and *CXCR4* mutation status may aid in the treatment decision-making. Currently, the two frequently utilized approaches include fixed-duration chemoimmunotherapy and BTK inhibitor-based continuous treatment until progression. Randomized trials comparing these two vastly divergent approaches are lacking. Recent studies demonstrating efficacy of B cell lymphoma-2 (BCL2) inhibitors and non-covalent BTK inhibitors in patients, previously exposed to a covalent BTK inhibitor, are a testament to the rapidly expanding options against WM.

1. Introduction

Waldenström macroglobulinemia (WM) is a low-grade B-cell lymphoplasmacytic lymphoma (LPL) of immunoglobulin M (IgM) subtype [1,2]. In 1944, Jan Waldenström reported on 3 patients, including two who had presented with hypergammaglobulinemia due to a large homogeneous, γ globulin with a molecular weight of approximately 1 million, normochromic anemia, thrombocytopenia, hypofibrinogenemia, hyperviscosity manifesting as oronasal bleeding, lymphadenopathy and marrow lymphocytosis, without any evidence of multiple myeloma [3]. This condition was subsequently referred to as WM. Eight years earlier, the initial accounts of the two women with rapid neurodegeneration by Jens Bing and Axel V. Neel, in the setting of hypergammaglobulinemia and a lymphoproliferative disorder were likely descriptions of a rare complication of WM, which is now recognized as the Bing-Neel Syndrome (BNS) [4]. Considered a clinicopathologic entity, WM is associated with symptoms attributable to the lymphoplasmacytic infiltration of the bone marrow and/or the large circulating monoclonal IgM protein that they generate. Fewer than 5% of LPL cases comprise the non-IgM subtypes, involving monoclonal IgA, IgG, or the nonsecreting type.

In 1988, WM became reportable as an independent hematologic malignancy in the US, and together with other LPLs it accounts for approximately 2% of newly diagnosed non-Hodgkin lymphoma (NHL). In contrast to MM, which is encountered twice as often among blacks, the rates of WM among whites (0.74 per 100,000) are markedly higher than blacks [5,6]. Rarely seen below the age of 30, WM is a markedly age dependent NHL. The reported age-adjusted incidence rate of 0.92 /100,000 person-years among males and 0.30 per 100,000 person-years among females for WM, translates to an estimated 2300 new cases of LPL diagnosed annually in the United States [7]. Older age, male sex, white race, and family history are well-established risk factors, with documented evidence of familial clustering and co-aggregation of certain B-cell malignancies, including other NHL and chronic lymphocytic leukemia (CLL). Besides the family history, environmental factors, including chronic antigenic stimulation, immune dysfunction, history of exposure to certain organic solvents, pesticides and wood dust may modulate familial WM as suggested by family-based analyses using unaffected relatives as controls [5,6,8,9]. A genome-wide approach was instrumental in gaining greater insights to the genetic susceptibility to this heritable malignancy when it identified loci at chromosome 6p25.3 and 14q32.13 as independent predisposition single nucleotide polymorphisms (SNPs) associated with the risk of WM/LPL [10]. Other potentially new loci have also been identified but require validation [11].

Despite a substantial increase in the choice of the LPL directed

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https://doi.org/10.1016/j.blre.2023.101129

Available online 26 August 2023

therapies and deeper insights of the pathophysiology, complete clonal eradication is exceedingly difficult to achieve in WM, and cure remains elusive. However, identification of novel "druggable" targets and improved access to drugs/regimens, with distinct mechanisms of action likely underpin the undeniable progress in the field. The success is aided in part by the indolent disease biology itself, leading to durable remission that allows the patients to benefit from the incremental gains, with sequential use of novel agents –even with modest efficacy–over the years.

2. Diagnosis of Waldenström macroglobulinemia

Clonally related small lymphocytes, plasmacytoid lymphocytes and plasma cells make up the bone marrow infiltrate in WM and secrete the monoclonal immunoglobulin M (IgM) protein, detectable in blood, that serves as a surrogate marker for response assessment. However, the size of IgM does not correlate with the degree of marrow infiltration. Per the Mayo Clinic Criteria, for an IgM secreting lymphoproliferative disorder to be considered WM and differentiated from IgM monoclonal gammopathy of undetermined significance (IgM MGUS), the clonal lymphoplasmacytosis should be at least 10% of the marrow cellularity and other B cell lymphomas with plasmacytic differentiation such as marginal zone lymphoma (MZL) must be ruled out [12]. The International Workshop on Waldenström Macroglobulinemia (IWWM) Consensus Criteria are, however, broader, permitting any degree of bone marrow infiltration by the IgM secreting lymphoplasmacytic infiltrate (even <10% of the marrow cellularity) provided the clonal cells are morphologically detectable [13]. However, we do not recommend considering patients with <10% bone marrow involvement as WM; instead we consider such patients as having IgM MGUS. With current diagnostic methods, clonal cells can be detected in the marrow in almost all patients with IgM MGUS, and considering them as having WM would incorrectly label people who have a benign disorder as having a malignancy. Studies from Italy show that patients defined as IgM MGUS by Mayo Clinic Criteria have an overall survival similar or even better than the general population [14]. Even in patients, with 10% or more clonal involvement, it is important to separate patients without evidence of end-organ damage (smoldering WM) who do not need therapy from those with symptomatic disease [15,16]. To establish the diagnosis of active or symptomatic WM, both the Mayo Clinic and the Consensus Criteria require evidence of end-organ damage that is unequivocally attributable to the LPL and variably manifests as cytopenias, constitutional symptoms, hyperviscosity, symptomatic lymphadenopathy, or hepatosplenomegaly, irrespective of the size of the circulating IgM monoclonal protein.

3. Genomics of Waldenström macroglobulinemia

3.1. Mutational landscape

In 2012, whole-genome sequencing (WGS) studies on paired tumor and normal tissue samples identified a highly recurrent somatic mutation in the myeloid differentiation primary response gene (*MYD88*) in WM cells but not in the normal tissue [17]. This finding was subsequently confirmed with Sanger sequencing and the highly sensitive allele-specific polymerase chain reaction (AS-PCR) assays by several groups [18]. Clonal *MYD88* mutations are nearly ubiquitous in WM, but not pathognomonic, and present in over 90% of the patients [19,20]. They are also common in lymphomas of immune privileged sites, but absent in IgM MM, with a rare occurrence in MZL with plasmacytic differentiation or CLL. Therefore, the presence of this somatic mutation, i.e., a positive test, in most cases, helps distinguish between WM and other B-LPDs with overlapping features. The major hot-spot mutation causes T to C transversion at position 38,182,641 in chromosome 3p22.2 [19]. This leads to leucine to proline single amino acid substitution, with resultant gain of function of the MYD88 adaptor protein that has a prominent role in the toll-like receptor signaling pathway. The mutated MYD88 serves as a scaffold for assembly of a multi-subunit signaling complex, leading to the downstream activation of several transcription factors, including nuclear factor-ab (NF-κB) signaling, that stimulate WM cell proliferation and survival (Fig. 1) [21]. The *MYD88* locus is altered in 50–80% of patients with IgM MGUS and represents an early oncogenic event that leads to the acquisition of a gain-of-function [19]. Non-L265P *MYD88* point mutations (M232T, V217F, R209C and S243N) are detectable in additional ~3%–5% of WM patients. However, the detection of the $MYD88^{mut}$ in phenotypically normal B-cells in a recent study suggests that this alteration may not by itself be the driver of oncogenesis [22].

Somatic subclonal mutations involving the regulatory cytosolic C-terminal domain (stretching from amino acid position 308 to 352) of C-X-C chemokine receptor type 4, CXCR4 (CD184), a G protein coupled receptor, are encountered in up to 40% of patients with WM [23]. These alterations, when present, almost always occur in patients that have an underlying *MYD88* mutation and resemble the germline mutations encountered in WHIM (warts, hypogammaglobulinemia, infection, and myelokathexis) syndrome. Therefore, these mutations are called $CXCR4^{WHIM}$ mutations [19,24]. The mutated *CXCR4*, while fully competent, leads to the loss of regulatory serines, with impaired CXCR4 desensitization and internalization, resulting in chemokine ligand, CXCL12, mediated persistent downstream signaling (involving enhanced phosphatidylinositol 3-kinase/AKT and mitogen-activated protein kinase/extracellular regulated kinase–1/2) that contributes to WM cell proliferation, survival, and dissemination [25] (Fig. 1). *CXCR4* mutations, almost unique to WM, with rare occurrence in MZL, confer a more aggressive clinical course, higher marrow burden, symptomatic hyperviscosity and resistance to a variety of therapies [19,24]. The presence of *CXCR4* mutation is also associated with a shorter time to active WM in patients with smoldering WM [26]. Both nonsense (NS) and frameshift (FS) variants exist, and the differential clinical impact of such alterations remains to be fully delineated [25,27]. The most frequently mutated region is S338X resulting in a premature stop codon [28]. Specifically, the presence of $CXCR4^{NS}$ mutations is associated with a lower response rate and shorter progression-free survival (PFS) with the use of Bruton tyrosine kinase (BTK) inhibitors [19,25,29,30].

Other somatic mutations that are frequently encountered include alteration in the *ARID1A* gene (modulates gene regulation, including *TP53)* that are identified in up to 17% of patients and the mutations in *CD79A* and *CD79B* (components of the B cell receptor pathway) found in 8–12% of patients [26,31–33]. These activating mutations trigger *SYK, BTK* and *PLCγ2* and are more frequently observed in $CXCR4^{WT}$ cells. Deletions involving *LYN* are noted in up to 70% of patients, and lead to the loss of regulatory kinase manifesting as hyperresponsive BCR signaling [34,35].

A recent biomarker study of the ASPEN trial presented at the IWWM-11 revealed a substantially higher rate of *TP53* alterations (12–22%) among patients with RR WM in comparison to 3–7% observed in the previously untreated setting. An additional novel finding was the presence of *TERT* (9%) mutations. Both these aberrations were associated with less favorable outcomes on BTK inhibitor therapy, exemplified by a trend toward reduced rates of deep response, translating into a shorter progression-free survival (PFS) in patients with *TP53* or *TERT* mutations compared to the sub-cohorts with the respective wild-type alleles (HR = 2.15, and 1.79, respectively) [11]. However, these results require validation in other studies.

Patients with $MYD88^{WT}$ WM harbor distinct NFKB-activating somatic mutations that are downstream of BTK as well as mutations causing epigenomic dysregulation or DNA damage repair impairment [36].

3.2. Cytogenetic abnormalities

WM is a genetically heterogeneous malignancy, with a median of 2 to

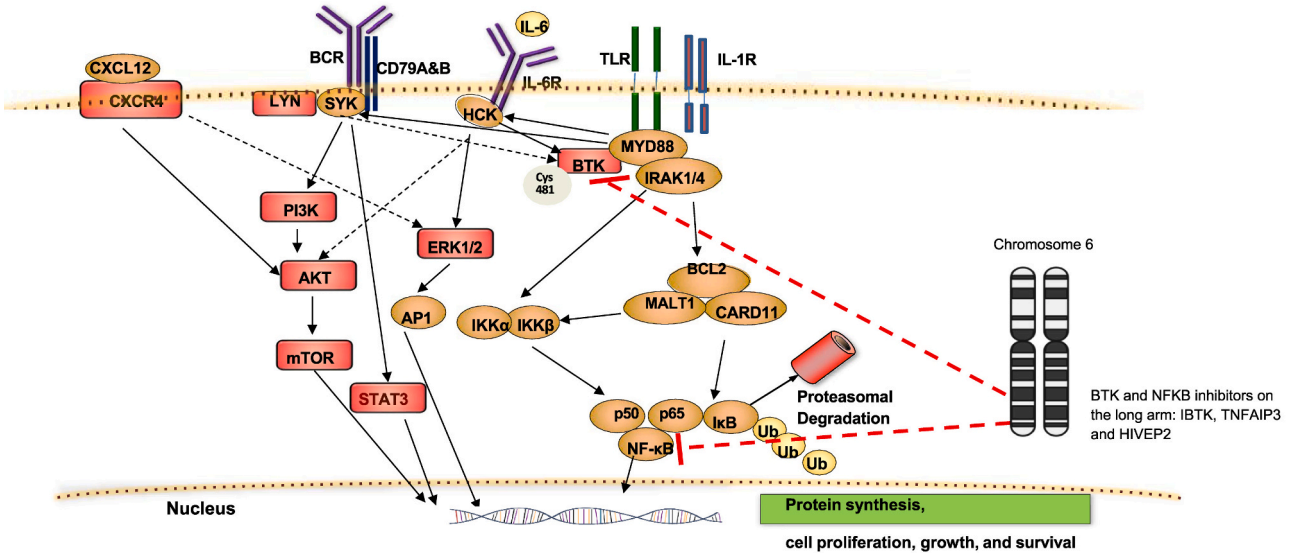


Fig. 1. Genomics of Waldenström Macroglobulinemia.
MYD88, an adapter protein downstream of Toll-Like Receptor (TLR), is critical for TLR signaling. TLRs recognize highly conserved motifs, DNA, RNA, and polysaccharides that are shared by pathogens. MYD88 is essential for induction of the downstream NFKB and MAP kinase activity. The N terminus of the MYD88 protein has a death domain (DD) that allows MYD88 oligomerization and interaction with IRAK4-IRAK1, forming Myddosome, a multimeric complex. Mutated MYD88 transactivates the SRC family member, HCK, cross talks with LYN-activated SYK, and spontaneously triggers the Myddosome assembly, with activated BTK and IRAK4 and IRAK1, which in turn activate NFKB. B-cell receptor (BCR) Is a transmembrane receptor, with a crucial role in B-cell development from early precursor to plasma cell differentiation. It also recognizes a variety of antigens, with a critical role in the adaptive immune response. The BCR signaling is mediated by coupling its immunoglobulin component with the heterodimerized signal transduction unit consisting of CD79A and CD79BBTK, a member of the TEC family plays a central role in the proximal BCR signal transduction pathway, and its absence can block maturation of cells at the pre-B cell stage. Loss of critical regulators of MYD88 signaling, IBTK and the NFKB regulators, TNFAIP3 and HIVEP2 occurs with the deletion of the long arm of chromosome 6.

3 chromosomal abnormalities observed per patient [37].Deletions in the long arm of chromosome 6 (del 6q21–25) are the most frequently detected abnormalities, observed in 30–50% of patients with WM, occurring primarily among patients that lack *CXCR4* mutations, and resulting in the loss of genes that modulate apoptosis, plasma cell differentiation and NFKB activity [38]. (Fig. 1) The prognostic impact of del6q is not definitively established. In a retrospective study ($N = 225$ including 27 with IgM MGUS) it was associated with other adverse prognostic features, including higher International Prognostic Scoring System for WM (IPSSWM) score [39]. Patients with smoldering WM ($n = 105$) in the setting of del6q show a shorter time to progression (TTP) to active WM (median TTP 30 months vs. 199 months in patients without del6q, $P < 0{\cdot}001$) and among those with active WM ($n = 93$) shorter PFS was evident (median 20 vs. 47 months, $P < 0{\cdot}001$), translating into a shorter overall survival (OS) (median 90 versus 131 months in non-del 6q patients ($P = 0{\cdot}01$) [39]. However, other studies have demonstrated no such unfavorable impact on OS [40,41]. Gain of 6p is the second most frequent chromosomal abnormality (17%) and is always in conjunction with 6q loss [42]. Trisomies involving chromosomes 4, 8, 12, and deletions of 13q and 17p have been observed, but balanced translocations are notably absent [41]. A linkage analysis conducted in WM families was the first genome-wide attempt, using a dense array of microsatellite markers, to identify regions harboring susceptibility genes showed linkage to 4 chromosomal regions (1q, 3p, 4q and 6q) [5,43]. Single nucleotide polymorphisms (SNPs) in 6 genes, *BCL6, IL6, IL10, IL8Ra, WRN, and TNFSF10* are associated with WM [44].

4. Asymptomatic precursor conditions

4.1. IgM monoclonal gammopathy of undetermined significance

The World Health Organization (WHO), Mayo Clinic, and the International Myeloma Working Group (IMWG) define IgM MGUS based on 3 criteria, all of which must be met for accurate diagnosis: i) The presence of circulating IgM monoclonal protein at a concentration < 3 g/dL. ii) Clonal lymphoplasmacytosis or plasmacytosis comprising $<10\%$ of the bone marrow cellularity, and iii) the absence of end-organ damage, manifesting as cytopenias, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly attributable to the lymphoplasmacytic cell or plasma cell proliferative process.

The risk of developing WM exceeds 260-fold among patients with IgM MGUS [45]. The International Consensus Classification of Mature Lymphoid Neoplasms has recently recognized IgM MGUS as two distinct entities: IgM MGUS, not otherwise specified (NOS) which is a precursor condition to WM, and the less-frequently encountered, IgM MGUS of plasma cell (PC) type that predisposes to IgM MM and not WM [46].IgM MGUS-NOS is characterized by the presence of monotypic or clonal B cells, without an abnormal lymphoplasmacytic infiltrate, with or without mutated *MYD88*, in the absence of other small B-cell malignancies. By contrast, the presence of clonal plasma cells alone, t(11;14) or other myeloma associated chromosomal abnormalities would support the diagnosis of IgM MGUS-PC type [46]. IgM MGUS-PC type lacks clonal B cells and exhibit $MYD88^{WT}$ signature [46]. AL amyloidosis may result from either entity.

Data from the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) population-based study that utilized 75,422 screened samples demonstrated MGUS in 3358 individuals, with IgM MGUS noted in 721 (21%) patients with MGUS. Unlike IgA MGUS [$n = 400$ (12%)], both IgM MGUS and IgG subtype [$n = 1923$ (57%)] showed increasing prevalence with age [47].

In a Mayo Clinic Study, involving 1384 patients with MGUS, 210 (15%) patients accounted for IgM MGUS. With an extended median follow up of 29 years, the relative risk of progression to WM, or a related disorder among patients with IgM MGUS was 10.8 (95%CI: 7.5–15). The overall rate of progression was 1.8 (95% CI 1.3–2.5%) per 100 person-years, and unlike non-IgM MGUS which was associated with a uniform rate of progression, the risk in patients with IgM MGUS varied with time: 2% per year in the first 10 years from the time of diagnosis, and 1.3% per year, subsequently [48].

The presence of two adverse risk factors at diagnosis: an abnormal serum free light chain (FLC) ratio and large serum M protein size (≥1.5 g per deciliter) increases the 20-year risk of progression to 55% (versus 41% among patients with one adverse risk factor and 19% among patients without any risk factor [48]. In the absence of any potential IgM-related symptom, a BM biopsy is not generally recommended in asymptomatic patients with IgM monoclonal protein <1.5 g/dL and normal FLC ratio [48].

Molecular somatic mutations, including the clonal *MYD88* mutations (in 50–80% of patients) [49,50] as well as the subclonal *CXCR4* mutations (in up to 20%) have been detected even at the precursor MGUS stage [51]. In an Italian study, the presence of *MYD88*^{L265P}mutation in IgM MGUS (IWWM-2 Consensus criteria defined) was associated with a greater risk of Bence Jones proteinuria, increased serum IgM size, concomitant immunoparesis, as well as clonal evolution [52]. A subsequent study specifically measured the impact of *MYD88*^{L265P} mutation, detected in 54% of 176 patients with IgM MGUS [53]. In a bivariate analysis, both the serum M protein at high concentration, using 1 g/dL as an arbitrary cut off and the presence of *MYD88*^{L265P} were independently associated with the progression of IgM MGUS. After a median follow up of 84 months, the cumulative incidence of progression for the patients with both the adverse features (24% of patients) was 12% and 38% at 5 and 10 years, respectively [53]. Notably, a low number of events and sparsity of data regarding additional risk factors for progression that were significant on a univariate analysis, including an abnormal serum free light chain ratio, elevated lactate dehydrogenase and detectable Bence Jones proteinuria precluded a multivariate analysis. As such, *MYD88*^{L265P}mutation could not be established unequivocally as an independent risk factor for progression to WM and the incremental benefit of using MYD88^{L265P} status as a prognostic marker remains unknown [52]. Further reducing the clarity is the recent observation of *MYD88*^{WT}genotype (rather than mutant MYD88) as an independent risk factor for progression to overt WM in patients with smoldering (asymptomatic) WM [54].

Paiva et al. have unequivocally established that patients with IgM MGUS exhibit clonal lymphoplasmacytic cells bearing a molecular and phenotypic signature that is largely indistinguishable from that of the patients with smoldering and active WM [55]. The accumulation of light-chain-isotype positive B-cells and acquisition of specific copy number abnormalities appears to be a multistep evolutionary process to malignancy [56].

4.2. Smoldering Waldenström macroglobulinemia

The term, 'smoldering WM' is defined by the presence of an IgM monoclonal protein of ≥3 g/dL and/or clonal ≥10% lymphoplasmacytic bone marrow infiltrate, in the absence of end-organ damage or symptoms e.g., constitutional symptoms, symptomatic anemia, hyperviscosity, lymphadenopathy, or hepatosplenomegaly, directly attributable to the plasma cell proliferative disorder [57] [16].Currently, the subset of patients with smoldering/asymptomatic disease should be actively surveilled since WM remains incurable, treatment related toxicities are not trivial and no benefits of early intervention have been identified. A substantial proportion of patients with smoldering WM will not progress to active WM requiring treatment. In the SWOG, S9003 study, 59 previously untreated asymptomatic patients and without high WM burden [defined as lymphadenopathy (>2 cm), palpable splenomegaly, hepatomegaly, or extensive bone marrow infiltration (> 50%)] were actively observed off therapy [58,59]. Ultimately, at median follow-up of 100 months, treatment was required by only 21% patients. A serum β2-microglobulin (β2M) level below 3 mg/L and a hemoglobin level of at least 12 g/dL at diagnosis predicted a lower likelihood of needing treatment [58,59]. Given the patients' variable risk of progression to active WM, a recent Mayo Clinic study examined a cohort of patients with smoldering WM ($n = 143$), and showed that the cumulative rate of progression was 11%, 38% and 55% at 1, 3 and 5 years, respectively [60]. In this cohort, with a median follow up of 9·5 [8·1–11·5] years, similar to the SWOG study, low hemoglobin (≤12.3 g/dL) and elevated β_2M ≥ 2·7 μg/ml were independent predictors of a shorter time-to-progression (TTP) to active WM, albeit the thresholds for the 2 parameters were slightly different (≤12.3 g/dL for hemoglobin and ≥ 2·7 for β_2 M) from those derived from SWOG S9003 study cohort [60]. A DFCI study identified IgM ≥4500 mg/dL, bone marrow lymphoplasmacytic infiltration ≥70%, β2-M ≥4.0 mg/dL, and albumin ≤3.5 g/dL as independent biomarkers of disease progression [54]. Among the patients who had progressed in this study, the indications for initiation of treatment were anemia with rising IgM levels and constitutional symptoms in 67% of the patients, peripheral neuropathy with increasing IgM levels in 20% of the patients, whereas symptomatic hyperviscosity and organomegaly, were the reasons to commence therapy in 15% and 10% of patients [54].

Interestingly, in the Mayo study, *MYD88*^{WT} cohort (as identified by the AS-PCR, with 1% sensitivity) also demonstrated a trend toward shorter TTP (median 1·7 years) compared to 4·7 years for the cohort with *MYD88*^{L265P} genotype [60]. This finding was strikingly similar to that observed in a cohort of patients ($n = 106$) from Greece and DFCI (median TTP was 4.9 years versus 1.8 years in patients with *MYD88* L265P and *MYD88* WT, respectively; HR 2.7 $P < 0.001$) [54]. However, a Spanish study, using more sensitive droplet digital PCR, refuted these findings, with only 6% patients who were *MYD88*^{WT} progressing to active/ symptomatic WM in contrast to 18% *MYD88*-mutated patients ($p = 0.112$) [61]. However, in this study, asymptomatic patients with ≤10% marrow involvement and the presence of immunophenotypical findings of LPL were categorized as smoldering WM instead of IgM MGUS. The study also suggested that high MYD88 and CXCR4 mutational burden (≥8% and ≥ 2%, respectively) among patients with precursor states (IgM MGUS and smoldering WM) were associated with faster rate of progression to active WM [61].

An Italian study that used the Consensus criteria for diagnosis of WM suggested that asymptomatic patients that harbored a *CXCR4* mutation had a shorter time to treatment/progression to active disease (51 months) than that of patients with wild-type *CXCR4* (median not reached) ($P = 0.007$) [62].

After the initial 5 years from the diagnosis, the rate of progression to active WM declines significantly. Surveillance can be tailored based on the patient risk profile. In previous studies the survival of patients with smoldering WM was similar to that of the age and sex-matched general population and there are no randomized data suggesting that early intervention prolongs OS [60,63]. A study from Mayo Clinic showed that the patients with smoldering WM and IgM >6000 mg/dL at diagnosis may be watched expectantly [64].

5. Diagnostic investigations and staging

If a diagnosis of WM is suspected or established, the history obtained should specifically elaborate on the presence of constitutional symptoms: (fever, chills, drenching night sweats, significant unintentional weight loss), bleeding (nasal, gingival), visual disturbance, headaches, Raynaud like symptoms, acrocyanosis, purpura, vasculitic rash, paresthesias and joint pain. Additionally, data pertaining to the family history of B cell malignancies should be obtained [65]. The physical examination should focus on the eye exam, including fundoscopy, preferably on a dilated eye, the presence of lymphadenopathy, hepatosplenomegaly, vasculitic rash and bruising [2].

At a minimum, molecular studies assessing *MYD88*^{L265P} and *CXCR4*^{S338X} mutations should be performed using AS-PCR on the diagnostic bone marrow specimen or prior to initiating therapy in a treatment-naïve (TN) patient, particularly before commencing a BTK inhibitor-based regimen as primary therapy [2,66]. The IWWM11 Consensus Panel also recommends examining the 6q and 17p chromosomal status on fluorescent in-situ hybridization (FISH) studies and, following CD19+ enrichment, sequencing for *TP53* (particularly in the

RR population in which incidence rate is markedly higher than at diagnosis) and the *CXCR4* gene in patients who do not exhibit $CXCR4^{S338X}$ mutations on AS-PCR [66]. The panel of investigations that should be performed at baseline is outlined in Table 1. The immunophenotypic studies (immunohistochemistry and flowcytometry), performed on the bone marrow biopsy specimen, indicate that both the clonal lymphocytic and plasma cell compartments share the light chain restriction. The lymphocytic component is CD19+, CD5+/−, CD10-, CD20+, $CD22^{low}$, CD23+/−, CD25+, CD38+/−, CD27+/−, CD79a+, Bcl2+ and Bcl6-. The smaller plasmacytic component is CD138+, CD38+, CD45+, CD56-, with diminished expression of CD19, CD20 and PAX5.

Although typically an indolent disease, the patients with WM have highly variable outcomes [67,68]. A collaborative multiinstitutional effort created the International Prognostic Scoring System for WM (IPSS-WM) which stratifies patients requiring treatment into 3 groups, with distinct outcomes, based on 5 parameters, including advanced age (>65 years), platelet count, hemoglobin, beta 2 microglobulin (β2M) and the IgM concentration [69]. In the originally proposed model, the 5-year survival rates were 87%, 68%, and 36%, respectively, for low-risk patients (27%), intermediate-risk patients (38%), and high-risk patients (35%) [69]. More recently, simplified prognostic models including the revised-IPSSWM and the Mayo Clinic model (Modified Staging System for Waldenström Macroglobulinemia) that have incorporated elevated serum lactate dehydrogenase (LDH), a marker of increased cell turnover) and albumin, among other parameters, have been proposed [70,71]. The $MYD88^{L265P}$ or $CXCR4^{WHIM}$ mutation status has either not been incorporated in the more recent models, or not deemed independently prognostic [70,71].

6. Response assessment

The duration of remission in WM is somewhat dictated by the magnitude of the response attained, the genomic signature of the WM cells, as well as the patients' ability to tolerate therapy, particularly the agents that are administered on a continuous basis. Response continues to deepen over time following completion of fixed duration chemo-immunotherapy in a sizeable proportion of patients with WM as well as patients on continuous BTK inhibitor-based therapy, although complete response (CR) is rare with the latter approach [72]. Recently, at IWWM-11, new "simplified" IgM-driven response assessment criteria have been proposed (Table 2) [73]. In addition to the monoclonal IgM disappearance/reduction following treatment if extramedullary disease (EMD) is present at baseline (typically encountered in ≤20% of patients at diagnosis), the standard IWWM-6 response criteria had required complete resolution of the EMD for patients to be considered as having achieved a CR or VGPR [74]. Similarly, previously, a reduction (the extent of reduction unspecified) in the EMD plus a 50–89% decline in the IgM size for patients to achieve PR was required, although the optimal timing of the EMD assessment was not clarified [74]. The IWWM-11 criteria, proposed by Treon et al. —using the ASPEN study data, on the basis of which zanubrutinib was approved— avoid repeated imaging among the patients with EMD at baseline, requiring only the serum IgM size to determine whether a VGPR or a PR is achieved. The definitions of CR and minor response (MR) remain unchanged [73]. The serum mass-fix that we currently use in clinical practice at Mayo Clinic in lieu of the serum immunofixation allows us to differentiate whether the test is positive as a result of using a monoclonal antibody, e.g., rituximab or daratumumab, or due to persistent monoclonal protein due to the residual disease [75].

7. Treatment

Given the paucity of high-level evidence, the approach to managing WM relies on the findings of a few phase 3 trials and predominantly single-arm phase 2 trials or retrospective studies. The therapeutic

Table 1
Diagnostic Investigations.

Test		Comments
Molecular Studies		
$MYD88^{L265P}$ mutation	• Allele-specific quantitative polymerase chain reaction PCR (AS-PCR) • Droplet Digital PCR (ddPCR) • Competitive allele-specific TaqMan PCR (Cast-PCR) • Next-Generation Sequencing (NGS)	• AS-PCR for L265P mutations is a targeted assay at Mayo Clinic with an analytical sensitivity of 1% MYD88 L265P in a wild type background and will not detect any alteration at codon 265 that does not result in the L- > P amino acid change or additional MYD88 alternations, including insertion or deletion events. Tumor burden may affect the assay's sensitivity. • ddPCR has improved sensitivity, precision, and reproducibility over AS-qPCR, especially in IgM MGUS and smoldering WM, overcoming technical issues in diagnostic samples with low tumor burden. • ddPCR may also be useful for MRD monitoring or assessing cell-free tumor DNA. • CD19+ enrichment not necessary unless less sensitive Sanger sequencing is being used for *non*-L265P MYD88 mutations. • Probes covering the entire *MYD88* gene in all NGS-targeted panels designs be used to avoid false negative results when assessing *non*-L265P MYD88 mutations. • The specimen source may be bone marrow or peripheral blood although the latter is less optimal than the marrow specimen, given high rates of false negative results.
CXCR4 mutations	• Sanger sequencing • NGS targeted panels • AS-PCR or ddPCR for $CXCR4^{WHIM\text{-}NS}$ may be used when NGS unavailable because ~90% of $CXCR4^{WHIM}$ NS mutations reside in S338.	• *CXCR4* mutations are frequently subclonal, therefore more sensitive tools needed. • Immunomagnetic approaches or flow cytometry based CD19+ cell enrichment, if available, is recommended to improve the sensitivity. • At Mayo Clinic, *CXCR4* mutation analysis is a reflex test on the marrow samples that exhibit $MYD88^{L265P}$ because these mutations are almost always in association with $MYD88^{L265P}$ and rarely observed in patients with $MYD88^{WT}$ signature. Using the bridged nucleic acids (BNA) clamped Sanger sequencing, an analytical sensitivity of 1% is established for the hotspot mutations c.1013C- > G/A (p.S338X) only. Routine Sanger sequencing, with a 15%–20% sensitivity is used

(*continued on next page*)

Table 1 (*continued*)

	Test	Comments
		to interrogate all other genetic variants in the test region.
TP53	• NGS targeted panels preferred. • Sanger sequencing	• CD19+ enrichment required since TP53 may occur in sub-clonal populations only • In TN WM the rates of *TP53* alterations, including mutations, deletions and copy-neutral LOH are infrequent at 3–7%; in RR WM such alterations occur more frequently at 15–22%.
Cytogenetic Studies		
Del 6q Del 17p	• Fluorescence in situ hybridization (FISH) • WGS/ WES	• CD19+ enrichment required. • Not routinely performed.
Blood Tests		
Mandatory	• Complete blood count with WBC differential count • LDH • Serum albumin • CMP • SPEP and immunofixation/ mass fix 24-h UPEP and IF/ Mass fix • Serum Ig A, G and M • Serum FLCs • Beta 2 microglobulin	• CBC with diff, CMP and monoclonal protein studies are performed in all patients at diagnosis and follow up. • Monoclonal protein studies help in diagnosis and response assessment.
Optional (Based on relevant history)	• Serum viscosity • Cold agglutinin titer • Cryocrit • DAT • Hepatitis C status • Hepatitis B status • vWD screen	
	• 2D echo with strain rate and cardiac biomarkers, troponin and NT-proBNP	• To rule out Immunoglobulin amyloidosis
Bone Marrow Examination		
Trephine Biopsy Aspirate	Multiparametric flow cytometry (MFC)	• FC analysis quantifies clonal cells, but may underestimate the amount of marrow infiltration compared to the BM biopsy WM cells express a single light chain, either kappa or lambda. • Both WM and MZL express pan B markers (CD19, CD20, CD22), but expression (particularly CD22) weaker in WM. SIgM expression higher in WM; marked predominance of K vs L in WM, in MZL, kappa and lambda relation is similar. CD5, CD23, CD103, and CD10 typically are negative in both WM and MZL; CD11c is + in 33% of WM vs 70% of MZL. CD25 expressed in most WM cases, whereas only in approx. 50% MZL; CD305 upregulated in MZL, usually - in WM. • CD52 and CD79b is overexpressed in WM. Increased numbers of mast cells are seen in WM
Radiographic Imaging		
	• CT scans: Chest, Abdomen and pelvis • PET-CT	• For assessment of extramedullary disease burden
		• If histological transformation is suspected
Neurologic Tests Assessment of Neuropathy	• Nerve Conduction study • Electromyography • Anti-MAG antibodies	• For patients with suspected DADS peripheral neuropathy, AL amyloidosis, Type 1 or 2 cryoglobulinemia or POEMS syndrome

approach has continuously evolved over the past 3 decades (Fig. 2).

8. Chemoimmunotherapy

Chemoimmunotherapy continues to retain its relevance in WM given the preponderance of evidence over the past few decades supporting integration of rituximab, a monoclonal anti-CD20 antibody, to the chemotherapy backbone [76]. Compared to rituximab monotherapy, marked improvement in outcomes were observed by combining rituximab with chemotherapy (Table 3). Besides substantial efficacy, chemoimmunotherapy is appealing due to a variety of reasons, including limited duration of treatment, resulting in low rates of cumulative chronic toxicities and greater affordability [76].

8.1. Bendamustine-rituximab

Bendamustine shares the characteristics of an alkylating agent and a purine nucleoside and has a favorable toxicity profile. Bendamustine-rituximab (BR) regimen has been widely used among patients with TNWM following a subset analysis ($n = 41$ patients with WM) of the landmark, StiLNHL1–2003 study, a phase 3 randomized controlled trial conducted in patients with mantle cell lymphoma and indolent lymphomas, including WM, demonstrating significantly longer PFS of BR arm (69.5 months compared to 28.1 months; hazard ratio [HR] 0.33, $p = 0.003$) with R-CHOP [77]. No CRs were observed with either regimen, and the overall response rate (ORR) and OS rates were comparable at last follow up (Table 3) [77].

The BRIGHT trial ($N = 447$) compared BR and R-CHOP/R-CVP in indolent lymphomas and redemonstrated a longer PFS with BR (5-year PFS rate of 65% versus 56%, HR 0.6, $p = 0.002$). However, only a small subset of patients enrolled in this study carried a diagnosis of LPL/WM ($n = 11$) [78,79]. The results of the MAINTAIN trial, a subsequent large study reaffirmed the findings of the previous StiLNHL1–2003 study and were inarguably instrumental in solidifying the role of BR as primary therapy (Table 3) [80].

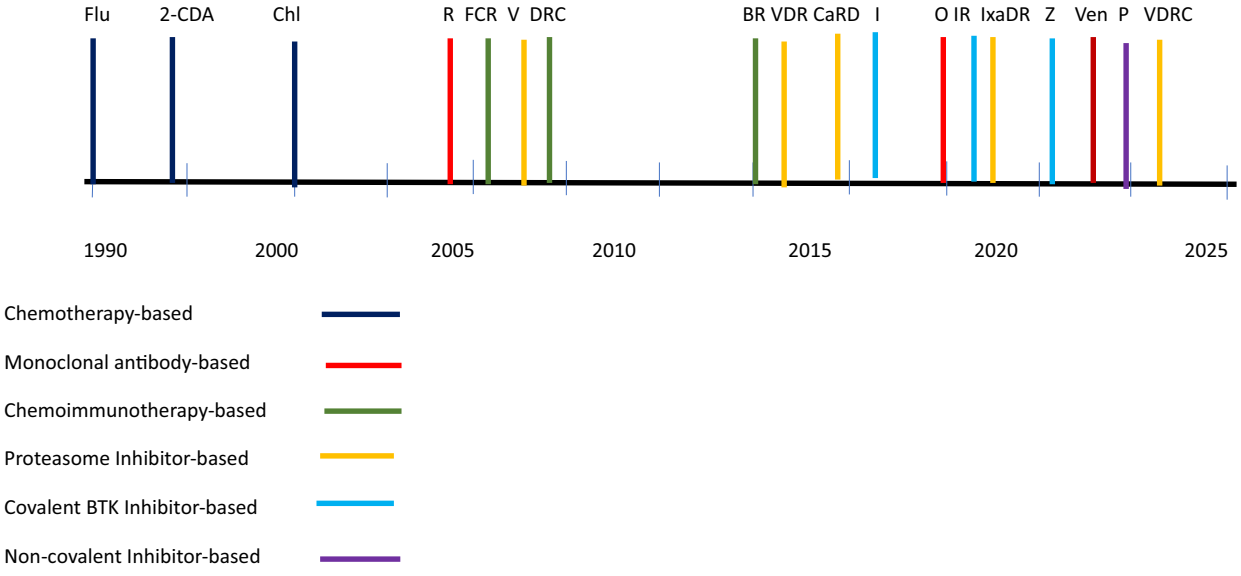
The French Innovative Leukemia Organization (FILO) retrospective study involved 69 patients with TN WM [81]. The CR rates were impressive at 19% and the VGPR rates were 37%. The responses deepened over time, with cumulative ORR improving from 70% at 3 months to 97% at 18 months [81]. The presence of MYD88 did not impact the response rates and survival outcomes. A course of 6 cycles at full dose was completed by 56%, with remaining 44% requiring dose reduction or receiving an abbreviated course of fewer than 6 cycles. At a median follow-up of nearly 2 years, the 2-year PFS rate was 87%, with 2-year OS of 97%. In the updated analysis (median follow up 68.5 months), the median OS was not reached and the median PFS was notably 82 months (range: 75-NR) [81].

Overall, there was no impact of reduced dose or shorter course of BR on the PFS, akin to the findings of a few other retrospective studies suggesting equivalent outcomes with 4 and 6 cycles. However, these findings of comparable efficacy with the lower dose could not be replicated in another study from the UK that clearly demonstrated inferior PFS outcomes with dose reduction (<800 mg/m2 cumulative dose of bendamustine) highlighting the importance of completing the 6

Table 2
New Response Assessment Criteria for Waldenström Macroglobulinemia by IWWM*.

Response category	Serum IgM level change	Extramedullary Disease[a]	Signs or symptoms of active disease	Other criteria
Complete response (CR)	Undetectable by immunofixation/ Mass-Fix and absence of M protein on SPEP. *Re*-confirmation is not required.	Complete resolution[¥c]	None	Normal bone marrow aspirate and biopsy No evidence of LPL
Very good partial response (VGPR)	≥ 90% reduction from baseline or within normal range. Re-confirmation is not required.	Assessment for EMD not required	No new	
Partial response (PR)	≥ 50% to <90% from baseline[b] Re-confirmation is not required.	Assessment for EMD not required	No new	
Minor response (MR)	≥ 25% but <50% from baseline[b] Re-confirmation is not required.	Assessment for EMD not required	No new	
Stable disease (SD)	< 25% reduction to <25% increase from baseline[b] Re-confirmation is not required.		No new	
Progressive disease (PD)	≥ 25%* increase from lowest nadir (requires reconfirmation by 2 sequential measurement)	Progressive, bulky adenopathy/ organomegaly[c] as suggested by any new lesion (>1.5 cm in any axis) or clear evidence of an increase by >50% in any axis to >1.5 cm in size of previously involved EMD from their nadir measurements. Any new lesion consistent with HT	Yes	Cytopenias or hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis attributable to WM
Non evaluable (NE)	Suspected IgM flare or IgM rebound, absence of data or suspected error in data reporting			

Abbreviations:
SPEP, serum protein electrophoresis; WM,Waldenström Macroglobulinemia; HT Histologic Transformation.
[a] Extramedullary disease (e.g, lymphadenopathy and/or splenomegaly) if present at baseline.
[b] Sequential changes in IgM levels may be determined by nephelometry.
[c] By computerized tomography For CR attainment, normalization of EMD if present at baseline will be considered complete resolution or mere decrease in size of lymph nodes (≤1.5 cm) or spleen (≤15 cm), or complete resolution of any other non-lymph node or non-splenic extramedullary mass(es) related to WM disease.
[*] International Workshop for Waldenstrom Macroglobulinemia.



Regimens: Flu Fludarabine; 2CDA Cladrabine; Chl Clhorambucil; R Rituximab; FCR: Fludarabine, Cyclophosphamide, Rituximab; V Bortezomib; DRC Dexamethasone, Cyclophosphamide, Rituximab, BR Bendamustine, Rituximab; VDR Bortezomib, dexamethasone, Rituximab; CaRD Carfilzomib, Rituximab, Dexamethasone; I Ibrutinib; O Ofatumumab; IR Ibrutinib, Rituximab; Ixa-RD Ixazomib Dexamethasone Rituximab; Ven Venetoclax; P Pirtobrutinib; VDRC Bortezomib, Dexamethasone, Cyclophosphamide, Rituximab

Fig. 2. Evolution of Treatment in Waldenström Macroglobulinemia.

Table 3
Efficacy of Frontline Chemoimmunotherapy in Waldenström Macroglobulinemia

Treatment	Phase	# (TN)	ORR (%)	MRR %,	CR%/ VGPR %	PFS (m)*	OS (m)*	General Comments
Dexamethasone/ Rituximab/ Cyclophosphamide (DRC)	2	72	83	74	7	35	95	Six 21-day cycles is moderately effective regimen and well tolerated. May be preferred for frail patients
	2	96	91	82	1/20	73% at 2 years	Not reached at 2 years	Six 28-day cycles with SQ rituximab from C2-C6 shows comparable 2-year PFS to the six 3-week cycles of the original regimen.
Rituximab/ Bendamustine (BR)	3 (subgroup analysis of WM cohort in StiLNHL1–2003)	41	96		0	69.5	unavailable	Markedly higher PFS with BR compared to R-CHOP control arm (median 28 m), with more manageable toxicity
	3 StiL NHL7–2008 MAINTAIN trial	266	93	88	1/24	69	unavailable	Rituximab maintenance post BR among pts. achieving at least a PR did not substantially impact the PFS or OS. An unplanned post hoc analysis showed PFS advantage with R maintenance among patients >65 years of age
Bortezomib/Dex/ Rituximab/ Cyclophosphamide (B-DRC)	2	96	95	85	5/27	81% at 2 years	Not reached at 2y	The quadruplet showed no PFS advantage over DRC, although the time to deeper responses was shorter. The quadruplet also resulted in increased neurotoxicity.
Lenalidomide/ Rituximab/ Cyclophosphamide/ Dex (L-RCD)	2	15	80	80	7	38	Not reached at 23 months	In cross trail comparison there was no benefit in outcomes noted with the addition of lenalidomide to the DRC backbone.
Fludarabine/ Rituximab (FR)[	2	27	96	89	5¥/33	78**	Not reported	Opportunistic infections, stem cell toxicity, risk of myeloid neoplasms and transformation to aggressive lymphoma are major limitations
Rituximab/ Cladribine (R-2CDA)	2	16	94	79	24¥	Not reached***	93% at 43 months follow-up.	Interestingly no major infections or transformation were noted in this small study at 43 months follow-up.
Fludarabine/ Cyclophosphamide/ Rituximab (FCR)[	2 R2W	17	82	77	0/18	Not reached at 18 months	88% at 18 m	Compared to BCR high grade hematologic toxicities were more frequently encountered with FCR
Bortezomib/ Cyclophosphamide/ Rituximab (BCR)	2 R2W	42	98	79	1/19	Not reached at 18 months	98% at 18 m	Grade 3 or higher neuropathy was avoided due to modified SQ weekly dose of bortezomib.
Hensel et al.	2	9	77¥	62¥	15¥	Not reported	Not reported	Higher ORR with the addition of R to PC.
Pentostatin/ Cyclophosphamide +/− Rituximab (PCR)] Herth et al.	2	21	88¥	68¥	0/16¥	84% at 2 years¥	100% at 2 years¥	A small study demonstrating that combining adenosine deaminase inhibitor, pentostatin, with cyclophosphamide and rituximab leads to good disease control, but this strategy is not frequently used.

For studies that include both relapsed/refractory and treatment naïve patients with WM, the results are reported for the TN cohort only *Median unless specified, ** Time to progression (TTP), *** time-to-treatment failure (TTF) ¥ for treatment-naïve and relapsed/refractory patients combined.

cycles of therapy [76]. Importantly, in the FILO study, protracted cytopenias occurred in almost 50% of the patients, with 2 patients developing treatment-related myeloid neoplasms [81].

In a more recent multiinstitutional retrospective study with a median follow-up of 4 years, the median PFS was 67.2 months with an outstanding 5 year overall survival of 90%. The progression of disease within 24 months (POD 24) noted in 11% of the patients led to an inferior overall survival translating into a 5-year OS of 75% versus 94% for those patients that did not progress within 24 months of starting BR [82].

8.2. Dexamethasone, rituximab, and cyclophosphamide

The DRC regimen omits the vinca alkaloid, vincristine, and the anthracycline, doxorubicin, from the RCHOP regimen, but retains the steroid (dexamethasone, instead of prednisone), the alkylating agent (cyclophosphamide) and the monoclonal anti-CD20 antibody (rituximab) components [83]. With low rates of neutropenia and thrombocytopenia as well as low non-hematologic toxicity, it is particularly well suited for the less fit/ frail patient. In a phase 2 trial involving patients with untreated WM ($n = 72$), the DRC regimen induced an ORR of 83%, PR rate of 67%, CR rate of 7%. The median PFS was approximately 3 years (Table 3) [83]. However, the median time-to-next treatment (51 months) was appreciably longer suggesting that biochemical progression may precede the reemergence of clinical symptoms that warrant treatment by more than a year. After a long follow up (median 8 years), myelodysplastic syndrome (MDS) was reported in 3% of patients and approximately 10% patients transformed to diffuse large B-cell lymphoma (DLBCL) [84].

8.3. Other chemo-immunotherapy regimens

Currently, the use of R-CHOP in WM is largely confined to the patients that have transformed to DLBCL [85,86]. As discussed earlier, there is no advantage of R-CHOP over rituximab-bendamustine in WM.

A single arm Mayo Clinic trial involving patients with indolent

lymphomas, examined the benefits of adding lenalidomide (20 mg PO, days 1–21) to the modified DRC regimen for previously untreated patients. Among the evaluable patients with WM, the ORR was 80%, (7% CR and 73% PR). The median PFS was 38 months, and comparable to the median PFS achieved with DRC, displaying no incremental value of adding lenalidomide (Table 3) [87].

Another more recently conducted (ECWM-1 NCT01788020) randomized controlled study evaluated a modified DRC regimen with or without the first-generation proteasome inhibitor, bortezomib (V). Overall, 204 patients were enrolled and following 3 cycles, a higher proportion of patients who were treated with the investigational quadruplet (V-DRC) achieved a response (ORR: 79 versus 57% and MRR 65% versus 33%, $p < 0.01$) [88]. Additionally, the responses were attained more rapidly among patients on V-DRC (median time-to-first response for B-DRC was 3.0 versus 5.5 months) and the VGPR rates were higher [88]. Despite these initial promising data, the ORR following six cycles of therapy become comparable (95% for V-DRC versus 87% for DRC, $p = 0.07$) as did the best response rates (MRR 85% and 82%, respectively with V-DRC and DRC $p = 0.60$). Notably, the 2-year PFS rates were similar as well (81% versus 73% with DRC $p = 0.32$) [88]. Expectedly, the treatment emergent peripheral neuropathy rates were greater with V-DRC (18% versus 3%). These findings once again confirmed a lack of benefit with the addition of a fourth agent to the DRC backbone (Table 3) [88].

8.4. Purine/ nucleoside analog-based chemo-immunotherapy regimens

Extensive data, over the past 3 decades, are available in the frontline and salvage setting with purine analogs, fludarabine and cladribine (2-CDA), which incorporate into the DNA and RNA strands and inhibit DNA replication and gene transcription, impacting both the dividing as well as non-dividing cells [89–98]. There is evidence of high ORR, particularly in the frontline setting [92]. A synergistic interaction with cyclophosphamide has been observed as induced DNA breaks remain unrepaired in the presence of fludarabine. In vitro data suggesting a synergistic activity with rituximab exist as well, translating into a more durable response with chemoimmunotherapy [91,94,96,99].

Oral fludarabine was compared with oral chlorambucil as primary therapy in 339 patients with WM in a large, multicenter phase 3 trial, demonstrating longer OS with fludarabine [92]. However, the associated toxicities, including protracted neutropenia and thrombocytopenia, risk of opportunistic infections, stem cell toxicity and the risk of histological transformation as well as treatment-related myeloid malignancies has dampened enthusiasm for its use in general [92].

Fludarabine has been examined in combination with alkylators and CD20 monoclonal antibodies, rituximab and ofatumumab, but not directly compared to cladribine. In cross study comparisons, their efficacy and tolerability are comparable.

In a non-comparative, phase 2 trial (R2W) 60 previously untreated patients were randomly assigned to subcutaneous bortezomib (weekly), oral cyclophosphamide and intravenous rituximab (BCR) or fludarabine cyclophosphamide and rituximab for six 28-day cycles, showing an ORR and MRR of 98% and 82% and MRR of 79% and 77%, respectively, with BCR and FCR [100]. Lower rates of treatment-emergent peripheral neuropathy in the BCR arm resulted from altering the route and frequency of bortezomib administration. Notably, 2 MDS-related deaths were encountered in the FCR arm [100].

As effective and safer alternatives emerge, the use of fludarabine and other purine analog-based chemoimmunotherapies has profoundly declined, but these regimens continue to serve as late line salvage options in heavily pretreated patients [1,76].

9. BTK inhibitors

Ibrutinib is a first-generation, orally absorbed, BTKi that occupies an active site in the ATP binding domain of the BTK enzyme and forms an irreversible covalent bond with the cystine residue at position 481, leading to prolonged kinase activity inhibition and degradation of the enzyme [101–110]. Ibrutinib is, however, less selective and interacts with other kinases with a cognate cystine at IC50 that is markedly lower than that of the second-generation BTKi [110–112].

A phase 1 trial, involving patients with B-cell malignancies, including four patients with RR WM, hinted at the activity of ibrutinib monotherapy in WM, with 3 of 4 patients achieving a response (Table 4) [113]. This study paved way for additional Phase 2 and 3 trials focusing on WM. Ibrutinib was granted a Breakthrough Therapy Designation for WM by the U.S. Food and Drug Administration (FDA). The pivotal study of ibrutinib monotherapy enrolled sixty-three patients with RR WM who had received a median of two prior therapies and confirmed the phase 1 trial results [114]. It was also the first study to demonstrate differential response and outcomes based on the *MYD88* and *CXCR4* mutational profile of the patients' WM cells [114].

Higher response rates were observed among patients with $MYD88^{L265P}CXCR4^{WT}$ signature as compared to those with $MYD88^{mut}CXCR4^{WHIM}$ and $MYD88^{WT}CXCR4^{WT}$ genotypes. The 2-year and 5-year progression-free survival (PFS) rates were 69% and 54%, respectively, for the entire cohort. The 5-year PFS rate was 70% and 38% for those with $MYD88^{Mut}CXCR4^{WT}$ and $MYD88^{Mut}CXCR4^{Mut}$ WM, respectively ($P = 0.02$), translating to a median PFS of 4.5 years for the latter group [108]. Interestingly, compared to the patients with $MYD88^{Mut}CXCR4^{WT}$ signature, those with the frameshift *CXCR4* mutations showed similar PFS ($P = 0.57$), whereas those with nonsense *CXCR4* mutations had a shorter PFS [108]. A subsequent analysis showed that that two of the seven patients who were previously categorized as $MYD88^{WT}$ on the AS-PCR assay, and had shown a partial response to ibrutinib, had indeed harbored non-L265P mutations in the *MYD88* gene that were ultimately detected on Sanger sequencing [115]. The updated findings revealed that no patients with an $MYD88^{WT}$ genotype had attained at least a partial response, underscoring the importance of assessing the mutation status before commencing ibrutinib monotherapy [108]. Among the patients with a true $MYD88^{WT}$ signature, the median PFS was merely 0.4 years, with all patients experiencing disease progression within 2 years of initiation of ibrutinib [108]. On the basis of the results of this single arm multicenter trial, ibrutinib, which was already previously approved for patients with MCL and CLL, received a supplemental indication for WM, irrespective of the number of prior lines of therapies. Ibrutinib's high efficacy was subsequently documented in patients with previously untreated WM as well although all patients in the study carried the *MYD88* mutation (Table 4) [107].

The randomized portion of the iNNOVATE trial was a placebo-controlled, double-blind, phase 3 study which enrolled 150 patients with both RR and TN WM that were not refractory to rituximab [116]. The patients were randomly assigned to receive either ibrutinib 420 mg orally or an oral placebo once daily until progression or intolerable side effects in addition to intravenous R 375 mg/m^2 once weekly for four consecutive weeks (weeks 1–4), followed by a second four-weekly rituximab course after a three-month hiatus (weeks 17–20) [116]. The protocol allowed patients in the placebo-rituximab arm to cross over to receive ibrutinib monotherapy upon disease progression and, thirty-eight such patients (51%) crossed over (three off-study and thirty-five on study) utilizing ibrutinib as the next-line therapy. The IR doublet led to a longer PFS, the primary end point, compared with R monotherapy (Table 4) [117]. Notably, the efficacy of IR seemed to be comparable among patients with TN and RR disease, suggesting that relegating this BTKi-based regimen to the RR setting would not compromise its efficacy. Reduced-infusion related reaction (IRR) rates, presumably attributable to lower cytokine release associated with simultaneous ibrutinib use, as well as lower rituximab-induced flare rates were observed in the IR arm [117]. The study however lacked a head-to head comparison with ibrutinib monotherapy and due to the study design, the true value of incorporating rituximab to the BTKi was unascertainable. Only one patient in each arm achieved a CR by month

Table 4
Efficacy of BTK Inhibitors in Waldenström Macroglobulinemia.

Study	N	Population	ORR (%)	MRR (%)	PR (%)	VGPR (%)	PFS (%)
Ibrutinib	4	RR	75	75	75	0	NA
Ibrutinib	63	RR	91	79	49	30	5y 54
Ibrutinib	30	TN	100	87	57	30	4y 76
iNNOVATE		TN/RR	92	76	45	29	4.5y
Ibrutinib+ Rituximab Placebo + Rituximab	150		44	31	25	4	68
	75						25
	75						
iNNOVATE ARM C ibrutinib		Rituximab	87	77	48	29	5y
	31	refractory					40
Acalabrutinib	106	TN	93	79	71	7	5.5y
	14	RR	95	84	57	23	84 (TN)
	92						52 (RR)
Zanubrutinib AU-003	77	TN/RR	96	83	37	44	2-yr 81
ASPEN Cohort 1(MYD88^{mut})	201	TN/RR	95	81	45	28 36	1y 90 78
Zanubrutinib	102		94	80	55	19 22	3.5y 87 70
Ibrutinib	99						
ASPEN Cohort 2	26	TN/RR	81	65	35	31	1.5 3.5y
Zanubrutinib (MYD88^{WT})							68 NA
Tirabrutinib	27	TN/RR	96	89	78	11	NR
Orelabrutinib	47	RR	87	75	NA	NA	1y 88%
Pirtobrutinib	17	RR cBTKi naive	88	88	59	29	NR
	63	cBTKi exposed	81	67	43	24	19 m
Ibrutinib-venetoclax	45	TN	100	93	53	40	1y 92%

18, and the median OS was not reached in either treatment arm at the time of the final analysis at a median follow-up of 50 months [117]. High overall (100%) and MRR (77%) rates were achieved in patients with *CXCR4* mutations. Although a lower proportion of patients with *MYD88^{MUT} CXCR4^{MUT}* attained at least a VGPR compared with patients with *MYD88^{MUT} CXCR4^{WT}* genotype (23% vs. 44%), the 54-month PFS rates seemed comparable (63% versus 72%, respectively). Similarly, among the patients with the *MYD88^{WT}/CXCR4^{WT}* genotype, the VGPR rate was 27% and 54-month PFS rate was 70% [117]. The results suggest that the IR may serve to overcome the adverse impact of the *MYD88*^{WT} and *CXCR4* mutations observed with ibrutinib monotherapy. However, the *MYD88* mutation status was assessed with a non-PCR based assay in the iNNOVATE study and only 78% of the patient population harbored the *L265P* mutation, raising doubts about the sensitivity of the assay, and in turn, the genotypic categorization of the subjects [117].

A separate, open-label, non-randomized arm in the iNNOVATE trial enrolled rituximab-refractory patient population and demonstrated the efficacy of ibrutinib monotherapy in that subset of patients that had been exposed to a median of four prior lines of therapy (Table 4) [118].

A Mayo Clinic study evaluating ibrutinib monotherapy use outside of a clinical trial setting reported outcomes that were similar to those observed in clinical trials [119]. Importantly, 18% of patients required a dose reduction and the ibrutinib discontinuation rates for reasons other than the disease progression were high at 20%. Patients on continuous ibrutinib therapy may experience cytopenias, diarrhea, fatigue, myalgia and bruising. Clinicians should also remain vigilant for cardiovascular toxicity, including cardiac arrhythmias (predominantly atrial fibrillation) and hypertension [102,120].

In another large retrospective study involving 353 patients, 27% (n = 96) patients required at least one dose reduction owing to ibrutinib intolerance, a rate that is nearly 1.5-fold higher than that noted in the pivotal trial [121]. The dose reductions were more common among patients who were at least 65 years of age (38% vs. 14% for patients<65 years; HR 2.46) and in females (38% vs. 23% in males; HR 2.2), with both variables being independently associated with dose reductions. Although in most patients, the adverse effects improved or even resolved with dose reduction, twenty-seven patients (28%) remained symptomatic despite this intervention, prompting a second dose reduction to 140 mg P0 daily among twenty-four of those twenty-seven patients. Interestingly, at a median follow up of 3 years, the hematologic responses were maintained (79%) and even improved (14%), despite the dose reduction [121].

10. Acalabrutinib

Acalabrutinib, a potent oral second-generation BTKi demonstrates greater selectivity for BTK and unlike its predecessor, ibrutinib, does not substantially inhibit EGFR, ITK, HCK, ERBB2, and JAK3 [122].

Although acalabrutinib is not approved in the US for use in WM it is commercially available for other indications. A dedicated single-arm, multicenter, phase II trial involving 106 patients with WM [RR (n = 92); TN (n = 14)] demonstrated MRR rates of 72% and 79% in RR and TN, respectively, at 27 months of follow up, translating to 2-year PFS rates of 82% and 90%, respectively (Table 4) [123]. No CRs were attained. At 2 years, the OS rate was 89% and 92%, in RR and TN population, respectively. In a subset analysis, among thirty-six patients with *MYD88*^{L265P} mutation, MRR was 78%. By contrast, 57% with *MYD88*^{WT} signature (n = 14) achieved a major response. The *CXCR4* mutational analysis was not performed, precluding assessment of the impact of concurrent *CXCR4* mutation [123].

Finally, at a follow-up of nearly 5 years, the median PFS was 68 months in the RR population and not reached the TN population [124]. Nearly two-thirds of patients experienced some degree of hemorrhage, with one fatal case of intracranial hematoma. The other most common adverse effects included headache, diarrhea, fatigue, arthralgia, nausea and dizziness. Twelve patients (11%) were diagnosed with atrial fibrillation/flutter and about 5% had hypertension [124]. Although acalabrutinib has not been directly evaluated against ibrutinib in patients with WM, a large trial, comparing the two BTK inhibitors in CLL patients, showed higher rates of atrial fibrillation and flutter (16.0% vs 9.4%; p = 0.002) as well as treatment discontinuation rate due to adverse effects (21% vs 15%) in the ibrutinib arm [125].

11. Zanubrutinib

Zanubrutinib is another potent, selective second-generation covalent BTKi with reduced off-target effects in comparison to ibrutinib as demonstrated in the ASPEN study [102]. The twice daily administration of 160 mg pill may be preferred over 320 mg once daily dosing due to more sustained lymphoid tissue BTK receptor occupancy. Zanubrutinib was approved for treating patients with TN and RR WM in 2021 on the basis of the phase 3 ASPEN trial that compared it to ibrutinib

monotherapy.

The phase 1–2 AU003 study in RR and TN patients showed that the magnitude of response deepened with treatment duration as VGPR rates improved from 21% at 6 months to 33% at 1 year to 44% at 2 years, with evidence of plateauing of response in the RR population beginning at about 20 months [126]. A VGPR or higher rate of 33% and 51% was observed in the TN and RR cohorts, respectively. Major responses were seen in 83% of patients (Table 4) [126]. Among the patients with $MYD88^{L265P}/CXCR4^{WT}$ ($n = 39$), ORR and MRR were 97% and 87%, respectively. In patients with $MYD88^{L265P}/CXCR4^{WHIM}$ ($n = 11$), ORR and MRR were 100% and 91%, respectively. The estimated 3-year PFS was 81%, and the OS rate was 85%.

In Cohort 1 of the ASPEN trial (Table 4), the patients were randomly assigned to receive either of the two BTKi and their efficacy and tolerability was compared in 201 patients with $MYD88^{L265P}$ mutation who were either TN ($n = 37$) or had relapsed refractory disease ($n = 164$) [120]. Complete response (CR) was not observed in either arm. A higher proportion of patients achieved VGPR with zanubrutinib (28%) compared to ibrutinib (19%) in the initial analysis, although, this difference was not statistically significant ($P = 0.09$), demonstrating the trial's failure to meet its primary endpoint. Furthermore, the MRR were similar in both arms (zanubrutinib: 77%; ibrutinib: 78%). The toxicity profile, however, was largely more favorable with zanubrutinib. In the zanubrutinib arm, there was a lower rate of all-grade atrial fibrillation (8% vs 24%), bleeding (56% vs. 62%), diarrhea (23% vs. 35%), hypertension (15% vs. 26%), anemia (18% vs.22%) but neutropenia occurred more frequently (35% vs 20%) as compared to ibrutinib, albeit without greater rates of grade 3 infections in the zanubrutinib arm. The rates of thrombocytopenia and second primary malignancies were similar in both arms. Unsurprisingly, the rates of therapy discontinuation due to AEs also favored zanubrutinib (9% vs. 20%).

In an updated analysis with a median follow-up of 44 months, 36% VGPR or better response rates were noted with zanubrutinib versus 25% with ibrutinib. Median PFS were still not reached in either arm, but the initial signs of longer PFS started with zanubrutinib (78.3% vs. 69.7% with ibrutinib; HR 0.63 (CI: 0.36–1.12) have started to emerge [127].

In a subset of twenty-six patients (23 RR; 5 TN) with $MYD88^{WT}$ signature (Cohort 2), the efficacy of zanubrutinib monotherapy was assessed [128]. Among this subset, a cross trial comparison showed that the outcomes were superior with zanubrutinib in comparison to ibrutinib (ORR 81%, MRR 54% and a VGPR rate of 23% with zanubrutinib). In contrast to the dismal PFS rates with ibrutinib in a prior study (median 0.4 years), with all patients that harbored $MYD88^{WT}$ signature succumbing within 2 years, the PFS rates at 42 months were 54% with zanubrutinib in the $MYD88^{WT}$ subset [128].

Given its superior toxicity profile over ibrutinib, strong efficacy irrespective of the patients' MYD88 mutation status, zanubrutinib is our preferred approved BTK inhibitor for patients with WM (Fig. 3). It is being evaluated among patients with intolerance to ibrutinib or acalabrutinib (NCT04116437). The preliminary findings have suggested that switching to zanubrutinib therapy avoids recurrence of any prior BTKi intolerance among the majority of the patients and durable remission is maintained in over 90% of such patients, demonstrating that patients have another viable safe and effective option within the same class [129,130]. However, the need for continuous therapy and the lack of deep remissions, despite extended use, make it less appealing than BR, particularly for the frontline setting.

Other second-generation covalent, irreversible BTKi, including tirabrutinib and orelabrutinib have been evaluated in single arm trials, with a short follow-up duration (Table 4) [131,132]. Since direct comparative data are lacking, it is unlikely that these "me too" covalent BTKi will succeed in supplanting zanubrutinib as the covalent BTKi of choice.

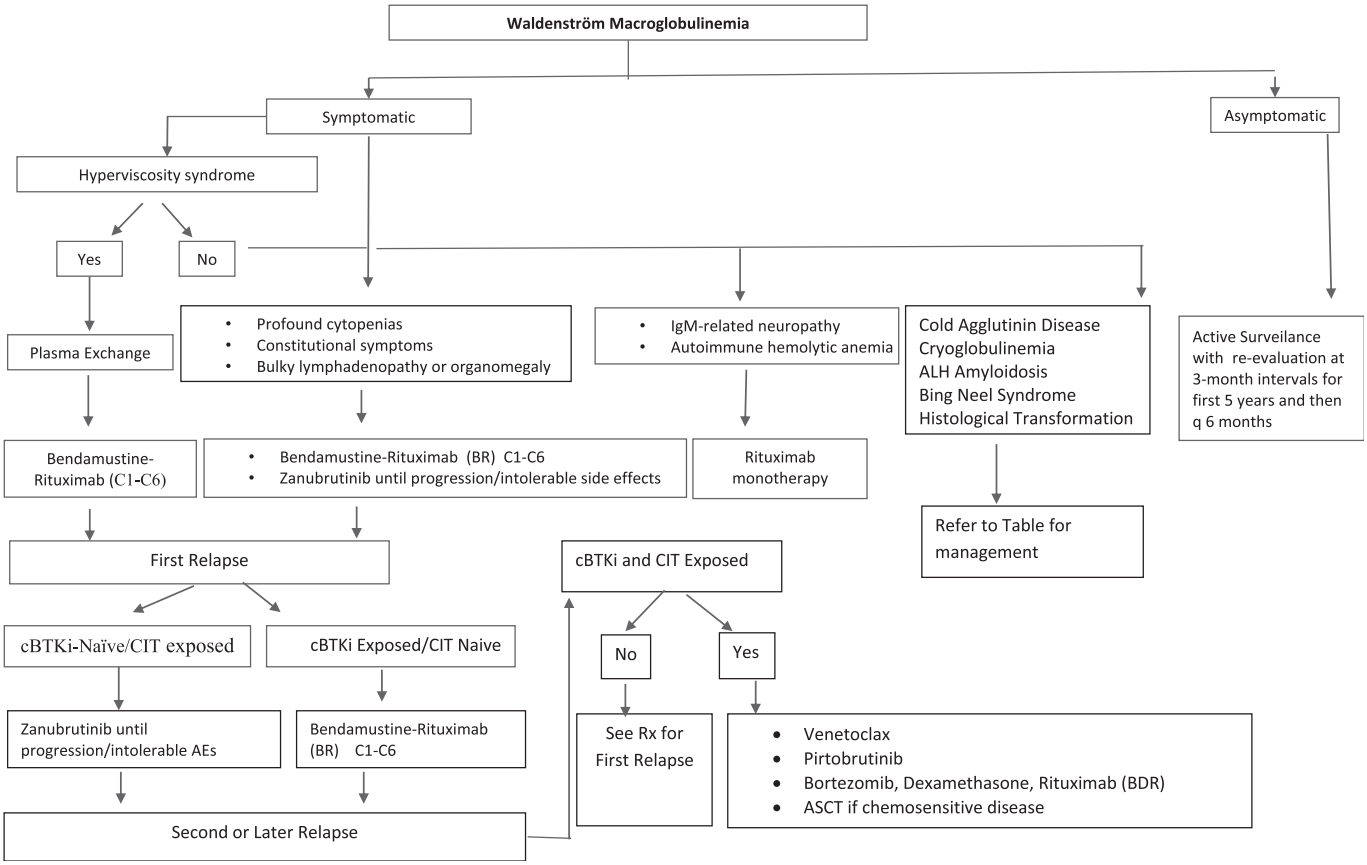


Fig. 3. Our Approach to the Management of Waldenström Macroglobulinemia.

11.1. Non-covalent bruton tyrosine kinase inhibitors

Pirtobrutinib is a reversible inhibitor of BTK, with efficacy in WM cells that harbor BTK^{WT}, BTK^{C481S} or BTK^{C481R} mutations [133–135]. In a subset analysis of the BRUIN study, a phase 1/2, multicenter, open-label trial that enrolled patients with B cell malignancies, 80 patients had RRWM of whom 17 were BTKi-naive and 63 were exposed previously exposed to a covalent BTKi but had either relapsed while on therapy (67%) or had covalent BTKi intolerance (33%) [134,135]. The recommended phase 2 dose (RP2D) of 200 mg once daily was given to 91% of WM patients. Among the BTKi-exposed patients, MRR was 67% and ≥ VGPR rate was 24%, with a median PFS of 19 months and 18-month OS rate 82% (Table 4). Data specifically delineating outcomes of patients with covalent BTK exposed, but intolerant, and covalent BTKi-refractory WM are not available yet. The response rates were even better in the BTKi-naïve population (MRR 88%; ≥VGPR 29%) [134,135]. Pirtobrutinib is commercially available, but not yet approved for WM. The cardiovascular safety profile of pirtobrutinib is particularly appealing in comparison to the covalent BTKis. The most common all grade AEs observed in all patients with B-cell malignancies treated with pirtobrutinib ($n = 725$) included fatigue in 29% diarrhea in 24% and bruising in 24%, with neutropenia observed in 24%, hypertension 9%, atrial fibrillation/flutter in 2.8% (1%), rash in 13%, arthralgia in 14% of patients. Grade 3 or higher toxicities, barring hematologic adverse effects, were exceedingly infrequent [136]. A clinical trial with another reversible, non-covalent BTKi nemtabrutinib, is ongoing (NCT03162536).

Abrupt cessation or interruption of BTKi therapy may result in withdrawal symptoms, including fever, body aches, night sweats, arthralgias, chills, headaches, and fatigue in up to 20% of patients [,138]. IgM rebound, a term denoting >25% increase in IgM levels upon withholding of a BTKi, may occur with or without BTKi withdrawal symptoms and arises from a hyperactive immune state that typically resolves with reinitiation of the BTKi [119,137,138].

12. Approach to frontline therapy

Randomized trials comparing BR with DRC have not been conducted. Similarly, high level evidence comparing fixed-duration therapy with BR and novel therapies, administered until progression, is absent. Cross-trial comparisons and retrospective studies, however, demonstrate superior efficacy of BR in comparison to DRC, including ORR (98% *v* 78% with DRC), as well as an improved TTNT and a PFS of approximately 62–70 months with BR (*v* 35–52 months with DRC). Similarly, B-DRC, with its neurotoxic potential, inability to improve PFS rates over DRC despite improved MRR in patients with underlying CXCR4 mutation (71% *v* 50%) does not appear to be superior to DRC and therefore unlikely to supplant BR as frontline regimen. Moreover, unlike ibrutinib, BR is effective, irrespective of the MYD88 mutation status. Although among the age-matched patients with *MYD88* mutation, BR and continuous ibrutinib monotherapy showed comparable outcomes (4-year PFS rate of 72% with BR versus 78% with ibrutinib and 4-year OS of 92% with BR versus 86% with continuous ibrutinib), ibrutinib was prematurely discontinued in 33% of patients. By contrast, 13% of patients could not complete the course of BR. As such, a course of 6 cycles of BR remains our preferred approach for the management of patients with newly diagnosed symptomatic WM (Fig. 3). BR is also well suited to serve as the control arm (comparator) regimen against which novel targeted agents may be evaluated as frontline therapies for WM in high-quality trials.

13. Proteasome inhibitors

Proteasome inhibitors (PI), in general, have shown rapid and durable responses in WM. Bortezomib, a boronic acid dipeptide that reversibly inhibits 26S proteasome, is the most extensively evaluated PI in WM. By inhibiting the proteasomal degradation of ubiquitinated proteins, PIs facilitate accumulation of the tagged proteins, thereby triggering unfolded protein response-mediated apoptosis. An ORR of 78–98% with bortezomib alone or in combination has been documented in several phase 2 studies (Table 5) [139–142]. With the exception of two, all are single arm non-randomized studies [100,143–153]. Peripheral neuropathy is the most frequently encountered treatment emergent non-hematologic adverse effect of bortezomib and in both NCIC CTG and WMCTG trials involving bi weekly bortezomib monotherapy, high-grade neuropathy was noted in one of every 5–6 patients with WM [100,144,145,150]. This major deterrent to its use is, in part, mitigated with the less frequent administration of bortezomib, from biweekly to once weekly (grade 3 neuropathy rates reduced to 5%), increasing the length of the cycle, and more recently, switching over from intravenous to weekly subcutaneous route of administration (grade 3 neuropathy is rarely encountered with this approach) [100,144,145,150].{.

The second-generation PIs, carfilzomib, oprozomib and ixazomib are also quite effective, and cause less neuropathy.{Kapoor, 2017 #876} Carfilzomib is a tetrapeptide epoxyketone, analog of epoxomicin that irreversibly inhibits 20S proteasome. The CaRD (carfilzomib, rituximab, and dexamethasone) regimen has demonstrated high response in WM, irrespective of the MYD88/CXCR4 mutational status [152,154]. Although largely neuropathy sparing, cardio renal toxicity, asymptomatic hyperlipasemia, and substantial decline in uninvolved immunoglobulins are some of the deleterious effects that have been observed with carfilzomib [152,154]. Ixazomib, an oral PI, showed ORR of 88–96% when combined with rituximab and dexamethasone in two phase 2 trials [155,156]. To reduce the risk of IgM flare, rituximab therapy was initiated only after two cycles of ixazomib and dexamethasone. In the trial involving TN patient population (Table 5), all patients exhibited $MYD88^{L265P}$ mutation, and 15 (58%) patients carried *CXCR4* mutations. The presence of *CXCR4* mutation was associated with a longer time to achievement of response (8 weeks vs 12 weeks, $p = 0.03$). Similarly, IDR has been investigated in patients with RR WM and showed that at 24 months, the PFS for the $MYD88^{L265P}/CXCR4^{WT}$, $MYD88^{L265P}/CXCR4^{MUT}$, and $MYD88^{WT}/CXCR4^{WT}$ patients was 75%, 57%, and 67%, respectively. Oprozomib is another oral PI that showed promising results in patients with RR WM in a phase Ib/2 dose escalation study (Table 5) [157]. Despite demonstrable efficacy, gastrointestinal toxicity, with fatalities, was a major limitation, precluding its further development. Marizomib, an irreversible PI leads to dose dependent apoptosis of WM cells and downregulates anti apoptotic protein Mcl-1, but data regarding its clinical efficacy and tolerability in WM are absent.

Although PI-based regimens offer several advantages; finite duration of therapy, rapidly reduce IgM levels and do not enhance the risk of second malignancies, currently their use is relegated to the third line in RR population, or among patients in whom an alkylator-rituximab combination or a BTK inhibitor is not being considered as primary therapy. Both bortezomib and ixazomib our best avoided in patients with an underlying peripheral neuropathy. Similarly, carfilzomib is unsuitable for the patients with cardiopulmonary comorbidities. However, bortezomib-based regimens are highly effective as frontline therapies among patients with ALH amyloidosis (Table 6) which is encountered in approximately 7–8% of the patients with WM [158].

14. BCL-2 inhibitors

Dysregulation of apoptosis is a hallmark of WM cell which relies heavily on anti-apoptotic protein, B-cell leukemia also leads to BCL2 upregulation [159–161]. Oblimersen sodium, an antisense oligonucleotide designed to hybridize to the first six codons of the *bcl-2* open reading frame to inhibit its translation into protein, was investigated nearly 2 decades ago in a phase 1 / 2 trial in patients with symptomatic RRWM [162]. High-grade hematologic toxicities occurred in five of the first six patients following the toxicity observation period of Cycle 1, requiring dose reduction in subsequent cycles. Efficacy signal was noted

Table 5
Efficacy of Proteasome Inhibitors in Waldenström Macroglobulinemia.

Trial	Phase	Regimen	Cohort	Trial size	ORR (%)	MRR (%)	PFS (median in months)
Chen et al. NCIC CTG	2	V	TN and RR	27	78	44	16
Treon et al. WMCTG Trial 03–248	2	V	TN and RR	27	85	48	7.9*
Ghobrial	2(	VR	TN	26	88	65	NR
Ghobrial	2	VR	RR	37	81	51	16*
Avramopoulos et al.	2(	VDR	TN	59	85	68	43
Treon et al.	2 (	VDR	TN	23	96	83	2-yr 78%
Auer et al.	2	VCR	TN	42	98	79	NA
Buske et al.	2	V-DRC	TN	102	91	81	2-yr 81%
Treon et al. Meid et al.	2(	CaRD	TN and RR	31	81	71	46
Castillo et al.	2(	IRD	TN	26	96	77	40
Kirsten et al. HOVON/ECWM-R2	1/2	IRD	RR	59	85	61	NR 2-yr 56%
Ghobrial et al.	1b/2	O	RR	1b 19	38** 82#		NA
				2 31	71** 47#	50 29	17 22

NA, not available; NR, not reached TTP, Time to progression; ORR, overall response rate; MRR, minor response rate; V, Bortezomib; I, ixazomib; Ca, carfilzomib; D, dexamethasone; R, Rituximab; C, cyclophosphamide; O, oprozomib.
**schedule 2/7: oprozomib administered 2 of 7 days or #5 of 4 days.

when a single patient achieved a PR, with IgM decreasing from approximately 6000 mg/dL to 1000 mg/dL over five 21-day cycles [162].

More recently, venetoclax, a commercially available highly selective BCL2 oral antagonist, has been shown to induce response in WM, even in patients that have been previously exposed or are refractory to BTK inhibitor-based therapy. In the Phase 1 study, M12–175, involving 106 patients with RR NHL, including a very small subset patients with WM ($n = 4$), the maximal tolerated dose (MTD) could not be determined, but the RP2D was 1200 mg [163]. Interestingly, an ORR of 100% was observed in patients with WM in contrast to 44% observed in the entire cohort [163]. Although no CRs were noted, the duration of response (DOR) for two of the four patients with WM was over 3 years. In another Phase 2 study (NCT02677324) for patients with RRWM ($n = 32$; all exhibiting $MYD88^{L265P}$ mutation and 53% with concurrent $CXCR4^{WHIM}$ mutation), venetoclax was given at 800 mg daily for a fixed duration of up to 2 years, following a dose escalation from 200 mg/day for the first week and 400 mg daily in the second week [160]. The median number of prior therapies was two, and 50% of patients were BTK inhibitor exposed. With a median follow-up of 33 months, the ORR and MRR were high at 84% and 81%, respectively. However only 19% of patients achieved VGPR [160]. The estimated median PFS was 30 months and a sizable proportion of the cohort progressed within 6 months of completing the 24-month finite duration therapy, suggesting the need for indefinite treatment even among the responding patients. Prior BTK inhibitor exposure adversely impacted the time to major response. The frequent adverse events included neutropenia ($n = 15$), anemia ($n = 8$), nausea ($n = 13$), diarrhea ($n = 4$) and headache ($n = 5$). A single patient experienced a laboratory, but not clinical, tumor lysis syndrome (TLS). IgM rebound was not noted after stopping therapy. Venetoclax is not yet approved for patients with WM [160].

Preclinical studies in WM support the rationale for BCL2 and BTK co-inhibition [159,164]. WM cells devoid of BTK^{C481S} or $CXCR4^{WHIM}$ mutations may acquire resistance to ibrutinib through Bcl-2 upregulation and increased BCL2 protein expression, making them vulnerable to venetoclax. Venetoclax has shown to induce direct apoptosis and enhance ibrutinib-triggered apoptosis in both $CXCR4^{WT}$ and $CXCR4^{WHIM}$ WM cells. Venetoclax through BCL2 inhibition leads to loss of viability and mitochondrial-mediated apoptosis of ibrutinib-resistant WM cells [159,164].

.A single arm, phase 2 trial in TN patients with WM examined the efficacy of a fixed duration venetoclax-ibrutinib combination, a doublet that has been previously studied in other B cell malignancies [165]. The response rates were impressive: ORR 100%, MRR 93%, VGPR 40%, but notably after a median follow of 11 months, no patients achieved CR, underscoring that unlike CLL, patients with WM do not achieve very deep responses with this strategy. Among the patients with $CXCR4^{WT}$ genotype, however, the VGPR rates were 50% (MRR 96%) versus 24% (MRR 89%) among patients with $CXCR4^{mut,}$ with similar time to response (median 1.9 months) in the two subsets. The time to major response was expectedly longer for the $CXCR4^{mut}$ population (2.8 months vs. 1.9 months; $p = 0.048$). The 12-month PFS rate was remarkably high (92%) [165]. However, the trial was prematurely closed after enrollment of forty-five of the planned fifty patients owing to unexpected occurrence of ventricular arrhythmias in four patients (9%), accounting for two fatalities. Consequently, another recently opened SWOG trial (NCT04840602), evaluating ibrutinib and rituximab +/− venetoclax in the same patient population is suspended [165]. A randomized, phase 2 trial, viWA-1 (NCT05099471) is designed to compare fixed duration (12 cycles) venetoclax-rituximab doublet (ramp up with target dose 800 mg daily) and DRC (6 cycles) in patients with TN WM.

Sonrotoclax (BGB-11417), a highly selective Bcl-2 inhibitor, with over tenfold higher potency than that of venetoclax is currently under investigation as monotherapy and in combination with zanubrutinib in B cell malignancies, including WM [166,167]. Similarly, another orally bioavailable selective BCL-2 inhibitor, lisaftoclax (APG-2575), is under evaluation in WM [168]. The dose ramp of both these next-generation BCL2 inhibitors is faster than the weekly dose escalation traditionally followed with venetoclax use.

15. Mammalian target of rapamycin (mTOR) inhibitors

Everolimus inhibits mTOR, a serine-threonine kinase downstream of the PI3K/AKT pathway (Fig. 4). Discordance between serum IgM levels and marrow disease burden is notable with everolimus as is the IgM rebound upon treatment discontinuation [169–171]. A phase 2 trial demonstrated an ORR of 70% in patients with RR WM (PR 42%, MR 38%) and ORR of 73%, with MRR of 61% in TN WM [169–171]. Due to an unfavorable toxicity profile, with unacceptably high rates of mucositis/stomatitis, treatment-emergent pneumonitis and rash, its use has considerably declined in the face of increasing salvage therapeutic options for WM.

Table 6
Management of Specific Clinical Scenarios in Waldenström Macroglobulinemia.

Condition	Symptoms and diagnostic tests	Management nuances	Treatment
Hyperviscosity Syndrome (HVS)	**Symptoms:** Epistaxis (bilateral), gingival or retinal bleeding, blurring/ visual disturbance, papilledema, central retinal vein occlusion, hearing loss, somnolence, cerebral bleed, seizure, ataxia, headache, lightheadedness, and rarely heart failure Symptoms may occur even with viscosity <4cp. **Diagnostic Tests:** Serum viscosity, IgM cryoglobulin. Ophthalmoscopy on dilated eyes if HVS suspected or even in asymptomatic pts. with IgM >4000 mg/dL.	• HV alone, without symptoms and signs of HV is not an indication to start treatment. • HVS is seen in up to 15% of pts. with WM and does not impact OS. • Pts may have significant anemia due to plasma volume expansion; to avoid rheological impact in hemodynamically stable pts., withhold RBC transfusion until normalization of viscosity. • Typically, only 1–3 PLEX sessions required to reverse symptoms. IgM reduction by 25% mostly eliminates symptoms. • Avoid rituximab until viscosity normalizes due to IgM flare which may exacerbate HV symptoms. Preemptive PLEX prior to rituximab use when IgM is ≥4000 mg/dL is an infrequently used alternative approach.	• Prompt PLEX (Category A evidence) and rapidly acting cytoreductive therapy. • PLEX associated AEs include hypotension, allergic reactions to replacement fluids, hypocalcemia, citrated related paresthesias, catheter related thrombosis and infection, rarely capillary leak like syndrome due to sudden fall in oncotic pressure. • BTKi avoided due to delay in time to response, particularly among pts. with *CXCR4*^{NS} that are more prone to HV.
WM-associated Peripheral Neuropathy (PN) Pathophysiologic mechanisms: i) Immune mediated via IgM autoantibody against peripheral nerve antigens ii) IgM mediated cryoglobulinemic vasculitis related PN (Discussed separately) iii) Monoclonal protein-mediated amyloid deposition; rarely IgM deposition PN iv) PN infiltration or peripheral neurolymphomatosis (pNL) involving spinal nerve roots	**Symptoms:** Classic anti-MAG phenotype: progressive distal bilateral sensory loss, unsteady, broad-based gait, side-to-side finger tremor and jerkiness with reduced/absent reflexes, reduced pinprick, minimally impaired proprioception and usually no/minimal weakness (DADS neuropathy). Motor weakness may be delayed. I-RODS may be used for disability assessment. MMNCB: Motor PN, with distal asymmetric upper limb weakness. CANOMAD: chronic sensory ataxia (100%), ophthalmoplegia (40%), CAs (30–50%), and disialosyl antibodies; Pts have areflexia, distal limb and perioral paresthesias, oculomotor/bulbar weakness; rarely respiratory muscle weakness. pNL: progressive proximal/distal weakness, frequently painful PN or radiculopathy. **Diagnostic Tests:** EMG with NCS; if axonal PN, r/o ALH amyloidosis; cryoglobulins**:** Anti MAG PN is classically patchy demyelinating, with prolonged distal motor latency; IgM anti-MAG Ab titer + in ~50%. Anti-ganglioside Ab panel GM1 titer in MMNCB; in CANOMAD demyelinating or axonal pattern and IgM is against disialosyl epitopes on gangliosides in dorsal root ganglion and occulomotor nerves. Nerve biopsy can be usually avoided. pNL: challenging to diagnose. Combined MRI (thickening and enhancement of nerve, plexus, or nerve roots, increased signal on T2-weighted and FLAIR sequences) + PET-CT (FDG avid nerve roots); perform LP (post MRI); doppler US (nerve thickening and increased blood flow around the enlarged nerves); CSF findings: non specific, high CSF protein, +/− pleocytosis, cytology (usually negative), immunophenotyping, flowcytometry and molecular studies may be required to detect clonal cells and distinguish from inflammatory infiltrate. Nerve biopsy may be needed to detect WM cell infiltration.	• Concomitant IgM monoclonal gammopathy and PN, both of which are common conditions, does not signify causality as they may be coincidental; rule out other etiologies: ETOH, DM, and age. • A difficult to treat condition; weigh risks and benefits of commencing immunosuppressive therapy which has at best typically stabilizes the disease. Avoid in pts. with only mild symptoms, given indolent course, but monitor closely. • Rituximab studies were under powered. • Beware of IgM flare associated transient worsening of PN. • High rate of treatment emergent neuropathy with IV bortezomib • pNL: a rare complication, with limited data on management. Therefore, no consensus. Steroid effect is short lived, and its use is best deferred if a nerve biopsy is planned.	• Rituximab x 4 weeks (26% experienced improvement and 52% stabilization vs. 3% and 36%, respectively with placebo on self-assessment in one study; meaningful in 10 m time to walk with rituximab vs. placebo. • IVIg short-term effect. • BTKi may improve or stabilize PN, including in pts. who are rituximab exposed. Chemoimmunotherapy (BR, DRC) may rarely be used in pts. with progressive neuropathy and persistent WM clone. • CANOMAD syndrome: IVIg (RR 40–60%); plasmapheresis (RR 50%) or rituximab. • pNL: systemic chemotherapy+/− intrathecal chemotherapy preferred for multifocal disease. Data with BTKi are sparse. RT may be used for focal lesions.

(*continued on next page*)

Table 6 (*continued*)

Condition	Symptoms and diagnostic tests	Management nuances	Treatment
Bing-Neel Syndrome (BNS) A neurological condition resulting from CNS infiltration by LPL cells.	**Symptoms:** Headache, visual and/or gait disturbances, focal neurological deficits, and cranial neuropathies manifesting as slurred speech, paresthesias, limb weakness, gait imbalance, vision loss, chin numbness, hearing loss and altered mentation, etc. **Diagnostic tests:** Contrast enhanced MRI Brain and Spine before lumbar puncture. CSF analysis: elevated protein, lymphocytic pleocytosis, cytology to confirm LPL cells. Flowcytometry Biopsy of the suspected site (cerebral lesion or meninges) required if CSF negative. CSF *MYD88* mutational testing or immunoglobulin gene rearrangement as an adjunct to cytology.	• Goal is to control symptoms and prevent disease progression. • Only a minority show complete symptomatic recovery and long-term control. • No distinct prognostic parameters, but age $<$ 65 years and platelet count $>100 \times 10^9$/L and TN status may suggest favorable prognosis. • Rituximab has poor BBB penetration. • HD MTX, although effective, has high toxicity. • Monotherapy with intrathecal agents leads to short-lived responses. • symptomatic responses to ibrutinib and 2-year EFS rate of 80% in one study.	• BTKi: ibrutinib (higher dose 560 mg/ daily), zanubrutinib and tirabrutinib, and BBB-penetrating chemotherapies such as bendamustine, cytarabine and fludarabine are effective; If chemosensitive WM relapse, ASCT is an alternative, using BEAM or thiotepa-based conditioning. • May use RT for localized involvement.
Cold Agglutinin Syndrome (CAS) WM associated chronic AIHA with CA-mediated RBC agglutination and destruction when CAs bind to RBC surface antigens (mostly I) at specific temperature range (thermal amplitude). Classical CP activation initiated by C1; sequential splitting of complement proteins, results in C3b coating of RBCs. These are prone to mononuclear phagocytic system mediated opsonization, with ensuing extravascular hemolysis. Intravascular hemolysis may occur in severely affected pts. and acute exacerbations when additional complement amplifying conditions are present, with cleavage of C5, and formation of MAC (C5b-9 complex).	**Symptoms:** Fatigue related to anemia and anaphylatoxins released due to complement activation. Cold-induced symptoms from the acral circulation, including acrocyanosis, Raynaud-like phenomena, livedo reticularis, and rarely gangrene; symptoms depend on thermal amplitude at which the pt.'s IgM CA binds to RBC antigens. Pts with high thermal amplitude have clinically significant disease. An increased risk of thrombosis (RR 1.7–3.1) compared with an age-matched population. **Diagnostic tests:** CBC, peripheral smear: anemia with evidence of chronic hemolysis: indirect hyperbilirubinemia, reticulocytosis, spherocytosis, elevated LDH. Monospecific direct antiglobulin test strongly positive for C3d Cold agglutinin titer $\geq$64 (termed CAD in the absence of a clinically or radiologically overt lymphoma or infection) Hemoglobinuria in 15% with intravascular hemolysis. Mostly $MYD88^{WT}$ Post-translational glycosylation of LCs is significantly more frequent (64%) on serum mass-fix in pts. with CAD compared to pts. with other IgM monoclonal gammopathies (5%)	• Aim of treatment is to destroy cold agglutinin-producing LPL cells and reduce RBC destruction. • Rituximab monotherapy: ORR 50%. CR rare. Median DOR 6–15 months, with often repeated response of relapsed pts. to rituximab. • Efficacy substantially improved with BR x 4 cycles: ORR, 71% CR 40%. • FR: ORR 76%; CR 21%; PR 55%; DOR NR at 66 m • Ibrutinib: ORR 100% • Bortezomib x 1 cycle (ORR 32%, CR 16%, PR 16%); anecdotal reports of daratumumab monotherapy. • Sutimlimab, a monoclonal Ab, binds to C1s. Given weekly IV for 2 weeks and then q2 weeks; most respond well, with rapid anemia and fatigue improvement; vaccination against meningococci, pneumococci and *Haemophilus influenzae* type B mandatory. • Complement inhibition alone is inappropriate if the main indication for treatment is cold-induced circulatory symptom(s).	• Mild symptoms often managed with thermal protection. • Plasmapheresis in critical situations, with concomitant initiation of systemic therapy. • Frail pts.: Rituximab • Young fit pts.: BR, BTKi, bortezomib • Sutimlimab usually as salvage therapy unless unique circumstances such as severely anemic pts. requiring rapid response (as a bridge to slow acting definitive therapies) or in acute exacerbations and in pts. in whom CIT is not feasible. • Phase 2/3 trials of Sutimlimab excluded pts. with $>$10% clonal lymphoid infiltration. • Agents under investigation: Subcutaneous pegcetacoplan (C3 and C3b inhibitor), iptacopan (a complement factor B inhibitor) ANX005 (a C1q inhibitor), IVV020, (C1s inhibitor), ARGX-117 (C2 inhibitor). • Folic acid as adjunct.
ALH Amyloidosis	**Symptoms:** Fatigue, weight loss, macroglossia, bruising, bilateral CTS, jaw claudication, DOE edema, erectile dysfunction, GI mobility changes polyneuropathy and/or dysautonomia. Signs: Ecchymoses (periorbital purpura), orthostatic, hypotension, or resolution of hypertension, albuminuria, hepatomegaly, splenomegaly, **Diagnostic tests:** BM biopsy and aspirate (IHC, flow FISH, and Congo red staining) CT scan: CAP, fat aspirate or salivary glands/lip biopsy, and eventually, if needed, organ biopsy Subtyping mandatory by MS or immunoelectron microscopy NT-proBNP/BNP, troponin, 2D Echo with strain, cardiac MRI, EKG and DPD/ PYP scintigraphy if ATTR suspected. 24-h albuminuria, LFTs and liver imaging if needed.	• Develops in about 7.5% of pts. with WM. • Use response criteria validated for non-IgM AL or WM response criteria for AH. • Lymph nodes may contain amyloid, and their involvement should not be considered for the hematological response assessment. • BTKi poorly tolerated, with pronounced bleeding and cardiotoxicity.	• Goal: to attain VGPR/CR rapidly • Consider BEAM or Melphalan conditioning followed by ASCT as frontline or as consolidation. • BR in ASCT ineligible • R-CyBorD is an alternative. • Venetoclax is an alternative.
Cryoglobulinemia (Type 1 or 2) A condition characterized by the	**Symptoms:** Cutaneous: Purpura, skin ulcers, Raynaud's phenomenon, acrocyanosis, livido reticularis, digital ischemia, cold	• Asymptomatic/Incidental diagnosis: observe; LPL-directed therapy reserved for symptomatic pts.	• High-grade evidence regarding management is limited. • Bortezomib based regimen. Avoid bortezomib in pts. with PN.

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Table 6 (*continued*)

Condition	Symptoms and diagnostic tests	Management nuances	Treatment
presence of cryoglobulins [immunoglobulins that precipitate in vitro at temperatures below normal body temperature (<37 °C and redissolve upon rewarming) in the serum] Cryoglobulin composition is monoclonal IgM in type 1 or monoclonal IgM with RF activity +polyclonal IgG in type 2. RF activity may be increased, particularly in type 2.	urticaria. Glomerulonephritis Arthralgia Sensory PN (70%), sensorimotor or mononeuritis multiplex. Involvement of lung (hemorrhage), heart (dilated cardiomyopathy, ischemia), GI tract (abdominal pain, bleed), CNS (stroke, confusion) rare. **Diagnostic tests:** Cryocrit (take samples into prewarmed tubes until serum is separated, as the cryoglobulin may not otherwise be detectable due to precipitation). Complement assays (CH50, C4, C3) may be decreased, SPEP, UPEP, mass-fix, serum viscosity, Hepatis B and C viral panel, creatinine, EMG/NCS (axonal length dependent sensorimotor neuropathy), urinalysis (proteinuria, microscopic hematuria, RBC casts); Biopsy: Skin, leukocytoclastic vasculitis Kidney, MPGN Nerve Marrow LPL/other B cell cancer	• Symptoms do not correlate with the cryocrit; minimal amount of measurable cryoglobulin may cause symptoms/end-organ damage by precipitating in vessels. • Educate pts. to avoid exposure to cold and regarding foot care. • Skin ulcers do not heal easily due to impaired blood supply; may increase the risk for sepsis; may require prophylactic antibiotics to prevent serious infection. • In pts. with MGUS-range infiltrate with lower clonal cell burden rituximab monotherapy may be used and PLEX may considered first to avoid rituximab flare associated worsening of the symptoms. • PLEX is also used in life threatening or rapidly evolving disease. • Single-agent prednisone (median dose 60 mg/day) may improve symptoms in nearly 3 of 4 pts., 50% of responders relapse requiring a second line of therapy.	• CIT: BR or DRC • BTKi
Histologic Transformation (HT) WM course may be complicated by HT into an aggressive lymphoma, usually DLBCL of ABC subtype. May be clonally related or independent.	**Symptoms:** Suspect in pts. with progressive constitutional symptoms, rapidly enlarging lymph nodes, extranodal involvement, sudden rise in LDH **Diagnostic tests:** Tissue biopsy required; guided by clinical +/− radiological features, e.g., rapidly enlarging LNs, or by site of increased ^{18F}FDG activity on PET-CT. Decrease in serum monoclonal IgM. 80–90% are non-GCB subtype. Most cases negative (83–100%) for EBV-encoded RNA (EBER) in-situ hybridization. *MYC* rearrangement (11–38%) by FISH.	• Occurs in upto 4–6% of pts. with WM • Associated with a poor outcome. • 15–25% pts. are TN at HT • Incidence higher (15%) in pts. with *MYD88*^{WT} genotype, along with shorter time to HT (OR ~ 8). Other possible biomarkers include *PIM1*, *FRYL*, *PER3*, *PTPRD*, *HNF1B* and *CD79B* mutations. • High rates of extranodal involvement, including CNS, testis, skin. • *MYD88*^{L265P} associated with higher CNS relapse rate and shorter OS. • A prognostic score based on 3 risks, elevated LDH, platelet count <100 × 10^9/L, and h/o any previous WM therapy	• Enrollment in clinical trials with novel therapies preferred. • CIT such as R-CHOP • Consolidation with ASCT in fit responders to CIT. • If feasible, consider CNS prophylaxis with HD-MTX
WM in the Elderly	**Symptoms:** Similar to those in the young. **Diagnostic tests:** Similar to those in the young. May have lower IgM levels and serum albumin, and higher serum LDH and serum β2M compared to pts. <75 years. Frequency of *MYD88*^{L265P} mutation is similar to the young.	• Age > 65 years is an established unfavorable prognostic factor in all staging systems. • WM adversely affects OS of elderly pts. compared to matched general population. • In the Mayo series, over time, an increase in the proportion of pts. ≥75 years with active WM (12% during the 1996–2003, 18% during 2004–2010, 25% during 2011–2018) was noted	• CIT such as BR (reduced dose of bendamustine). In frail pts., DRC may be preferred, given its favorable toxicity profile • BTKi may be an alternative in pts. without cardiovascular comorbidities.

Abbreviations: HVS, hyperviscosity syndrome; cp, centipoise; pts., patients; IgM, immunoglobulin M; HV, hyperviscosity; OS, overall survival; PLEX, plasma exchange, RBC, red blood cells; AEs, adverse events; BTKi, Bruton's tyrosine kinase inhibitors; PN, peripheral neuropathy; pNL, peripheral neurolymphomatosis; MAG, myelin associated glycoproteins; DADS, Distal Acquired Demyelinating Symmetric; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; MMNCB, IgM paraproteinemic multifocal motor neuropathy with conduction block; CANOMAD, chronic ataxic neuropathy, ophthalmoplegia, immunoglobulin M [IgM] paraprotein, cold agglutinins, and disialosyl antibodies; EMG, electromyography; NCS nerve conduction study; r/o rule out; ETOH, ethyl alcohol; DM, diabetes mellitus; IV, intravenous; vs. versus; IVIg IVIg intravenous immunoglobulin; BR, bendamustine rituximab; DRC, dexamethasone, rituximab, cyclophosphamide; MRI, magnetic resonance image; FLAIR, fluid-attenuated inversion recovery; US ultrasonography PET-CT, positron emission tomography; FDG, fluorodeoxyglucose; BNS, Bing Neel syndrome; CNS, central nervous system; LPL, lymphoplasmacytic; CSF, cerebrospinal fluid; US, ultrasonography; RR, response rate; RT, radiotherapy; MYD88, myeloid differentiation primary response gene; TN, treatment naïve; BBB, blood-brain barrier; HD-MTX, high-dose methotrexate; EFS, event free survival; ASCT, autologous stem cell transplantation BEAM, BCNU, etoposide, cytarabine and melphalan; AIHA, autoimmune hemolytic anemia; CA, cold agglutinin; MAC, membrane attack complex; CBC, complete blood count; CAD, cold agglutinin disease; LDH, lactate dehydrogenase; LCs, light chains; WT, wild-type; CR, complete response; ORR, overall response rate; PR, partial response; q, every; ALH, amyloid light heavy chain; CTS, carpal tunnel syndrome; DOE, dyspnea on exertion; GI gastrointestinal; BM, bone marrow; IHC, immunohistochemistry; flow, flow cytometry; FISH, fluorescence in-situ hybridization; CT computed tomography, CAP, chest abdomen pelvis MS, mass spectrometry; NT-proBNP/BNP, N-terminal pro b-type natriuretic peptide/ brain natriuretic peptide; EKG, electrocardiogram; DPD/PYP, Technetium-99 m 3,3-diphosphono-1,2-propanodicarboxylic acid/ technetium-99 m sodium pyrophosphate; ATTR, transthyretin amyloidosis; LFTs, liver function tests; pts., patients; AL, amyloidosis light chain type; AH amyloidosis heavy chain type; VGPR, very good partial remission; R-CyBorD, rituximab, cyclophosphamide, bortezomib, dexamethasone; RF, rheumatoid factor; CP complement pathway, CH50, complement total; C complement; SPEP, Serum protein electrophoresis; UPEP urine protein electrophoresis, MPGN, membranoproliferative glomerulonephritis; MGUS, monoclonal gammopathy of undetermined significance; CIT, chemoimmunotherapy; HT, histologic transformation DLBCL, diffuse large B-cell lymphoma; ABC, activated B-cell; non-GCB non-germinal center B, R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; β2M beta 2 microglobulin; h/o, history of.

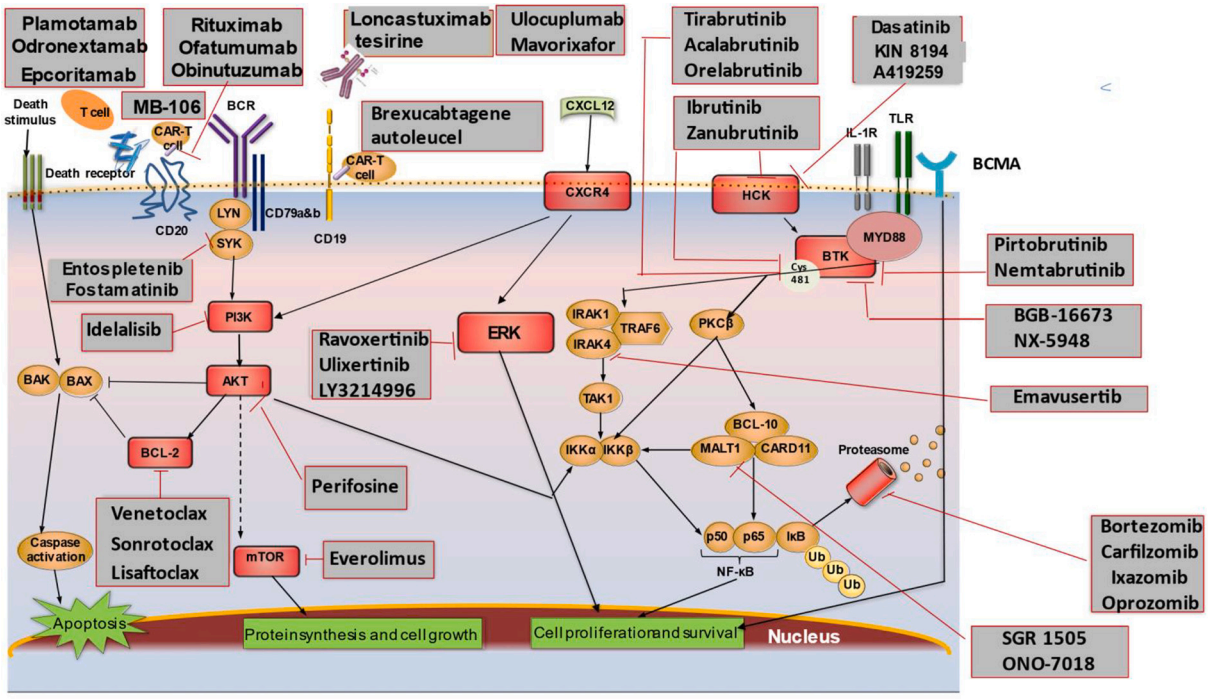

Fig. 4. Targets in Waldenström Macroglobulinemia.

16. Stem cell transplantation

Although data show that patients with a high WM burden may benefit from early autologous stem cell transplantation (ASCT), increasing use of novel therapies has relegated ASCT as a salvage option further down, beyond chemoimmunotherapy and BTK inhibitors [172–175]. Maximal efficacy of ASCT, with long-term disease control, is observed in patients with chemosensitive disease. However, data to support survival advantage of ASCT are lacking. Deferring ASCT to third or a later line of treatment, offering it to a transplant-eligible patient who has been previously treated with a BTK inhibitor (if available), is therefore considered reasonable (Fig. 3). The number of prior therapies and disease chemosensitivity at the time of ASCT dictated post ASCT survival among 202 patients in the European Bone Marrow Transplant Registry (EBMTR) who underwent ASCT [174]. In this analysis the non-relapse mortality rate was 3.8% at 1 year, with an estimated 5-year PFS and OS rates of approximately 40% and 69%, respectively. In a multi-institutional retrospective study, median OS of patients who relapsed post ACST was not reached after a median follow up of 3 years. There was a trend toward shorter survival among patients who relapsed within a year (median 18.4 months vs. NR; $p = 0.06$) [176]. The post relapse OS in patients who were rescued with ibrutinib salvage therapy post-transplant was longer compared to those who did not receive ibrutinib (median NR vs. 18.4 months; $p = 0.02$) [176].

Among the patients with concurrent AHL amyloidosis, ASCT continues to play a crucial role, particularly as the tolerability to BTK inhibitors in this specific patient population is poor, and the options are limited. However, only a minority of such patients are ASCT eligible. Additionally, patients with BNS may benefit from this approach. Allogeneic transplantation, with its associated morbidity and mortality, is best avoided in patients with WM with expanding therapeutic options [173,177].

17. Cellular immunotherapy

On the heels of success in other non-Hodgkin lymphomas, among the first constructs to be examined in WM, which expresses both CD19 and CD20, are CAR-T products against CD19 and CD20. Preliminary results in 3 patients who had received a CD19 directed CAR-T demonstrated a response in 2 (1 CR, 1 PR and 1 stable disease), but the disease control was short-lived (3–26 months) following CAR-T therapy [178]. A CD20-targeted CAR, MB 106, is also currently being evaluated in an ongoing phase 1/2 basket trial that includes refractory LPL among other non-Hodgkin lymphomas [179]. Preliminary data in 2 patients with WM were promising, with both patients responding; the response appeared to be maintained at 15 months after treatment in one patient, while COVID-19 related non-relapse mortality was observed at 6 months following CAR-T treatment in the other patient.

18. T cell engagers

Bispecific or tri-specific T-cell engagers (TCEs) are antibodies with binding sites directed against the tumor and the T cell antigens to facilitate creation of an immunologic synapse, leading to neoplastic cell death [180]. Approval of the off-the-shelf anti-BCMA bispecific for RR MM (teclistamab) and anti CD20 bispecifics for RR lymphomas (glofitamab, mosunetuzumab epcoritimab) have indisputably established their strong efficacy in B cell malignancies, although the paucity of TCE related data in WM speaks to their sluggish development specifically for a rare malignancy such as WM. Several ongoing studies, examining odronextamab, epcoritamab and plamotamab will likely show the efficacy and tolerability of this novel class of agents for the WM patient population.

Several trials outside of T cell directed immunotherapies, including those with fixed-duration novel-novel combinations, with potential to impact patient outcomes, are ongoing (Table 7).

19. Severe acute respiratory syndrome coronavirus 2 in patients with WM

Several new variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have emerged since the original Wuhan strain that caused the COVID-19 pandemic. Breakthrough infections occur despite the use of vaccines. The IWWM-11 Consensus Panel 5 has

Table 7
Ongoing Trials Utilizing Novel Approaches in Waldenström Macroglobulinemia.

Trial identifier	Intervention	Phase	Cohort	Primary outcome measure
BTK Inhibitor Combinations				
MK-1026-003 NCT04728893	Nemtabrutinib (ARQ 531/MK-1026)	2	Refractory to CIT, cBTKi Part-2 (Cohort H) WM Specific	ORR
NCT05065554	Acalabrutinib (C1–48) Rituximab (C1& 4)	2	TN/R exposed WM and MGUS Anti MAG PN	ORR
RAINBOW NCT04061512	Ibrutinib, Rituximab X (C1–6) followed by Ibrutinib vs. DRC	2/3	TN	ORR at week 24; PFS at 2 years
CZAR-1 NCT04263480	Ibrutinib, carfilzomib vs. ibrutinib	2	TN/RR	≥ VGPR at 12 m
SWOG 2005 NCT04840602	Ibrutinib (C1–24), Rituximab (C1 & C5) +/− Venetoclax (C1–24)	2 RT	TN prior Rituximab allowed if given >12 m (ARM 1: IR may switch IRV if progressing on IR; Arm B IRV)	CR rate with IRV vs IR
NCT03679624	Daratumumab (C1–19), Ibrutinib	2	TN (Cohort A; ibrutinib naïve) Previously treated but ibrutinib plateau	Safety Terminated
NCT04883437	Acalabrutinib (C1–12), Obinutuzumab (C3–8) After C12 pts. in CR randomized o D/c Rx or continue. Pts < CR continue Acalabrutinib	2	TN LPL	CR rate ≥ Grade 3 AE rates
BCL2 Inhibitor Combinations				
NCT05734495	Pirtobrutinib (C1–24), Venetoclax (C2–24)	2	RR ≥1 prior Rx; Prior cBTKi permitted	≥ VGPR
ViWA NCT05099471	Venetoclax, Rituximab vs. DRC	2	TN	≥ VGPR
MAPLE-1 NCT04260217	Lisaftoclax (APG2575) +/−Rituximab+/ − ibrutinib	1b/2	TN Arm B RR Arm A (1 Prior Rx and I-refractory) Arm C (BTKi naïve)	DLT/MTD
NCT04277637	Sonrotoclax (BGB-11417), Zanubrutinib	1/2	RR Part 1 Monotherapy dose finding	MTD/RP2D
NCT05734495	Pirtobrutinib (C1–24), Venetoclax (C2–24)	2	RR ≥1 prior Rx; Prior cBTKi permitted	≥ VGPR
NCT04830137	NX-2127 (BTK Degrader)	1a/ 1b	RR ≥1 prior Rx and refractory to BTKi	DLT/MTD; ORR at Ph1b dose
NCT05131022	NX-5948 (BTK Degrader)	1a/ 1b	RR ≥2 prior Rx, BTKi exposed, BNS	DLT/MTD; ORR at Ph1b dose
NCT05544019	SGR-1505 (MALT Inhibitor)	1	RR WM, LPL	DLT/MTD
NCT03147885	Selinexor-RCHOP (C1-C6) followed by selinexor (XPO inhibitor) maintenance (1 year) among pts. achieving ≥PR	1/2	RR WM (only Ph 1) 1 prior non-anthracycline based Rx	DLT/MTD
NCT04450069 CLOVER-WaM	Iopofosine (CLR-131)	2	RR WM/LPL, ≥2 prior Rx BNS4 total infusions of CLR 131 (15 mCi/m2) over 2 cycles	MRR
NCT05065554	Acalabrutinib (C1–48) Rituximab (C1& 4)	2	TN/R exposed WM and MGUS Anti MAG PN	ORR PN neuropathy response rate (secondary outcome measure)

recently released an updated approach for the prevention and management of COVID-19 related issues [181]. The key recommendations suggest using variant-specific booster vaccines (annually, together with the flu vaccine) at least 3 months from the last vaccine dose or COVID-19 infection in all patients with WM. Encouraging data suggest emergence of protective neutralizing antibody titers following the booster dose in a third of patients with B-cell malignancies, including patients with WM, who had previously demonstrated suboptimal responses following the second dose. Preventive measures, including continued use of masks are advocated, particularly among patients on BTK inhibitors and/or anti-CD20 monoclonal antibodies used within the previous year. As certain WM-directed therapies attenuate post vaccination humoral response, if feasible, temporary interruption in the treatment prior to vaccination/boosters may improve vaccination response. Pre-exposure prophylaxis is recommended for all patients receiving WM-directed therapy. The role of immunoglobulin administration against COVID-19 inpatients with WM remains unclear, although high SARS-CoV-2 anti spike titers have been detected in patients receiving prophylactic immunoglobulins [181].

Owing to the increased risk of developing severe COVID-19 infection, oral ritonavir/nirmatrelvir antiviral drug combination should be promptly initiated in all WM patients experiencing mild to moderate COVID-19 related symptoms, and in select asymptomatic patients, irrespective of their prior vaccination or WM status. Given the drug-drug interactions, to minimize toxicity, ibrutinib, zanubrutinib and venetoclax should be temporarily held, considering the risk of IgM rebound upon withholding therapy. For patients in whom ritonavir/nirmatrelvir combination is contraindicated, remdesivir may be administered within 7 days of symptom onset. Despite lack of interaction with ibrutinib or venetoclax, molnupiravir is not considered the first line antiviral because of its reduced efficacy in comparison to the other 2 agents [181].

20. Surveillance

For patients with an established diagnosis of IgM MGUS, we recommend active surveillance that involves careful history taking, focussing on the emergence of symptoms associated with progression to WM, ALH amyloidosis and MM, full physical examination (focussing on the evaluation of lymphadenopathy, organomegaly, fluid overload, bruising, peripheral neuropathy, etc) and laboratory assessment (CBC, serum and urine monoclonal protein studies, serum calcium, alkaline

phosphatase and serum LDH) at 6 months initially, and annually thereafter, if the patient is asymptomatic, clinical examination is unremarkable and the laboratory assessment is stable. Patients with SWM also require lifelong active surveillance, preferably every 4 months for the first 3 years from diagnosis, every 6 months for the subsequent 2 years, and, if stable, annually thereafter. We do not perform imaging studies during surveillance unless otherwise dictated by the clinical evaluation. For patients with active WM on chemoimmunotherapy, we suggest evaluating at least once at the commencement of each new cycle of treatment and on an as needed basis. We typically do not advocate the use of rituximab maintenance therapy among responders. Upon completion of the treatment, we evaluate the responders once every 3 months for 2 years and every 4–6 months subsequently focussing on persistent cytopenias, age-appropriate cancer screening and patient vaccination status. Patients may continue to show an improvement in the depth of response even several months beyond the completion of the chemoimmunotherapy course. An increasing IgM level, meeting the criteria of biochemical progression, in the absence of reemergence of symptoms or cytopenia(s) does not warrant reinitiation of therapy. For patients on BTK inhibitors, we recommend assessment once every cycle for the first few cycles, focussing on cardiovascular, gastrointestinal, and musculoskeletal and cutaneous issues. If patients are tolerating therapy well, we reduce the frequency of face-to-face evaluation to every 3 months, but suggest checking complete blood count with the differential count on a monthly basis, blood pressure monitoring and modifying the dose as needed.

21. Future considerations

Although WM remains incurable, the plethora of drugs, currently available, and in development (Fig. 4) underscore that the management of WM is evolving, as more evidence from unique approaches, including CAR-T, bispecific antibodies, BTK degraders, and radiotherapeutics, emerges from the ongoing trials. Although CR remains elusive with novel therapies, our aim to achieve CR should not be abandoned as it may be a prerequisite to cure. The lack of disease eradication with BTKi suggests inherent resistance of WM cells to this class of drugs. However, deeper responses have not consistently translated into improved outcomes. This is especially true for the lack of superior OS among patients achieving a CR and the debate of 'cure' versus 'control' of WM persists. Rational combination strategies that simultaneously target different proteins/pathways in WM cells will eventually aid in advancing the field, provided the tolerability of such combinations, and in turn, the patients' quality of life, is not compromised.

If the transformative progress over the past few years is prologue, the pace of advances over the next decade would be unprecedented as researchers continue to explore rationale combination and sequential strategies utilizing newer-generation agents with non-overlapping toxicities. The seminal discovery of *MYD88* L265P mutation served as an inflection point inducing extraordinary enthusiasm to identify newer druggable targets, which coupled with the typically indolent course of WM has permitted sizeable proportion of patients to benefit from the introduction of novel agents that offer a viable alternative to the traditional chemoimmunotherapy. However, an inherent advantage associated with the chemoimmunotherapeutic approach is the finite duration of its delivery and clinical trials in development will focus on examining whether potent novel-novel agent combinations given for a fixed period can ultimately supplant frontline chemoimmunotherapy. The success of such trials would arguably be the next landmark in this dynamic field.

Practice points

- Clonal lymphoplasmacytic involvement of the marrow, without evidence of end-organ damage such as anemia or lymphadenopathy is considered IgM MGUS if the level of involvement is <10%, and smoldering WM if the level of involvement is 10% or higher; these asymptomatic disorders do not require therapy.
- To establish the diagnosis of symptomatic WM, there must be evidence of end-organ damage that is unequivocally attributable to the lymphoplasmacytic lymphoma such as cytopenias, constitutional symptoms, hyperviscosity, symptomatic lymphadenopathy, or hepatosplenomegaly.
- A monoclonal anti-CD20 antibody, most commonly rituximab, is typically added to a chemotherapy backbone to treat WM.
- The two most frequently used regimens for initial therapy are either rituximab plus bendamustine or a covalent BTK inhibitor such as zanubrutinib or ibrutinib.
- *MYD88*^{L265P} and *CXCR4* mutation status may aid in the treatment decision-making
- Other classes that have a role in the treatment of WM, especially in relapsed disease include proteasome inhibitors and purine nucleoside analogs.
- B cell lymphoma-2 (BCL2) inhibitors and non-covalent BTK inhibitors are effective in patients who have been previously exposed to a covalent BTK inhibitor

Research agenda

- Randomized trials comparing fixed-duration rituximab-bendamustine versus continuous therapy with rituximab plus BTK inhibitors are needed. We also need randomized trials investigating fixed-duration BTK inhibitor combinations.
- Clinical trials to determine the optimal BTK inhibitor to be used in treatment of newly diagnosed and relapsed WM are needed.
- We also need trials investigating CART cells and bispecific antibodies in WM.
- Relapse in WM is common, and strategies investigating additional plasma cell compartment directed therapy, specifically anti-CD38 antibodies should be investigated as consolidation approaches.
- Translational studies to determine the appropriate use of predictive biomarkers to selecting therapy are needed.

Declaration of Competing Interest

Prashant Kapoor, MD is the principal investigator of trials for which Mayo Clinic has received research funding from Amgen, Regeneron, Bristol Myers Squibb, Loxo Pharmaceuticals, Ichnos, Karyopharm, Sanofi, AbbVie and GlaxoSmithKline. Prashant Kapoor has served on the Advisory Boards of BeiGene, Pharmacyclics, X4 Pharmaceuticals, Kite, Oncopeptides, Angitia Bio, GlaxoSmithKline, AbbVie and Sanofi.

S. Vincent Rajkumar, MD has no conflict of interest to declare.

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