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Report of consensus Panel 4 from the 11th International Workshop on Waldenstrom's macroglobulinemia on diagnostic and response criteria

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ABSTRACT

Consensus Panel 4 (CP4) of the 11th International Workshop on Waldenstrom's Macroglobulinemia (IWWM-11) was tasked with reviewing the current criteria for diagnosis and response assessment. Since the initial consensus reports of the 2nd International Workshop, there have been updates in the understanding of the mutational landscape of IgM related diseases, including the discovery and prevalence of MYD88 and CXCR4 mutations; an improved recognition of disease related morbidities attributed to monoclonal IgM and tumor infiltration; and a better understanding of response assessment based on multiple, prospective trials that have evaluated diverse agents in Waldenstrom's macroglobulinemia. The key recommendations from IWWM-11 CP4 included: (1) reaffirmation of IWWM-2 consensus panel recommendations that arbitrary values for laboratory parameters such as minimal IgM level or bone marrow infiltration should not be used to distinguish Waldenstrom's macroglobulinemia from IgM MGUS; (2) delineation of IgM MGUS into 2 subclasses including a subtype characterized by clonal plasma cells and MYD88 wild-type, and the other by presence of monotypic or monoclonal B cells which may carry the MYD88 mutation; and (3) recognition of "simplified" response assessments that use serum IgM only for determining partial and very good partial responses (simplified IWWM-6/new IWWM-11 response criteria). Guidance on response determination for suspected IgM flare and IgM rebound related to treatment, as well as extramedullary disease assessment was also updated and included in this report.

Introduction

Consensus Panel 4 (CP4) of the 11th International Workshop on Waldenstrom's Macroglobulinemia (IWWM-11) was tasked with reviewing the current criteria for diagnosis and response assessment [1,2]. Since the initial consensus reports of the 2nd International Workshop, there have been updates in our understanding of the mutational landscape of IgM related diseases, including

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the discovery and prevalence of MYD88 and CXCR4 mutations; an improved recognition of disease related morbidities attributed to monoclonal IgM and tumor infiltration; and a better understanding of response assessment based on multiple, prospective trials that have evaluated diverse agents in Waldenstrom's macroglobulinemia (WM). A main contention in the classification of IgM related diseases is whether arbitrary measures should be employed in delineating IgM MGUS from WM, and if IgM MGUS represents a heterogeneous entity. Recently, the International Consensus Classification of mature lymphoid neoplasms (ICC) addressed this important concern and noted that a diagnosis of WM could be rendered in patients with abnormal lymphoplasmacytic aggregates in the bone marrow (BM) and evidence of clonal B cells and plasma cells, even when the aggregates represent <10% of cellularity of the trephine biopsy [3].

Both MYD88 and CXCR4 mutations are highly prevalent in WM, with estimates of 95% to 97% and 30% to 40% respectively [4]. The ICC strongly encouraged molecular studies for MYD88 and CXCR4 mutations in the workup of suspected lymphoplasmacytic lymphoma (LPL) [3]. The use of mutated MYD88 as a marker to demarcate IgM MGUS from WM has also been investigated. Expression of mutated MYD88 by allele specific polymerase chain reaction assay (AS-PCR) was found in 50% to 90% of cases of IgM MGUS and was an independent risk factor for progression in 1 study [5–7]. In another study, the level of mutated MYD88 was associated with progression to WM [5]. However, the presence of mutated MYD88 did not delineate IgM MGUS from WM in any of these studies. Similarly, CXCR4 mutations which are found in up to 20% of patients with IgM MGUS did not discern IgM MGUS from WM [8,9]. However, the use of more sensitive digital droplet PCR did show that mutational burden of MYD88 as well as CXCR4 was associated with an increased risk for progression to symptomatic WM in both IgM MGUS and smoldering (asymptomatic) WM [10].

Interestingly, the use of MYD88 did clarify distinct IgM MGUS subclasses: 1 subclass comprised of cases with clonal B-cells that included MYD88 mutated cases [5–9]; and another subclass comprised of cases with plasma cells only that was devoid of clonal B-cells and wild-type for MYD88 [11]. Data on the latter remains limited as it occurs less frequently. Given these findings, the ICC has adopted a subclassification of IgM MGUS recognizing IgM MGUS of plasma cell type (IgM MGUS-PC) that is considered a precursor of MM and is defined as showing clonal plasma cells without a detectable B-cell component and with wild-type MYD88; and IgM MGUS, not otherwise specified (NOS) that includes cases with monotypic or monoclonal B cells that may harbor the MYD88 mutation [3].

CP4 of IWWM-11 was also tasked with evaluating a simplified response assessment for WM based on IgM criteria. As part of the "standard" IWWM-6 response criteria, reductions in adenopathy and/or splenomegaly were required to fulfill partial response (PR) and resolution of adenopathy and/or splenomegaly for very good partial response (VGPR) in only those patients who demonstrated extramedullary disease at baseline [2]. Moreover, the extent of the reduction, and timing of assessment were not specified. As extramedullary disease in WM is uncommon at time of diagnosis (≤20%) the requirement for such measures was restricted to a minority of patients, though at relapse extramedullary disease may be more common [12]. Study costs, exposure of patients to the burden of repeat imaging and radiation exposure limited compliance by both investigators and patients. As such, IgM driven criteria to assess PR and VGPR responses have largely been utilized in most WM studies. These criteria referred to as "modified IWWM-6″ criteria have differed in various prospective clinical trials ranging from requiring reduction in adenopathy and/or splenomegaly for PR and VGPR as per NCCN criteria [12] (exemplified in refs [13–18]) to utilizing IgM alone for PR and VGPR attainment (exemplified in refs. [19–23]). The definitions of complete response (CR) and minor response (MR) have been the same across all these criteria, as has the definition of progressive disease. As such, CP4 sought to clarify the most optimal approach to PR and VGPR response assessment in WM. Important to these efforts was the availability of data from a large, prospective, multicenter, randomized study (ASPEN) that evaluated ibrutinib vs zanubrutinib in patients with MYD88 mutated WM in Cohort 1, and zanubrutinib alone in patients with MYD88 wild-type WM in Cohort 2 [25,26]. The findings from this study supported FDA and EMA approval of zanubrutinib, and were updated at the 11th International Workshop on WM [27]. The data base from this study with a median follow-up of 44.4 months for Cohort 1, and 43 months for Cohort 2 were made available to the CP4 panel and permitted comparison of (1) "standard" IWWM-6 response criteria that required decreased adenopathy and/or splenomegaly for PR and resolution of adenopathy and/or splenomegaly for VGPR[2]; (2) "modified" IWWM-6 response criteria driven by categorical decreases in IgM for PR and VGPR and reduction in adenopathy and/or splenomegaly in those with baseline extramedullary disease[12]; and (3) a more "simplified" modification of IWWM-6 response criteria which rely on categorical decreases in IgM alone for PR and VGPR attainment.

The findings and recommendations from CP4 on revising the current criteria for diagnosis and response assessment are reported herein.

Should the current IWWM workshop definition for IgM MGUS and WM remain as is?

The panel reaffirmed the diagnostic criteria adopted at the Second International Workshop on WM (IWWM-2), including those that distinguish IgM MGUS from WM [1]. As part of the diagnostic criteria set forth at IWWM-2, patients with an IgM monoclonal protein and unequivocal evidence of BM involvement by lymphoplasmacytic lymphoma were considered as meeting diagnostic criteria for WM irrespective of their total IgM concentration, provided an IgM monoclonal protein was present. Patients were considered to have IgM MGUS if they had an IgM monoclonal gammopathy but no morphological evidence of BM involvement by lymphoma. Flow cytometric or molecular evidence of a clonal B-cell disease would not suffice for the diagnosis of WM without morphological evidence for a BM infiltrate. The updated guideline recommendations from IWWM-11 maintain the previous position of the IWWM-2 consensus panel that disease definitions should not use arbitrary values for laboratory parameters such as minimal IgM level or BM infiltration to render the diagnosis of WM. The recommendations re-affirmed at IWWM-11 are consistent with clinical practice since treatment-naïve patients with BM disease involvement of less than 10% may present with symptomatic disease and require therapy as evidenced by their participation in numerous clinical trials with treatment-naïve patients [14,15,19,22,24,25,28-33]. Many of these patients have morbidity attributable to the monoclonal IgM protein including but not limited to demyelinating peripheral neuropathy, cryoglobulinemia, cold agglutinemia, anti-phospholipid antibody syndrome, and hyperviscosity syndrome [34]. Moreover, morbidity attributable to monoclonal light chains such as light chain deposition disease and amyloidosis can be found in patients with WM with BM disease burden under 10% [35,36]. Consistent with these recommendations, the diagnostic criteria for LPL (inclusive of WM) have recently been refined in the ICC of Mature Lymphoid Neoplasms: *"In keeping with the diagnostic criteria proposed by the International Workshop on Waldenstrom's Macroglobulinemia, a diagnosis of LPL may be rendered in patients with abnormal lymphoplasmacytic aggregates in the bone marrow and evidence of clonal B cells and plasma cells, even when the aggregates represent <10% of cellularity of the*

Table 1
Classification of IgM MGUS, IgM related disorders, and Waldenstrom macroglobulinemia.

Classification of IgM monoclonal gammopathies						
	IgM monoclonal protein*	Bone marrow infiltration†	Clonal or monotypic B-cells‡	Clonal plasma cells; no clonal or monotypic B-cells§	Symptoms attributable to monoclonal IgM or light chain‖	Symptoms attributable to tumor infiltration¶
IgM MGUS, Not otherwise specified (IgM MGUS-NOS)	+		+			
IgM MGUS, Plasma cell type (IgM MGUS-PC)	+			+		
IgM related disorders#	+		+	+	+	
Waldenstrom macroglobulinemia, asymptomatic	+	+	+			
Waldenstrom macroglobulinemia, symptomatic	+	+	+		+	+

* The presence of a monoclonal IgM protein by serum protein electrophoresis is required, regardless of concentration. A positive immunofixation is insufficient to meet this criterion.

† Bone marrow (BM) involvement by lymphoplasmacytic lymphoma (LPL) with clonal B cells and plasma cells, even if LPL involvement represents <10% of cellularity of the trephine biopsy is sufficient for the diagnosis of WM.

‡ The presence of clonal or monotypic B-cells, no BM morphological involvement of LPL, the presence of mutated MYD88 (if detected), and no evidence for other small B-cell malignancies supports the diagnosis of IgM MGUS, not otherwise specified (IgM MGUS-NOS) (see reference [3]).

§ The presence of clonal plasma cells without a detectable B-cell component, no BM LPL involvement, the presence of wild-type MYD88, and t(11;14)(q13;q32) or other cytogenetic abnormalities typical of MM (if present) supports the diagnosis of IgM MGUS, Plasma Cell Type (IgM MGUS-PC) (see reference [3]).

‖ Symptoms attributable to the monoclonal IgM or light chain protein include but are not limited to demyelinating peripheral neuropathy, cryoglobulinemia, cold agglutinemia, anti-phospholipid antibody syndrome, hyperviscosity syndrome, light chain deposition disease, and amyloidosis.

¶ Symptoms attributable to tumor infiltration include but are not limited to constitutional symptoms, cytopenias, central nervous system infiltration (Bing Neel Syndrome), organomegaly (adenopathy, splenomegaly, extramedullary mass). Primary Cold Agglutinin Disease should be considered and excluded in suspected WM and IgM Related Disorders (IgM RD) patients who are wild-type for MYD88 (see references [3,46]).

Criteria for IgM Related Disorders (IgM RD) may be fulfilled by either presence of IgM MGUS-NOS; or the presence of clonal plasma cells with no clonal or monotypic B-cells, consistent with IgM MGUS-PC (as per reference [3]). The panel acknowledges a paucity of data for IgM RD in patients with IgM MGUS-PC.

trephine biopsy" [3]. Moreover, symptomatic patients with <10% BM involvement have been included in many clinical trials, including FDA and EMA enabling studies, indicative of their symptomatic status for participation in these studies [14,15,19,22,24,25,28-33]. Since patients can be symptomatic at IgM levels <1000 mg/dL, a minimum cutoff for total serum IgM levels is not appropriate to fulfill WM diagnostic criteria so long as a monoclonal IgM protein is detected [1]. Importantly, while IgM levels can be used to track BM disease burden for a particular patient, serum IgM levels show great variability in their relationship to BM disease burden across patients with WM [34].

It is important to note that patients can fulfill the diagnostic criteria for WM without symptoms related to their disease. These patients are termed as having "Asymptomatic WM," an entity also referred to as "smoldering WM". Asymptomatic patients do not meet criteria for initiation of treatment based on consensus criteria adopted at IWWM-2 [37]. Some of these asymptomatic patients with WM may not require therapy for prolonged periods of time. The cumulative probability of progression for asymptomatic WM patients was 6% at 1 year, 39% at 3 years, 59% at 5 years, and 65% at 10 years in a series by Kyle et al [38] with 285 person-years of follow-up. Patients with WM are considered symptomatic if they have features attributable to tumor infiltration that is, constitutional symptoms, cytopenias, central nervous system infiltration (Bing Neel Syndrome), organomegaly (adenopathy, splenomegaly, extramedullary mass), and/or symptoms attributable to the IgM or light chain monoclonal protein itself (ie, hyperviscosity syndrome, cryoglobulinemia, cold agglutinemia, light chain deposition disease, amyloidosis, IgM demyelinating peripheral neuropathy, IgM deposition disease). It is also recognized that some patients have clinical features attributable to the monoclonal protein but do not fulfill diagnostic criteria for WM. It is considered that these patients constitute a distinct clinical group termed IgM related disorders that corresponds to the entity of monoclonal gammopathy of clinical significance (MGCS) in the revised ICC classification [1]. The criteria for the above entities were previously published and are further clarified in Table 1.

Should IgM MGUS be clarified as either a B-cell or Plasma-Cell IgM MGUS?

The panel affirms the revised ICC classification which recently recognized 2 subtypes of IgM MGUS: IgM MGUS of plasma cell type (IgM MGUS-PC) and IgM MGUS, NOS (IgM MGUS-NOS) [3]. "IgM MGUS of plasma cell type (IGM MGUS-PC) is considered a precursor of MM and is defined as showing clonal plasma cells without a detectable B-cell component and with wild-type MYD88." IgM MGUS-PC also includes patients with t(11;14)(q13;q32) or other cytogenetic abnormalities typical of MM [3]. "Patients with IgM MGUS, NOS include those with a MYD88 mutation, detectable monotypic or monoclonal B cells but without abnormal lymphoplasmacytic aggregates diagnostic of LPL, and those without evidence for other small B-cell neoplasms." Routine fluorescence in situ hybridization (FISH) myeloma studies and MYD88 mutation analysis may provide additional support to morphological and flow cytometric studies to clarify subtype of IgM MGUS, and patients with IgM MGUS more likely to progress to MM vs WM or another B-cell neoplasm.

Should the presence of clonal cells B-cells or plasma cells impact the definition of IgM MGUS?

As discussed above, in patients with IgM MGUS showing clonal plasma cells without a detectable B-cell component and with wild-type MYD88, the entity of IgM MGUS of plasma cell type (IgM MGUS-PC) should be made [3,11]. IgM MGUS-PC can be considered a precursor to IgM multiple myeloma, and may manifest

Table 2
Categorical response assessments from updated ASPEN study findings using standard, modified and simplified IWWM-6 response criteria.

A	Cohort 1	Standard IWWM-6	Modified IWWM-6	Simplified IWWM-6/ New IWWM-11
	CR	0 (0%)	0 (0%)	0 (0%)
	VGPR	27 (13.4%)	62 (30.8%)	63 (31.3%)
	PR	135 (67.2%)	100 (49.8%)	107 (53.2%)
	MR	28 (13.9%)	28 (13.9%)	20 (10%)
	Other	11 (5.5%)	11 (5.5%)	11 (5.5%)
	Major RR	162 (80.6%)	162 (80.6%)	170 (84.6%)
	Overall RR	190 (94.5%)	190 (94.5%)	190 (94.5%)
B	Cohort 2	Standard IWWM-6	Modified IWWM-6	Simplified IWWM-6/ New IWWM-11
	CR	1 (3.8%)	1 (3.8%)	1 (3.8%)
	VGPR	3 (11.5%)	7 (26.9%)	8 (30.7%)
	PR	13 (50.0%)	9 (34.6%)	8 (30.7%)
	MR	4 (15.3%)	4 (15.3%)	4 (15.3%)
	Other	5 (19.2%)	5 (19.2%)	5 (19.2%)
	Major RR	17 (65.4%)	17 (65.4%)	17 (65.4%)
	Overall RR	21 (80.8%)	21 (80.8%)	21 (80.8%)

Categorical responses using standard, modified and simplified IWWM-6 (new IWWM-11) criteria are presented for MYD88 mutated patients who received either ibrutinib or zanubrutinib in Cohort 1 (A); and for MYD88 wild-type patients who received zanubrutinib in Cohort 2 of the ASPEN study (B). 201 patients were included in this analysis for Cohort 1; and 26 patients for the analysis for Cohort 2. CR, complete response; VGPR, very good partial response; PR, partial response; MR, minor response; Other, includes stable disease and non-response. Major Response Rate includes PR, VGPR and CR. Overall Response Rate includes MR, PR, VGPR and CR. Concordance coefficients for categorical responses were as follows: VGPR (0.82); PR (0.83); MR (0.92) for Cohort 1, and VGPR (0.79); PR (0.84) for Cohort 2, suggesting high to very high agreement rates. Friedman's Chi-square tests for concordance performed on the coefficients were all highly significant (see text for details).

with t(11;14)(q13;q32) or other cytogenetic abnormalities typical of MM [3]. Patients with monotypic or monoclonal B cells but without abnormal lymphoplasmacytic aggregates diagnostic of LPL, and those without evidence for other small B-cell neoplasms should be considered IgM MGUS, NOS [3]. IgM MGUS-NOS may manifest mutated MYD88 and considered a precursor to WM and other B-cell neoplasms [5,6,7,9,10]. Individuals who will lack monotypic B cells and who are MYD88 wild type but also lack monotypic PC should be considered IgM MGUS-NOS. IgM MGUS-PC should only be used when a monotypic PC population is demonstrable.

Should the presence or absence of mutated *MYD88* impact the definition of IgM MGUS?

The detection of mutated MYD88 by itself is insufficient for the diagnosis of WM. Up to 90% of patients with IgM MGUS may express mutated MYD88 [5,6,7,9,10]. In a patient who shows a MYD88 mutation along with detectable monotypic or monoclonal B cells, but without abnormal lymphoplasmacytic aggregates diagnostic of WM, and without evidence for other small B-cell neoplasms, the entity of IgM MGUS, NOS (IgM MGUS-NOS) should be made [3].

Should simplified response driven criteria based on IgM only be adopted for assessment in WM?

The panel assessed the updated ASPEN data for both arms (ibrutinib and zanubrutinib) of Cohort 1 (N = 201) and the single arm (zanubrutinib) of Cohort 2 (N = 26). The categorical responses using "standard," "modified," and simplified" criteria are shown in Table 2A for cohort 1 which consisted of MYD88 mutated patients who received either ibrutinib or zanubrutinib; and Table 2B which consisted of MYD88 wild-type patients who received zanubrutinib. The panel noted that the overall response rate (ie, the response rate that includes minor responses or better was the same (94.5%) by all 3 criteria for Cohort 1. The major response rate (ie, the response rate that includes partial responses or better) in Cohort 1 were 80.6%, 80.6%, and 84.5%, respectively using "standard," "modified," and "simplified" criteria, and reflected an upgrade of MR to PR for 8 patients with the latter, with a very high concordance coefficient of 0.94 ($P < .0001$ by Friedman's Chi-square test). Given the interdependence of categorical responses between response criteria, Kendall's W concordance coefficient was calculated, wherein a coefficient of 1 suggests complete agreement, 0.9 a very high agreement, and 0.7 a strong agreement. Friedman's chi-squared test for concordance was performed on the coefficient, wherein for the null hypothesis, the coefficient is 0 (the variables have no agreement); and rejecting the null hypothesis ($P < .05$) supported that the response criteria being compared were highly concordant.

The panel next examined categorical response attainment for Cohort 1. Numerically, more VGPRs occurred with "modified" (30.8%) and "simplified" (31.3%) vs "standard" (13.4%) IWWM-6 response criteria (concordance coefficient = 0.82; $P < .0001$ by Friedman's Chi-square test). As expected, these shifts largely resulted from upgrades from PR to VGPR, with PR rates for "modified" and "simplified" of 49.8% and 53.2%, respectively, vs 67.2% using "standard" IWWM-6 response criteria (concordance coefficient = 0.83; $P < .0001$ by Friedman's Chi-square test). Upgrades from MR to PR also occurred using "simplified" criteria resulting in MR response rates of 13.9%, 13.9%, and 10% for "standard," "modified," and "simplified" criteria (concordance coefficient = 0.92; $P < .0001$ by Friedman's Chi-square test). No differences in "other" category that included stable (SD) or progressive disease (PD) were noted between the 3 criteria. As shown in Table 3, 2-way and 3-way comparisons of response criteria showed that categorical responses were highly concordant in Cohort 1.

For Cohort 2, both overall (80.8%) and major (64.5%) response rates were the same using all 3 criteria. The panel next examined categorical response attainment for Cohort 2. Numerically, more VGPRs occurred with "modified" (26.9%) and "simplified" (30.7%) vs "standard" (11.5%) IWWM-6 response criteria (concordance coefficient = 0.79; $P = .0001$ by Friedman's Chi-square test). As expected, these shifts largely resulted from upgrades from PR to VGPR, with PR rates for "modified" and "simplified" of 34.6% and 30.7%, respectively, vs 50% using "standard" IWWM-6 response criteria (concordance coefficient = 0.84; $P < .0001$ by Friedman's Chi-square test). The MR response rate was the same (15.3%) in all 3 response criteria. No differences in other category that included

Table 3
Calculations using Kendall's co-efficient of between the standard, modified, and simplified IWWM-6 (new IWWM-11) response criteria.

Concordance coefficient (p-values)		
	Cohort 1	Cohort 2
Standard IWWM-6 vs. Modified IWWM-6	0.91 (<0.0001)	0.96 (0.004)
Standard IWWM-6 vs Simplified IWWM-6/New IWWM-11	0.88 (<0.0001)	0.96 (0.004)
Modified IWWM-6 vs Simplified IWWM-6/New IWWM-11	0.98 (<0.0001)	0.99 (0.002)

A co-efficient of concordance greater than 0.9 suggests a very high agreement . Friedman's chi-squared test was performed on the co-efficient of concordance, wherein for the null hypothesis, the coefficient is 0 (the variables have no agreement); and rejecting the null hypothesis ($P < .05$) supported that the response criteria being compared were highly concordant.

Table 4
Progression free survival estimates for ASPEN study using standard, modified and simplified IWWM-6 criteria.

A	Standard IWWM-6	Modified IWWM-6	Simplified IWWM-6/ New IWWM-11
VGPR	0.848(0.645,0.94)	0.832(0.71,0.906)	0.819(0.696,0.896)
PR	0.792(0.709,0.853)	0.781(0.681,0.853)	0.753(0.654,0.828)
MR	0.472(0.265,0.655)	0.472(0.265,0.655)	0.566(0.312,0.758)
Others*	0.311(0.015,0.723)	0.311(0.015,0.723)	0.286(0.01,0.711)
B	Standard IWWM-6	Modified IWWM-6	Simplified IWWM-6/ New IWWM-11
CR	1(1,1)	1(1,1)	1(1,1)
VGPR	0.667(0.054,0.945)	0.571(0.172,0.837)	0.5(0.152,0.775)
PR	0.462(0.192,0.696)	0.444(0.136,0.719)	0.5(0.152,0.775)
MR	0.75(0.128,0.961)	0.75(0.128,0.961)	0.75(0.128,0.961)
Others*	0.4(0.052,0.753)	0.4(0.052,0.753)	0.4(0.052,0.753)

Estimates at 42 months are shown with confidence intervals for standard, modified and simplified IWWM-6 criteria for Cohort 1 (A) and Cohort 2 (B) of the ASPEN Study. The median study follow-up was 44.4 months in Cohort 1, and 43 months in Cohort 2.
* Others, includes stable disease and non-response.

stable (SD) or progressive disease (PD) were noted between the 3 criteria as well. Kendall's correlation coefficient of concordance (with ties correction) was also calculated for comparison of response criteria for Cohort 2. As shown in Table 3, comparisons of response criteria showed that categorical responses were highly concordant also for Cohort 2.

Given these findings, the panel next evaluated progression-free survival (PFS) by categorical responses for Cohorts 1 and 2 using "standard," "modified," and "simplified" IWWM-6 response criteria. As shown in Figure 1, categorical response attainment similarly impacted PFS across for all 3 response criteria for MYD88 mutated patients in Cohort 1 demonstrating similar long term (42 months) estimates and overlapping confidence intervals as shown in Table 4A. Similar findings were also observed across all 3 response criteria for MYD88 wild-type patients from Cohort 2 as shown in Figure 2 and Table 4B.

In view of the above data, and common use of "simplified" IWWM-6 response criteria in clinical studies and practice, the panel determined that "simplified" response criteria utilizing IgM response for categorical response for VGPR, PR, MR, and SD assessments was reasonable and comparable to standard IWWM-6 response assessment. *For purposes of clarity, the simplified IWWM-6 criteria were recommended to be referred to as IWWM-11 WM response criteria.* The panel reiterated that for CR attainment, normalization of BM and resolution of extramedullary disease if present at baseline would need to be demonstrated along with absence of monoclonal IgM protein by serum immunoelectrophoresis (SPEP) and immunofixation studies along with demonstration of normalized IgM levels. Reconfirmation of absence of monoclonal IgM protein by these studies and normalization of IgM levels is not required to meet CR criteria. A BM biopsy and imaging should be done within 12 weeks to support CR attainment following demonstration of absence of monoclonal IgM protein by SPEP and immunofixation studies and normalization of IgM levels (Table 4).

Should the categorical response criteria currently in place be used as part of a modified IgM only response assessment?

The panel agreed that categorical response criteria currently in place can be used as part of "simplified" WM response assessment (Table 4).

Should confirmation of a categorical response be required for anything other than progressive disease?

Re-confirmation of CR, VGPR, PR, MR or SD is not required. Progressive disease (PD) must be re-confirmed by back-to-back measurements if the IgM is being used to support PD. To meet criteria for progressive disease, a ≥25% increase in serum IgM level with a minimum serum IgM increase of 500 mg/dL from the nadir is required on 2 sequential (back-to-back) measurements. In the event an IgM measurement meets PD criteria, and the subsequent measurement does not, the patient will not have met PD criteria until 2 back-to-back measurements show PD. Demonstration of PD by imaging does not require re-confirmation. In the event of discordant response findings, that is, IgM measurement shows a response but imaging shows PD related to WM, then the assessment should be considered PD.

Should a molecular complete response category be adopted for patients with MYD88 mutated disease?

At present, CR attainment remains rare. The panel believes that insufficient data currently exists for adoption of molecular response category as part of WM response criteria. Moreover, while quantitative assessment of MYD88 represents a potentially useful biomarker for assessing molecular responses, such determination is not feasible for those with MYD88 wild-type WM. The panel encouraged further studies by investigators to clarify the methods for

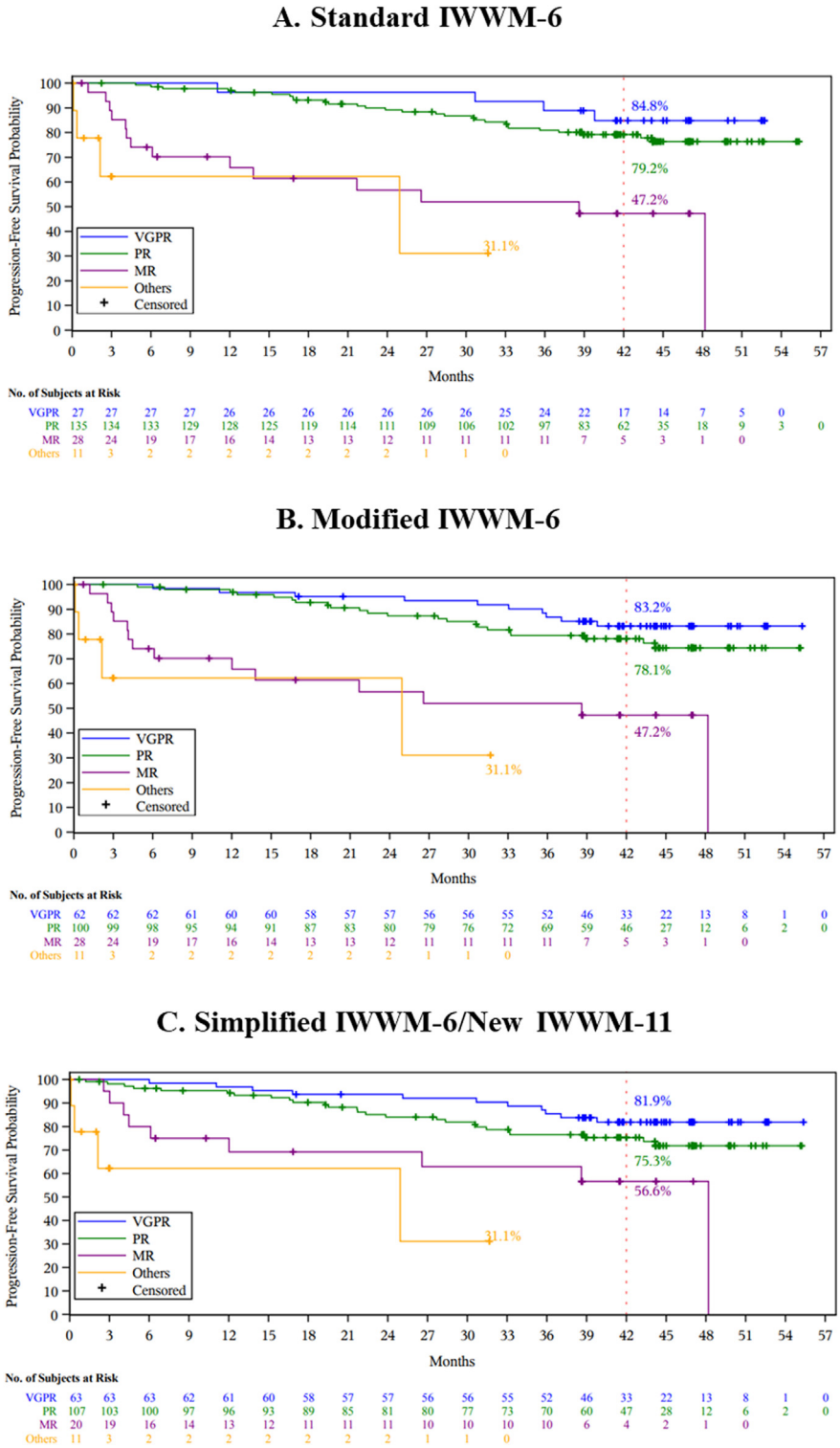

Fig. 1. Progression-free survival (PFS) curves for 201 WM patients on Cohort 1 of the ASPEN study. PFS is depicted by categorical response attainment using standard (A), modified (B), and simplified (C) IWWM-6 criteria. Patients at risk at various time points are shown below. PFS estimates at 42 months are shown for patients attaining categorical responses. The median study follow-up was 44.4 months in Cohort 1.

Table 5
IWWM-11 response criteria (also referred to as simplified IWWM-6 response criteria) for assessment of disease response in Waldenstrom's macroglobulinemia.

		Serum Monoclonal IgM	Serum IgM Level	Bone Marrow Aspirate and Trephine Biopsy	Extramedullary disease
Complete response	CR	Absence of monoclonal IgM protein by SPEP and IFX.	Within normal range	Normal morphology; no evidence of LPL involvement.	Absence of extramedullary disease if present at baseline. See criteria for determination of resolution of extramedullary disease.*
Very good partial response	VGPR		≥90% reduction in serum IgM levels or within normal range		
Partial response	PR		≥50% to <90% reduction in serum IgM levels		
Minor response	MR		≥25% to <50% reduction in serum IgM levels		
Stable disease	SD		<25% reduction to <25% increase in serum IgM levels		
Progressive disease	PD		≥ 25% increase in serum IgM levels with a minimum increase of 500 mg/dL from nadir. Reconfirmation is required by 2 sequential (back-to-back) measurements if the serum IgM is being used to support PD. Demonstration of PD by imaging does not require re-confirmation.†,‡		Any new lesion (>1.5 cm in any axis) or unequivocal evidence of an increase by >50% in any axis to >1.5 cm in size of previously involved extramedullary disease sites from their nadir measurements. Any new lesion consistent with transformed disease.
Nonevaluable	NE		Suspected IgM flare or IgM rebound, absence of data or suspected error in data reporting§		

Categorical response assessment for CR, VGPR, PR, MR or SD assumes no signs or symptoms consistent with disease progression are present. The overall response rate includes MR, PR, VGPR, and CR responses, whereas the major response rate includes PR, VGPR and CR responses.

* For CR attainment, normalization of extramedullary disease if present at baseline will be considered complete resolution or decrease in size of lymph nodes (≤1.5 cm) or decrease in the size of spleen (≤15 cm), or complete resolution of any other non-lymph node or non-splenic extramedullary mass(es) related to WM disease consistent with revised response criteria for malignant lymphoma (see reference [39]).

† Re-confirmation of CR, VGPR, PR, MR, or SD is not required. Progressive disease (PD) must be re-confirmed if the IgM is being used to support PD. To meet criteria for progressive disease, a ≥25% increase in serum IgM level with a minimum serum IgM increase of 500 mg/dL from the nadir is required on 2 sequential (back-to-back) measurements. In the event an IgM measurement meets PD criteria, and the subsequent measurement does not, the patient will not have met PD criteria until 2 back-to-back measurements show PD. Demonstration of PD by imaging does not require re-confirmation. In the event of discordant response findings, that is, IgM measurement shows a response but imaging shows PD related to WM, then the assessment should be considered PD.

‡ Suspected IgM flare or IgM rebound related to therapy will not be considered as progressive disease.

§ A nonevaluable response assessment should be specified in cases of suspected IgM flare or IgM rebound; absence of data, or suspected error in data reporting (ie, contradictory central vs local laboratory measurements).

determining molecular responses, and importance of molecular responses to treatment outcomes in WM.

Additional questions submitted to consensus panel from the audience at IWWM-11.

Should immunofixation positive vs immunofixation negative disease be distinguished as a separate response category for VGPR in WM?

The panel believes that insufficient data currently exists for adoption of distinct subclass of response for VGPR attainment based on immunofixation.

How should extramedullary disease be evaluated as part of any response assessment?

Extramedullary disease can be present in up to 20% of WM patients at diagnosis, though at relapse may be more common [12]. Repeat imaging should be performed as part of assessment for CR attainment, and in suspected cases of disease progression for patients who demonstrated extramedullary disease at baseline, as well as in those in whom new extramedullary disease is suspected. For purposes of defining extramedullary disease, pathological lymph nodes will be considered those >1.5 cm, and splenomegaly if the spleen size is >15 cm in any axis, or the presence of any other non-lymph node or splenic extramedullary mass determined to be related to WM disease. Normalization will be considered complete resolution or decrease in size of lymph nodes (≤1.5 cm) or decrease in the size of spleen (≤15 cm), or complete resolution of any other non-lymph node or splenic extramedullary mass(es) related to WM disease consistent with revised response criteria for malignant lymphoma [39]. The requirement for extramedullary disease re-assessment is only necessary for meeting the definition of CR. In the event of suspected progression, any new lesion (>1.5 cm in any axis) or unequivocal evidence of an increase by ≥50% in any axis to >1.5 cm in size of previously involved extramedullary disease sites from their nadir measurements will be considered as evidence of progressive disease. Demonstration of a new lesion consistent with transformed disease will also be considered as evidence of progressive disease.

Discuss the role of minimal residual disease in response assessment

At present, CR attainment remains rare. The panel felt that insufficient data currently exists for inclusion of a minimal residual disease assessment as part of the response assessment.

What is the role of free light chains in WM response assessment. Should it be included in response criteria or just for amyloidosis response assessment?

At present, there is insufficient data to include a role for free light chain assessment in WM response. Free light chain assessment is essential in determining treatment efficacy in patients with WM related amyloidosis. Additional clarification is provided in the report by IWWM-11 Consensus Panel 6.

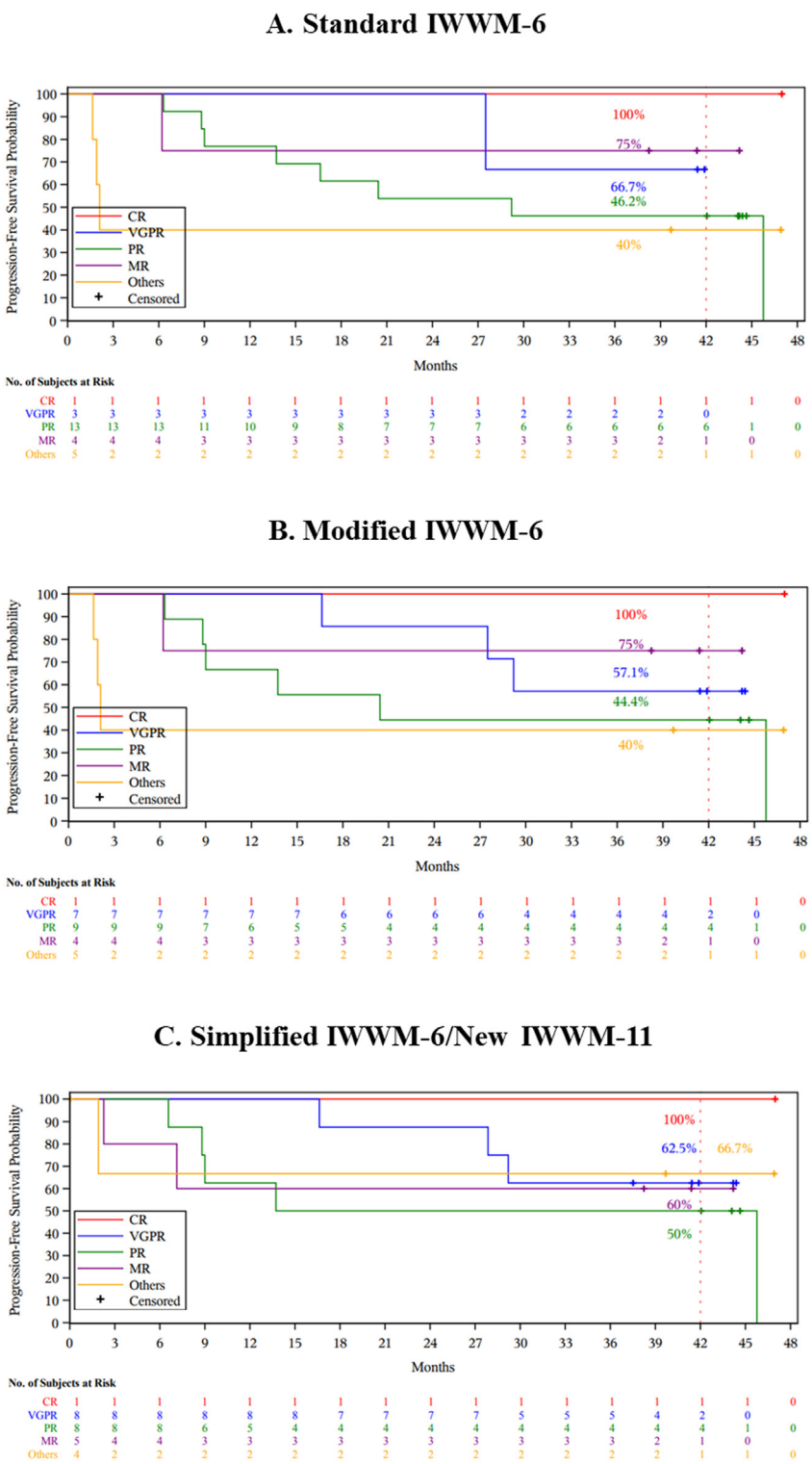

Fig. 2. Progression-free survival (PFS) curves for 26 WM patients on Cohort 2 of the ASPEN study. PFS is depicted by categorical response attainment using standard (A), modified (B), and simplified (C) IWWM-6 criteria. Patients at risk at various time points are shown below. PFS estimates at 42 months are shown for patients attaining categorical responses. The median study follow-up was 43 months in Cohort 2.

Clarify criteria for IgM flare and IgM rebound

Treatment related effects on serum IgM levels independent of underlying tumor burden is well recognized in WM. IgM flare can occur with antibody therapies such as rituximab and ofatumumab, and may be accentuated or attenuated by concurrent administration of other agents [40–44]. The IgM flare has been defined as a greater than 25% increase in total serum IgM levels following administration of a suspected agent [41,42]. For purposes of response assessment, an IgM flare should not count as a progression event. IgM flares may last weeks to months and a patient should be deemed unevaluable for response purposes in the event of a suspected IgM flare. A BM biopsy and/or imaging can be considered to clarify an IgM flare vs disease progression in circumstances

when clinical management warrants clarification. IgM rebound can occur following cessation or holding of certain therapeutics such as inhibitors of Bruton's Tyrosine Kinase (BTK) [21]. The IgM rebound has been defined as a greater than 25% increase in total serum IgM levels following withholding of a suspected therapy associated with IgM rebounds such as BTK-inhibitors [21]. A rebound may resolve upon reinstitution of treatment. For purposes of response assessment, an IgM rebound should not count as a progression event in the appropriate clinical context, such as an abrupt IgM increase following withholding of an agent associated with an IgM rebound, and absence otherwise of any signs or symptoms of progressive disease. IgM rebounds may last weeks, and a patient should be deemed unevaluable for response purposes in the event of a suspected IgM rebound. A BM biopsy and/or imaging can be considered to clarify an IgM rebound vs disease progression in circumstances when clinical management warrants clarification.

Clarify that withdrawal symptoms following BTK-inhibitor cessation occur and if such symptoms should be factored in when making response assessment for progressive disease

Withdrawal symptoms including fever, body aches, night sweats, arthralgias, chills, headaches and fatigue may occur in up to 20% of patients with WM following cessation or withholding of ibrutinib [45]. Such symptoms may not have been present at baseline. In the proper clinical context, when ibrutinib and possibly other BTK-inhibitors are held or stopped, such symptoms should not be considered as evidence of disease progression.

How should patients with very low IgM levels be considered for response assessment?

For patients with ultra -low IgM levels (ie, below 500 mg/dL), response assessment using serial changes in serum may be less reliable. Laboratory sensitivity for accurate serum IgM determination, as well as “normal” IgM background may complicate assessment. As there is a paucity of data to guide IgM response assessment in this population, further study is needed to identify more reliable methods for assessing changes in underlying WM disease burden.

Conclusions

The key recommendations from IWWM-11 CP4 included: (1) reaffirmation of IWWM-2 consensus panel recommendations that arbitrary values for laboratory parameters such as minimal IgM level or BM infiltration should not be used to distinguish WM from IgM MGUS; (2) delineation of IgM MGUS into 2 subclasses including a subtype characterized by clonal plasma cells and MYD88 wild-type (IgM MGUS-PC), and the other by presence of monotypic or monoclonal B cells which may carry the MYD88 mutation (IgM MGUS-NOS); and (3) recognition of a “simplified” (new IWWM-11) response criteria that supports use of IgM only for determining partial and VGPR assessments. Guidance on response determination for suspected IgM flare and IgM rebound related to treatment, and extramedullary disease assessment was also updated and included in this report.

Author contributions

SPT, RO, AT, RGS, JSM, and MD prepared, reviewed and submitted key questions for Consensus Panel 4 (CP4). Questions were reviewed in an open general assembly by attendants of IWWM-11, and additional questions for CP4 deliberations were formulated and submitted. SPT wrote the first draft of CP4 responses, and draft was reviewed and modified by RO, AT, RGS, JSM, and MD. Final draft was submitted to CP4 general panel for review and commentary. CP4 general panel was composed of individuals with experience in the care of WM patients who attended IWWM-11 and volunteered to be on CP4 panel. The ASPEN Study Team at Beigene provided data and supportive data analyses.

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Conflicts of interest

SPT received research funding, and/or consulting fees from Abbvie/Pharmacyclics Inc., Janssen Oncology Inc., Beigene Inc., Eli Lilly Pharmaceuticals, and Bristol Myers Squibb. JSM, declares participation on advisory boards and consulting services, on behalf of my Institution, for Abbvie, Amgen, BMS, Celgene, GSK, Haemalogix, Janssen-Cilag, Karyopharm, MSD, Novartis, Pfizer, Takeda, Regeneron, Roche, Sanofi, and SecuraBio. JJC received research funds from Abbvie, AstraZeneca, Beigene, Cellectar, LOXO, Pharmacyclics, TG Therapeutics, and honoraria from Abbvie, Beigene, Cellectar, Kite, LOXO, Janssen, Pharmacyclics, and Roche Pharmaceuticals. ET declares honoraria from Amgen, Astra/Zeneca, BMS, GSK, Integris Pharma, Janssen, Pfizer, Sanofi and Takeda Research Grants: Amgen, GSK, Janssen, Sanofi and Takeda Travel Grants: Amgen and Takeda. QL declares participation on advisory boards and consulting services for Beigene, Xi‘an Janssen, Pfizer, Sanofi, AstraZeneca. GB declares participation on advisory boards and speakers bureau for Janssen-Cilag, Bristol Myers Squibb and Novartis. MCM received research funding and/or consulting fees from Beigene, Jansen Cilag, BMS, CDR life and GSK, all paid to institution. PM reports honoraria from Janssen, Astra Zenecca and Incyte; consultancy or advisory role for Janssen and Beigene; and travel support from Abbvie. EK reports consulting fees from Abbvie, Janssen, Pierre Fabre, Celgene, honoraria from Abbvie, Janssen, expert testimony from Pierre Fabre, and participation on a DSMB for Genmab. AT declares being on the Advisory Board and Speaker Bureau for Janssen SPA, AbbVie, Astrazeneca, and Beigene. RGS declares honoraria from Amgen, Takeda, Janssen, Incyte, Astellas, BeiGene, AstraZeneca, Pfizer; and research funding from Novartis, Gilead, Astellas, Janssen; and participation in advisory boards for Amgen, Pharmacyclics, Takeda. CST reports research funding from Janssen, AbbVie and Beigene; and honoraria from Janssen, Pharmacyclics, Beigene and AbbVie. KCA reports Advisory Role: Pfizer, Astrazeneca, Janssen, Oncopeptides Board Membership: C4 Therapeutics, Dynamic Cell Therapies, Window, Starton. Ownership Interests: C4 Therapeutics, Oncopep, NextRNA, Dynamic Cell Therapies. MAD received honoraria from Amgen, Bristol Myers Squibb, GSK, Janssen, Beigene Inc, Sanofi and Takeda. RGO reports honoraria from Janssen, Beigene, Astra-Zeneca, and serving as an advisor for Janssen, Beigene.

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