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Letter
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What Prognostic Markers Should Be Evaluated in Marginal Zone Lymphoma? A Survey Among Leading International Experts

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Marginal zone lymphoma (MZL) is an indolent and heterogeneous disease. It includes three main entities: extra nodal MZL (EMZL), splenic MZL (SMZL), and nodal MZL (NMZL), with specific diagnostic criteria, clinical behavior, and therapeutic implications. Response assessment criteria are either based on Cheson criteria in nongastric EMZL and NMZL, or on Matutes criteria in SMZL.[1,2] For the specific case of localized gastric mucosae-associated lymphoid tissue (MALT) lymphoma, the response assessment also includes histological criteria evaluated on the gastric biopsy.[3] Furthermore, while Cheson criteria discarded the use of ^{18}FDG-Positron emission tomography-computed tomography (^{18}FDG-PET/CT) in indolent lymphomas because of the supposed lack of avidity, this question is now debated in regard with the new acquisition modalities.[4] At baseline, MALTI-IPI score in EMZL, HPLL score, and IIL score in SMZL have displayed substantial prognostic values, while there is no dedicated score in NMZL.[5–7] In this latter case, by analogy with follicular lymphoma the FLIPI score is often used even if it does not provide guidance for treatment choice (clinical presentation and GELF criteria are used on this purpose). During follow-up, early progression of disease within 24 months (POD24) has recently shown to be associated with shorter survival in MALT lymphomas patients receiving systemic treatment.[8,9]

MZL indolent course requires long and costly trials to evaluate novel therapeutics. In hematological malignancies, FDA and EMA have granted that progression-free survival (PFS) could be a surrogate endpoint to support accelerated and traditional approval. Nevertheless, shorter endpoints would be needed in MZL, which makes appealing novel assessment tools such as PET-CT and cell-free DNA (cfDNA). To note, surrogate markers capture the treatment effect on the true endpoint and are originally prognostic markers, whereas those latter are simply markers that are associated with a poor or good outcome.

The main objective of this survey among experts was to draw up a list of potential prognostic markers for PFS in MZL trials, that will serve as basis to perform future prognostic analyses.

In March 2021, an online questionnaire was sent to a panel of 105 leading international experts involved in the conduct of lymphoma clinical trials. Experts were selected for their commitment in published phase 2/phase 3 indolent lymphoma trials or for their membership in international lymphoma study groups (International Extranodal Lymphoma Study Group or Lymphoma Research Foundation) to whom the protocol of the survey was presented during a scientific council sitting. Panelists were contacted by email up to 3 times and were given 3 months to answer the questionnaire on the REDCap web application. The questionnaire addressed the topic of prognostic markers at baseline and during follow-up in MZL using a branching logic. For markers at baseline, respondents could make their choice among next-generation sequencing (NGS) variants, cytogenetic abnormalities, cfDNA and PET-CT measurements. Concerning the markers after treatment start,[18] FDG-PET/CT, cfDNA, and minimal residual disease (MRD) measurements were proposed in accordance with the recent lymphoma literature. Experts could make a multiple choice for every question (full questionnaire is available in see Supplemental Digital Content Data; http://links.lww.com/HS/A217). After extraction, descriptive statistics were performed as well as comparisons between Northern Americans/Others experts using Fisher's Exact test, on RStudio Software Version 1.1.463.

A total of 74 experts (participation rate 70%) from 16 different countries (Europe 66%, Northern America 26%, Asia 4%, Oceania 2%, Southern America 2%) took the questionnaire. Forty-nine (69%) of them were clinicians hematologists, and the other were oncologists, pathologists, biologists, radiologists, nuclear medicine physicians, or radiotherapists. As shown in Table 1, 43 (61%) and 44 (64%) of them had already been primary investigator or coinvestigator in a prospective clinical trial including either MZL-only patients or MZL patients merged with other lymphoma patients, respectively.

Among the different tools proposed to measure a prognostic marker at baseline, NGS (n = 48, 65%) was chosen more frequently than[18] FDG-PET/CT (n = 39, 53%), cfDNA (n = 29, 39%), and cytogenetics (n = 21, 28%, see Table 2). Six other responses were suggested by respondents such as RNA sequencing (RNASeq), gene expression programming (GEP), epigenetic reprogramming, proteomics, microbiome analysis, or number of clinical sites involved. No differences of choices were observed between Northern Americans and others (P = 0.78).

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Table 1.

Respondents' Characteristics

	N = 74
Sex (n, %)	
Male	38 (54%)
Female	33 (46%)
Age (median [IQR])	51 [44;60]
Region	
Europe	49 (66%)
Northern America	19 (26%)
Other	6 (8%)
Main activity (n, %)	
Clinical hematology	49 (69%)
Pathology	5 (7%)
Biological hematology	4 (6%)
Radiology or nuclear medicine	3 (4%)
Other	10 (14%)
Involvment in a dedicated MZL trial (n, %)	
Primary investigator	26 (37%)
Coinvestigator	17 (24%)
Methodologist	0 (0%)
Trial steering committee	1 (1%)
Trial management group	1 (1%)
No	25 (36%)
Involvment in a trial with MZL and non-MZL patients (n, %)	
Primary investigator	28 (41%)
Coinvestigator	16 (23%)
Methodologist	2 (3%)
Trial steering committee	0 (0%)
Trial management group	1 (1%)
No	34 (48%)
Involvment in MZL observational cohorts (n, %)	37 (52%)

IQR = interquartile range; MZL = marginal zone lymphoma.

Among experts who deemed NGS relevant at baseline, *TP53* (n = 43, 58%) and *NOTCH2* (n = 30, 41%) were chosen as the more interesting variants, before *KLF2* (n = 19, 26%), *KMT2D* (n = 16, 22%), and *TNFAIP3* (n = 15, 20%). Among experts who deemed PET-CT relevant at baseline, they elected the total metabolic tumor volume (TMTV) as most interesting prognostic marker (n = 25, 34%), before the maximum standardized uptake value (SUVmax) of the main lesion (n = 16, 22%) and the Deauville score (n = 14, 19%). Among experts who deemed Cytogenetics relevant at baseline, they considered del(17p), t(11;18), and t(14;18) to be the more valuable cytogenetic abnormalities to be tested as prognostic markers in MZL (n = 11 [15%], n = 11 [15%], and n = 8 [11%], respectively).

Concerning the prognostic tools to use after treatment start, the panelists prioritized ^{18}FDG-PET/CT (n = 42, 57%) and cfDNA (n = 41, 55%), and gave less credit to a potential minimal residual disease (MRD, n = 27, 36%, see Table 2). Epigenetic reprogramming, circulating tumor DNA and biopsy of PET-CT-positive lesions to assess microenvironment and B-cell component were otherwise proposed by 3 panelists. No differences of choices were observed between Northern Americans and others (P = 0.52). Among experts who chose ^{18}FDG-PET/CT, most of them (n = 23, 31% of all panelists) deemed interesting to evaluate the Deauville score at interim or end-of-treatment, which was more frequent than TMTV (n = 17, 23%), ΔSUVmax (n = 14, 19%), SUVmax (n = 13, 18%), and ΔTMTV (n = 8, 11%). Among experts who deemed cfDNA as a good prognostic tool during follow-up, the majority of them preferred ΔcfDNA both at interim (n = 20, 27%) and at end-of-treatment (n = 24, 32%), rather than discrete values given by cfDNA levels (n = 14, 19%). Finally, concerning MRD in MZL, the panelists opted for a blood evaluation (n = 21, 78%) but deemed flow cytometry and PCR as very similar technique options (n = 14 [52%] and n = 13 [48%], respectively).

Table 2.

Choice Made by Leading Experts of Prognostic Markers at Baseline and After Treatment Start in MZL to be Evaluated in the Near Future

	N = 74
Prognostic markers at baseline	
NGS	**48 (65%)**
TP53	43 (58%)
NOTCH2	30 (41%)
KLF2	19 (26%)
KMT2D	16 (22%)
TNFAIP3	15 (20%)
PTPRD	5 (7%)
Other	2 (3%)
PET-CT	**39 (53%)**
TMTV	25 (34%)
SUVmax	16 (22%)
Deauville score	14 (19%)
Any measurement	9 (12%)
Other	3 (4%)
cfDNA	**29 (39%)**
Cytogenetics	**21 (28%)**
del(17p)	11 (15%)
t(11;18)	11 (15%)
t(14;18)	8 (11%)
del(7q)	5 (7%)
t(1;14)	5 (7%)
+3	3 (4%)
+18	3 (4%)
6q23-	2 (3%)
Any abnormality	6 (8%)
Other	1 (1%)
Other	**6 (8%)**
Prognostic markers during follow-up	
PET-CT	**42 (57%)**
Deauville score	23 (31%)
TMTV	17 (23%)
ΔSUVmax	14 (19%)
SUVmax	13 (18%)
ΔTMTV	8 (11%)
Any measurement	9 (12%)
Other	3 (4%)
cfDNA	**41 (55%)**
ΔcfDNA baseline-EOT	24 (32%)
ΔcfDNA baseline-interim	20 (27%)
cfDNA levels	14 (19%)
Any measurement	7 (10%)
Other	1 (1%)
MRD	**27 (36%)**
Sample: Blood	21 (78%)
Sample: Bone marrow	6 (22%)
Technique: Flow cytometry	14 (52%)
Technique: PCR	13 (48%)
Other	**2 (3%)**

Statistics presented: n(%).

cfDNA = cell-free DNA; EOT = end-of-treatment; NGS = next-generation sequencing; PCR = polymerase chain reaction; PET-CT = ^{18}FDG-Positron emission tomography-computed tomography; SUVmax = Maximum Standardized Uptake Value; TMTV = total metabolic tumor volume.

Participants of our survey highlighted key markers of whose prognostic value should be tested in MZL on the basis of large prospective cohorts and clinical trials. To note, none of these markers are currently recommended for clinical routine management of individual patients. They gave much importance to NGS at baseline, confirmed the interest of ^{18}FDG-PET/CT evaluation and showed great interest in cfDNA measurements after treatment start. In our

opinion, these answers are very valuable in regard with the high rate of participation, the high proportion of primary and coinvestigators of prospective MZL clinical trials among respondents and their representability in the international community in MZL research.

NOTCH2 variant was described as an independent marker of short time to first treatment in SMZL.[10] Concomitantly, it has been associated with higher-promoter methylation and a poorer overall survival in a set of 98 patients in SMZL, but the validation set on prospective data included only 36 patients.[11] Its prognostic value on treatment-free survival has been described more consistently by Campos-Martin et al in a set of 150 SMZL patients.[12] Although *NOTCH2* is retrieved in 10%–25% of SMZL and 25% of NMZL, it is almost absent in EMZL.[10,13] Along with *TP53*, mutations of *NOTCH2* shall then be a marker of interest in the coming years especially in SMZL and NMZL.

Deletions of 7q and aberrations of 14q have been associated with a bad prognosis in SMZL on limited retrospective and prospective data.[11,14] Although t(11;18) BIRC3/MALT1 is an independent predictor of resistance to *Helicobacter pylori* eradication, it has never been validated as a prognostic marker in EMZL. This contrasts with the curiosity of experts in the role of t(11;18) and t(1;18) in EMZL, and suggests that further studies would be undertaken in this prospect.

The use of ^{18}FDG-PET/CT in MZL was first reported in 2007 on a cohort of 33 patients,[15] and it is now certain that a large majority of MZL are FDG-avid. Across all subtypes, the prognostic value of baseline ^{18}FDG-PET/CT was firstly suggested in 2014 on a limited set of 25 patients.[16] Later, Albano et al published three larger cohorts in which only lesion-to-liver SUVmax ratio and lesion-to-blood pool SUVmax ratio at baseline were independently associated with PFS in SMZL.[17,18] In response assessment, Song et al highlighted the prognostic value of a Deauville score-base interim ^{18}FDG-PET/CT response assessment on PFS in a set of 146 patients and across all subtypes (but mostly EMZL and NMZL).[19] In this paper, ΔSUVmax had no prognostic impact and TMTV was not assessed. Finally, Vaxman et al reported the prognostic role of SUVmax value at end-of-treatment on PFS in a set of 110 patients.[20] Both visual and semiquantitative approaches were applied in the response evaluation and while the role of ^{18}FDG-PET/CT in MZL remains uncertain, IELSG44 PIMENTO trial and IELSG47 MALIBU trial will provide consistent data in regard of its prognostic value across all subtypes. In parallel, a recent study on 22 newly-diagnosed MZL patients raised interest on CXCR4-directed ^{68}Ga-pentixafor PET/CT as a primary staging tool, although larger series are still expected before recommending this modality.[21]

Eventually, while a droplet digital PCR has been proposed in Hairy cell leukemia or multicolor flow cytometry with a sensitivity of 10^{-4} in chronic lymphocytic leukemia, MRD has never been studied across all subtypes of MZL. It is an avenue for the coming years that has been promoted by a third of our panelists, and one could wonder if this percentage would be higher if our panel had involved more biologists.

In conclusion, our survey highlights the main prognostic markers that shall be prioritized to be statistically evaluated in the near future among ongoing and coming trials and large cohorts involving MZL patients. This will be the first step before considering later surrogacy analyses.

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AUTHOR CONTRIBUTIONS

CB, JL, and CT conceived of the presented idea and set up the questionnaire. CB, EZ, GN, and CT presented the survey to the experts. CB and JL performed the statistical analysis. All authors participated to the writing of the draft and reviewed the final paper.

DISCLOSURE

EZ and CT are part of the International Extranodal Lymphoma Study Group (IELSG) board, in which the survey was presented to experts. The authors have no other conflicts of interest to disclose.

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