

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

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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 (β 2M) 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 β 2M 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.

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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 (HR-SWM), 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

$\geq 70\%$, serum IgM ≥ 4500 mg/dL, serum β_2 -microglobulin ≥ 4 mg/dL, and serum albumin < 3.5 g/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_2 M 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_2 M ≥ 4 mg/dL OR A. $\dagger$ 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 β_2 -microglobulin did not emerge as prognostic (Table 1). However, high β_2 -microglobulin levels tracked with elevated LDH, low albumin and older age, and a consistent rise in the por-

portion of high β_2 -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 β_2 -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- κ B) 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 occurring alongside a TP53 mutation on the other allele [22]. Furthermore, TP53^{Alt}

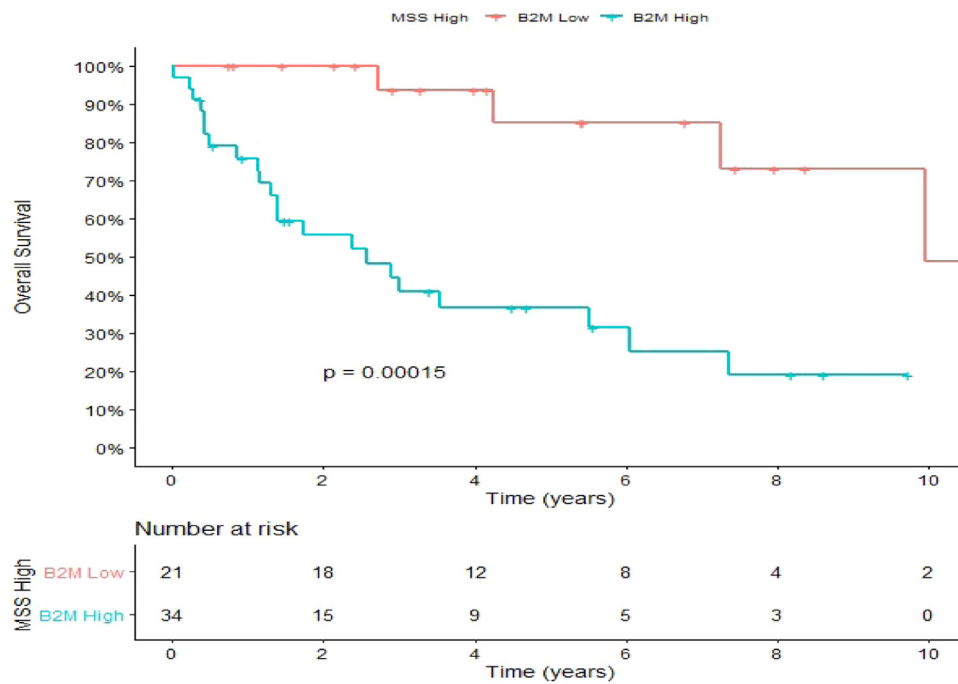


Fig. 1. Among treatment-naïve patients with active WM staged as high-risk MSS-WM, those with β_2 -microglobulin ≥ 4 mcg/mL had markedly worse overall survival compared to the remainder of the high-risk MSS-WM patients.

may coexist with *CXCR4* mutations [22,31,50]. A preponderance of evidence suggests that *TP53*^{Alt}, although infrequently encountered in treatment-naïve (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*^{Alteration} in WM.

Study/Year	Cohort	N	Method	Frequency of <i>TP53</i> ^{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% <i>TP53</i> ^{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 • <i>TP53</i> sequences were analyzed in only 3 pts (all with Del 17p)
DFCI	TN/RR TNWM RRWM	30 26 04	WGS	<i>TP53</i> ^{MUT} 7%	NA	• 1 of 2 cases with <i>TP53</i>^{mut} was of biallelic mutation. • Deletion of both PRDM2 and TOP1 participating in <i>TP53</i>-related signaling was also noted.
French Study 2017 [22]	SWM Active WM	125	Sanger ultradeep-targeted NGS SNP array	<i>TP53</i> ^{Alt} 11.2% <i>TP53</i> ^{MUT} 7.3%	TTP Active WM: 1.5y vs 4y, <i>P</i> < .001 TTP SWM: 2y vs 5y (<i>P</i> = .001) OS: Active WM: 4y vs NR SWM: 9y vs 18y (<i>P</i> = .002)	• <i>TP53</i>^{Alt} characterized by shorter TTP & OS for active WM & SWM. • <i>TP53</i>^{Alt} associated with shorter OS for active WM, regardless of IPSSWM. • All mutations localized to the DNA-binding domain. • No correlation with <i>CXCR4</i>^{mut} • Pts with <i>TP53</i>^{Alt} had more genomic abnormalities • Deletion 17p and <i>TP53</i> 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 <i>TP53</i>^{mut} effect in this study.
DFCI 2018 [69]	TN/RR TNWM RRWM	265 116 149	NGS Sanger	<i>TP53</i> ^{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	• <i>TP53</i>^{mut} uncommon but associated with aggressive disease. • All mutations localized to the DNA-binding domain. • 5/6 (83%) with <i>TP53</i>^{mut} but without concurrent Del 17p. • All 3 pts. on ibrutinib harbored <i>CXCR4</i>^{mut} & attained a PR. • Biallelic inactivation in 4 pts, 2 of whom died of progression. • CHIP-associated <i>DNMT3A</i>^{mut} in one pt.
Study/ Year	Cohort	N	Method	Frequency of <i>TP53</i> ^{Alt}	PFS & [OS If available]	• Comments

(continued on next page)

Table 2 (continued)

Study/Year	Cohort	N	Method	Frequency of <i>TP53</i> ^{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) <i>TP53</i> ^{MUT} 11.8% 22%	NA	- Heterogeneous variants but all in DNA-binding domain (exons 5–8). <i>TP53</i>^{mut} associated with symptomatic disease and shorter TTT. - For the entire cohort, <i>TP53</i>^{mut} associated with shorter PFS/ OS. <i>TP53</i> deletion was detected in 10% in the validation set but did not appear to affect prognosis. - Rituximab maintenance in pts <i>TP53</i>^{mut} associated better PFS1. - In a regression model for genetic and treatment factors in all patients <i>TP53</i>^{mut} was associated with inferior OS from diagnosis. - In patients <i>TP53</i>^{mut}, <i>CXCR4</i>^{WT/FS} single agent ibrutinib was associated with a trend for better PFS1 (<i>P</i> = .085).
ASPEN Bio-marker post-hoc analysis 2023 [55]	TN/RR Cohort 1 <i>MYD88</i> ^{mut} Cohort 2 <i>MYD88</i> ^{WT}	210 190 20	NGS	<i>TP53</i> ^{MUT} 24.8%	Ibrutinib: 42m-PFS <i>TP53</i> ^{mut} 58% vs 72% in <i>TP53</i> ^{WT} . Zanu: 42m-PFS <i>TP53</i> ^{mut} 62% vs 85% in <i>TP53</i> ^{WT} . Median PFS NR in Zanu arm vs 44.2 m in ibrutinib arm (HR, 0.66; <i>P</i> = .37) 1y-PFS 25% in <i>TP53</i> ^{mut} vs 75% in <i>TP53</i> ^{WT}	- Patients with <i>TP53</i>^{mut} had poorer prognosis regardless of the BTKi used. However, outcomes were more favorable with zanubrutinib (vs ibrutinib) among pts with <i>TP53</i>^{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 <i>TP53</i>^{WT} populations in the 2 arms. - In Cohort 1, 11.6% patients had <i>TP53</i>^{mut} at VAF <1% whereas 13.7% had <i>TP53</i>^{mut} at VAF ≥1% or had a <i>TP53</i> deletion. Patients with <i>TP53</i>^{mut} at VAF of ≥1% or <i>TP53</i> deletion had higher rate of <i>CXCR4</i>^{NS}. - A dosage-dependent unfavorable impact on PFS was observed among patients with <i>TP53</i>^{mut} with VAF of ≥1%. - Pts with <i>TP53</i>^{mut} had shorter PFS on a multivariate analysis.
DFCI 2024 [31]	<i>MYD88</i> ^{mut} TNWM	119	RNA Seq WES	Del 17p 3% <i>TP53</i> ^{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 <i>ROR1</i> 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 1, 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 <i>MYD88</i> ^{L265P} mutation	H&E, IHC, Multiparametric flow cytometry Allele-specific quantitative polymerase chain reaction PCR (AS-PCR) Droplet Digital PCR (ddPCR)	- Required to establish diagnosis, risk stratify SWM, & to assess HR molecular/genetic features and for deep response to therapy [98,99]. - Patients with SWM who harbor <i>MYD88</i>^{WT} genotype have a higher (1.7 to 1.8 fold) risk of progressing to overt WM. - Patients with WM who harbor <i>MYD88</i>^{WT} genotype have a 7-fold higher risk of histological transformation. - AS-PCR for L265P mutation with an analytical sensitivity of 1% or lower <i>MYD88</i>^{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 <i>MYD88</i> alterations, including insertion or deletion events. - 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 <i>MYD88</i> mutations	Next-Generation Sequencing (NGS)	- All NGS-targeted panels designs should use probes covering the entire <i>MYD88</i> gene to assess <i>non</i>-L265P <i>MYD88</i> mutations. - CD19+ enrichment not required unless less sensitive Sanger sequencing is being used for <i>non</i>-L265P <i>MYD88</i> mutations.
<i>CXCR4</i> mutations (<i>CXCR4</i> ^{MUT})	AS-PCR or ddPCR for <i>CXCR4</i> ^{NS338X} Sanger sequencing NGS targeted panels	- CD19+ enrichment is recommended for improved sensitivity to detect subclonal mutations. <i>CXCR4</i> mutations occur are almost always in association with <i>MYD88</i>^{L265P}. - Over 40 different <i>CXCR4</i> nonsense and frameshift variants have been identified so far. - Given the constraints of <i>CXCR4</i>^{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 <i>CXCR4</i>^{NS} as a very proportion of <i>CXCR4</i>^{MUT-NS} reside in S338 region. - Less sensitive routine Sanger sequencing is used to interrogate all other genetic variants in the test region.
<i>TP53</i> mutation	NGS targeted panels preferred. Sanger sequencing if NGS unavailable.	CD19+ enrichment suggested as <i>TP53</i> 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 ($\pm$ 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 Peripheral Neuropathy Myopathy	vWF assessment Coagulation profile Serum viscosity Nerve Conduction study Anti-MAG antibodies Serum cryoglobulin Electromyography Creatine kinase	- 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.

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

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Table 4 (continued)

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

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Table 4 (continued)

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

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 Zeneca 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.

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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.

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