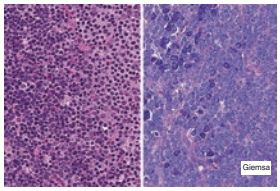
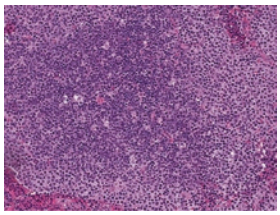
Nodal Marginal Zone Lymphoma

8

Luca Arcaini and Andreas Viardot

Nodal marginal zone lymphoma (NMZL)

Clinical outline
Primarily nodal disease, as localized or generalized lymphadenopathy in adults, without evidence of relevant extranodal or splenic disease.

Cytology	Small to medium sized cells ranging in morphology from lymphocyte- and centrocyte-like to monocytoid. Features of plasmacytic differentiation may be observed. Variable content of blasts.	Nodal margina zone lymphoma, cytology	
Histology	Expanded marginal zone around reactive germinal centers, which become progressively infiltrated by the neoplastic cells. Outwards growth to the paracortical zone may ultimately lead to a diffuse pattern	Nodal marginal zone lymphoma, hystology	

	CD20	CD5	CD23[1]	CD10	BCL6	cyclin D1	CD103	FMC7	IgM	light chains
notes	[1]partial/weak expression occacionally observed									
other marker	EMZL lacks a specific phenotype and the antibody panel primarily aims at exclusion of other lymphoma subtypes. IRTA1 and MNDA may be helpful marker but less frequently used or not widely available.									

= majority of cases positive = variable fraction of cases positive = negative

Main differential diagnosis	CLL (should be CD23 positive), MCL (sould be cyclin D1 positive). Subtypes of marginal zone lymphomas (extranodal, nodal, splenic, cutaneous) distinguished mainly by clinical presentation (pattern of involved organs). LPL (should be MYD88 mutated) needs to be excluded based on clinical findings (IgM gammopathy) and extent of bone marrow involvement (expected to be the predominant site of presentation in LPL).

M. Dreyling, M. Ladetto (eds.), *Indolent Lymphomas*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-55989-2_8

Key molecular features		
Activation of Notch and nuclear factor kappa B pathways. IGH genes rearranged, somatic hypermutation and IGHV3 and IGHV4 usage bias. Frequent translocations: Non reported. Frequent copy number alterations: Gains of chromosome 3 and 8, loss of 6q23. Frequent mutations: *NOTCH2, MLL2/KMT2D, PTPRD, KLF2, TNFAIP3* rarer: *MYD88, CARD11*		
Precursor lesions		
Not reported. In contrast to ENMZL no association with inflammation reported.		
Progression		
May progress/transform to defuse large B-cell lymphoma. Definition of transformation currently purely morphologically by detection of sheets of blasts.		
Clinically relevant pathologic features	**Relevance**	**Evidence**
Mutations	prognostic: *KLF2* and *NOTCH2* mutations (unfavourable)	**C**
Proliferation/blasts	High proliferation and/or blast content (unfavourable)	**C**
Legend: A = verified in multiple studies, randomized trials and/or integrated in guidelines; B = variable between studies/needs definitive validation; C = preliminary/discrepant results.		

8.1 Definition

Nodal marginal zone lymphoma (NMZL) is a non-Hodgkin lymphoma of mature B-cells, with similarities to the extranodal (EMZL) or splenic marginal zone lymphoma (SMZL), but with predominant nodal involvement and without extranodal or splenic involvement [1]. Since diagnosis is made by exclusion, some inaccuracy in the distinction from other marginal zone lymphomas (MZL) or indolent lymphomas might be possible. However, there are several arguments based on immunohistological, genetic, and molecular genetic findings, suggesting that NMZL presents a distinct entity.

The NMZL was originally described as a "monocytoid" or "parafollicular" B-cell lymphoma in 1986 (historical review in [2]). Only later, the relationship to other MZL became clear. In 1994, the "nodal marginal zone lymphoma with or without monocytoid B-cells" was included as a separate entity in the REAL classification, also adopted in the WHO classification of lymphoid neoplasia of 2001 and of 2008 and in the revision of 2016.

The NMZL presents less than 2% of all lymphoid neoplasia and only a small proportion (about 10–20%) of MZL [2]. The annual incidence is 0.8 patients in 100,000 men and women

L. Arcaini (✉)
Division of Hematology, Fondazione IRCCS Policlinico San Matteo & Department of Molecular Medicine, University of Pavia, Pavia, Italy
e-mail: arcaini@unipv.it

A. Viardot
Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany
e-mail: andreas.viardot@uniklinik-ulm.de

per year. However, the incidence might be increasing in the last decade (25% from 2001 to 2009) [3]. This increase may be partly explained by a raised awareness of pathologists for this entity.

The typical age of onset is about 60 years (slightly younger than patients with SMZL), the male-to-female ratio is approximately equal. In the majority of patients, there is an advanced stage and bone marrow is involved (43%; [4]). In 10% of patients, there is a leukemic disease without marked splenic enlargement. At diagnosis, the majority of patients have a good performance status and no B symptoms [4–6].

An exception might be the pediatric NMZL, an entity included into the recent revision of the WHO classification of lymphoid neoplasia, typically in younger patients. The majority of patients are male (ratio 20–1) and have a localized stage (I or II), usually affecting cervical lymph nodes. Relapses are infrequent, even after local resection of radiotherapy [7]. There are no clear histological or molecular pathologic criteria for delineation to the adult forms. However, enlarged lymph follicle with the extension of the mantle zone and frequent CD43 expression might be characteristic but not exclusive for the pediatric NMZL [1].

8.2 Pathogenesis

Like other MZL, an association with hepatitis C virus (HCV) infection with geographical variability and chronic inflammatory disease have been reported. In a first series, 24% of patients with NMZL had a HCV infection [5, 6]. In a recent publication [8], patients with NMZL and HCV were found less frequently, in contrast to series from Asia [9]. Since the treatment of HCV infection can induce a remission of the lymphoma, screening for HCV is mandatory at diagnosis of NMZL [8].

The association with autoimmune disease is less frequently reported in comparison to EMZL; in a French series there were only four out of 47 patients (9%) with autoimmune diseases [4].

8.3 Histologic and Biologic Characteristics

The typical histopathological picture is the proliferation of small-sized lymphocytes into the marginal zone (which surrounded the reactive lymph follicle) with a secondary infiltration of the interfollicular areas of the lymph node [1]. By immunophenotyping, NMZL have typical Pan-B-cell markers like CD19 and CD20. CD23, CD5, and germinal center markers (CD10, BCL6, HGAL and LMO2) are rarely positive, Cyclin D1 is usually negative.

Like follicular lymphoma (FL), BCL2 is frequently positive; MNDA and IRTA1 are regarded as distinctive markers to differentiate FL and MZL. There is no immunological marker to differentiate to NMZL from other MZL [1, 10].

There are typical genetic markers for all MZL like gains on chromosome 3 and 18 as well as losses on chromosome arm 6q23–24. All MZL shows an activation of NFkappaB and epigenetic modifications [11]. The NMZL shares with the SMZL the lack of specific translocations like the t(11;18)(q21;q21) translocation—a hallmark of gastric EZML. Other similarities between NMZL and SMZL are the mutations of NOTCH pathway and of the transcription factor KLF2. In contrast to SMZL, deletions on chromosome arm 7q31 are unusual [11]. More specific characteristics for the NMZL may be the inactivation of PTPRD, a receptor-type protein tyrosine phosphatase (up to 20% of cases) and a high frequency of KMT2D (formerly MML-2) [12]. MYD88 L265P mutations are detected rarely in MZLs. KLF2 and NOTCH2 mutations might have a possible prognostic impact; however, larger series are necessary [12].

In a recent analysis using high-throughput sequencing, NMZL shows a higher mutational load than in EMZL. The most frequent mutated genes code for epigenetic modifiers (e.g. KMT2D 28%, CREBPA 20%, TET2 20%), followed by mutations of BRAF (17%). BRAF mutations are typically on V600E comparable to hairy cell leukemia, which might offer new therapeutic options in a subset of these patients. Moreover, this mutations seems to be restricted to MZL [13].

Similar to EMZL and SMZL, ongoing mutations and a restricted VH gene usage argue for a causal relationship to an antigenic stimulus supporting an ongoing B-cell expansion. In NMZL, the IGHV4–34 gene is used in 20–30% of cases, which is rarely reported in EMZL or SMZL with the exception of the ocular adnexal lymphoma [10].

8.4 Prognosis

Before the implementation of the CD20 antibody rituximab into the treatment, the prognosis of NMZL was considered as worse in contrast to EMZL and comparable to SMZL [14]. In recent series, this difference is not pronounced and more comparable to EZML. In the US SEER registry (Suirvellance, Epidemiology, and End Results database), the 5-year survival of patients between 1995 and 2009 was 76.5% (in contrast EZML: 79.0%) [15]. In contrast to SZML, the prognosis was improved within 15 years.

In different case series, the overall survival at 5 years was between 57% and 97% [15]. The high difference in data from epidemiological registries may be partially explained by the heterogeneity of the diagnosis due to changes in the pathological delineation and in the staging procedures, and also by changes in the treatment. Prognostic differences between EZML and NMZL can be explained by the fact that EZML is very often localized: indeed, the prognosis of EZML and NMZL in stage I is comparable [16].

For risk assessment, the international prognostic index (IPI) and the follicular lymphoma international prognostic index (FLIPI) were evaluated in a retrospective series in NMZL [17]. There are a large amount of molecular risk factors evaluated in NMZL without a clear candidate for prognostication (e.g. negative results: loss of Survivin, active Caspase 3, overexpression of Cyclin E; positive results: loss of expression of MUM1/IRF4 and Ki67 less than 5%, overview in [2]). In contrast to many hematologic neoplasia, the loss of chromosome arm 17p might be no strong prognostic factor in NMZL [11].

Recently, the progression of disease within 24 months (POD24) was established as a risk factor for relapsed marginal zone lymphoma [18]. Since NMZL represents only a small proportion of all patients of this series (10%), the impact for overall survival was not significant compared to EMZL and SMZL.

The transformation into a high-grade lymphoma is a possible event in NMZL. In a series of 340 patients with MZL, the incidence of transformation was 3% at 5 years in the group of NMZL patients [19], and possibly slightly lower than in FL or other MZL. A histological transformation is associated with a poorer prognosis: the 2-years survival after transplantation is only 57% [19].

8.5 First-Line Treatment

Due to the rarity, the heterogeneity and the diagnostic uncertainty, there are no treatment recommendations evaluated prospectively in patients with NMZL. Since NMZL and MZL were often treated in clinical trials together with other indolent lymphoma, the guidelines for treatment of FL were transferred directly to the NMZL (e.g. ESMO guidelines [20]; NCCN [21] Guidelines Non-Hodgkin's Lymphoma, Version 4.2014). Regarding to clinical trials, the NMZL were included in trials of other MZLs or indolent lymphoma.

In localized stages (stage I, II without bulky disease), involved field radiotherapy is widely accepted as a standard. However, the value of radiotherapy in contrast to "watch and wait" or systemic treatment is not well-defined. A localized NMZL in a young patient could represent a pediatric NMZL which is difficult to delineate to the adult form. In few case reports [22, 23], patients with pediatric NMZL had an excellent prognosis even after resection of the involved lymph node only. In a recent publication, there was only one patient with relapse after local resection in 20 children with pediatric NMZL [23]. Therefore, "watch and wait" might be a useful strategy as alternative to radiotherapy in (young) patients after surgical removal of the involved lymph node.

In asymptomatic patients with advanced stages, "watch and wait" is an accepted standard

comparable to the strategy in FL. Symptomatic patients were treated with a combination of chemotherapy and a CD20 antibody. Like in other B-cell neoplasia, the addition of rituximab improves the outcome. Analogue to EMZL, a monotherapy with rituximab could be an alternative to the combination. However, prospective data are scarce. In the RESORT trial [24], 28 patients with NMZL and low tumor burden received a monotherapy with rituximab. The response rate in NMZL was higher than in EMZL or CLL/CL (complete response 3.8%, partial response 57.1%, others stable disease), but lower than in FL (overall response 70.8%).

There are several combination therapies, like R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), R-F (rituximab, fludarabine), R-FC (rituximab, fludarabine, cyclophosphamide), R-CHOP (rituximab, cyclophosphamide, vincristine, prednisone), or R-Benda (rituximab, bendamustine) (review in Table 8.1). In a small series, the response rates were after R-CVP, R-F, and R-FC 88%, 85, and 99%, respectively. The PFS after 3 years was 59%, 79.5%, and 90.1% [26, 27, 32]. However, treatment with fludarabine is sometimes associated with fatal complications particularly in elderly patients.

In the StIL-001 trial, 549 patients with indolent lymphomas were randomized between R-CHOP and R-Bendamustine, including 67 patients with MZL [33]. In contrast to the other subgroups, there was no difference in PFS between two arms. The toxicity was lower with R-bendamustine compared to R-CHOP, so that R-bendamustine is often used in European countries. In the GALLIUM trial, Rituximab in combination with chemotherapy (bendamustine, CVP, CHOP) was compared with the new CD20 antibody Obinutuzumab. In a subgroup analysis of 195 patients with MZL including 66 patients with NMZL, the PFS could not be improved by Obinutuzumab in contrast to the patients with FL [34]. However, there was an unexpectedly high toxicity in both arms with treatment-associated fatal events (6% in the rituximab arm, 12% in the obinutuzumab arm). The fatal events occur mostly in patients treated with the combination with bendamustine, which was observed also in the whole collective of the GALLIUM trial. The high rate of severe infections after bendamustine, and also after fludarabine, might be caused by a long-term T-cell depletion after treatment.

In an analysis of patients of the US cancer registry (SEER-Medicare; [35]), there was no significant

Table 8.1 Clinical trials of first-line treatment including patients with NMZL

Reference	Treatment	All patients/patients with MZL/with NMZL	OR/CR	Outcome
Leblond et al. [25]c	Chlorambucil	414/33/n.a.	38.6%/5.3%	mPFS 27.1 months
	Fludarabine		38.6%/2.0%	mPFS 36.1 months
Kang [26]	R-CVP	42/42/n.a.	88%/60%	3 years PFS 59%
Brown [27]	R-Fludarabine	24/24/14	85%/54%	3 years PFS 79%
Ferrario [32]	R-Fludarabine/ cyclophosphamide	46/46/6	89%/67%	3 years PFS 90.1%
Samaniego [28]	R-Pentostatin/ cyclophosphamide	83/83/n.a.	75%/70%	3 years PFS 73%
Rummel [33]	R-CHOP	463/59/n.a.	93%/42%	mPFS 31.5 months
	R-Bendamustine		93%/47%	mPFS: 69.5 months
Flinn [29]	R-CVP/R-CHOP	224/24/n.a.	91%/25%	n.a.
	R-Bendamustine		97%/31%	
Herold [34]	R-chemo	96/96/31	82%/19%	3 years PFS 78.1%
	G-chemo		83%/16%	3 years PFS 75.0%
Rummel [30]	R-Bendamustine ± R-maintenance	119/119/n.a.	91%/23%	2 years PFS 92%
Oh [31]	R-CVP + R-maintenance	45/45/15	93%/44%	3 years PFS 83%

difference between use of Rituximab-Bendamustine versus Rituximab monotherapy in 903 patients with NMZL. With all limitations and unexpected confounding factors, the authors resume to be consider the risk and benefit of the combination particularly in elderly patients.

In a subgroup analysis of the MAINTAIN-trial, including 119 patients with SMZL and NMZL, the 2-years maintenance treatment with rituximab after immunochemotherapy prolonged significantly the progression-free survival without adding any new toxicity [30].

8.6 Treatment of Relapse and New Options

In FL, the early progression within 24 months after immunochemotherapy (POD24) is regarded as a prognostic marker. POD24 was shown to be of prognostic relevance also in MZL—however the proportion of NMZL was too small (appr. 10%; [18]). However, intensive treatment options like high-dose chemotherapy with autologous stem cell support can be offered to younger patients with early progress and other high-risk factors. In later relapse, repeated immunochemotherapy is the usual standard in these patients.

In January 2017, the US Food and Drug Administration (FDA) approved the Bruton tyrosine kinase (BTK) inhibitor Ibrutinib for the treatment of patients with relapsed and refractory MZL, who had already received a CD20 antibody based pretreatment (data on novel drugs are summarized in Table 8.2). In the pivotal phase-II trial, 17 patients with NMZL were included. The overall response rate—the primary endpoint of this trial—was lower in NMZL patients than in other (41% vs. 48%), as well as the median PFS (8.3 months vs. 14.2 months [41]). Next-generation BTK inhibitors like Acalabrutinib and Zanubrutinib are under clinical investigation in MZL (NCT02180711, NCT03846427).

In the pivotal phase-II trial using the PI3Kδ inhibitors idelalisib [44], 15 patients with MZL were included, respectively. The overall response rates were approximately 50% in MZL, so that this principle may be effective. However, in contrast to FL, idelalisib is not approved for the treatment of MZL.

Copanlisib is a PI3K inhibitor which combines activity against the PI3K subunit α and δ and has a different spectrum of side effects. In a phase II trial, coplanlisib has an overall response rate of 78% in all MZLs and particularly 87% in 15 patients with NMZL. The duration of response was 17.4 months [37].

The combination of lenalidomide and rituximab (so-called R^2) may be an option in MZL with a response rate up to 89% [45]. In the AUGMENT phase III trial [40], 63 patients with MZL underwent a randomization between ritux-

Table 8.2 Novel drugs in marginal zone lymphoma

Reference	Drug	All patients/with MZL/with NMZL	OR/CR in MZL	Outcome
Wagner-Johnston [36]	Idelalisib	125/15/5	47%/6%	mPFS 6.6 months
Dreyling [37]	Copanlisib	23/23/15	83%/13%	mPFS 24.2 months
Conconi [38]	Everolimus	30/30/6	20%/3%	mPFS 14 months
Rosenthal [39]	Lenalidomide, rituximab, Cyclophosphamid, Dexamethason	33/33/5	87.9%/30.3%	mPFS: 39.7 months
Leonard [40]	R-Lenalidomide	178/31/8	65%/29%	mPFS: 20.2 months
	R-mono	180/32/10	44%/13%	mPFS: 25.2 months
Noy [41]	Ibrutinib	63/63/17	48%/3%	mPFS 14.2 months
Lossos [42]	Yttrium $^{90-}$ ibritumomab	16/16/n.a.	87.5%/56%	mPFS 47 months
Samaniego [43]	Yttrium ^{90} ibritumomab	11/11/n.a.	100%/97%	mPFS >56 months

OR overall response, *CR* complete remission, *mPFS* median progression-free survival, *R* rituximab, *CVP* cyclophophamide, vincristin, prednisone, *CHOP* cyclophosphamide, vincristine, prednisone, *n.a.* not evaluable

imab monotherapy and R^2. With regard to the endpoint PFS, the whole collective, but not the subgroup of MZL shows a significant improvement. Nevertheless, the combination of lenalidomide and rituximab (R^2) was approved by FDA also for the treatment of refractory or relapsed MZL in May 2019. In contrast, the EMA approved this combination only for follicular lymphoma in January 2020.

8.7 Summary

The NMZL is a rare lymphoma entity which is partially difficult to differentiate from other indolent lymphomas. Using new techniques including high-throughput sequencing, the classification might be improved in the next years and more targeted treatment strategies might be established. Following the treatment guidelines of FL is proved of value in NMZL. However, novel drugs like BTK or PI3K inhibitor might be particularly efficient in this entity. The majority of patients with NMZL have a favorable prognosis.

References

1. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: International Agency of Cancer Research; 2016.
2. Thieblemont C, Molina T, Davi F. Optimizing therapy for nodal marginal zone lymphoma. Blood. 2016;127:2064–71. https://doi.org/10.1182/blood-2015-12-624296.
3. Khalil MO, Morton LM, Devesa SS, Check DP, Curtis RE, Weisenburger DD, Dores GM. Incidence of marginal zone lymphoma in the United States, 2001–2009 with a focus on primary anatomic site. Br J Haematol. 2014;165:67–77. https://doi.org/10.1111/bjh.12730.
4. Berger F, Felman P, Thieblemont C, Pradier T, Baseggio L, Bryon PA, Salles G, Callet-Bauchu E, Coiffier B. Non-MALT marginal zone B-cell lymphomas: a description of clinical presentation and outcome in 124 patients. Blood. 2000;95:1950–6.
5. Arcaini L, Burcheri S, Rossi A, et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. Ann Oncol. 2007a;18:346–50. https://doi.org/10.1093/annonc/mdl388.
6. Arcaini L, Paulli M, Burcheri S, Rossi A, et al. Primary nodal marginal zone B-cell lymphoma: clinical features and prognostic assessment of a rare disease. Br J Haematol. 2007b;2007(136):301–4. https://doi.org/10.1111/j.1365-2141.2006.06437.x.
7. Taddesse-Heath L, Pittaluga S, Sorbara L, Bussey M, Raffeld M, Jaffe ES. Marginal zone B-cell lymphoma in children and young adults. Am J Surg Pathol. 2003;27:522–31.
8. Arcaini L, Besson C, Frigeni M, et al. Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. Blood. 2016;128:2527–32. https://doi.org/10.1182/blood-2016-05-714667.
9. Chuang SS, Liao YL, Chang ST, et al. Hepatitis C virus infection is significantly associated with malignant lymphoma in Taiwan, particularly with nodal and splenic marginal zone lymphomas. J Clin Pathol. 2010;63:595–8. https://doi.org/10.1136/jcp.2010.076810.
10. Bertoni F, Rossi D, Campo E. Recent advances in understanding the biology of marginal zone lymphoma. F1000Res. 2018;7:406. https://doi.org/10.12688/f1000research.13826.
11. Rinaldi A, Mian M, Chigrinova E, et al. Genome-wide DNA profiling of marginal zone lymphomas identifies subtype-specific lesions with an impact on the clinical outcome. Blood. 2011;117:1595–604. https://doi.org/10.1182/blood-2010-01-264275.
12. Spina V, Khiabanian H, Messina M, Monti S, Cascione L, Bruscaggin A. The genetics of nodal marginal zone lymphoma. Blood. 2016;128:1362–73. https://doi.org/10.1182/blood-2016-02-696757.
13. Pillonel V, Juskevicius D, Ng CKY, et al. High-throughput sequencing of nodal marginal zone lymphomas identifies recurrent BRAF mutations. Leukemia. 2018;32:2412. https://doi.org/10.1038/s41375-018-0082-4.
14. Thieblemont C. Improved biological insight and influence on management in indolent lymphoma. Talk 3: update on nodal and splenic marginal zone lymphoma. Hematology Am Soc Hematol Educ Program. 2017;2017:371–8.
15. Olszewski AJ, Castillo JJ. Survival of patients with marginal zone lymphoma: analysis of the surveillance, epidemiology, and end results database. Cancer. 2013;119:629–38. https://doi.org/10.1002/cncr.27773.
16. Kuper-Hommel MJ, van de Schans SA, Vreugdenhil G, van Krieken JH, Coebergh JW. Trends in incidence, therapy and outcome of localized nodal and extranodal marginal zone lymphomas: declining incidence and inferior outcome for gastrointestinal sites. Leuk Lymphoma. 2013;54:1891–7. https://doi.org/10.3109/10428194.2013.764421.
17. Heilgeist A, McClanahan F, Ho AD, Witzens-Harig M. Prognostic value of the follicular lymphoma international prognostic index score in marginal zone lymphoma: an analysis of clinical presentation and outcome in 144 patients. Cancer. 2013;119:99–106. https://doi.org/10.1002/cncr.27704.
18. Luminari S, Merli M, Rattotti S, et al. Early progression as a predictor of survival in marginal zone

lymphomas: an analysis from the FIL-NF10 study. Blood. 2019;134:798–801. https://doi.org/10.1182/blood.2019001088.
19. Conconi A, Franceschetti S, Aprile von Hohenstaufen K, Margiotta-Casaluci G, Stathis A, Moccia AA, Bertoni F, Ramponi A, Mazzucchelli L, Cavalli F, Gaidano G, Zucca E. Histologic transformation in marginal zone lymphomas†. Ann Oncol. 2015;26:2329–35. https://doi.org/10.1093/annonc/mdv368.
20. Zucca E, Arcaini L, Buske C, et al. Marginal zone lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:17–29. https://doi.org/10.1016/j.annonc.2019.10.010.
21. NCCN guidelines non-Hodgkin's lymphoma, version 4.2014, p 225. https://www.nccn.org/about/nhl.pdf.
22. Gitelson E, Al-Saleem T, Robu V, Millenson MM, Smith MR. Pediatric nodal marginal zone lymphoma may develop in the adult population. Leuk Lymphoma. 2010;51:89–94. https://doi.org/10.3109/10428190903349670.
23. Ronceray L, Abla O, Barzilai-Birenboim S, Bomken S, Chiang A, Jazbec J, Kabickova E, Lazic J, et al. Children and adolescents with marginal zone lymphoma have an excellent prognosis with limited chemotherapy or a watch-and-wait strategy after complete resection. Pediatr Blood Cancer. 2018;65:65. https://doi.org/10.1002/pbc.26932.
24. Williams ME, Hong F, Gascoyne RD, Wagner LI, Krauss JC, Habermann TM, Swinnen LJ, Schuster SJ, et al. Rituximab extended schedule or retreatment trial for low tumour burden non-follicular indolent B-cell non-Hodgkin lymphomas: eastern cooperative oncology group protocol E4402. Br J Haematol. 2016;173:867–75. https://doi.org/10.1111/bjh.14007.
25. Leblond V, Johnson S, Chevret S, et al. Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenström macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma. J Clin Oncol. 2013;31:301–7. https://doi.org/10.1200/JCO.2012.44.7920.
26. Kang HJ, Kim WS, Kim SJ, et al. Phase II trial of rituximab plus CVP combination chemotherapy for advanced stage marginal zone lymphoma as a first-line therapy: consortium for improving survival of lymphoma (CISL) study. Ann Hematol. 2012;91:543–51. https://doi.org/10.1007/s00277-011-1337-6.
27. Brown JR, Friedberg JW, Feng Y, et al. A phase 2 study of concurrent fludarabine and rituximab for the treatment of marginal zone lymphomas. Br J Haematol. 2009;145:741–8. https://doi.org/10.1111/j.1365-2141.2009.07677.x.
28. Samaniego F, Hagemeister F, Romaguera JE, et al. Pentostatin, cyclophosphamide and rituximab for previously untreated advanced stage, low-grade B-cell lymphomas. Br J Haematol. 2015;169(6):814–23. https://doi.org/10.1111/bjh.13367.
29. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123:2944–52. https://doi.org/10.1182/blood-2013-11-531327.
30. Rummel M, Koenigsmann M, Chow KU, et al. Two years rituximab maintenance vs. observation after first line treatment with bendamustine plus rituximab (B-R) in patients with marginal zone lymphoma (MZL): results of a prospective, randomized, multicenter phase 2 study (the StiL NHL7-2008 MAINTAIN trial). J Clin Oncol. 2018;36(15 Suppl):7515. https://doi.org/10.1200/JCO.2018.36.15_suppl.7515.
31. Oh SY, Kim JS, Kim WS, et al. Phase II study of R–CVP followed by rituximab maintenance therapy for patients with advanced marginal zone lymphoma: consortium for improving survival of lymphoma (CISL) study. Cancer Commun (London). 2019;39:58. https://doi.org/10.1186/s40880-019-0403-7.
32. Ferrario A, Pulsoni A, Olivero B, et al. Fludarabine, cyclophosphamide, and rituximab in patients with advanced, untreated, indolent B-cell nonfollicular lymphomas: phase 2 study of the Italian Lymphoma Foundation. Cancer. 2012;118:3954–61. https://doi.org/10.1002/cncr.26708.
33. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, et al. Study group indolent lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381:1203–10. https://doi.org/10.1016/S0140-6736(12)61763-2.
34. Herold M, Hoster E, Janssens A, et al. Immunochemotherapy with obinutuzumab or rituximab in patients with previously untreated marginal zone lymphoma (MZL) in the randomised GALLIUM trial. IMCL (abstract). J Clin Oncol. 2017;36(23):239.
35. Olszewski AJ, Ollila TA, Reagan JL. Bendamustine-rituximab does not improve survival over rituximab monotherapy for older patients with nodal or splenic marginal zone lymphoma. Blood. 2019;134(Suppl_1):2824.
36. Wagner-Johnston N, Schuster S, de Vos S, et al. Long-term follow-up of Idelalisib monotherapy in patients with double-refractory marginal zone lymphoma or lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia. Blood. 2019;134(Suppl_1):4006. https://doi.org/10.1182/blood-2019-121936.
37. Dreyling M, Panayiotidis P, Follows GA, et al. Long-term efficacy and safety of Copanlisib in multiply relapsed or refractory patients with marginal zone lymphoma. Blood. 2019;134(Suppl 1):1531.
38. Conconi A, Raderer M, Franceschetti S, et al. Clinical activity of everolimus in relapsed/refractory marginal zone B-cell lymphomas: results of a phase II study of the international Extranodal Lymphoma Study Group. Br J Haematol. 2014;166:69–76. https://doi.org/10.1111/bjh.12845.
39. Rosenthal A, Dueck AC, Ansell S, et al. A phase 2 study of lenalidomide, rituximab, cyclophosphamide, and dexamethasone (LR-CD) for untreated low-grade

non-Hodgkin lymphoma requiring therapy. Am J Hematol. 2017;92:467–72. https://doi.org/10.1002/ajh.24693.

40. Leonard JP, Trneny M, Izutzu K, et al. AUGMENT: a phase III study of Lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37:1188–99. https://doi.org/10.1200/JCO.19.00010.
41. Noy A, de Vos S, Thieblemont C, Martin P, Flowers CR, Morschhauser F, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood. 2017;129:2224–32. https://doi.org/10.1182/blood-2016-10-747345.
42. Lossos IS, Fabregas JC, Koru-Sengul T, Miao F, Goodman D, Serafini AN, Hosein PJ, Stefanovic A, Rosenblatt JD, Hoffman JE. Phase II study of (90) Y Ibritumomab tiuxetan (Zevalin) in patients with previously untreated marginal zone lymphoma. Leuk Lymphoma. 2015;56:1750–5. https://doi.org/10.3109/10428194.2014.975801.
43. Samaniego F, Berkova Z, Romaguera JE, Fowler N, Fanale MA, Pro B, Shah JJ, McLaughlin P, Sehgal L, Selvaraj V, Braun FK, Mathur R, Feng L, Neelapu SS, Kwak LW. 90Y-ibritumomab tiuxetan radiotherapy as first-line therapy for early stage low-grade B-cell lymphomas, including bulky disease. Br J Haematol. 2014;167:207–13. https://doi.org/10.1111/bjh.13021.
44. Gopal AK, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent non-Hodgkin lymphoma refractory to both rituximab and an alkylating agent. N Engl J Med. 2014;370:1008–18. https://doi.org/10.1056/NEJMoa1314583.
45. Fowler NH, Davis RE, Rawal S, Nastoupil L, Hagemeister FB, McLaughlin P, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. Lancet Oncol. 2014;15:1311–8. https://doi.org/10.1016/S1470-2045(14)70455-3.