



GUIDELINE

Guideline for the diagnosis and management of marginal zone lymphomas: A British Society of Haematology Guideline

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SCOPE

The objective of this guideline is to provide healthcare professionals with clear guidance on the diagnosis and management of patients with marginal zone lymphoma (MZL).

METHODOLOGY

These guidelines were compiled according to the BSH process: <https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf>.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength

of recommendations. The GRADE criteria can be found at <http://www.gradeworkinggroup.org>.

Recommendations are based on a review of the literature using Medline/Pubmed. Search terms included: marginal zone, MZL, extranodal MZL, MALT, nodal, splenic, treatment, randomised, clinical trial, radioimmunotherapy, hepatitis C, *Helicobacter pylori*. The search was limited to English language publications and conference abstracts from 1 January 1998 to 20 September 2022. Titles/abstracts obtained were curated and manually reviewed by the writing group, which conducted additional searches using subsection heading terms.

The manuscript was reviewed by the BSH Guidelines Haemato-oncology Task Force, the BSH Guidelines Executive Committee and the haemato-oncology sounding board of the BSH.

INTRODUCTION

The MZLs are a group of clinically indolent mature B-cell lymphomas derived from memory B cells of the 'marginal' zones of secondary lymphoid tissues. Marginal zone B cells are at the centre of inflammation, autoimmunity and malignant transformation through the coordination of innate and adoptive immunity. MZLs, especially extranodal marginal zone lymphomas (EMZL), frequently arise in the context of chronic infection or autoimmune disease, and, while the various subtypes share many biological, diagnostic and clinical features, they manifest subtype-specific features, resulting in a multisystem presentation.

The 5th World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues recognises distinct MZL subtypes according to the microenvironment of involved tissue¹—EMZL of mucosa-associated lymphoid (MALT) tissue, splenic marginal zone lymphoma (SMZL) and nodal marginal zone lymphoma (NMZL).^{2,3} Paediatric marginal zone lymphoma and primary cutaneous MZL, originally included under NMZL and EMZL/MALT, respectively, are now classified as separate entities.

MZL is the third most common lymphoma,⁴ comprising up to 15% of non-Hodgkin Lymphoma (NHL) in the Western World. Over 60% are EMZL/MALT (which can arise from any site following chronic antigenic stimulation), 20% are SMZL and <10% are NMZL. Incidence increases with age, suggesting cumulative exposure to risk factors. Age-adjusted incidence has increased by 1.1% per year⁵ with a current UK

incidence of 2.62 per 100 000 and a male-to-female ratio of 1.6.⁴

DIAGNOSIS

Diagnosis requires a representative tissue biopsy, bone marrow or peripheral blood sample, depending on the subtype. Diagnostic material should be reviewed by an expert haematopathologist⁶ in the context of clinical and laboratory features and classified according to the 5th WHO classification of haematolymphoid tumours and/or the International Consensus Classification of Lymphoid Neoplasms.^{2,3} Which classification has been used should be stated in the report.

There are currently no widely specific diagnostic markers for MZL. Immunohistochemical (IHC) evaluation of tissue relies upon excluding other low-grade B-cell NHL entities. Commonly used IHC markers are listed in [Table 1](#).

Extranodal marginal zone lymphomas of mucosal-associated lymphoid tissue (EMZL/MALT)

EMZL/MALT recapitulates Peyer's patch-type lymphoid tissue² and presents at a variety of extra-nodal sites. Tumours are composed of morphologically heterogeneous small B cells, including marginal zone (centrocyte-like) cells,

TABLE 1 Diagnostic tissue markers.

Test	Type	Expected result	Reason
CD20	IHC	+	B-cell neoplasm
BCL2	IHC	+	Demonstrates partly colonised follicles
BCL6	IHC	+	Residual germinal centre cells positive in colonised follicles
CD21	IHC	+	Expanded follicular dendritic cell meshworks help demonstrate follicular colonisation
CD43	IHC	+/-	Aberrant expression in MZL and useful in differentiating neoplastic from reactive proliferations
CD5	IHC	-	Rare positive MZL cases described
CD23 and LEF1	IHC	-	Distinguish from CLL
CD10	IHC	-	Rare positive cases described (BCL6 negative)
Cyclin D1 and SOX11	IHC	-	Especially useful in CD5+ cases to rule out MCL
IgD	IHC	-	IgD is expressed by SMZL cells and not in EMZL/NMZL-residual mantle zones will be positive.
Congo Red	Histological staining	+/-	Detects amyloid (EMZL/MALT lymphoma)
Immunoglobulin light chains	IHC/ISH	Restriction	Demonstration of restriction in neoplastic B cells and in cases with plasma cell differentiation
MYD88	PCR	Unmutated	Distinguish from lymphoplasmacytic lymphoma (LPL). <i>Note:</i> MYD88 mutations may occur in 7%–15% of SMZL (see Table 2)
B-cell clonality	PCR	Clonal	PCR should not be solely relied upon in the absence of morphological clinical correlation-oligo/mono clonal B-cell expansions can arise in the setting of chronic inflammation

Abbreviations: CLL, chronic lymphocytic leukaemia; EMZL, extranodal marginal zone lymphomas; IHC, immunohistochemistry; ISH, in situ hybridization; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; PCR, polymerase chain reaction; SMZL, splenic marginal zone lymphoma.

TABLE 2 Site-specific characteristics of EMZL/MALT (modified from Refs. [2,20,23,24]).

Anatomical site	Frequency of location for MZL, %	Confirmed and potential/possible aetiological factors	Genetic alterations	Reported immunoglobulin-gene usage IGHV
Gastrointestinal tract				
Stomach	70	<ul style="list-style-type: none"> <i>Helicobacter pylori</i> (38%–85%)⁸ <i>H. heilmannii</i> (<1%) 	<ul style="list-style-type: none"> t(11;18)(q21;q21)/BIRC3::MALT1 (6%–26%). Higher incidence in <i>H. pylori</i>-negative gastritis, associated with aggressive behaviour and nuclear expression of BCL10²⁵ t(14;18)(q32;q21)/IGH::MALT1 (1%–5%) Trisomy 3 (11%) Trisomy 18 (6%) TNFAIP3 (A20) Inactivation (5%–18%) 	
Intestinal tract	2	<ul style="list-style-type: none"> <i>Campylobacter jejuni</i> (up to 50%) 	<ul style="list-style-type: none"> t(11;18)(q21;q21)/BIRC3::MALT1 (12%–56%) t(1;14)(p22;q32)/IGH::BCL10 (0%–13%) Trisomy 3 (75%) Trisomy 18 (25%) 	
Liver	10	<ul style="list-style-type: none"> Hepatitis C virus (23%) Hepatitis B virus (16%) Other viral hepatitis (10%) <i>H. pylori</i> (13%) Autoimmune hepatitis/primary biliary cirrhosis/Sjögren syndrome (12%) Ascariasis (4%) Synchronous malignant tumours (11%) 	<ul style="list-style-type: none"> t(14;18)(q32;q21)/IGH::MALT1 (0%–67%) t(3;14)(p14;q32)/IGH::FOXPI Trisomy 3 Trisomy 18 	
Gallbladder and extra-hepatic bile duct	14	<ul style="list-style-type: none"> Gallstones 	<ul style="list-style-type: none"> t(11;18)(q21;q21)/BIRC3::MALT1 	
Head and neck				
Ocular adnexa ²⁶	60	<ul style="list-style-type: none"> <i>Chlamydia psittaci</i> (geographical variation) Hepatitis C virus (25%) IgG4-related disease (10%) 	<ul style="list-style-type: none"> t(14;18)(q32;q21)/IGH::MALT1 (0%–25%) t(3;14)(p14.1;q32)/IGH::FOXPI (0%–20%) Trisomy 3 (38%) Trisomy 8 (13%) TNFAIP3 (A20) inactivation (26%) Gain 6p Loss 6q CABIN1 (30%) RHOA (26%) TBLIXR1 (22%) CREBBP (17%) 	4–34
Salivary glands	30–40	<ul style="list-style-type: none"> Sjögren syndrome IgG4-related disease/sialadenitis Hepatitis C virus 	<ul style="list-style-type: none"> t(14;18)(q32;q21)/IGH::MALT1 (0%–16%) t(11;18)(q21;q21)/BIRC3::MALT1 (0%–5%) t(1;14)(p22;q32)/IGH::BCL10 (0%–2%) Trisomy 3 (55%) Trisomy 8 (19%) Mutated GPR34 	1–69
Thyroid gland	2	<ul style="list-style-type: none"> Chronic lymphocytic (Hashimoto) thyroiditis IgG4-related disease 	<ul style="list-style-type: none"> t(3;14)(p14.1;q32)/IGH::FOXPI (0%–50%) t(11;18)(q21;q21)/BIRC3::MALT1 (0%–17%) Trisomy 3 (17%) TNFAIP3 (A20) inactivation (22%) Mutations of CD274, TNFRSF14 and/or TET2 	3–23
Pulmonary				
Lung	70–90	<ul style="list-style-type: none"> <i>H. pylori</i>, <i>Achromobacter xylosoxidans</i> Human immunodeficiency virus Hepatitis C virus Sjögren syndrome/systemic lupus erythematosus Smoking Common variable immunodeficiency syndrome 	<ul style="list-style-type: none"> t(11;18)(q21;q21)/BIRC3::MALT1 (31%–53%) t(14;18)(q32;q21)/IGH::MALT1 (6%–10%) t(1;14)(p22;q32)/IGH::BCL10 (2%–7%) Trisomy 3 (20%) Trisomy 8 (7%) TNFAIP3 (A20) inactivation (12%) 	

(Continues)

TABLE 2 (Continued)

Anatomical site	Frequency of location for MZL, %	Confirmed and potential/possible aetiological factors	Genetic alterations	Reported immunoglobulin-gene usage IGHV
Thymus		<ul style="list-style-type: none"> Sjögren syndrome (>60%)/rheumatoid arthritis/scleroderma, predominantly in Asian females 	<ul style="list-style-type: none"> Trisomy 3 (50%) 	
Skin	7	<ul style="list-style-type: none"> <i>Borrelia burgdorferi</i> IgG4-related disease (15%–39%) Tattoo pigments Vaccines 	<ul style="list-style-type: none"> t(14;18)(q32;q21)/<i>IGH::MALT1</i> (0%–14%) t(3;14)(p14.1;q32)/<i>IGH::FOXP1</i> (0%–10%) t(11;18)(q21;q21)/<i>BIRC3::MALT1</i> (0%–8%) Trisomy 3 (20%) Trisomy 8 (4%) <i>FAS</i> mutations 	
Other sites				
Breast	3	<ul style="list-style-type: none"> Sjögren syndrome 	<ul style="list-style-type: none"> t(11;18)(q21;q21) t(14;18)(q32;q21) 	
Dura ²⁷		<ul style="list-style-type: none"> IgG4-related disease 	<ul style="list-style-type: none"> <i>TNFAIP3</i> 67% (of cases with plasmacytic differentiation) <i>NOTCH2</i> 80% (of cases with monocytoid morphology) <i>TBLXR1</i>, <i>HLHL6</i>, <i>MLL2</i>, 6p25.3 gains, 1p36.32 losses 	

Abbreviations: EMZL, extranodal marginal zone lymphomas; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma.

monocytoid cells, small lymphocytes and centroblast-like cells. There is plasmacytic differentiation in some cases. Neoplastic cells reside in the marginal zones of reactive B-cell follicles, extend into the interfollicular region and colonise the follicles. In epithelial tumours, lymphoepithelial lesions are seen. These are aggregates of ≥ 3 neoplastic cells with distortion or destruction of the epithelium, often with eosinophilic degeneration of epithelial cells. These are not essential for diagnosis and are not specific for EMZL.⁷

Helicobacter pylori infection is strongly implicated in the pathogenesis of gastric EMZL/MALT.⁸ Autoimmunity-associated chronic inflammation (Sjögren syndrome and Hashimoto thyroiditis) may precede EMZL/MALT-affecting salivary glands and thyroid respectively.

Primary cutaneous marginal zone lymphoproliferations are now recognised as a distinct entity because of their indolent behaviour and disease-specific survival approaching 100% without the need for aggressive therapies.³ The term 'primary cutaneous marginal zone LPD' is proposed in the International Consensus Classification of mature lymphoid neoplasms. The 5th WHO classification of haematolymphoid tumours categorises the same entity as a 'Primary cutaneous marginal zone lymphoma'.² Approximately 75% are class-switched (predominantly IgG+), with up to 40% expressing IgG4. Abundant reactive T cells and peripherally located clustered plasma cells are often seen. Cases that are IgM+ (non-class-switched) and show monocytoid B cells warrant exclusion of non-cutaneous primary disease.³

MZLs rarely involve the central nervous system (CNS), either primarily or secondarily. Most CNS MZL is dural EMZL/MALT lymphoma, with lesions often radiologically indistinguishable meningioma^{9–13}; however, MRI may distinguish from meningioma by a more prominent dural tail.¹⁴ Histological confirmation has important implications for

prognosis and management, as dural EMZL/MALT lymphoma has a better prognosis than high-grade primary central nervous system lymphomas.^{15,16} IgG4 expression in light-chain-restricted clonal plasma cells is a feature of MZL involving the CNS. Other EMZL/MALT lymphomas may also develop in the context of IgG4-related disease, and an aetiological association has been suggested.^{17–21} Site-specific aetiology and reported genetic alterations²² are summarised in Table 2.

Splenic marginal zone lymphoma

A diagnosis can usually be established through a combination of morphology and flow cytometry on peripheral blood or aspirated bone marrow, marrow trephine biopsy histology and IHC, but in a minority of cases, a definitive diagnosis may require splenectomy.⁷ Splenic histology reveals a B-cell neoplasm composed of small lymphocytes that surround and replace the splenic white pulp germinal centres, efface the follicle mantle and merge with a peripheral (marginal) zone of larger cells, including scattered transformed blasts; both small and larger cells infiltrate the red pulp. SMZL shares features with other splenic lymphomas and, without splenectomy, may be indistinguishable from splenic diffuse red pulp lymphoma (Table 3).

Nodal marginal zone lymphoma

NMZL is a primary nodal B-cell neoplasm morphologically resembling lymph nodes involvement by EMZL/MALT or SMZL but without evidence of extranodal or splenic disease. Peripheral blood involvement may occur, and bone marrow involvement is seen in one third of cases.^{2,41}

TABLE 3 Pathology and differential diagnosis of SMZL (modified from Ref. [28]).

	SMZL	SDRPL	HCL	HCLv
Male:Female	1:1	1:1	4:1	M > F
Age	>60 years	>40 years	Median: 58 years	Mid age-elderly
Atypical cells and findings in peripheral blood	Villous lymphocytes with polar cytoplasmic projections	Polar cytoplasmic projections; basophilic cytoplasm	Hairy cells with circumferential hairy projections (may be infrequent); low monocyte count; low lymphocyte count	Hairy cells with variable cytoplasmic projections; prominent nucleoli; monocyte count preserved; high lymphocyte count
Immunophenotype	CD20+ CD103- CD25-/+ CD27+ CD11c+/- CD123- DBA44+ Annexin A1- Cyclin D1- IgD+	CD20 bright+ CD103-/+ CD25- CD27+ CD11c-/+ CD123- DBA44+ Annexin A1- Cyclin D1- IgG+ (rare IgD/IgM+ cases)	CD20 bright+ CD103+ CD25+ CD27- CD11c+ CD123+ DBA44+ Annexin A1+ Cyclin D1+ (weak) IgG+	CD20 bright+ CD103+ CD25- CD27+ CD11c+ CD123- DBA44+ Annexin A1- Cyclin D1- IgG+
Marrow involvement	Nodular and intrasinusoidal	Intrasinusoidal, interstitial and nodular	Diffuse and interstitial—'honeycomb' pattern; minor intrasinusoidal component may be seen; fibrosis marked	Interstitial rarely diffuse; predilection to sinusoidal infiltration; reticulin fibrosis not significant (easier to aspirate than classical HCL)
Spleen histology	Marked expansion of white pulp and infiltration of red pulp; micronodular pattern	Diffuse red pulp involvement of cords and sinusoids; white pulp spared	Red pulp infiltration with red blood cell lakes; atrophic white pulp	Red pulp infiltration with red blood cell lakes; atrophic white pulp
Molecular genetics	<ul style="list-style-type: none"> Del7q22-36 (with a minimal common deletion of a 3 Mb region at 7q32.1-32.2) (45% of cases)^{22,29,30} <i>NOTCH2</i> (10%–25%) and <i>KLF2</i> (10%–40%) mutations^{31–33} 17p13 (<i>TP53</i>) deletion (3%–17%)²² <i>IGHV</i> gene somatic mutations: frequent <i>IGHV1-2*04</i> segment use, low mutational load^{24,34,35} <i>MYD88 L256P</i> mutation (7%–15%)^{36,37} 	<ul style="list-style-type: none"> <i>CCND3</i> PEST domain mutations <i>IGHV</i> gene somatic mutations (79%): overrepresentation of <i>IGHV3-23</i> and <i>IGHV4-34</i> usage^{24,38} 	<ul style="list-style-type: none"> <i>BRAF</i> V600E mutation in most cases <i>IGHV3-23</i> and less commonly <i>IGHV4-34</i> usage³⁸ <i>TP53</i> deletion rare^{39,40} 	<ul style="list-style-type: none"> <i>BRAF</i> V600E not present <i>MAP2K1</i> mutations <i>IGHV4-34</i> usage³⁸ Common complex karyotypes and <i>TP53</i> deletion^{39,40}

Abbreviations: HCL, hairy cell leukaemia; HCLv, HCL variant (splenic B-cell lymphoma/leukaemia with prominent nucleoli²); SDRPL, splenic diffuse red pulp lymphoma; SMZL, splenic marginal zone lymphoma.

Table 1 describes IHC that is useful in establishing the diagnosis. Where plasma cell differentiation is prominent, distinction from lymphoplasmacytic lymphoma (LPL) may be difficult. Demonstration of remnants of follicular dendritic

cell meshworks favours a diagnosis of NMZL.² *MYD88* gene mutations are usually detected in LPL and rarely in NMZL.

A mixture of cell types is seen in NMZL, but the presence of >20% large B cells is concerning for high-grade

transformation (HGT).² However, a diagnosis of diffuse large B-cell lymphoma should only be made if clearly delineated sheets of large B cells are identified. In some cases, an abundant PD1+ follicular helper T-cell infiltrate has been described and may pose a diagnostic challenge in distinction from T-cell lymphoma; this can also be seen in EMZL/MALT.⁴² Trisomy of chromosomes 3 and 18, gains of 2p and 6p and loss of 1p and 6q are common in NMZL, with frequent somatic variants of *KMT2D*, *PTPRD*, *NOTCH2* and *KLF2*.²

Paediatric nodal MZL, now a separate entity in the 5th WHO classification,² is an indolent disease with a favourable prognosis. It occurs predominantly in boys (M:F, 20:1) presenting with asymptomatic, localised disease involving lymph nodes of the head and neck. Involved nodes display progressive transformation of germinal centres.⁴³ Differential diagnosis includes atypical marginal zone hyperplasia and marginal zone hyperplasia associated with *Haemophilus influenzae*, wherein the marginal zone cells are IgD-positive.⁴⁴ Genetic studies are advised in this setting, in view of the differential diagnoses.

Transformation to high-grade disease

Population-based long-term data on the transformation of MZL is limited; however, in some studies, a cumulative

incidence of transformation to aggressive large B-cell lymphoma of 4.7% at 10 years is described.⁴⁵ In this study, the highest risk of transformation was observed in patients with SMZL (14%); a range of 4%–15% is described in other studies.^{46,47} Risk factors for transformation are discussed in Section “Transformed disease”.

Histologically, the common form of transformation is to a diffuse large B-cell lymphoma (DLBCL) of non-germinal centre immunophenotype; a diagnosis of DLBCL should only be made if clearly delineated sheets of large B cells are identified.² A variable proportion of large B cells are present within the neoplastic population in all histological subtypes of MZL. Rarer cases of transformation to classical Hodgkin Lymphoma and plasma cell leukaemia have been described.^{48,49} A clonal relationship between the MZL and transformed disease can be demonstrated in many cases, but apparent transformations may in some cases represent clonally unrelated second lymphomas.

WORK UP AND STAGING

All patients require a history and full physical examination, blood tests, radiological imaging for staging and baseline measurement of disease (summarised in Table 4).

TABLE 4 Work up and staging investigations.

Investigations	
All patients	
<ul style="list-style-type: none"> • Full blood count and blood film • Peripheral blood flow cytometric immunophenotyping (SMZL and NMZL) • Renal and liver function tests, LDH, beta-2-microglobulin (B2M) • Protein electrophoresis • Viral serology (HCV, HBV and HIV) • Contrast-enhanced CT neck, thorax, abdomen and pelvis 	
Selected patients	Indication
<ul style="list-style-type: none"> • Bone marrow aspirate and trephine biopsy (for morphology and IHC ± flow cytometry, FISH, IGHV genes) 	<ul style="list-style-type: none"> • All patients with SMZL • Associated cytopenias, and confirmation of early stage disease in non-gastric EMZL/MALT, NMZL
<ul style="list-style-type: none"> • PET scan 	<ul style="list-style-type: none"> • Suspected HGT • Evaluation of early stage disease suitable for radiotherapy
<ul style="list-style-type: none"> • MRI scan 	<ul style="list-style-type: none"> • Evaluation of specific EMZL/MALT sites, for example orbits, brain
<ul style="list-style-type: none"> • Oesophago-gastro-duodenoscopy ± endoscopic ultrasound 	<ul style="list-style-type: none"> • Diagnosis and prognosis of gastric EMZL/MALT
<ul style="list-style-type: none"> • Testing for <i>Helicobacter pylori</i> (faecal antigen testing; carbon-13 urea breath test [CLO] ± serology) 	<ul style="list-style-type: none"> • Gastric and non-gastric EMZL/MALT
<ul style="list-style-type: none"> • Direct antiglobulin test (DAT), reticulocytes, haptoglobin 	<ul style="list-style-type: none"> • Presence of haemolysis (SMZL)
<ul style="list-style-type: none"> • Clotting 	<ul style="list-style-type: none"> • Suspected acquired clotting disorder (SMZL)
<ul style="list-style-type: none"> • C1 esterase 	<ul style="list-style-type: none"> • Associated angioedema (SMZL)
<ul style="list-style-type: none"> • Autoimmune screen; vasculitis screen; IgG4 level 	<ul style="list-style-type: none"> • Suspected underlying pathology
<ul style="list-style-type: none"> • Cryoglobulin concentration and C3/4 levels 	<ul style="list-style-type: none"> • Suspected cryoglobulinaemia or if HCV-positive (SMZL)

Abbreviations: CLO, campulobacter-like organism test; CT, computed tomography; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoid tissue; MRI, magnetic resonance imaging; NMZL, nodal marginal zone lymphoma; PET, positron emission tomography; SMZL, splenic marginal zone lymphoma.

Extranodal marginal zone lymphomas of mucosal-associated lymphoid tissue

Gastric EMZL/MALT lymphoma

Gastric EMZL/MALT lymphoma accounts for 35% of MZL and ~50% of all EMZL. Rarer subtypes of gastrointestinal MALT lymphoma include small intestinal MALT or its variant immunoproliferative small intestinal disease (IPSID) and colonic MALT lymphoma.⁵⁰

Patients with gastric EMZL/MALT lymphoma should undergo oesophago-gastro-duodenoscopy (OGD) with biopsies and careful documentation of lesions.⁵¹ Mapping biopsies are not essential, but high-quality photography and a detailed description of the site of lesions are advised for comparison. Repeat OGD is recommended in cases of diagnostic uncertainty. Fluorescence in situ hybridisation (FISH) for t(11:18)(q21;q21) and fusion of *BIRC3* (formerly *API2*) and *MALT1* is recommended in all cases, as its presence is associated with more advanced disease and a lower rate of response to *H. pylori* eradication.⁵²

Helicobacter pylori is strongly implicated in the pathogenesis of gastric EMZL/MALT lymphoma. Despite the apparently decreasing incidence of *H. pylori*-positive gastric EMZL/MALT lymphomas,⁵³ most cases are still thought to be *H. pylori* positive, particularly in older patients. *H. pylori* testing should be performed in every patient, with proton pump inhibitor (PPI) and antibiotics discontinued at least 2 weeks before.⁵⁴ *H. pylori* infection is primarily evaluated by tissue IHC. In addition, faecal antigen testing (or a carbon-13 urea breath test; CLO) and *Helicobacter* serology are recommended. Serology is useful with low-level infection and if histology/CLO is negative.⁵⁵ *H. heilmannii* in gastric EMZL/MALT and *Campylobacter jejuni* in IPSID are less frequent causative organisms.^{56,57}

Bone marrow involvement is rare—just 4.3% in one study⁵⁸—and bone marrow biopsy is not essential except in patients with cytopenia.

The role of positron emission tomography (PET) is not well defined in MZL; PET is, however, increasingly used in MZL for staging of both nodal and extranodal disease⁵⁹ and subsequent response assessment if fluorodeoxyglucose (FDG) is avid at baseline.^{7,60,61} Since uptake in extranodal sites can vary by extranodal location and lesional size, it is anticipated that baseline scans may be used more often in the future to determine whether PET is the most appropriate modality for response assessment. Gastric EMZL/MALT lymphomas show variable FDG avidity, with reported rates of 50%–60%.⁵⁹ A retrospective study reported inferior overall survival (OS) and a higher incidence of HGT in gastric EMZL/MALT lymphoma when standardised uptake value was ≥ 10 .⁶² PET may therefore be considered when HGT is suspected.

There is a lack of consensus on the best staging classification for gastrointestinal MALT lymphoma. The 1994 Lugano classification⁶³ is most widely used in the UK but is based primarily on imaging, while the modified Ann-Arbor staging system^{64,65} takes into account depth of infiltration and distant lymph node involvement. The more recent Paris staging involves a TNM system using the same principles.⁶⁶ Table 5 compares the three staging systems.

Non-gastric EMZL/MALT lymphoma

Non-gastric EMZL/MALT lymphomas involving the ocular adnexa, skin, lung, salivary gland, thyroid and breast have site-specific genetic profiles that may affect prognosis, in addition to the potential for organ-specific clinical considerations.⁶⁸ Concomitant autoimmune disease is reported to

TABLE 5 Comparison of staging systems for gastrointestinal EMZL/MALT lymphoma.

Ann Arbor modified staging ^{64,65,67}	Paris staging ⁶⁶	Tumour/lymphoma extent	Lugano staging (1994) ⁶³
	TX	Lymphoma extent not specified	
	T0	No evidence of lymphoma	
Stage IIE	T1m N0M0	Mucosa	Stage I
	T1sm N0M0	Submucosa	
Stage I2E	T2 N0M0	Muscularis propria	
	T3 N0M0	Serosa but not adjacent structures	
	T4 N0M0	Invasion of adjacent structures	Stage II
Stage III1E	T1-4 N1M0A165402	Regional LNs	II1 = Regional LNs
Stage II2E	T1-4 N2M0	Distant intraabdominal LNs	II2 = Distant intraabdominal LNs
			III = invasion of adjacent structures
Stage III3E	T1-4 N3M0	Extra-abdominal LNs	Stage IV
Stage IV	T1-4 N0-3M1	Distant (non-contiguous) GI sites	
	B1	Bone marrow involvement	

Abbreviations: EMZL, extranodal marginal zone lymphomas; GI, gastrointestinal; LN, lymph node; MALT, mucosa-associated lymphoid tissue.

be more frequent in non-gastric than gastric EMZL/MALT lymphomas, but the prognostic impact is unknown.⁶⁹

Diagnosis and staging should be tailored to the site involved and include testing for underlying infectious or autoimmune causes (Table 6).

Splenic marginal zone lymphoma

SMZL involves the spleen, splenic and hilar nodes, bone marrow and frequently the peripheral blood as villous lymphocytes,²³ and can present as isolated lymphocytosis. Cytopenias occur in 25% and are related to hypersplenism and less commonly to auto-antibodies or marrow infiltration.^{2,75} Aside from splenic hilar nodal enlargement, lymphadenopathy and other organ involvement are rare at diagnosis.⁷⁶

Work-up investigations include testing for associated autoimmune phenomena, which occur in ~20%, and testing for hepatitis C. Proposed investigations are summarised in Table 4.

Nodal marginal zone lymphoma

The majority of patients with NMZL present with disseminated, albeit often non-bulky nodal disease,⁷⁷ without splenic or extranodal involvement. Bone marrow involvement is evident in one third of cases.⁴¹ Peripheral blood involvement is very rare.⁷⁸ All patients should undergo computed tomography (CT) or PET/CT staging, which is also helpful to exclude nodal dissemination of EMZL/MALT, which occurs in one

third of EMZL/MALT cases.⁷⁸ HGT occurs at ~1% per year and conveys an inferior OS.⁷⁹

FIRST-LINE MANAGEMENT

Localised gastric EMZL/MALT

The strong aetiopathogenic link with *H. pylori* makes eradication therapy with a PPI and two antibiotics (triple therapy) the mainstay of first-line therapy in gastric EMZL/MALT, irrespective of disease stage and *H. pylori* status. The NICE recommendation (CG184)⁸⁰ is a 7-day, twice-daily course of PPI given with amoxicillin and either clarithromycin or metronidazole. In patients allergic to penicillin or with previous exposure to clarithromycin, quadruple therapy for 7 days with twice-daily PPI, bismuth, metronidazole and tetracycline is recommended. European guidelines (Maastricht VI/Florence consensus) recommend 14-day clarithromycin-based triple therapies on the basis of an increased cure rate without significantly increased side effects compared to 7-day regimens.^{54,81} The importance of adhering to treatment to improve successful eradication should be explained to patients. Antibiotic therapy should be considered even when evidence of *H. pylori* is lacking, to cover false negative cases and other *Helicobacter* species.⁸² A meta-analysis of published studies reported an overall pooled CR rate of 29.3% in *H. pylori*-negative cases.⁵³

Response to the first-line *H. pylori* eradication should be assessed with a stool antigen test or urea breath test ≥6 weeks after starting eradication and ≥2 weeks after stopping PPI.⁵¹

TABLE 6 Non-gastric EMZL/MALT: staging, associated conditions and antibiotic therapy.

Site (frequency)	Site-specific staging and additional evaluations ^{7,70}	Associated autoimmune condition/pathogen	First-line antibiotic regimen; reported response rate	Response assessment
Ocular adnexa (13%)	<ul style="list-style-type: none"> CT or MRI orbits Ophthalmology examination PCR for <i>C. psittaci</i> on tumour biopsy, peripheral blood mononuclear cells, conjunctival swabs Anti-SSA and anti-SSB antibodies 	Sjögren syndrome (lacrimal gland MZL) <i>C. psittaci</i>	Doxycycline 100 mg BD for 21 days; up to 65% ⁷¹⁻⁷³	3 months ⁷⁰ Reported range 3–36 months ^{7,71}
Skin (9%)	<ul style="list-style-type: none"> PCR tumour biopsy 	<i>Borrelia burgdorferi</i>	Ceftriaxone 2 g/day for 14 days; case reports only ^{72,74}	-
Lungs (9%)	<ul style="list-style-type: none"> Bronchoscopy and bronchoalveolar lavage 	Lymphocytic interstitial pneumonia <i>Achromobacter xylosoxidans</i>	-	-
Salivary glands (8%)	<ul style="list-style-type: none"> ENT examination US or CT or MRI Anti-SSA and anti-SSB antibodies 	Sjögren syndrome	-	-
Breast (3%)	<ul style="list-style-type: none"> Mammography and US MRI 	-	-	-
Thyroid (2%)	<ul style="list-style-type: none"> Ultrasound CT scan of the neck Thyroid function tests 	Hashimoto thyroiditis	-	-

Abbreviations: CT, computed tomography; EMZL, extranodal marginal zone lymphomas; ENT, ear nose and throat; MALT, mucosa-associated lymphoid tissue; MRI, magnetic resonance imaging; MZL, marginal zone lymphoma; PCR, polymerase chain reaction; US, ultrasound.

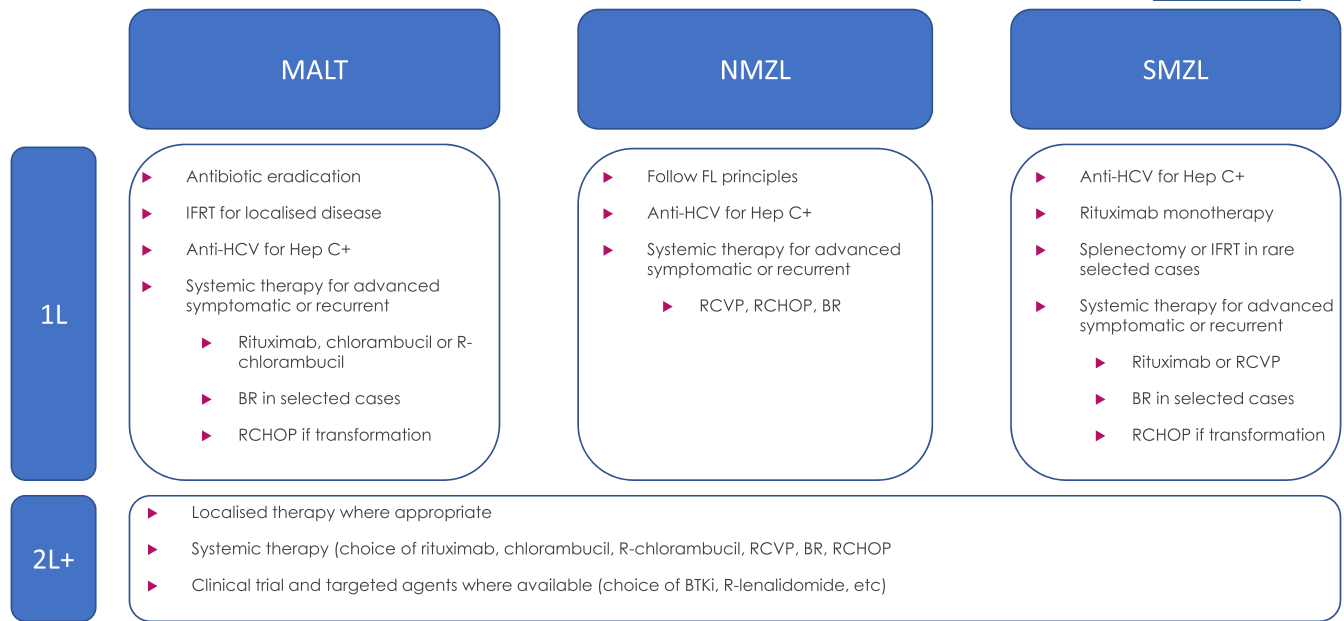


FIGURE 1 Summary and recommendations for marginal zone lymphomas. FL, follicular lymphoma; IFRT, involved field radiotherapy; MALT, mucosa-associated lymphoid tissue; NMZL, nodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma.

Late responses up to a year after treatment are reported, and ~62% achieve a CR 12 months after *H. pylori* eradication.⁸³ Eradication is less effective in the presence of t(11;18) (q21;q21), when disease extends through the gastric serosa, or where there is perigastric lymph node involvement.⁸⁴ After successful eradication therapy, a positive serology result may persist for up to 2 years, consistent with the previous infection; follow-up serology is therefore unhelpful to confirm *H. pylori* eradication. Second-line therapy is recommended for patients with a persistent positive result. Non-responding patients may be resistant to clarithromycin, and samples should be sent for culture and antibiotic sensitivity.

In both *H. pylori*-positive and -negative cases, repeat OGD with multiple biopsies and comparison with previous biopsies is recommended at 3–6 months to assess response. Management thereafter is guided by OGD findings, symptoms and adverse signs such as deep invasion, overt progression, bulk or impending organ damage (Figure 1). Persistent clonality following *H. pylori* eradication is an acceptable outcome and can be monitored,⁸⁵ as well as presence of microscopic disease in the absence of symptoms and endoscopic findings.⁸⁶ The Groupe d'Etude des Lymphomes de l'Adulte (GELA) scoring system^{87,88} may be helpful to document histological response when diagnostic biopsies are available for comparison (Table 7).

Radiotherapy (RT) is indicated for stage I/IIe gastric EMZL/MALT lymphoma that has failed to respond to or relapses after *H. pylori* eradication and in the presence of overt progression, deep invasion, lymphadenopathy or presence of t(11;18).^{89–92} This is highly successful, with reported histological complete responses of 95%–100% on endoscopic follow-up.^{93–95} Involved-site radiotherapy (ISRT) should include the entire stomach and, if involved, adjacent lymph nodes. Treatment should be given with an empty stomach

and planned with an advanced technique such as intensity modulation to minimise radiation dose to the heart, liver and kidneys.^{95–98}

While most studies have included patients treated with ≥ 30 Gy, a recent series shows that 24 Gy is likely to be adequate⁹⁷ and unlikely to cause significant acute toxicity. With appropriate RT planning, the dose delivered to critical structures can be kept well below organ tolerance, reducing the risk of long-term complications.

Systemic therapy, together with *H. pylori* eradication, is indicated for first-line management of patients with advanced stage gastric EMZL/MALT if they are symptomatic, have deeply invasive disease, tumour bulk or impending organ damage. Systemic therapy treatment is discussed in Section “Management of relapsed MZL”.

The prognosis of gastric EMZL/MALT lymphoma is excellent, with 5-year survival exceeding 90% and 75%–80% 10-year survival. The EMZL/MALT international prognostic index (IPI) is prognostic in both gastric and non-gastric EMZL/MALT. It defines three prognostic categories based on age >70 years, Ann Arbor stage III/IV and elevated lactate dehydrogenase (LDH) with 0, 1 or ≥ 2 risk factors predicting 5-year event-free survival of 70%, 56% and 29% respectively.⁹⁹

In a study of 1408 gastric EMZL/MALT patients by Zullo et al., the annual recurrence rate was 2.2%. Due to a small increased risk of gastric cancer in patients with gastric EMZL/MALT lymphoma,^{100,101} long-term follow-up with clinical examination, blood counts and OGD is recommended for surveillance of second cancers, including patients achieving complete lymphoma remission. Although the optimal follow-up interval is not defined, follow-up every 12–18 months under gastroenterology services is recommended, in line with EGILS and ESMO guidelines.^{51,102}

TABLE 7 GELA histological grading system for post-treatment evaluation of gastric EMZL/MALT lymphoma.

Score	Lymphoid infiltrate	LEL	Stromal changes
Complete histological remission (CR)	Absent or scattered plasma cells and small lymphoid cells in the LP	Absent	Normal or empty LP and/or fibrosis
Probable minimal residual disease (pMRD)	Aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM	Absent	Empty LP and/or fibrosis
Responding residual disease (rRD)	Dense, diffuse or nodular, extending around glands in the LP	Focal LEL or absent	Focal empty LP and/or fibrosis
No change (NC)	Dense diffuse or nodular	Present 'may be absent'	No changes

Abbreviations: EMZL, extranodal marginal zone lymphomas; GELA, Groupe d'Etude des Lymphomes de l'Adulte; LP, lamina propria; MALT, mucosa-associated lymphoid tissue; MM, muscularis mucosa; SM, submucosa.

Localised non-gastric EMZL/MALT

Unlike primary gastric EMZL/MALT lymphoma, less is known about the value of antibiotic therapy in non-gastric EMZL/MALT lymphoma. In patients with localised ocular adnexal EMZL/MALT where a causative organism has been identified, antibiotic therapy can be considered (Table 6). Doxycycline in *C. psittaci*-negative cases can cause disease regression in some cases and can be considered in first-line management of ocular adnexal EMZL/MALT,^{71–73} with a reported overall response rate (ORR) of 45%–65%.⁷⁴ In other non-gastric EMZL/MALT lymphomas where a causative agent has been identified, for example *Borrelia burgdorferi* in cutaneous EMZL/MALT lymphoma, evidence is limited to case reports, and routine use of antibiotics is not recommended. The median time-to-response after antibiotics is 6 months, but it may be up to 36 months. Patients with hepatitis C-associated EMZL/MALT lymphoma should receive initial treatment with anti-viral therapy, which may lead to regression of disease and improved outcomes.¹⁰³ Patients with non-gastric EMZL/MALT lymphoma who have completed treatment can be evaluated every 3 months for the first 2 years and every 6 months thereafter.⁷

Less than 5% of patients develop extra-cutaneous disease¹⁰⁴ and bone marrow involvement is extremely rare.¹⁰⁵ For this reason, routine bone marrow examination is not recommended for clinical staging.¹⁰⁶ Where *B. burgdorferi* infection is endemic, PCR on a skin biopsy should be performed. Initial treatment of localised disease, in the absence of *B. burgdorferi*, is either involved lesion RT for T1 disease (solitary skin involvement¹⁰⁷) or surgical excision.¹⁰⁸ 24 Gy is recommended for curative treatment of primary cutaneous marginal zone lymphoma based on randomised trial data.¹⁰⁹ For T2 disease (regional skin involvement), with a small number of lesions, treatment for each individual lesion may also be beneficial.¹⁰⁸ Where multiple lesions are present, a 'watch and wait' approach may be adopted, with treatment of symptomatic lesions with low doses of RT (4 Gy), rituximab or single agent or combination chemotherapy.¹⁰⁶

RT offers excellent treatment for localised disease where regression is not achieved with antibiotic therapy. Moderate doses achieve excellent outcomes in EMZL/MALT, with 24 Gy now considered the standard of care based on the

results of a large, randomised phase III trial.^{109,110} Response rates exceed 90%, in-field recurrences are rare, and most patients are cured.^{111–113} A recent published phase II trial of involved field RT for localised non-gastric EMZL/MALT lymphoma reported 5-year progression-free survival (PFS) and OS of 79% and 95% respectively.¹¹⁴ Low-dose RT (4 Gy in two fractions) is also an option for Sjogren's-associated parotid EMZL/MALT lymphoma^{115,116} and ocular EMZL/MALT lymphoma when there is concern about the risk of cataract or dry eye.

Randomised data comparing RT to surgery, immunotherapy or surveillance are lacking, but several retrospective studies have demonstrated that patients treated with first-line RT have better outcomes, including OS.^{91,111} A randomised study investigating the addition of adjuvant chemotherapy to RT for parotid EMZL did not show benefit.¹¹⁷

Advanced stage gastric, non-gastric EMZL/MALT and NMZL

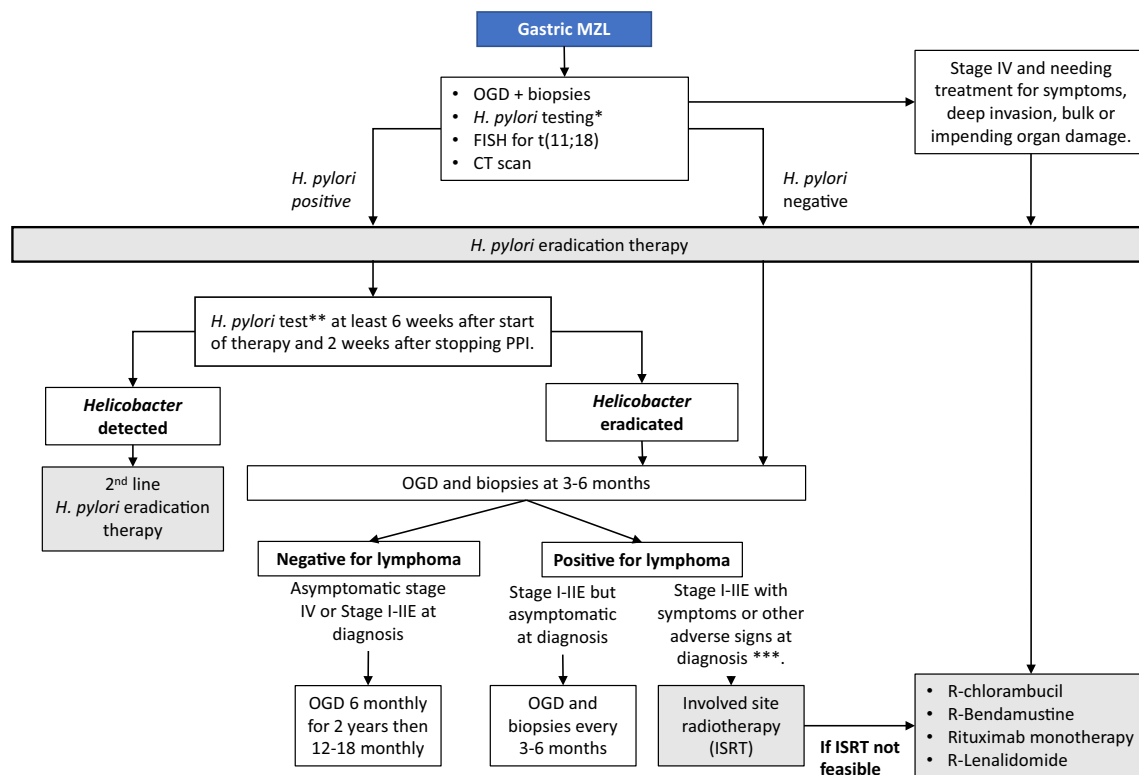
Advanced stage EMZL/MALT lymphoma is incurable, and for asymptomatic patients, a 'watch and wait' approach is appropriate. EMZL, when it disseminates, favours other extranodal sites rather than lymph nodes (Figure 2).

RT can provide rapid and effective palliation for patients with advanced EMZL/MALT and symptomatic local sites. Very low doses (e.g. 4 Gy) produces good local control with minimal to no toxicity^{96,110,118} and can be repeated.

Systemic therapy is indicated for patients with symptomatic, advanced disease, after failure of antibiotics or RT, or where there is evidence of HGT.

The randomised IELSG-19 trial comparing rituximab, chlorambucil and rituximab–chlorambucil is the largest study in EMZL/MALT lymphoma, involving 454 patients. Rituximab–chlorambucil was more effective than monotherapy (EFS not reached vs. 5.1 years for chlorambucil and 5.6 years for rituximab),¹¹⁹ but did not improve OS. Treatment with rituximab plus chlorambucil is reasonable for elderly and frail patients; monotherapy of each can also be offered if combination therapy is not well tolerated.

The phase II MALT2008-01 trial reported efficacy for bendamustine–rituximab (BR) in gastric and non-gastric



*Faecal antigen testing (and/or a carbon-13 urea breath test), serology and immunohistochemistry.

** Faecal antigen or Carbon-13 urea breath test.

*** These include overt progression, deep invasion, lymphadenopathy and presence of t(11:18).

FIGURE 2 Diagnosis and management for gastric marginal zone lymphomas. CT, computed tomography; FISH, fluorescence in situ hybridisation; OGD, oesophago-gastro-duodenoscopy.

EMZL/MALT. ORR was >85% and the estimated 5-year OS was 85.6%,¹²⁰⁻¹²² with added scope to limit treatment to 4 cycles in patients achieving complete remission (CR). In clinical practice, the choice of BR must balance efficacy against higher toxicity, especially in older and/or comorbid patients.

Two phase II trials from the same group evaluated RCVP (rituximab–cyclophosphamide–vincristine–prednisolone) in EMZL/MALT and NMZL. Reported 3-year PFS was 59% for RCVP without maintenance¹²³ and 81% for RCVP with maintenance rituximab (375 mg/m² every 8 weeks for up to 12 cycles).¹²²

A subanalysis of previously untreated MZL patients enrolled in the phase III GALLIUM trial showed no improvement in outcomes for obinutuzumab compared to rituximab combinations, and obinutuzumab was also more toxic than rituximab.¹²⁴ Obinutuzumab-chemotherapy is therefore not recommended for the treatment of MZL. Table 8 summarises frontline studies in EMZL/MALT.

EMZL/MALT lymphoma involving CNS

Due to its rarity, therapy for CNS MZL is not standardised. ISRT or ISRT plus whole brain radiotherapy (WBRT) to 24–30 Gy is most common, especially for dural tumours^{15,134} and achieves excellent long-term disease

control^{10,11,14,15,134-136} even in the presence of concomitant leptomeningeal disease.¹³⁵ Doses of 30–36 Gy produce high CR rates and low neurotoxicity,^{14,135} with outcomes similar to chemotherapy alone and combined chemoradiotherapy.¹⁵ However, as this is an indolent lymphoma, lower doses (e.g. 24 Gy) may also be very effective and significantly less toxic.^{109,110} The decision to use ISRT or WBRT depends on the site and number of lesions.

Treatment of dural EMZL/MALT with systemic high-dose methotrexate (HD-MTX) and non-HD-MTX regimens are reported¹¹ but combined chemoradiotherapy carries a high risk of neurotoxicity¹³⁷ and is neither necessary nor recommended.

Chemotherapy may be preferred for rare patients presenting with secondary CNS MZL. The literature includes cases treated with BR,^{138,139} RCHOP, followed by maintenance rituximab¹⁴ and R-ibrutinib.¹⁴⁰ The efficacy of rituximab monotherapy is uncertain.¹³⁹

Patients with CNS MZL need long-term surveillance due to an increased risk of late disease recurrence.¹³⁵

Splenic marginal zone lymphoma

SMZL patients with hepatitis C infection should receive up-front anti-viral therapy.^{103,141}

TABLE 8 Summary of frontline studies in MZL.

MZL subtype	Study (reference)	Treatment	No. patients	ORR, CR (%)	PFS/EFS (years)	OS (years)
All subtypes	GALLIUM ¹²⁵	R-chemo	66	81, 19	PFS 75% (3 years)	Not reported
		O-chemo	61	83, 16	PFS 78% (3 years)	
		(Both arms with maintenance)	68		(ns)	
	BRIGHT ¹²⁶	BR	28	92, 20	Not reported	Not reported
		RCHOP/RCVP	18	71, 24 (ns)		
	STIL NHLI ¹²⁷	BR	37	93, 40	Median 57 months	Not reported
RCHOP		30	91, 30 (ns)	Median 47 months (ns)		
EMZL/MALT	MALT 2008-01 ¹²⁸	BR	57	100, 75	93% (7 years)	96% (7 years)
	IELSG38 ^{129,130}	R-chlorambucil + maintenance	112	95, 69 (after 1 year of maintenance)	87% (5 years)	93% (5 years)
		R	138	78, 56	EFS 50% (5 years)	90% (5 years)
		Chlorambucil	131	86, 63	EFS 51% (5 years)	
	Oh et al. ¹²²	R-Chlorambucil	132	95, 79	EFS 68% (5 years)	PFS 72% (5 years)
		RCVP + maintenance	30	93, 44	PFS 81% (3 years)	90% (3 years)
Kang et al. ¹²³	RCVP	28	88, 60	PFS 59% (3 years)	83% (4 years)	
SMZL	MAINTAIN ¹³¹	BR	61	91, 19	Median 92 months	86% (6 years)
		BR + maintenance	59		Not reached (p=0.008)	92% (6 years) (ns)
	BRISMA ¹³²	BR	56	91, 73	PFS 90% (3 years)	96% (3 years)
	Kalpadakis et al. ¹³³	Rituximab + maintenance	76	92, 65	79% (5 years)	93% (5 years)
NMZL	MAINTAIN ¹³¹	BR	61	91, 19	Median 92 months	86% (6 years)
		BR + maintenance	59		Not reached (p=0.008)	92% (6 years) (ns)
	Oh et al. ¹²²	RCVP + maintenance	15	93, 44	PFS 81% (3 years)	90% (3 years)
	Kang et al. ¹²³	RCVP	12	88, 60	PFS 59% (3 years)	83% (4 years)

Abbreviations: CR, complete remission; EFS, event-free survival; EMZL, extranodal marginal zone lymphoma; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SMZL, splenic marginal zone lymphoma.

Many patients are asymptomatic and can be monitored at 3–6 monthly intervals. Perrone et al. reported a median time-to-first-treatment of 58.5 months, and at 10 years, 30% of patients remained untreated.¹⁴² The main criteria for treatment include constitutional symptoms, symptomatic or progressive splenomegaly, bulky lymphadenopathy, autoimmune phenomena and progressive cytopenias,⁷⁶ as shown in Table 9.

There are no published randomised trials of treatment for SMZL. Systemic therapy options for symptomatic patients include rituximab monotherapy, immunochemotherapy and splenectomy, based on a few small prospective phase II trials.¹³²

Rituximab monotherapy, 375 mg/m² weekly for 6 weeks followed by 2 monthly maintenance for 1 year, is well tolerated and has achieved durable responses in retrospective data series. In the largest retrospective study of 106 patients, outcomes postinduction were 92% ORR and 44% CR.

TABLE 9 Indications for treatment in SMZL and NMZL.

Symptoms and signs
B symptoms (weight loss >10% in <6 months, fever, drenching sweats)
Progressive cytopenia
Symptomatic splenomegaly (for SMZL)
Compromised vital organs or bulky disease

Abbreviations: NMZL, nodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma.

Ten-year PFS and OS rates were 64% and 85% respectively.¹³³ As results are comparable to the largest retrospective series of 100 SMZL patients undergoing splenectomy (median PFS 8 years and 10-year OS 67%),¹⁴³ rituximab has largely surpassed splenectomy in modern practice. Splenectomy may still have a role in managing fit patients with a large

spleen and minimal bone marrow disease or lymphadenopathy.¹⁴⁴ A splenectomy should be performed after appropriate vaccinations.

Immunochemotherapy combining rituximab with CVP, CHOP and bendamustine has shown ORR and OS similar to rituximab monotherapy.^{145–147} In the BRISMA/IELSG36 involving 56 SMZL patients, ORR was 91% and CR 73%, with a 3-year PFS of 90% and a 3-year OS of 96%. Although highly effective, 25% of patients had a serious adverse event.^{132,148} A large, retrospective observational study of 317 older, symptomatic patients showed no significant OS benefit of BR versus rituximab monotherapy.^{149,150} Taken together, the evidence suggests that BR should be reserved for fitter/younger patients.

The MAINTAIN randomised phase III trial demonstrated a PFS advantage for maintenance rituximab when given to SMZL and NMZL patients responding to induction BR or RCVP; PFS 92.2 months in the observation arm vs. not reached in the maintenance arm (HR 0.35, $p = 0.008$). No difference in OS at 6 years was observed.¹³¹

For patients unfit for systemic therapy or splenectomy, RT can provide rapid, effective palliation leading to a significant reduction of splenic size and pain, even with very low dose schedules of 4–10 Gy. A higher 24 Gy dose may provide more durable control but carries a greater risk of cytopenias during and after RT.^{151–153} A full blood count should be monitored weekly during treatment.

The choice of tools used for response assessment in SMZL depends upon the results of staging investigations (Table 10).

MANAGEMENT OF RELAPSED MZL

MZL is an incurable malignancy, and although initial therapy often leads to long remissions, relapse is common, especially with advanced stage presentation. Early progression within 24 months of initial systemic therapy (POD24) is unusual but associated with inferior survival.¹⁵⁴

Treatment for relapsed MZL follows a similar paradigm to relapsed/refractory follicular lymphoma,¹⁵⁵ including RT for localised relapse and active surveillance for asymptomatic, advanced stage relapse. Standard immunochemotherapy produces ORR of 85%–93% and CR in 54%–78% of cases, with no specific therapeutic strategies for POD24 patients.¹⁵⁶ Based on the randomised IELSG-19 trial, less intensive therapy consisting of rituximab (R) monotherapy or R-chlorambucil offers excellent disease control for EMZL/MALT that has persisted after local therapy, with outcomes similar to those of first-line treated patients.¹¹⁹ There is limited evidence that rituximab monotherapy can be effective for relapsed/refractory SMZL, including those who have progressed after rituximab monotherapy or splenectomy.¹⁵⁷ BR is active in small subgroups analysed alongside other low-grade B-cell lymphomas,^{158,159} achieving ORR > 80%, but with significant grade 3–4 haematological toxicity and an increased risk of secondary malignancy.¹⁶⁰

Although chemotherapy can be effective, many patients are older or have comorbidities, leading to unacceptable

TABLE 10 Response criteria SMZL (Adapted from Ref. [7]).

Complete response	Resolution of splenomegaly (spleen length <13 cm) Resolution of cytopenias, with Hb >120 g/L, platelets >100 × 10 ⁹ /L, neutrophils >1.5 × 10 ⁹ /L No evidence of clonal B-cell population in peripheral blood by flow cytometry No evidence of bone marrow infiltration by immunohistochemistry No residual FDG-avid disease above background by PET (if positive at pretreatment assessment)
Partial response	≥50% Regression of measurable disease No new sites of disease 10%–99% Improvement of cytopenias 10%–99% Reduction of bone marrow infiltration
Stable disease/no change	≤10% Improvement in disease parameters
Progressive disease	>10% Increase in measurable disease from nadir or best response
Progressive disease	Reappearance of any measurable disease

Abbreviations: FDG, fluorodeoxyglucose; PET, positron emission tomography.

toxicities. This has generated interest in targeted, non-chemotherapy agents.

Bruton tyrosine kinase (BTK) plays a critical role in MZL pathogenesis, and several covalent BTK inhibitors (cBTKi) are approved for relapsed/refractory MZL. The pivotal PCYC-1121 phase II trial of ibrutinib monotherapy in 63 patients with a median of 2 prior lines demonstrated an ORR of 58%, a median duration of response (DOR) 27.6 months and a median PFS 15.7 months at 33 months.¹⁶¹ Responses were observed across all MZL subtypes, and exploratory analysis demonstrated an association between NF-κB pathway gene mutations and improved outcomes.

In the MAGNOLIA trial, zanubrutinib monotherapy (a second-generation selective cBTKi) demonstrated ORR 68.2% and CR 25.8%, 12-month DOR 93.0% and 15-month PFS 82.5%, leading to FDA and EMA approval in relapsed/refractory MZL after prior anti-CD20 treatment. Patients aged ≥75 years (ORR 94%) and those refractory to last therapy (ORR 67%) also benefitted. Zanubrutinib has a favourable safety profile; common adverse events include diarrhoea (22.1%), bruising (20.6%) and constipation (14.7%). Atrial fibrillation/flutter and grade 3 hypertension are rare.¹⁶² These data suggest an important emerging role for zanubrutinib in relapsed/refractory MZL. A recently published pilot study demonstrated the activity of acalabrutinib in relapsed/refractory MZL. Other BTK is under investigation include the reversible, non-covalent BTKis pirtobrutinib¹⁶³ and MK-1026 (NCT03162536).¹⁶⁴

Lenalidomide–rituximab (R2) was FDA-approved for relapsed/refractory MZL based on the randomised AUGMENT and MAGNIFY trials.¹⁶⁵ In the MZL subset of AUGMENT ($n = 63$), adding lenalidomide to rituximab improved ORR

TABLE 11 Summary of standard and targeted treatments for relapsed and refractory MZL.

Study	Treatment	Subtypes, setting	Patients	ORR %	CR %	PFS/EFS, median months or %
Conconi et al. (2003) ¹⁷¹	Rituximab	EMZL/MALT r/r	11	45	36	-
Salar et al. (2017) ¹²⁸	R-bendamustine	EMZL/MALT de novo + r/r	60	100	75	EFS 88% at 84 months PFS 93% at 84 months
Rummel et al. (2005) ¹⁵⁸	R-bendamustine	EMZL/MALT r/r	6	83	67	-
Kiesewetter et al. (2014) ¹⁵⁹	R-bendamustine	EMZL/MALT r/r	14	92	71	-
Murukami et al. (2021) ¹⁵⁷	R-bendamustine	All r/r	6	92 ^a	65 ^a	-
Vannata et al. (2021) ¹⁷²	Bendamustine + ofatumumab	All r/r	16	93	57	PFS 33 months
Noy et al. (2020) ¹⁷³	Ibrutinib	All r/r	63	48	3	PFS 15.7 months
Opat et al. (2021) ¹⁶²	Zanubrutinib	All r/r	68	68	26	PFS 82% at 15 months
Vanazzi et al. (2014) ¹⁷⁴	90Y-ibritumomab tiuxetan	EMZL/MALT r/r	30	90	77	Not reached
Lolli et al. (2020) ¹⁷⁵	90Y-Ibritumomab tiuxetan	EMZL/MALT de novo + r/r	16	94	63	PFS 37.3 months
Kiesewetter et al. (2019) ¹⁷⁶	Lenalidomide	EMZL/MALT de novo + r/r	16	69	38	-
Kiesewetter et al. (2017) ¹⁷⁷	Lenalidomide + rituximab	EMZL/MALT de novo + r/r	46	80	54	-
Leonard et al. (2019) ¹⁶⁶	Lenalidomide + rituximab	All r/r	63	65	29	PFS 20 months
Jacobson et al. (2020) ¹⁷⁸	Axicabtagene ciloleucel	All r/r	14	86	71	-
Jurczak et al. (2018) ¹⁶⁷	Tafasitamab	All r/r	9	33	18 ^a	NR at 21 months median follow-up ^a
Conconi et al. (2014) ¹⁷⁹	Everolimus	All r/r	30	25	3	PFS 14 months
Kirschbaum et al. (2011) ¹⁸⁰	Vorinostat	All r/r	9	22	11	PFS 18.8 months
De Vos et al. (2009) ¹⁸¹	R-bortezomib	All r/r	11	67	-	-
Conconi et al. (2011) ¹⁸²	Bortezomib	EMZL/MALT r/r	32	48	31	PFS 25 months
Andorsky et al. (2019) ¹⁸³	Entospletinib	All r/r	17	18	0	-

Abbreviations: CR, complete remission; EFS, event-free survival; EMZL, extranodal marginal zone lymphoma; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; ORR, overall response rate; PFS, progression-free survival; r/r, relapsed or refractory; NR, not reached.

^aShowing results for all low-grade B-NHL histologies.

(65% vs. 44%) but not PFS compared to rituximab alone. Infections (63% vs. 49%), neutropenia (58% vs. 23%) and skin reactions (32% vs. 12%) were more common in R2-treated patients.¹⁶⁶ R2 is not yet approved for relapsed/refractory MZL in the United Kingdom or European Union.

Tafasitamab, an anti-CD19-directed humanised monoclonal antibody, has modest activity in relapsed/refractory MZL¹⁶⁷ and is undergoing phase III investigation in combination with lenalidomide-rituximab (NCT04680052).¹⁶⁸ Several small molecules inhibiting HDAC, proteasome, mTOR and SYK have also demonstrated modest activity in MZL (Table 11).

Chimeric antigen receptor T-cell therapy with axicabtagene ciloleucel has demonstrated activity in relapsed/refractory MZL, but with high rates of cytokine release syndrome and neurotoxicity compared to FL and less durable responses.¹⁶⁹ CD3-CD20 bispecific antibodies may also be active in MZL, but the data are immature.

Autologous stem-cell transplantation (ASCT) has a role in selected patients.¹⁷⁰ A historic series (1994–2003) of 199 patients (median age 56 years, median prior lines 2 and 71% rituximab-exposed) reported 5-year EFS and OS rates of

53% and 73% respectively. ASCT can be considered for chemosensitive relapsed MZL in selected fit patients, but benefits should be weighed against the availability of alternative novel approaches.

Finally, it should be noted that phosphoinositide 3-kinase (PI3Ki) inhibitors are active in relapsed/refractory MZL, but due to their significant toxicity, they are no longer in clinical development or licensed for use.

TRANSFORMED DISEASE

HGT, typically to DLBCL, occurs in 3%–20%, with a median time of 3.7 years from MZL diagnosis to HGT.¹⁸⁴ A large single-centre retrospective study of 564 biopsy-proven cases from 1990 to 2016, including mostly EMZL/MALT cases (86%), identified elevated LDH and failure to achieve CR as independent predictors of HGT.⁷⁹ HGT was associated with inferior survival (5-year OS 65% for HGT vs. 86% without HGT, $p < 0.001$), especially if occurring within 12 months of diagnosis (4-year OS 43% vs. 81% for HT >12 months, $p < 0.001$). If suspected, PET-CT may be helpful to identify a

suitable biopsy site for diagnostic confirmation. Treatment follows similar management principles as for transformed FL.

SUPPORTIVE CARE AND PATIENT INFORMATION

All patients should be advised on importance of being physically active, exercise and healthy eating.

All patients should be offered annual flu and COVID-19 vaccination (with frequency as specified by present recommendations <https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a>, alert patients that vaccinations have reduced efficacy after rituximab and possibly also BTK inhibitors). Splenectomised patients should be offered specific prophylaxis: <https://www.gov.uk/government/publications/immunisation-of-individuals-with-underlying-medical-conditions-the-green-book-chapter-7>. Patient with recurrent infections and low immunoglobulin levels should be reviewed by an immunologist.

Lymphoma Action <https://lymphoma-action.org.uk/>, Blood Cancer <https://bloodcancer.org.uk/>, <https://www.macmillan.org.uk>, <https://www.maggies.org/> and other groups provide valuable personalised support to newly diagnosed patients and throughout their lymphoma journey. Patients should be involved in shared decision making to guide their management <https://www.nice.org.uk/guidance/ng197>. For the information on specific regimens refer patients to <https://www.macmillan.org.uk> and <https://lymphoma-action.org.uk/>.

Patients should provide written informed consent for treatment using the dedicated systemic anticancer therapy (SACT) consent form (https://www.cancerresearchuk.org/health-professional/treatment-and-other-post-diagnosis-issues/consent-forms-for-sact-systemic-anti-cancer-therapy#sact_consent5) or equivalent local document.

SUMMARY AND RECOMMENDATIONS

Diagnosis

Histomorphology and a panel of IHC markers should be used for diagnosis of EMZL/NMZL (A1).

SMZL can usually be diagnosed by a combination of morphology and flow cytometry on peripheral blood and marrow aspirate/trephine biopsy histology/IHC (A1).

Work up and staging

Staging should include full body CT with contrast (B1).

PET-CT can be considered in cases where RT is planned for early stage disease and to investigate suspected high-grade transformation (C1).

Bone marrow biopsy is recommended for staging of NMZL and SMZL, and in cases of non-gastric EMZL/MALT to investigate cytopenias or confirm localised disease where RT is planned (B1).

Due to a low incidence of involvement, bone marrow examination is not routinely recommended for staging of gastric EMZL/MALT, except to investigate cytopenias (B1).

Initial work-up for patients with gastric EMZL/MALT should include oesophago-gastro-duodenoscopy (OGD). High-quality photography and detailed description of the site of lesions are advised for comparison over time; repeat OGD is recommended in the case of diagnostic uncertainty (A1).

FISH testing for t(11;18) (q21;q21) (fusion of BIRC3 and MALT1) is also recommended during initial work-up for gastric EMZL/MALT as the presence is a predictor of advanced disease and lower response to *H. pylori* eradication (B1).

Other imaging modalities (MRI, ultrasound and mammography) may be helpful for additional characterisation of non-gastric EMZL/MALT, according to disease site (B1).

DISEASE MANAGEMENT

Localised gastric EMZL/MALT

Helicobacter eradication therapy should be given to all patients at diagnosis, irrespective of stage and *H. pylori* infection status (A1).

Response to eradication therapy should be assessed by stool antigen test or urea breath test at least 6 weeks after starting eradication and at least 2 weeks after discontinuing PPI therapy (C1).

Patients with a persistent *H. pylori* infection should be offered second-line eradication therapy, ideally guided by results of repeat OGD and sample cultures for clarithromycin resistance (C1).

OGD and biopsies should be performed at 3–6 months to assess lymphoma response, with further management guided by symptoms, OGD findings and adverse signs (deep invasion, overt progression, bulky disease or impending organ damage); long-term OGD surveillance is recommended, the frequency is guided by degree of gastritis and atrophy (C1).

The GELA scoring system is recommended to document histological response (A1).

ISRT should be considered for patients with localised disease after eradication therapy if they are symptomatic or have adverse signs. 24 Gy in 12 fractions is recommended for treatment delivered with curative intent (B1).

Active monitoring and patient triggered follow-up is appropriate for patients with residual disease after eradication therapy if they are asymptomatic and have no adverse signs (B1).

OGD at 12- to 18-month intervals is recommended for surveillance for gastric carcinoma (C1).

Localised non-gastric MALT lymphoma

Anti-viral treatment is recommended in patients with active hepatitis C infection (B4).

Antibiotic therapy should be considered in first-line management of ocular adnexal EMZL/MALT (B3).

Routine antibiotics are not recommended in other non-gastric EMZL/MALT lymphomas in the absence of an identified causative organism (C5).

ISRT is recommended for localised non-gastric EMZL/MALT lymphoma (A3).

Advanced stage EMZL/MALT lymphoma, NMZL

H. pylori eradication and systemic therapy should be offered to patients presenting with symptomatic advanced stage disease, deep invasion, bulky disease or impending organ damage (C1).

Rituximab with chlorambucil are recommended first-line systemic treatment options; however, as there is no OS benefit, monotherapy can be offered especially to older/frailer patients or if combination is not tolerated (A1).

Bendamustine and rituximab (BR) is also effective but more toxic (A3).

RCVP is also effective and responding patients can be considered for maintenance rituximab if available (A3).

Obinutuzumab in combination with chemotherapy is not recommended for treatment of MZL (A1).

Low-dose RT (4 Gy in two fractions) can provide effective palliation for local symptomatic sites (B1).

CNS EMZL/MALT lymphoma

ISRT or ISRT + RT to a total dose of 24–30 Gy is recommended to treat dural EMZL/MALT lymphoma (C1).

Systemic HD-MTX- and non-HD-MTX-based therapy can be considered in selected cases, but HD-MTX-based chemotherapy followed by WBRT is unnecessarily toxic (C1).

Systemic chemotherapy with CNS-penetrating agents or targeted therapy such as a BTK inhibitor (if available) are options for patients with secondary CNS MZL (C1).

Long-term clinical active surveillance for late relapse is recommended (C1).

Splenic marginal zone lymphoma

Anti-viral treatment is recommended in patients with active hepatitis C infection (B2).

Asymptomatic SMZL patients can be actively monitored, including patient triggered follow-up (B1).

Rituximab monotherapy ± maintenance rituximab is recommended for symptomatic patients meeting criteria for treatment (B1).

BR, RCVP, rituximab + chlorambucil are alternative options for patients requiring systemic therapy, with choice depending on patient age, fitness and treatment goals (B2).

RCHOP should be used if there is a clinical suspicion of high-grade transformation (B2).

Splenectomy can be considered for patients with splenomegaly without significant bone marrow disease or lymphadenopathy (C2).

Splenic RT can be considered for frail symptomatic patients (C2).

Nodal marginal zone lymphoma

Treatment options depend on stage and patient fitness and broadly follow those for FL (B4).

Asymptomatic patients can be actively monitored (B1).

Immunochemotherapy is recommended for symptomatic advanced stage disease (B4).

CBL-MZL

CBL-MZL is usually indolent and should not be considered a manifestation of lymphoma unless progression occurs (C1).

After specialist assessment and appropriate patient education, patients can be monitored annually for primary care for symptoms and signs of splenomegaly and progressive cytopenias (C1).

Treatment of relapsed MZL

Active monitoring should be considered for asymptomatic patients with relapsed disease (any stage) (B1).

RT should be considered for patients with localised, symptomatic relapsed disease (B1).

Single-agent rituximab is an option for patients with symptomatic relapsed SMZL and EMZL/MALT who have previously achieved a durable response to rituximab monotherapy (B2).

Splenectomy is an option for selected patients with relapsed SMZL when rituximab monotherapy is ineffective or contraindicated (B2).

Immunochemotherapy is recommended for patients with symptomatic relapsed disease who are unsuitable for RT or rituximab monotherapy, relapsing <24 months after rituximab monotherapy, or with clinically suspected or histologically confirmed high-grade transformation (HGT) (B1).

Consolidation ASCT is an option for selected fit patients with MZL, and high-grade transformation had been ruled out for patients experiencing early relapse after immunochemotherapy (C2).

Targeted therapies, ideally within a clinical trial, should be offered to patients with multiply relapsed disease who are unsuitable for standard therapy. Licensed options, including ibrutinib, zanubrutinib, lenalidomide ± rituximab

are not funded in the UK at present but may be available on compassionate use programmes (B2).

Transformed disease

High-grade transformation is associated with elevated LDH, failure to achieve CR, FLIPI/IPI >2 and sheets of B-cell blasts. Wherever possible, the diagnosis must be histologically confirmed to guide management (B1).

AUTHOR CONTRIBUTIONS

Renata Walewska proposed this guideline and Chaired the Writing Group. All the authors contributed to the writing and revising of this guideline.

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CONFLICT OF INTEREST STATEMENT

All authors have made a full declaration of interests to the BSH and Task Force Chairs, which may be viewed on request.

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REFERENCES

1. Nemazee D. Natural history of MZ B cells. *J Exp Med.* 2021;218(4):e20202700.

2. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia.* 2022;36(7):1720–48.
3. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of mature lymphoid neoplasms: a report from the Clinical Advisory Committee. *Blood.* 2022;140(11):1229–53.
4. Smith A, Crouch S, Lax S, Li J, Painter D, Howell D, et al. Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network. *Br J Cancer.* 2015;112(9):1575–84.
5. Cerhan JR, Habermann TM. Epidemiology of marginal zone lymphoma. *Ann Lymphoma.* 2021;5:5.
6. NICE. Haematological cancers: improving outcomes, NICE Guideline [NG47]; 2016.
7. Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2020;31(1):17–29.
8. Mendes LST, Attygalle AD, Wotherspoon AC. *Helicobacter pylori* infection in gastric extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma: a re-evaluation. *Gut.* 2014;63(9):1526–8.
9. Tu PH, Giannini C, Judkins AR, Schwalb JM, Burack R, O'Neill BP, et al. Clinicopathologic and genetic profile of intracranial marginal zone lymphoma: a primary low-grade CNS lymphoma that mimics meningioma. *J Clin Oncol.* 2005;23(24):5718–27.
10. Villeneuve A, Rubin F, Bonfils P. Meningeal marginal zone B-cell lymphoma: the meningioma trap. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2018;135(2):131–2.
11. Desjardins C, Larrieu-Ciron D, Choquet S, Mokhtari K, Charlotte F, Nichelli L, et al. Chemotherapy is an efficient treatment in primary CNS MALT lymphoma. *J Neurooncol.* 2022;159(1):151–61.
12. Hajtovic S, Yu E, Bershadskiy A, Sacho R, Gilad R. Primary intracranial marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue arising in the lateral ventricle: case report and review of pathogenesis. *Surg Neurol Int.* 2022;13:181.
13. Bayraktar S, Stefanovic A, Montague N, Davis J, Murray T, Lossos IS. Central nervous system manifestations of marginal zone B-cell lymphoma. *Ann Hematol.* 2010;89(10):1003–9.
14. de la Fuente MI, Haggiagi A, Moul A, Young RJ, Sidani C, Markoe A, et al. Marginal zone dural lymphoma: the Memorial Sloan Kettering Cancer Center and University of Miami experiences. *Leuk Lymphoma.* 2017;58(4):882–8.
15. Chihara D, Fowler NH, Oki Y, Fanale MA, Nastoupil LJ, Westin JR, et al. Impact of histologic subtypes and treatment modality among patients with primary central nervous system lymphoma: a SEER database analysis. *Oncotarget.* 2018;9(48):28897–902.
16. Ayanambakkam A, Ibrahim S, Bilal K, Cherry MA. Extranodal marginal zone lymphoma of the central nervous system. *Clin Lymphoma Myeloma Leuk.* 2018;18(1):34–37.e8.
17. Sato Y, Takata K, Ichimura K, Tanaka T, Morito T, Tamura M, et al. IgG4-producing marginal zone B-cell lymphoma. *Int J Hematol.* 2008;88(4):428–33.
18. Venkataraman G, Rizzo KA, Chavez JJ, Streubel B, Raffeld M, Jaffe ES, et al. Marginal zone lymphomas involving meningeal dura: possible link to IgG4-related diseases. *Mod Pathol.* 2011;24(3):355–66.
19. Sato Y, Ohshima K, Takata K, Huang X, Cui W, Ohno K, et al. Ocular adnexal IgG4-producing mucosa-associated lymphoid tissue lymphoma mimicking IgG4-related disease. *J Clin Exp Hematop.* 2012;52(1):51–5.
20. Sohn EJ, Ahn HB, Roh MS, Jung WJ, Ryu WY, Kwon YH. Immunoglobulin G4 (IgG4)-positive ocular adnexal mucosa-associated lymphoid tissue lymphoma and idiopathic orbital inflammation. *Ophthal Plast Reconstr Surg.* 2018;34(4):313–9.
21. Bledsoe JR, Wallace ZS, Stone JH, Deshpande V, Ferry JA. Lymphomas in IgG4-related disease: clinicopathologic features in a Western population. *Virchows Arch.* 2018;472(5):839–52.

22. Nakamura S, Ponzoni M. Marginal zone B-cell lymphoma: lessons from Western and Eastern diagnostic approaches. *Pathology*. 2020;52(1):15–29.
23. Piris MA, Onaindia A, Mollejo M. Splenic marginal zone lymphoma. *Best Pract Res Clin Haematol*. 2017;30(1–2):56–64.
24. Traverse-Glehen A, Baseggio L, Bauchu EC, Morel D, Gazzo S, Ffrench M, et al. Splenic red pulp lymphoma with numerous basophilic villous lymphocytes: a distinct clinicopathologic and molecular entity? *Blood*. 2008;111(4):2253–60.
25. Ye H, Liu H, Raderer M, Chott A, Ruskone-Fourmesttraux A, Wotherspoon A, et al. High incidence of t(11;18)(q21;q21) in *Helicobacter pylori*-negative gastric MALT lymphoma. *Blood*. 2003;101(7):2547–50.
26. Magistri M, Happ LE, Ramdial J, Lu X, Stathias V, Kunkalla K, et al. The genetic landscape of ocular adnexa MALT lymphoma reveals frequent aberrations in NFAT and MEF2B signaling pathways. *Cancer Res Commun*. 2021;1(1):1–16.
27. Ganapathi KA, Jobanputra V, Iwamoto F, Jain P, Chen J, Cascione L, et al. The genetic landscape of dural marginal zone lymphomas. *Oncotarget*. 2016;7(28):43052–61.
28. Parry-Jones N, Joshi A, Forconi F, Dearden C, BSH Guidelines Committee. Guideline for diagnosis and management of hairy cell leukaemia (HCL) and hairy cell variant (HCL-V). *Br J Haematol*. 2020;191(5):730–7.
29. Ruiz-Ballesteros E, Mollejo M, Mateo M, Algara P, Martinez P, Piris MA. MicroRNA losses in the frequently deleted region of 7q in SMZL. *Leukemia*. 2007;21(12):2547–9.
30. Watkins AJ, Hamoudi RA, Zeng N, Yan Q, Huang Y, Liu H, et al. An integrated genomic and expression analysis of 7q deletion in splenic marginal zone lymphoma. *PLoS One*. 2012;7(9):e44997.
31. Rossi D, Trifonov V, Fangazio M, Bruscazzin A, Rasi S, Spina V, et al. The coding genome of splenic marginal zone lymphoma: activation of NOTCH2 and other pathways regulating marginal zone development. *J Exp Med*. 2012;209(9):1537–51.
32. Clipson A, Wang M, de Leval L, Ashton-Key M, Wotherspoon A, Vassiliou G, et al. KLF2 mutation is the most frequent somatic change in splenic marginal zone lymphoma and identifies a subset with distinct genotype. *Leukemia*. 2015;29(5):1177–85.
33. Kiel MJ, Velusamy T, Betz BL, Zhao L, Weigelin HG, Chiang MY, et al. Whole-genome sequencing identifies recurrent somatic NOTCH2 mutations in splenic marginal zone lymphoma. *J Exp Med*. 2012;209(9):1553–65.
34. Bikos V, Darzentas N, Hadzidimitriou A, Davis Z, Hockley S, Traverse-Glehen A, et al. Over 30% of patients with splenic marginal zone lymphoma express the same immunoglobulin heavy variable gene: ontogenetic implications. *Leukemia*. 2012;26(7):1638–46.
35. Traverse-Glehen A, Davi F, Ben Simon E, Callet-Bauchu E, Felman P, Baseggio L, et al. Analysis of VH genes in marginal zone lymphoma reveals marked heterogeneity between splenic and nodal tumors and suggests the existence of clonal selection. *Haematologica*. 2005;90(4):470–8.
36. Martinez-Lopez A, Curiel Del Olmo S, Martinez N, Montes-Moreno S, Mollejo M, Mazorra F, et al. MYD88 L265P in marginal zone lymphomas. *Hematol Oncol*. 2013;31:152.
37. Ruben ALG, Anne MRS, Marie José K, Steven TP, Joost SPV. MYD88 in the driver's seat of B-cell lymphomagenesis: from molecular mechanisms to clinical implications. *Haematologica*. 2019;104(12):2337–48.
38. Traverse-Glehen A, Verney A, Gazzo S, Jallades L, Chabane K, Hayette S, et al. Splenic diffuse red pulp lymphoma has a distinct pattern of somatic mutations amongst B-cell malignancies. *Leuk Lymphoma*. 2017;58(3):666–75.
39. Wotherspoon A, Matutes E. Recent advances in understanding small B-cell leukaemias and lymphomas. *Curr Diagn Pathol*. 2004;10(5):374–84.
40. Vallianatou K, Brito-Babapulle V, Matutes E, Atkinson S, Catovsky D. p53 gene deletion and trisomy 12 in hairy cell leukemia and its variant. *Leuk Res*. 1999;23(11):1041–5.
41. Thieblemont C, Molina T, Davi F. Optimizing therapy for nodal marginal zone lymphoma. *Blood*. 2016;127(17):2064–71.
42. Egan C, Laurent C, Alejo JC, Pileri S, Campo E, Swerdlow SH, et al. Expansion of PD1-positive T cells in nodal marginal zone lymphoma: a potential diagnostic pitfall. *Am J Surg Pathol*. 2020;44(5):657–64.
43. Campo E, Pileri S, Jaffe E, Nathawani B, Stein H, Mueller-Hermelink H. Nodal marginal zone B-cell lymphoma. In: Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al., editors. *WHO classification of tumours of haematopoietic and lymphoid tissues*. Revised 4th ed. Lyon: IARC; 2017. p. 263–5.
44. Kluin PM, Langerak AW, Beverdam-Vincent J, Geurts-Giele WR, Visser L, Rutgers B, et al. Paediatric nodal marginal zone B-cell lymphadenopathy of the neck: a *Haemophilus influenzae*-driven immune disorder? *J Pathol*. 2015;236(3):302–14.
45. Kalashnikov I, Tanskanen T, Viisanen L, Malila N, Jyrkkio S, Leppä S. Transformation and survival in marginal zone lymphoma: a Finnish nationwide population-based study. *Blood Cancer J*. 2023;13(1):62.
46. Casulo C, Friedberg J. Transformation of marginal zone lymphoma (and association with other lymphomas). *Best Pract Res Clin Haematol*. 2017;30(1–2):131–8.
47. Bastidas-Mora G, Bea S, Navarro A, Gine E, Costa D, Delgado J, et al. Clinico-biological features and outcome of patients with splenic marginal zone lymphoma with histological transformation. *Br J Haematol*. 2022;196(1):146–55.
48. Cook JR, Amador C, Czader M, Duffield A, Goodlad J, Ott G, et al. Transformations of marginal zone lymphomas and lymphoplasma-cytic lymphomas: report from the 2021 SH/EHP Workshop. *Am J Clin Pathol*. 2023;159(6):614–25.
49. Menter T, Dirnhofer S, Tzankov A. Transformation of a splenic marginal zone lymphoma into classic Hodgkin lymphoma. *J Clin Pathol*. 2019;72(5):391–2.
50. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375–90.
51. Ruskone-Fourmesttraux A, Fischbach W, Aleman BM, Boot H, Du MQ, Megraud F, et al. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. *Gut*. 2011;60(6):747–58.
52. Liu H, Ye H, Ruskone-Fourmesttraux A, De Jong D, Pileri S, Thiede C, et al. t(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to *H. pylori* eradication. *Gastroenterology*. 2002;122(5):1286–94.
53. Jung K, Kim DH, Seo HI, Gong EJ, Bang CS. Efficacy of eradication therapy in *Helicobacter pylori*-negative gastric mucosa-associated lymphoid tissue lymphoma: a meta-analysis. *Helicobacter*. 2021;26(2):e12774.
54. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. *Gut*. 2022;71(9):1724–62.
55. Eck M, Greiner A, Schmausser B, Eck H, Kolve M, Fischbach W, et al. Evaluation of *Helicobacter pylori* in gastric MALT-type lymphoma: differences between histologic and serologic diagnosis. *Mod Pathol*. 1999;12(12):1148–51.
56. Zullo A, Hassan C, Ridola L, De Francesco V, Rossi L, Tomao S, et al. Eradication therapy in *Helicobacter pylori*-negative, gastric low-grade mucosa-associated lymphoid tissue lymphoma patients: a systematic review. *J Clin Gastroenterol*. 2013;47(10):824–7.
57. Lecuit M, Abachin E, Martin A, Poyart C, Pochart P, Suarez F, et al. Immunoproliferative small intestinal disease associated with *Campylobacter jejuni*. *N Engl J Med*. 2004;350(3):239–48.
58. Choi SI, Kook MC, Hwang S, Kim YI, Lee JY, Kim CG, et al. Prevalence and implications of bone marrow involvement in patients with gastric mucosa-associated lymphoid tissue lymphoma. *Gut Liver*. 2018;12(3):278–87.
59. Treglia G, Zucca E, Sadeghi R, Cavalli F, Giovannella L, Ceriani L. Detection rate of fluorine-18-fluorodeoxyglucose positron emission

- tomography in patients with marginal zone lymphoma of MALT type: a meta-analysis. *Hematol Oncol*. 2015;33(3):113–24.
60. Rossi D, Bertoni F, Zucca E. Marginal-zone lymphomas. *N Engl J Med*. 2022;386(6):568–81.
 61. NCCN Clinical Practice Guidelines in Oncology B-Cell Lymphomas [Internet]. National Comprehensive Cancer Network; 2023 [cited Feb 2023]. Available from: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1480>
 62. Qi S, Huang MY, Yang Y, Schöder H, Teckie S, Noy A, et al. Uptake of [18F]fluorodeoxyglucose in initial positron-emission tomography predicts survival in MALT lymphoma. *Blood Adv*. 2018;2(6):649–55.
 63. Rohatiner A, d'Amore F, Coiffier B, Crowther D, Gospodarowicz M, Isaacson P, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. *Ann Oncol*. 1994;5(5):397–400.
 64. Musshoff K. Klinische Stadieneinteilung der Nicht-Hodgkin's lymphoma. *Strahlenther Onkol*. 1977;153:218–21.
 65. Radaszkiewicz T, Dragosics B, Bauer P. Gastrointestinal malignant lymphomas of the mucosa-associated lymphoid tissue: factors relevant to prognosis. *Gastroenterology*. 1992;102(5):1628–38.
 66. Ruskone-Fourmestraux A, Dragosics B, Morgner A, Wotherspoon A, De Jong D. Paris staging system for primary gastrointestinal lymphomas. *Gut*. 2003;52(6):912–3.
 67. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res*. 1971;31(11):1860–1.
 68. Kwee I, Rancoita PM, Rinaldi A, Ferreri AJ, Bhagat G, Gascoyne RD, et al. Genomic profiles of MALT lymphomas: variability across anatomical sites. *Haematologica*. 2011;96(7):1064–6.
 69. Wöhrer S, Troch M, Streubel B, Zwerina J, Skrabs C, Formanek M, et al. MALT lymphoma in patients with autoimmune diseases: a comparative analysis of characteristics and clinical course. *Leukemia*. 2007;21(8):1812–8.
 70. Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. *Blood*. 2016;127(17):2082–92.
 71. Ferreri AJ, Ponzoni M, Guidoboni M, Resti AG, Politi LS, Cortelazzo S, et al. Bacteria-eradicating therapy with doxycycline in ocular adnexal MALT lymphoma: a multicenter prospective trial. *J Natl Cancer Inst*. 2006;98(19):1375–82.
 72. Ferreri AJ, Govi S, Pasini E, Mappa S, Bertoni F, Zaja F, et al. *Chlamydomphila psittaci* eradication with doxycycline as first-line targeted therapy for ocular adnexae lymphoma: final results of an international phase II trial. *J Clin Oncol*. 2012;30(24):2988–94.
 73. Kim TM, Kim KH, Lee MJ, Jeon YK, Lee SH, Kim DW, et al. First-line therapy with doxycycline in ocular adnexal mucosa-associated lymphoid tissue lymphoma: a retrospective analysis of clinical predictors. *Cancer Sci*. 2010;101(5):1199–203.
 74. Kiesewetter B, Raderer M. Antibiotic therapy in nongastrointestinal MALT lymphoma: a review of the literature. *Blood*. 2013;122(8):1350–7.
 75. Behdad A, Bailey NG. Diagnosis of splenic B-cell lymphomas in the bone marrow: a review of histopathologic, immunophenotypic, and genetic findings. *Arch Pathol Lab Med*. 2014;138(10):1295–301.
 76. Matutes E, Oscier D, Montalban C, Berger F, Callet-Bauchu E, Dogan A, et al. Splenic marginal zone lymphoma proposals for a revision of diagnostic, staging and therapeutic criteria. *Leukemia*. 2008;22(3):487–95.
 77. van den Brand M, van Krieken JH. Recognizing nodal marginal zone lymphoma: recent advances and pitfalls. A systematic review. *Haematologica*. 2013;98(7):1003–13.
 78. Traverse-Glehen A, Bertoni F, Thieblemont C, Zucca E, Coiffier B, Berger F, et al. Nodal marginal zone B-cell lymphoma: a diagnostic and therapeutic dilemma. *Oncology (Williston Park)*. 2012;26(1):92–9, 103–4.
 79. Alderuccio JP, Zhao W, Desai A, Gallastegui N, Ramdial J, Kimble E, et al. Risk factors for transformation to higher-grade lymphoma and its impact on survival in a large cohort of patients with marginal zone lymphoma from a single institution. *J Clin Oncol*. 2018;36(34):3370–80.
 80. NICE. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management CG184. Clinical Guideline 2014. September 3, 2014. Contract No: [CG184].
 81. Calvet X, Garcia N, Lopez T, Gisbert JP, Gene E, Roque M. A meta-analysis of short versus long therapy with a proton pump inhibitor, clarithromycin and either metronidazole or amoxicillin for treating *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2000;14(5):603–9.
 82. Takigawa H, Yuge R, Masaki S, Otani R, Kadota H, Naito T, et al. Involvement of non-*Helicobacter pylori* helicobacter infections in *Helicobacter pylori*-negative gastric MALT lymphoma pathogenesis and efficacy of eradication therapy. *Gastric Cancer*. 2021;24(4):937–45.
 83. Fischbach W, Goebeler-Kolve ME, Dragosics B, Greiner A, Stolte M. Long term outcome of patients with gastric marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT) following exclusive *Helicobacter pylori* eradication therapy: experience from a large prospective series. *Gut*. 2004;53(1):34–7.
 84. Liu H, Ruskon-Fourmestraux A, Lavergne-Slove A, Ye H, Molina T, Bouhnik Y, et al. Resistance of t(11;18) positive gastric mucosa-associated lymphoid tissue lymphoma to *Helicobacter pylori* eradication therapy. *Lancet*. 2001;357(9249):39–40.
 85. Fischbach W, Goebeler-Kolve M, Starostik P, Greiner A, Muller-Hermelink HK. Minimal residual low-grade gastric MALT-type lymphoma after eradication of *Helicobacter pylori*. *Lancet*. 2002;360(9332):547–8.
 86. Wündisch T, Thiede C, Morgner A, Dempfle A, Günther A, Liu H, et al. Long-term follow-up of gastric MALT lymphoma after *Helicobacter pylori* eradication. *J Clin Oncol*. 2005;23(31):8018–24.
 87. Copie-Bergman C, Gaulard P, Lavergne-Slove A, Brousse N, Flejou JF, Dordonne K, et al. Proposal for a new histological grading system for post-treatment evaluation of gastric MALT lymphoma. *Gut*. 2003;52(11):1656.
 88. Copie-Bergman C, Wotherspoon AC, Capella C, Motta T, Pedrinis E, Pileri SA, et al. Gela histological scoring system for post-treatment biopsies of patients with gastric MALT lymphoma is feasible and reliable in routine practice. *Br J Haematol*. 2013;160(1):47–52.
 89. De Leo AN, Bates JE, Lockney NA, Mendenhall NP, Shaikh ME, Morris CG, et al. Radiotherapy in early-stage gastric MALT: improved survival without increased cardiac death. *Am J Clin Oncol*. 2020;43(11):770–5.
 90. Tsang RW, Gospodarowicz MK, Pintilie M, Bezjak A, Wells W, Hodgson DC, et al. Stage I and II MALT lymphoma: results of treatment with radiotherapy. *Int J Radiat Oncol Biol Phys*. 2001;50(5):1258–64.
 91. Ling DC, Vargo JA, Balasubramani GK, Beriwal S. Underutilization of radiation therapy in early-stage marginal zone lymphoma negatively impacts overall survival. *Pract Radiat Oncol*. 2016;6(4):e97–e105.
 92. Thieblemont C, Conconi A, Laszlo D, Tucci A, Vitolo U, Martelli M, et al. A simple and effective malt lymphoma-specific prognostic index generated from the dataset of the IELSG-19 controlled clinical trial. *Hematol Oncol*. 2015;33:167–8.
 93. Yahalom J, Xu AJ, Noy A, Lobaugh S, Chelius M, Chau K, et al. Involved-site radiotherapy for *Helicobacter pylori*-independent gastric MALT lymphoma: 26 years of experience with 178 patients. *Blood Adv*. 2021;5(7):1830–6.
 94. Ruskone-Fourmestraux A, Matysiak-Budnik T, Fabiani B, Cervera P, Brix H, Le Malicot K, et al. Exclusive moderate-dose radiotherapy in gastric marginal zone B-cell MALT lymphoma: results of a prospective study with a long term follow-up. *Radiation Oncol*. 2015;117(1):178–82.
 95. Taguchi S, Yoshioka Y, Mishima Y, Nishimura N, Yokoyama M, Takeuchi K, et al. Assessment of late toxicities of liver and kidney after definitive radiotherapy for gastric MALT lymphoma. *Int J Radiat Oncol Biol Phys*. 2019;105(1 Suppl):E475.

96. Chan EK, Fung S, Gospodarowicz M, Hodgson D, Wells W, Sun A, et al. Palliation by low-dose local radiation therapy for indolent non-Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys.* 2011;81(5):e781–6.
97. Pinnix CC, Gunther JR, Milgrom SA, Cruz Chamorro RJ, Medeiros LJ, Khoury JD, et al. Outcomes after reduced-dose intensity modulated radiation therapy for gastric mucosa-associated lymphoid tissue (MALT) lymphoma. *Int J Radiat Oncol Biol Phys.* 2019;104(2):447–55.
98. Katsuta T, Kashiwado K. Analysis of chronic renal failure following radiotherapy for gastric/duodenal mucosa-associated lymphoid tissue lymphoma at a single institution. *Int J Radiat Oncol Biol Phys.* 2019;105(1 Suppl):E478.
99. Thieblemont C, Cascione L, Conconi A, Kiesewetter B, Raderer M, Gaidano G, et al. A MALT lymphoma prognostic index. *Blood.* 2017;130(12):1409–17.
100. Copie-Bergman C, Locher C, Levy M, Chaumette MT, Haioun C, Delfau-Larue MH, et al. Metachronous gastric MALT lymphoma and early gastric cancer: is residual lymphoma a risk factor for the development of gastric carcinoma? *Ann Oncol.* 2005;16(8):1232–6.
101. Capelle LG, de Vries AC, Looman CW, Casparie MK, Boot H, Meijer GA, et al. Gastric MALT lymphoma: epidemiology and high adenocarcinoma risk in a nation-wide study. *Eur J Cancer.* 2008;44(16):2470–6.
102. Zucca E, Copie-Bergman C, Ricardi U, Thieblemont C, Raderer M, Ladetto M, et al. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24(Suppl 6):vi144–vi148.
103. Arcaini L, Vallisa D, Rattotti S, Ferretti VV, Ferreri AJM, Bernuzzi P, et al. Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi. *Ann Oncol.* 2014;25(7):1404–10.
104. Servitje O, Muniesa C, Benavente Y, Monsalvez V, Garcia-Muret MP, Gallardo F, et al. Primary cutaneous marginal zone B-cell lymphoma: response to treatment and disease-free survival in a series of 137 patients. *J Am Acad Dermatol.* 2013;69(3):357–65.
105. Senff NJ, Kluin-Nelemans HC, Willemze R. Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma. *Br J Haematol.* 2008;142(1):52–6.
106. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M, Committee EG. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018;29(Suppl 4):iv30–iv40.
107. Kim YH, Willemze R, Pimpinelli N, Whittaker S, Olsen EA, Ranki A, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood.* 2007;110(2):479–84.
108. Specht L, Dabaja B, Illidge T, Wilson LD, Hoppe RT, International Lymphoma Radiation Oncology Group. Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys.* 2015;92(1):32–9.
109. Lowry L, Smith P, Qian W, Falk S, Benstead K, Illidge T, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. *Radiation Oncol.* 2011;100(1):86–92.
110. Hoskin P, Popova B, Schofield O, Brammer C, Robinson M, Brunt AM, et al. 4 Gy versus 24 Gy radiotherapy for follicular and marginal zone lymphoma (FoRT): long-term follow-up of a multicentre, randomised, phase 3, non-inferiority trial. *Lancet Oncol.* 2021;22(3):332–40.
111. Teckie S, Qi S, Chelius M, Lovie S, Hsu M, Noy A, et al. Long-term outcome of 487 patients with early-stage extra-nodal marginal zone lymphoma. *Ann Oncol.* 2017;28(5):1064–9.
112. Elsayad K, Reinartz G, Oertel M, Rehn S, Eismann J, Scobioala S, et al. Radiotherapy of extranodal low-grade follicular and marginal zone lymphomas: long-term follow-up of 159 patients. *Strahlenther Onkol.* 2020;196(2):117–25.
113. Yahalom J, Teckie S, Qi S, Hsu M, Lovie S, Chelius M, et al. Long-term outcome of 490 patients with early-stage extra-nodal marginal zone lymphoma. *Haematologica.* 2015;100:4.
114. MacManus MP, Roos D, O'Brien P, Capp A, Wirth A, Tsang R, et al. Prospective phase II trial of radiation therapy in localised non-gastric marginal zone lymphoma with prospective evaluation of autoimmunity and *Helicobacter pylori* status: TROG 05.02/ALLG NHL15. *Eur J Cancer.* 2021;152:129–38.
115. Shelley C, Brady J, Rahman F, Mikhael G. Efficacy of low dose radiotherapy in head & neck MALT lymphoma. *Int J Radiat Oncol Biol Phys.* 2020;108(3 Suppl):S142–3.
116. Gunther JR, Park C, Dabaja BS, Milgrom SA, Cruz Chamorro RJ, Medeiros LJ, et al. Radiation therapy for salivary gland MALT lymphoma: ultra-low dose treatment achieves encouraging early outcomes and spares salivary function. *Leuk Lymphoma.* 2020;61(1):171–5.
117. Aviles A, Delgado S, Huerta-Guzman J. Marginal zone B cell lymphoma of the parotid glands: results of a randomised trial comparing radiotherapy to combined therapy. *Eur J Cancer B Oral Oncol.* 1996;32B(6):420–2.
118. Hoskin PJ, Kirkwood AA, Popova B, Smith P, Robinson M, Gallop-Evans E, et al. 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. *Lancet Oncol.* 2014;15(4):457–63.
119. Zucca E, Conconi A, Martinelli G, Bouabdallah R, Tucci A, Vitolo U, et al. Final results of the IELSG-19 randomized trial of mucosa-associated lymphoid tissue lymphoma: improved event-free and progression-free survival with rituximab plus chlorambucil versus either chlorambucil or rituximab monotherapy. *J Clin Oncol.* 2017;35(17):1905–12.
120. Zucca E, Conconi A, Laszlo D, López-Guillermo A, Bouabdallah R, Coiffier B, et al. Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 Randomized Study. *J Clin Oncol.* 2013;31(5):565–72.
121. Salar A, Domingo-Domenech E, Panizo C, Nicolás C, Bargay J, Muntañola A, et al. First-line response-adapted treatment with the combination of bendamustine and rituximab in patients with mucosa-associated lymphoid tissue lymphoma (MALT2008-01): a multicentre, single-arm, phase 2 trial. *Lancet Haematol.* 2014;1(3):e104–11.
122. Oh SY, Kim WS, Kim JS, Kim SJ, Yoon DH, Yang DH, et al. Phase II study of R-CVP followed by rituximab maintenance therapy for patients with advanced marginal zone lymphoma: Consortium for Improving Survival of Lymphoma (CISL) study. *Cancer Commun (Lond).* 2019;39(1):58.
123. Kang HJ, Kim WS, Kim SJ, Lee JJ, Yang DH, Kim JS, et al. Phase II trial of rituximab plus CVP combination chemotherapy for advanced stage marginal zone lymphoma as a first-line therapy: Consortium for Improving Survival of Lymphoma (CISL) study. *Ann Hematol.* 2012;91(4):543–51.
124. Herold M, Hoster E, Janssens A, McCarthy H, Tedeschi A, Pocock C, et al. Immunochemotherapy and maintenance with obinutuzumab or rituximab in patients with previously untreated marginal zone lymphoma in the randomized GALLIUM trial. *HemaSphere.* 2022;6(3):e699.
125. Herold M, Hoster E, Janssens A, McCarthy H, Tedeschi A, Pocock C, et al. Immunochemotherapy with obinutuzumab or rituximab in a subset of patients in the randomised gallium trial with previously untreated marginal zone lymphoma (MZL). *Hematol Oncol.* 2017;35(Suppl 2):146–7.
126. Flinn IW, van der Jagt R, Kahl BS, Wood P, Hawkins TE, Macdonald D, et al. Randomized trial of bendamustine-rituximab

- or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood*. 2014;123(19):2944–52.
127. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grunhagen U, Losen C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203–10.
 128. Salar A, Domingo-Domenech E, Panizo C, Nicolas C, Bargay J, Muntanola A, et al. Long-term results of the multicenter phase II trial with bendamustine and rituximab as first line treatment for patients with MALT lymphoma (MALT-2008-01). *Hematol Oncol*. 2017;35(Suppl 2):147–8.
 129. Stathis A, Gregorini A, Gressin R, Orsucci L, Perrot A, Tani M, et al. IELSG-38: a phase II study of chlorambucil in combination with rituximab followed by maintenance therapy with subcutaneous rituximab in patients with extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT). *Blood*. 2017;130:1506.
 130. Piroso M, Orsucci L, Feugier P, Tani M, Ghesquieres H, Musuraca G, et al. Phase II trial of rituximab plus chlorambucil followed by a 2-year subcutaneous rituximab maintenance in MALT lymphoma patients (IELSG38). Lugano, Switzerland: Wiley; 2021.
 131. Rummel MJ, Koenigsmann M, Chow KU, Knauf W, Lerchenmuller CA, Losen C, et al. Two years rituximab maintenance vs. observation after first line treatment with bendamustine plus rituximab (B-R) in patients with marginal zone lymphoma (MZL): results of a prospective, randomized, multicenter phase 2 study (the StiL NHL7-2008 MAINTAIN trial). *J Clin Oncol*. 2018;36(15 Suppl 1):7515.
 132. Iannitto E, Bellei M, Amorim S, Ferreri AJM, Marcheselli L, Cesaretti M, et al. Efficacy of bendamustine and rituximab in splenic marginal zone lymphoma: results from the phase II BRISMA/IELSG36 study. *Br J Haematol*. 2018;183(5):755–65.
 133. Kalpadakis C, Pangalis GA, Sachanas S, Tsirkinidis P, Kontopidou FN, Moschogiannis M, et al. Rituximab monotherapy in splenic marginal zone lymphoma: prolonged responses and potential benefit from maintenance. *Blood*. 2018;132(6):666–70.
 134. Sunderland AJ, Steiner RE, Al Zahrani M, Pinnix CC, Dabaja BS, Gunther JR, et al. An international multicenter retrospective analysis of patients with extranodal marginal zone lymphoma and histologically confirmed central nervous system and dural involvement. *Cancer Med*. 2020;9(2):663–70.
 135. Puri DR, Tereffe W, Yahalom J. Low-dose and limited-volume radiotherapy alone for primary dural marginal zone lymphoma: treatment approach and review of published data. *Int J Radiat Oncol Biol Phys*. 2008;71(5):1425–35.
 136. Iwamoto FM, DeAngelis LM, Abrey LE. Primary dural lymphomas: a clinicopathologic study of treatment and outcome in eight patients. *Neurology*. 2006;66(11):1763–5.
 137. Grommes C, Rubenstein JL, DeAngelis LM, Ferreri AJM, Batchelor TT. Comprehensive approach to diagnosis and treatment of newly diagnosed primary CNS lymphoma. *Neuro Oncol*. 2019;21(3):296–305.
 138. Tsutsumi Y, Ito S, Nagai J, Tateno T, Teshima T. Patients with marginal zone dural lymphoma successfully treated with rituximab and bendamustine: a report of two cases. *Mol Clin Oncol*. 2021;15(4):208.
 139. Okimoto RA, Perry A, Rubenstein JL. 77-Year-old woman with a dural-based mass. Marginal zone B-cell lymphoma (MZBCL). *Brain Pathol*. 2015;25(1):111–2.
 140. Estevez M, Chu C, Pless M. Small B-cell lymphoma presenting as diffuse dural thickening with cranial neuropathies. *J Neurooncol*. 2002;59(3):243–7.
 141. Arcaini L, Besson C, Frigeni M, Fontaine H, Goldaniga M, Casato M, et al. Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. *Blood*. 2016;128(21):2527–32.
 142. Perrone S, D'Elia GM, Annechini G, Stefanizzi C, D'Urso P, Pulsoni A. A retrospective analysis on splenic marginal zone lymphoma: prognostic factors, role of watch and wait and other therapeutic approaches in the rituximab era. *Hematol Oncol*. 2015;33:293.
 143. Lenglet J, Traulle C, Mounier N, Benet C, Munoz-Bongrand N, Amorim S, et al. Long-term follow-up analysis of 100 patients with splenic marginal zone lymphoma treated with splenectomy as first-line treatment. *Leuk Lymphoma*. 2014;55(8):1854–60.
 144. Kalpadakis C, Pangalis GA, Angelopoulou MK, Sachanas S, Vassilakopoulos TP. Should rituximab replace splenectomy in the management of splenic marginal zone lymphoma? *Best Pract Res Clin Haematol*. 2018;31(1):65–72.
 145. Morigi A, Argnani L, Lolli G, Broccoli A, Pellegrini C, Nanni L, et al. Bendamustine-rituximab regimen in untreated indolent marginal zone lymphoma: experience on 65 patients. *Hematol Oncol*. 2020;38(4):487–92.
 146. Sindel A, Al-Juhaishi T, Yazbeck V. Marginal zone lymphoma: state-of-the-art treatment. *Curr Treat Options Oncol*. 2019;20(12):90.
 147. Castelli R, Bergamaschini L, Delilieri GL. First-line treatment with bendamustine and rituximab, in patients with intermediate-/high-risk splenic marginal zone lymphomas. *Med Oncol*. 2018;35(2):15.
 148. Ferrero S, Ladetto M, Beldjord K, Drandi D, Stelitano C, Bernard S, et al. First application of minimal residual disease analysis in splenic marginal zone lymphoma trials: preliminary results from BRISMA/IELSG36 phase II study. *Hematol Oncol*. 2019;37(Suppl 2):224–5.
 149. Olszewski AJ, Ollila T, Reagan JL. Rituximab alone (R) versus rituximab plus bendamustine (BR) for splenic (SMZL) and nodal marginal zone lymphoma (NMZL). *Hematol Oncol*. 2019;37(Suppl 2):225–6.
 150. Olszewski AJ, Ollila TA, Reagan JL. Bendamustine-rituximab does not improve survival over rituximab monotherapy for older patients with nodal or splenic marginal zone lymphoma. *Blood*. 2019;134(Suppl 1):2824.
 151. Oliveira LC, Fardilha C, Louro M, Pinheiro C, Sousa A, Marques H, et al. Palliative splenic irradiation for symptomatic splenomegaly in non-Hodgkin lymphoma. *Ecancermedicallscience*. 2018;12:887.
 152. Zaorsky NG, Williams GR, Barta SK, Esnaola NF, Kropf PL, Hayes SB, et al. Splenic irradiation for splenomegaly: a systematic review. *Cancer Treat Rev*. 2017;53:47–52.
 153. Kriz J, Micke O, Bruns F, Haverkamp U, Mucke R, Schafer U, et al. Radiotherapy of splenomegaly: a palliative treatment option for a benign phenomenon in malignant diseases. *Strahlenther Onkol*. 2011;187(4):221–4.
 154. Luminari S, Merli M, Rattotti S, Tarantino V, Marcheselli L, Cavallo F, et al. Early progression as a predictor of survival in marginal zone lymphomas: an analysis from the FIL-NF10 study. *Blood*. 2019;134(10):798–801.
 155. McNamara C, Montoto S, Eyre TA, Ardeshta K, Burton C, Illidge T, et al. The investigation and management of follicular lymphoma. *Br J Haematol*. 2020;191(3):363–81.
 156. Denlinger NM, Epperla N, William BM. Management of relapsed/refractory marginal zone lymphoma: focus on ibrutinib. *Cancer Manag Res*. 2018;10:615–24.
 157. Murakami H, Yoshioka T, Moriyama T, Ishikawa T, Makita M, Sunami K. Bendamustine plus rituximab as salvage treatment for patients with relapsed or refractory low-grade B-cell lymphoma and mantle cell lymphoma: a single-center retrospective study. *Acta Med Okayama*. 2021;75(4):461–9.
 158. Rummel MJ, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin Oncol*. 2005;23(15):3383–9.
 159. Kiesewetter B, Mayerhoefer ME, Lukas J, Zielinski CC, Mullauer L, Raderer M. Rituximab plus bendamustine is active in pre-treated patients with extragastric marginal zone B cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma). *Ann Hematol*. 2014;93(2):249–53.

160. Martin P, Chen Z, Cheson BD, Robinson KS, Williams M, Rajguru SA, et al. Long-term outcomes, secondary malignancies and stem cell collection following bendamustine in patients with previously treated non-Hodgkin lymphoma. *Br J Haematol.* 2017;178(2):250–6.
161. Noy A, de Vos S, Thieblemont C, Martin P, Flowers CR, Morschhauser F, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood.* 2017;129(16):2224–32.
162. Opat S, Tedeschi A, Linton K, McKay P, Hu B, Chan H, et al. The MAGNOLIA trial: zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, demonstrates safety and efficacy in relapsed/refractory marginal zone lymphoma. *Clin Cancer Res.* 2021;27(23):6323–32.
163. Mato AR, Shah NN, Jurczak W, Cheah CY, Pagel JM, Woyach JA, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet.* 2021;397(10277):892–901.
164. Woyach JA, Flinn IW, Awan FT, Eradat H, Brander DM, Tees M, et al. Preliminary efficacy and safety of MK-1026, a non-covalent inhibitor of wild-type and C481S mutated Bruton tyrosine kinase, in B-cell malignancies: a phase 2 dose expansion study. *Blood.* 2021;138(Suppl 1):392.
165. Coleman M, Andorsky DJ, Yacoub A, Melear JM, Fanning SR, Kolibaba KS, et al. Patients with relapsed/refractory marginal zone lymphoma in the MAGNIFY phase IIIb interim analysis of induction R2 followed by maintenance. *Blood.* 2020;136:24–5.
166. Leonard JP, Trneny M, Izutsu K, Fowler NH, Hong X, Zhu J, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol.* 2019;37(14):1188–99.
167. Jurczak W, Zinzani PL, Gaidano G, Goy A, Provencio M, Nagy Z, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Ann Oncol.* 2018;29(5):1266–72.
168. Sehn LH, Scholz CW, Luminari S, Salar A, Wahlin BE, Gopal AK, et al. A phase 3 study to evaluate the efficacy and safety of tafasitamab plus lenalidomide and rituximab versus placebo plus lenalidomide and rituximab in patients with relapsed/refractory (R/R) follicular lymphoma (FL) or marginal zone lymphoma (MZL). *J Clin Oncol.* 2021;39(15_Suppl):7568.
169. Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles GA, et al. Interim analysis of ZUMA-5: a phase II study of axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory indolent non-Hodgkin lymphoma (R/R iNHL). *J Clin Oncol.* 2020;38(15_suppl):8008.
170. Avivi I, Arcaini L, Ferretti VV, Boumendil A, Finel H, Milone G, et al. High-dose therapy and autologous stem cell transplantation in marginal zone lymphomas: a retrospective study by the EBMT Lymphoma Working Party and FIL-GITMO. *Br J Haematol.* 2018;182(6):807–15.
171. Conconi A, Martinelli G, Thieblemont C, Ferreri AJ, Devizzi L, Peccatori F, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. *Blood.* 2003;102(8):2741–5.
172. Vannata B, Vanazzi A, Negri M, Liptrott SJ, Bartosek AA, Miani M, et al. A phase II trial of bendamustine in combination with ofatumumab in patients with relapsed or refractory marginal zone B-cell lymphomas. *Hematol Oncol.* 2021;39(1):60–5.
173. Noy A, de Vos S, Coleman M, Martin P, Flowers CR, Thieblemont C, et al. Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis. *Blood Adv.* 2020;4(22):5773–84.
174. Vanazzi A, Grana C, Crosta C, Pruneri G, Rizzo S, Radice D, et al. Efficacy of ⁹⁰Yttrium-ibritumomab tiuxetan in relapsed/refractory extranodal marginal-zone lymphoma. *Hematol Oncol.* 2014;32(1):10–5.
175. Lolli G, Argani L, Broccoli A, Marangon M, Pellegrini C, Morigi A, et al. (90) Y-ibritumomab tiuxetan in patients with extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) – the Zeno Study. *Br J Haematol.* 2020;189(1):e6–e9.
176. Kiesewetter B, Lamm W, Neuper O, Mayerhoefer ME, Simonitsch-Klupp I, Raderer M. Prolonged follow-up on lenalidomide-based treatment for mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) – real-world data from the Medical University of Vienna. *Hematol Oncol.* 2019;37(4):345–51.
177. Kiesewetter B, Willenbacher E, Willenbacher W, Egle A, Neumeister P, Voskova D, et al. A phase 2 study of rituximab plus lenalidomide for mucosa-associated lymphoid tissue lymphoma. *Blood.* 2017;129(3):383–5.
178. Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. IBCL-124: interim analysis of ZUMA-5: a phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients with relapsed/refractory indolent non-Hodgkin lymphoma (R/R iNHL). *Clin Lymphoma Myeloma Leuk.* 2020;20(Suppl 1):S278.
179. Conconi A, Raderer M, Franceschetti S, Devizzi L, Ferreri AJ, Magagnoli M, et al. Clinical activity of everolimus in relapsed/refractory marginal zone B-cell lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group. *Br J Haematol.* 2014;166(1):69–76.
180. Kirschbaum M, Frankel P, Popplewell L, Zain J, Delioukina M, Pullarkat V, et al. Phase II study of vorinostat for treatment of relapsed or refractory indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol.* 2011;29(9):1198–203.
181. de Vos S, Goy A, Dakhil SR, Saleh MN, McLaughlin P, Belt R, et al. Multicenter randomized phase II study of weekly or twice-weekly bortezomib plus rituximab in patients with relapsed or refractory follicular or marginal-zone B-cell lymphoma. *J Clin Oncol.* 2009;27(30):5023–30.
182. Conconi A, Martinelli G, Lopez-Guillermo A, Zinzani PL, Ferreri AJM, Rigacci L, et al. Clinical activity of bortezomib in relapsed/refractory MALT lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group (IELSG). *Ann Oncol.* 2011;22(3):689–95.
183. Andorsky DJ, Kolibaba KS, Assouline S, Forero-Torres A, Jones V, Klein LM, et al. An open-label phase 2 trial of entospletinib in indolent non-Hodgkin lymphoma and mantle cell lymphoma. *Br J Haematol.* 2019;184(2):215–22.
184. Rusconi C, Guerrero ML, Tedeschi A, Zancanella M, Gotti M, Nichelatti M, et al. Outcome of transformed marginal zone lymphomas treated in the rituximab era. *Blood.* 2015;126(23):5098.

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