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AML: DEVASTATING

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A *FLT3-ITD* mutation drives progression and may lead to lower patient survival.[1-3]

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Prescribing information for: XOSPATA™ ▼ 40 mg film coated tablets (gilteritinib). **Indications:** Gilteritinib is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation. **Posology and administration:** Treatment with gilteritinib should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Before taking gilteritinib, relapsed or refractory AML patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test. The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) orally once daily, with or without food, swallowed whole with water and should not be broken or crushed. Gilteritinib should be administered at about the same time each day. See *Special warnings and precautions for use* section on tests to be conducted prior to initiation e.g. blood chemistries, ECG & pregnancy test. Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response. In the absence of a response (patient did not achieve a composite complete remission (CRc) after 4 weeks of treatment), the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted. Gilteritinib may be re-initiated in patients following haematopoietic stem cell transplantation (HSCT), Planned HSCT: Interrupt treatment one week prior to administration of the conditioning regimen for HSCT. Treatment can be resumed 30 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in CRc. Elderly: No dose adjustment is required in patients ≥65 years of age. Gilteritinib is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment. Please refer to SPC, section 4.2 for full instructions for use in hepatic & renal impairment. Paediatric population: The safety and efficacy of gilteritinib in children aged below 18 years has not yet been established. No data are available. Due to in vitro binding to $5HT_{2B}$, there is a potential impact on cardiac development in patients less than 6 months of age. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. **Special warnings and precautions for use:** Differentiation syndrome: Gilteritinib has been associated with differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with haemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, gilteritinib should be interrupted until signs and symptoms are no longer severe. Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2 or lower. Posterior reversible encephalopathy syndrome: There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving gilteritinib. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of gilteritinib in patients who develop PRES is recommended. Prolonged QT interval: Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT interval). QT prolongation can be observed in the first three months of treatment with gilteritinib. Therefore, ECG should be performed prior to initiation of treatment, on day 8 and 15 of cycle 1, and prior to the start of the next three subsequent months of treatment. Caution is warranted in patients with relevant cardiac history. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during gilteritinib treatment. Gilteritinib should be interrupted in patients who have a QTcF >500 msec.The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on careful consideration of benefits and risks. Resume gilteritinib at a reduced dose (from 120 mg to 80 mg or from 200 mg to 120 mg) when QTcF interval returns to within 30 msec of baseline or ≤480 msec. Patients with QTcF interval increase by >30 msec on day 8 of cycle 1 should have a further ECG on day 9; if QTcF increase is confirmed gilteritinib dose should be reduced to 80 mg. If gilteritinib is re-introduced at a reduced dose, ECG should be performed after 15 days of dosing, and prior to the start of the next three subsequent months of treatment. In clinical studies, 12 patients had QTcF >500 msec. Three patients interrupted and re-initiated treatment without recurrence of QT prolongation. Pancreatitis: There have been reports of pancreatitis. Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored. Gilteritinib should be interrupted and can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg) when the signs and symptoms of pancreatitis have resolved. Toxicity: If the patient experiences other Grade 3 or higher toxicity considered related to treatment, interrupt treatment until the toxicity resolves or improves to Grade 1. If deemed clinically appropriate gilteritinib can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg). Interactions: Co-administration of CYP3A/P-gp inducers may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided. Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A,P-gp and/or breast cancer resistant protein (BCRP) (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of gilteritinib. Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient. Embryofoetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus. Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with gilteritinib and to use effective contraception during treatment with gilteritinib and for at least 6 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of gilteritinib. **Interactions:** Gilteritinib is primarily metabolised by CYP3A enzymes, which can be induced or inhibited by a number of concomitant medicinal products. See Special Warnings and Precautions for Use section above for further information on this and the effects of gilteritinib on products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. *Gilteritinib as an inhibitor or inducer:* gilteritinib is not an inhibitor or inducer of CYP3A4 or an inhibitor of MATE1 *in vivo*. Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 (organic cation transporter 1) *in vitro*. As no clinical data is available, it cannot be excluded that gilteritinib could inhibit these transporters at a therapeutic dose. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, methotrexate, rosuvastatin) and OCT1 (e.g., metformin). **Fertility, pregnancy and lactation:** Pregnancy: Gilteritinib is not recommended during pregnancy and in women of childbearing potential not using effective contraception. See Special Warnings and Precautions for Use section above for information on pregnancy testing and contraception. Breastfeeding: Breastfeeding should be discontinued during treatment with gilteritinib and for at least two months after the last dose. Fertility: There are no data on the effect of gilterinitib on human fertility. **List of adverse reactions:** *Prescribers should consult the SPC for full information on adverse events* **List of adverse reactions:** Very common (≥1/10): Dizziness, Hypotension, Cough, Dyspnoea, Diarrhoea, Nausea, Constipation, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Blood alkaline phosphatase increased, Pain in extremity, Arthralgia, Myalgia, Fatigue, Peripheral oedema and Asthenia. Common (≥1/100 to <1/10): Anaphylactic reaction, Electrocardiogram QT prolonged, Pericardial effusion, Pericarditis, Cardiac failure, Differentiation syndrome, Musculoskeletal pain, Acute kidney injury and Malaise. Serious adverse reactions: The most frequent serious adverse reactions noted from evaluation of 319 patients with relapsed or refractory AML who have received at least one dose of 120 mg gilteritinib were acute kidney injury, diarrhoea, ALT increased, dyspnea, AST increased and hypotension. Other clinically significant serious adverse reactions included differentiation syndrome, electrocardiogram QT prolonged and posterior reversible encephalopathy syndrome. **Overdose:** There is no known specific antidote for gilteritinib. In the event of an overdose, treatment should be stopped. Patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated, taking into consideration the long half-life estimated at 113 hours. **Cost (excluding VAT):** United Kingdom (UK): XOSPATA 40 mg film-coated tablets x 84: £14,188.00. **Legal classification:** POM. **Marketing authorisation number:** Great Britain (GB): PLGB 00166/0425. Northern Ireland NI: EU/1/19/1399/001. **Marketing authorisation holder:** GB: Astellas Pharma Ltd., 300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX. NI: Astellas Pharma Europe B.V. Sylviusweg 62, 2333 BE Leiden, The Netherlands. **Date of preparation:** March 2023. **Document number:** MAT_UK_XOS_2023_00039. **Further information available from:** Astellas Pharma Ltd., Medical Information: 0800 783 5018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.

AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplication.

References: 1. Chevallier P, et al. Leukemia 2011;25(6):939-44. **2.** Gale RE, et al. Blood 2008;111(5):2776-84. **3.** Smith CC, et al. Nature 2012;485(7397):260-3.

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GUIDELINE

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

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Keywords: CBMZL, clinical guidelines, clonal B-cell lymphocytosis of marginal-zone origin, extranodal MZL, marginal zone lymphoma, mucosa-associated lymphoid tissue, nodal NMZL, splenic SMZL

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 tissue[1]—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 year[5] 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 haematopathologist[6] 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 tissue[2] 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). *Note*: 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	• *Helicobacter pylori* (38%–85%)[8] • *H. heilmannii* (<1%)	• t(11;18)(q21;q21)/*BIRC3::MALT1* (6%–26%). Higher incidence in *H. pylori*-negative gastritis, associated with aggressive behaviour and nuclear expression of BCL10[25] • t(14;18)(q32;q21)/*IGH::MALT1* (1%–5%) • Trisomy 3 (11%) • Trisomy 18 (6%) • *TNFAIP3 (A20)* Inactivation (5%–18%)	
Intestinal tract	2	• *Campylobacter jejuni* (up to 50%)	• 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	• Hepatitis C virus (23%) • Hepatitis B virus (16%) • Other viral hepatitis (10%) • *H. pylori* (13%) • Autoimmune hepatitis/primary biliary cirrhosis/Sjögren syndrome (12%) • Ascariasis (4%) • Synchronous malignant tumours (11%)	• t(14;18)(q32;q21)/*IGH::MALT1* (0%–67%) • t(3;14)(p14;q32)/*IGH::FOXP1* • Trisomy 3 • Trisomy 18	
Gallbladder and extra-hepatic bile duct	14	• Gallstones	• t(11;18)(q21;q21)/*BIRC3::MALT1*	
Head and neck				
Ocular adnexa[26]	60	• *Chlamydia psittaci* (geographical variation) Hepatitis C virus (25%) IgG4-related disease (10%)	• t(14;18)(q32;q21)/*IGH::MALT1* (0%–25%) • t(3;14)(p14.1;q32)/*IGH::FOXP1* (0%–20%) • Trisomy 3 (38%) • Trisomy 8 (13%) • *TNFAIP3 (A20)* inactivation (26%) • Gain 6p • Loss 6q • *CABIN1* (30%) • *RHOA* (26%) • *TBL1XR1* (22%) • *CREBBP* (17%)	4–34
Salivary glands	30–40	• Sjögren syndrome • IgG4-related disease/sialadenitis • Hepatitis C virus	• 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	• Chronic lymphocytic (Hashimoto) thyroiditis IgG4-related disease	• t(3;14)(p14.1;q32)/*IGH::FOXP1* (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	• *H. pylori*, *Achromobactor xylosoxidans* • Human immunodeficiency virus • Hepatitis C virus • Sjögren syndrome/systemic lupus erythematosus • Smoking • Common variable immunodeficiency syndrome	• 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		• Sjögren syndrome (>60%)/rheumatoid arthritis/scleroderma, predominantly in Asian females	• Trisomy 3 (50%)	
Skin	7	• *Borrelia burgdorferi* • IgG4-related disease (15%–39%) • Tattoo pigments • Vaccines	• t(14;18)(q32;q21)/*IGH::MALT1* (0%–14%) • t(3;14)(p14.1;q32)/*IGH::FOXP1* (0%–10%) • t(11;18)(q21;q21)/*BIRC3::MALT1* (0%–8%) • Trisomy 3 (20%) • Trisomy 8 (4%) • *FAS* mutations	
Other sites				
Breast	3	• Sjögren syndrome	• t(11;18)(q21;q21) • t(14;18)(q32;q21)	
Dura[27]		• IgG4-related disease	• *TNFAIP3* 67% (of cases with plasmacytic differentiation) • *NOTCH2* 80% (of cases with monocytoid morphology) • *TBL1XR1*, *HLHL6*, *MLL2*, 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 alterations[22] 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	• Del7q22-36 (with a minimal common deletion of a 3 Mb region at 7q32.1-32.2) (45% of cases)[22,29,30] • *NOTCH2* (10%–25%) and *KLF2* (10%–40%) mutations[31–33] • 17p13 (*TP53*) deletion (3%–17%)[22] • *IGHV* gene somatic mutations: frequent IGHV1-2*04 segment use, low mutational load[24,34,35] • *MYD88 L256P* mutation (7%–15%)[36,37]	• *CCND3* PEST domain mutations • *IGHV* gene somatic mutations (79%): overrepresentation of IGHV3-23 and IGHV4-34 usage[24,38]	• *BRAF* V600E mutation in most cases • IGHV3-23 and less commonly IGHV4-34 usage[38] • *TP53* deletion rare[39,40]	• *BRAF* V600E not present • *MAP2K1* mutations • IGHV4-34 usage[38] • Common complex karyotypes and *TP53* deletion[39,40]

Abbreviations: HCL, hairy cell leukaemia; HCLv, HCL variant (splenic B-cell lymphoma/leukaemia with prominent nucleoli[2]); 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	
• Full blood count and blood film • Peripheral blood flow cytometric imunophentyping (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**
• Bone marrow aspirate and trephine biopsy (for morphology and IHC ± flow cytometry, FISH, IGHV genes)	• All patients with SMZL • Associated cytopenias, and confirmation of early stage disease in non-gastric EMZL/MALT, NMZL
• PET scan	• Suspected HGT • Evaluation of early stage disease suitable for radiotherapy
• MRI scan	• Evaluation of specific EMZL/MALT sites, for example orbits, brain
• Oesophago-gastro-duodenoscopy ± endoscopic ultrasound	• Diagnosis and prognosis of gastric EMZL/MALT
• Testing for *Helicobacter pylori* (faecal antigen testing; carbon-13 urea breath test [CLO] ± serology)	• Gastric and non-gastric EMZL/MALT
• Direct antiglobulin test (DAT), reticulocytes, haptoglobin	• Presence of haemolysis (SMZL)
• Clotting	• Suspected acquired clotting disorder (SMZL)
• C1 esterase	• Associated angioedema (SMZL)
• Autoimmune screen; vasculitis screen; IgG4 level	• Suspected underlying pathology
• Cryoglobulin concentration and C3/4 levels	• Suspected cyroglobulinaemia or if HCV-positive (SMZL)

Abbreviations: CLO, campulobacter-like organism test; CT, computed tomography; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; LDH, lactate dehyrogenase; MALT, mucosa-associated lymphoid tissue; MRI, magnetic resonance imging; 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 study[58]—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 disease[59] 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 classification[63] 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 I1E	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 II1 = Regional LNs II2 = Distant intraabdominal LNs IIE = invasion of adjacent structures
Stage II1E	T1-4 N1M0A165402	Regional LNs	
Stage II2E	T1-4 N2M0	Distant intraabdominal LNs	
Stage IIIE	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 amoxycillin 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%)	• CT or MRI orbits • Ophthalmology examination • PCR for *C. psittaci* on tumour biopsy, peripheral blood mononuclear cells, conjunctival swabs • Anti-SSA and anti-SSB antibodies	Sjögren syndrome (lacrimal gland MZL) *C. psittaci*	Doxycycline 100 mg BD for 21 days; up to 65%[71–73]	3 months[70] Reported range 3–36 months[7,71]
Skin (9%)	• PCR tumour biopsy	*Borrelia burgdorferi*	Ceftriaxone 2 g/day for 14 days; case reports only[72,74]	-
Lungs (9%)	• Bronchoscopy and bronchoalveolar lavage	Lymphocytic interstitial pneumonia *Achromobacter xylosoxidans*	-	-
Salivary glands (8%)	• ENT examination • US or CT or MRI • Anti-SSA and anti-SSB antibodies	Sjögren syndrome	-	-
Breast (3%)	• Mammography and US • MRI	-	-	-
Thyroid (2%)	• 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 imging; MZL, marginal zone lymphoma; PCR, polymerase chain reaction; US, ultrasound.

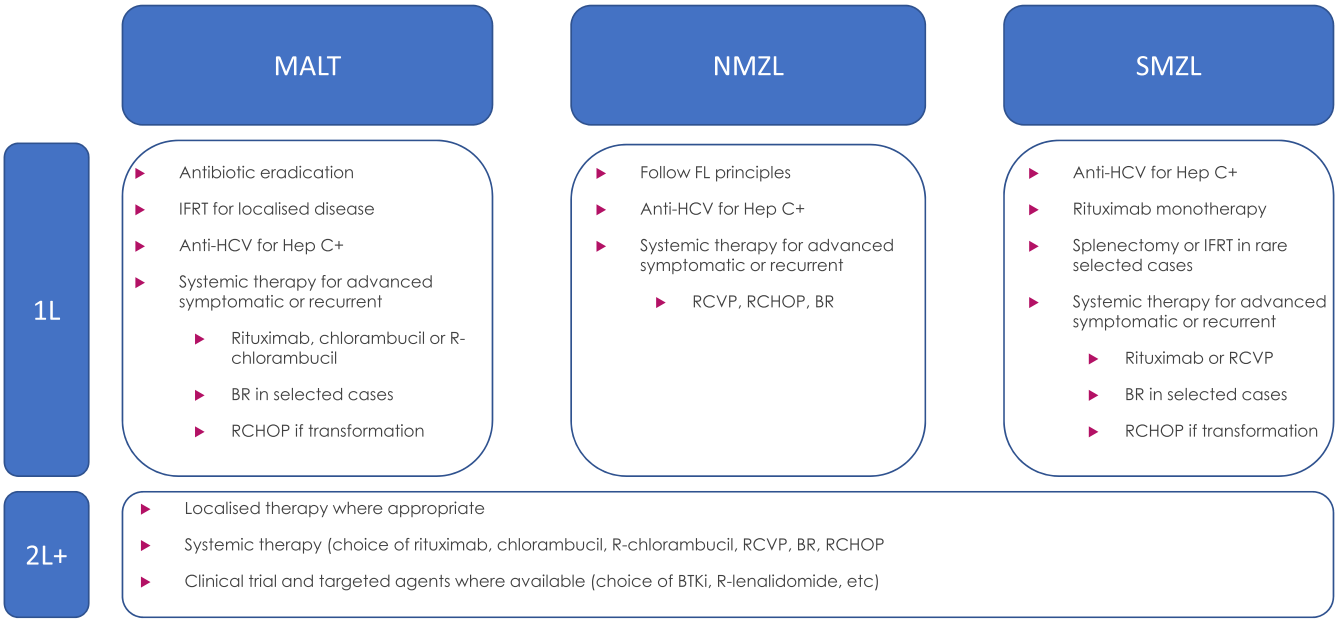


FIGURE 1 Summary and recommendations for marginal zone lymphomas. FL, follicular lymphoma; IFRT, involved field radiotherapy; MALT, mucosa-associated lymphoid tissue; NMZL, nodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma.

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 adequate[97] 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 dehyrogenase (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 disease[104] 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 involvement[107]) 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, immunochemotherapy 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

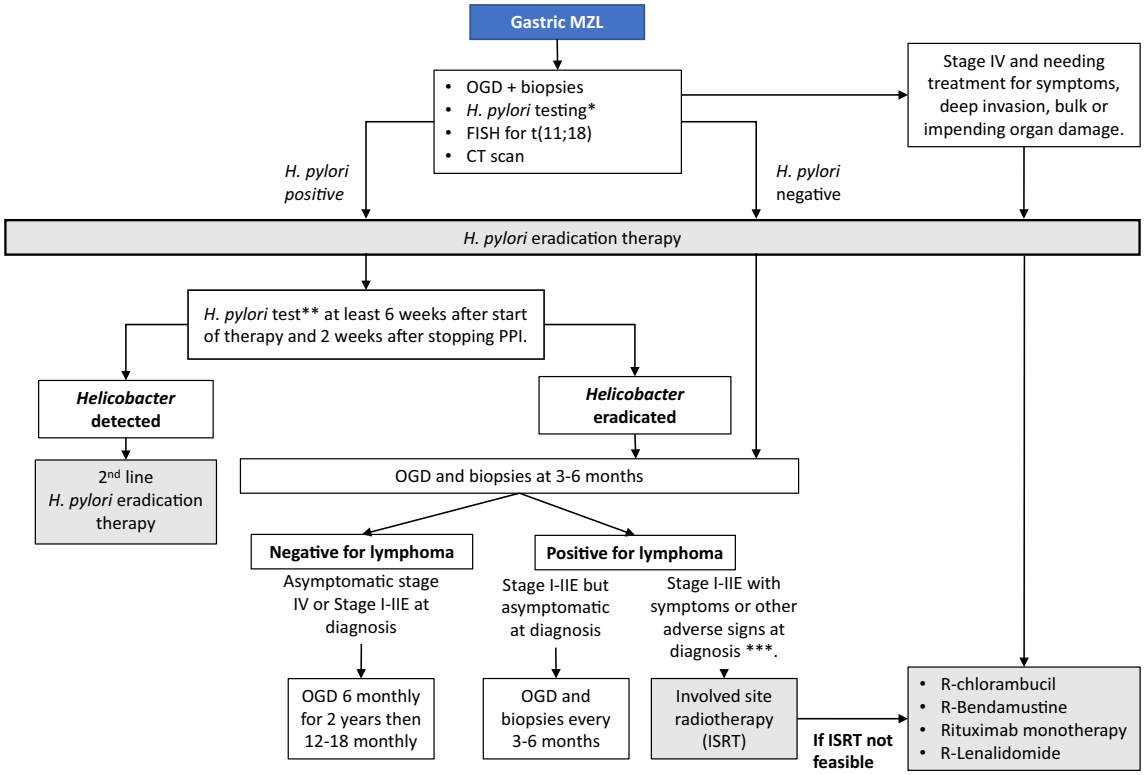
Advanced stage EMZL/MALT lymphoma is incurable, and for asymptomatic patients, a 'watch and wait' approach is appropriate. EMZL, when it disseminates, favours other extranodal sites rather than lymph nodes (Figure 2).

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 maintenance[123] and 81% for RCVP with maintenance rituximab (375 mg/m^2 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 reported[11] but combined chemoradiotherapy carries a high risk of neurotoxicity[137] 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 rituximab[14] 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 upfront 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 NHL1[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)
	IELSG-19[119]	R	138	78, 56	EFS 50% (5 years)	90% (5 years)
		Chlorambucil	131	86, 63	EFS 51% (5 years)	
		R-Chlorambucil	132	95, 79	EFS 68% (5 years) PFS 72% (5 years)	
	Oh et al.[122]	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/m^2 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).

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.

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 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 pirtobrutinib[163] 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.

[a]Showing 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 MZL[167] 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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