Seminars in Hematology 62 (2025) 90–105

Contents lists available at ScienceDirect

Seminars in Hematology

journal homepage: www.elsevier.com/locate/seminhematol

Report of Consensus Panel 3 from the 12th International Workshop on Waldenstrom's Macroglobulinemia on the management of patients with high-risk disease

Prashant Kapoor[a,*], Meletios A. Dimopoulos[b,c], Stephen M. Ansell[a], Efstathios Kastritis[b], Ranjana Advani[d], Eric Durot[e], Pierre Morel[f], Charalampia Kyriakou[g], Roman Hajek[h], Daniela Drandi[i], Jithma P. Abeykoon[a], Signy Chow[j], Xinxin Cao[k], Christopher J. Patterson[l], Jeffrey V. Matous[m], Christian Buske[n], Steven P. Treon[l], Marie J. Kersten[o]

[a] *Mayo Clinic, Rochester MN*
[b] *Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece*
[c] *Department of Medicine, Korea University, Seoul, South Korea*
[d] *Stanford University Medical Center, Stanford CA*
[e] *Department of Hematology, University Hospital of Reims and UFR Médecine, Reims, France*
[f] *Department of Hematology, University Hospital of Amiens, Amiens, France.*
[g] *Department of Haemato-Oncology, St Bartholomew's Hospital, London, UK*
[h] *Department of Haemato-oncology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic*
[i] *Department of Molecular Biotechnology and Health Sciences, Hematology Division, University of Torino, Italy*
[j] *Odette Cancer Centre, Sunnybrook Health Sciences Centre, Division of Medical Oncology and Hematology, Faculty of Medicine, University of Toronto, Toronto, Canada*
[k] *National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[l] *Dana Farber Cancer Institute, Harvard Medical School, Boston MA*
[m] *Colorado Blood Cancer Institute, Sarah Cannon Research Institute, Denver, CO*
[n] *University Hospital Ulm, Institute of Experimental Cancer Research, Ulm, Germany*
[o] *Department of Hematology, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam/LYMMCARE, Amsterdam, the Netherlands*

ARTICLE INFO

Keywords:
IgM lymphoplasmacytic lymphoma
Risk stratification
TP53 mutation
Deletion 17p
Prognosis

ABSTRACT

The Consensus Panel 3 (CP3) of the 12th International Workshop on Waldenström macroglobulinemia (IWWM-12) has reviewed and incorporated current data to make recommendations for the management of patients with high-risk WM (HR-WM). Recognizing the considerable heterogeneity in survival outcomes and identifying a subgroup of patients with a very poor prognosis, the key recommendations from CP3 include: (1) Risk stratifying patients with smoldering WM (SWM) and active (symptomatic) WM at diagnosis (2) Using the degree of i) bone marrow lymphoplasmacytosis, ii) serum beta-2 microglobulin (β2M) elevation, iii) IgM increase, iv) serum albumin decrease and the presence of wild-type *MYD88* status markers that adversely dictate the time-to-progression from smoldering to active WM to the define HR-SWM. (3) Among patients with active WM, the presenting parameters: advanced chronological age, low serum albumin, elevated serum lactate dehydrogenase, elevated β2M and the presence of *TP53* alterations *(TP53* mutation or deletion 17p) unfavorably impact the prognosis and should be utilized to risk-stratify patients into the HR category. (4) The panel encourages screening for genetic alterations at diagnosis, prior to initiating therapy and also with rapidly advancing disease or refractoriness to ongoing therapy, which might result from clonal evolution. Although limited data directing the selection and sequencing of therapies exist, a risk-adapted approach and clinical trial participation for patients with HR-WM are highly encouraged.

* Corresponding author: Prashant Kapoor, MD, Mayo Clinic, Rochester, MN 55905.
E-mail address: kapoor.prashant@mayo.edu (P. Kapoor).

https://doi.org/10.1053/j.seminhematol.2025.04.001
0037-1963/© 2025 Published by Elsevier Inc.

Introduction

Various staging systems, developed over the years for patients with active (symptomatic) Waldenström macroglobulinemia (WM), attest to the substantial disease heterogeneity, exemplified by considerable disparity in overall survival (OS), particularly between the low- and very advanced-stage patient populations [1–6]. The benefits of the steadily expanding treatment landscape, with increasing incorporation of novel agents, are not yet apparent for the high risk patients that continue to have a dismal outcome (5-year OS rate ~35%) [7]. Furthermore, optimal sequencing of therapies remains unclear, particularly for this high-risk (HR) subset of patients [8]. At IWWM-12, the Consensus Panel 3 (CP3) was tasked with making recommendations regarding the management of HRWM. The panel chairs (PK and MJK) initially formulated a series of questions spanning the topic, foremost focusing on defining HRWM, including HR smoldering WM (HRSWM), then developing an approach to accurately capture the prognosis, building a consensus regarding the most suitable initial therapies and subsequent optimal sequencing in the contemporary era, and ultimately emphasizing potential research strategies that should be prioritized for the management of HR patients.

At the outset, the CP3 members acknowledged the obvious knowledge gaps and paucity of evidence to support many recommendations solely based upon the existing data for HRWM. Their appraisal served to highlight the deficiencies and challenges, underpinning the urgency to facilitate much-needed research and bolster efforts toward finding evidence to support a risk-adapted approach. The goal is to improve outcomes of the most difficult-to-treat (and currently ill-defined) subset of patients, with short-lived remission-duration(s), that ultimately succumbs to WM. To that end, CP3 attempted to make consensus statements addressing the following relevant questions to provide a framework to build upon hereafter for optimal management of HRWM.

How should high-risk smoldering WM be defined?

The CP at the IWWM-2 had used the term "smoldering WM" (SWM), specifically for patients with bona fide WM, not meeting the criteria for initiating treatment because of the absence of symptoms and/or end-organ damage attributable to WM [9]. Not all patients with SWM will progress to active WM during their lifetime and they are generally observed until an indication warranting clinical intervention is met [10]. Up to 25% to 28% of patients are categorized as SWM at diagnosis, and they enjoy survival comparable to their age- and gender-matched general population [11–13]. However, patients with SWM —an 'intermediate' precursor disease between IgM monoclonal gammopathy of undetermined significance (MGUS) and active WM— demonstrate widely-divergent outcomes, with a subset at one end of the spectrum, that inarguably qualifies as HR-SWM and progresses to active disease in a short timeframe (~ 2-3 years), and a subset at the other extreme mimicking IgM MGUS, with a low probability of progression [10,14–17].

Retrospective studies examining the natural history of SWM have identified numerous factors impacting the risk of progression, including the degree of bone marrow lymphoplasmacytic lymphoma (LPL) infiltration, serum β_2-microglobulin, serum albumin, serum IgM, circulating tumor cells (CTCs), concomitant immunoparesis or clonal hematopoiesis, as well as the presence of certain cytogenetic abnormalities, mutations or lack thereof, contributing to clonal evolution [18–25].

In a recent analysis led by Dana Farber Cancer Institute (DFCI) involving 439 patients with "asymptomatic WM" — classified as such based on any degree of marrow lymphoplasmacytic lymphoma infiltrate and absence of symptoms — marrow infiltration of ≥70%, serum IgM ≥4500 mg/dL, serum β_2-microglobulin ≥4mg/dL, and serum albumin <3.5g/dL emerged as independent markers of progression, with each of these parameters at their respective cut-offs associated with ~60% 2-year risk of progression [14]. To avoid biases, hemoglobin level was omitted from the model because anemia is already factored into decision-making regarding treatment initiation. This model categorized patients into 3 distinct groups (risk-score below the first quartile, interquartile and above the third quartile) based on the likelihood of progression to overt WM [14]. Interestingly, in two studies, including the aforementioned study, patients with wild-type myeloid differentiation factor 88 (*MYD88*^{WT}) had a short time-to-progression (median TTP, ~1·7 to 1.8 years) [13,14]. This signature was not integrated with the other features in the proposed models as the MYD88 related data were available only for a small subset of the subjects. One study showed *MYD88*^{WT} genotype to be an independent risk factor for progression in a multivariate analysis [14]. However, other studies with somewhat conflicting these findings have suggested that the presence of *MYD88*^{L265P} mutation, as well as its allele burden, are actually risk factors for shorter progression [26,27]. Similarly, scant data regarding the CXC motif chemokine receptor 4 (CXCR4) mutational status have precluded its incorporation into the current stratification models of SWM [13,27,28]. Data regarding *TP53* alterations (*TP53*^{Alt}) are limited in SWM [22].

- The panel considers patients with SWM to have high-risk disease if the projected risk of progressing to active WM is within 3 years of the diagnosis.
- Because the DFCI model, incorporating routinely used tests, could differentiate a subset that had a high risk of progressing within 3 years of diagnosis and has been externally validated in 3 additional cohorts from Mayo Clinic, Greece and Italy (median TTP for HR-SWM, 2.2-2.9 years) [14,29] CP3 considers it to be among the most robust and easily adoptable existing models. The panel recognizes the deficiencies that could conceivably be overcome in the future, incorporating additional biomarkers, including genomic features (*MYD88*, *CXCR4* and *TP53* alteration status) if deemed independently prognostic in the progression dynamics to overt WM.
- The panel appreciates the absence of evidence to suggest that early therapeutic intervention would lead to improved OS in HR-SWM and reaffirms the IWWM-2 consensus recommendations to watch and wait, outside of well-designed clinical trials, irrespective of the risk factors.
- The panel recommends that patients with HR-SWM be actively surveilled every 3-4 months. If a biomarker(s) changes rapidly to suggest disease evolution during surveillance, complete re-evaluation is warranted to ensure that the patient still does not meet the criteria for initiating therapy. Clinicians should reinforce with their patients, the importance of remaining vigilant for any "red flag" symptoms and continue to monitor even more closely [10].
- The panel recommends that the proposed definition (Table 1) be uniformly adopted to identify and classify patients with HR-SWM for any clinical trials/ studies pertaining to SWM in the future.

How should high-risk active WM be defined?

The median OS of patients with overt WM is over 10 years and continues to improve particularly in the elderly [6,30]. A subset of patients, however, has dismal survival (median ~3 years from the diagnosis) [5]. Chronological age at presentation has repeatedly emerged as the strongest prognostic factor, with advanced age consistently correlating with poor outcome [3,5,6,31], despite some studies adjusting for the cause of death [6,32]. Even

Table 1
Consensus panel definitions for high-risk smoldering and active WM.

Disease entity	Criteria	Outcome
High-risk smoldering WM	Risk score >1.8512 calculated by Asymptomatic WM Patient Risk Calculator (www.awmrisk.com) based on the following biomarkers: i) Immunoglobulin M ii) Bone marrow lymphoplasmacytic infiltration iii) Serum β_2M iv) Serum albumin OR Presence of *MYD88*^{WT} genotype OR *Presence of *TP53*^{Alt} *[TP53*^{MUT} and/or Del 17p]	Median TTP 1.8 y
High-risk active (symptomatic) WM	High-risk MSS-WM (Composite Score 3-5, Calculator www.myelomarisk.com) using the following variables: i) Age: ≤65 y (Score 0), 66-75 y (Score 1), >75 y (Score 2) ii) Serum LDH > ULN (Score 2) iii) Serum albumin <3.5 g/dL (Score1) *Plus* Serum β_2M ≥4 mg/dL OR A. †A total score 4 or 5 using the following variablesi) Age 66-75 y (1 point), >75 years (2 points) i) Serum β_2-microglobulin ≥4 mg/dL (1 point) ii) Serum LDH >250 U/L (1 point) Serum albumin <3.5 g/dL (1 point) OR a) Presence of *TP53*^{Alt} *[TP53*^{MUT*} and/or Del 17p]	5-y OS 35%-40%, Median OS ~2.5 y

Abbreviations: WM Waldenström macroglobulinemia, β_{2M} Beta2microglobulin, WT wild-type *TP53*^{Alt} Tumor protein 53 alteration, *TP53*^{MUT*} Tumor protein 53 mutation, Del 17p Deletion 17p, TTP time to progression, MSS-WM Modified Staging System for WM, LDH, Lactate dehydrogenase; ULN, upper limit of normal; OS, overall survival.
†Patients categorized as very-high risk in the Revised International Prognostic Staging System for WM (rIPSS-WM).
*Variant allele frequency (VAF) cutoff for *TP53* mutation is not well established but should be at least 1% to be considered high-risk.

among patients ≥75 years of age at diagnosis, the most frequent cause of death is WM [33,34] and the survival of patients with WM is inferior to the matched general population [35]. Several other traditional baseline features (hepatosplenomegaly, low albumin, high β_2-microglobulin, elevated serum lactate dehydrogenase (LDH), high IgM, anemia, thrombocytopenia), molecular or cellular markers (*MYD88*^{WT}, circulating tumor cells) are considered unfavorable [3,5,6,32,36–40]. In addition, the development of complications (histologic transformation (HT), extramedullary disease, coexisting AL/AH/AHL amyloidosis) is associated with poor prognosis [32,38,41–44]. However, many variables are either not independently and accurately able to capture the prognosis, or encountered infrequently, precluding their inclusion in prognostic models. For example, mutated *CXCR4* is associated with resistance to therapies and inferior outcomes but mutated CXCR4 alone does not lead to markedly poor (<3 years) OS [45–55].

The International prognostic staging system (IPSS-WM) has been most widely used, although a few subsequent iterations of the staging systems have highlighted its limitations. Among these, the revised International Prognostic Scoring System (rIPSS-WM) aimed to capture the high-risk population by a priori considering a 3-year timepoint from treatment initiation, to determine the cut-off for the most significant variables for WM-related death by 3 years. Although it could only be partially replicated in external cohorts, with poor discrimination of the intermediate risk groups, a distinct subset of patients (12%) at the highest risk of WM-related death was identified (score 4-5), with a 3-year WM-related mortality of 48% (Table 1). However, molecular parameters and cytogenetics have not been integrated in rIPSS-WM [5,7].

Another, externally validated prognostic tool, the Modified Staging System (MSS-WM) was subsequently proposed, and it further simplified the rIPSS-WM. Importantly, the MSS-WM also demonstrated no incremental value of incorporating *MYD88*^{L265P} genotype for staging [6]. MSS-WM relied only on age, albumin and LDH at diagnosis as β2-microglobulin did not emerge as prognostic (Table 1). However, high β2-microglobulin levels tracked with elevated LDH, low albumin and older age, and a consistent rise in the proportion of high β2-microglobulin with increasing stage was noted (36%, 63%, 69%, and 80% within MSS-WM low, low-intermediate, intermediate, and high-risk cohorts). Although at the lower stages elevated β_2-microglobulin failed to further risk-stratify the patients, among those stratified as high-risk MSS-WM, an ultra-HR cohort, comprising 14% of the study population, could be further delineated on the basis of β2-microglobulin ≥4 mcg/mL (Fig. 1; Kapoor, personal communication). Notably, both disease burden-based scores, rIPSS-WM and MSS-WM that include similar variables, still require validation in patient-populations treated with frontline BTKi.

Deletion 6q is the most frequently encountered cytogenetic abnormality in WM and results in the loss of B-lymphocyte-induced maturation protein 1 (*BLIMP1*) and tumor necrosis factor alpha-induced protein 3 (*TNFAIP3*), a negative regulator of the nuclear factor kappa B (NF-κB) pathway [45,47,56–60]. Its impact as an independent prognosticator for OS is not well-established. With the available data demonstrating conflicting findings, it is not currently included in any risk-stratification [61–63].

CXCR4 mutation(s), detected in up to 40% of patients, confers resistance to many therapies [46,48–50,52,64,65]. *MYD88*^{L265P}/*CXCR4*^{Mut} signature is associated with inferior progression-free survival (PFS) in some trials although their negative effect on OS is only beginning to emerge with longer follow-up, indirectly suggesting that upon relapse, salvage therapies may, to an extent, still effectively rescue such patients [66]. A recent Chinese study showed that the IPSS-WM independently risk-stratified patients on non-BTKi therapies, but *CXCR4* and *MYD88* mutations did not [67]. Conversely, the IPSS-WM failed to risk-stratify patients on BTKi therapies in whom these two molecular markers were independently prognostic for OS [67].

The short arm of chromosome 17 houses the tumor protein P53 (*TP53),* encoding a tumor suppressor protein [68]. In WM *TP53*^{Alt} predominantly comprise *TP53* mutations (*TP53*^{MUT}) in the DNA binding domain and monoallelic 17p loss (deletion 17p) [22]. Biallelic inactivation may occur, with deletion 17p occuring alongside a *TP53* mutation on the other allele [22]. Furthermore, *TP53*^{Alt}

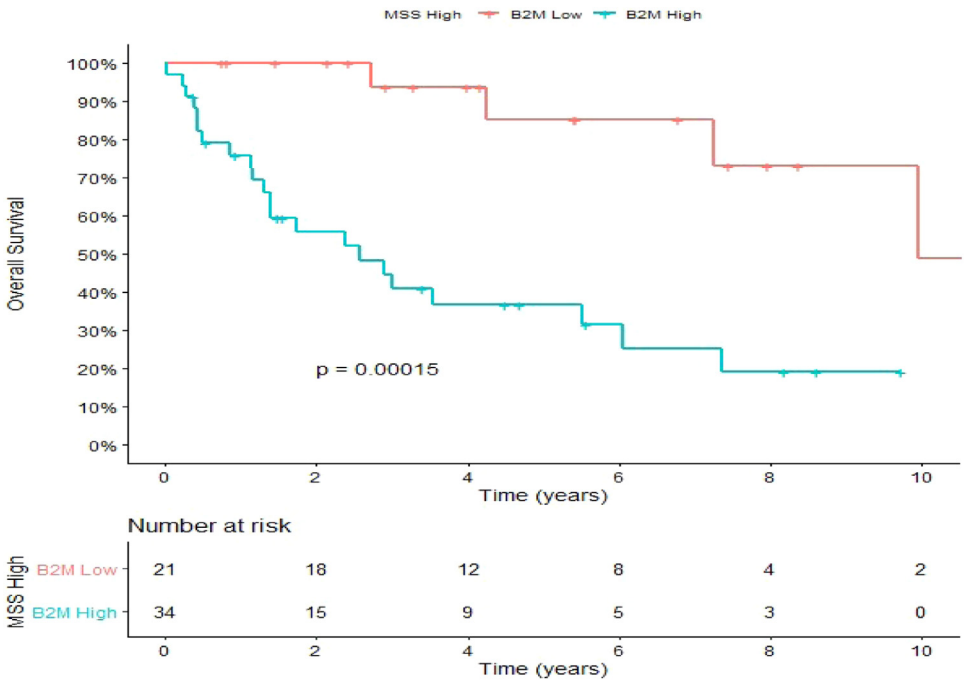

Fig. 1. Among treatment-naïve patients with active WM staged as high-risk MSS-WM, those with β2-microglobulin ≥4 mcg/mL had markedly worse overall survival compared to the remainder of the high-risk MSS-WM patients.

may coexist with *CXCR4* mutations [22,31,50]. A preponderance of evidence suggests that *TP53*^{Alt}, although infrequently encountered in treatment-naive (TN) WM patients, are associated with an increased tumor burden and aggressive disease course [22,69]. The detection rate increases to up to 25% to 30% in relapsed/refractory (RR) disease (Table 2) [46,55]. *TP53*^{Alt} are associated with inferior outcomes, although only a few trials have systematically studied and reported their effect, and tests assessing *TP53*^{Alt} have not been regularly employed in routine practice (Table 2). To what extent their presence incrementally adversely impacts the prognosis, not already captured by the more conventional biomarkers or disease-burden-based scores, remains to be determined.

A post-hoc biomarker analysis of the phase 3 ASPEN trial that compared 2 different BTK inhibitors, ibrutinib and zanubrutinib among patients with TN or RR WM was recently performed (Table 2) [55]. It showed that besides *MYD88*^{MUT}, the most frequently detected genetic alterations that were detectable on the baseline next-generation sequencing (NGS) occurred in *CXCR4* (25.7%), *TP53* (24.8%), *ARID1A* (15.7%), and *TERT* (9%) [55]. The high assay sensitivity (LOD: ~0.1%-0.25%; 11.6% of patients had VAF<1%), along with relapsed/refractory disease comprising the bulk of the study population, could explain the remarkably high *TP53*^{MUT} rate. A high *TP53*^{MUT} acquisition rate may also reflect the genotoxic effects of prior alkylating-agent or purine-analog based regimens [70,71].

- Synthesizing the currently available data, the panel defined HR-WM, recognizing that the proposed definition (Table 1) is subject to further refinement as new evidence regarding the independent prognostic impact of cytogenetic and molecular alterations emerges.

Which tests should be performed to risk stratify WM patients at diagnosis and how should patients be assessed for clonal evolution at progression?

Table 3, outlining the required tests, also underscores the value of a symptom-directed streamlined evaluation at diagnosis for a malignancy with myriad clinical manifestations of differing implications.

MYD88 mutational status serves as a predictive marker for BTKi monotherapy but has not uniformly shown to be prognostic across different treatments, and it is therefore not currently included in the WM risk stratification.

- The panel recommends that all patients undergo baseline serum albumin, serum β_2-microglobulin, serum LDH assessment at diagnosis for risk stratification.
- The panel does not recommend conventional cytogenetic analyses routinely, given the low mitotic index of WM cells and the absence of disease-defining chromosomal aberrations. However, prospectively examining the value of CD19+ enriched FISH studies both in SWM and active WM for del17p as well as *TP53*^{MUT} analysis in CD19+ sorted cells by Sanger sequencing, or preferably, the more sensitive *TP53*-specific NGS panel (because the mutation may be subclonal), is important to advance the field. The panel recommends using the chronic lymphoid malignancies targeted NGS panels that are becoming more easily available.
- Notably, *TP53* alterations may appear during clonal evolution and at relapse if not detectable at diagnosis and should be assessed at later timepoints, prior to starting a new line of treatment in patients previously genotyped as wild type. Among the patients with *TP53* mutation in whom del17p is not previously captured, FISH analysis should be performed prior to starting any line of treatment to specifically rule out del17p cytogenetic abnormality, an established marker of poor prognosis.

What are the best available frontline therapies to treat HR-WM and which therapies should be avoided in these patients?

The panel recognizes that the absence of a uniform definition for HR-WM has resulted in paucity of evidence for the management of this subset of patients. Nonetheless, more recent studies have demonstrated a differential effect of therapies in certain sub-

Table 2
Studies examining the significance of *TP53*$^{\text{Alteration}}$ in WM.

Study/Year	Cohort	N	Method	Frequency of *TP53* $^{\text{Alt}}$	PFS & [OS If available]	Comments
Mayo Clinic 2002 [95]	TN/RR TNWM RRWM	40 11 29	FISH	Del 17p 15% (total) 9% TN 21% RR	NA	• Pts with Del 17p13.1(p53) had higher marrow LPL burden. • The deletion pattern was interstitial deletion with loss of one 17p13.1 signal and 2 CEP17 probe signals
Mayo Clinic 2004 [96]	TN/RR TNWM RRWM	22 9 13	FISH	Del 17p 9%	NA	• Interstitial deletion was the most common pattern of deletion. • Outcome analysis not performed
WM1 Trial subset analysis 2013 [57]	TNWM	140	FISH/ Cytogenetics	Del 17p 8% *TP53*^{MUT} 0%	19 m vs 30 m without Del17p	• Del 17p presence associated with higher LPL burden. • After adjusting for treatment arms (Chlorambucil vs Fludarabine) and IPSSWM risk groups, Del 17p was associated with shorter PFS • *TP53* sequences were analyzed in only 3 pts (all with Del 17p)
DFCI	TN/RR TNWM RRWM	30 26 04	WGS	*TP53*^{MUT} 7%	NA	• 1 of 2 cases with *TP53* $^{\text{mut}}$ was of biallelic mutation. • Deletion of both PRDM2 and TOP1 participating in TP53-related signaling was also noted.
French Study 2017 [22]	SWM Active WM	125	Sanger ultradeep-targeted NGS SNP array	*TP53* $^{\text{Alt}}$ 11.2% *TP53*^{MUT} 7.3%	TTP Active WM: 1.5y vs 4y, $P < .001$ TTP SWM: 2y vs 5y ($P = .001$) OS: Active WM: 4y vs NR SWM: 9y vs 18y ($P = .002$)	• *TP53* $^{\text{Alt}}$ characterized by shorter TTP & OS for active WM & SWM. • *TP53* $^{\text{Alt}}$ associated with shorter OS for active WM, regardless of IPSSWM. • All mutations localized to the DNA-binding domain. • No correlation with *CXCR4*$^{\text{mut}}$ • Pts with *TP53*$^{\text{Alt}}$ had more genomic abnormalities • Deletion 17p and *TP53* mutation co-occurred in 58%.
Chinese Study 2017 [97]	WM	98	FISH	Del 17p 8.9%	OS 36% (3y) vs 87% (3y) among pts without del17p	• Only a minority of pts with WM harboring Del 17p (25%) had CCF>20% in this study and unlike the CLL pts on the study, WM pts with Del17p >20% had no significant difference in the survival (3y OS 50%) outcome compared to OS of pts with Del17p CCF threshold of 6.5% (3y OS 36%). • In MVA, neither Del 17p nor Del 13q emerged as an independent unfavorable prognostic marker, but elevated LDH did. • No data on *TP53* $^{\text{mut}}$ effect in this study.
DFCI 2018 [69]	TN/RR TNWM RRWM	265 116 149	NGS Sanger	*TP53*^{MUT} 4.9% 2.3% (TN 2.6% RR: 2.0%)	NA 2/ 6 pts died at 0.5 m & 15 m Alive pts FU range: 10-31m	• *TP53* $^{\text{mut}}$ uncommon but associated with aggressive disease. • All mutations localized to the DNA-binding domain. • 5/6 (83%) with *TP53* $^{\text{mut}}$ but without concurrent Del 17p. • All 3 pts. on ibrutinib harbored CXCR4$^{\text{mut}}$ & attained a PR. • Biallelic inactivation in 4 pts, 2 of whom died of progression. • CHIP-associated *DNMT3A*$^{\text{mut}}$ in one pt.
Study/ Year	Cohort	N	Method	Frequency of *TP53* $^{\text{Alt}}$	PFS & [OS If available]	• Comments

(*continued on next page*)

Table 2 (*continued*)

Study/Year	Cohort	N	Method	Frequency of *TP53* ^{Alt}	PFS & [OS If available]	Comments
MDACC 2021 [21]	TN/RR WM SWM Non-IgM LPL	219 12	29-gene targeted NGS (Training Cohort, $N=68$) AS-PCR and 4 targeted NGS Validation Cohort ($n=18$)	*14%* (Overall) *TP53^{MUT} 11.8%* *22%*	NA	• Heterogeneous variants but all in DNA-binding domain (exons 5-8). • *TP53*^{mut} associated with symptomatic disease and shorter TTT. • For the entire cohort, TP53 ^{mut} associated with shorter PFS/ OS. • *TP53* deletion was detected in 10% in the validation set but did not appear to affect prognosis. • Rituximab maintenance in pts *TP53* ^{mut} associated better PFS1. • In a regression model for genetic and treatment factors in all patients *TP53*^{mut} was associated with inferior OS from diagnosis. • In patients *TP53*^{mut}, CXCR4$^{WT/FS}$ single agent ibrutinib was associated with a trend for better PFS1 ($P=.085$).
ASPEN Bio-marker post-hoc analysis 2023 [55]	TN/RR Cohort 1 *MYD88*^{mut} Cohort 2 *MYD88*^{WT}	210 190 20	NGS	*TP53^{MUT}* 24.8%	Ibrutinib: 42m-PFS *TP53*^{mut} 58% vs 72% in *TP53*^{WT}. Zanu: 42m-PFS *TP53*^{mut} 62% vs 85% in *TP53*^{WT}. Median PFS NR in Zanu arm vs 44.2 m in ibrutinib arm (HR, 0.66; $P=.37$) 1y-PFS 25% in *TP53*^{mut} vs 75% in P*53*^{WT}	• Patients with *TP53*^{mut} had poorer prognosis regardless of the BTKi used. However, outcomes were more favorable with zanubrutinib • (vs ibrutinib) among pts with *TP53*^{mut}. • The study was underpowered to detect a difference between the treatment arms. However, the 42-month PFS rate was only marginally higher in the zanubrutinib arm (62% vs 58% with ibrutinib). By contrast, the PFS rates were 84.6% and 72.1%, respectively in the TP53WT populations in the 2 arms. • In Cohort 1, 11.6% patients had *TP53*^{mut} at VAF <1% whereas 13.7% had *TP53*^{mut} at VAF ≥1% or had a TP53 deletion. Patients with *TP53*^{mut} at VAF of ≥1% or TP53 deletion had higher rate of *CXCR4*^{NS} • A dosage-dependent unfavorable impact on PFS was observed among patients with *TP53*^{mut} with VAF of ≥1%. • Pts with *TP53*^{mut} had shorter PFS on a multivariate analysis.
DFCI 2024 [31]	*MYD88* ^{mut} TNWM	119	RNA Seq WES	Del 17p 3% *TP53^{MUT} 2.5%*	NA	• Long median follow-up (~ 10 y) from diagnosis. • Only age and del 17p were significant predictors of OS. • When top 500 high variance genes within WM that were also differentially expressed between WM and healthy donor memory B cells were incorporated to the multivariate model, age and Del 17p were retained but high *ROR1* expression also emerged as a poor prognostic factor.

Abbreviations: N number, *TP53*^{Alt} Tumor protein 53 alteration, PFS Progression-free survival, OS Overall survival, TTP time to progression. Del 17p Deletion 17p, *TP53*^{MUT} Tumor protein 53 mutation, TN Treatment naïve, RR Relapsed and/or refractory, FISH fluorescence *in-situ* hybridization, NA Not available, Pts patients, LPL lymphoplasmacytic lymphoma, CEP Chromosome enumeration probe, IPSSWM International Prognostic Staging System for WM, WGS Whole genome sequencing, DFCI Dana-Farber Cancer Institute, MDACC Munroe Dunaway Anderson Cancer Center, SNP Single nucleotide polymorphism, AS-PCR Allele specific polymerase chain reaction, TTT Time to therapy, RNA seq Ribonucleic acid sequencing, SWM smoldering Waldenström macroglobulinemia, PRDM2 Positive regulatory domain zinc finger protein 2, TOP1 DNA topoisomerase I, MVA multivariable analysis, RNA-seq Ribonucleic acid sequencing, NGS Next-generation sequencing, *MYD88* Myeloid differentiation primary response gene, WT while type, Mut mutation, CXCR4 C-X-C chemokine receptor type 4, FS frame shift, NS nonsense, Zanu: Zanubrutinib, CHIP clonal hematopoiesis of indeterminate potential, *DNMT3A* Deoxyribonucleic acid methyl transferase 3 alpha, VAF variant allele frequency, WES Whole exome sequencing, ROR1, Receptor tyrosine kinase-like orphan receptor 1.

Table 3
Investigations for risk stratification of patients with WM.

Parameter	Assay/Test	Comments
A. Mandatory Tests		
• **Histopathology and Molecular Markers Assessment**		
Bone marrow biopsy & aspirate	H&E, IHC, Multiparametric flow cytometry	• Required to establish diagnosis, risk stratify SWM, & to assess HR molecular/genetic features and for deep response to therapy [98,99].
MYD88^{L265P} mutation		• Patients with SWM who harbor *MYD88*^{WT} genotype have a higher (1.7 to 1.8 fold) risk of progressing to overt WM. • Patients with WM who harbor *MYD88*^{WT} genotype have a 7-fold higher risk of histological transformation.
	Allele-specific quantitative polymerase chain reaction PCR (AS-PCR)	• AS-PCR for L265P mutation with an analytical sensitivity of 1% or lower *MYD88*^{L265P} in a wild- type background. • Limitation: This assay will fail to detect any alteration at codon 265 that does not result in the L->P amino acid change or other MYD88 alterations, including insertion or deletion events.
	Droplet Digital PCR (ddPCR)	• Although the specimen source may be obtained from either bone marrow or peripheral blood, the tumor burden could affect the assay's sensitivity, and peripheral blood is considered less optimal and increase the risk of false-negative result. • ddPCR is more sensitive, precise, and reproducible than AS-qPCR and is particularly useful in precursor conditions, IgM MGUS and smoldering WM, with low tumour burden. • Useful for MRD assessment (molecular remission) or cell-free tumor DNA [100] although scientific initiatives aimed at standardizing molecular methods are needed.
Non-L265P MYD88 mutations	Next-Generation Sequencing (NGS)	• All NGS-targeted panels designs should use probes covering the entire *MYD88* gene to assess *non*-L265P MYD88 mutations. • CD19+ enrichment not required unless less sensitive Sanger sequencing is being used for *non*-L265P MYD88 mutations.
CXCR4 mutations (*CXCR4*^{MUT})	AS-PCR or ddPCR for CXCR4^{NSS338X} Sanger sequencing NGS targeted panels	• CD19+ enrichment is recommended for improved sensitivity to detect subclonal mutations. • *CXCR4* mutations occur are almost always in association with *MYD88*^{L265P}. • Over 40 different CXCR4 nonsense and frameshift variants have been identified so far. • Given the constraints of *CXCR4*^{MUT} analysis, assays with an analytical sensitivity of 1% may be used for the hotspot mutations c.1013C->G/A (p.S338X) only, e.g., AS-PCR or ddPCR for *CXCR4*^{NS} as a very proportion of *CXCR4*$^{MUT\text{-}NS}$ reside in S338 region. • Less sensitive routine Sanger sequencing is used to interrogate all other genetic variants in the test region.
TP53 mutation	NGS targeted panels preferred. Sanger sequencing if NGS unavailable.	• CD19+ enrichment suggested as *TP53* mutations may be subclonal.
• **Cytogenetic Studies**		
Deletion 17p	FISH WGS/ WES (not routinely done)	• CD19+ enrichment advisable.
• **Blood tests**		
Serum LDH Serum albumin Serum β_2-microglobulin	Peripheral blood	• CBC with differential count, comprehensive metabolic profile, IgM, IgA & IgG immunoglobulins and monoclonal protein studies (e.g. mass-quant if available) are performed in all pts [101]. • Monoclonal protein studies aid in the diagnosis and subsequent response assessment. • Baseline serum LDH, albumin and β_2-microglobulin help risk-stratify pts with TN active WM.
• **Radiographic Imaging**		
Extramedullary Disease (EMD)	PET-CT	• EMD (excluding nodal and splenic involvement) is identified in 4-6% of pts; 15y cumulative incidence ~13% [44,102]. • Most frequently affected sites are lungs (including pleura), kidneys and CNS (which requires separate tests, discussed below, for evaluation); 5y OS ~65% in the most recent Danish study, with no difference compared to pts without EMD [103].
• **Clinical Presentation-Directed Tests**		
Optional (based on relevant history and exam) Cardiac, renal, gastrointestinal or neurological symptoms, rash, and macroglossia.	Cardiac biomarkers, troponin (T or I) and NT-proBNP (or BNP) 2D echo with strain rate (± Cardiac MRI) Fat aspirate/ involved organ biopsy 24-hour UPEP	• Rule out coexisting **AL/AHL amyloidosis**. Seen in 7-8% of patients with WM and associated with worse survival compared to WM without AL/AHL amyloidosis [43]. • Involved organ biopsy may be needed if bone marrow biopsy or fat aspirate negative for Congo-red stain. • Amyloid subtyping required prior to initiating clone-directed therapy.
Unexplained bruising or bleeding	vWF assessment Coagulation profile Serum viscosity	• Suspect immunoglobulin amyloidosis, acquired von Willibrand disease (3-4% at diagnosis) [106] or hyperviscosity. • Symptomatic hyperviscosity (characterized by headache, bilateral epistaxis, gingival or retinal bleeding, blurring/ visual disturbance, papilledema, central retinal vein occlusion, hearing loss, somnolence, cerebral bleed, seizure, ataxia, lightheadedness, and rarely heart failure) at diagnosis or during the disease course) has not been shown to adversely affect OS, but prompt intervention is warranted to avoid catastrophic clinical sequelae.
Peripheral Neuropathy	Nerve Conduction study Anti-MAG antibodies Serum cryoglobulin	
Myopathy	Electromyography Creatine kinase	

(*continued on next page*)

Table 3 (*continued*)

Parameter	Assay/Test	Comments
Unexplained fatigue, DVT, cold-induced symptoms from the acral circulation, including acrocyanosis, Raynaud-like phenomena, livedo reticularis, gangrene.	Monospecific direct antiglobulin test (DAT) positive for C3d. Cold agglutinin titer ≥64 Serum cryoglobulin	• For patients with suspected DADS peripheral neuropathy, AL amyloidosis, Type 1 or 2 cryoglobulinemia or POEMS syndrome. • If suspecting AL/AHL associated myopathy • If suspecting **cold agglutinin syndrome (CAS)** or WM associated chronic AIHA with CA-mediated RBC agglutination and destruction • Mostly MYD88^{WT}
Headache, cranial nerve palsies, visual and/or gait disturbances including limb weakness, imbalance, focal neurological deficits, slurred speech, paresthesias, chin numbness, hearing loss and altered mentation, seizures, etc.	Contrast enhanced MRI Brain and spine followed by CSF analysis including cytology to confirm LPL cells. mutational testing or immunoglobulin gene rearrangement as adjunct. PET-CT followed by targeted tissue biopsy.	• For suspected Bing Neel syndrome [107,108]
Rapidly enlarging lymph nodes, progressive constitutional symptoms, extranodal involvement	FISH EBV-encoded RNA (EBER) *in-situ* hybridization [18,42,104,105]. Serum LDH	• If **histological transformation (HT)** is suspected anytime during the disease course. Seen in ~4% [42]. • Pts with WM who transform have a 5-fold higher risk of death vs. pts who do not [42]. • Majority (80-90%) are non-GCB subtype. • *MYC* rearrangement noted (11-38%) by FISH • Cases mostly negative (83-100%) for EBER *in-situ* hybridization [18,42,104,105]. • Abrupt increase in LDH and thrombocytopenia [41]

Abbreviation: NGS, next-generation sequencing; FISH, fluorescent in-situ hybridization; WGS/ WES, whole genome sequencing /whole exome sequencing; DADS, Distal acquired demyelinating symmetric neuropathy; *TP53* total protein *53*, LDH lactate dehydrogenase; Ig, immunoglobulin; MRI, magnetic resonance imaging; PET-CT, positron emitting tomography; CBC, complete blood count; AL, amyloidosis light chain; AHL, immunoglobulin heavy and light chain amyloidosis, MAG, myelin associated glycoprotein; CSF, cerebrospinal fluid; *MYD88,* myeloid differentiation primary response gene; CXCR4 C-X-C, chemokine receptor type 4, who OS, overall survival; vWF, von Willebrand factor; UPEP, Urine protein electrophoresis; LPL, lymphoplasmacytic lymphoma; EBER, Epstein-Barr encoding region.

sets of patients. Patients with *MYD88*^{WT} genotype demonstrate a lower major response rate (MRR) and shorter PFS on ibrutinib and patients on bendamustine rituximab (BR) or any BTKi demonstrate shorter PFS in the presence of *CXCR4*^{MUT}.

BTK inhibitors are unable to overcome chemoresistance conferred by *TP53*^{MUT}.The ASPEN biomarker substudy clearly demonstrated inferior outcome with both ibrutinib and zanubrutinib in the presence of *CXCR4*^{MUT} and/or *TP53*^{MUT}, although zanubrutinib resulted in more favorable outcomes in comparison to ibrutinib. A Chinese study showed that the presence of *CXCR4* mutations negatively impacted the survival outcome of patients treated with BTKi but not of patients managed with cyctotoxic therapy [67].

In a subset analysis of an international, retrospective, multi-institutional study, among TN patients with known *CXCR4* mutation status ($n=89$) receiving BR, the subcohort with *CXCR4*^{MUT} (28%) demonstrated markedly inferior PFS at 42 months (Table 4, manuscript in preparation) [72]. Interestingly, the cohort that progressed within 24 months (POD24) of initiating BR was enriched for patients with *CXCR4*^{MUT} (70% vs 21% in late progressors). Additionally, *CXCR4*^{MUT} was associated with shorter OS. However, a multivariate analysis revealed that only POD24 status and not *CXCR4*^{MUT} unfavorably impacted OS. In cross-study comparisons, interestingly the efficacy data with frontline BR appears to be comparable to that of ibrutinib (42-month PFS rate 49% with either approach) [72], but inferior to that achieved with zanubrutinib (42-month PFS, 73.2%) in the presence of *CXCR4*^{MUT}, despite the ASPEN cohort including both the TN and RR patient populations [55,73].

Another Phase 2 trial (#NCT00422799) employing the proteasome inhibitor, bortezomib plus rituximab showed that the CXCR4 status had no effect on PFS or OS [54]. However, in the randomized-controlled ECWM1 trial, with limited follow up, no PFS improvement was evident in the patients with or without *CXCR4* mutation when bortezomib was added to the DRC backbone (control) [74]. Although resistance to bortezomib in cancer cell lines with higher CXCR4 expression has been shown previously, *CXCR4*^{MUT} does not correlate with its expression in WM [54].

A subset analysis of a single-institution, retrospective study (Table 2) involving 11 patients with *TP53*^{MUT} demonstrated that rituximab maintenance may be associated with longer PFS ($P=.035$). An unplanned post-hoc analysis of the StiLNHL7-2008 trial, examining the impact of rituximab maintenance among patients >65 years of age (who had responded to initial BR induction) showed a significantly longer PFS with maintenance, suggesting that the benefit may be confined to the elderly patients that are more likely to be categorized as HRWM owing to their higher age [75]. This approach of utilizing rituximab maintenance in HRWM warrants more studies to draw definitive conclusions.

- Recognizing the inferior outcomes of patients with *TP53*^{MUT} in general with all available therapies, and the sparse data regarding this subset of patients, the panel prefers to use zanubrutinib, if available, over other therapies in patients with mutated *TP53*^{MUT}.
- Among the patients harboring *CXCR4*^{MUT}, zanubrutinib appears to have a superior PFS rate compared to ibrutinib and is the preferred agent. However, the panel members appreciate that in countries without access to zanubrutinib, ibrutinib plus rituximab may be the only BTKi-based option that has shown genotypic independent activity. Alternatively, BR may be used in such circumstances if fixed- duration approach is desired.
- In patients with bulky disease or coexisting AL/AHL amyloidosis LPL-directed chemoimmunotherapy is recommended. Ibrutinib should be specifically avoided in patients with AL/AHL amyloidosis due to its poor tolerability, with increased risk of bleeding and cardiovascular adverse effects, in this subset [76] that is already inherently predisposed to such complications from the underlying AL.

Which regimen(s) should be used upon first relapse of patients with high-risk WM and does stem cell transplantation have a role in managing these patients?

In general, the evidence for sequencing of therapies in patients with WM is exceedingly limited. In the ASPEN trial, patients with

Table 4
Prognostic impact of *CXCR4* mutational status in WM.

Study/Type	Cohort	N (%)	ORR (%)	MRR (%)	≥VGPR (%)	TTMR (m)*	PFS% (at)	OS % (at)	Comment
Ibrutinib	RRWM	63	91	79	30	2	54% (5y)	87 (5y)	1st trial to demonstrate differential
Pivotal Trial	*MYD88*^{MUT}/*CXCR4*^{WT}	36 (57)	100	97	47	1.8	70% (5y)	93 (5y)	impact of *CXCR4*^{MUT} on outcome.
Phase 2 [109,110]	*MYD88*^{MUT}/*CXCR4*^{MUT}	22 (35)	86	68	9	4.7	38% (5y)	80 (5y)	Markedly poor outcome with *MYD88*^{WT}
	MYD88^{WT}/*CXCR4*$^{WT/UK}$	4 (6)	50	0	0	NA	0.4 m*	UA	genotype.
ASPEN Trial	TNWM/RRWM; I/Z (Cohort	99/ 102	94/95	80/81	25/36	2.9/	70/78 (3.5y)	85/88	First trial to compare 2 BTKi.
Phase 3	1)					2.8		(3.5y)	*CXCR4*^{mut} was associated with lower
I/Z [71,77]	*MYD88*^{MUT}/*CXCR4*^{WT} I/Z	72 (78)/	94/97	85/83	31/45	2.8/	49/73 (3.5y)	79/84 (3.5y)	≥VGPR rates on MVA.
		65 (66)				2.8			Among pts with *CXCR4*^{mut}, ≥VGPR rates
	MYD88^{MUT}/*CXCR4*^{MUT} I/Z	20 (22)/	95/91	65/79	10/21	6.6/	75/81 (3.5y)	86/8(3.5y)	were more than 2-fold higher with Z.
		23 (23)				3.4			
	MYD88^{WT}/*CXCR4*$^{WT\ or\ UK}$	26	81	65	27	3	54 (3.5y)	84 (3.5y)	
	(Cohort 2; Z only)								
iNNOVATE	TNWM and RRWM IR/R	75/75	92/44	76/31	31/5	3	68 (4.5y)	86 4.5y)	The study does not include single
Trial							25 (4.5y)	84 4.5y)	agent ibrutinib as a comparator arm.
Phase 3	*MYD88*^{MUT}/*CXCR4*^{WT} IR/R	32 (43)	94/43	81/26	44/14	2/5	72/25 (4.5y)	UA	Clinical benefit with IR (vs R) appeared
IR/R [111,112]		/35(47)							to be independent of mutational status,
	MYD88^{MUT}/*CXCR4*^{MUT} IR/R	26 (35)	100/48	77/43	23/8	3/9	63/21 (4.5y)	UA	but NGS instead of the more sensitive,
		/23(31)							AS-PCR, was used *MYD88* genotypic
	MYD88^{WT}/*CXCR4*^{WT} IR/R	11 (15) /9	82/56	73/22	27/0	7/5	70/30 (4.5y)	UA	assessment.
		(12)							
iNNOVATE	RRWM	31	87	77	29	2	39*; 40 (5y)	NR*;73(5y)	Pts with *CXCR4*^{MUT}appeared to have
Phase 3 Sub-study for	*MYD88*^{MUT}/*CXCR4*^{WT}	17 (68)	88	88	41	1	NR *	NR*	lower VGPR and PFS rates.
Rituximab refractory [113,114]	*MYD88*^{MUT}/*CXCR4*^{MUT}	7 (28)	86	71	14	4	18 m*	50 m*	Markedly poor outcome with *MYD88*^{WT}
	MYD88^{WT}/*CXCR4*^{WT}	1 (4)	0	0	0	NA	6 m	9 m	genotype.
Ibrutinib	TNWM; all*MYD88*^{MUT}	30	100	87	30	1.9	76 (4y)	100 (4y)	5/6 (83%) pts who progressed had
Phase 2 [115,116]	*MYD88*^{MUT}/*CXCR4*^{WT}	16 (53)	100	94	44	1.8	92 (4y)	100 (4y)	*CXCR4*^{MUT}.PFS rate in pts with
	MYD88^{MUT}/*CXCR4*^{MUT}	14 (47)	99	78	14	7.3	59 (4y)	100 (4y)	*CXCR4*^{MUT} was lower ($p = 0.06$)

(*continued on next page*)

Table 4 (*continued*)

Study/Type	Cohort	N (%)	ORR (%)	MRR (%)	≥VGPR (%)	TTMR (m)*	PFS% (at)	OS % (at)	Comment
DFCI	TNWM/RRWM	180	94	76	25	NA	NR* 77 (3y)	NR* 89 (3y)	PFS shorter for *CXCR4*$^{MUT/NS}$ vs pts with
Ibrutinib	*CXCR4*^{WT}		97	85	33	NA	NR* 83(3y)	92 (3y)	CXCR4^{WT} or with *CXCR4*$^{MUT/FS}$
Retrospective [117]	*CXCR4*$^{MUT/NS}$	(27)	88	55	6	NA	40* 60(3y)	86 (3y)	OS similar across 3 groups.
	CXCR4$^{MUT/FS}$	(11)	90	79	26	NA	NR* 76(3y)	78(3y)	
Venetoclax	RRWM	32	84	80	19	5	80 (2y)	100 (2.5y)	*CXCR4*^{MUT} status did not impact
Phase 2 [80]	*MYD88*^{MUT}/*CXCR4*^{WT}	17 (53)	86	86	29	UA	50 (2.5y)	100 (2.5y)	outcomes with venetoclax
	MYD88^{MUT}/*CXCR4*^{MUT}	15 (47)	82	77	12	UA	50 (2.5y)	100 (2.5y)	monotherapy.
	MYD88^{WT}/*CXCR4*$^{WT\ or\ UK}$	0	NA	NA	NA	NA	NA	NA	
Venetoclax	RRWM/non-IgM LPL	76	70	63	23	NA	29m*, 57(2y)	NR*, 80 (2y)	Pts with *CXCR4*^{MUT}had a numerically
Multicenter,	*CXCR4*^{WT}	34	76	73	24	NA	71	93 (2y)	(but not statistically) inferior PFS and
Retrospective	*CXCR4*^{MUT}	23	70	52	22	NA	53	79 (2y)	OS ($p = 0.4$).
(Personal communication Y Sawalha) [79]									
Pirtobrutinib [82]	RRWM	80	80	71	26	2	61 (1.5y)	82% (1.5y)	78% of pts previously exposed to a
(Personal communication	*MYD88*^{MUT}	65(81)	NA	71	NA	NA	NA	NA	covalent BTKi and this study showed
Palomba, L) [82]	*MYD88*^{WT}	8(10)	NA	88	NA	NA	NA	NA	efficacy in such patients. Additional
	CXCR4^{WT}	42(53)	NA	76	NA	NA	NA	NA	details awaited as follow-up is
	CXCR4^{MUT}	12(15)	NA	50	NA	NA	NA	NA	currently short.
Tirabrutinib [118]	TNWM/RRWM	27, 18/9	96	93	30	2m	93 (2y)	100 (2y)	Very few pts with *CXCR4*^{MUT} for a
	MYD88^{MUT}/*CXCR4*^{WT}	22	96	91	36	2m	NA	100 (2y)	meaningful analysis.
	MYD88^{MUT}/*CXCR4*^{MUT}	3	100	100	0	4m	NA	100 (2y)	
	MYD88^{WT}/*CXCR4*^{MUT}	1	100	100	0	6m	NA	100 (2y)	
Orelabrutinib [119]	RRWM	47	89	81	21	2	72% (3y)		Very few pts with *CXCR4*^{MUT} for a
	MYD88^{MUT}/*CXCR4*^{WT}	39 (83)	95	85	NA	1.9	86 (2.5)	NA	relevant analysis.
	MYD88 ^{MUT}/CRCR4 ^{S338X}	4 (8.5)	100	100	NA	3.6	75 (2.5)	NA	
	MYD88^{WT}/*CXCR4*^{WT}	4 (8.5)	25	25	NA	NR	75 (2.5)	NA	
IDR	TNWM	26	96	77	19	6	40m*	100 (4y)	Pts with *CXCR4*^{MUT} took longer to
Phase 2 [120,121]	*MYD88*^{MUT}/*CXCR4*^{WT}	11 (42)	100	81	36	3	36m*	100 (4y)	respond (3m* vs 1m*; $P = .003$)
	MYD88^{MUT}/*CXCR4*^{MUT}	15 (58)	93	74	7	10	40m*	100 (4y)	No PFS difference in *CXCR4*^{MUTNS} vs
	MYD88^{WT}/*CXCR4*$^{WT\ or\ UK}$	0	NA	NA	NA	NA	NA	NA	*CXCR4*^{MUTFS} ($P = .90$); 1 pt with
									CXCR4^{MUTNS} had *TP53*^{MUT}& PFS 47 m

(*continued on next page*)

Table 4 (*continued*)

Study/Type	Cohort	N (%)	ORR (%)	MRR (%)	≥VGPR (%)	TTMR (m)*	PFS% (at)	OS % (at)	Comment
HOVON124/ ECWM-R2	RRWM	59	85	61	15	5	56(2y)	88(2y)	Shorter PFS for pts with *CXCR4*^{MUT},but
IDR	*MYD88*^{MUT}/*CXCR4*^{WT}	34 (65)	92	68	21	NA	NR*, 75 (2y)	NA	not statistically significant because the
Phase 1/ 2 [78]	*MYD88*^{MUT}/*CXCR4*^{MUT}	14 (27)	72	43	0	NA	36m*,63 (2y)	NA	study was underpowered to detect a
	MYD88^{WT}/*CXCR4*$^{WT\ or\ UK}$	06 (8)	66	66	33	NA	NR*, 67(2y)	NA	difference.
ZID [122]	TNWM	24	100	96	46	NA	40*	NR*	First study, albeit small to examine
	MYD88^{MUT}	23 (96)	100	NA	NA	NA	NA	NA	time limited ZID combination
	MYD88^{WT}	1 (4)	NA	NA	NA	NA	NA	NA	75% experienced IgM rebound upon
	CXCR4^{WT}	19 (78)	100	94	50	2	40	NR*	completing therapy.
	CXCR4^{MUT}	5 (22)	100	100	40	2	32	32*	Deep responses similar in pts with and without CXCR4^{MUT}
ECWM-1	TNWM	100/102	91/95	82/85	33/21	NA	73/81(2y)	NR*	*CXCR4* mutational analysis was
Phase 3									performed only in some patients by
DRC/B-DRC	*MYD88*^{MUT}/*CXCR4*^{WT}	19(53)/ 26(65)	94/100	82/73	12/12	NA	NR/NR*	NA	either Sanger sequencing or NGS in CD19+-selected or unselected cells.
	MYD88^{MUT}/*CXCR4*^{MUT}	12(33)/ 9(23)	83/86	50/71	8/0	NA	NA/NA	NA	DRC and B-DRC showed comparable PFS in pts with or without CXCR4
	MYD88^{WT}/*CXCR4*^{WT}	5(14)/ 5(14)	100/ 100	80/ 100	20/25	NA	NA/NA	NA	mutation, but follow-up was short and sample size was small.
Ixazomib-Ibrutinib (Personal communication, Laplant B) [123]	TNWM/RRWM	21	90	90	24		23m* (44.5 (2y)	95 (2y)	Study examined time-limited (24 cycles) treatment for WM. Primary endpoint (CR attainment) not
	MYD88^{MUT}/*CXCR4*^{WT}	8	88	75	38		54 (2y)	100 (2y)	met.
	MYD88^{MUT}/*CXCR4*^{MUT}	5	100	80	20		NR(2y)	100 (2y)	Disease progressed shortly after
	MYD88^{WT}/*CXCR4*^{MUT}	1	100	100	0		NR (2y)	100 (2y)	treatment discontinuation with a
	CXCR4^{MUT}	6 (28)		83					median TTNT of 1.3 months.
BR	TNWM	253	95	94	46	NA	6.7y*	NR*, 89 (5y)	*CXCR4*^{MUT} was associated with higher
Multicenter, Retrospective [72] (Personal communication, Kapoor, P)	*MYD88*^{MUT}	154 (90)	NA	93	55	NA	64 (5y)	90 (5y)	WM burden. *CXCR4*^{MUT} was associated with shorter
	MYD88^{WT}	18 (10)	NA	94	47	NA	64 (5y)	81 (5y)	PFS and OS.
	CXCR4^{WT}	25 (28)	NA	83	20	NA	78 (5y)	91 (5y)	Early progressors (POD24 cohort) were
	CXCR4^{MUT}	64 (72)	NA	97	57	NA	43 (5y)	80 (5y)	enriched for pts with *CXCR4*^{MUT}

Abbreviations: ORR, overall response rate; MRR, Major response rate; VGPR, Very good partial response; TTMR, Time to major response; PFS, Progression free survival; OS, overall survival; NA, not available; I, ibrutinib; Z, Zanubrutinib; R, Rituximab; UK, unknown; IR, ibrutinib-rituximab; IDR, Ixazomib, Dexamethasone and Rituximab; ZID, Zanubrutinib Ixazomib and Dexamethasone; DRC, Dexamethasone, Rituximab and Cyclophosphamide; B-DRC, Bortezomib, Dexamethasone, Rituximab and Cyclophosphamide; MVA, multivariable analysis; BR, Bendamustine and Rituximab; MUT, Mutation; WT, wild type; UK, Unknown; TTNT, Time to next therapy; NA, Not available; NR, Not reached; pts patients *Median.

RRWM primarily comprised the study population [77]. Although the final analyses did not provide separate data for the RRWM cohort, zanubrutinib appeared to have somewhat superior efficacy for patients with unfavorable parameters (e.g., CXCR4, TP53) in the analysis incorporating both treatment-naïve and RR populations [71]. The data with BR and other chemo-immunotherapy-based regimens are sparse for the RRWM population and absent, specifically regarding *TP53*^{MUT} and *CXCR4*^{MUT} subcohorts [72].

In the post hoc analysis of the ECWM-R2/HOVON124 study involving ixazomib, rituximab and dexamethasone (IDR) induction followed by rituximab maintenance in patients with RRWM, PFS was inferior for the *MYD88*^{L265P}/*CXCR4*^{MUT} cohort (Table 4) [78]. Importantly, only 2% of patients had received a BTKi previously [78].

In a multicenter study examining the efficacy and safety of BCL2 inhibitor, venetoclax, in RR LPL (majority were RRWM), 2-year PFS rates were lower among the patients previously exposed to a BTKi (47% vs 92%; HR = 2.97, $P = .012$) or harboring *TP53*^{MUT} (38% vs 64%; HR = 2.62; $P = .035$), although the presence of *CXCR4*^{MUT} did not reveal such differences (manuscript under review) [79]. These findings were consistent with the results of a small phase 2 study of venetoclax in which *CXCR4*^{MUT} mutations did not adversely impact PFS, unlike prior BTKi exposure (Table 4) [80].

Pirtobrutinib is a highly selective, non-covalent BTKi that reversibly inhibits both WT and C481-mutant BTK with equal potency. Pirtobrutinib also inhibits the phosphorylation of tyrosine 551, resulting in an inactive conformation, thereby inhibiting scaffolding interactions that support kinase-independent BTK signaling [81]. At IWWM-12, the RRWM subset-related BRUIN trial findings involving patients on pirtobrutinib were presented. Of 80 patients, 63 were BTKi-exposed; most (65%) had discontinued covalent BTKi due to progression [81]. VGPR and MRR rates were 35% and 88%, respectively in the BTKi-naïve cohort and 24% and 67% in the BTKi-exposed cohort (Personal communication, Lia Palomba).[82] However, neither the outcome data specifically for the BTKi-exposed cohort nor any *TP53*^{MUT} related data were discussed.

In the era of novel agents, high-dose chemotherapy followed by either autologous (ASCT) or allogeneic (allo-SCT) hemopoietic stem cell transplantation as a salvage treatment is relegated to a lower-level, after BTKi therapy and chemoimmunotherapy. Additionally, in patients with AL/AHL amyloidosis in whom rapidly achieving at least a very good partial response to arrest and eventually reverse the involved organ damage is critical, ASCT may be considered for consolidation in the frontline setting provided the patients' transplant-eligibility is established [83–85]. There are no prospective studies but limited data, mainly from the registry studies suggesting that patients with WM may benefit from SCT, exist. However, specific details regarding the risk factors are sparse. In one EBMT study of 158 patients with WM (54% of whom were HRWM per IPSSWM), undergoing ASCT between 1991 and 2005, the outcomes were significantly inferior among patients who had received ≥3 prior lines of therapy or were chemorefractory at ASCT [86]. The results from an updated analysis involving 772 patients treated with ASCT between 2000 and 2021 were presented at the IWWM 12. Over a third of patients had previously received ≥3 lines of therapy [86]. The estimated 5-year PFS was 77% and OS was 70%, with 5-year non-relapse mortality (NRM) of 4.5% [87]. Interestingly, a sub analysis, comparing the outcomes at different intervals (2000-2009, 2010-2015, 2016-2021) coinciding with new drug development, did not show a significant difference in OS over those time periods [87]. These data, on difficult-to-treat patients that were considered predominantly high-risk but ASCT-eligible by their treatment centers suggest that a subset may still be rescued by ASCT. The data are even more scant among patients undergoing allo-SCT, which is rarely considered a suitable option, even among the young and fitter patients, especially with the advent of novel therapies [88]. A recent EBMT analysis of 330 patients with WM who underwent allo-SCT —the largest cohort so far— presented at the IWWM12 showed 5-year PFS and OS rates of 45% and 54%, respectively, with a 2-year relapse rate of 21% and a prohibitively high 2-year non-relapse mortality rate of 20%.[87]

- The panel recommends zanubrutinib for RRWM with HR features in patients not exposed to a BTKi, rather than BR or an ixazomib-based regimen.
- Among patients with *CXCR4*^{MUT}, venetoclax is a suitable alternative, although prior BTKi exposure is known to adversely affect PFS.
- Among the covalent BTKi-resistant or intolerant and chemoimmunotherapy-exposed patients, it is reasonable to employ pirtobrutinib, recognizing that data are absent specifically for the HR subset, including patients with *TP53*^{Alt}.
- Global access to novel therapies has been a vexing issue. If drug inavailability and unaffordability are major barriers to most effectively managing patients with HRWM, the duration of response to prior fixed-duration regimen(s) used, as well as the feasibility of approaches such as ASCT should be considered in selecting the subsequent salvage therapy.

Which type of clinical trials should be developed and prioritized for HRWM?

Clinical trials, conducted particularly in the RRWM population have been instrumental in the unprecedented progress that has been made over the past decade. Their impact in the HRWM patients is, however, yet to be intensively scrutinized. Importantly, for the TN HR subset in which the risk-benefit ratio is even more favorably altered toward pursuing an 'outside-the-box' strategy (in comparison to TN standard-risk patients), utilization of therapies deemed promising in the RRWM space has a greater chance of benefiting through a meaningful impact on the outcomes of those at the highest risk of WM-related mortality. The efficacy data generated by the use of fixed-duration potentially promising novel approaches, including antibody-drug conjugates (loncastuximab) [89], phospholipid drug conjugates (iopofosine) [90], T-cell engagers (plamotamab [91] and epcoritamab), CAR-T cell therapy (MB-106), BCL2/BTK-I combination therapy (sonrotoclax-zanubrutinib, pirtobrutinib-venetoclax), BTK degraders (NX-5848, BGB-16673), specifically in patients stratified under the newly created HRWM category would be especially useful, as this subset clearly constitutes an area of unmet need [92–94]. By effectively transforming their overall outlook, such approaches are consequently more likely to be adopted earlier in the HRWM population.

- The panel champions the successful development of clinical trials targeting the HR patient population.
- The panel encourages clinicians to facilitate enrollment of the high-risk patients to the ongoing clinical trials examining the efficacy and safety of promising novel approaches to generate robust data that are likely to lay the groundwork for safe and effective risk-adapted strategies in the future.

We envision these consensus statements regarding a subset of patients – that exhibit distinctly poor prognosis with the existing treatments – to serve as the guiding principles, providing a framework to spur acquisition of data-driven evidence identifying the risk factors for early progression and the development of effective strategies aimed at confronting HRWM.

Declaration of competing interest

PK is the principal investigator of trials for which Mayo Clinic has received research funding from Amgen, Regeneron, Bristol My-

ers Squibb, Loxo Pharmaceuticals, Ichnos, Karyopharm, Sanofi, AbbVie and GlaxoSmithKline. Prashant Kapoor has received honorarium from Keosys and served on the Advisory Boards of BeiGene, Mustang Bio, Janssen, Pharmacyclics, X4 Pharmaceuticals, Kite, Oncopeptides, Ascentage, Angitia Bio, GlaxoSmithKline, Sanofi and AbbVie.

MAD has received honoraria from participation in advisory boards and satellite symposia from Amgen, Sanofi, Regeneron, Menarini, Takeda, GS, BMS, Janssen, BeiGene, Swixx and Astrazeneca.

SMA is the principal investigator of trials for which Mayo Clinic has received research funding from Bristol Myers Squibb, Takeda, AstraZeneca, Pfizer, Regeneron, Affimed, ADC Therapeutics and Step Pharma.

EK has received honoraria from Pfizer, GSK, Janssen, Prothena; Research funding from Pfizer, GSK, Janssen.

RA Relevant Research funding: BeiGene, Roche, Merck, Gilead.

Advisory board: Roche, Genentech, Genmab.

ED has been reimbursed for travel accommodations from Roche, AbbVie, Johnson and Johnson**.**

PM reports honoraria from Janssen, Astra Zenecca and Incyte; consultancy or advisory role for Janssen and Beigene; and travel support from Abbvie.

CK Research grant from BMS and support for meeting attendance from Takeda**.**

RH has had a consultant or advisory relationship with Janssen, Amgen, Celgene, AbbVie, BMS, Novartis, PharmaMar, and Takeda; has received honoraria from Janssen, Amgen, Celgene, BMS, PharmaMar, and Takeda; has received research funding from Janssen, Amgen, Celgene, BMS, Novartis, and Takeda; is member of Advisory Boards: BMS, Takeda, Amgen, Oncopeptides, Sanofi, Janssen, GSK; has received support for attending meetings and/or travel from Amgen, Celgene, Takeda, Janssen.

JPA No conflicts of interest.

DD No conflicts of interest.

SC No conflicts of interest.

XC No conflicts of interest.

CJP No conflicts of interest.

JVM has served as a consultant to Johnson and Johnson.

CB Honoraria: Roche/Genentech, Janssen, BeiGene, Novartis, Pfizer, Incyte, AbbVie, Gilead Sciences, Celltrion, MorphoSys, Regeneron, Sobi, Lilly.

Consulting or Advisory Role: Gilead Sciences, Janssen, Roche, Pfizer, BeiGene, Celltrion, AbbVie, Incyte, Regeneron, MorphoSys, Novartis, Sobi, Lilly.

Speakers' Bureau: Roche, Janssen, BeiGene, Celltrion, AbbVie, Pfizer, Gilead Sciences, Novartis, Gilead, Incyte, Pfizer, MorphoSys, Sobi, Lilly.

Research Funding: Roche/Genentech, Janssen, Celltrion, MSD, Pfizer, Amgen, Bayer.

SPT received research funding, and/or consulting fees from Abbvie/Pharmacyclics Inc., Janssen Oncology Inc., Beigene Inc., Eli Lilly Pharmaceuticals, Bristol Myers Squibb, and Ono Pharmaceuticals. ST is a named inventor for MYD88 and CXCR4 testing for WM and has assigned all interests to his institution.

MJK: Honoraria from and consulting/advisory role for BMS, Kite, a Gilead Company, Miltenyi Biotech, Novartis, Adicet Bio, Mustang Bio, Beigene and Roche; research funding from Kite, and travel support from Kite, Miltenyi Biotech, Novartis, AbbVie and Roche.

CRediT authorship contribution statement

Prashant Kapoor: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Meletios A. Dimopoulos:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Stephen M. Ansell:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Efstathios Kastritis:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Ranjana Advani:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Eric Durot:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Pierre Morel:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Charalampia Kyriakou:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Roman Hajek:** Formal analysis, Methodology, Writing – review & editing. **Daniela Drandi:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Jithma P. Abeykoon:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Signy Chow:** Formal analysis, Investigation, Writing – review & editing. **Xinxin Cao:** Formal analysis, Investigation, Writing – review & editing. **Christopher J. Patterson:** Data curation, Formal analysis, Investigation, Project administration, Resources, Writing – review & editing. **Jeffrey V. Matous:** Conceptualization, Formal analysis, Writing – review & editing. **Christian Buske:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Steven P. Treon:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Marie J. Kersten:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Acknowledgments

The authors gratefully acknowledge Beigene Pharmaceuticals, Cellectar Biosciences, Inc. Abbvie/Pharmacyclics, Johnson&Johnson, Eli Lilly, and the International Waldenstrom's Macroglobulinemia Foundation for their support of the 12th International Workshop on Waldenstrom's Macroglobulinemia. Consensus panel reports of the 12th International Workshop on Waldenstrom's Macroglobulinemia are for educational purposes and should not be construed as offering specific medical advice for patients.

The authors thank Yazeed Sawalha, MD, Betsy R. Laplant, MS, Patrick J. O'Brien,

Saurabh Zanwar, MD and Lia Palomba, MD for generously providing additional data related to their research work cited and utilized in this manuscript.

References

[1] Merlini G, Baldini L, Broglia C, et al. Prognostic factors in symptomatic Waldenstrom's macroglobulinemia. Semin Oncol Apr 2003;30(2):211–15. doi:10.1053/sonc.2003.50064.

[2] Gobbi PG, Bettini R, Montecucco C, et al. Study of prognosis in Waldenstrom's macroglobulinemia: a proposal for a simple binary classification with clinical and investigational utility. Blood May 15 1994;83(10):2939–45.

[3] Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. Multicenter Study Research Support, Non-U.S. Gov't. *Blood* Apr 30 2009;113(18):4163–70. doi:10.1182/blood-2008-08-174961.

[4] Dhodapkar MV, Jacobson JL, Gertz MA, et al. Prognostic factors and response to fludarabine therapy in patients with Waldenstrom macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). Blood, The Journal of the American Society of Hematology 2001;98(1):41–8.

[5] Kastritis E, Morel P, Duhamel A, et al. A revised international prognostic score system for Waldenström's macroglobulinemia. Leukemia 2019;33(11):2654–61 2019/11/01. doi:10.1038/s41375-019-0431-y.

[6] Zanwar S, Le-Rademacher J, Durot E, et al. Simplified Risk Stratification Model for Patients With Waldenstrom Macroglobulinemia. J Clin Oncol Jul 20 2024;42(21):2527–36. doi:10.1200/JCO.23.02066.

[7] Zanwar S, Kapoor P. Diagnosis and Risk Stratification in Waldenstrom Macroglobulinemia. J Natl Compr Canc Netw Sep 2024;22(7). doi:10.6004/jnccn.2024.7024.

[8] Kapoor P, Rajkumar SV. Current approach to Waldenstrom macroglobulinemia. Blood Rev Nov 2023;62:101129. doi:10.1016/j.blre.2023.101129.

[9] Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Consensus Development Conference Review. Seminars in oncology Apr 2003;30(2):116–20. doi:10.1053/sonc.2003.50038.
[10] Kyle RA, Ansell SM, Kapoor P. Prognostic factors and indications for treatment of Waldenstrom's Macroglobulinemia. Best practice & research Clinical haematology Jun 2016;29(2):179–86. doi:10.1016/j.beha.2016.08.014.
[11] Pophali PA, Bartley A, Kapoor P, et al. Prevalence and survival of smouldering Waldenström macroglobulinaemia in the United States. Br J Haematol 2019;184(6):1014–17. doi:10.1111/bjh.15201.
[12] Gobbi PG, Baldini L, Broglia C, et al. Prognostic validation of the international classification of immunoglobulin M gammopathies: a survival advantage for patients with immunoglobulin M monoclonal gammopathy of undetermined significance? Research Support, Non-U.S. Gov't Validation Studies. Clin Cancer Res Mar 1 2005;11(5):1786–90. doi:10.1158/1078-0432.CCR-04-1899.
[13] Zanwar S, Abeykoon JP, Ansell SM, et al. Disease outcomes and biomarkers of progression in smouldering Waldenstrom macroglobulinaemia. Br J Haematol Oct 2021;195(2):210–16. doi:10.1111/bjh.17691.
[14] Bustoros M, Sklavenitis-Pistofidis R, Kapoor P, et al. Progression Risk Stratification of Asymptomatic Waldenstrom Macroglobulinemia. J Clin Oncol Apr 16 2019 Jco1900394. doi:10.1200/jco.19.00394.
[15] Kyle RA, Benson JT, Larson DR, et al. Progression in smoldering Waldenstrom macroglobulinemia: long-term results. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. Blood May 10 2012;119(19):4462–6. doi:10.1182/blood-2011-10-384768.
[16] Kyle RA, Therneau TM, Rajkumar SV, et al. Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. Research Support, U.S. Gov't. P.H.S. *Blood* Nov 15 2003;102(10):3759–64. doi:10.1182/blood-2003-03-0801.
[17] Kapoor P, Ansell SM, Fonseca R, et al. Diagnosis and Management of Waldenstrom Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016. JAMA Oncol Sep 1 2017;3(9):1257–65. doi:10.1001/jamaoncol.2016.5763.
[18] Alexanian R, Weber D, Delasalle K, Cabanillas F, Dimopoulos M. Asymptomatic Waldenstrom's macroglobulinemia. Seminars in oncology Apr 2003;30(2):206–10. doi:10.1053/sonc.2003.50051.
[19] European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society–first revision. Guideline. J Peripher Nerv Syst Sep 2010;15(3):185–95. doi:10.1111/j.1529-8027.2010.00278.x.
[20] Baldini L, Goldaniga M, Guffanti A, et al. Immunoglobulin M monoclonal gammopathies of undetermined significance and indolent Waldenstrom's macroglobulinemia recognize the same determinants of evolution into symptomatic lymphoid disorders: proposal for a common prognostic scoring system. J Clin Oncol 2005;23(21):4662–8.
[21] Wang Y, Gali VL, Xu-Monette ZY, et al. Molecular and genetic biomarkers implemented from next-generation sequencing provide treatment insights in clinical practice for Waldenstrom macroglobulinemia. Neoplasia Apr 2021;23(4):361–74. doi:10.1016/j.neo.2021.02.002.
[22] Poulain S, Roumier C, Bertrand E, et al. TP53 Mutation and Its Prognostic Significance in Waldenstrom's Macroglobulinemia. Clin Cancer Res Oct 15 2017;23(20):6325–35. doi:10.1158/1078-0432.Ccr-17-0007.
[23] Varettoni M, Zibellini S, Boveri E, et al. A risk-stratification model based on the initial concentration of the serum monoclonal protein and MYD88 mutation status identifies a subset of patients with IgM monoclonal gammopathy of undetermined significance at high risk of progression to Waldenström macroglobulinaemia or other lymphoproliferative disorders. Br J Haematol 2019;187(4):441–6. doi:10.1111/bjh.16086.
[24] Kapoor P. The MYD88(L265P) conundrum in IgM monoclonal gammopathy of undetermined significance. Br J Haematol Nov 2019;187(4):413–15. doi:10.1111/bjh.16085.
[25] Tahri S, Mouhieddine TH, Redd R, et al. Clonal hematopoiesis is associated with increased risk of progression of asymptomatic Waldenstrom macroglobulinemia. Blood Adv Apr 12 2022;6(7):2230–5. doi:10.1182/bloodadvances.2021004926.
[26] Moreno DF, Jimenez C, Escalante F, et al. Prognostic risk and survival of asymptomatic IgM monoclonal gammopathy: Results from a Spanish Multicenter Registry. Hemasphere Nov 2024;8(11):e70029. doi:10.1002/hem3.70029.
[27] Moreno DF, Lopez-Guerra M, Paz S, et al. Prognostic impact of MYD88 and CXCR4 mutations assessed by droplet digital polymerase chain reaction in IgM monoclonal gammopathy of undetermined significance and smouldering Waldenstrom macroglobulinaemia. Br J Haematol Jan 2023;200(2):187–96. doi:10.1111/bjh.18502.
[28] Varettoni M, Zibellini S, Defrancesco I, et al. Pattern of somatic mutations in patients with Waldenström macroglobulinemia or IgM monoclonal gammopathy of undetermined significance. Haematologica 2017;102(12):2077.
[29] Merli M, Bianchi B, Bertu L, et al. Validation and further potentialities of the novel AWM score for progression risk stratification in patients with asymptomatic Waldenstrom macroglobulinemia. Leuk Lymphoma Apr 2020;61(4):987–9. doi:10.1080/10428194.2019.1689393.
[30] Chohan KL, Paludo J, Vallumsetla N, et al. Survival trends in young patients with Waldenström macroglobulinemia: Over five decades of experience. Am J Hematol 2023;98(3):432–9.
[31] Hunter Z. Multi-Omic Analysis Identifies Deletions in Chr17p and High ROR1 Expression, but Not TP53 Mutations As Predictors of Overall Survival in Patients with Untreated Waldenstrom's Macroglobulinemia (WM). Blood 2024;144(Suppl 1):2968.
[32] Ruan G, Zanwar S, Abeykoon JP, et al. Predictors of short-term survival in Waldenstrom Macroglobulinemia. Leuk Lymphoma Dec 2020;61(12):2975–9. doi:10.1080/10428194.2020.1789625.
[33] Zanwar S, Abeykoon JP, Ansell SM, et al. Waldenström Macroglobulinemia in the Very Elderly (≥75 years):Clinical Characteristics and Outcomes. Blood 2020;136(Suppl 1):44–5. doi:10.1182/blood-2020-142884.
[34] Kastritis E, Kyrtsonis MC, Morel P, et al. Competing risk survival analysis in patients with symptomatic Waldenstrom macroglobulinemia: the impact of disease unrelated mortality and of rituximab-based primary therapy. Haematologica Nov 2015;100(11):e446–9. doi:10.3324/haematol.2015.124149.
[35] Amaador K, Kersten MJ, Visser O, et al. Conditional relative survival in Waldenstrom's macroglobulinaemia: a population-based study in The Netherlands. Br J Haematol Mar 2022;196(5):1205–8. doi:10.1111/bjh.17926.
[36] Kastritis E, Kyrtsonis MC, Hadjiharissi E, et al. Validation of the International Prognostic Scoring System (IPSS) for Waldenstrom's macroglobulinemia (WM) and the importance of serum lactate dehydrogenase (LDH). Leuk Res Oct 2010;34(10):1340–3. doi:10.1016/j.leukres.2010.04.005.
[37] Kastritis E, Gavriatopoulou M, Kyrtsonis MC, et al. Prognostication of the high-risk WM patient. Clin Lymphoma Myeloma Leuk Feb 2011;11(1):127–9. doi:10.3816/CLML.2011.n.028.
[38] Treon SP, Gustine J, Xu L, et al. MYD88 wild-type Waldenstrom Macroglobulinaemia: differential diagnosis, risk of histological transformation, and overall survival. Br J Haematol Feb 2018;180(3):374–80. doi:10.1111/bjh.15049.
[39] Boccon-Gibod C, Sourdeau E, Morel P, et al. Circulating tumor cells in Waldenstrom macroglobulinemia. Leukemia Apr 2024;38(4):903–7. doi:10.1038/s41375-024-02156-3.
[40] Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Research Support, Non-U.S. Gov't. Blood May 1 2014;123(18):2791–6. doi:10.1182/blood-2014-01-550905.
[41] Durot E, Kanagaratnam L, Zanwar S, et al. A prognostic index predicting survival in transformed Waldenström macroglobulinemia. Haematologica 2020;106(11):2940–6 11/12. doi:10.3324/haematol.2020.262899.
[42] Zanwar S, Abeykoon JP, Durot E, et al. Impact of MYD88(L265P) mutation status on histological transformation of Waldenström Macroglobulinemia. Am J Hematol Mar 2020;95(3):274–81. doi:10.1002/ajh.25697.
[43] Zanwar S, Abeykoon JP, Ansell SM, et al. Primary systemic amyloidosis in patients with Waldenstrom macroglobulinemia. Leukemia 2019;33(3):790–4. doi:10.1038/s41375-018-0286-7.
[44] Cao X, Ye Q, Orlowski RZ, et al. Waldenstrom macroglobulinemia with extramedullary involvement at initial diagnosis portends a poorer prognosis. J Hematol Oncol Jun 24 2015;8:74. doi:10.1186/s13045-015-0172-y.
[45] Poulain S, Roumier C, Venet-Caillault A, et al. Genomic Landscape of CXCR4 Mutations in Waldenstrom Macroglobulinemia. Clin Cancer Res Mar 15 2016;22(6):1480–8. doi:10.1158/1078-0432.ccr-15-0646.
[46] Treon SP, Sarosiek S, Castillo JJ. How I use genomics and BTK inhibitors in the treatment of Waldenstrom macroglobulinemia. Blood Apr 25 2024;143(17):1702–12. doi:10.1182/blood.2022017235.
[47] Treon SP, Xu L, Guerrera ML, et al. Genomic Landscape of Waldenström Macroglobulinemia and Its Impact on Treatment Strategies. J Clin Oncol Apr 10 2020;38(11):1198–208. doi:10.1200/jco.19.02314.
[48] Cao Y, Hunter ZR, Liu X, et al. CXCR4 WHIM-like frameshift and nonsense mutations promote ibrutinib resistance but do not supplant MYD88(L265P)-directed survival signalling in Waldenstrom macroglobulinaemia cells. Research Support, Non-U.S. Gov't. Br J Haematol Mar 2015;168(5):701–7. doi:10.1111/bjh.13200.
[49] Tawfiq RK, Abeykoon JP, Kapoor P. Bruton Tyrosine Kinase Inhibition: an Effective Strategy to Manage Waldenstrom Macroglobulinemia. Curr Hematol Malig Rep Jun 2024;19(3):120–37. doi:10.1007/s11899-024-00731-0.
[50] Hunter ZR, Yang G, Xu L, Liu X, Castillo JJ, Treon SP. Genomics, Signaling, and Treatment of Waldenstrom Macroglobulinemia. J Clin Oncol Mar 20 2017;35(9):994–1001. doi:10.1200/jco.2016.71.0814.
[51] Kaiser LM, Hunter ZR, Treon SP, Buske C. CXCR4 in Waldenström's Macroglobulinema: chances and challenges. Leukemia Feb 2021;35(2):333–45. doi:10.1038/s41375-020-01102-3.
[52] Roccaro AM, Sacco A, Jimenez C, et al. C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. Blood Jun 26 2014;123(26):4120–31. doi:10.1182/blood-2014-03-564583.
[53] Ravi G, Kapoor P. Current approach to Waldenstrom Macroglobulinemia. Cancer Treat Res Commun 2022;31:100527. doi:10.1016/j.ctarc.2022.100527.
[54] Sklavenitis-Pistofidis R, Capelletti M, Liu C-J, et al. Bortezomib overcomes the negative impact of CXCR4 mutations on survival of Waldenstrom macroglobulinemia patients. Blood 2018;132(24):2608–12. doi:10.1182/blood-2018-07-863241.
[55] Tam CS, Opat S, D'Sa S, et al. Biomarker analysis of the ASPEN study comparing zanubrutinib with ibrutinib for patients with Waldenstrom macroglobulinemia. Blood Adv Apr 9 2024;8(7):1639–50. doi:10.1182/bloodadvances.2023010906.
[56] Schop RF, Kuehl WM, Van Wier SA, et al. Waldenstrom macroglobulinemia neoplastic cells lack immunoglobulin heavy chain locus translocations but have frequent 6q deletions. Research Support, Non-U.S. Gov't Research

Support, U.S. Gov't, P.H.S. Blood Oct 15 2002;100(8):2996–3001. doi:10.1182/blood.V100.8.2996.
[57] Nguyen-Khac F, Lambert J, Chapiro E, et al. Chromosomal aberrations and their prognostic value in a series of 174 untreated patients with Waldenström's macroglobulinemia. Haematologica 2013;98(4):649.
[58] Guerrera ML, Tsakmaklis N, Xu L, et al. MYD88 mutated and wild-type Waldenstrom's Macroglobulinemia: characterization of chromosome 6q gene losses and their mutual exclusivity with mutations in CXCR4. Haematologica Sep 2018;103(9):e408–11. doi:10.3324/haematol.2018.190181.
[59] Paiva B, Corchete LA, Vidriales MB, et al. The cellular origin and malignant transformation of Waldenstrom macroglobulinemia. Research Support, Non-U.S. Gov't. Blood Apr 9 2015;125(15):2370–80. doi:10.1182/blood-2014-09-602565.
[60] Kapoor P, Ansell SM, Braggio E. Waldenstrom macroglobulinemia: genomic aberrations and treatment. Plasma Cell Dyscrasias 2016:321–61.
[61] García-Sanz R, Dogliotti I, Zaccaria GM, et al. 6q deletion in Waldenström macroglobulinaemia negatively affects time to transformation and survival. Br J Haematol 2021;192(5):843–52.
[62] Ocio EM, Schop RF, Gonzalez B, et al. 6q deletion in Waldenstrom macroglobulinemia is associated with features of adverse prognosis. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't. Br J Haematol Jan 2007;136(1):80–6. doi:10.1111/j.1365-2141.2006.06389.x.
[63] Forgeard N, Baron M, Caron J, et al. Inflammation in Waldenstrom macroglobulinemia is associated with 6q deletion and need for treatment initiation. Haematologica Nov 1 2022;107(11):2720–4. doi:10.3324/haematol.2022.281053.
[64] Cao Y, Hunter ZR, Liu X, et al. The WHIM-like CXCR4(S338X) somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenstrom's Macroglobulinemia. Leukemia Jan 2015;29(1):169–76. doi:10.1038/leu.2014.187.
[65] Gustine JN, Xu L, Tsakmaklis N, et al. CXCR4(S338X) clonality is an important determinant of ibrutinib outcomes in patients with Waldenstrom macroglobulinemia. Blood Adv Oct 8 2019;3(19):2800–3. doi:10.1182/bloodadvances.2019000635.
[66] Zanwar S. A multicenter, International collaborative study evaluating frontline therapy with bendamustine rituximab Waldenstrom macroglobulinemia. Abstract *Hemasphere* 2022(6):1046–7 2022 Jun 23.
[67] Yan Y, Yu Y, Xiong W, et al. Determination of MYD88 and CXCR4 Mutations for Clinical Detection and Their Significance in Waldenstrom Macroglobulinemia. Clin Cancer Res Dec 2 2024;30(23):5483–93. doi:10.1158/1078-0432.CCR-23-3939.
[68] Garcia-Sanz R, Varettoni M, Jiménez C, et al. Semin Hematol 2023;60(2):90–6.
[69] Gustine JN, Tsakmaklis N, Demos MG, et al. TP53 mutations are associated with mutated MYD88 and CXCR4, and confer an adverse outcome in Waldenstrom macroglobulinaemia. Br J Haematol Jan 2019;184(2):242–5. doi:10.1111/bjh.15560.
[70] Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood 2020;136(18):2038–50. doi:10.1182/blood.2020006844.
[71] Dimopoulos MA, Opat S, D'Sa S, et al. Zanubrutinib Versus Ibrutinib in Symptomatic Waldenström Macroglobulinemia: Final Analysis From the Randomized Phase III ASPEN Study. Journal of Clinical Oncology 2023 JCO.22.02830. doi:10.1200/JCO.22.02830.
[72] Zanwar S. A multicenter, international collaborative study evaluating frontline therapy with bendamustine rituximab for Waldenstrom macroglobulinemia. Abstract Hemasphere 2022;6(Suppl):1046–7.
[73] Dimopoulos MA, Opat S, D'Sa S, et al. Zanubrutinib Versus Ibrutinib in Symptomatic Waldenstrom Macroglobulinemia: Final Analysis From the Randomized Phase III ASPEN Study. J Clin Oncol Nov 20 2023;41(33):5099–106. doi:10.1200/JCO.22.02830.
[74] Buske C, Dimopoulos MA, Grunenberg A, et al. Bortezomib-dexamethasone, rituximab, and cyclophosphamide as first-line treatment for waldenström's macroglobulinemia: a prospectively randomized trial of the european consortium for waldenström's macroglobulinemia. Journal of Clinical Oncology 2023;41(14):2607–16.
[75] Rummel MJ, Lerchenmüller C, Hensel M, et al. Two Years Rituximab Maintenance Vs. Observation after First Line Treatment with Bendamustine Plus Rituximab (B-R) in Patients with Waldenström's Macroglobulinemia (MW): Results of a Prospective, Randomized, Multicenter Phase 3 Study (the StiL NHL7-2008 MAINTAIN trial). Blood 2019;134(Suppl_1):343. doi:10.1182/blood-2019-121909.
[76] Pika T, Hegenbart U, Flodrova P, Maier B, Kimmich C, Schonland SO. First report of ibrutinib in IgM-related amyloidosis: few responses, poor tolerability, and short survival. Blood Jan 18 2018;131(3):368–71. doi:10.1182/blood-2017-09-806463.
[77] Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenstrom macroglobulinemia: the ASPEN study. Blood Oct 29 2020;136(18):2038–50. doi:10.1182/blood.2020006844.
[78] Kersten MJ, Amaador K, Minnema MC, et al. Combining Ixazomib With Subcutaneous Rituximab and Dexamethasone in Relapsed or Refractory Waldenström's Macroglobulinemia: Final Analysis of the Phase I/II HOVON124/ECWM-R2 Study. Journal of Clinical Oncology 2021;40(1):40–51 2022/01/01. doi:10.1200/JCO.21.00105.
[79] Sawalha Y, Sarosiek SR, Welkie RL, et al. Outcomes of Patients with Relapsed/Refractory Lymphoplasmacytic Lymphoma Treated with Venetoclax: A Multicenter Retrospective Analysis. Blood 2023;142(Suppl 1):3045. doi:10.1182/blood-2023-187237.
[80] Castillo JJ, Allan JN, Siddiqi T, et al. Venetoclax in Previously Treated Waldenstrom Macroglobulinemia. J Clin Oncol Jan 1 2022;40(1):63–71. doi:10.1200/JCO.21.01194.
[81] Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. The Lancet 2021;397(10277):892–901 2021/03/06/. doi:10.1016/S0140-6736(21)00224-5.
[82] Palomba ML, Patel MR, Eyre TA, et al. Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed /Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study. Blood 2022;140(Suppl 1):557–60. doi:10.1182/blood-2022-159123.
[83] Paludo J, Gertz Morie, Ansell Stephen M, Abeykoon Jithma P, Dispenzieri Angela Martha QLacy, Kyle Robert, Buadi Francis, Dingli David, Hayman Suzanne, Gonsalves Wilson I, Vincent Rajkumar S, Kumar Shaji, Kapoor Prashant. Impact of Day-100 Response Post Autologous Stem Cell Transplantation (ASCT) in Waldenström Macroglobulinemia (WM). Biology of Blood and Marrow Transplantation 2016;22(3) Supplement,.
[84] Merlini G, Sarosiek S, Benevolo G, et al. Report of Consensus Panel 6 from the 11th International Workshop on Waldenström's Macroglobulinemia on Management of Waldenström's Macroglobulinemia Related Amyloidosis. Elsevier; 2023.
[85] Sidiqi MH, Buadi FK, Dispenzieri A, et al. Autologous Stem Cell Transplant for IgM-Associated Amyloid Light-Chain Amyloidosis. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation Mar 2019;25(3):e108–11. doi:10.1016/j.bbmt.2018.12.003.
[86] Kyriakou C, Canals C, Sibon D, et al. High-dose therapy and autologous stem-cell transplantation in Waldenstrom macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Comment Multicenter Study. J Clin Oncol May 1 2010;28(13):2227–32. doi:10.1200/JCO.2009.24.4905.
[87] Kyriakou C, Fekom M, Khvedelidze I, et al. Long Term Outcomes of Hematopoietic Stem Cell Transplantation in Patients with Waldenström's Macroglobulinemia. Report from the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (LWP EBMT). Blood 2024;144(Suppl 1):3010. doi:10.1182/blood-2024-197901.
[88] Kyriakou C, Canals C, Cornelissen JJ, et al. Allogeneic stem-cell transplantation in patients with Waldenstrom macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol Nov 20 2010;28(33):4926–34. doi:10.1200/JCO.2009.27.3607.
[89] Castillo J. A Phase II Trial of Loncastuximab Tesirine in Patients with Previously Treated Waldenström Macroglobulinemia. Abstract *Blood* 2024;144(Suppl 1):4404.
[90] Ailawadhi S, Stiff P, Ibrahim E, et al. CLR 131 (Iopofosine I-131) Treatment in Triple Class Refractory and Beyond Multiple Myeloma Patients: Preliminary Efficacy and Safety Results from the Phase 2 Clover-1 Trial. Blood 2021;138(Suppl 1):1652. doi:10.1182/blood-2021-152682.
[91] Parrondo RD, Paulus A, Alegria V, et al. Plamotamab (XmAb((R))13676) for Ibrutinib- refractory CXCR4-mutated extramedullary Waldenstrom macroglobulinemia. Leuk Lymphoma Mar 2022;63(3):738–42. doi:10.1080/10428194.2021.2005045.
[92] Castillo J. A Phase II Study of Pirtobrutinib and Venetoclax in Previously Treated Patients with Waldenström Macroglobulinemia: An Interim Analysis. Abstract *Blood* 2024;144(Suppl 1):3011.
[93] Shadman M, Yeung C, Redman MW, et al. Third Generation CD20 Targeted CAR T-Cell Therapy (MB-106) for Treatment of Patients with Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma. Blood 2020;136(Suppl 1):38–9. doi:10.1182/blood-2020-136440.
[94] Tam CS, Kapoor P, Castillo JJ, et al. Report of consensus panel 7 from the 11th international workshop on Waldenstrom macroglobulinemia on priorities for novel clinical trials. Semin Hematol Mar 2023;60(2):118–24. doi:10.1053/j.seminhematol.2023.03.006.
[95] Schop RF, Jalal SM, Van Wier SA, et al. Deletions of 17p13.1 and 13q14 are uncommon in Waldenstrom macroglobulinemia clonal cells and mostly seen at the time of disease progression. Cancer Genet Cytogenet Jan 1 2002;132(1):55–60. doi:10.1016/s0165-4608(01)00526-x.
[96] Chang H, Samiee S, Li D, Patterson B, Chen CI, Stewart AK. Analysis of IgH translocations, chromosome 13q14 and 17p13.1(p53) deletions by fluorescence in situ hybridization in Waldenstrom's macroglobulinemia: a single center study of 22 cases. Leukemia Jun 2004;18(6):1160–2. doi:10.1038/sj.leu.2403369.
[97] Yi S, Li Z, Zou D, et al. Del17p does not always significantly influence the survival of B-cell chronic lymphoproliferative disorders. Oncotarget Jan 9 2018;9(3):3353–64. doi:10.18632/oncotarget.23261.
[98] Varettoni M, Arcaini L, Rattotti S, Ferretti V, Cazzola M. Bone marrow assessment in asymptomatic immunoglobulin M monoclonal gammopathies. Comment Letter. Br J Haematol Jan 2015;168(2):301–2. doi:10.1111/bjh.13091.
[99] Varghese AM, Rawstron AC, Ashcroft AJ, Moreton P, Owen RG. Assessment of bone marrow response in Waldenstrom's macroglobulinemia. Clin Lymphoma Myeloma Mar 2009;9(1):53–5. doi:10.3816/CLM.2009.n.013.
[100] Varettoni M, Zibellini S, Merli M, et al. Molecular remission is an independent predictor of progression-free survival in patients with Waldenstrom macroglobulinemia treated with chemo-immunotherapy: Results from the FIL_BIOWM study. Hematol Oncol Aug 2023;41(3):574–7. doi:10.1002/hon.3082.

[101] Uljon SN, Treon SP, Tripsas CK, Lindeman NI. Challenges with serum protein electrophoresis in assessing progression and clinical response in patients with Waldenstrom macroglobulinemia. Clin Lymphoma Myeloma Leuk Apr 2013;13(2):247–9. doi:10.1016/j.clml.2013.03.001.
[102] Banwait R, Aljawai Y, Cappuccio J, et al. Extramedullary Waldenstrom macroglobulinemia. Am J Hematol Feb 2015;90(2):100–4. doi:10.1002/ajh.23880.
[103] Ostergaard S, Munksgaard L, Nielsen TH, et al. Extramedullary disease in Waldenstrom macroglobulinemia: A population-based observational study. EJHaem Dec 2024;5(6):1269–73. doi:10.1002/jha2.1037.
[104] Castillo JJ, Gustine J, Meid K, Dubeau T, Hunter ZR, Treon SP. Histological transformation to diffuse large B-cell lymphoma in patients with Waldenstrom macroglobulinemia. Am J Hematol Oct 2016;91(10):1032–5. doi:10.1002/ajh.24477.
[105] Durot E, Tomowiak C, Michallet AS, et al. Transformed Waldenstrom macroglobulinaemia: clinical presentation and outcome. A multi-institutional retrospective study of 77 cases from the French Innovative Leukemia Organization (FILO). Br J Haematol Nov 2017;179(3):439–48. doi:10.1111/bjh.14881.
[106] Chohan KL, Pruthi RK, Zanwar S, et al. The clinical impact of acquired von Willebrand syndrome secondary to Waldenstrom macroglobulinemia: an underrecognized source of major bleeding events. Leukemia Nov 2024;38(11):2497–500. doi:10.1038/s41375-024-02393-6.
[107] Zanwar S, Abeykoon JP, Ansell SM, et al. Central nervous system involvement (Bing-Neel Syndrome) in patients with Waldenstrom macroglobulinemia. Leuk Lymphoma Jul-Aug 2023;64(8):1490–3. doi:10.1080/10428194.2023.2214026.
[108] Minnema MC, Kimby E, D'Sa S, et al. Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome. Haematologica 2017;102(1):43–51. doi:10.3324/haematol.2016.147728.
[109] Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. Clinical Trial Multicenter Study Research Support, Non-U.S. Gov't. N Engl J Med Apr 9 2015;372(15):1430–40. doi:10.1056/NEJMoa1501548.
[110] Treon SP, Meid K, Gustine J, et al. Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenstrom Macroglobulinemia. J Clin Oncol Feb 20 2021;39(6):565–75. doi:10.1200/JCO.20.00555.
[111] Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenstrom's Macroglobulinemia. N Engl J Med Jun 21 2018;378(25):2399–410. doi:10.1056/NEJMoa1802917.
[112] Buske C, Tedeschi A, Trotman J, et al. Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenstrom's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study. J Clin Oncol Jan 1 2022;40(1):52–62. doi:10.1200/JCO.21.00838.
[113] Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib for patients with rituximab-refractory Waldenstrom's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. The Lancet Oncology Feb 2017;18(2):241–50. doi:10.1016/s1470-2045(16)30632-5.
[114] Trotman J, Buske C, Tedeschi A, et al. Single-Agent Ibrutinib for Rituximab-Refractory Waldenstrom Macroglobulinemia: Final Analysis of the Substudy of the Phase III Innovate(TM) Trial. Clin Cancer Res Nov 1 2021;27(21):5793–800. doi:10.1158/1078-0432.CCR-21-1497.
[115] Treon SP, Gustine J, Meid K, et al. Ibrutinib Monotherapy in Symptomatic, Treatment-Naive Patients With Waldenstrom Macroglobulinemia. J Clin Oncol Sep 20 2018;36(27):2755–61. doi:10.1200/jco.2018.78.6426.
[116] Castillo JJ, Meid K, Gustine JN, et al. Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia. Leukemia Feb 2022;36(2):532–9. doi:10.1038/s41375-021-01417-9.
[117] Castillo JJ, Xu L, Gustine JN, et al. CXCR4 mutation subtypes impact response and survival outcomes in patients with Waldenström macroglobulinaemia treated with ibrutinib. Br J Haematol 2019;187(3):356–63. doi:10.1111/bjh.16088.
[118] Sekiguchi N, Rai S, Munakata W, et al. Two-year outcomes of tirabrutinib monotherapy in Waldenstrom's macroglobulinemia. Cancer Sci Jun 2022;113(6):2085–96. doi:10.1111/cas.15344.
[119] Cao XX, Jin J, Fu CC, et al. Evaluation of orelabrutinib monotherapy in patients with relapsed or refractory Waldenstrom's macroglobulinemia in a single-arm, multicenter, open-label, phase 2 study. EClinicalMedicine Oct 2022;52:101682. doi:10.1016/j.eclinm.2022.101682.
[120] Castillo JJ, Meid K, Flynn CA, et al. Ixazomib, dexamethasone, and rituximab in treatment-naive patients with Waldenstrom macroglobulinemia: long-term follow-up. Blood Adv Aug 25 2020;4(16):3952–9. doi:10.1182/bloodadvances.2020001963.
[121] Castillo JJ, Meid K, Gustine JN, et al. Prospective Clinical Trial of Ixazomib, Dexamethasone, and Rituximab as Primary Therapy in Waldenstrom Macroglobulinemia. Clin Cancer Res Jul 15 2018;24(14):3247–52. doi:10.1158/1078-0432.CCR-18-0152.
[122] Xiong W, Yan Y, Wang T, et al. Zanubrutinib plus Ixazomib and Dexamethasone in newly diagnosed symptomatic Waldenström macroglobulinemia:a phase II study. Clinical Cancer Research 2025. doi:10.1158/1078-0432.Ccr-24-3490.
[123] Parrondo RD, Dutta N, LaPlant BR, et al. A phase II study of ibrutinib in combination with ixazomib in patients with Waldenstrom macroglobulinaemia. Br J Haematol May 2024;204(5):1825–9. doi:10.1111/bjh.19320.