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Current Treatments in Marginal Zone Lymphoma

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ABSTRACT: Marginal zone lymphoma (MZL) is a heterogeneous group of indolent non-Hodgkin lymphomas (NHLs). Three subtypes are recognized based on the site of involvement: extranodal MZL, splenic MZL, and nodal MZL. MZL represents 7% of all mature NHLs that exhibit geographical variability in their incidence and association with infectious agents. Each MZL subtype is characterized by unique biology, clinical presentation, therapeutic approach, and natural history. Recent findings have improved risk stratification of patients at diagnosis and after frontline therapy; however, these data are not incorporated into treatment decisions or selections of therapeutic agents. Moreover, a limited number of patients with MZL have been enrolled in randomized clinical trials, and all subtypes have been analyzed as a single group. This approach precludes a full characterization of the efficacy of treatment platforms, and current recommendations are largely derived from experience with follicular lymphoma. Emerging data have demonstrated that novel agents have higher efficacy and safety, expanding the landscape of treatment options. However, despite recent advances, several unmet needs remain in this field, including the discovery of prognostic biomarkers, utility of PET/CT at different extranodal sites, and appropriate sequence of therapies. There is a significant need to design clinical trials with the power to establish standard therapies as well as to assess their effects on patient-reported outcomes. In this review, we will provide an updated analysis of the literature and discuss our approach to the diagnosis and treatment of patients with MZL.

Introduction

Marginal zone lymphoma (MZL) is an indolent disease that represents 7% of all non-Hodgkin lymphomas (NHLs).¹ The World Health Organization classification recognizes 3 subtypes according to primary site of involvement: extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), nodal MZL (NMZL), and splenic MZL (SMZL).² In the United States, EMZL is the most common subtype (60.8%), followed by NMZL (30.3%) and SMZL (8.9%).¹ A similar immunophenotype marks all MZLs, but they exhibit unique clinical features that have therapeutic

implications.^{3,4} However, few clinical trials have enrolled a significant number of patients with MZL, and current recommendations are largely borrowed from treatments of follicular lymphoma and other indolent NHLs. In this manuscript, we will review recent advances in MZL and describe current evidence supporting the appropriate management for each subtype.

Current Standards For Diagnosis and Molecular Testing

EMZL has been described in nearly all tissues. The most

common extranodal sites include the stomach (30%), ocular adnexal (OA; 12%), skin (10%), lung (9%), and salivary gland (7%).¹ Clinical manifestations are variable and depend on the site of origin. EMZL arises as a consequence of chronic inflammation within extranodal sites, with the strongest evidence associated with *Helicobacter pylori* and gastric EMZL.^{5,6} *Chlamydia psittaci* infection was associated with OA EMZL in Europe,⁷ although this association remains unclear in the United States.⁸⁻¹⁰ In addition, chronic inflammation caused by autoimmune conditions such as Sjögren syndrome or Hashimoto thyroiditis were seen in salivary gland and thyroid EMZL, respectively.¹¹⁻¹³

EMZL is diagnosed based on the histopathologic identification of an abnormally expansile population of marginal zone B cells, usually with diffuse or nodular extension into interfollicular zones with associated follicular colonization. Neoplastic cells are small- to medium-sized lymphoid cells with round to slightly irregular nuclei, moderately dispersed chromatin, and inconspicuous nucleoli with relatively abundant pale cytoplasm.² Neoplastic cells have an immunophenotype similar to that of normal marginal zone B cells, including expression of pan B-cell markers (CD19, CD20, CD79a, PAX5) and general lack of expression of CD5, CD10, LEF1, and cyclin D1. Some EMZLs coexpress CD43 and show plasmacytic differentiation with a monotypic plasma cell component. Recent reports highlighted IRTA1 as a possible specific biomarker for EMZL, although integration in clinical practice remains limited.^{14,15}

NMZL is characterized by pathologic lymphadenopathy without evidence of extranodal or splenic involvement.^{2,16} A minority of patients experience B symptoms (drenching night sweats, unintentional weight loss of >10% of body weight over the past six months or fever defined as temperature >100.4°F) or demonstrate bone marrow or peripheral blood involvement.¹⁷ Diagnosis is based on the histology of the lymph node and it requires the exclusion of secondary nodal involvement by EMZL and SMZL. Lymph nodes demonstrate partial or total nodal architectural effacement by a small- to medium-sized lymphoid proliferation that surrounds reactive follicles and expands into the interfollicular areas. Follicular colonization is commonly identified and is a useful feature in making this diagnosis. Neoplastic cells are composed of variable numbers of marginal zone (centrocyte-like and monocytoid) B cells with occasional plasma cells and scattered transformed B cells.² The antigen expression profile is similar to that of other MZLs.¹⁶ There are no specific recurrent cytogenetic abnormalities associated with NMZL; as in other MZLs, there are gains of chromosomes 3, 7, 12, and 18, and losses of 6q23-24.¹⁸ MYD88 L265P mutation is usually absent but has been occasionally reported.^{19,20}

In contrast with EMZL and NMZL, SMZL is characterized by splenomegaly with bone marrow involvement and variable presence of peripheral blood villous lymphocytes. Peripheral lymphadenopathy is uncommon.² Cytopenias may be present, and these are secondary to hypersplenism, autoimmune phenomena, or bone marrow infiltration. An increased risk of SMZL has been reported in patients with chronic hepatitis C (HCV) infection.^{21,22} To establish a definitive diagnosis of SMZL, a bone marrow biopsy is frequently required, because the aspirate is not always sufficient for an accurate diagnosis.²³ The combination of atypical and expansile interstitial nodular involvement with prominent intrasinusoidal infiltration is typical of SMZL.^{18,24} When spleen histology is not available, SMZL diagnosis relies on the integration of clinical features and lymphocyte immunophenotype coupled with the histopathologic evaluation of the bone marrow.²⁵ Although no ancillary biomarker exist, deletion 7q22-36 (seen in 30%-40% of cases of SMZL), mutations in *KLF2* (12%-42%) and *NOTCH2* (10%-25%) are frequently seen, facilitating the diagnosis.²⁶⁻²⁸ Nonmutated IGHV as well as mutations in *NOTCH2*, *KLF2*, and *TP53* have been associated with inferior outcomes.^{26,29,30} Importantly, mutations in *MYD88* L265P can be also observed in 7% to 15% of SMZL cases, underscoring the need for an appropriate clinicopathological diagnosis to avoid an erroneous diagnosis of lymphoplasmacytic lymphoma.¹⁹

CT with contrast remains the prefer imaging for staging and for assessing treatment response in MZL.^{31,32} MRI is valuable in specific locations such as dural, OA, salivary gland, and breast.^{11,33-36} The Lugano Classification considers MZL to be a nonfluorodeoxyglucose (FDG)-avid disease without recommending PET/CT, although the National Comprehensive Cancer Network (NCCN) guidelines list PET/CT as useful in selected patients.^{31,37} The role of PET/CT in EMZL remains questionable because of variable FDG-avidity in extranodal sites. Better detection rates were described in certain locations, such as lung (50%-100%) and head and neck (50%-100%), compared with OA (22%-100%) and stomach (0%-100%).^{38,39} In SMZL and NMZL, the reported FDG-avidity is above 76%, supporting its clinical implementation.^{40,41} PET/CT sensitivity to detected bone marrow involvement in MZL was described in 36%, underscoring the need for bone marrow biopsy in those patients where specific kinds of disease involvement has implications for therapeutic selections.⁴² Nevertheless, in patients with stage I EMZL that has been established by physical examination and imaging, then treated with frontline involved site radiation therapy (ISRT), bone marrow status does not affect lymphoma specific-survival (LSS).⁴³

Stratification For Treatment Selection

Gastric EMZL

The stomach remains the most common EMZL disease location; it is typically associated with chronic gastritis induced by *H pylori*. However, a declining frequency in *H pylori*-associated gastric EMZL has been observed in Italy; it remains unclear whether this association is also decreasing in other regions globally.⁴⁴ Using endoscopic ultrasound to determine involvement of submucosa or regional lymph nodes may help predict a potentially lower success rate of *H pylori* eradication therapy, which underlines the value of this test in the initial work-up.³¹ The presence of t(11;18) confers low probability of response to *H pylori* eradication therapy; patients with this characteristic should be considered for ISRT (Figure 1).^{31,45} The presence of t(11;18) is observed in about 40% of gastric cases; such cases usually present at an advanced stage but they have a lower frequency of higher-grade transformation than patients without this abnormality.⁴⁵⁻⁴⁷ Eradicating the infection is still recommended, in the attempt to decrease the risk of other *H pylori*-associated complications as well as eliminate a source of chronic antigen stimulation that may contribute to lymphoma recurrence.⁴⁷ *H pylori* eradication should be confirmed by urea breath or stool antigen tests at least 6 weeks after starting eradication therapy and at least 2 weeks after the withdrawal of proton-pump inhibitors.³² If initial treatment fails to eradicate *H pylori*, a second-line treatment is recommended. After frontline therapy, upper endoscopy with biopsy is repeated in 3 months to assess response. In those who achieve endoscopic lymphoma remission but have persistent asymptomatic microscopic disease, current guidelines recommend observation for at least 12 months before starting a new line of therapy, because most patients achieve subsequent complete response (CR).^{32,48,49} After eradication therapy, detection of monoclonal rearrangement of the IgVH gene in patients with histological response can persist for years without increasing risk for lymphoma relapse.⁵⁰ Still, the risk of gastric adenocarcinoma remains higher in patients with gastric EMZL, so it remains unclear whether these patients should undergo regular endoscopic surveillance.^{51,52}

Alterations in NF- κ B signaling, with frequent *TNFAIP3* inactivating mutations and translocations in *MALT1/IGH*, are characteristics of *H pylori*-negative gastric EMZL.⁵³ Compared with *H pylori*-associated gastric EMZL, patients without *H pylori* appear to have more advanced-stage disease at diagnosis.^{54,55} ISRT remains the preferred treatment modality in *H pylori*-negative gastric EMZL; it is associated with long-term disease control.⁵⁶ Consensus guidelines recommend a dose of 30 Gy; however, lower

doses (23.5-27 Gy) seem to achieve comparable results.^{31,57} Importantly, eradication therapy in *H pylori*-negative gastric EMZL may still be beneficial a subset of patients.^{58,59}

Nongastric EMZL

Stratification for treatment selection in nongastric EMZL is less well established, but in those with localized disease who are treated with ISRT, the primary extranodal site does not affect survival.⁴³ The most common EMZL location after the gastrointestinal tract is OA. In a large (n = 182) single-center retrospective analysis, Desai et al identified age >60 years and ISRT dose <30.6 Gy as independent factors associated with shorter progression-free survival (PFS) in OA EMZL.³⁴ However, consensus guidelines recommend a dose of 24 Gy; clearly, the appropriate dose in EMZL remains under debate.³¹ Cutaneous EMZL is commonly localized to the skin; relatively few patients (6%) demonstrate extracutaneous spreading.⁶⁰ Most patients exhibit a single skin lesion (58%), and treatment with ISRT is the preferred approach.^{60,61} In patients with asymptomatic widespread cutaneous involvement, the watch-and-wait approach is acceptable. In symptomatic patients, however, single-agent rituximab (Rituxan) is preferred, given the indolent course of the disease.

Pulmonary EMZL is commonly associated with a smoking history. Rarely, there are presenting B symptoms, elevated lactate dehydrogenase (LDH), or bone marrow involvement. Cavitory and large lesions, multifocal parenchymal disease, concomitant extrapulmonary disease, thrombocytopenia, and elevated LDH are features associated with shorter PFS.^{39,62} Regardless of the features of initial presentation, watch-and-wait is suitable in a significant proportion of patients.⁶²

Colorectal EMZL can present during colonoscopy as subepithelial tumors, mucosa granularity, polyps, exophytic lesions, and enlarged folds. In asymptomatic patients without evidence of advanced-stage disease, watch-and-wait after complete endoscopic resection is a valid option.^{63,64}

Therapy Selection

Although molecular data and prognostic factors have been recently described (Table 1), these features are not incorporated into clinical practice for treatment initiation or for selection of a specific regimen. Similarly, no studies have been done regarding therapies for patients with EMZL who progress within 24 months. Based on expert opinion, current guidelines recommend therapy initiation in patients with lymphoma-related symptoms, gastrointestinal bleeding, deep organ invasion, threatened end-organ function, bulky disease, and rapid disease progression; patient preference must be considered as well.^{31,32} The Groupe d'Etude des Lymphomes Folliculaires

(GELF)⁶⁵ criteria correlate with those for high-tumor-burden follicular lymphoma (FL) and are commonly included in the treatment decision for patients with MZL. However, the applicability of those criteria in MZL remains to be determined.

EMZL

EMZL typically remains localized within the tissue of origin for a prolonged period, making ISRT the preferred approach in limited-stage disease (Figure 1). This has been shown to achieve long-term remissions across studies.^{34,66-69} One exception to this recommendation is salivary gland EMZL, in which ISRT can be associated with significant long-term toxicities. Patients with Sjögren syndrome have a higher risk for future contralateral gland EMZL; therefore, other approaches, including single-agent rituximab, should be considered.⁷⁰ Although surgery is not recommended in the management of EMZL, it can provide long-term remission in patients who have had a complete resection for diagnostic purposes, with subsequent watch-and-wait usually advised.^{39,62,71}

TABLE 1. Established Prognostic Factors in MZL

Risk factors	Risk group	Number of factors	Survival rate
Extranodal marginal zone lymphoma			
MALT-IPI¹¹⁷	5-year EFS		
Age ≥70 years	Low	0	70%
Stage III/IV	Intermediate	1	56%
Elevated LDH	High	≥2	29%
POD within 24 months¹¹⁸	10-year OS		
	Early POD	-	64%
	No early POD	-	85%
Splenic marginal zone lymphoma			
HPLL^{119,120}	5-year LSS		
Hemoglobin <9.5 g/dL	A	0	95%
Platelets <80,000/mm³	B	1-2	87%
Elevated LDH	C	3-4	68%
Extrahilar lymphadenopathy	-	-	-

EFS, event free-survival; HPLL, hemoglobin, platelet count, lactate dehydrogenase, and extrahilar lymphadenopathy; LDH, lactate dehydrogenase; LSS, lymphoma-specific survival; MALT-IPI, Mucosa-Associated Lymphoid Tissue International Prognostic Index; MZL, marginal zone lymphoma; OS, overall survival, POD, progression of disease.

In symptomatic patients experiencing advanced-stage disease, who have relapsed after *H pylori* therapy or ISRT, immunotherapy and chemoimmunotherapy are established options in EMZL. Several regimens were tested across indolent NHL (including a small number of patients with MZL), which prevents the selection of one platform as the standard of care. We will discuss the most common therapeutic platforms. **Bendamustine with rituximab (BR)**. Work by the Study group indolent Lymphomas (StiL) and the BRIGHT study established BR as the preferred regimen for indolent lymphomas.^{72,73} These 2 randomized noninferiority clinical trials tested BR vs R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride [Adriamycin], vincristine, and prednisone) or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) in mantle cell lymphoma and indolent NHL. The studies differed in their primary end points: PFS in the StiL trial (NCT00991211) and CR rate in the BRIGHT study (NCT00877006). BR was associated with better tolerance. The efficacy of BR was comparable with that of R-CHOP and R-CVP, with favorable response rates (CR; 31% vs 25%, respectively; *P* = .0225). The median PFS approached 5 years for patients treated with BR.

The MALT2008-01 trial demonstrated the efficacy of BR in 57 patients with EMZL.⁷⁴ The trial tested a response-adapted strategy, and most patients achieved CR or unconfirmed CR (CRu) after 3 cycles with only 14 (25%) patients requiring more than 4 cycles of treatment. Responses did not differ by primary site or t(11;18) status, and the reported 7-year event-free survival (EFS) rate was 88%.⁷⁵

Through studies, BR demonstrated acceptable safety. The main grade ≥3 adverse events (AEs) were lymphopenia (34%-74%) and neutropenia (5%-49%). The most common all-grade

nonhematological toxicity was drug hypersensitivity (6%-15%); only 4% developed alopecia.^{72,73,75} Notably, bendamustine leads to prolonged T-cell depletion, which increases the risk for opportunistic infections.⁷⁶ Prophylaxis for *Pneumocystis jirovecii* and varicella-zoster virus is recommended. In a recent 5-year update of the BRIGHT study,⁷⁷ authors reported a higher incidence of nonmelanoma skin carcinomas in patients treated with bendamustine-based regimens, underscoring the need for regular dermatologic surveillance of such individuals.

R-CVP and R-CHOP. As previously described, R-CVP and R-CHOP demonstrated efficacy similar to that of BR, although both regimens were associated with more frequent AEs. In the StiL trial, R-CHOP exhibited more hematological toxicity (68% vs 30%; $P < .0001$), infections (50% vs 27%; $P = .0025$), peripheral neuropathy (29% vs 7%; $P < .0001$), and stomatitis (19% vs 6%; $P < .0001$) compared with BR. Further, all patients developed alopecia.⁷² The most common AEs associated with R-CVP were neutropenia (56%), infections (50%), peripheral neuropathy (47%), and constipation (44%).⁷³ NCCN guidelines list R-CHOP and R-CVP as preferred first-line therapy regimens for MZL. However, based on comparable efficacy with improved toxicity, we favor the selection of BR as frontline therapy in EMZL.

Lenalidomide with rituximab (R²). Lenalidomide (Revlimid) at a dose of 25 mg on days 1 to 21 demonstrated efficacy in EMZL, with an overall response rate (ORR) of 61.1% (CR rate, 33.3%).⁷⁸ Commonly, lenalidomide is combined with rituximab to enhance single-agent activity. In a single-institution study, the combination of lenalidomide (20 mg on days 1 to 21) with rituximab (day 1 of each cycle) was tested in patients with advanced-stage indolent NHL; GELF criteria were not required for enrollment.^{79,80} The study enrolled 30 patients with MZL (NMZL, 60%; EMZL, 37%; SMZL, 3%), and the ORR was 93% with a CR rate of 70% and a median PFS of 59.8 months. Responses were similar across MZL subtypes. The most common all-grade AEs were fatigue (93%) and nausea/vomiting (73%). R² demonstrated similar efficacy (ORR, 80%; CR rate, 54%) in a multicenter EMZL study with no new safety concerns.⁸¹

Single-agent rituximab. Rituximab demonstrated efficacy in the treatment of indolent lymphomas and was associated with an acceptable safety profile. Conconi et al proved clinical activity ($n = 23$) of frontline rituximab in EMZL; patients' ORR was 87% (CR rate, 48%) with a median time to treatment failure (TTF) of 22 months.⁸² Similar results were seen in patients with gastric EMZL ($n = 27$) who were refractory to *H pylori* eradication therapy or not eligible for this approach.⁸³ However, these results were not reproduced in subsequent studies, which

frequently saw PR or stable disease as best responses and shorter median TTFs.⁸⁴⁻⁸⁶ Single-agent rituximab is a reasonable approach in patients who are not candidates for combination chemotherapy regimens. It has a favorable safety profile, but the trade-off is a low likelihood of durable remissions.

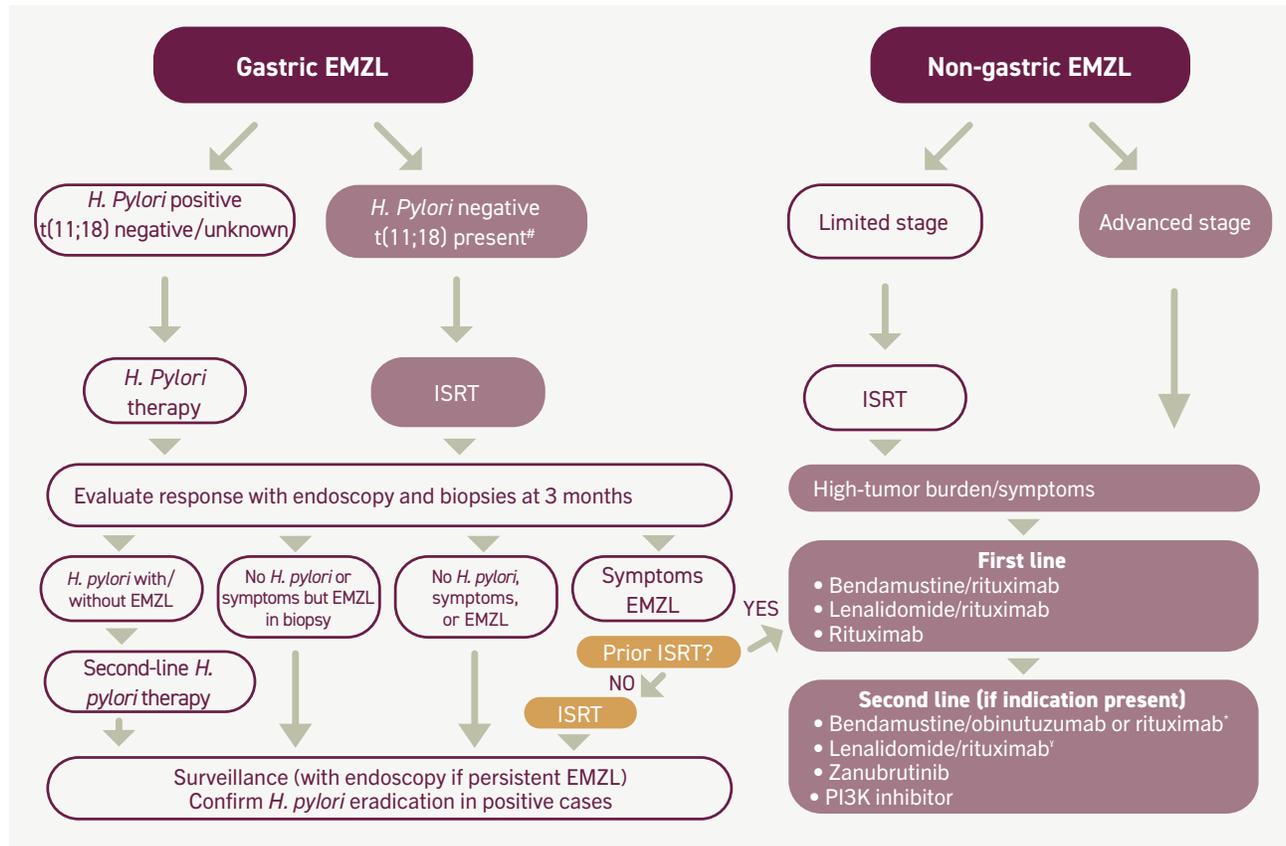
Chlorambucil with rituximab. A total of 454 patients participated in the IELSG-19 (NCT00210353), the only randomized clinical trial exclusively focused on untreated EMZL; its primary end point was EFS.⁸⁷ The combination arm with chlorambucil and rituximab resulted in significantly longer 5-year EFS (68%) compared with single-agent chlorambucil (51%) or single-agent rituximab (50%; $P = .0009$). Despite proven efficacy, this combination is not commonly selected in the United States. The NCCN guidelines suggest this approach for elderly or infirm patients.³¹

⁹⁰Y-Ibritumomab tiuxetan. ⁹⁰Y-Ibritumomab tiuxetan (⁹⁰Y-IT) is a radio-conjugated murine monoclonal antibody approved for certain patients with FL: those with relapsed/refractory (R/R) CD20-positive disease or as consolidation following induction therapy in untreated patients.⁸⁸ Its use encompasses a single treatment plan and induces cell death via antibody-stimulated cytolysis and apoptosis caused by emitted ionizing radiation.⁸⁹ Two single-institution studies tested this approach in untreated indolent NHL including MZL ($n=11$ and 17 , respectively).^{90,91} Although baseline characteristics differed between the patients in the studies, both studies reported an ORR above 88.4%, with most patients achieving CR/CRu (59%-96.7%). The 5-year PFS rate was between 41.2% and 82%, with grade 3 or greater neutropenia (53%-61.3%) and thrombocytopenia (35% in both studies) as common toxicities. One case of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) occurred after ⁹⁰Y-IT. In the FDA Adverse Event Reporting System database analysis, this treatment approach has yielded incidence rates of MDS and AML of 6.9% and 3.6%, respectively.⁸⁹ The selection of this treatment by clinicians has been limited by concerns about secondary myeloid malignancies as well as by significant logistic considerations that are involved in delivering this compound. It is currently unclear where ⁹⁰Y-IT fits into the MZL landscape, but this approach can be considered in patients with appropriate marrow cellularity who request a short treatment program.

SMZL

There is no full agreement regarding the treatment of SMZL; watch-and-wait is an acceptable approach in asymptomatic patients.³² Consensus guidelines support treatment initiation in those with symptomatic splenomegaly, systemic

FIGURE 1. Algorithm Approach to Newly Diagnosed and Relapsed/Refractory Gastric (A) and Nongastric (B) Extranodal Marginal Zone Lymphoma



EMZL, extranodal marginal zone lymphoma; H pylori, Helicobacter pylori; ISRT, involved site radiation therapy; PI3K, phosphatidylinositol 3-kinase.
 #Patients with H pylori infection and presence of t(11;18) still require eradication therapy.
 *If not previously treated with bendamustine.
 †If not previously treated with lenalidomide.

symptoms, and cytopenias (hemoglobin <10 g/dL, platelets <80,000/mm³, and neutrophils <1000/mm³). In patients with chronic HCV infection, antiviral therapy is recommended.^{32,92} Patients with concomitant autoimmune cytopenias should receive conventional treatments for these diseases prior to lymphoma therapy.²³ Treatment options include splenectomy, chemoimmunotherapy, and single-agent rituximab; none has a clear survival benefit over the others (Figure 2).⁹³⁻⁹⁶

Single-agent rituximab. Rituximab is the preferred approach in patients with SMZL requiring therapy. In a retrospective analysis, patients (n = 106) received an induction phase of 6 weekly doses of rituximab 375 mg/m² followed by maintenance every 2 months for up to 2 years or follow up in responders.^{94,97} The ORR at the end of induction was 92%, with 44% CR, 21% CRu, and 27% partial response (PR) rates. Clinical splenomegaly resolved in a median of 4 weeks (range, 1-48) and hematologic response was seen in a median of 2 weeks (range, 1-32). The 5-year freedom from

progression (FFP), overall survival (OS), and LSS rates were 71%, 93%, and 99%, respectively. Among responders, maintenance therapy was associated with better 5-year FFP rates (79% vs 52%; P = .0006) without difference by maintenance duration (P = .90). The role of rituximab maintenance was also tested in the E4402 study (NCT01406782) in patients with asymptomatic, low-tumor-burden, non-FL indolent lymphomas.⁸⁵ Maintenance was associated with longer median TTF compared with retreatment (4.8 vs 1.4 years; P = .012) without OS benefit.⁹⁵ As a result, maintenance treatment can be considered optional and should be only considered after a careful evaluation of potential infectious complications.

Bendamustine with rituximab. The BRISMA/IELSG-36 trial (NCT02853370) tested BR in 56 patients with untreated SMZL or who relapsed after splenectomy.⁹⁸ The ORR was 91% (CR rate, 73%) with estimated 3-year PFS and OS rates of 90% and 96%, respectively. Notably, treatment discontinuation occurred in 9% due to toxicity; 68% experienced grade 3 or greater toxicity, largely hematologic; and

1 patient died from infection. BR is an effective platform in patients with SMZL, however, the toxicity profile appears worse than in other indolent NHL preventing its generalization as preferred frontline therapy.

Splenectomy. Splenectomy facilitates SMZL diagnosis; it also provides quick symptom control associated with splenomegaly, resolution of cytopenias, and prolonged disease control.⁹⁹ However, while this approach was once popular, the practice of splenectomy has steadily declined in the United States.⁹⁶ Splenectomy does not address disease in bone marrow and/or blood and it is associated with potential perioperative and infectious complications. It should be reserved for symptomatic patients who are refractory to systemic agents.¹⁰⁰

NMZL

Few data exist on the management of NMZL, and there is no standard of care.¹⁶ Consensus guidelines recommend the same treatment as for other MZL subtypes, with ISRT in patients with limited-stage disease. In those patients with advanced-stage disease that is asymptomatic and has a

low-tumor-burden, a watch-and-wait approach, similar to that used in FL, is reasonable. In patients who are symptomatic or presenting with a high-tumor-burden, single-agent rituximab or BR are appropriate options (Figure 2).

Relapsed/Refractory MZL

Obinutuzumab. Obinutuzumab (Gazyva) is a recombinant type II glycoengineered anti-CD20 and immunoglobulin G Fc-optimized monoclonal antibody. It has the potential to generate an effect in the recipient more potent than that of rituximab.¹⁰¹ In the GAUGUIN study (NCT00517530), 40 patients with indolent NHLs (MZL, n = 3) were randomly assigned to receive 8 cycles of obinutuzumab at 400 mg on days 1 and 8 of cycle 1 and day 1 of cycles 2 to 8 (400/400 mg arm) or 1600 mg on days 1 and 8 of cycle 1 and 800 mg on day 1 of cycles 2 to 8 (1600/800 mg arm). In patients with rituximab-refractory indolent NHL (n = 22; 55%), obinutuzumab achieved an ORR of 50% (CR/CRu rate, 22.7%) in the 1600/800 mg arm compared with 8.3% (CR/CRu rate, 11.1%) in the 400/400mg arm.¹⁰² The most

FIGURE 2. Algorithm Approach to Newly Diagnosed and Relapsed/Refractory Nodal Marginal Zone Lymphoma (A) and Splenic Marginal Zone Lymphoma (B)

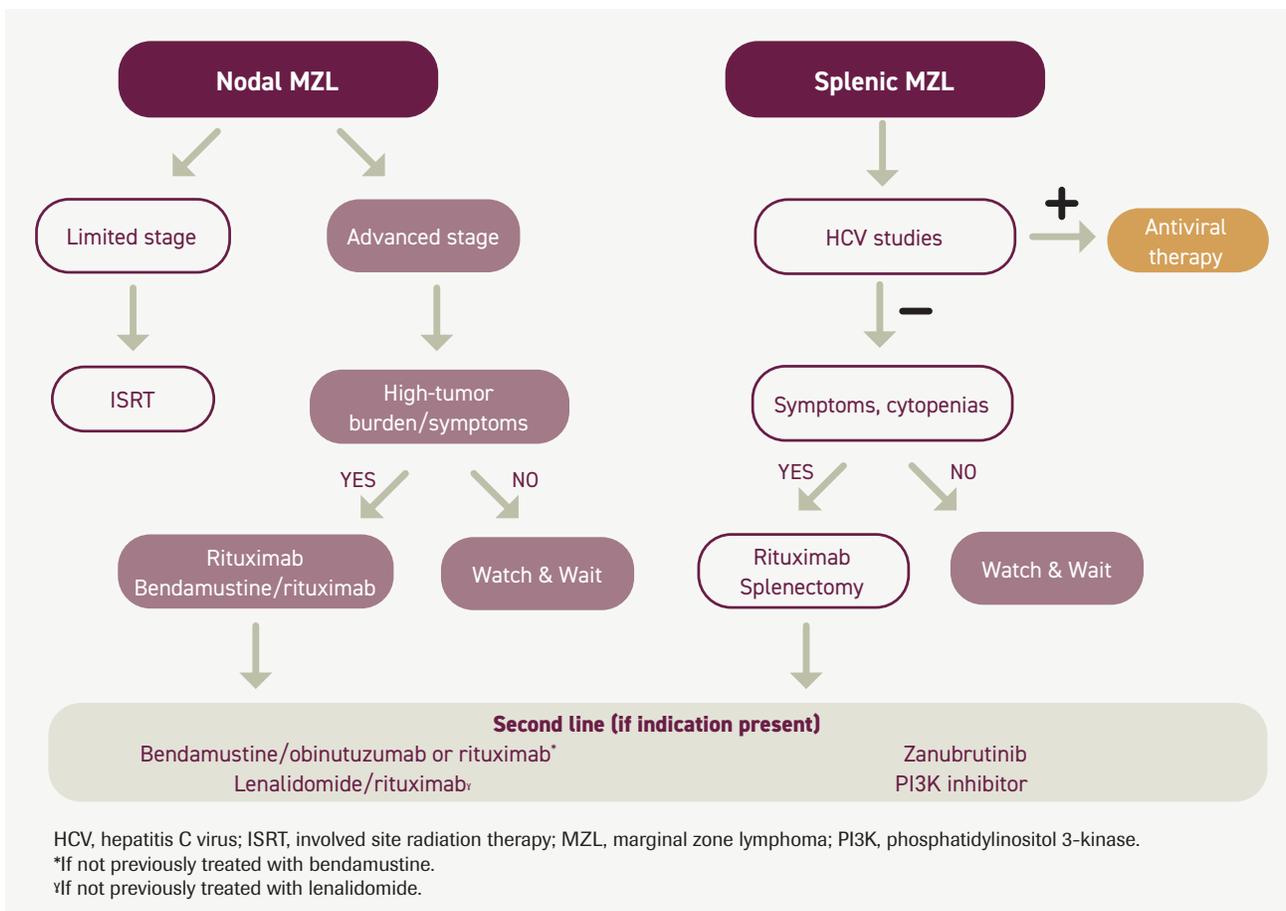


TABLE 2. Clinical Trials Testing Phosphatidylinositol 3-Kinase (PI3K) Inhibitors in Relapsed/Refractory MZL

PI3K inhibitor	Route	Total number of patients	Patients with MZL	ORR (CR)	ORR% in MZL (CR)	Median PFS (mo)	Grade 3/4 AEs
Idelalisib (2014) ^{111*}	PO	125	15	57% (6%)	47% (6.6%)	11	Neutropenia (27%), AST/ALT elevation (13%), diarrhea (13%), pneumonia (7%)
Copanlisib (2017) ^{113,114}	IV	142	23	59% (12%)	70% (9%)	12.5	Hyperglycemia (40.1%), hypertension (23.9%), pneumonia (10.6%), diarrhea (8.5%)
Duvelisib (2019) ¹¹²	PO	129	18	47.3% (1.6%)	39.0% (5.6%)	9.5	Neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), thrombocytopenia (11.6%)
Parsaclisib (2020) ^{121†}	PO	-	94	-	54.3% (6.4%)	13.8	Neutropenia and diarrhea (8.1% each)
Umbralisib (2021) ¹²²	PO	208	69	47.1% (25.5%)	49.3 (16%)	Not reached in MZL	Neutropenia (11.5%), diarrhea (10.1%)
Copanlisib with rituximab (2021) ¹¹⁵	IV	652	95	81% (34%)	26% (39%)	22.1 in MZL	Hyperglycemia (56%), hypertension (40%), neutropenia (16%), pneumonia (7%), diarrhea (5%)

ALT, alanine transaminase; AST, aspartate transaminase; CR, complete response; IV, intravenous; mo, months; MZL, marginal zone lymphoma; ORR, overall response rate; PFS, progression-free survival; PO, by mouth.

*Voluntary withdrawal from the United States for follicular lymphoma and small lymphocytic lymphoma.

†Voluntary withdrawal of FDA submission for approval in follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma.

common AEs included infusion-related reactions, infection, asthenia, and nausea.

Bendamustine with obinutuzumab. The randomized phase 3 GADOLIN trial (NCT01059630) tested bendamustine with obinutuzumab followed by obinutuzumab maintenance (n = 194; MZL = 27) vs bendamustine monotherapy (n = 202; MZL = 19) in rituximab-refractory indolent NHL.¹⁰³ Median PFS was significantly longer in the combination cohort (not reached vs 14.9 months; *P* = .0001) with common grade 3 or greater AEs including neutropenia (33%), thrombocytopenia (11%), anemia (8%), and infusion-related reactions (11%). In an updated analysis,¹⁰⁴ authors confirmed initial observations of longer median PFS in the combination arm (25.8 vs 14.1 months) with an HR for progression or death of 0.57 (*P* < .001) associated with OS benefit (HR, 0.67; *P* = .027). However, 51.3% experienced infections during maintenance. Cardiac toxicity was more common in the combination arm with grade 3 or greater atrial fibrillation (n=2) and heart failure (n=2).

Lenalidomide with rituximab (R²). R² is an active combination in MZL, currently FDA approved after 1 line of therapy. The AUGMENT trial (NCT01938001) randomly enrolled 358 patients who required treatment per investigator

assessment to R² (n = 178) vs placebo with rituximab (n = 180).¹⁰⁵ The treatment schedule was lenalidomide 20 mg, or placebo, on days 1 through 21 of a 28-day cycle, for 12 cycles, with rituximab 375 mg/m² weekly in cycle 1 and on day 1 of cycles 2 through 5. As in prior trials, most patients enrolled in this study had FL (n = 295; 82%); in those with MZL (n = 63; 18%), EMZL (n = 30) was the most common (NMZL, n = 18; SMZL, n = 15). ORR at 78% (CR, 34%) vs 53% (CR, 18%; *P* = .001) and the primary study end point of median PFS (HR, 0.46; *P* < .0001) favored R². Common AEs associated with R² were neutropenia (58%; grade ≥3, 50%), diarrhea (31%), constipation (26%), cough (23%), and fatigue (22%). A subgroup analysis in MZL demonstrated a trend toward better ORR (65% [CR, 29%] vs 44% [CR, 13%]; *P* = .1313) in the R² arm without improving PFS (unstratified HR, 1.00). Although no PFS benefit was observed in the AUGMENT trial, the results of several other studies support the incorporation of lenalidomide-based programs in MZL.⁷⁸⁻⁸¹

Emerging and Novel Therapies for Relapsed/Refractory MZL

Ibrutinib. Ibrutinib (Imbruvica) is a potent and irreversible

inhibitor of Bruton tyrosine kinase (BTK), an integral component of the B-cell receptor pathway. Ibrutinib was evaluated in a single-arm phase 2 study in patients with MZL treated with at least 1 prior therapy.¹⁰⁶ Patients received ibrutinib 560 mg daily until progression or unacceptable toxicity, for up to 3 years. Most had EMZL (n = 32; 51%) followed by NMZL (n = 17; 27%) and SMZL (n = 14; 22%). In 60 evaluable patients, the ORR (primary end point) was 48% (95% CI, 35%-62%) with only 3% (n = 2) achieving CR. ORRs by MZL subtype were 47% in EMZL (CR, 6%), 50% in SMZL (no CRs), and 41% in NMZL (no CRs). There was a median PFS of 15.7 months.¹⁰⁷ Common grade 3 or greater AEs included anemia (14%), pneumonia (8%), and fatigue (6%). Importantly, 62% of the patients discontinued treatment, with disease progression (32%) and AEs (17%) as common causes. Atrial fibrillation occurred in 6% (all grade 1-2). Exploratory biomarker analysis demonstrated shorter response in cases with mutations in *KMT2D* and *CARD11*.

Zanubrutinib. The MAGNOLIA trial (NCT03846427) demonstrated safety and efficacy of the second-generation BTK inhibitor zanubrutinib (Brukinsa) in MZL.^{108,109} Investigators provided zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity. The study enrolled 68 patients (EMZL, 38%; NMZL, 38%; SMZL, 18%; and unknown, 6%) with R/R MZL; the ORR (primary end point) was 68.2% (CR rate, 25.8%). Median duration of response and PFS were not reached. Most common cause of treatment discontinuation (41.2%) was disease progression, observed in 23.5%. Frequent AEs included diarrhea (22.1%), bruising (20.6%), and constipation (14.7%). Neutropenia (7.3%) was the most common grade ≥ 3 AE. Atrial fibrillation/flutter occurred in 2 patients. Based on these data, zanubrutinib is the BTK inhibitor of choice in MZL.

Phosphatidylinositol 3-kinase (PI3K) inhibitors. The PI3K family is classified into 3 distinct classes. Class I is most relevant to cell growth and survival and has been the target for drug development. The class I PI3K pathway includes 4 isoforms— α , β , δ , and γ —with the last 2 isoforms largely expressed in leukocytes.¹¹⁰ Several PI3K inhibitors have been tested in R/R indolent NHL after at least 2 prior lines of therapy. Idelalisib is a potent, small-molecule inhibitor of PI3K δ , and it was the first agent of this group evaluated in clinical trials. Duvelisib is a dual inhibitor of PI3K- δ and - γ ; copanlisib is an intravenous pan-class I PI3K inhibitor, with predominant activity against PI3K- α and - δ isoforms; and umbralisib is a dual inhibitor of PI3K δ /casein kinase-1 ϵ . Table 2 summarizes the safety and efficacy of these agents.

Idelalisib. In a single-group, open-label, phase 2 study, the response rate (primary end point) to idelalisib (Zydelig) 150 mg twice daily was 57%, with only 6% achieving CR. The

median PFS was 11 months, with similar results across MZL subtypes. The most common AEs (all grades) included diarrhea (43%), fatigue (30%), nausea (30%), cough (29%), and pyrexia (28%).¹¹¹ Idelalisib was voluntarily withdrawn for R/R FL and small lymphocytic lymphoma from the United States market in January 2022.

Duvelisib. In the phase 2 DYNAMO trial (NCT01882803), duvelisib (Copiktra) 25 mg twice daily demonstrated an ORR of 47.3% (95% CI, 38%-56%) largely based on PRs (45.7%).¹¹² With a median follow-up of 32.1 months, the median PFS was 9.5 months (95% CI, 8.1-11.8). Frequent all-grade AEs included diarrhea (48.8%), nausea (29.5%), neutropenia (28.7%), fatigue (27.9%), and cough (27.1%).

Copanlisib. In the CHRONOS-1 trial (NCT01660451), copanlisib (Aliqopa) at a dosage of 60 mg on days 1, 8, and 15 of a 28-day cycle achieved an objective response rate of 59%, with 12% attaining CRs. Common AEs included hyperglycemia (50%), diarrhea (34%), hypertension (30%), fatigue (30%), neutropenia (30%), and fever (25%).¹¹³ Most AEs decreased in incidence and grade after 6 months, except for grade 3 diarrhea, which increased from 4.9% to 10.8% after 1 year.¹¹⁴ To improve single-agent efficacy, rituximab was incorporated with copanlisib in the randomized CHRONOS-3 trial (NCT02367040). The combination arm demonstrated a better PFS compared with placebo with rituximab (HR, 0.52; 95% CI, 0.39-0.69; $P < .0001$). Similar to effects seen with single-agent copanlisib, hyperglycemia and hypertension were substantial: 64% and 37% of the patients enrolled in the combination arm required medications to address these AEs, respectively.¹¹⁵

Umbralisib. In the phase 2b UNITY-NHL trial (NCT02793583), treatment consisted of umbralisib (Ukoniq) 800 mg once daily. Across all indolent NHLs, the ORR was 47.1%. Umbralisib achieved higher CR rates (Table 2) compared with other single-agent PI3K inhibitors. Furthermore, with a median follow-up of 27.8 months, the median PFS (95% CI, 12.1 months to not estimable) was not reached in the MZL subgroup. Common AEs included diarrhea (59.1%), nausea (39.4%), fatigue (30.8%), vomiting (23.6%), and cough (20.7%). These observations encouraged the selection of umbralisib over other agents, but in February 2022, the FDA released a notice with information regarding a possible increased risk of death associated with umbralisib. The agency suspended the enrollment of new patients in clinical trials while the investigation is undergoing.¹¹⁶

Conclusions

MZL is commonly characterized by an indolent course, with patients experiencing long survival. Patients with limited-stage EMZL can achieved prolonged remissions with ISRT, and that treatment remains the preferred approach.

Patients with SMZL are best managed with single-agent rituximab. For patients with advanced-stage but asymptomatic, low-tumor-burden NMZL, watch-and-wait is a reasonable approach, with a significant number of patients not needing therapy for years. Patients with symptoms and/or a high-tumor-burden appear best served by the BR regimen. Several treatment platforms have demonstrated efficacy in R/R MZL, but potential toxicities should be carefully considered before treatment selection. The current therapeutic landscape in MZL allows clinicians to limit the use of cytotoxic chemotherapy, and future studies should delineate the appropriate sequence of novel agents in MZL. ■

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CONFLICT OF INTEREST:

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