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Real-world data for marginal zone lymphoma patients in the French REALYSA cohort: The REALMA study

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Abstract

Marginal Zone Lymphoma (MZL) comprises three subtypes: extranodal MZL (EMZL), splenic MZL (SMZL) and nodal MZL (NMZL). Since clinical trials have limited representativeness, there is a need for real-world data (RWD) evidence in MZL. Real-world data in Lymphoma and survival in Adults (REALYSA) is a prospective multicentric French cohort of newly diagnosed lymphoma patients. This study consists of the first abstraction of MZL patients prospectively included in REALYSA between 12/2018 and 01/2021 with at least 1 year of follow-up. It provides a landscape description of clinical characteristics, initial workup, quality of life and first-line therapy performed in routine practice. Among 207 included patients, 122 presented with EMZL, 51 with SMZL and 34 with NMZL. At baseline, median age was 67 years (range 28–96), and patients reported a favorable global health status (75/100 (IQR 58,83)) – which was higher in NMZL and lower in SMZL patients ($p = 0.006$). ^{18}FDG-PET/CT was frequently performed at initial workup (EMZL 72%, SMZL 73%, NMZL 85%). Active surveillance was the initial management for 58 (28%) patients. The most prescribed therapies were rituximab-chlorambucil in the EMZL population (30%), rituximab monotherapy in the SMZL population (37%) and R-CHOP (24%)/bendamustine-rituximab (15%) in the NMZL population. At end of first line, overall response rate was 93% among treated patients with 75% of complete response. This French nationwide study provided for the first time prospective RWD on clinical characteristics, initial management and treatment response of MZL patients.

KEYWORDS
epidemiology, lymphoma, marginal zone lymphoma, real-world data, real-world evidence

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1 | INTRODUCTION

In 2018, according to the last national report of the French National Cancer Institute on lymphomas, the number of newly diagnosed marginal zone lymphoma (MZL) patients in France was estimated at 2790 (1457 in men and 1333 in women), accounting for over 13% of all newly cases of non-Hodgkin lymphomas.[1] With a median age of 71 years, a male-to-female ratio of 1.4, and a standardized incidence rate based on the age structure of the global population of 2.0/100,000 person-years, MZL showed the highest average annual increase in incidence between 2003 and 2018 (4.7% [95% CI 3.4–5.9] in men, 4.0% [95% CI 2.0–6.0] in women). This standardized incidence rate is closed to that reported by the SEER program registries in the United States (2.1/100,000 person-years), despite a lower increase in this rate between 2006 and 2015.[2]

Initial management of MZL patients remains heterogeneous and mainly depends on MZL subtypes, presence of symptoms, disease bulk and patients status (age, comorbidities). According to the ESMO guidelines,[3] for patients with symptomatic extranodal MZL (EMZL) that need systemic therapies, combination of rituximab with chlorambucil (R-Clb) is recommended. Under this treatment, a large international randomized phase III trial reported 5-year PFS and OS rates of 72% and 90%.[4] Efficacy of bendamustine-rituximab (BR) was demonstrated in phase II trials or observed series of patients (ORR ranging from 93% to 100%, 5-year PFS from 90% to 93%)[5,6] and has been widely implemented in the routine practice. For patients with a symptomatic splenic MZL (SMZL), splenectomy has been progressively replaced by rituximab-monotherapy (induction + maintenance) which provides rapid response, minimal toxicity and prolonged PFS (5-year PFS 79%).[7] Finally, in patients with nodal MZL (NMZL) presenting with B symptoms, deterioration of peripheral blood counts, rapid enlargement of lymph nodes or compression of vital organs by bulky disease, the current guidelines support the combination of rituximab and a chemotherapy (BR or cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) or cyclophosphamide/vincristine/prednisone (R-CVP)). Since MZL is an indolent disease, patients' preference should also be considered.

In France, for patients diagnosed of MZL in 2015, the overall 5-year net standardized survival was 90% (CI95% 87–92), according to the French National Cancer Institute. Over the 2005–2015 period, the 5-year net survival improved by 4% overall and by 6% in patients aged 80+.[8]

Real-world data (RWD) in MZL field came mainly from retrospective studies, which were associated with severe limitations by design (e.g., missing data, biased sampling). In 2002, a first observational epidemiology cohort study – the *Molecular Epidemiology Resource* (MER) – was initiated in the Upper Midwest (USA). In 2004, UK's Haematological Malignancy Research Network started the collection of detailed information about all haematological malignancies diagnosed in two adjacent Yorkshire Cancer Networks. In 2010, the prospective NF10 study, led by the *Fondazione Italiana Limfomi* (FIL), was initiated to allow the follow-up of patients with low-grade non-follicular lymphoma. In November 2018, the French REALYSA (RWD in LYmphoma in Adults) study was initiated as a nationwide multicentric prospective cohort of 6000 adult patients with newly diagnosed lymphoma.[9] The duration of study is to span over 10 years (5 years of patients enrollment (2018–2023) and 4–9 years of follow-up). In this study, patients are prospectively recruited in one of the 35 hematology centers after signing an informed consent form. Patients are managed according to physician's choice with no compulsory visits. The REALYSA study population, inclusion procedure, data collection and management, pathology and clinical review, were already described elsewhere.[9,10] In this study, we described the current population of MZL patients included in REALYSA cohort between 12/2018 to 01/2021 with initial clinical characteristics, comorbidities, baseline quality of life (QoL), care pathways, initial workup, therapeutic management and end-of-first line (EO1L) response rates.

2 | METHODS

2.1 | Study registration and Patient consent statement

As part of the REALYSA protocol, this study was approved by a French ethics committee (Comité de Protection des Personnes Ouest II - file number: 2018/46) and by the National Commission for data protection and freedom of information (CNIL - decision number: DR-2018-238). The REALYSA study is registered on ClinicalTrials.gov identifier (NCT number: NCT03869619). Written informed consent was obtained from patients before any data collection. Patients were informed of this specific analysis through a dedicated webpage on the LYSA website (https://lymphoma-research-experts.org/) before data abstraction.

2.2 | Data abstraction

Adult patients were enrolled within 6 months following their initial diagnosis of lymphoma and came from 35 participating French hematology services. Data on medical history and lymphoma diagnosis were provided by clinicians; lifelong history of residences and occupations were provided by patients through self-administered questionnaires; professional and domestic exposures, leisure time activities, lifestyle factors and women's health were collected during a face-to-face interview. Only adult patients with MZL (splenic, extranodal including cutaneous, or nodal subtypes) were included in REALMA study. Abstraction was performed on 1 January 2023, to ensure MZL patients had at least one year of follow-up, thus having completed first-line therapy. Each diagnosis was centrally reviewed by expert pathologist (M. D.) based on pathology report, and integrative diagnosis (see *Definitions*) was finally scored after harmonization with an expert clinician (C. B.). For clinical information and treatments, specific processes were set up to ensure high-quality data.[10] An automatic "patient profile" was generated for each

patient included in REALYSA and was reviewed for this study by expert physicians. For this study, abstracted data included patients' medical history, baseline characteristics, patients' healthcare pathway, initial workup, first-line therapy and overall (ORR) and complete (CRR) response rates at the end of first line. The MALT-IPI score, HPLL/ABC score and FLIPI score were applied for EMZL, SMZL and NMZL, respectively.

2.3 | Definitions

All included patients had a diagnosis of either EMZL, SMZL or NMZL. Final diagnosis integrated histological, biological and clinical data. Biomarkers could orientate towards a specific subtype (e.g., t(11; 18)(q21; q21) BIRC3/MALT1 for EMZL, del(7q31-32) for SMZL, *KLF2* or *NOTCH2* mutations for both SMZL and NMZL). In case of difficult diagnosis (e.g., disseminated disease with multiple sites involved), a clinical classification algorithm was applied: cases with a extranodal involvement (precluding bone marrow and blood) were labeled as EMZL; cases without extranodal involvement but with spleen or isolated blood/bone marrow involvement were labeled as SMZL; and nodal MZL was a diagnosis of elimination.

Watch and wait management was defined as the decision to start an active surveillance after diagnosis. The definition of systemic therapy in first line was applied to the use of systemic immunotherapy, chemotherapy or targeted therapy, alone or in combination. The definition of local therapy consisted of the use of antibiotics for *H.pylori* eradication, radiation therapy, or surgery.

Diagnosis-to-Treatment Interval (diagnosis to treatment interval (DTI)) was investigated and defined as the time from first diagnosis of MZL to the date of the first therapy, whether local or systemic. Response rates at end of first line of therapy were assessed by local investigators.

2.4 | Quality of life

Quality of life (QoL) was assessed at baseline using the EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 questionnaire along with the specific modules for patients with Non-Hodgkin Lymphoma – Low Grade: QLQ-NHL-LG20.[11] The QLQ-C30 was composed of both multi-item scales and single-item measures. These include a global health status/QoL scale, five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), three symptom scales (fatigue, nausea and vomiting, pain), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). After using a linear transformation to standardize the raw scores into scores ranging from 0 to 100, a high score for a functional scale represented a healthy level of functioning, a high score for the global health status/QoL represented a high QoL, but a high score for a symptom scale or item represented a high level of symptomatology. The QLQ-NHL-LG20 module was composed of multi-item scales which allow the measurement of four dimensions: (i) symptom burden due to disease; (ii) physical fatigue; (iii) emotional impacts; and (iv) worries/fears about health and functioning.

2.5 | Sampling representativeness assessment and statistical methods

In order to assess the cohort's representativeness, we compared the age distribution of incident cases in this study with the national incidence estimates derived from the FRANCIM data (national cancer registries network).[8]

Data were described using median (IQR, range) for quantitative variables and count and percentages for qualitative variables. Patients' characteristics were compared between subtypes using Chi-square test of independence, Fisher's exact test or Kruskal-Wallis test, depending on the nature of variables to be compared. The QLQ-C30 questionnaire and QLQ-NHL-LG20 module were also compared between MZL subtypes using the Kruskal-Wallis test. All statistics were performed with R software (Version 1.1.463–2009–2018 RStudio, Inc).

3 | RESULTS

3.1 | Baseline characteristics and initial workup

From 11 December 2018, to 31 December 2021, a total of 207 patients with MZL were included in the study (Figure 1). Among them, 122 (59%) presented with EMZL, 51 (25%) with SMZL and 34 (16%) with NMZL (Table 1).

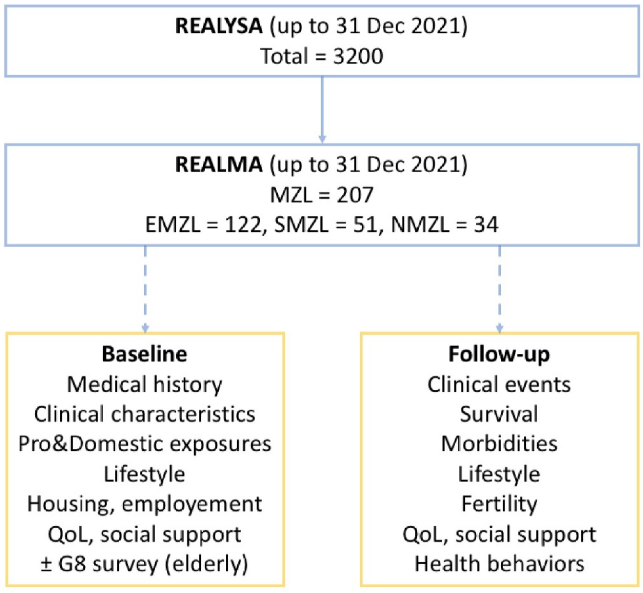

FIGURE 1 Flow chart of REALMA patients and design of the REALYSA study.

TABLE 1 Patients' characteristics at inclusion.

	Overall *N = 207*	EMZL *N = 122*	SMZL *N = 51*	NMZL *N = 34*	*p*-value
Female sex	109 (53%)	69 (57%)	27 (53%)	13 (38%)	0.2
Age (years)	67 (60, 75)	66 (59, 76)	71 (60, 75)	69 (63, 74)	0.5
BMI (kg/m2)	25.0 (22.2, 28.0)	24.9 (22.3, 27.9)	24.2 (21.6, 27.4)	27.2 (23.7, 30.0)	0.077
PS ECOG					0.2
0–1	190 (92%)	115 (94%)	45 (88%)	30 (88%)	
2–4	11 (5%)	5 (4%)	4 (8%)	2 (6%)	
Missing	6 (3%)	2 (2%)	2 (4%)	2 (6%)	
B-symptoms	39 (19%)	14 (11%)	17 (33%)	8 (24%)	0.003
Bulky mass >7cm	31 (20%)	16 (18%)	11 (31%)	4 (13%)	0.2
Compressive syndrome	12 (5.8%)	7 (5.7%)	3 (5.9%)	2 (5.9%)	>0.9
Extranodal involvement (excl. bone marrow/blood)	122 (59%)	122 (100%)	0 (0%)	0 (0%)	<0.001
Spleen involvement	49 (60%)	0 (NA%)	49 (96%)	0 (0%)	<0.001
Bone marrow involvment	48 (62%)	12 (32%)	29 (94%)	7 (70%)	<0.001
Nodal involvement	123 (59%)	58 (48%)	31 (61%)	34 (100%)	<0.001
Ann Arbor stage 3–4	145 (70%)	77 (63%)	50 (98%)	18 (53%)	<0.001
Hemoglobin (g/dl)	13.20 (11.53, 14.28)	13.40 (12.30, 14.40)	11.60 (9.75, 13.45)	13.40 (12.30, 14.45)	<0.001
Hemoglobin <12 g/dl	60 (29%)	26 (21%)	28 (55%)	6 (18%)	<0.001
WBC (G/L)	6.9 (5.7, 9.2)	6.8 (5.8, 8.3)	8.4 (4.6, 14.3)	6.6 (5.5, 7.9)	0.3
ALC (G/L)	1.6 (1.1, 2.5)	1.6 (1.1, 2.1)	2.3 (1.2, 8.5)	1.4 (1.1, 2.4)	0.017
ANC (G/L)	3.87 (3.03, 5.22)	4.14 (3.17, 5.34)	3.51 (2.23, 4.56)	3.70 (3.31, 5.19)	0.036
Platelets (G/L)	232 (178, 271)	244 (203, 299)	156 (109, 215)	246 (214, 268)	<0.001
LDH>ULN	57 (31%)	26 (24%)	20 (48%)	11 (33%)	0.016
Albumin (g/L)	40.0 (37.0, 44.0)	40.0 (37.0, 43.0)	39.0 (35.8, 42.0)	43.5 (39.0, 45.0)	0.043
ß2-microglobulin	2.40 (2.00, 3.27)	2.30 (1.90, 2.75)	3.80 (3.10, 4.80)	2.30 (2.08, 3.10)	<0.001
M-protein	28 (14%)	14 (11%)	5 (9.8%)	9 (26%)	0.044
Types of M-protein	IgG (54%)	IgG (57%)	IgG (100%)	IgM (78%)	0.018
IPI score					<0.001
Low	57 (32%)	43 (39%)	1 (2.5%)	13 (42%)	
Intermediate	97 (54%)	57 (52%)	23 (57%)	17 (55%)	
High	26 (14%)	9 (8.3%)	16 (40%)	1 (3.2%)	
HPLL/ABC score					
B			20 (53%)		
C			18 (47%)		
MALT-IPI score					
Low		29 (30%)			
Intermediate		49 (51%)			
High		19 (20%)			

TABLE 1 (Continued)

	Overall *N = 207*	EMZL *N = 122*	SMZL *N = 51*	NMZL *N = 34*	*p*-value
FLIPI score					
Low				10 (34%)	
Intermediate				11 (38%)	
High				8 (28%)	

Note: Statistics presented: n (%); median (IQR). Statistical tests performed: Kruskal-Wallis test; Chi-square test of independence; Fisher's exact test.

TABLE 2 Patients' comorbidities at MZL diagnosis.

	Overall *N = 207*	EMZL *N = 122*	SMZL *N = 51*	NMZL *N = 34*
General comorbidities				
High blood pressure	69 (33%)	38 (31%)	19 (37%)	12 (35%)
Dyslipidemia	34 (16%)	19 (16%)	7 (14%)	8 (24%)
Diabetes	17 (8.2%)	10 (8.2%)	4 (7.8%)	3 (8.8%)
Asthma	10 (4.8%)	4 (3.3%)	2 (3.9%)	4 (12%)
Cancers				
Breast cancer	12 (5.8%)	6 (4.9%)	4 (7.8%)	2 (5.9%)
Melanoma	9 (4.3%)	5 (4.1%)	1 (2.0%)	3 (8.8%)
Prostate cancer	7 (3.4%)	5 (4.1%)	1 (2.0%)	1 (2.9%)
Immune disorders	32 (15.5%)	18 (14.8%)	7 (13.7%)	7 (20.6%)
Number of comorbidities	3 (2,5)	3 (2,5)	3 (1,5)	4 (2,6)
Charlson comorbidity index (patients of 80+ yo, N = 57)				
0-1	52 (91%)	32 (94%)	12 (86%)	8 (89%)
2-5	5 (9%)	2 (6%)	2 (14%)	1 (11%)

Note: Statistics presented: *n* (%).

At baseline, median age was of 67 years old (IQR 60,75) and 53% of patients were females. Only 5% of patients had a PS ≥ 2. Ann Arbor stage III-IV was reported in 70% of patients; 19% presented with B-symptoms, 20% with a bulky mass >7cm and 6% with a compressive syndrome. Bone marrow involvement was assessed in 83 patients (40%; EMZL 34%, SMZL 61%, NMZL 29%) and bone marrow was infiltrated in 48 (62%) patients. Blood flow cytometry was performed in 46 (22%) cases. In terms of imaging, ^{18}FDG-PET/CT (EMZL 72%, SMZL 73%, NMZL 85%) was more frequently performed than CT-scan (EMZL 72%, SMZL 63%, NMZL 74%), although 98 (47%) of patients underwent both. In EMZL patients, the most frequent extranodal sites were as follows: lung (n = 33 (27%), stomach (n = 24 (20%)), pleura (n = 14 (11%)), orbit (n = 11 (9%)), bone (n = 11 (9%)), liver (n = 8 (7%), skin (n = 6 (5%)). Among the 35 (29%) EMZL patients presenting with 2+ extranodal sites, the most frequent associations was lung-pleura (n = 3 (2%)). None of the SMZL patients presented with a HPLL A-score disease,[12] although at least 29 (57%) of them had a bone marrow involvement (information was missing for 20 SMZL patients). A M-component spike was observed in 14% of patients, mainly in NMZL patients (26%). In NMZL only, IgM was more frequent than IgG. Higher lymphocytes count and ß-2 microglobulin were observed in patients with SMZL, along with lower hemoglobin and platelets levels, as compared to EMZL and NMZL patients.

3.2 | Comorbidities

At baseline and across all subtypes, patients had a median of 3 (IQR 2,5) comorbidities (Table 2). Interestingly, 15% of patients presented a history of immune disorders (EMZL 15%, SMZL 14%, NMZL 18%). Among the 129 (62%) patients who completed epidemiological questionnaires, 55% of patients were or had been smokers, with a median of 10 packs-years (IQR 0–24).

3.3 | Quality of life

Patients reported a good global health status (75 out of 100 (IQR 58,83)), which was significantly higher in NMZL (83 (IQR 67,94)) and

TABLE 3 Quality of life assessment at MZL diagnosis using EORTC QLQ-C30 questionnaire and NHL-LG20 module.

	EMZL *N = 110*	SMZL *N = 50*	NMZL *N = 32*	*p*-value
QLQ-C30 questionnaire				
Global health status/QoL	75 (67, 83)	67 (50, 77)	83 (67, 94)	0.006
Scales				
Physical functioning	93 (80, 100)	87 (72, 100)	93 (78, 100)	0.3
Role functioning	100 (83, 100)	100 (67, 100)	100 (83, 100)	0.2
Emotional fucntioning	75 (65, 92)	75 (67, 96)	83 (58, 100)	0.7
Cognitive functioning	83 (83, 100)	100 (83, 100)	100 (83, 100)	0.9
Social functioning	100 (67, 100)	83 (67, 100)	100 (100, 100)	0.019
Fatigue	33 (11, 33)	33 (6, 67)	17 (0, 42)	0.2
Single-items				
Nausea	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.11
Pain	0 (0, 33)	17 (0, 33)	0 (0, 4)	0.037
Dyspnea	0 (0, 33)	0 (0, 33)	0 (0, 33)	0.7
Insomnia	33 (0, 33)	33 (0, 67)	33 (0, 67)	0.5
Appetite loss	0 (0, 33)	0 (0, 33)	0 (0, 0)	0.004
Constipation	0 (0, 33)	0 (0, 33)	0 (0, 33)	0.2
Diarrhea	0 (0, 8)	0 (0, 0)	0 (0, 0)	0.3
Financial difficulties	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.3
QLQ-NHL-LG20 module				
Scales				
Symptom burden due to disease	17 (0, 25)	17 (8, 33)	17 (0, 29)	0.5
Physical fatigue	25 (8, 42)	29 (8, 52)	8 (0, 50)	0.3
Emotional impacts	17 (8, 33)	17 (8, 33)	8 (0, 31)	0.5
Worries about health/functioning	46 (33, 58)	46 (33, 58)	46 (38, 58)	>0.9

Note: Statistics presented: median (IQR). Statistical tests performed: Kruskal-Wallis test.

lower in SMZL (67 (IQR 50,77), $p = 0.046$, Table 3). Global fatigue at baseline was moderate (33 out of 100 (IQR 0,44)) and mainly explained by the physical fatigue (25 (IQR 8,42)) and the symptom burden due to the disease (46 (IQR 33,58)). Main symptoms were insomnia, pain and appetite loss, the two latter being associated with the splenic subtype of MZL. Diagnosis of MZL altered the emotional functioning of patients across all subtypes (overall 75/100 (IQR 62,92)).

3.4 | Care pathways

Only 6% ($n = 10/158$) of MZL diagnoses were initially suspected by hematologists ($n = 8$ (5%)) or oncologists ($n = 2$ (1%)). In comparison, 45% ($n = 71$) of these were suspected by general practitioners, 8% ($n = 13$) at the emergency room, 6% ($n = 10$) in internal medicine and in ophthalmology. Finally, treatments were mostly administered by hematologists ($n = 160/164$, 98%) from university hospital ($n = 119/166$, 72%), which was consistent across all subtypes (Figure 2). Out of 88 patients aged 70+, only 9 (10%) were referred to an onco-geriatrician before treatment start.

3.5 | Initial management

The median follow-up was 20.8 months (CI95% 18.3,22.3). Median DTI was 2.7 months (IQR 1.2, 8.6), and the longest DTI was 39 months. Among the 207 MZL patients included in this study, 58 (28%) of patients had an active surveillance. Only 10 (5%) patients exclusively received local therapy and 21 (10%) patients received local and systemic therapy altogether. Antibiotics targeting *H.pylori* were administered in 11 patients (46% of gastric EMZL patients). Surgery was only offered in 2 cases of EMZL, and one case (splenectomy) for a patient with SMZL. Radiation therapy was performed on only 6 patients (sites involved: stomach & orbit). As to systemic therapies in EMZL, R-Clb was the most offered in EMZL (30% of all

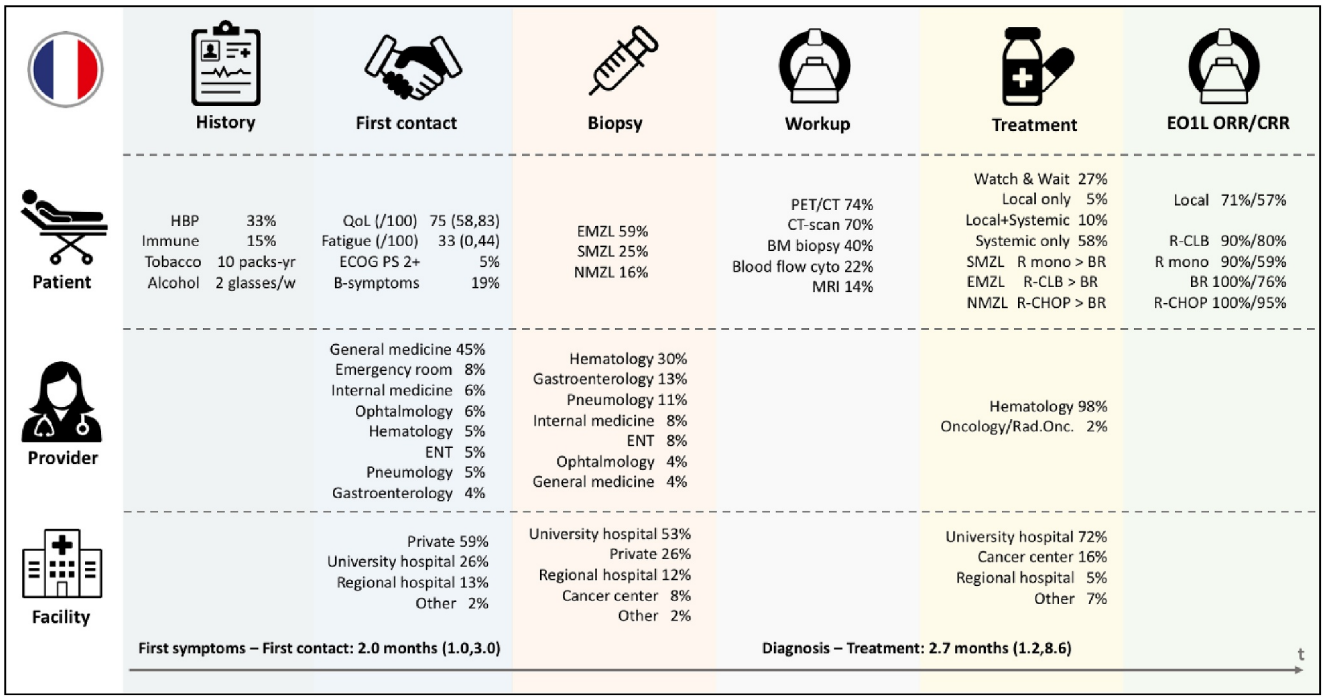

FIGURE 2 Overview of REALMA patients and healthcare pathways, from first symptoms due to marginal zone lymphoma (MZL) to end of first line therapy (EO1L). *ORR/CRR: overall/complete response rate, HBP: high blood pressure, PS: performance status, EMZL: extranodal MZL, NMZL: nodal MZL, SMZL: splenic MZL, BM: bone marrow, R mono: rituximab monotherapy, BR: bendamustine-rituximab, CLB: chlorambucil, ENT: otolaryngology, Rad.Onc.: radiation oncology. Statistics presented: n (%), median (inter-quartile range).*

EMZL cases), before BR (13%), rituximab-monotherapy (8%), R-CHOP (7%) and ibrutinib-rituximab (6%). In SMZL, rituximab-monotherapy was the most administered (37% of all SMZL cases), before BR (12%) and R-Clb (10%). Finally, in NMZL, physicians mainly offered R-CHOP (24% of all NZML cases) and BR (15%). Across all subtypes, a total of 13 patients (9% of patients receiving systemic therapy) received a maintenance therapy (ibrutinib = 7, rituximab = 6, see Table 4).

3.6 | Response to initial therapy

Out of 149 patients with initial active treatment, response at end of first line was available in 141 patients. Among these, a total of 131 (93%) of patients achieved at least a partial response, while 106 (75%) achieved a complete response. Among the 58 patients evaluated by ^{18}FDG-PET/CT, 52 (90%) achieved a metabolic complete response.

3.7 | Population representativeness

As indicator or representativeness, the study population was compared to the national MZL incidence registry,[8] according to age group and sex (see Figure 3). These data suggest a good comparability in terms of age distribution, though with a lower median age at diagnosis (67 vs. 71), and a slight under-representation of elderly women (over 75).

4 | DISCUSSION

The REALMA study is the first French nationwide prospective real-world study in MZL with the objective of landscaping clinical practices and initial patients' characteristics in this under investigated NHL subtype.

First and foremost, in terms of population representativeness, all French MZL patients are not included in the REALYSA study which enrolled patients in only 35 out of 71 LYSA centers (*Lymphoma Research Association* is the French lymphoma cooperative group). For instance, a nested study showed, in one REALYSA center over a 1-year period, that only 54% of all patients were included in REALYSA, which was higher than the clinical trial inclusion rate (near 10%). This study showed that clinicians tended to include lymphoma patients with advanced stage and those for whom a curative treatment was planned – thus the majority of MZL patients were not included in REALYSA (20/35 patients) in this center.[13] In addition, it is well known that many patients diagnosed with EMZL may be referred to the organ-specialist practitioners and not systematically to hematologist-oncologists as long as they do not require a systemic therapy. In our analysis, only 23% of EMZL patients were offered active surveillance (vs. 32% in the MER prospective cohort[14]).

	Overall N = 207	EMZL N = 122	SMZL N = 51	NMZL N = 34
Watch & wait	54 (26%)	28 (23%)	11 (22%)	15 (44%)
Local therapies				
Anti-infectives	12 (6%)	11 (9%)	1 (2%)	0 (0%)
Surgery	3 (1%)	2 (2%)	1 (2%)	0 (0%)
Radiation therapy	6 (3%)	6 (5%)	0 (0%)	0 (0%)
Systemic therapies				
rituximab-Chlorambucil	43 (21%)	37 (30%)	5 (10%)	1 (3%)
rituximab Monotherapy	30 (15%)	10 (8%)	19 (37%)	1 (3%)
bendamustine-Rituximab	27 (13%)	16 (13%)	6 (12%)	5 (15%)
rituximab-CHOP	21 (10%)	9 (7%)	4 (8%)	8 (24%)
rituximab-Chemotherapy (other)	14 (7%)	5 (4%)	5 (10%)	4 (12%)
ibrutinib-Rituximab	7 (3%)	7 (6%)	0 (0%)	0 (0%)
Maintenance therapy				
ibrutinib Monotherapy	7 (3%)	7 (6%)	0 (0%)	0 (0%)
rituximab Monotherapy	6 (3%)	2 (2%)	3 (6%)	1 (3%)

Note: Statistics presented: *n* (%). Nota bene: 10 patients with extranodal MZL received both local and systemic therapies.

TABLE 4 Treatments received according to subtypes of marginal zone lymphoma.

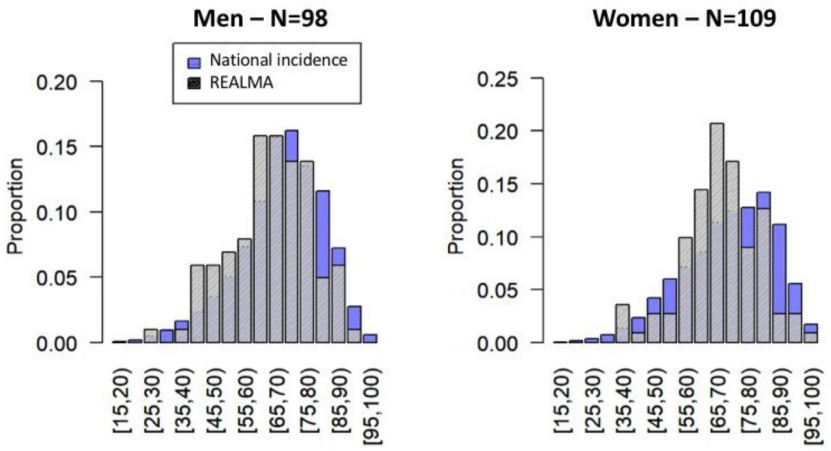

FIGURE 3 Age distribution of patients from the REALMA cohort and from the FRANCIM dataset (national incidence).

When comparing our population to the national incidence data, we observed similarities in terms of age distribution, though with a slight under-representation of older patients (median age at diagnosis: 67 vs. 71 years). This trend can be explained by a recruitment bias through tertiary care hospitals where patients are overall younger at baseline. Indeed, in first-line MZL clinical trials (i.e., selected patients from tertiary care hospitals), median age is even lower (61 (range 28–81) in the IELSG19, 63 (range 22–88) in the GALLIUM, 59 (range 36–77) in NCT00695786)[4,15,16] – which highlights the problem of representativeness of patients included in clinical trials.[17] In real-world studies (NF10 (Italy),[18,19] MER,[14] *Lymphoma Epidemiology of Outcomes* (LEO, USA),[20] Memorial Sloan Kettering (MSK) Lymphoma Outcomes Database)[21]), median age was found to be similar to our study (64 (range (18–92)) in the MER, 64 (range 24–89) in the LEO, 66 (range 28–90) in the NF10, 62 (range 50–69) in the MSK cohort). Altogether, these data suggest that our inclusion criteria were very close to the patients' routine management. Nonetheless, low-risk patients were underrepresented in our study: indeed, although 26% were initially observed, the median DTI was short (2.7 months (IQR 1.2, 8.6)) and proportion of low-risk IPI patients was low (32%, vs. 53% in the MER). This shift may be explained by the fact that patients in the REALMA study were those seen by a hematologist, therefore with the intent de be treated. This peculiarity of late referral to a hematologist may also explain the lower rate of H. pylori eradication in our cohort (i.e., early-stage gastric EMZL being initially seen by gastrologists/internists).

One of the strengths of this cohort is that it relies on most accurate diagnoses, in a field wherein experts may diverge about how MZL subtypes should be ascertained, either clinically only (as in the NF10 cohort, therefore using a fourth "disseminated MZL" subtype) or by integrating the clinical presentation to pathological and molecular results as we decided to proceed (see the recent controversies between WHO-5HEAM[22] and ICC[23]). REALYSA takes advantage of the LYMPHOPATH network – which provides expert-review of all newly diagnosed lymphomas in France.[24] In previous publications, it had been shown that the rate of diagnosis correction after expert review in MZL was ranging from 17% in EMZL, 20% in SMZL, to 41% in NMZL.[24,25] As comparison, for example, in the BRISMA/IELSG36 trial, 16/78 (21%) of initially registered patients had finally been considered ineligible for unconfirmed diagnosis.[26]

For initial workup, we reported that ^{18}FDG-PET/CT and bone marrow biopsy/aspiration were performed in 74% and 38% of our patients, respectively. In the LEO cohort (8 US centers), 44% of the patients had undergone both ^{18}FDG-PET/CT and bone marrow biopsy.[20]

In our cohort, a lower rate of initial observation was observed as compared to the LEO cohort (EMZL 17% vs. 32%, SMZL 36% vs. 44%, NMZL 39% vs. 49%[14,21]) or the NF10 cohort (overall, 27% vs. 47%[19]). However, a 10% rate of initial observation has already been reported in another US study (accrual period from 1995 through 2016) – variations may be explained by both clinical opinion and initial presentation in certain populations.[27] We also reported the very low rate of splenectomy in first line management of SMZL in France, in contrast with the other cohorts,[19,20] which can be explained by the later accrual period in our study with current clinical practices in accordance with international guidelines.[3] As compared to other cohorts, REALMA study presented a higher rate of systemic therapy administration (51% vs. 41% in the NF10% and 27% in the MER), mainly in EMZL (61% vs. 26% in the MER) and in SMZL (76% vs. 18% in the MER).[14] This was associated with a lower use of BR regimen (13% vs. 18% in the NF10) and a higher use of R-Clb (21% vs. 14% in the NF10).[19]

The REALMA study is the only prospective one to report CRR every 6 months throughout follow-up as in a clinical trial – which makes it pretty unique. In this analysis, we observed an overall CRR of 75% at the end of 1st line therapy. Given the short follow-up at the time of analysis, we were not able to report early endpoints assessments such as POD24,[19,28] CR24 or time-to-CR within 24 months.[29]

In recent years, QoL was studied in indolent lymphoma survivors in the US but it was done using FACT-G score.[30,31] Here, using EORTC QoL questionnaires, we outlined the higher global health status for patients with NMZL (median (IQR): 83 (67, 94) versus 75 (67, 83) in EMZL and 67 (50, 77) in SMZL, $p = 0.006$) and the prevalence of symptoms such as pain, insomnia and appetite loss in patients with SMZL at diagnosis. This supports the idea that MZL subtypes have various clinical presentations and should be analyzed separately in clinical studies.[32,33]

This is the first analysis describing RWD of patients with MZL in France using the prospective REALYSA cohort. With a multi-step rigorous data validation process, this cohort allowed the generation of high-quality data on epidemiology, clinical characteristics, patients-reported outcomes (i.e., QoL) and possibly biological studies to improve knowledge's in MZL and these first results are consistent with the real-world literature. With the objective of 6.000 included patients in the REALYSA cohort, we estimate a total of approximately 400 MZL assessable patients at the end of the study – allowing further characterization of this lymphoma subtype in the French population.

AUTHOR CONTRIBUTIONS

C. Bommier, C. Thieblemont, M. Donzel, F. Cherblanc, A. Belot, A. Monnereau and H. Ghesquieres, conceived the presented idea and set up the methodology. C. Bommier and A. Belot performed the statistical analysis. All authors are active contributors to the REALYSA study. All authors participated to the writing of the draft and reviewed the final paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the authors HG and CB upon reasonable request.

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