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Report of Consensus Panel 4 from the 12th International Workshop on Waldenstrom's Macroglobulinemia on the management of patients with non-IgM lymphoplasmacytic lymphoma

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ABSTRACT

Approximately 95% of lymphoplasmacytic lymphomas (LPL) are IgM secreting and are characterized as Waldenstrom Macroglobulinemia (WM). Conversely, non-IgM secreting LPL are rare. As part of the 12th International Workshop on WM (IWWM-12), a consensus panel of experts was tasked to develop recommendations for the management and response assessment of non-IgM LPL. The panel considered that in view of available molecular, pathological and clinical data, non-IgM LPL should be considered as a separate sub-entity of LPL. The panel further recommended that the IWWM-2 consensus criteria used for IgM LPL (WM) treatment initiation, should also be used for non-IgM LPL and be independent of IgG or IgA paraprotein level unless symptomatic hyperviscosity is present. The panel agreed that based on current evidence, there is insufficient data to support a different clinical management for non-IgM vs IgM (WM) LPL. Moreover, the panel advised that patients with non-IgM LPL should be treated in a similar manner to patients with IgM LPL independent of MYD88 mutation status until more is known about its impact on treatment outcomes for non-IgM LPL patients. The panel therefore recommends the use of the IWWM-11 IgM LPL (WM) response criteria for cases of non-IgM LPL with a monoclonal IgA or IgG paraprotein component, but creating a specific panel to develop formal response criteria for this LPL subset was also recommended.

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Introduction

Consensus Panel 4 (CP4) of the 12th International Workshop on Waldenström's Macroglobulinemia (IWWM-12) was tasked with developing consensus recommendations for the management of non-IgM lymphoplasmacytic lymphoma (LPL) [1]. LPL is a rare indolent subtype of non-Hodgkin lymphoma characterized by a spectrum of B-cell differentiation, including clonal small lymphocytes, plasmacytoid lymphocytes, and plasma cells. In most cases LPL is associated with a serum immunoglobulin M (IgM) paraprotein and a bone marrow involvement, corresponding to the clinical and pathologic entity of Waldenström's Macroglobulinemia (WM) [1]. In a minority of LPL cases, the paraprotein is absent or is of an IgG or IgA isotype or is characterized as free light chain only. Additionally, there are also a small fraction of cases in which, although an IgM monoclonal component is present, the diagnosis of WM cannot be made as the tumor infiltration is outside the bone marrow. In aggregate, relative to WM, cases of non-IgM LPL are uncommon making up about 5% of all LPL cases. In a recent analysis of data from a nationwide population-based lymphoma registry that included 1511 LPL patients, only 2.1% of patients did not meet the criteria for the diagnosis of IgM LPL (WM) [2].

In the current version of the International Consensus Classification of Mature Lymphoid Neoplasms (ICC) the only entity that is recognized under LPL is IgM LPL (WM), which is defined as the presence of a monoclonal IgM component and abnormal lymphoplasmacytic aggregates in the bone marrow even if the aggregates represent <10% of cellularity of the trephine biopsy. There is no consideration of how non-IgM LPL should be considered [3]. (Table 1). Conversely, the 5th edition of the World Health Organization Classification of Haematolymphoid Tumours (WHO–HAEM5) recognizes 2 subtypes of LPL, the most common being IgM LPL (WM) and the less common type being non-IgM LPL (~5%) which includes: (1) cases with IgG or IgA monoclonal proteins, (2) non-secretory LPL, and (3) IgM LPL without bone marrow involvement (Table 1) [4].

Considering that non-IgM LPL cases are rare and reported cohorts of this entity are limited, it has been difficult to define how these cases should be characterized and what their pathobiological relationship to WM entails. Furthermore, although the genetic profile of WM is very well characterized, less is known of the molecular characteristics of non-IgM LPL. A better insight into the genetic profile could inform the question of whether non-IgM LPL should be considered as a separate entity. This is relevant as patients with this rare diagnosis are usually excluded from interventional studies focusing on WM or other indolent lymphomas. Moreover, their specific characterization may support diagnostic and therapeutic procedure reimbursements.

The aim of the recommendations from CP4 was to review existing literature and to formulate and agree by consensus on how to best approach the management of non-IgM LPL patients, and to stimulate specific studies of this entity. These goals were addressed in the panel through the consideration of a series of questions.

Should non-IgM lymphoplasmacytic lymphoma be considered a distinct pathological entity from Waldenstrom's Macroglobulinemia?

Currently, the only classification recognizing non-IgM LPL as a separate entity but always being included in the category of LPL together with LPL/WM is the WHO–HAEM5. The literature review conducted during the development of this consensus allowed us to consider LPL patients from different series who did not fulfill the WM criteria (Table 2) [2,5–10]. The distribution of the paraprotein isotypes in these patients was: IgG 65%, IgA 21%, only light chain 4%, and nonsecretory 8%. Finally, 2% of this group of patients had an IgM monoclonal paraprotein with no BM infiltration detected. For the cases with identified paraprotein, the kappa/lambda ratio was 76:24, and the mean size of the M component was 3804 mg/dL for IgG and 2483 mg/dL for IgA. One of the concerns that emerged in the panel was how to consider bi-clonal cases, when 2 or more isotypes can be recognized as paraproteins. According to the molecular structure of the heavy chain immunoglobulin gene and the B-cell development that informs the basis of WM [11], if one of the paraproteins is of IgM isotype and the bone marrow is infiltrated with LPL cells, the case should be considered as an IgM LPL (WM). This is explained by a noncompleted immunoglobulin class switching in the tumor clone and the presence of IgG and IgA should be attributed to alternative splicing rather than a real step in B-cell differentiation [12]. Although the rare cases of light chain only and the dual IgG and IgA secretion cases are not included in the classification of the WHO–HAEM5 (Table 1), they are usually considered within the entity of non-WM LPL [5,13,14]. It should be highlighted that cases of gamma heavy chain disease are not considered a variant of LPL since the previous WHO–HAEM4 [15,16] LPL cases with an IgM paraprotein and without bone marrow infiltration, not fulfilling WM criteria, and those without a monoclonal component may take advantage of more sensitive techniques for a better definition. The lack of the IgM paraprotein could be due to the use of serum protein electrophoresis or IgM quantification of insufficient sensitivity for detecting very low levels of IgM. In these cases, immunofixation should be carried out to confirm the lack of an IgM monoclonal component. This is even more problematic, since serum immunofixation could be insufficient to detect very low amounts of monoclonal proteins that could be detected with the use of free light chain assessment [17], heavy chain/light assessment [18,19], or mass spectrometry [20,21]. The same can be said for the BM infiltration, which is usually evaluated by conventional pathological studies, whose sensitivity could be relatively poor for detecting cases with low numbers of infiltrating cells. Thus, the use of techniques with greater sensitivities, such as multiparametric flow cytometry [22,23] or real time or digital

Table 1
Lymphoplasmacytic lymphoma categorization according to the in the International Consensus Classification of lymphoid neoplasms and fifth edition of World Health Organization Classification.

Classification	The International Consensus Classification of mature lymphoid neoplasms: a report from the ClinicalAdvisory Committee	The fifth edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms
Category/Entity	**Mature B-cell neoplasm** ***Lymphoplasmacytic lymphoma*** ***(Waldenstrom macroglobulinemia)*** The diagnostic criteria proposed by the International Workshop on Waldenstrom's Macroglobulinemia have been maintained: LPL diagnosis: 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 trephine biopsy.	**Mature B-cell neoplasm** ***2 subtypes Lymphoplasmacytic lymphoma:*** ***- IgM-LPL/Waldenström Macroglobulinaemia (WM) type.*** ***(Most common)*** ***- Non-WM type LPL (~5%)*** - cases with IgG or IgA monoclonal proteins, FLC only - non-secretory LPL - IgM LPL without bone marrow involvement

Table 2
Disease, patient characteristics, and outcomes of non-WM LPL in retrospective studies considering more than 5 patients.

	Varettoni et al. [5]	Brandefors et al. [2]	Castillo et al. [6]	Yu et al. [7]	Cao et al. [10]	Kang et al. [9]
Category of pts considered	Non IgM LPL	Non-WM LPL	Non IgM LPL	Non IgM LPL	IgG and IgA LPL	Non IgM LPL
N° pts	45	33	31	23	17	8
Median Age	66y	69 y	63 y	69 y	63 y	61.5 y
Male	40%	45.5%	39%	74%	53%	91%
Lymphadenopathy or splenomegaly	53%/22%	NR	NR	NR/60%	47%/6%	50%/37.5%
Extranodal involvement	20%	NR	NR	22%	NR	NR
BM involvement	84%	91%	100%	NR	82%	100%
Hemoglobin g/dL	Median 11.5 g/dL (range 7-16)	≤11.5 g/dL ($n=28$): 71.4%	NR	NR	≤11.5 g/dL: 70.6%	≤11.5 g/dL: 50%
Platelets 10^9/L	NR	≤100 10^9/L ($n=21$): 5%	NR	NR	<140 10^9/L: 12%	<150 10^9/L: 25%
Secretory LPL	69%	88%	87%	70%	100%	75%
IgG	NR	54.5%	64.5%	61%	53%	62.5%
IgA	NR	16%	16%	9%	47%	12.5%
IgM	Not Considered	6%	Not Considered	Not Considered	Not Considered	Not Considered
Only serum Free Light Chain	-	3%	6.4%	-	NR	25%
Type of light chain						
kappa or lambda	71%/23%	NR	NR	NR	NR	NR
K and lambda	6%	NR	NR	NR	NR	NR
Non secretory LPL	31%	12%	13%	30%	Not considered	25%
COMPARISON WITH WM/LPL COHORT						
Difference in clinical features	Higher nodal and extranodal involvement	younger higher LDH anemia lymphocytosis More symptomatic at diagnosis	-Higher extramedullary involvement -lower neuropathy -lower hyperviscosity	-Higher extramedullary involvement	similar clinical and pathologic features	Higher extramedullary involvement
Prognosis	No different PFS No different OS	Shorter TTFT No different OS	No differences in RR No different OS	No different PFS No different OS	Higher mortality within the first year after diagnosis ($P<.001$) Worse OS ($P=.024$) No different PFS or DSS	Trend of lower OS

BM = Bone Marrow; DSS = disease specific survival; NR = not reported; OS = overall survival; PFS = progression free survival; RR = response rate; Y = years.

PCR [24,25] could detect the existence of small B-cell clones in the bone marrow with the same characteristics of the extramedullary LPL thus, confirming a final diagnosis of LPL/WM.

According to our literature analysis and review of case reports of non-IgM LPL, differences in clinical behavior have been described between non-WM LPL and LPL/WM raising the question as to whether such differences are relevant to clinical practice, especially if they are important enough to consider non-WM LPL as a completely distinct entity for clinical management and regulatory procedures. The limited data that exist on non-WM LPL does not help us in drawing this conclusion. Some of the clinical and biological differences have been seen in just a few cases, which has impeded its confirmation because of the heterogeneity of published series and case reports. For instance, some patients with non-WM LPL have been described as presenting more commonly with extramedullary disease with less frequent BM involvement [6]. The frequency of neuropathy and hyperviscosity are lower in non-WM LPL than in WM patients [6], an expected finding if we consider the physiopathology of these complications. The lack of the IgM paraprotein results in a lower serum viscosity and a lower probability of immune interactions. However, these results have not been confirmed since formal statistically significant differences are very difficult to achieve based on the low numbers of cases analyzed in each report. Concerning the outcome, some groups have reported a shorter time to first treatment for non-WM LPL compared to LPL/WM [5,6], as well as some trends to poorer progression free survival, but again, with no statistically significant differences; furthermore any impact on overall survival seems to be very marginal.

Therapy and response of non-IgM LPL cases to treatment are also difficult to ascertain because the reported series are small and heterogeneous, and the major response criterion used is that of paraprotein reduction which is uninformative for nonsecretory cases. However, most non-WM LPL patients received similar treatments to LPL/WM and no relevant differences in response rates were reported. Something similar can be said for biological studies. Immunophenotyping studies by flow cytometry have not identified differences between these 2 entities and pathologically, the expression of CD19 and CD20 is universally present, and the proportion of cases expressing CD5, CD10, CD23 appears similar to WM [6]. We have virtually no information on conventional cytogenetics and FISH, and studies on gene mutations are scanty and do not show significant differences (see below).

Based on the available data for non-IgM LPL, the panel considers that taking into consideration the lack of criteria to fulfill the LPL/WM criteria, non-WM LPL should be considered as a sub-entity of LPL as it is considered within the WHO–HAEM5 classification [4]. No sufficient data are available to support a different clinical management for non-IgM LPL from IgM LPL (WM).

Should *MYD88, CXCR4* or *TP53* mutations be evaluated in the work-up of non-IgM LPL?

The presence of genomic alterations in LPL has been evaluated in several series, but they were usually evaluated for IgM LPL (WM) cases. In most series where non-IgM LPL was evaluated for the $MYD88^{L265P}$ mutation, it has been reported at a lower rate for non-IgM vs IgM LPL (WM) cases [5,26,27] although some groups have reported a highly comparable mutation $MYD88^{L265P}$ rate (Table 3) [2,6–8,26,28]. Considering all published series and some reported single cases, it can be concluded that the $MYD88^{L265P}$ mutation is a common event in non-WM LPL, although at a lower rate, of approximately 57% (Table 3). *CXCR4* has been less extensively explored in these patients, but when tested was found to be mutated in 20% of patients (Table 3). Other genes have been rarely analyzed in these patients. *KMT2D* is mutated in about 15% of non-WM LPL cases, which is very similar to the rate found in LPL/WM [29]. Finally, a few non-IgM LPL patients have demonstrated mutations in *TRAF* and *TP53*. As for other characteristics, the number of patients that could be evaluated was so low that it is not possible to add reliable information for clinical decision making.

Accordingly, the panel recommends performing genomic studies in non-WM LPL similar to those recommended for LPL/WM [30]. It is also recommended to perform the evaluation using appropriate samples that ensure the presence of sufficient tumor DNA. For patients with BM infiltration, fresh cells obtained with BM aspiration are considered the most appropriate source for DNA extraction, especially if clonal cells can be counted by flow cytometry [31]. However, if BM is not infiltrated or the number of medullary tumor cells is low, lymph node material, preferentially fresh/frozen material should be provided for DNA extraction. Peripheral blood is rarely involved but, in such a case, it could be an alternative. Finally, more and more frequently cell free DNA from plasma is being used with good results, so it is also a potential source of material for molecular genomics [32].

Should the paraprotein levels be considered for initiating treatment in non-IgM LPL?

According to published series, the most common triggers for treatment initiation in non-IgM LPL are cytopenias, extramedullary disease (lymphadenopathy, splenomegaly) and extranodal sites for disease involvement. Demyelinating neuropathy, hyperviscosity, renal impairment and other disorders frequently attributed to the IgM paraprotein are rarely described. Accordingly, the criteria for starting therapy in non-IgM LPL cases entail many of those usually applied to IgM LPL [33]. During the panel discussions, the question of whether the level of the monoclonal paraprotein should be

Table 3
Genotype in non-WM LPL.

	Disease entity considered	Method	% $MYD88^{m}$ (n° mut/n° evaluated)	% $CXCR4^{m}$ (n° mutated/n° evaluated)
Varettoni et al. [5]	Non-IgM LPL	AS-PCR	42% (8/19)	24% (4/17)
Varettoni et al. [5]*	Non-IgM LPL	NGS	44% (7/16)	25% (4/16)
Awata-Shiraiwa et al. [28]^	Non-IgM LPL	NGS	70% (7/10)	20% (2/10)
Brandefors et al. [2]	Non-WM LPL	AS-PCR	73% (8/11)	NR
Castillo et al. [6]	Non-IgM LPL	AS-PCR	80% (16/20)	25% (5/20)
Yu et al. [7]	Non-IgM LPL	AS-PCR	56% (10/18)	NR
Qiu et al. [8]	Non-IgM LPL	AS-PCR	71% (17/24)	25% (6/24)
Cao et al. [10]	Non-IgM LPL	AS-PCR	40% (6/15)	NR
Jimenez et al. [26]	Non-WM LPL	AS-PCR	0 (0/9)	NR

* $KMT2D^{m}$ 19%, $TP53^{m}$ 6%, $TRAF^{m}$ 6% (No ARID1-A, NOTCH2, PRDM1, CD79B, MYBBP1A, TNFAIP3 mutations).
^ ARID1-A: 10%, KMTD2 10%.
NR = not reported.

Table 4
Treatment characteristics in non-WM LPL retrospective studies.

	Varettoni et al. [5]	Brandefors et al. [2]	Castillo et al. [6]	Cao et al. [10]	Kang et al. [9]
Category of pts considered	Non-IgM LPL	Non-WM LPL	Non-IgM LPL	Non-IgM LPL	Non-IgM LPL
Treated pts	36	13	22	14	6
TTFT median	5.3 m	NR	4 m	Treated at diagnosis	NR
Rituximab alone	2.7%	7.7%	18%	7%	0
Immuno-CHT	67%	77%	77%	64%	17%
Type of first line CHT					17%
alkylating-based regimens	36%	31%	NR	7%	
Anthracycline-based regimens	28%	31%	NR	28.5%	0
Bendamustine	25%	31%	NR	-	17%
PI	2.7%	-	14%	7%	0
BTKi	.	-	4%	-	0
Other	8.3%	-	4%	28.5%	67%

CHT = chemotherapy; PI = proteasome inhibitors; TTFT = time to first treatment.

used to trigger treatment was raised, but all panelists agreed that as in IgM LPL, the level of the monoclonal protein as a single factor should not be a criterion for starting therapy in non-IgM LPL.

Therefore, the panel recommends that for non-IgM LPL cases, the consensus criteria used for IgM LPL (WM) treatment decision making [33] should also be used for initiation of treatment. Initiation of treatment in non-IgM LPL cases should be independent of IgG or IgA paraprotein level, per se, though if patients have symptomatic hyperviscosity treatment should be initiated as per the consensus criteria for IgM LPL [33].

Should the treatment of non-IgM LPL follow the therapeutic guidelines for WM?

Most of the non-IgM LPL patients described in the literature received therapy regimens containing rituximab. The most frequently used chemotherapies were chlorambucil, bendamustine, or cyclophosphamide containing regimens, with more cases receiving anthracyclines vs IgM LPL cases (Table 4). Reported treatment with single agent rituximab was uncommon for non-IgM LPL (Table 4). Although small differences can be seen with respect to outcomes vs IgM LPL (WM), these differences are insufficient to make distinctive treatment recommendations for non-IgM vs IgM LPL. Importantly, in the largest series in which a comparison with IgM LPL was performed, no difference in overall survival was observed. This lack of information is even more evident for BTK inhibitors, which is further exacerbated by the exclusion of these patients in clinical trials for IgM LPL.

The panel therefore recommends a similar therapeutic approach for non-IgM LPL patients as those used in IgM LPL (WM) and emphasizes the recommendation of the allowance of non-IgM LPL patients in trials designed for IgM LPL (WM). In addition, the panel recommends the development of stratification for any LPL in trials focused on indolent lymphomas as to not hamper the development of therapeutics for these patients.

Should the presence or absence of *MYD88* mutation impact the choice of treatment with BTK-inhibitors in non-IgM LPL?

Most patients with non-IgM LPL are positive for mutations at the *MYD88* gene, mainly for the L265P variant. When this variant is absent in IgM LPL, the disease responds poorly to ibrutinib monotherapy with no major responses [34,35]. This has prompted the avoidance of the use of ibrutinib in WM with no mutations in the *MYD88* gene [36]. Conversely, major responses have occurred in 65% of MYD88 wild-type WM patients receiving zanubrutinib [36]. In non-WM LPL, there is insufficient experience with BTKi to assess the real impact by MYD88 mutation status.

Accordingly, most panelists agreed that considering the similar molecular characteristics of both entities, as well as the above recommendation of using a similar management approach for non-IgM and IgM LPL, patients with non-IgM LPL should be treated in a similar manner to patients with IgM LPL independent of MYD88 mutation status until more is known about its impact on treatment outcomes for non-IgM LPL patients.

Should proteosome inhibitors be used only in lymphoplasmacytic lymphoma associated with the presence of a paraprotein?

Proteasome inhibitors (PI) demonstrated activity in multiple myeloma with high potential in reducing the monoclonal component size [37]. Based on this capacity, several PI (Bortezomib, Carfilzomib, Ixazomib) have demonstrated high levels of activity in IgM LPL (WM) [38–40], including cases with a high monoclonal IgM component. This prompted the recommendation for the use of PI in patients with high IgM component [41]. In the opposite situation, PIs are infrequently used in indolent lymphomas with no monoclonal protein [42]. This stimulated the panel discussion about the possibility of restricting the use of PI only in cases with non-WM LPL and monoclonal component. Although this argument could be considered logical on first principles, there are no clinical data available to support this position.

Accordingly, the recommendation is that non-IgM LPL should be treated as IgM LPL (WM) and the use of PI should be based on clinical presentation.

How should response be assessed in non-IgM LPL?

There are no prior reports for response evaluation in non-IgM LPL. Accordingly, most panelists expressed their favorable opinion for using the IWWM-11 consensus criteria adopted for IgM LPL (WM) [43]. Obviously, this recommendation applies only for those non-IgM LPL cases with a paraprotein. In cases without a monoclonal immunoglobulin component, the Lugano Criteria should be considered [44,45]. There is concern about the practical use of the PET-CT scan, since it is being recommended to use [^{68}Ga]pentioxafor instead of [^{18}F]Fluoro-desoxyglucose based on a better avidity for indolent lymphomas, especially LPL [46]. In addition, when extramedullary disease is absent, bone marrow infiltration can only estimate disease burden. Some therapies such as BTK inhibitors are active, while they do not impact the disease burden as other agents. Some panelists expressed the need of developing new criteria of response that are better adapted to non-IgM LPL. Another concern was expressed by the panelists on how criteria for progressive disease should be assessed. In IgM LPL (WM), a serum IgM increase of 5 g/L is required [47], a level that could be different for IgG or IgA isotypes. The panel highlighted here that this level of increase to establish progression is also used for IgG and

IgA multiple myeloma, so the application of IgM LPL (WM) consensus criteria can be considered. In addition, for the rare patients with non-IgM LPL with only light chain paraprotein, the same criteria that are used for light chain MM could be considered for response evaluation [48]. The assessment of Heavy/Light chains (such as Heavylite) is potentially a useful tool [19], although there is no data for a formal recommendation of this methodology.

The panel therefore recommends the use of the IWWM-11 IgM LPL (WM) response criteria for cases of non-IgM LPL with a monoclonal IgA or IgG paraprotein component, but creating a specific panel to develop formal response criteria for this LPL subset was also recommended.

Declaration of competing interest

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CRediT authorship contribution statement

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