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Lymphoma (DO Persky, Section Editor)

Marginal Zone Lymphoma: State-of-the-Art Treatment

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Opinion statement

Despite being the second most common indolent non-Hodgkin's lymphoma (iNHL), marginal zone lymphoma (MZL) remains largely understudied, and given its underlying disease heterogeneity, it is challenging to define a single treatment approach for these patients. For localized disease, local therapy is recommended such as triple therapy for *H. pylori* in gastric extranodal MZL, splenectomy for splenic MZL, and radiotherapy for nodal MZL. For disseminated disease with low tumor burden, a watch and wait or single-agent rituximab can be used. However, for symptomatic disease, a similar approach to follicular lymphoma (FL) can be used with chemoimmunotherapy approaches such as bendamustine and rituximab. High FDG uptake is not common in MZL and is not diagnostic by itself of transformation to high-grade lymphoma but informs the choice of the site to be biopsied. Transformation into a large B cell lymphoma is treated with R-CHOP-like regimens. Patients with relapsing disease after at least one CD20-based therapy have several recently approved chemotherapy-free options including B cell receptor inhibitors such ibrutinib (approved specifically in MZL) and immunomodulatory agents such as lenalidomide and rituximab (FDA approved in MZL and FL). Phosphoinositide 3-kinase (PI3K) inhibitors have shown excellent activity in iNHL, specifically in MZL, with breakthrough designation status for copanlisib and umbralisib, allowing off label use of this class of agents in clinical practice. With the availability of prospective clinical trials using chemo-free approaches, specifically those targeting abnormal signaling pathways activated in MZL tumors and its microenvironment, treating physicians are encouraged to enroll patients on these clinical trials in order to better understand the underlying biology, mechanisms of response, and resistance to current therapies and help design future rationale combination strategies.

Introduction

Marginal zone lymphoma (MZL) is the second most common subtype of indolent B cell non-Hodgkin's lymphoma (iNHL). It is derived from post-germinal center memory B cells present in the marginal zone of lymphoid organs [1]. MZL comprises approximately 6% of all lymphoid malignancies [2]. Based on the 2016 World Health Organization (WHO) Classification of Lymphoid Neoplasms, MZL has been subdivided into 3 major categories: extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), nodal MZL (NMZL), and splenic MZL (SMZL) representing 70%, 20%, and 10% of all MZL, respectively [3]. The median age differs by subtype but is close to 67 for all MZL subtypes [2]. Of the extranodal sites, the most common is stomach/gastric (GALT lymphoma) followed by ocular/adnexal, lung, skin, and salivary gland [2]. There appears to be an association between chronic immune stimulation (bacterial, viral, autoimmune) and MZL [8, 9]. Of the infectious causes of MZL, *Helicobacter pylori* has the strongest association, notoriously causing GALT lymphoma, *Chlamydophylia psittaci* is associated with ocular/adnexal lymphoma, *Borrelia burgdorferi* with cutaneous MZL, and *Campylobacter jejuni* with immunoproliferative small intestinal disease (IPSID) [10–13]. IPSID "mediterranean lymphoma" is a variant of EMZL characterized by oversecretion of defective immunoglobulin alpha heavy chains [14, 15]. Hepatitis C (HCV), an RNA virus is linked to the pathogenesis of several B cell NHL, including MZL. Among HCV-positive patients with MZL, skin involvement is the most common (35%) followed by salivary glands (25%) and orbit (15%) [16]. Autoimmune conditions such as Hashimoto's and Sjogren's syndrome have been associated with thyroid and parotid/lung MZL, respectively [17, 18]. MZL has been associated with several genetic alterations including chromosomal translocations (Table 1): Trisomy 3, t(11;18), t(3;14), mutations of NOTCH2, MLL2, KLF2 in NMZL and SMZL, but PTPRD mutation is only observed in 20% of NMZL providing potential diagnostic tool differentiating NMZL from other subtypes of MZL [4]. Although, there are no specific pathognomonic genetic alteration for MALT lymphomas, the majority of these alterations lead to the activation of the NF-κB pathway [5]. MZL is characterized by invasion of the marginal zone, with subsequent interfollicular expansion by predominantly small abnormal B cells with the following immunophenotype: kappa/lambda-positive, CD20-positive, BCL-2-positive, cyclin D1-negative, CD5-negative, CD10-negative, CD103-negative, with or without CD23 positivity. Plasmacytic differentiation and follicular colonization can be observed. Work up of MZL involves obtaining a complete blood count, comprehensive metabolic panel, lactate dehydrogenase (LDH), and Hepatitis B and C viral panels as well as *H. pylori* if GALT lymphoma is suspected. Computed tomography of the chest, abdomen, and pelvis and or whole-body PET-CT are usually obtained. For GALT lymphoma, endoscopy should be performed. With the exception of gastric MALT lymphoma, staging is done utilizing the Ann Arbor Staging system.

Table 1. Summary of the main genetic alterations in marginal zone lymphomas

Genetic alterations	Site
PTPRD mutation [4]	NMZL (20%)
MLL2 mutation [4]	SMZL (15%), NMZL (34%)
NFKB pathway mutation [4]	SMZL (34%), NMZL (54%)
NOTCH2 mutation [4]	SMZL (10–21%), NMZL (20%)
KLF2 mutation [4]	SMZL (10–40%), NMZL (17%)
Trisomies 3 and 18 [5–7]	Several Sites
t(11;18)(q21;q21)–API2-MALT1 [5–7]	Most commonly lung (45%), stomach (23%), and intestine (19%)
t(1;14)(p22;q32)–BCL10-IGH [5–7]	Stomach (2%), lung (8%), and intestine (7%)
t(14;18)(q32;q21)–IGH-MALT1 [5–7]	Salivary (6%), ocular adnexa (16%), and skin (7%)
t(3;14)(p14.1;q32)–FOXP1-IGH [5–7]	Thyroid (50%), ocular adnexa (20%), and skin (10%)

SMZL, splenic marginal zone lymphoma; *NMZL*, nodal marginal zone lymphoma

GALT lymphoma is usually staged using the Lugano Modification of the Ann Arbor Staging System [19]. The Follicular Lymphoma International Prognostic Index score has been validated and used in MZL [20], but the development of the MALT-IPI is more specific to the disease [21]. MALT-IPI utilizes 3 risk factors: age ≥ 70 years, Ann Arbor stage III–IV, and an elevated LDH [21]. While the majority of MZL have a relatively indolent course, like other iNHLs, it too can transform to a more aggressive lymphoma. Histologic transformation to DLBCL occurs in 7.5% of cases, with the majority (73.5%) from EMZL, followed by NMZL (14.7%) [22, 23]. Rarely, MZL can transform to Hodgkin lymphoma [22, 23].

Current treatment options

Given the heterogeneity of MZL, there is no consensus on its management, expect *Helicobacter pylori* eradication for localized GALT. Current guidelines recommend starting therapy for patients with high tumor burden or once they become symptomatic. Patients with nodal marginal zone lymphomas are managed similarly to follicular lymphomas, with radiotherapy for localized disease, watch and wait for disseminated low tumor burden, and chemoimmunotherapy for disseminated disease with high tumor burden. For patients with splenic marginal zone lymphoma that require treatment, weekly rituximab is preferred over splenectomy that is usually reserved for fit patients with symptomatic splenomegaly without bulky lymphadenopathy. For patients with hepatitis C virus, antiviral therapy should be the first-line approach as it can lead by itself to regression of the lymphoma. For patients with localized non-gastric MALT lymphoma, radiotherapy is preferred, but surgery can be considered for certain locations such as the breast or thyroid. For advanced stage MZL who require treatment, regardless of subtype, a rituximab-based regimen such as with bendamustine/chlorambucil is appropriate for frontline therapy. In the relapsed/refractory setting, there is a plethora of options that are currently available with anti-CD20 monoclonal antibodies either alone or in combination with chemotherapy, and novel targeted agents as detailed below.

Frontline therapy

Antibiotics

H. pylori eradication therapy—frontline therapy for H. pylori+GALT

Chronic *H. pylori* infection has been strongly associated with GALT lymphomagenesis. Therefore, *H. pylori* eradication therapy remains the only standard treatment modality for localized disease IE-IIE, with several effective anti-H pylori regimens available with an overall remission rate close to 80% [24, 25]. However, EMZL harboring t(1;14) and t(11;18) are associated with resistance to *H. pylori* eradication regimens. Interestingly, *H. pylori*-negative patients still have good response (close to 50%) to antibiotics-based regimen, suggesting that other microorganisms are involved in the pathogenesis of GALT. However, antibiotic treatment for non-gastric MALT lymphomas remains investigational. Unlike *H. pylori*, the link between *Chlamydophila psittaci* and MZL for example is weak. Doxycycline, a

tetracycline antibiotic, commonly used for the treatment of community-acquired pneumonia and tick-borne infections was evaluated in a phase 2 trial in 47 patients with stage 1 ocular/adnexal MZL [26], with an overall response rate (ORR) of 65%, complete response (CR) of 17%, and 5-year progression-free survival (PFS) of 55% [26].

Radiotherapy—frontline therapy, particularly nodal/extranodal early stage

MALT lymphomas, especially GALT, remain localized for a long period of time, and NMZL can be managed similar to FL. Therefore, for early stage, localized disease, radiotherapy is an option. In a retrospective analysis of stage I-II E of MALT lymphomas, patients received primary RT [27]. For those with ocular/adnexal MALT, the majority of patients received 25 Gy, the majority of salivary gland or thyroid MALT received 25–30 Gy [27]. Those with GALT received a standard dose of 30–35 Gy to the stomach, paragastric, and celiac lymph nodes. This approach resulted in CR/CRu of 99% and 10-year OS of 87% [27].

Radioimmunoconjugate—extranodal and nodal MZL

^{90}Y ibritumomab tiuxetan is a radioactive yttrium 90 attached to rituximab that targets CD20. In a single center, non-randomized phase 2 study that included both extranodal and nodal subtypes of MZL, a total of 2 doses were given, and patients were followed up for 5 years [28]. Sixteen patients were enrolled and there was an ORR of 87.5% at 12 weeks with a CR of 50% that increased to 63% at 9 months. The median PFS was 47.6 months. The 5-year PFS and OS were 40% and 72%, respectively. Overall, ^{90}Y ibritumomab tiuxetan was well tolerated and led to long-term responses, but with a trend for an increased risk of MDS.

Anti-CD20 monoclonal antibody—frontline MZL

Rituxan is the first-in-class anti-CD20 type I monoclonal antibody to receive initial FDA approval in 1997 for patients with relapsed/refractory (R/R) iNHL [29]. It is currently indicated for frontline therapy in patients with low tumor burden or those with high tumor burden not able to tolerate conventional chemoimmunotherapy. In the GAUSS trial, the second-generation type II monoclonal antibody, obinutuzumab was compared with rituximab in patients with R/R iNHL, each administered weekly 4 times, followed by 2 years of maintenance [30]. Obinutuzumab showed an increase in ORR (45% vs 33%) compared with rituximab in patients with R/R iNHL that did not translate into improvement in progression-free survival, but with an increase in infusion-related reaction. Currently, single-agent rituximab 375 mg/m^2 administered weekly 4 times, remains the preferred initial therapy for MZL.

Chemoimmunotherapy

Chlorambucil and rituximab—frontline therapy for advanced MALT lymphomas

Chlorambucil is an alkylating agent historically used in the treatment of several B cell lymphoproliferative disorders, particularly CLL. IELSG-19 was an open label, randomized phase 3 trial of frontline MALT lymphoma: currently one of the largest studies for MALT lymphomas [31••]. Patients were randomized to chlorambucil monotherapy, rituximab monotherapy, or the combination of

rituximab and chlorambucil. A total of 454 patients were enrolled. The ORR was 85.5% with chlorambucil monotherapy, 78.3% with rituximab monotherapy, and 94.7% with the combination therapy (Table 2) [31••]. The CR was 63.4%, 55.8%, and 78.8% in chlorambucil, rituximab, and the combination respectively [31••]. The primary endpoint of the study was event-free survival (EFS), with the combination showing significantly longer EFS (median not reached) compared with each single agent alone: chlorambucil (5.1 years) or rituximab (5.6 years) with a $p = 0.0009$. The median PFS was again not reached in combination therapy vs. chlorambucil (8.3 years) and rituximab (6.9 years) with $p = 0.0119$. However, the 5-year OS was similar in the 3 arms: 89% in chlorambucil, 92% in rituximab, and 90% in the combination arm. Treatment was generally well tolerated in all 3 arms.

CVP and rituximab—frontline therapy for advanced MZL, any subtype

Given the efficacy of rituximab in FL as a single agent, and particularly in combination with alkylating agents, there was an interest in assessing its activity specifically in MZL. This phase 2 study evaluated the combination of rituximab with cyclophosphamide, vincristine, and prednisolone (R-CVP) in frontline advanced stage MZL [32]. Treatment of naïve patients with stage 3 or 4 MZL were included and received a total of 6–8 cycles. Of the 40 patients that received treatment, the ORR was 88% with a CR of 60% (Table 2). The 3-year PFS was 59% with an OS of 95%. The regimen was fairly well tolerated with 10.5% of patients having a grade 3 or 4 neutropenia. While there were no treatment-related deaths, 6 patients did require hospitalization for toxicity-related events [32].

Bendamustine and anti-CD20 antibodies—frontline therapy for advanced MZL, any subtype

Bendamustine is an alkylating agent with clinical activity in CLL and several iNHL, in particular, in combination with anti-CD20 antibodies (rituximab and obinutuzumab).

The BRIGHT trial was a multicenter, phase 3 randomized non-inferiority study looking at BR vs R-CHOP/R-CVP in untreated patients with iNHL and mantle cell lymphoma (MCL) [33]. This study included patients with follicular lymphoma, lymphoplasmacytic lymphomas, MCL, and splenic, extranodal, and nodal MZL. Patients were randomized to either BR or R-CHOP or R-CVP, 6–8 cycles. A total of 46 patients had the MZL subtype. For all patients, the ORR was 97% in the BR arm and 91% in the standard arm ($p = 0.0102$), and the CR rate was 31% vs 25%, respectively, which met the non-inferiority threshold with $p = 0.0225$, but did not meet the superiority threshold ($p = 0.1269$) [33]. In a subgroup analysis of MZL, ORR/CR were 92/20% for BR compared with 71%/24% for R-CHOP/R-CVP but not statistically significant (Table 2) [33].

The GELTAMO MALT2008-01 was a multicenter, phase 2 trial that studied BR specifically in untreated patients with MALT lymphomas, but also included patients with GALT failing *H. pylori* eradication and primary cutaneous MALT lymphoma failing local therapies [34, 35]. Using a response-adapted approach, all patients were given 3 cycles of BR initially: those achieving CR, received a total of 4 cycles, while those achieving a PR, received a total of 6 cycles [34, 35]. A total of 60 patients were enrolled with 57 evaluable for the primary endpoint: 2 years EFS. The EFS was 93% and 87.7% at 2 and 7 years, respectively, with no

Table 2. Activity of established and novel therapies for patients with MZL

Regimen	MOA	Phase	Trial setting	No. of MZL	ORR
PPI+clarithromycin +amoxicillin	Antibiotic and proton-pump inhibitor	none	Retrospective chart review	33	80.9%
Doxycycline	Antibiotic	II	Frontline ocular/adnexae MZL	47	65%
Chlorambucil	Alkylating	III	Frontline MALT	131	85.5%
Rituximab	CD20 mAb	III		138	78.3%
Chlorambucil and rituximab	CIT	III		132	94.7%
R-CVP	CIT	II	Frontline MZL	40	88%
BR	CIT	III	Frontline iNHL	46 (28 received BR)	92%
BR	CIT	II	Frontline MALT	60	100%
BR	CIT	II	Frontline SMZL		91%
BO	CIT	III	Rituximab refractory iNHL	46 (27 received BO)	79%
O-chemo	CIT	III	Frontline MZL	88	82.8%
Rituximab maintenance	CD20 inhibitor	III	Frontline indolent NHL	71	52.1%
^{90}Y Ibritumomab tiuxetan	Radioimmunoconjugate	III	Frontline MZL	16	87.5%
Bortezomib	Proteasome Inhibitor	II	Frontline and R/R MZL	16	80%
Lenalidomide+ Rituximab (R^2)	CD20 inhibitor and immunomodulator	III	R/R FL and MZL	63 (31 received R^2)	65%
Lenalidomide+ Rituximab (R^2)	CD20 inhibitor and immunomodulator	II	Frontline MZL	30	93%
Ibrutinib	BTK inhibitor	II	R/R MZL	63	48%
Idelalisib	PI3K-delta isoform	II	R/R iNHL	15	57%
Copanlisib	PI3K-alpha and delta isoform inhibitor	II	R/R iNHL	23	58.5%
Duvelisib	PI3K-delta and gamma isoform inhibitor	II	R/R iNHL	18	47%
Parsaclisib	PI3K-delta inhibitor	I/II	R/R iNHL	9	78%
Umbralisib	PI3K delta inhibitor	II	R/R MZL	38	55%
Venetoclax	BCL-2 inhibitor	1b	R/R iNHL	3	67%
Venetoclax+BR	BCL-2 inhibitor	1b	R/R iNHL	6	100%

Regimen	CRR	MedianPFS/FFS	Major (G3–4) toxicities	Reference
PPI+clarithromycin +amoxicillin	80.8%	13 M[1]	None	Kim et al. 2016 [25]
Doxycycline	17%	††55%	None	Ferreri et al. 2012 [26]
Chlorambucil	63.4%	*51%	Leukopenia (2%), neutropenia (2%), lymphopenia (2%)	Zucca et al. [31••]
Rituximab	55.8%	*50%	Infections (4%), transaminases (3%), neutropenia (2%)	
	78.8%	*68%		

Table 2. (Continued)

Regimen	CRR	MedianPFS/FFS	Major (G3–4) toxicities	Reference
Chlorambucil and rituximab			Leukopenia (5%), neutropenia (19%), febrile neutropenia (3%), infections (4%)	
R-CVP	60%	†59%	Neutropenia (11%)	Kang et al. 2012 [32]
BR	20%	††65%[2]	Lymphopenia (63%), leukopenia(43%), neutropenia (49%), infection (7%)	Flinn et al. 2014 [33]
BR	98%	**88%	Lymphopenia (33%), neutropenia (20%), leukopenia (5%)	Salar et al. 2017 [34, 35]
BR	73%	†90%	Neutropenia (43%), thrombocytopenia (16%), anemia (9%)	Iannitto et al. 2018 [36•]
BO	17%	NR	Neutropenia (33%), thrombocytopenia (11%), infusion-related reactions (11%)	Sehn et al. 2016 [37]
O-chemo	16.2%	†75%	Neutropenia (45%), thrombocytopenia (10%), pneumonia (10%)	Herold et al. 2017 [38]
Rituximab maintenance	12.7%	4.8 Y[3]	Minimal	Williams et al. 2016 [39]
^{90}Y Ibritumomab tiuxetan	50%	47.6 M	Neutropenia (44%), thrombocytopenia, anemia	Lossos et al. 2015 [28]
Bortezomib	43%	22 M	Vomiting (6%) diarrhea (18%)	Troch et al. 2009 [40]
Lenalidomide+ Rituximab (R^2)	29%	20.2 M	Neutropenia (50%), leukopenia (7%), anemia (5%),	Leonard et al. 2019 [41••]
Lenalidomide+ Rituximab (R^2)	70%	59.8 M	Neutropenia (33%), leukopenia (7%), myalgia (10%)	Becnel et al. 2019 [42]
Ibrutinib	3%	14.2 M	Anemia (14%), diarrhea (5%), pneumonia (8%), neutropenia (5%), leukopenia (5%)	Noy et al. 2017 [43••]
Idelalisib	6%	11 M	Neutropenia (27%), diarrhea, increased ALT	Gopal et al. 2014 [44]
Copanlisib	14.1%	11.3 M	Hyperglycemia (34%), Pneumonia, (14%) Neutropenia (16% G4)	Dreyling et al. 2017 [45•]
Duvelisib	2%	9.5 M	Neutropenia (25%), thrombocytopenia (12%), diarrhea (15%), anemia (15%)	Flinn et al. 2019 [46]
Parsaclisib	33%	4.4 M[4]	Lymphopenia (10%), neutropenia (10%), diarrhea (9%), thrombocytopenia (10%)	Forero-Torres et al. 2019 [47]
Umbralisib	10%	71% at 1 year	Diarrhea (45%), nausea (29%), fatigue (26%), headache (26%), cough (24%), and decreased appetite (21%)	Fowler et al. 2019 [48•] Davids et al. 2017 [49]
Venetoclax	0%	6 M	Neutropenia (14%), anemia (15%), fatigue (7%), diarrhea (3%)	Davids et al. 2017 [49]
Venetoclax+BR	50%	10.7 M	Neutropenia (60%), lymphopenia (38%), thrombocytopenia (28%), anemia (17%)	De Vos et al. 2018 [50]

M, months; *MOA*, mechanism of action; *MZL*, marginal zone lymphoma; *NA*, not applicable; *NR*, not reached; *SMZL*, splenic marginal zone lymphoma; *ORR*, overall response rate; *CRR*, complete response rate; *PFS*, progression-free survival; *FFS*, failure-free survival; *B*, bendamustine; *F*, fludarabine; *R*, rituximab; *O*, obinutuzumab; *PI3K*, phosphoinositol 3 kinase; *Bcl-2*, B cell lymphoma 2; *R/R*, relapse/refractory; *Y*, year. [1]Median time to recurrence in *H. pylori*-positive patients. [2]Updated data from 2017. [3]Median time to treatment failure. [4]Median duration of response. †3 years PFS, ††5 years PFS, *5 years EFS (event-free survival), **7 years EFS

difference between the gastric and non-gastric sites [35]. The ORR was 100% with a CR of 98% (Table 2) [34, 35].

The BRISMA/IELSG36 study, was a multicenter, open label, phase 2 trial studying BR as frontline therapy specifically in SMZL [36•]. A total of 56 patients were enrolled and eligible. The ORR was 91% with a CR of 73% at the end of treatment (Table 2) [36•]. The 3-year PFS and OS were 90% and 96% respectively.

Chemotherapy and obinutuzumab—frontline iNHL

The GALLIUM study is a randomized phase III trial that compared obinutuzumab in combination with different chemotherapy backbones vs. rituximab in untreated patients mainly with follicular lymphoma but also included patients with MZL [38]. The chemotherapy regimens consisted of CHOP, CVP, or bendamustine. After induction, patient achieving CR or PR continued to get maintenance rituximan or obinutuzumab every 2 months for 2 years or until progression. [38] A total of 195 MZL patients were included: 71% received bendamustine, 16% received CHOP, and 12% received CVP. The study was not sufficiently powered to detect PFS differences. The ORR in the obintuzumab arm was 82.8% with a CR of 16.2% [38]. Of note, this study did not perform a subgroup analysis for MZL patients.

Immunomodulatory agent

Lenalidomide and rituximab—frontline MZL, any subtype

Lenalidomide (Revlimid) is an immunomodulatory agent currently approved in MM, MCL and myelodysplastic syndromes (MDS). Due to the important role of the tumor microenvironment in iNHL, it has been extensively studied in indolent lymphomas including MZL. Revlimid plus rituximab (R^2) was evaluated in both the frontline setting as well as in the R/R setting. In a single-institution of untreated stage 3/4 MZL, R^2 was given for a maximum of 12 cycles [42]. The primary endpoint was ORR. In this study, the combination was extremely active with and ORR of 93% and CR/CRu of 70%. The median PFS was 59.8 months and the 5-year OS was 96% [42].

Maintenance therapy

Rituximab as maintenance therapy

The RESORT Trial was a randomized, phase 3 trial that compared maintenance rituximab vs retreatment in iNHLs [39]. This study enrolled untreated SLL, nodal MZL, splenic MZL, and MALT lymphomas. All patients received 4 doses of weekly rituximab followed by restaging scans at week 13. Patients with PR, CR, or CRu were then randomized to maintenance dosing or retreatment with rituximab. Maintenance dosing received 1 dose of rituximab every 3 months until treatment failure. The ORR for MZL at induction was 52.1% with a CR of 12.7% (Table 2). The median time for maintenance rituximab failure was 4.83 years ($p = 0.012$) [39]. At the 7 year follow-up, no patients in the maintenance treatment arm underwent cytotoxic or radiation therapy. The median time to failure in the retreatment arm was 1.39 years and the median time until first cytotoxic therapy was 6.3 years [39]. The 5-year OS was 90% and 91% in

the maintenance and retreatment arms, respectively. Severe grade 3 or 4 toxicities were infrequent but consisted of 1 grade 4 neutropenia in the maintenance arm [39]. Other maintenance strategies with chlorambucil±rituximab and lenalidomide have not been wildly adopted.

Relapsed/refractory setting

Chemoimmunotherapy

Bendamustine and obinutuzumab—relapsed/refractory MZL, any subtype

The GADOLIN trial was a randomized, phase 3 trial comparing obinutuzumab with bendamustine vs bendamustine monotherapy in patients with iNHL that were refractory to rituximab-based therapy [37]. Patients were randomized to obinutuzumab plus bendamustine for 6 cycles and if they had no evidence of progression following induction, then they received obinutuzumab every 2 months for 2 years or until progression [37]. The combination showed an ORR of 79% and CR of 17% that was similar to bendamustine monotherapy (Table 2). However, median PFS was 25.8 months for the combination vs 14.1 months for bendamustine monotherapy ($p < 0.0001$), and this lead to an increase in OS (HR, 0.67; $p = .027$) [51•]. A total of 68% of patients receiving bendamustine and obinutuzumab experienced grade 3–5 events compared with 62% in the bendamustine monotherapy arm. There were 12 patients in each group that had a grade 5 fatal event. There was no subgroup analysis of the MZL patients.

Proteasome inhibitors

Bortezomib—investigational, MALT subtype

Bortezomib is a proteasome inhibitor currently approved for multiple myeloma (MM), and MCL. It was evaluated for MALT lymphomas in a prospective phase 2 study [40]. The median number of administered cycles was 8, with an ORR of 80% and CRR of 43% (Table 2). The median PFS was 22 months [40]. Three patients developed grade 3 diarrhea, and 1 patient developed grade 3 emesis. A total of 75% of patients developed polyneuropathy with the majority being grade 2. There were no episodes of grade 3 or 4 thrombocytopenia, neutropenia, or infections [40].

Immunomodulatory agents

Lenalidomide—R/R MZL, any subtype

The AUGMENT trial is a randomized phase 3, multicenter trial in patients with R/R MZL and FL [41••]. This trial compared R^2 with rituximab (R) monotherapy. In the MZL subgroup, the ORR was 65% with a CR of 29% (Table 2). This was not statistically different compared with rituximab monotherapy. The median PFS was 20.2 months that was also not statistically different from rituximab. In the MZL subgroup, the OS was not different compared with rituximab monotherapy (HR, 2.89; 95% CI, 0.56–14.92) [41••]. In this trial, 50% of R^2 had grade 3 or 4 neutropenia, and 7% with leukopenia [41••].

The MAGNIFY trial is a phase IIIb evaluating the optimal duration of lenalidomide for patients with R/R FL and MZL [52]. Patients received induction with R^2, and those achieving SD or better were randomized to R^2 vs maintenance R. Of the 370 patients enrolled, 20% were MZL. Induction with R^2 lead to an ORR/CR 65/38%, median TTR 2.7 months, median DOR 35.8 months and median PFS of 38.4 months. The most common grade 3/4 AE was neutropenia at 34% [52].

The AUGMENT and MAGNIFY trials were the basis for FDA approval for this first chemotherapy-free combination regimen in patients with R/R MZL and FL.

Bruton tyrosine kinase inhibitors

Ibrutinib—R/R MZL, any subtype

Bruton tyrosine kinase (BTK) is a key enzyme of the B cell receptor signaling pathway leading to cell proliferation and survival. In a multicenter, nonrandomized, phase 2 study, patients with R/R extranodal, splenic and nodal MZL were treated with the BTK inhibitor ibrutinib until disease progression or unacceptable toxicity, for up to 3 years [43••]. The ORR was 48% with a CR of 3% (Table 2). While, the median PFS was 14.2 months, the median OS had not been reached. By MZL subtype, the median PFS was 13.8 months in extranodal, 19.4 months in splenic, and 8.3 months in nodal MZL. The most common grade 3 adverse event was anemia at 14%. Additional grade 3 AEs included pneumonia (8%), fatigue (6%), leukopenia (5%), and neutropenia (5%). A total of 8 patients died during the study [43••]. This pivotal trial was the basis for FDA approval of ibrutinib in patients with R/R MZL after prior anti-CD20 therapy.

PI3K inhibitors—R/R MZL, any subtype

The phosphoinositide 3-kinase (PI3K) pathway is part of the B cell receptor signaling pathway and integrates survival signals from the tumor's microenvironment.

Idelalisib

Idelalisib is the first-in-class PI3K inhibitor of the isoform delta. In a non-randomized, phase 2 study of patients with R/R iNHL,that included 15 patients with MZL, in addition to follicular, SLL, and lymphoplasmacytic lymphoma, idelalisib showed an ORR of 57% with a 6% CR (Table 2) [44]. The median PFS and OS were 11 and 20.3 months, respectively.

Duvelisib

Duvelisib is another PI3K inhibitor with a predominant activity on PI3K-δ and PI3K-γ. DYNAMO is a phase 2 study that evaluated duvelisib in patients with R/R iNHL, includeding all subtypes of iNHL [46]. There were 18 patients enrolled who had MZL. Patients were given duvelisib until progression of disease, unacceptable toxicity, or death. Overall, duvelisib showed an ORR/CR of 47/2% and in the MZL subtype the ORR was 39% [46]. The median PFS was 9.5 months (Table 2). Duvelisib toxicity profile seems similar to idelalisib.

Copanlisib

Copanlisib is a pan-class 1 PI3K inhibitor, with a predominant activity against the PI3K-α and PI3K-δ isoforms. CHRONOS-1 is a phase 2 trial that evaluated copanlisib in patients with R/R iNHL after at least 2 prior lines of therapy, including patients with FL, MZL, SLL, and lymphoplasmacytoid/Waldenstrom macroglobulinemia [45•]. Treatment was continued until disease progression or unacceptable toxicities. Copanlisib showed an ORR of 58.5% with a CR of 14.1%, and among MZL patients, the CR was 13% [45•]. The median PFS was 11.3 months and the median OS had not been reached (Table 2). Based on the data from the CHRONOS-1 trial, copanlisib was granted FDA breakthrough designation for patients with R/R MZL. Copanlisib seems to have a better toxicity profile than the prior 2 agents.

Novel agents

Our understanding of the role of the tumor microenvironment and the molecular alterations underlying the different subtypes of MZL are contributing to the continuous development of novel targeted therapies for this disease.

PI3K inhibitors

Parsaclisib

Parsaclisib is a potent PI3K inhibitor which has an increased selectivity (≥ 19,000-fold) for PI3K-δ isoform [47]. The CITADEL-101 trial is a phase 1/2 trial with multiple cohorts: parsaclisib monotherapy, parsaclisib plus itacitinib, and parsaclisib plus rituximab, ifosfamide, carboplatin, and etoposide (R-ICE). Parsaclisib monotherapy had 4 cohorts: B cell malignancies, Hodgkin's lymphoma, DLBCL, and iNHL. MZL patients were only enrolled in the parsaclisib monotherapy arm. Of the MZL patients, the ORR was 78% with a CR of 33% (Table 2). The median duration of response (DOR) was 4.4 months [47].

Umbralisib

Umbralisib is a dual inhibitor of the PI3K-δ and casein kinase-1ε leading to potentially lower inhibition of regulatory T cells, and therefore lower immune-related side effects [48•, 53]. Sixty-nine patients with R/R MZL received umbralisib until disease progression or unacceptable toxicities. A total of 38 patients met criteria for analysis and found to have an ORR of 55% with a CR of 10% [48•, 53]. The 12 month PFS was 71% (Table 2). Based on this study, umbralisib was granted FDA breakthrough designation for patients with R/R MZL. In a safety study on umbralisib monotherapy or combined with other chemoimmunotherapies, which included CLL/SLL, DLBCL, iNHL, the most common grade 3/4 adverse event was neutropenia at 17%, anemia at 6%, and pneumonia at 5% [48•, 53].

Bcl-2 inhibitors

Venetoclax

Venetoclax is a selective inhibitor of the antiapoptotic B cell leukemia/lymphoma-2 (BCL-2) protein. It was assessed as monotherapy and in combination studies. The M12-175 study was a phase 1 trial of venetoclax monotherapy for patients with R/R iNHL that only enrolled 3 patients with MZL [49]. Patients in the dose-escalation cohorts were given doses ranging from 200 mg to a max target daily dose of 1200 mg [49]. Of the total patients, the ORR was 44%, and in the MZL cohort, ORR was 67% with no CR (Table 2). The duration of response (DOR) was 2.3 and 23.6 months between the 2 patients [49].

In another phase 1 study in R/R iNHL, venetoclax was studied in combination with BR and demonstrated an ORR of 65% [53]. Six of the studied patients had MZL, and of those 6, 100% had an ORR with 50% achieving CR (Table 2) [50].

Chemotherapy-free combinations such of venetoclax and copanlisib NCT03886649 are being actively investigated across the spectrum of B cell malignancies with expansion cohorts in MZL. More importantly, we are witnessing an increased number of trials that are specifically designed for patients with MZL: OLYMP-1 (obinutuzumab in untreated MZL-NCT03322865) and MALIBU (ibrutinib and rituximab in untreated MZL-NCT03697512).

Finally, immunotherapy continues to revolutionize cancer therapy, and given the important role of the tumor microenvironment in MZL, there are several ongoing studies looking at immune checkpoint inhibitors such as pembrolizumab, the PD-1 inhibitor, in frontline iNHL NCT03498612, or in the R/R setting as a single agent and in combination with B cell receptor inhibitors NCT02332980, while other studies are evaluating CAR-T cell therapy in R/R iNHL, including MZL-NCT03105336.

While immunochemotherapy has been the therapy backbone for disseminated MZL, we are witnessing a shift toward targeted therapies with approval of several agents that modulate the tumor microenvironment and its interaction with the underlying tumor. A precision medicine approach for this disease would require an integration of different molecular signatures, immune profiling, and clinicopathological features in order to create accurate prognostic and therapeutic strategies that will be tailored for each individual patient. This can only be achieved through international collaborative efforts and the implementation of prospective clinical studies dedicated to patients with MZL.

Compliance with Ethical Standards

Conflict of Interest

Ariel Sindel declares that he has no conflict of interest.

Taha Al-Juhaishi declares that he has not conflict of interest.

Victor Yazbeck has received research funding through grants from Gilead and has received honoraria from Pharmacyclics, Celgene, and Seattle Genetics for service on advisory boards.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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