



Guidelines



Waldenström's macroglobulinemia: The LYSA pragmatic guidelines

Damien Roos-Weil^{a,b,*}, Cécile Tomowiak^c, Stéphanie Poulain^d, Florence Nguyen-Khac^{b,e}, Florian Bouclet^f, Marine Armand^{b,e}, Thérèse Aurran^g, Eric Durot^h, David Ghezⁱ, Bénédicte Hivert^j, Kamel Laribi^k, Magali Le Garff Tavernier^{b,e}, Stéphane Lepretre^f, Lydia Montes^l, Amine Moslemi^m, Laurence Simonⁿ, Véronique Leblond^a, Pierre Morel^l, Olivier Tournilhac^o

^a Sorbonne Université, AP-HP, Service d'Hématologie Clinique, GH Pitié-Salpêtrière, Paris, France

^b Centre de Recherche des Cordeliers, Sorbonne Université, Université Paris Cité, Inserm UMRS 1138, Drug Resistance in Hematological Malignancies Team, F, Paris 75006, France

^c Service d'Hématologie Et Thérapie Cellulaire, Pôle Régional de Cancérologie, CHU de Poitiers, Poitiers, France

^d INSERM 1277-CNRS 9020 UMRS 12. University of Lille, Lille, France. Laboratory of Hematology, Biology and Pathology center, CHU de Lille, F, LILLE 59000, France

^e Sorbonne Université, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Service d'Hématologie Biologique, F, Paris 75013, France

^f Centre Henri Becquerel, department of clinical haematology, Rouen 76038, France

^g Service d'Hématologie, Institut Paoli Calmettes, Marseille, France

^h Service d'Hématologie, University Hospital of Reims and UFR Médecine, Reims, France

ⁱ Département d'Hématologie, Institut Gustave Roussy, Villejuif, France

^j Hématologie Clinique, Groupement des Hôpitaux de l'Institut Catholique de Lille Hôpital St Vincent de Paul, Lille, France

^k Service d'Hématologie, Centre Hospitalier Le Mans, Le Mans, France

^l Service d'Hématologie, CHU Amiens, Amiens, France

^m Service d'Anatomopathologie, CHU Amiens, Amiens, France

ⁿ Centre Hospitalier Sud Francilien, service d'hématologie clinique, Corbeil-Essonnes, France

^o Service d'Hématologie Et Thérapie Cellulaire, Centre Hospitalier Universitaire (CHU), UCA, EA7453 Chelater, Clermont-Ferrand CIC-1405, France

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ABSTRACT

Waldenström's macroglobulinemia (WM) is a rare, indolent B-cell lymphoma that predominantly affects older adults. In recent years, significant progress has been made in understanding its pathogenesis, identifying relevant biomarkers, and developing novel therapeutic approaches to complement traditional chemoimmunotherapy—collectively reshaping the management landscape of WM. In this article, we provide comprehensive, evidence-based recommendations for the diagnosis, molecular evaluation, and treatment of WM, including strategies for both frontline and relapsed disease. These guidelines are informed by the latest clinical research, expert consensus, and current practice standards, with the goal of equipping clinicians with a practical and effective framework for delivering optimal care to patients with WM.

1. Introduction

Waldenström's macroglobulinemia (WM) is a rare indolent B-cell lymphoma that typically affects the elderly, with a median age at diagnosis around 70 years. Although the disease remains incurable, the current range of available therapies enables satisfactory long-term disease control and, in the majority of cases, prolonged survival. First-line (1 L) therapy classically consists of fixed-duration chemoimmunotherapy (CIT) and relapse treatments typically include covalent

BTK inhibitors (cBTKi) or the use of a different CIT to that used in 1 L. Furthermore, recent studies have evaluated the tolerance and efficacy of continuous cBTKi in the context of 1 L treatment.

The current main questions in WM are: What is the best 1 L approach between fixed-duration CIT and continuous cBTKi? Which (genetic) tools can we use to choose between these two options? Which therapeutic options are available for patients in relapse after CIT and cBTKi?

Due to its rarity, the number of randomised prospective studies in WM remains limited, but there are numerous non-randomized

* Correspondence to. Sorbonne Université, AP-HP, Hôpital Pitié-Salpêtrière, Service d'Hématologie Clinique, 47-83 Bd de l'Hôpital, Paris, Cedex 75651, France.
E-mail address: damien.roosweil@aphp.fr (D. Roos-Weil).

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prospective and retrospective studies compiling large numbers of patients, which enable treatment recommendations to be made. The Lymphoma Study Association (LYSA) group proposes consensus guidelines that reflect the best available evidence-based medicine (EBM) while considering reasonable proposals that have been widely adopted and are applied in clinical practice by LYSA experts in the field.

Levels of evidence and grades of recommendations were applied in accordance with the Grading of Recommendations Assessment Development and Evaluation (GRADE) nomenclature (see **Supplemental Table S1**), with the exception of the elements included in the section entitled "Definition and diagnosis work-up", for which this grading system was not enough relevant.

1.1. Definition and diagnosis work-up

According to the 5th edition of the World Health Organization (WHO) classification of tumors, lymphoplasmacytic lymphoma (LPL) is defined as the proliferation of small lymphocytes, lymphoplasmacytic cells, and plasma cells, which typically infiltrate the bone marrow (BM) or, occasionally, the lymph nodes or spleen. LPL may or may not secrete monoclonal immunoglobulin (Ig), typically of the IgM isotype [1,2]. As per the International Workshop on Waldenström's Macroglobulinemia (IWWM) 2 recommendations [3] and the WHO classification, the diagnosis of Waldenström macroglobulinemia (WM) requires the fulfillment of the following criteria: (i) the presence of clonal lymphoplasmacytic cells in the BM, and (ii) the presence of circulating monoclonal IgM in any quantity. The International Consensus Classification (ICC) on Lymphoid Neoplasms [2] does not provide a different stance on this matter.

The highly recurrent p.L265P somatic mutation of the *MYD88* gene (*MYD88* L265P, also called L252P), observed in more than 95 % of patients, is a key feature and should be tested for. However, it is not specific, as it can also be found, albeit less frequently, in other B-cell lymphoproliferative disorders. Additionally, testing for *CXCR4* mutations, which are less common but rare in other lymphoid malignancies, is also recommended by both the WHO and ICC.

Rare nosologically related entities, such as LPL secreting a monoclonal Ig other than IgM, non-secretory LPL, or LPL secreting IgM but without BM involvement, do not fall within the definition of WM. Lymphoproliferations associated with chronic cold agglutinin disease (CAD), which do not typically harbor the *MYD88* L265P mutation, are likely distinct entities, as recognized by the ICC.

1.2. Which investigations are required for WM diagnosis? Can we avoid bone marrow biopsy?

Waldenström macroglobulinemia (WM) can be suspected in the presence of IgM monoclonal gammopathy, with or without symptoms related to the monoclonal protein itself or the proliferation of clonal lymphoplasmacytic cells that secrete the monoclonal protein. WM is not the only B-cell malignancy responsible for the secretion of IgM, as it can also be found in marginal zone lymphoma (MZL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and, though less frequently, mantle cell lymphoma or IgM myeloma. The presence of clonal cells in the bone marrow (BM) can be detected in nearly all patients with IgM monoclonal gammopathy of undetermined significance (IgM-MGUS), suggesting a continuum with multistep events from IgM-MGUS to WM. The critical distinction lies in identifying asymptomatic patients who do not require treatment versus those with target organ damage who do, regardless of the rate of BM infiltration or IgM levels. This has led to the conceptualization of asymptomatic WM and IgM-related disorders, also known as monoclonal gammopathy of clinical significance (MGCS).

BM assessment is a key component of the pathological diagnosis of WM and is strongly recommended for all patients suspected of having symptomatic WM or another IgM-related disorder. Notably, BM

assessment helps to differentiate between WM and IgM-MGUS/IgM-MGCS, as well as MZL. While the value of this assessment in asymptomatic individuals is not yet fully established, it may provide prognostic information regarding the risk of progression, which can be discussed with individual patients.

A BM evaluation, including aspirate and trephine biopsy, is recommended for most patients. The recent update from the ICC [2] emphasizes the importance of demonstrating aberrant lymphoplasmacytic aggregates and the presence of clonal B cells and plasma cells on trephine biopsy for diagnosing WM. The diagnosis does not require a minimum level of infiltration, in accordance with the diagnostic criteria proposed by the IWWM in 2023 [4]. A trephine biopsy offers a more comprehensive assessment of disease burden and provides clearer evidence of plasmacytic differentiation, along with other diagnostic clues, such as the presence of reactive mast cells and immunoglobulin inclusions. Histological examination typically reveals a diffuse or nodular infiltrate, characterized by small B lymphocytes, plasmacytoid cells, and plasma cells in the paratrabecular and interstitial regions. In MZL, the infiltrate predominantly appears as an interstitial pattern, with occasional intrasinusoidal involvement. However, distinguishing between these two entities based solely on this criterion can be challenging.

Therefore, additional diagnostic tools, including multiparametric flow cytometry (MFC) methods, cytogenetic analysis, and molecular testing, are utilized on BM aspirates. The assessment of clonal B-cells is facilitated by MFC from BM aspirates, showing the expression of pan-B antigens (CD19, CD20), with CD79b+ IgM+, CD25 + CD27 + CD22low CD38 +low FMC7 +low, and monotypic light-chain expression. The expression of CD10, CD23, CD11c, or CD103 is often negative, which helps distinguish WM from other low-grade B-cell lymphomas. CD5 expression is seen in 5–20 % of cases, with a Matutes score of < 3 [5]. The myeloid marker CD13 can help differentiate WM/LPL from other B-cell lymphomas [6]. Plasma cells in WM are clonally related and express CD38, CD138, and low levels of CD19 and CD20. While WM and MZL can have overlapping phenotypic profiles, WM usually shows homogeneous CD25 expression with low CD22 and CD27 expression, whereas MZL typically presents as CD22 + CD25- with higher CD27 expression.

In select circumstances, notably those with hemorrhagic risk (e.g. acquired von Willebrand syndrome, active anticoagulation therapy), BM aspirate with MFC, cytogenetic, and molecular studies could be considered as a substitute for BM biopsy, contingent upon the presence of a compelling rationale for the diagnosis of WM (i.e., a compatible phenotype and the existence of a *MYD88* L265P mutation).

Experts point of view:

- **BM assessment including trephine biopsy and aspirate for MFC, cytogenetic, molecular studies is still the gold standard for WM diagnosis.**
- **BM aspirate with MFC, cytogenetic and molecular studies could represent an alternative in selected circumstances.**

1.3. Which genomic assessment and by which technique?

The recently updated ICC [2] has emphasized the value of genetic abnormalities associated with the diagnosis of WM. Although not specific to WM, the demonstration of *MYD88* L265P has clear diagnostic utility allowing a precise genomic diagnosis in the correct clinical and pathological context.

Although the *MYD88* L265P mutation is a molecular marker that is highly recurrent (> 95 %) in WM patients, the presence of the *MYD88* L265P mutation in itself is not pathognomonic of WM, as it is also detectable in a significant proportion of patients with IgM-MGUS, and albeit rarely, in other B-cell lymphoproliferative disorders, including MZL, DLBCL, and CLL/SLL [7]. Its absence does not exclude the diagnosis of WM although it should at least raise questions regarding the validity of a WM diagnosis.

In circumstances where a *MYD88* L265P mutation has not been identified, alternative *MYD88* mutations, particularly those delineated in DLBCL-ABC, may be detected using next-generation sequencing (NGS) [8–11]. Rarely, any *MYD88* mutation is identified. In such instances, subsequent to the exclusion of a technical issue (i.e., a low tumor cell load or a detection technique with limited sensitivity), the presence of a *MYD88* WT WM may be considered, with subsequent implications for prognosis [12]. In such *MYD88* WT cases, a thorough re-evaluation of bone marrow cytology and cytogenetic testing is also warranted—particularly for the t(11;14) translocation—to exclude the diagnosis of IgM-secreting multiple myeloma.

Mutations in the *CXCR4* gene have been identified as the second most common alterations in WM (30%–40% patients) [8,13,14]. *CXCR4* mutations are essentially unique to WM, as they have not been described so far in other diseases, with the exception of a few MZL and DLBCL cases [15]. The *CXCR4* mutational landscape is complex, with > 50 nonsense and frameshift mutations described, the most frequently observed in 50% of cases being *CXCR4* S338X. Unlike *MYD88* L265P, *CXCR4* mutations in WM are generally subclonal and a patient may harbor several mutations in distinct clones. They are associated with increased BM infiltration, higher serum IgM levels, symptomatic hyperviscosity, thrombocytopenia and acquired von Willebrand factor deficiency [9,13,16]. However, *CXCR4* mutations are relevant not only for diagnosis, but also for prognosis and response to cBTKi [16,17].

Other mutations include *ARID1A*, *MLL2*, *TP53*, *CD79A*, *CD79B* or *SPI1* ranging from 5% to 20% of cases [13,18,19]. *TP53* mutations are rare in WM (5–10%), but have been associated with poor survival [8,20,21] and their frequency increases in patients beyond the first-line therapy [22].

The prognostic impact of genetic abnormalities according to the therapies used is also discussed below.

DNA for *MYD88* or *CXCR4* mutational analysis can be extracted from BM, peripheral blood or plasma. Bone marrow is the cell source of reference, bearing in mind that in the case of limited infiltration or diluted sampling, there is still a risk of false negative results. The use of peripheral blood carries a high risk of false negatives and is not recommended for routine diagnosis [23]. Several studies indicate that mutational analysis of cell-free DNA from plasma could be used reliably to identify *MYD88* L265P and *CXCR4* S338X, although this is not yet recommended in clinical practice [24–26].

For *MYD88* L265P detection, a high sensitivity test is recommended. Accepted techniques in terms of reproducibility and sensitivity (1%) include allele-specific PCR (AS-PCR) and digital droplet PCR (ddPCR) on unselected marrow. A NGS sequencing approach requires CD19 + immunoselection to achieve a sufficient level of sensitivity. A detection limit of 1% is required when using NGS to detect *MYD88* or *CXCR4* variants. In *MYD88* L265P negative patients where a diagnosis of WM is strongly suspected, NGS can be used, if possible on CD19 + selected cells to provide reliable results, to identify other *MYD88* mutations or mutations associated with other lymphoproliferative syndromes, such as *KLF2* or *NOTCH2* in MZL.

There are no specific chromosomal abnormalities (CA) that define WM [27]. A complex karyotype (CK, ≥ 3 CA) is observed in 15–30% of cases, including 5% with a highly complex karyotype (HCK, ≥ 5 CA). The most prevalent CA are del6q (20–40%), del13q (10–15%), tri18/18q (10–15%), tri4/4q (8%), del17p (8%), tri12 (8%), tri3/3q (6%) [8,28,29]. Cytogenetic analysis can facilitate the differential diagnosis, particularly in cases of *MYD88* WT patients. Indeed, while del6q and tri4 are non-specific, they are useful recurrent abnormalities, given the high frequency of del6q and the rarity of tri4 in other mature B-cell disorders.

Furthermore, a multitude of cytogenetic abnormalities have been documented to be associated with progression-free survival (PFS) and overall survival (OS), including CK/HCK [8], del6q [31], tri4 [8,32], and *TP53* abnormalities (del17p and/or *TP53* mutations) [8,20,21,29].

It is recommended that karyotype and FISH testing for del6q (6q21/

6q23), and also tri4 if possible, be performed as it could help WM diagnosis. Given its prognostic impact, FISH with the *TP53* probe (in parallel with the analysis of *TP53* mutations) is mandatory. The aforementioned analyses are to be performed on BM samples. Stimulation with ODN-CpG + IL2 is mandatory for duration of 72 h, with a cell concentration of 1 to 2M/ml for cell culture.

Experts point of view:

- At diagnosis, assessment of *MYD88* L265P mutation on BM sample using an assay of established sensitivity is mandatory while it is recommended to perform karyotype and FISH analysis for del6q detection.
- Before first-line therapy, the presence of *TP53* abnormalities (del17p [FISH] and/or *TP53* mutations [NGS]) should be assessed as it deeply impacts prognosis and will guide therapeutic choice (see below).
- Detection of *CXCR4* mutation is not mandatory but desirable as it could help for both WM diagnosis and prognostic stratification.

1.4. Which baseline investigations are required?

Recommended investigations for patients suspected of or diagnosed with WM are indicated in Table 1 and Supplemental Table S2. Evaluation for complications such as neuropathy, amyloidosis, and central nervous system (CNS) involvement should be tailored to the individual clinical situation [33].

The propensity of IgM to form multimers in serum makes sample evaluation particularly challenging and IgM gammopathy should be identified through serum protein electrophoresis (SPE) and quantified via densitometric analysis of the SPE result (peak integration). Alternatively, the total IgM concentration could be assessed by nephelometry, which is a suitable method, though it generally yields higher values than densitometric analysis. Ideally, IgM concentration should be assessed sequentially using the same technique within the same laboratory. It is also important to measure IgG and IgA levels, as their reduction may indicate immune deficiency. Although the level of involved serum free light chains (FLC) has been associated with the risk of progression [34,35], the dosage of serum FLC is not recommended in

Table 1
Baseline evaluations of patients with WM.

Types of tests	Techniques	
Tests to establish the diagnosis		
Serum protein electrophoresis and immunofixation	Mandatory	
Marrow aspirate and biopsy	Mandatory	
<i>MYD88</i> L265P mutation	Mandatory	AS-PCR, ddPCR (or NGS)
del6q, tri4	Recommended	FISH
Conventional karyotype	Recommended	72 h, ODN-CpG+IL2
Assessment before first-line treatment		
Age, performance status, comorbidities	Mandatory	
CBC and differential count	Mandatory	
Serum protein electrophoresis, serum chemistry	Mandatory	
Marrow aspirate	Mandatory	
<i>MYD88</i> L265P mutation*	Mandatory*	AS-PCR, ddPCR (or NGS)
<i>TP53</i> mutations	Mandatory	NGS
<i>CXCR4</i> mutations	Recommended	NGS
del17p	Mandatory	FISH
CT-scan (neck, chest, abdomen, and pelvis)	Recommended	
Infectious disease status	Mandatory	

*If not performed previously (at diagnosis). Could also help to assess to determine sample representativeness and clone abundance.

Abbreviations: AS-PCR, allele-specific PCR; ddPCR, digital droplet PCR; NGS, next-generation sequencing.

all IgM-MGUS/WM patients but reserved to those who are suspected to have associated AL amyloidosis or more rarely cast nephropathy or others renal gammopathies. CT-scan is recommended before the initiation of therapy and could be useful to evaluate therapeutic response in patients with bulky disease and profound tumor syndrome.

1.5. Management of first-line Waldenström macroglobulinemia

WM is a disease that is predominantly indolent but nevertheless incurable, with a wide range of clinical manifestations. WM is preceded by an early precursor stage, designated as IgM monoclonal gammopathy of undetermined significance (IgM-MGUS), and a subsequent stage, termed smoldering WM (SWM). Both stages are asymptomatic, although SWM is associated with an increased risk of progression, which necessitates closer follow-up and monitoring. The majority of patients are asymptomatic at the time of diagnosis. Some will never require treatment, while others present with symptomatic disease at diagnosis, including hyperviscosity syndrome, bulky adenopathy and/or profound cytopenia. The asymptomatic WM risk score proposed by Bustoros et al. (<https://www.awmrisk.com>) [36] may be used to estimate time-to-first-treatment, although it requires further validation before routine use. Symptomatic patients should receive therapy that will mainly rely on two types of regimens: fixed-duration CIT and continuous cBTKi.

Management of specific situations related to symptoms attributable to the IgM or light chain monoclonal protein itself (i.e., cryoglobulins, cold agglutinins, AL amyloidosis, IgM-related neuropathy, ...) will not be discussed in this review.

Developing evidence-based treatment algorithms in WM is challenging as the majority of published studies are non-randomised. Optimal choice and sequence of therapies is therefore unknown. Patients should be considered for clinical trials where possible.

1.6. When do we need to initiate therapy for WM?

A significant proportion of WM patients are asymptomatic at presentation and can be safely observed. The risk of progression to symptomatic WM is 31 % at 2 years [36] and 55–60 % at 5 years [36,37]. Progression risk stratification for patients with asymptomatic WM has been created to predict time to first treatment, including four factors (BM infiltration, serum IgM, β 2-microglobulin, and albumin) [36]. For patients with asymptomatic disease, the gold-standard approach remains watch-and-wait. Follow-up for these patients should include repeated assessments of IgM levels, blood count, and clinical examination. The frequency of evaluation can be adjusted based on the risk of progression. Low-risk patients can be seen every 6–12 months, intermediate-risk patients every 4–6 months, and high-risk patients every 3–4 months. It is important to note that being in the high-risk category does not indicate a need for treatment.

Criteria for initiating treatment (proposed by the IWWM-2 consensus group) [38] include IgM-related complications and/or symptoms associated with tumor cell infiltration of the bone marrow, such as cytopenia, constitutional symptoms and bulky extramedullary disease (Supplemental Table S3). The decision to start treatment should not be based solely on the level of IgM.

1.7. What is the role of prognostic scores in clinical practice?

The International Prognostic Scoring System for WM (IPSSWM) [39] and revised IPSSWM (rIPSSWM) [40] enable the classification of WM patients into different risk groups, distinguishing those with a favorable prognosis from those with poor long-term outcomes. However, it is not advisable to stratify treatment based on these scores in routine clinical practice due to a lack of prospective data identifying the superiority of specific treatments in distinct risk groups.

1.8. Which investigations are required before initiating therapy?

Mandatory and desirable investigations before first-line therapy are summarized in Table 1.

1.9. What are therapeutic options for first-line symptomatic WM?

The main therapeutic options currently available for first-line treatment are fixed-duration CIT regimens and continuous cBTKi. Both options are effective, though they present distinct risk-benefit profiles. CIT is a cost-effective, time-limited treatment that clinicians are experienced in administering. However, it requires parenteral administration, hospital admissions, and may lead to infectious complications or therapy-related myeloid neoplasms in some patients [41]. In contrast, cBTKi is an oral, outpatient therapy, but it is associated with high costs and requires continuous treatment, which can lead to resistance and toxicity, including certain cardiovascular adverse events.

1.10. Chemoimmunotherapy (CIT)

1.10.1. Bendamustine and rituximab (BR)

The BR regimen consists of six cycles, each lasting four weeks, with rituximab 375 mg/m² on D1 and bendamustine 90 mg/m² on D1 and D2 (Supplemental Table S4). For more fragile patients or those with poor tolerance, the bendamustine dose can be reduced to 70 mg/m² and/or the number of cycles can be limited to four [42]; however, this may impact disease control [43,44].

While no prospective study has directly compared the efficacy of different CIT regimens, the BR combination appears to yield the most profound responses, with the longest PFS and time-to-next-treatment (TNT). Specifically, the overall response rate (ORR) ranges from 90 % to 98 %, with a median PFS of 60–65 months and a 4-year TNT of 80–85 %, with acceptable tolerability [43–47]. A French retrospective analysis of 69 patients reported a high ORR of 95 %. With a median follow-up of 76.1 months, the 5-year PFS and overall survival (OS) rates were 67 % (95 % CI, 56–79) and 80 % (95 % CI, 71–90), respectively [48]. Two additional retrospective analyses demonstrated significantly higher ORR and longer PFS with BR (n = 83 and 245) compared to DRC (n = 92 and 116), although OS was equivalent [44,47]. BR also facilitates rapid disease control in highly symptomatic patients or those with large tumor masses.

1.11. Dexamethasone, rituximab and cyclophosphamide (DRC)

The DRC regimen consists of six cycles, either 21 or 28 days in length, with dexamethasone 20 mg and rituximab 375 mg/m² on D1, and cyclophosphamide 100 mg/m² twice daily from D1 to D5 (Supplemental Table S3). This regimen is an effective alternative, offering an ORR of 79–83 % and good hematological tolerance, particularly for fragile patients with slow disease progression and no urgent disease control. However, its median PFS of 35 months is shorter than that of BR [49,50].

In a recent randomized study [51], DRC was used as a control arm with a 28-day cycle interval, resulting in an ORR of 87 % and a 2-year PFS of 73 %, suggesting that this design is comparable to the 21-day cycle. The addition of bortezomib to DRC (administered subcutaneously at a dose of 1.6 mg/m² once daily on D1, 8, and 15) for six 28-day cycles provides more rapid disease control and symptom management but did not significantly improve PFS. Notably, both studies reported nausea in 40 % of patients, likely due to the oral administration of cyclophosphamide, which should be carefully managed to prevent this side effect.

1.12. Bortezomib, dexamethasone and rituximab (Bo-DR) and other proteasome inhibitor-based regimens

The Bo-DR regimen consists of single-agent bortezomib (1.3 mg/m²

IV on D1, 4, 8, and 11 of a 21-day cycle), followed by weekly IV bortezomib (1.6 mg/m² on D1, 8, 15, and 22) for four additional cycles, with IV dexamethasone 40 mg and IV rituximab (375 mg/m²) administered in cycles 2 and 5 (Supplemental Table S3). If exposure to alkylating agents or nucleoside analogues is to be avoided, Bo-DR therapy can be used, resulting in ORR of 85 % and a median PFS of 42 months [52,53]. Bortezomib has the advantage of rapidly reducing IgM levels. This protocol is generally well-tolerated and can be used in frail patients. Peripheral neuropathy is the most significant adverse event and limiting factor associated with bortezomib in WM, with grade 3 neuropathy occurring in up to 20–30 % of patients. Notably, even grade 2 neuropathy is associated with a meaningful decline in quality of life. Studies in both first-line and relapsed WM settings have shown that modifying the administration schedule—using weekly rather than twice-weekly dosing, SC instead of IV route, and adjusting the dose—can reduce the incidence of this toxicity [54]. These considerations are particularly important given that a subset of patients may already have peripheral neuropathy at baseline, sometimes as a result of the underlying disease itself.

1.13. BTK inhibitors

Covalent BTK inhibitors (cBTKi) offer a well-tolerated alternative for first-line treatment of WM patients, particularly for those ineligible for CIT. First-line continuous cBTKi therapy, including ibrutinib (with or without rituximab) and zanubrutinib, provides long-term disease control, with progression-free survival (PFS) rates ranging from 70 % to 90 % at 3–4 years [17,55,56]. In the randomized phase III ASPEN trial including 1 L and R/R WM patients, zanubrutinib showed a trend toward deeper and earlier responses, particularly in CXCR4-mutated patients with a median follow-up of 45 months. However, no significant differences in PFS or OS were observed between the two groups. Zanubrutinib demonstrated a better cardiovascular profile compared to ibrutinib, with lower rates of atrial fibrillation (8 % vs. 25 %) and hypertension (15 % vs. 26 %). However, zanubrutinib was associated with higher rates of neutropenia, though it did not result in an increased risk

of infections [22,56].

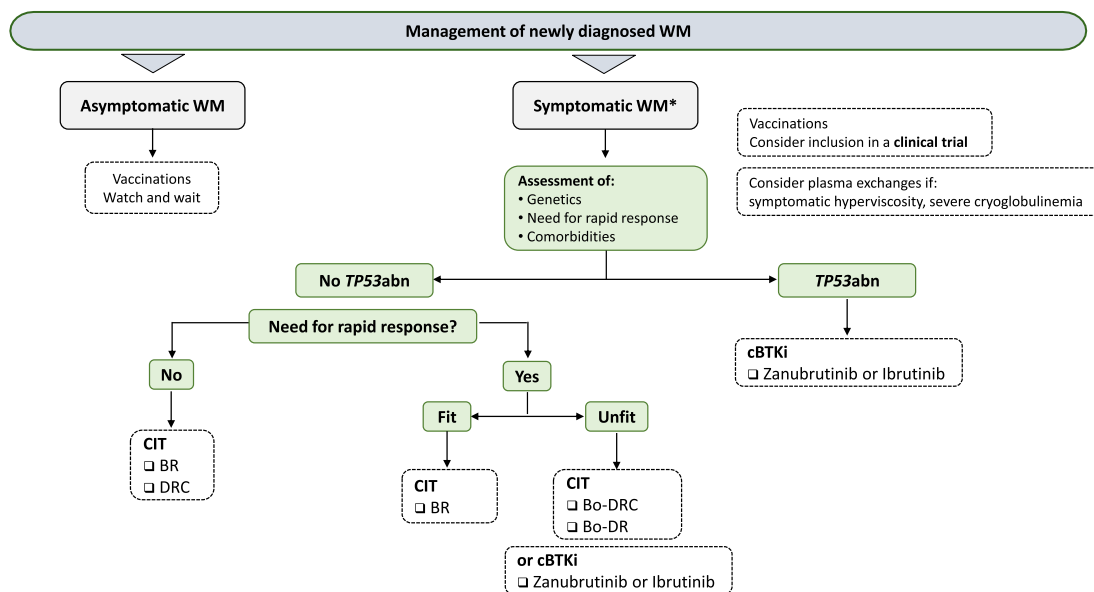
When switching treatments, it is recommended to continue cBTKi therapy until the next-line treatment is initiated. This approach helps minimize IgM rebound and mitigates the side effects associated with “BTKi withdrawal symptoms,” which can affect up to 20 % of patients after treatment cessation [57].

1.14. How to guide first-line therapy?

The primary goal of therapy in WM is to manage symptoms and reduce tumor burden, as achieving a complete response remains rare with current treatments. WM patients can vary in age, comorbidities, and symptomatology, experiencing complications that may require prompt disease control. Therefore, it is crucial to strike a balance between treatment efficacy and tolerability, tailored to the individual patient’s needs. When selecting first-line treatment for WM, three key factors should be considered: the need for rapid response, the patient’s age and comorbidities, and the presence and type of genetic abnormalities.

Treatment options may vary between countries due to differences in drug reimbursements and medical practices. Whenever possible, patients should be considered for inclusion in clinical trials. The LYSA group’s recommendations for frontline therapy are summarized in Fig. 1, while selected results from major trials evaluating CIT and cBTKi in WM are presented in Supplemental Table S5.

Currently, only a limited number of clinical trials incorporate comprehensive molecular (e.g., MYD88, CXCR4, TP53) and cytogenetic data (e.g., del6q, del17p, complex karyotype). Before firm conclusions can be drawn regarding the impact of molecular features on therapeutic response—particularly to cBTKi—it is essential to ensure the quality, reproducibility, and completeness of available data. Variability in results often stems from differences in assay sensitivity, methodological standardization, and the sorting of malignant versus non-malignant cell populations, all of which directly influence the accuracy of molecular profiling. A major unmet need in WM remains the absence of randomized controlled trials directly comparing CIT with cBTKi. Such studies



* Excluding situations related to MGCS/neuropathies

Fig. 1. Recommendations for management of newly diagnosed WM. Abbreviations: Bo-DRC, bortezomib-DRC; BR, bendamustine-rituximab; cBTKi, covalent BTK inhibitors; CIT, chemoimmunotherapy; DRC, dexamethasone–cyclophosphamide-rituximab; MGCS, monoclonal gammopathy of clinical significance; TP53abn, TP53 abnormalities (TP53 mutation and/or del17p).

are critical to defining optimal first-line and R/R treatment strategies, especially within distinct molecular subgroups. The current lack of head-to-head data limits our ability to determine whether molecular or cytogenetic abnormalities—or even clinical prognostic indices such as the IPSSWM—should guide therapeutic selection between these two fundamentally different approaches. Future prospective efforts must therefore integrate high-resolution molecular and genomic data into trial design and clinical decision-making. This includes the use of broad NGS panels on purified samples or those with well-defined VAF, harmonized sequencing methodologies, standardized reporting, and systematic correlation with clinical outcomes. Randomized trials comparing CIT and targeted therapies, stratified by genomic profiles, will be essential to advance precision-based treatment strategies.

However, recent prospective and retrospective data provide valuable insights into the prognostic significance of common genetic anomalies under both CIT and cBTKi, potentially aiding in the decision between these two treatment strategies.

TP53 abnormalities (*TP53abn*), including *TP53* mutations and/or del17p, are detected in 5–15 % of treatment-naïve patients [8,20,29] and in 25–30 % of those who have previously been treated, most of whom received alkylators and/or nucleoside analogues [22]. Patients with *TP53abn* typically have shorter OS and/or PFS with both CIT [30] and cBTKi [22]. However, the median PFS observed with cBTKi (mainly in patients in relapse/refractory [R/R] setting) is much longer than that observed with CIT in 1 L (approximately 48 vs. less than 24 months) [8, 20,22,29]. Therefore, although the evidence is largely derived from retrospective studies and indirect comparisons, we recommend cBTKi as the preferred option for *TP53abn* WM. No significant difference in efficacy has been observed between ibrutinib and zanubrutinib in this subgroup [22]. This recommendation aligns with the marketing authorizations granted by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for both ibrutinib and zanubrutinib. However, in settings where cBTKi and/or *TP53abn* testing are unavailable, CIT remains an acceptable alternative.

Several studies have shown that *CXCR4* mutations negatively affect the depth of response and PFS of patients treated with ibrutinib, whereas this was not the case with CIT, ibrutinib-rituximab [55] or zanubrutinib [56]. Notably, the PFS of *CXCR4*-mutated patients treated with 1 L CIT or cBTKi do not appear to significantly differ [17,30,55]. Given these current and conflicting data, we do not recommend basing the initial therapeutic strategy solely on *CXCR4* status.

There is conflicting evidence regarding the association of *MYD88*^{WT} and poorer survival [12,30,58], possibly due in part to diagnostic and technical issues [12]. The median PFS observed after CIT and cBTKi does not appear to significantly differ for these patients. Zanubrutinib or ibrutinib-rituximab could represent preferred options regarding the marked activity observed in small cohorts of *MYD88*^{WT} patients (median PFS, 45 months-not reached) [55,56,59]. However, more mature data are needed to better understand treatment outcomes in this specific population.

For patients without *TP53abn*, treatment choices should be guided by the need for a rapid response and the patient's comorbidities. In cases of high tumor burden, rapidly acting regimens such as BR, bortezomib-based regimens, or cBTKi are preferred (with a median time to partial response or better of 2–3 months, compared to 4–6 months with DRC). If a patient presents with hyperviscosity, plasmapheresis should be considered. A bortezomib-containing regimen (Bo-DR or Bo-DRC) can rapidly reduce IgM levels and may be an alternative for patients who are not fit for BR and have contraindications to cBTKi (e.g., cardiac comorbidities, recent intracranial hemorrhage, need for anticoagulation, or dual antiplatelet therapy). For patients who do not require immediate disease control, CIT is the first-line option. DRC is a safe, cost-effective choice due to its low toxicity and fixed duration. While BR is highly effective, it may cause more toxic side effects, so it is typically reserved for fit patients or used at reduced doses for others (Figure 1).

Experts point of view:

- In 1 L WM patients with *TP53abn*, we recommend the use of continuous cBTKi (Grade IIB).
- In 1 L WM patients without *TP53abn*, the preferred options rely on fixed-duration CIT: either BR or DRC for patients with slowly progressive disease; in case of disease that need rapid control, we recommend BR for fit patients and bortezomib-based regimens (Bo-DR, Bo-DRC) for unfit patients (Grade IB).

Is there still a place for rituximab monotherapy in first-line WM?

Aside from specific situations close to MGCS (anti-MAG neuropathy, cryoglobulin, CANOMAD, etc.), rituximab monotherapy has a very limited role in the first-line treatment of WM. The major response rates and median PFS are relatively modest, with only 20–40 % and 16–18 months respectively [60]. Additionally, approximately 50 % of patients receiving rituximab monotherapy may experience an IgM flare.

Experts point of view:

1.15. If a patient is not suitable for CIT, cBTKi should be considered rather than rituximab monotherapy (Grade IIIB)

Is there a place for rituximab maintenance in first-line WM?

Following the demonstration of its benefits in other B-cell lymphoid malignancies, maintenance treatment with rituximab has been proposed in WM. A retrospective single-center study suggested its benefit on PFS after different regimens of CIT [61]. However, a prospective randomized study showed no benefit after BR [62]. Given these results and the impact of prolonged anti-CD20 immunotherapy on infectious risk and vaccine response in treated WM patients [63], we do not recommend maintenance therapy.

Experts point of view:

2. There is a lack of evidence to support rituximab maintenance in WM (Grade IC)

2.1. How and when response should be evaluated?

Response criteria have been established by IWWM-6 and recently updated by IWWM-11 [4]. While the exact timing of evaluation is not clearly defined, it is recommended to assess response sequentially after treatment completion, due to the delayed IgM responses observed with purine analogues and monoclonal antibodies [4,64]. Finally, treatment response should be evaluated using uniform response criteria.

Experts point of view:

- Treatment response should be evaluated using uniform response criteria (Grade IA).
- Systematic bone marrow evaluation is not recommended in daily practice (Grade IA).

Supportive care

Infectious complications, particularly those affecting the respiratory tract, are common in WM. Due to the similarities between CLL and WM, and the limited data specifically on WM, we recommend following the CLL guidelines, which include supportive care [65]. These guidelines provide recommendations for the use of prophylactic antibiotics (targeting *Pneumocystis*, *Zoster*, B hepatitis, and fungal infections), as well as vaccination and immunoglobulin replacement therapy.

2.2. Management of relapsed WM

In WM, a relapse is defined [4,64] either by the reappearance of monoclonal IgM (if it had disappeared) or by an increase ≥ 25 % over the minimal IgM level (nadir of response obtained in the previous line)

or by other clinical or biological criteria related to WM.

2.3. How to identify a relapse?

There are several pitfalls to avoid. Care must be taken to define when the nadir of the response was, sometimes several weeks or months after the end of the previous line. SPE should always be used, if possible, in the same laboratory, using the same quantification technique, and beware of fluctuations caused by the possible presence of cryoglobulinemia. Beyond monoclonal IgM, the criteria for clinical and biological progression are diverse [4,64]. The reappearance of anemia is frequent but in this context of chronic, post-therapeutic disease, alternate explanation should be considered (including iron deficiency, myelodysplastic syndrome). There are many WM related mechanisms of anemia associated with WM (infiltration, hemodilution, autoimmunity). It should be noted that a significant proportion of WMs are inflammatory, which contributes to the anemia, and that once all other causes have been ruled out, the reappearance of elevated CRP may be a criterion of hematological activity, but not a criterion for treatment per se [66]. Upon cBTKi discontinuation, rebound phenomena with increased IgM peak and clinical manifestations have been described [67,68].

Expert's point of view:

- **Anemia being of miscellaneous mechanism, related or non-related to WM, an exhaustive blood +/- medullar assessment of potential case should be performed (Grade IA).**
- **A rebound effect following cBTKi discontinuation, which is not systematically followed by disease progression, requires careful monitoring before confirming a true relapse (Grade IA).**

2.4. What are the criteria for treating relapses of WM?

The presence of a relapse does not necessarily indicate the need of a new line of treatment. The criteria for resuming treatment are similar to those used in the 1 L [69]. In the absence of these criteria, patients should be monitored, and their vaccine status updated in preparation for future treatment. The frequency of blood tests and clinical evaluations should be guided by the disease's evolutionary history and the clinical and biological factors that led to the initiation of the previous line. At least initially, evaluations should be performed every 3 months for blood assessment and every 6 months for consultations. Imaging surveillance should not be systematic.

Which investigations are required before initiating therapy in the relapse setting?

While not required at the initial diagnosis of relapse, a BM re-evaluation is essential before initiating a new line of therapy. BM aspiration is generally sufficient, but it must include cytology, immunophenotyping, karyotyping with FISH, and molecular analysis. NGS should include key genes such as *MYD88*, *TP53*, and *CXCR4*. The *MYD88* mutation is stable over time; although it need not be reassessed for its presence, evaluating its allele frequency—along with cytology and immunophenotyping—helps to determine sample representativeness and clone abundance. In contrast, *TP53* abnormalities may increase with disease progression and successive treatments (notably CIT) [22,30]. *CXCR4* mutations may be absent at diagnosis but emerge at relapse, or vice versa, warranting reassessment. This molecular evaluation can also uncover clonal hematopoiesis of uncertain potential (CHIP) or signs of myelodysplasia, both of which carry important therapeutic implications. In situations where a new line of cBTKi is being discussed even though the patient has previously been exposed to it, the assessment of resistance mutations (*BTK*, *PLCG2*) should be performed to decide whether to opt for a new cBTKi therapy or another strategy [70].

A comprehensive cardiac assessment is also critical, ideally conducted by a cardio-oncology specialist, with a focus on evaluating risks associated with cBTKi. This should include a thorough clinical history, blood pressure measurement, echocardiography (including left

ventricular ejection fraction and left atrial surface area), and, when indicated, cardiac biomarkers, Holter ECG, and ambulatory blood pressure monitoring. Additionally, a full medication review is necessary to anticipate potential drug interactions. Renal function, history of infectious complications, and the possible need for immunoglobulin replacement therapy should also be carefully evaluated.

2.5. What are therapeutic options for relapsed or refractory symptomatic WM?

The current standard of care for relapsed or refractory (R/R) WM primarily involves cBTKi, with CIT reserved for selected cases. In instances of resistance or intolerance to cBTKi, alternative off-label therapies may be considered, including proteasome inhibitors, idelalisib, and BCL2 inhibitors (BCL2i). Emerging therapeutic strategies are also under investigation, such as non-covalent BTK inhibitors (ncBTKi) and BTK degraders, which may offer promising options for patients with treatment-refractory disease.

2.6. Chemoimmunotherapy (CIT)

Data on CIT in R/R WM are largely retrospective and, with few exceptions, do not include patients previously exposed to cBTKi. The regimens primarily consist of BR and DRC, as described in the 1 L section.

In a European study (n = 111), BR resulted in an ORR of 84 %, including 74 % major response rate (MRR) with median PFS and OS of 50 and 58 months, respectively [71]. In an older Mayo Clinic study (n = 50), DRC resulted in an ORR of 87 %, including a 68 % MRR, with a median PFS and TNT of 32 and 50 months, respectively [72]. Patients in both studies were 68–69 years old, and had received a median of one previous line, though the BR study population appeared to have been more heavily pretreated. A retrospective single-center comparison of DRC and BR in 1 L and R/R WM (with more relapsed patients in BR group) showed similar response rates, with a 2-year PFS of 66 % with BR versus 53 % with DRC (p = 0.08) [72,73]. In most studies, CIT re-treatment appeared more effective in relapsed WM patients than in those with refractory disease.

The combination of fludarabine, cyclophosphamide and rituximab (FCR) in R/R WM has been reported in retrospective series [74,75]. In the FILO study, FCR achieved an ORR of 84 % and a median PFS of 79 months, which may appear excellent. However, the regimen was associated with significant hematological (including prolonged cytopenia and myelodysplasia) and infectious toxicities, leading to the recommendation against its use.

The adverse impact of *TP53*abn on the outcomes of CIT has not been evaluated in these studies, but it has been demonstrated in other settings [8,20].

2.7. Proteasome inhibitors

Different regimens including proteasome inhibitors, dexamethasone and rituximab (PI-DR) have been investigated in R/R WM. As monotherapy in relapsed WM, bortezomib induces rapid responses with a ≥ 25 % reduction in IgM observed within 6–8 weeks. It has shown an ORR ranging from 27 % to 80 % and a median PFS from 8 to 16 months [76–79]. One of these studies showed the benefit of adding dexamethasone [78]. In R/R WM patients previously treated with a median of 2–3 lines (78 % including rituximab), the combination of bortezomib and rituximab achieved an 81 % ORR and a median PFS of 15.6 months [80].

More recently, a phase 1/2 study evaluated the combination of ixazomib (an oral, less neurotoxic PI) with dexamethasone and rituximab (IRD) in R/R WM (median of 2 prior lines, 63 % including rituximab). This regimen achieved 71 % ORR and 56 % 2-year PFS. Grade 1/2 neuropathy was present at baseline in 21 patients, with worsening during treatment in 3 patients. New-onset grade 1 or 2 neuropathy

occurred in 19 % and 3 % of patients, with no cases of grade 3 or higher [81]. Data on the impact of *TP53*abn on PI efficacy are lacking. A post hoc analysis of the IRD study suggests that *CXCR4* mutations may be associated with a lower depth of response, though no significant impact on PFS has been demonstrated [81].

2.8. Covalent BTK inhibitors

Two cBTKi, ibrutinib and zanubrutinib, have marketing authorization (AMM) in France for R/R WM.

The original study of ibrutinib as monotherapy included relatively young patients with a median age of 63 (range, 44–86) years, exposed to 2 (range, 1–9) previous lines. In the latest long-term evaluation (59 months), the ORR was 90.5 %, MRR 79.4 %, with a time to response (\geq PR) of 1.8 months, a 5-year PFS of 54 % and an OS of 93 % [82,83]. In the INNOVATE study, in 31 patients of similar median age but all refractory to rituximab and pre-exposed to 4 (1–7) lines, with a follow-up of 58 months, the 5-year PFS was 40 % [84,85]. This study also demonstrated the benefit of the combination of ibrutinib and rituximab compared to placebo and rituximab in older patients (median age 68–70 years) who were not refractory to rituximab, 45 % of whom were in 1 L [55]. The benefit of combining rituximab with ibrutinib has obviously not been demonstrated. Acalabrutinib was tested in phase 2 in 92 R/R WM patients with a median age of 69 years and pre-exposed to 2 (1–7) lines (without cBTKi). The ORR and MRR rates were 93 % and 80 % [86]. In a recent 66-month update, the median PFS and OS were 52 % and 71 %, respectively [87]. Acalabrutinib can be used in patients intolerant to the other two available cBTKi. Other cBTKi including tirabrutinib [88] and orelabrutinib [89] are currently being evaluated. The ASPEN trial compared zanubrutinib with ibrutinib [56,90]. In the R/R cohort, representing 82 % of patients, the MRR rate was 81.4 % with zanubrutinib compared to 79.8 % with ibrutinib, with a median time to response of 2.8 months in both arms. PFS at 42 months was 81.7 % with zanubrutinib versus 74.9 % for ibrutinib, which was not statistically significant, and OS was similar (87 vs. 85 %).

The adverse event (AE) profiles of cBTKi differ and are influenced by several factors, including patient age and length of follow-up (see [Supplemental Table S4–5](#)). In ASPEN, treatment discontinuation due to AEs occurred twice as often with ibrutinib. Notably, ibrutinib was associated with a significantly higher incidence of hypertension and cardiac arrhythmias, including atrial fibrillation and flutter. In contrast, zanubrutinib was linked to higher rates of grade \geq 3 neutropenia and anemia. The more favorable cardiovascular safety profile of zanubrutinib was also demonstrated in the ALPINE trial in chronic lymphocytic leukemia (CLL) [91], and further supported by a recent review. Importantly, all agents in this therapeutic class carry a bleeding risk, which poses a potential contraindication in patients with acquired von Willebrand disease. In such cases, cBTKi should be used with particular caution.

2.9. Non-covalent BTK inhibitors (ncBTKi) and BTK degraders

Following the initial report of first 26 WM patients treated with pirtobrutinib [92], the BRUIN study expanded its WM cohort to include 78 patients, 78 % of whom had been previously exposed to cBTKi. After a relatively short median follow-up of 7.7 months, the MRR among 72 evaluable patients was 68 % [93].

BTK degraders such as BGB-16673 (NCT05006716) and NX-2127 (NCT04830137) are being developed in B-cell malignancies, including WM. Early results have shown promising activity in heavily pretreated patients [94,95].

2.10. BCL2 inhibitors (BCL2i)

The first BCL2 inhibitor (BCL2i), venetoclax, was evaluated in R/R WM, in a cohort where 50 % of patients had prior exposure to cBTKi.

The ORR, MRR, and VGPR rate were 84 %, 81 %, and 19 %, respectively. Notably, the MRR was significantly lower in patients with refractory disease compared to those with relapsed disease (50 % vs. 95 %; $P = .007$). After a median follow-up of 33 months, the median PFS was 30 months [96]. Although venetoclax is not currently approved for use in WM, it may represent a valuable option for patients who relapse after treatment with cBTKi. The combination of ibrutinib and venetoclax, which has demonstrated efficacy in CLL has not yet been studied in R/R WM. However, it was tested in the 1 L setting, showing a rapid and high MRR. Unfortunately, the study was terminated early due to four cases of cardiac arrhythmia, including two fatal events [97]. Other strategies combining BTKi and BCL2i are being investigated. A second BCL2 inhibitor, sonrotoclax, is currently under evaluation as monotherapy (NCT05952037). It is also scheduled to be studied in combination with zanubrutinib in France, as part of the WAZABI trial (NCT06547866).

2.11. PI3K inhibitors

Idelalisib, the first selective PI3K inhibitor, has been evaluated in WM. In the REMODEL phase II trial, idelalisib was combined with obinutuzumab in patients with R/R WM. However, toxicity remained a significant issue, with 42 % of patients permanently discontinuing treatment—primarily due to gastrointestinal and hepatic adverse events. Despite these challenges, the combination showed clinical efficacy. Notably, the presence of *CXCR4* or *TP53* mutations did not appear to affect PFS, although *TP53* mutations were associated with inferior OS over the longer term [98,99].

2.11.1. How to guide R/R therapy?

The choice of treatment for R/R WM primarily depends on the initial treatment strategy, typically either CIT or cBTKi. However, several additional factors must be considered, including patient age, comorbidities, performance status, and the initial disease presentation—such as rapid progression or a history of hyperviscosity syndrome, which may necessitate a prompt reduction in IgM levels. Tumor burden, prior therapy-related toxicities, and cytogenetic or molecular features also play a critical role.

Patient preference is another important consideration, particularly in choosing between fixed-duration therapies (e.g., CIT) and continuous long-term treatments (e.g., cBTKi). Finally, the duration of response to the previous line of therapy is a key determinant when evaluating the feasibility of re-treatment with the same approach.

Molecular analysis of the BM should be repeated at relapse and integrated into treatment decision-making algorithms. Specific mutations can influence both treatment selection and expected outcomes. *CXCR4* mutations have been associated with reduced depth of response and shorter PFS, particularly with ibrutinib monotherapy. However, this negative impact appears to be mitigated when ibrutinib is combined with rituximab or when zanubrutinib is used, though further validation is needed.

Similarly, *MYD88* WT patients tend to have inferior responses and shorter PFS with ibrutinib. While efficacy remains lower than in *MYD88*-mutated cases, zanubrutinib has shown encouraging activity in this subgroup. Alterations in *TP53* are another important consideration, as they are associated with poor outcomes and should generally discourage the reuse of CIT. Preliminary evidence also suggests they may predict shorter PFS under cBTKi.

The LYSA group's recommendations for relapsed setting are summarized in [Figs. 2 and 3](#), while selected results from major trials in R/R WM are presented in [Supplemental Table S6](#).

Expert's point of view:

2.12. First relapse

- In R/R WM after 1 L CIT, we recommend the use of a cBTKi as second-line therapy (Grade IIIA)

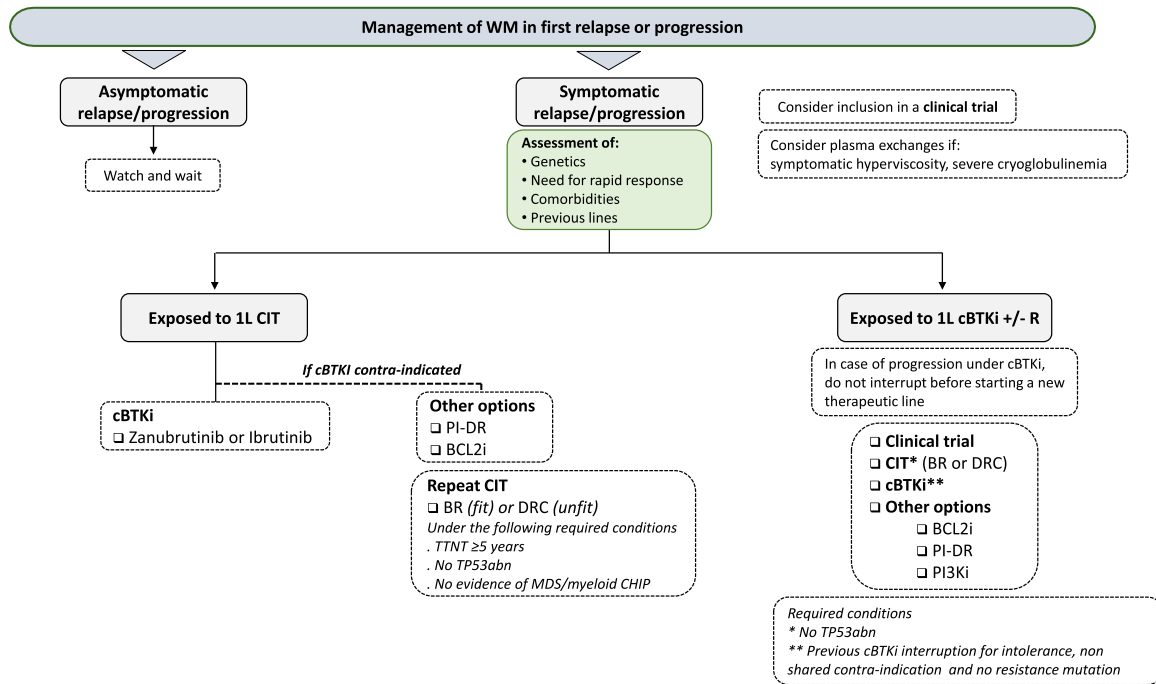


Fig. 2. Recommendations for management of WM in first relapse or progression. Abbreviations: 1 L, first-line; BCL2i, BCL2 inhibitor; Bo-DRC, bortezomib-DRC; BR, bendamustine-rituximab; cBTKi, covalent BTK inhibitors; CIT, chemoimmunotherapy; CHIP, clonal hematopoiesis of undetermined significance; DRC, dexamethasone–cyclophosphamide-rituximab; PI-DR, proteasome inhibitor-dexamethasone-rituximab; TP53abn, TP53 abnormalities (TP53 mutation and/or del17p); TTNT, time to next treatment.

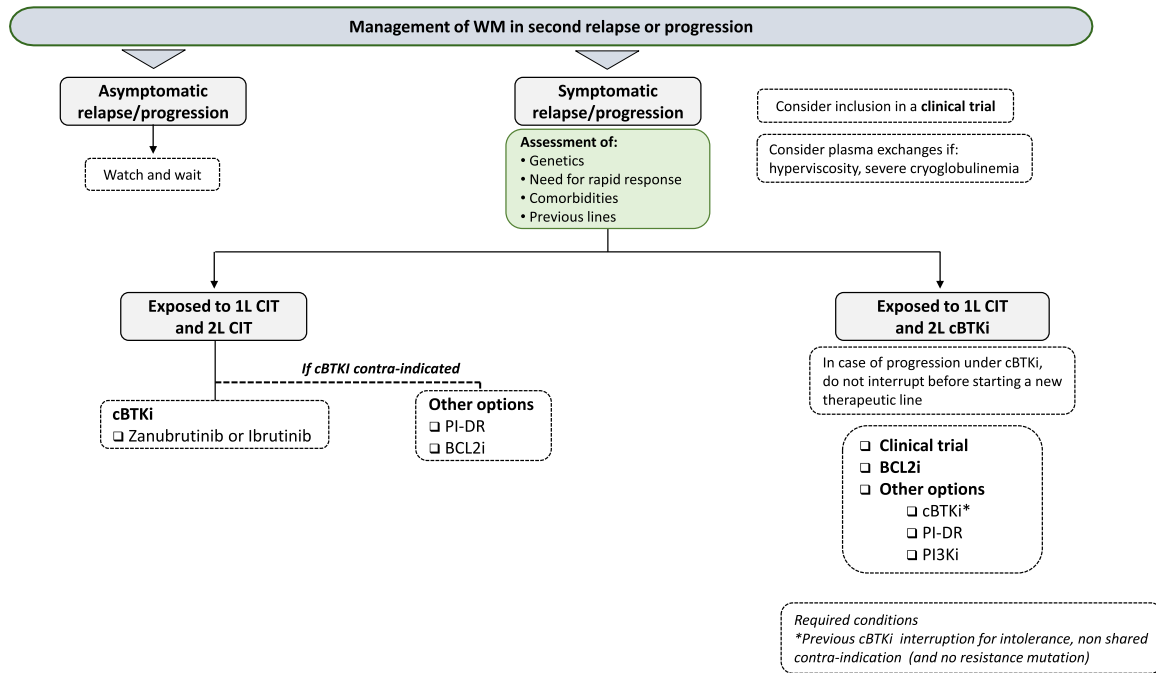


Fig. 3. Recommendations for management of WM in second relapse or progression. Abbreviations: 1 L, first-line; 2 L, second-line; BCL2i, BCL2 inhibitor; Bo-DRC, bortezomib-DRC; BR, bendamustine-rituximab; cBTKi, covalent BTK inhibitors; CIT, chemoimmunotherapy; CHIP, clonal hematopoiesis of undetermined significance; DRC, dexamethasone–cyclophosphamide-rituximab; PI-DR, proteasome inhibitor-dexamethasone-rituximab; PI3Ki, PI3K inhibitor.

- In R/R WM after 1 L CIT, cBTKi administration should not be discouraged by any specific mutation profile. However, the speed, depth, and duration of response may be influenced by the underlying molecular characteristics (Grade IIIA).
- In R/R WM, the choice of cBTKi should primarily be guided by patient comorbidities and the safety profile of each agent.

Zanubrutinib is associated with a lower incidence of cardiovascular adverse events (Grade IA).

- In R/R WM, the molecular profile may also influence cBTKi selection. Zanubrutinib is the most studied cBTKi in MYD88 WT cases (Grade IIIA). Its superiority in the presence of CXCR4 mutations remains less clearly defined (Grade ID).

- In R/R WM after 1 L CIT, for patients with contraindications to cBTKi, repeating CIT (e.g., DRC after DRC, or BR after DRC) is a valid option, provided there is no *TP53* abnormality, no evidence of myelodysplasia, and the initial response lasted at least 5 years (Grade IVB).
- In R/R WM after 1 L CIT or cBTKi, if neither standard alternate approach (cBTKi or CIT) is appropriate, off-label use of a proteasome inhibitor-based regimen or venetoclax may be considered (Grade IVB)

2.13. Subsequent relapses

- In R/R WM previously treated with repeated CIT, we strongly recommend the use of a cBTKi as third-line (Grade IIIA)
- In R/R WM previously treated with first-line CIT who develop intolerance or resistance to second-line cBTKi, compassionate use of venetoclax, ncBTKi or idelalisib may be considered. Proteasome inhibitor-based regimens remain a viable alternative (Grade IVB)

Is there a place for cell therapy in R/R WM?

Autologous and allogeneic hematopoietic cell transplantation (auto-HCT and allo-HCT) were historically explored as treatment options for R/R WM, particularly when therapeutic alternatives were limited. Today, the role of auto-HCT has become obsolete due to its toxicity and lack of curative potential, especially in the era of cBTKi, which have significantly improved treatment outcomes.

In cases of relapse following cBTKi—regardless of prior exposure to CIT—novel agents such as ncBTKi, BCL2i, and BTK degraders are emerging options. However, the durability of responses in patients previously treated with or resistant to cBTKi remains uncertain.

Cellular therapies, including CAR-T cells and bispecific antibodies, represent promising strategies, although clinical experience in WM is still limited except for series reporting this treatment in WM transformation (see below) [100]. Allo-HCT continues to be investigated, primarily through retrospective studies, with one prospective evaluation to date. While these studies suggest a potential for long-term disease control, the risk of significant toxicity must be carefully weighed [101–103] [104].

Experts point of view:

- Allo-HCT should be discussed in selected eligible R/R WM patients with a donor, who have been exposed to CIT, cBTKi and a new alternative such as a BCL2i and/or with a low bone marrow reserve and/or suspected or proven myelodysplasia (Grade IVC).

When to suspect and how to manage histological transformation of WM?

Histological transformation of WM (HT-WM) to aggressive lymphoma represents a rare but serious evolution, typically suspected in the presence of sudden clinical deterioration such as rapidly enlarging lymph nodes, B symptoms, or a marked rise in LDH levels. Diagnosis relies on histological confirmation through a tissue biopsy of the suspicious lesion, ideally reviewed by an experienced hematopathologist. Baseline evaluation should include a positron emission tomography-computed tomography (PET/CT) scan to assess disease extent and metabolic activity. In patients with neurological symptoms or a high risk of CNS involvement, brain magnetic resonance imaging (MRI) and cerebrospinal fluid analysis are recommended. Frontline treatment follows diffuse large B-cell lymphoma (DLBCL) protocols, using chemotherapy such as R-CHOP [105]. Consolidation approaches, including CNS prophylaxis and autologous stem cell transplantation, may be considered in selected patients according to DLBCL guidelines. In the R/R setting, encouraging results have been observed with CAR T-cells [100]. CAR-T cells and bispecific antibodies can be applied according to DLBCL treatment paradigms and local availability.

CRedit authorship contribution statement

David Ghez: Writing – review & editing, Validation, Investigation. **Hivert Benedicte:** Writing – review & editing, Validation, Methodology, Investigation. **Kamel Laribi:** Writing – review & editing, Validation, Methodology, Investigation. **Damien Roos-Weil:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Magali Le Garff Tavernier:** Writing – review & editing, Validation, Methodology, Investigation. **Florian Bouclet:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Laurence Simon:** Writing – review & editing, Validation, Methodology, Investigation. **Marine Armand:** Writing – review & editing, Validation, Methodology, Investigation. **Leblond Veronique:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Aurran Therese:** Writing – review & editing, Validation, Methodology, Investigation. **Pierre Morel:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Eric Durot:** Writing – review & editing, Methodology, Investigation. **Olivier Tournilhac:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Amine Moslemi:** Writing – review & editing, Validation, Investigation. **Tomowiak Cecile:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Lepretre Stephane:** Writing – review & editing, Validation, Methodology, Investigation. **Poulain Stephanie:** Writing – review & editing, Validation, Methodology. **Lydia Montes:** Writing – review & editing, Validation, Methodology, Investigation. **Florence Nguyen-Khac:** Writing – review & editing, Validation, Methodology, Investigation.

Author contribution

DRW and OT supervised the project and conceived the manuscript; all authors contributed to writing, drafting, reviewing, and approving the final version.

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2025.116120](https://doi.org/10.1016/j.ejca.2025.116120).

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