

A microscopic view of red blood cells, showing their characteristic biconcave disc shape and reddish color, set against a dark background.

# **Insights, Knowledge Gaps, and Priorities in Marginal Zone Lymphoma Research**

**Report of the Lymphoma Research  
Foundation's Marginal  
Zone Lymphoma Workshop**

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**A Lymphoma Research Foundation Publication**

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# Insights, Knowledge Gaps, and Priorities in Marginal Zone Lymphoma Research

## Abstract

Marginal zone lymphoma (MZL) is a rare, indolent form of non-Hodgkin lymphoma that arises from B cells in the marginal zone of lymphoid tissues. MZL is comprised of 3 key subtypes: extranodal, nodal, and splenic MZL. Despite being generally slow growing, MZL presents significant challenges due to its heterogeneous nature, inconsistently defined disease, and the limited efficacy and availability of current treatments. Advancements in targeted therapies and a deeper understanding of the molecular underpinnings of MZL are critical to improving patient outcomes and achieving more durable remissions. At the Lymphoma Research Foundation's 2024 Marginal Zone Lymphoma Virtual Scientific Workshop, researchers gathered to discuss recent developments in both basic scientific and clinical research so that together we can continue to develop our understanding of MZL and improve outcomes for patients. This report, which includes a summary of each presentation, aims to review the findings presented at the workshop. Additionally, it highlights opportunities, reviews questions, and assesses areas for future study to set the stage for treatment advancements in the coming decades.

## Introduction

Marginal zone lymphoma (MZL) is an indolent B-cell non-Hodgkin lymphoma that originates in the marginal zones of lymphoid tissues, encompassing the key subtypes of extranodal, nodal, and splenic MZL. Accurate diagnosis and effective prognostication are challenging due to MZL's heterogeneous presentation and overlapping features with other lymphomas. Current treatment

options are limited and often yield only partial remissions, highlighting the need for more effective and targeted therapies. Improved diagnosis and disease characterization are essential for optimizing outcomes, and recent research has made significant strides in understanding the genetic and molecular landscape of MZL. These advancements are poised to improve patient outcomes by enabling more precise diagnostics, prognostics, and therapeutic interventions.

Recognizing the need for accelerated MZL research, the Lymphoma Research Foundation has provided MZL-specific research grants and developed an MZL steering committee, a working group that includes both basic scientists and translational/clinical researchers from North America and Europe. Since April 2019, the group has met regularly to allow researchers to share their work and offer a unique opportunity for collaboration among investigators across a wide range of MZL areas of interest. Through this type of exchange, thoughts on the current and future direction of MZL research are shared, and researchers are provided with a unique opportunity to develop collaborations needed to continue to drive MZL research forward.

The 2024 MZL Virtual Scientific Workshop, held on May 3 and 4, 2024, included sessions on MZL pathology; molecular taxonomy; viral, microbial, and antigen factors linked to MZL; developmental therapeutics; MZL epidemiology, prognosis, and transformation; criteria for assessment and evaluation of response; an international overview of MZL clinical trials; and an open forum to establish a road map for MZL research priorities in the short (1 to 5 years) and long (5 years or more) terms.



Thomas M. Habermann, MD

**Q / What is the significance of the MZL Workshop?**

**Habermann /** In 1999 and then in 2024 we brought together the leading individuals internationally in MZL. We did this because it is one of the most complicated groups of lymphomas, as far as its biology, treatment, and outcomes. It is an incredibly heterogeneous group of disorders that most clinicians and even individuals in the field of lymphoma don't quite appreciate.

**Q / How does the MZL Workshop contribute to advancing research and improving outcomes for patients with MZL?**

**Habermann /** What we learned at this meeting is more of what we don't know and more of how to apply what we know, bringing together individuals in this format and then establishing what I referred to as our 1-year and our 5-year plans looking into which directions we think we need to go. It was fascinating in 2024 for us to see how many papers came out in MZL. It's my belief that this endeavor has done something to help contribute to the field.

**Q / Where do you hope to see this field advance in the future?**

**Habermann /** We're in need of different treatments. This disorder can be managed with observation, in some patients with just surgical resection, in some with chemotherapy, or with immunotherapy, and there is no uniform treatment approach. Secondly, low-grade lymphoproliferative disorders are not curable, although we know that at 10 years, the most common cause of death is not lymphoma, but it's other causes. This is in contradiction to follicular lymphoma. One of the things that we've done to help advance the field is to separate this group of disorders into [separate] clinical trials so that we can learn more. The other piece that we have to continue to advance is the biology. The genomics is very complicated, and

[later in the article **Figure 1**] demonstrates the different gene expression patterns of different types of MZL.

**Q / What was your favorite part of the workshop?**

**Habermann /** [My] favorite part was the interactions. We did it in person in 1999 and we did it virtually in 2024, and it was intriguing to see how interactive it [is now]. We required speakers to only speak for a [certain] period of time, and we made sure there was very adequate time for a question-and-answer session, and in both venues, it was quite remarkable. Not only that, but bringing all the information...the speakers did a remarkable job. Just the detail, and all of it was astute. These were the top people internationally on the topic, so it was fun.

**Q / What do you hope your colleagues took away from this workshop?**

**Habermann /** Each time we have this meeting, I hope we take away what we need to do with future directions in managing the disease. We saw between 1999 and 2024 that there were very significant contributions made. We also established some different collaborations over time, and we hope that's going to continue both nationally and internationally. The International Extranodal Lymphoma Study Group has done an extraordinary job in this disorder, and the interactions with them have been quite remarkable in recent years.

**Q / Is there anything else you'd like to highlight?**

**Habermann /** The meeting has always been closed, and that's been fortunate and unfortunate. We've done this in a way that we want it to be very interactive and inclusive of individuals with in-depth knowledge of the disorder. My hope is that we can potentially, over time, broaden this. My other hope is that we can find a place to publish this [information]. The previous meeting in 1999 had about 11 papers, but we want to broaden the knowledge of this disease to people and clinicians nationally and internationally.

## Proceedings

### Introduction:

#### The State of MZL Since 2019

To kick off the workshop, Davide Rossi, MD, PhD, deputy head of the Division of Hematology of the Oncology Institute of Southern Switzerland and head of the Laboratory of Experimental Hematology at the Institute of Oncology Research in Bellinzona, Switzerland, provided an overview of the research advancements that have occurred in MZL since the 2019 MZL workshop. Rossi utilized data from a PubMed search to illustrate that the annual number of MZL publications hovers around 400. Among the new publications, Rossi identified 86 studies with transformative research, most of which (n = 62) were clinical studies that fell into the following categories: staging and restaging, treatment, prognosis, and resistance. A total of 24 studies were translational and covered topics including predisposition, classification, genetics, microenvironment, and transformation. Given this background of new literature, Rossi expressed great excitement for the future of MZL research.

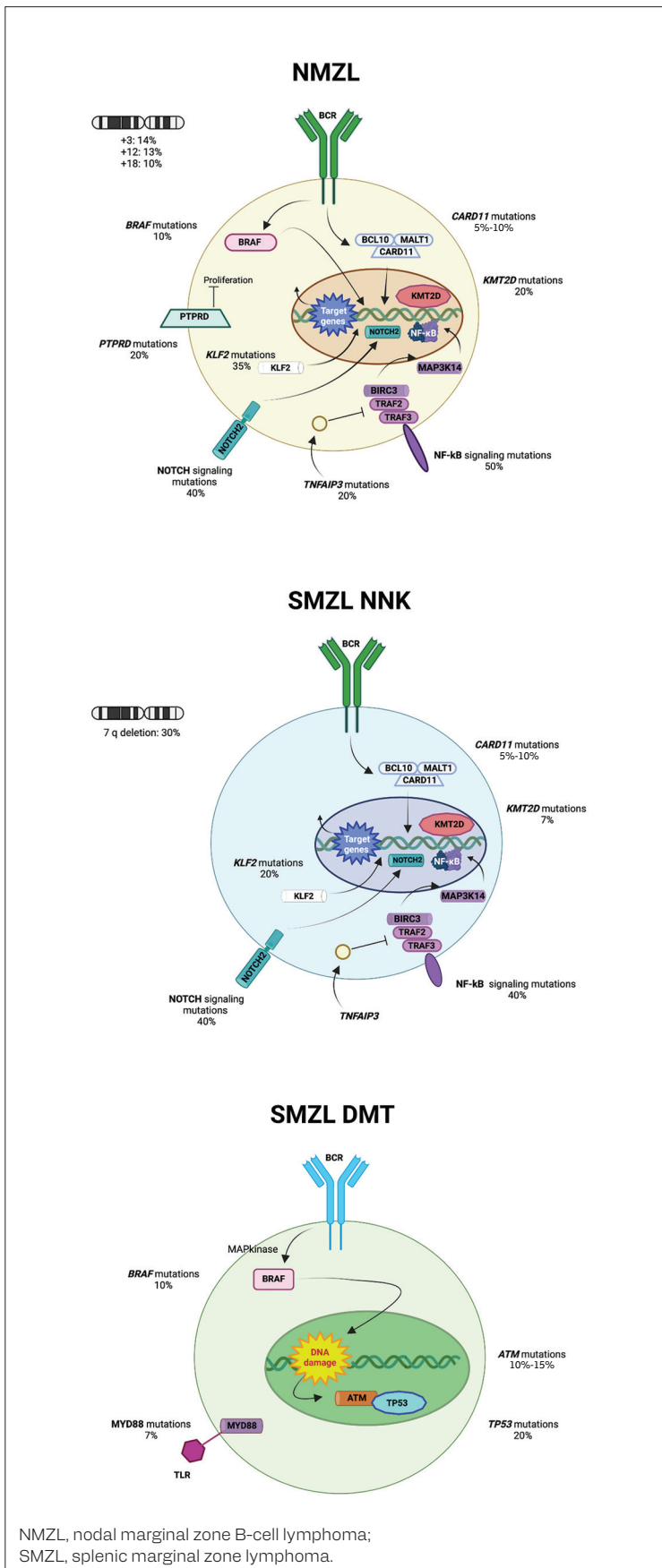
Next, Thomas Habermann, MD, professor of medicine at the Mayo Clinic, Rochester, MN, provided a road map and overview of MZL. Habermann revisited concerns and unanswered questions generated in the 2019 workshop and the corresponding long- and short-term solutions proposed to address those needs. The questions and concerns were categorized into the following sessions: biology and pathology; epidemiology and transformation; assessment criteria, response evaluation, and surrogate end points in MZL; MZL targeted pathways; etiology and natural history of MZL subtypes; and treatment of MZL. The following sessions share the community's progress toward understanding more about each of these important categories.

### Session I: Pathology

To open this session, Andrew Wotherspoon, MB BCh FRCPath, consultant histopathologist at the Royal Marsden Hospital, discussed the gray areas of diagnosing MZL (Figure 1). Currently, diagnosis of MZL is based on analysis of peripheral blood and bone marrow aspirate/biopsy in combination with evaluation of molecular disease characteristics, but some difficulties with differential diagnoses persist. Wotherspoon covered 6 specific challenges in MZL diagnosis, the first of which was differentiating between splenic MZL and other primary splenic small B-cell lymphomas. Wotherspoon's approach for differentiating between hairy cell leukemia, splenic MZL, and splenic diffuse red pulp small B-cell lymphoma relies on assessment of peripheral blood appearances, the degree of intrasinusoidal disease, and differentiating molecular findings. To distinguish between primary and secondary MZL in lymph nodes, Wotherspoon suggests searching for extranodal primary MZL only if a patient has stage I nodal MZL. Differential diagnosis of early MZL vs reactive lymphoid tissue can be difficult; useful differentiators that are often (but not always) indicative of early MZL overreactive tissue include lymphoepithelial lesions that are well formed and have eosinophilic appearance, the presence of Dutcher bodies, centrocyte-like cell morphology and cytological atypia, expression of CD43 and CD5, and light chain restriction. Clonality assessments may be helpful but should be interpreted with caution. Indicators of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (WM) vs splenic MZL include levels of immunoglobulin M (IgM), marrow infiltration pattern, the presence of mast cells, plasma cell count, and some immunohistochemical factors. Differentiating between extranodal MZL and follicular lymphoma (FL) can be aided by assessing the infiltrate pattern, determining the

presence of lymphoepithelial lesions, and careful immunophenotyping. Atypical marginal zone hyperplasia exhibits distorted follicular structures with infiltration in the marginal zone area. Features differentiating hyperplasia from MZL include aberrant CD43 expression, CD27 negativity, light chain restriction,  $\lambda$  light chain restriction, high proliferation, location (tonsil and appendix are most common), age, and clonality. The insights provided in this talk may help physicians and pathologists discriminate between difficult MZL diagnoses.

Next, James Cook, MD, PhD, professor of pathology at the Cleveland Clinic, discussed the existence of *MYD88*-negative WM and *MYD88*-positive MZL (Figure 2). In general, distinguishing between MZL and lymphoplasmacytic lymphoma (LPL) is challenging due to their overlapping clinical, morphological, and immunophenotype features. A 2012 study identified *MYD88* mutations in the vast majority of bone marrow WM samples and many LPL samples, leading to the recognition of the *MYD88* L265P mutation as a common but not exclusive feature of LPL (95% to 97% of cases).<sup>1</sup> A small percentage of patients with LPL are reported to have wild-type *MYD88*; *MYD88* wild-type LPL cells appear to have similar characteristics to *MYD88*-mutated LPL cells. *MYD88* mutations are not exclusive to LPL and can also occur in other lymphomas. In MZL, up to 10% of patients have been reported to harbor mutations in *MYD88*; however, most data on *MYD88* mutations in MZL come from patients with splenic disease and bone marrow biopsies, and most reported cases have plasmacytic differentiation and IgM protein, which makes the true disease for these samples difficult to ascertain. The *MYD88* L265P mutation has been reported in a small percentage of nodal and splenic MZL cases, and in mucosa-associated lymphoid tissue (MALT) lymphomas,



**FIGURE 1. Key Molecular Alterations in NMZL and SMZL With NNK and DMT Genotypes**

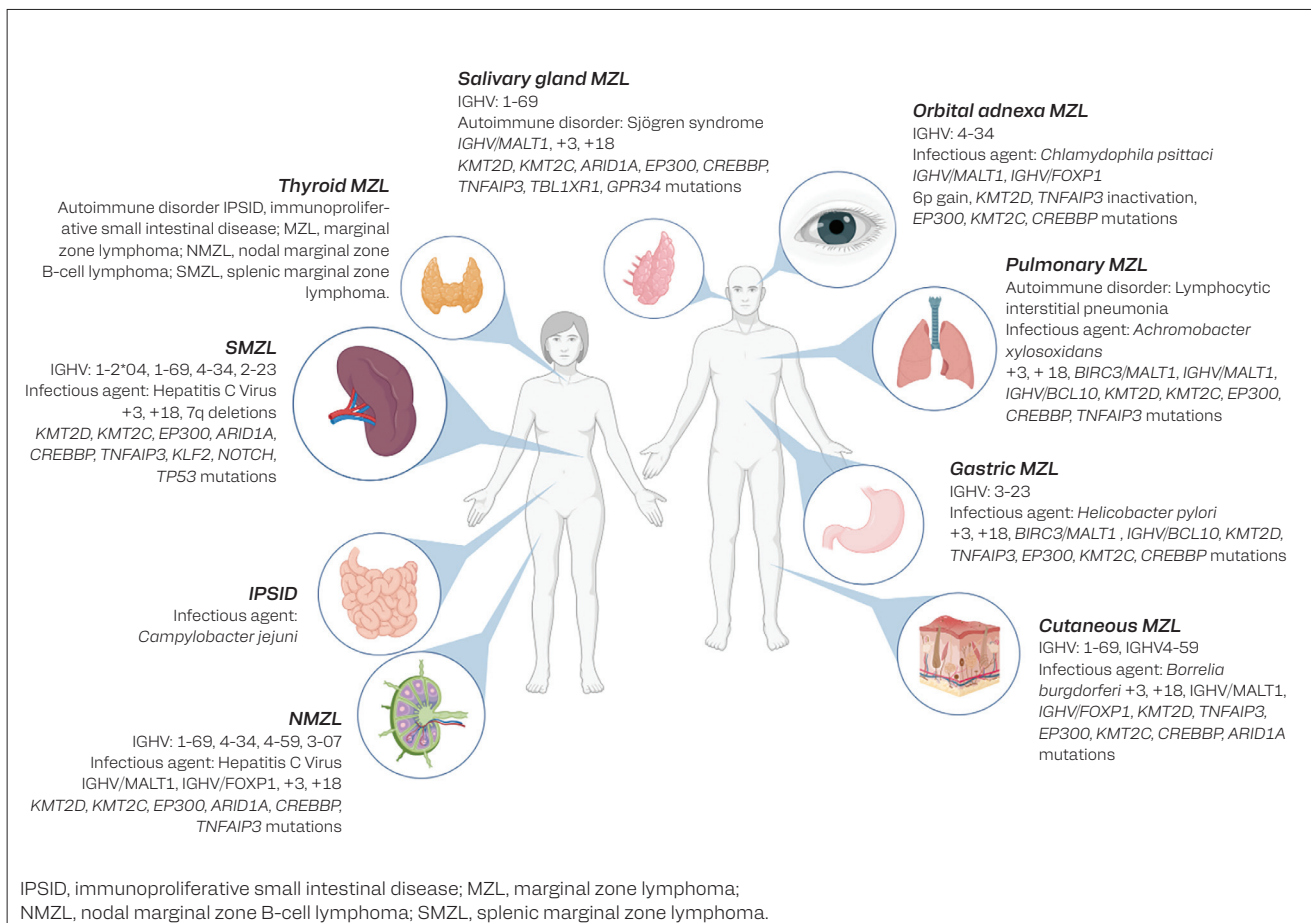
This is a schematic representation of the genes and pathways that are molecularly deregulated. The prevalence of these alterations are indicated alongside each gene or pathway, providing an overview of frequency and relevance.

*MYD88* mutations have been reported in gastric and ocular adnexa sites. Overall, Cook concluded that *MYD88*-negative WM and *MYD88*-positive MZL cases do seem to exist but are rare. In LPL, additional MZL biomarkers would be helpful to better understand *MYD88*'s relationship to MZL. In splenic MZL, the *MYD88* L265P mutation appears rare to absent; in extranodal MZL, *MYD88* L265P does occur at certain sites; and while there are nodal MZL cases with *MYD88* L265P, the criteria for nodal MZL need refinement. The presence of *MYD88* L265P favors a diagnosis of LPL over MZL but is not 100% sensitive or specific. While the diagnosis of extranodal MALT lymphoma is generally straightforward, distinguishing between splenic and nodal MZL from LPL remains a challenge.

**Session II: Molecular Taxonomy**

Ming-Qing Du, PhD, MB, FRCPath, professor of oncological pathology, Division of Cellular and Molecular Pathology at the University of Cambridge, discussed the genetic and immune characteristics of extranodal MZL. Du reviewed key genetic changes that have been implicated in MALT lymphomas. It has been established that marginal zone B-cell differentiation is largely driven by transcription factor signaling, but genetic disease varies by disease site. For example, gastric MALT lymphoma is characterized by *Helicobacter pylori*-specific T-cell signaling.

**FIGURE 2.** This figure illustrates the anatomical distribution, molecular characteristics, and associated triggers of various subtypes of MZL.



In thyroid MALT lymphoma, genetic changes affect B-cell and T-cell function via inactivation of PD-L1 and TNFRSF14 (herpesvirus entry mediator) signaling and the inactivation of FAS ligand signaling. In salivary MALT lymphomas, notable genetic changes include mutations (in the G-protein coupled receptor GPR34 and chemokine receptor CCR6) that promote lymphatic transcription programs. CCR6 signaling has also been implicated in gastric MALT; however, Du noted that CCR6 signaling is independent of genetic changes to the receptor and is commonly maintained by ligand stimulation in

inflammatory conditions (ie, *H pylori* infection). Du summarized the discussion by showing how similar mechanisms drive malignancy in the different MALT disease sites but involve different players: The *H pylori*-specific T cells in gastric extranodal MZL, the exaggerated T-cell function in thyroid extranodal MZL, and the enhanced GPCR signaling in salivary extranodal MZL all lead to increased transcription of MZL-related genes.

Next, Anne J. Novak, PhD, consultant, Division of Hematology, Department of Internal Medicine; consultant, Department of Immunology; and professor of medicine

at Mayo Clinic, described the genomic, transcriptomic, and biologic characterization of MZL. Novak discussed efforts to use next-generation sequencing strategies to identify shared biology and disease mechanisms across B-cell lymphoma subtypes. Using acquired tumor samples from 64 B-cell lymphomas, Novak's group performed bulk RNA sequencing, tumor-normal whole exome sequencing, and immune profiling to identify distinct clusters of patients with differences in event-free survival (EFS) and overall survival (OS).<sup>2</sup> The 5 patient clusters had distinct biological, genetic, and immune

features. A gene expression signature including 113 genes was identified and associated with inferior EFS and OS in low-grade B-cell lymphomas; using patient data, the gene signature identified those with significantly worse EFS and OS. Using the mining algorithm for genetic controllers, a tool for predicting transcription factors of gene sets, DEK was identified as a potential regulator of the genes included in the predictive gene signature. DEK expression was associated with aggressive disease in low-grade B-cell lymphoma and correlated with cell cycle gene expression. Cells collected from more aggressive tumors showed higher levels of DEK expression, and in cell-based experiments, DEK depletion inhibited proliferation and was accompanied by reduced expression of cell cycle genes, reduced Bcl-2 and Bcl-xL expression, and increased p53 expression. DEK knockout cells also showed increased susceptibility to apoptotic agents. Future research will continue to explore the role of DEK in lymphoma.

Alexandar Tzankov, MD, surgical pathologist and head of the Department of Histopathology and Autopsy at the Institute of Medical Genetics and Pathology at University Hospital Basel, University of Basel, followed with a discussion of nodal MZL from a pathologist's point of view. Nodal MZL is a diagnosis made in the absence of indicators of extranodal or splenic disease. Increasing age is the most important risk factor for nodal MZL. Histopathology often shows a nodular, inside-out pattern from the germinal center, occasionally exhibiting a blastoid morphology, and in some cases, the lymphoma cells have plasmacytoid differentiation. The nodal MZL phenotype is not very specific; samples may be positive for a range of immunohistochemical markers; the most common are Bcl-2, CD19, CD20, CD22, and CD79a. Tzankov noted that bone marrow involvement of nodal MZL is likely underestimated. There are no specific cytogenetic signatures of nodal

MZL, and molecular genetics generally overlap with other MZL subtypes, though PTPRD and BRAF are notable in nodal disease, and mutations in *MYD88* are rare. Genes mutated in nodal MZL are generally involved in chromatin remodeling, NOTCH signaling, and the p53 pathway. Transformation is poorly defined in MZL; it is often evidenced by the appearance of sheets of blasts. Other indicators of transformation may include the Ki-67 score, karyotype, and mutations in *NOTCH3*, *TP53*, and *TBL1XR1* (discussed further by Luca Arcaini on day 2). To summarize, Tzankov explained that in practice, the diagnosis of nodal MZL requires a thorough analysis of lymphadenectomy samples, clinical and radiologic data, and bone marrow biopsies. Mutations in several genes related to MZL can provide diagnostic and prognostic information when used in the context of other disease information, and genetic aberrations provide opportunities to identify novel drug targets for MZL treatment.

### Session III: Searching for New Pathogens/Antigens Associated with MZL

To open this session, Andrea Alimonti, MD, director of the Institute of Oncology Research, head of the Molecular Oncology Research Group, and full professor at Università della Svizzera italiana and ETH Zurich, discussed the microbiome of patients with lymphoma. In healthy individuals, the gut microbiome contains over 2000 different species of organisms with roles in metabolism, vitamin production, and xenobiotic and drug detoxification processes. Dysbiosis in the balance of the gut microbial environment can contribute to the onset of many diseases and is one of the canonical hallmarks of cancer. Microorganisms can induce tumorigenesis through a variety of mechanisms, including by inducing DNA damage, creating an inflammatory environment, or through secondary metabolite or hormone signaling.



Alexandar Tzankov, MD

#### Q / From a pathologist's point of view, what is nodal MZL?

**Tzankov** / Nodal MZL is challenging from the perspective of pathology since [it belongs] to low-grade lymphomas that are not defined by a specific phenotype, like mantle cell lymphomas that express [cyclin-dependent kinase] 1 or follicular lymphomas that express germinal center markers. They are also not defined by a single genetic operation, especially not by a specific translocation, although they occasionally show some recurrent genetic changes. This makes the diagnosis challenging, like the diagnosis of exclusion. If one reads the definition of this disease, it's a primary nodal B-cell neoplasm that morphologically resembles lymph node involvement by MZL but without evidence of extranodal or splenic disease. At the end of the day, establishing the diagnosis is not very easy.

On the one hand, you need some clinical and radiologic information on whether the spleen is involved and whether [the disease is] involved in external organs. This is something that you usually don't know at the time a biopsy of a lymph node is done, and you probably provide a descriptive diagnosis of a B-cell lymphoma without a specific phenotype that has to be contextualized based on findings of other disciplines. On the other hand, it makes things interesting, and this is for sure one of the lymphoma subtypes for which the lymphoma conferences, after the diagnosis, are quite useful to put all the information together.

**Q / How does bone marrow involvement play into nodal MZL, and does that impact prognosis and treatment decisions?**

**Tzankov /** The bone marrow involvement is a little bit underestimated and a poorly studied issue in this consideration, and it will never be sufficiently studied, especially nowadays in the times of sophisticated staging methods, especially PET scans. Nevertheless, it's rather more common than anticipated. It's nonspecific, and could be interstitial, peritubular, nodular, or diffuse, and depending on the extent of the involvement, it could be easy to diagnose or be more complicated to diagnose. There are several problems in that consideration; some MZLs [do not have much aspiration], so the aspirational cytology and the flow cytometry of the bone marrow may underestimate what is going on.

On the other hand, histopathology, [when it is used], because of the lack of specific phenotype, may also be difficult to interpret. The use of molecular techniques is decisive to reaching a final diagnosis, which is [an uphill] battle since MZLs appear analogous to some follicular lymphomas and limited stage, but no MZLs can be considered potential candidates for curative irradiation, and this may not be the case in cases involving the bone marrow. The most important issue here is to properly address the bone marrow involvement whenever a patient is considered for curative local radiotherapy. The diagnostic hematopathologist should be aware that reaching a final diagnosis may be tricky and that using sequencing techniques to discern the clonal relationship between the B cells in the bone marrow and in the lymph nodes may be applicable in that particular consideration. A tricky issue with many caveats, but all I have said is not based on prospective or retrospective large case studies, but rather on my personal opinion from the 25 years of practice that I have.

**Q / What are the important prognostic factors for MZL, and how do they influence treatment decisions?**

**Tzankov /** Beyond the clinical prognostic factors that are more or less summarized in [the Follicular Lymphoma International Prognostic Index] analogous scoring, there are not a lot of

well-established prognostic factors in nodal MZL. The involvement of the bone marrow that we discussed previously is probably not a sole prognostic marker, but it can discern between patients with limited-stage disease who may be potentially curable with the irradiation. This by no means [states] that patients with bone marrow involvement would for sure have poorer outcomes. Yet, the probability of having poor outcomes is higher. A high proliferation rate, over 50%, is rather suggestive of more aggressive behavior of the MZL; the presence of complex karyotypes is considered a probable negative prognostic factor, and there are some limited studies suggesting that *NOTCH3* mutations, or *TP53* mutations, or mutations of a gene called *TBL1XR1* may forecast more aggressive clinical behavior, but all this information is from a limited number of studies with a limited number of patients and rather retrospective ones.

In addition, maybe the detection of sheets of blasts by the hematopathologist when diagnosing MZL may be linked to more aggressive behavior. Yet the books are still not closed [on] how to define these sheets of blasts. It's suggested that the monotonous proliferation of large cells that are more than 20% of the neoplastic population would meet this criterion. Everything is not well established and is rather based on information from retrospective or limited numbers.

**Q / Looking toward the future, where do you hope to see this field go?**

**Tzankov /** Dealing with nodal MZL, we're probably not dealing with just 1 single disease, but maybe with diseases that rely on mutations in different pathways. Cases that are more linked to mutations in the NOTCH pathway compared with cases that are linked to more mutations in the WNT signaling pathway, and maybe for lymphomas relying on the activation of different mutational pathways, will go for more tailored treatment. This is something that I estimate should be in the far future in terms of diagnostics. I suppose that the mutational profiles that are useful in single cases would be helpful to discern difficult cases of nodal MZL.

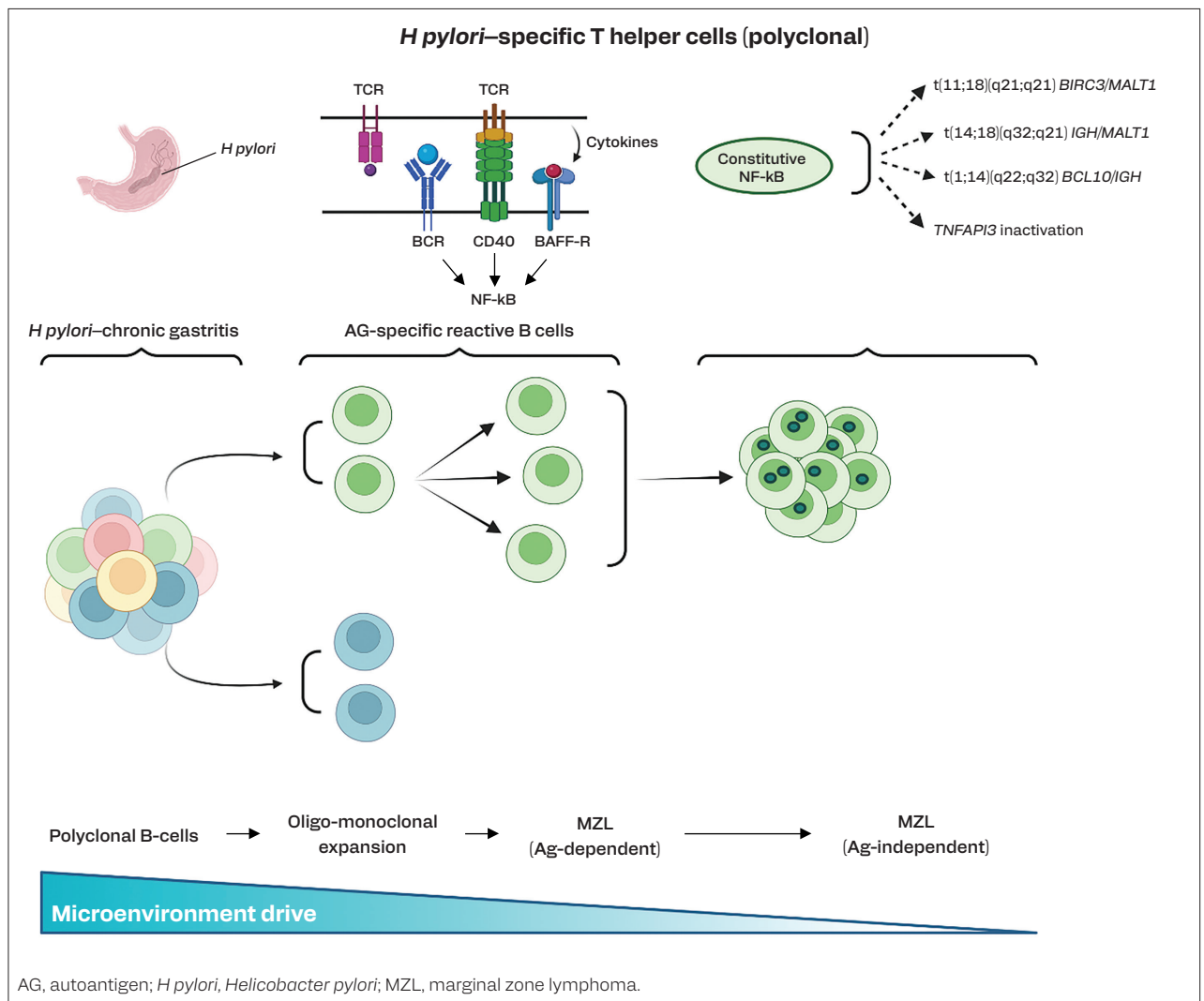
Gut bacteria can directly influence the onset and progression of cancer; the intra-tumoral microbiome is an ongoing subject of research in a number of different cancer types and has been implicated in metastatic colonization.

In non-Hodgkin lymphomas, specific bacteria have been linked to MALT lymphoma onset, including *H pylori*,

*Chlamydomphila psittaci*, *Campylobacter jejuni*, and *Borrelia burgdorferi* (Figure 3). In lymphoma, pathogen infections are proposed to promote malignancy via chronic stimulation of B-cell and T-cell lymphocytes and the formation of follicular lymphoid tissue, which subsequently leads to B-cell lymphoma. Antibiotic therapy has proven beneficial,

especially in *H pylori* gastric MALT. The microbiota-gut-lymphoma axis presents exciting opportunities for new MZL prevention and treatment strategies via the modulation of gut microorganisms. Alimonti concluded with a summary of the wide array of therapeutic interventions for gut microbiome modulation, including dietary and supplemental interventions,





**FIGURE 3. Overview of the Pathogenic Evolution of MZL.** This depicts the progression from polyclonal B cells to oligo-monoclonal expansion, leading to antigen-dependent MZL and eventually antigen-independent MZL. The role of *H. pylori* infection in chronic gastritis is illustrated, emphasizing the interaction between *H. pylori*-specific T helper cells, B cells, and the activation of pathways such as NF-κB via antigen stimulation (eg, CD40/CD40L interactions and cytokines such as BAFF). The figure also notes genetic alterations (eg, translocations involving *MALT1*, *IGH*, and *BCL10*, as well as *TNFAIP3* inactivation) that contribute to constitutive NF-κB signaling, underscoring the transition to antigen-independent lymphoma development

fecal microbiota transplantation, engineered bacterial therapies, and phage therapy. A growing number of clinical trials are underway to explore gut microbial modulation to combat cancer.

Following the microbiome discussion, Ethel Cesarman, MD, PhD, assistant director of the Molecular Hematopathology Laboratory of the New York-Presbyterian Hospital/Weil Cornell Medical

College, shared an update on the interplay between viral infections and lymphoma. Viruses have a significant impact on cancers; an estimated 13% of cancers are considered to be caused by viruses.<sup>3</sup> In lymphoma, the intersection between cancer, immunodeficiency, and herpesviral infection is of particular relevance. The Kaposi sarcoma-associated herpesvirus (KSHV, also known

as human herpesvirus 8 [HHV8]) is associated with lymphoproliferative disorders including primary effusion lymphomas, extracavitary primary effusion lymphoma (PEL), and KSHV-associated diffuse large B-cell lymphoma (DLBCL) not otherwise specified, and is linked to reactive lymphoid proliferation. PEL can occur in the spleen and other organs and is characterized by

large tumor cells and characteristics of latency-associated nuclear antigen staining pattern. In multicentric Castleman disease, KSHV is always found in B cells that are expressing  $\lambda$  light chains; further exploration of this phenomenon may provide insight into pathogenic mechanisms. In tumor cells, KSHV expresses approximately 7 different genes involved in the virus latency program. Existing antiviral treatments are targeted at the viral lytic program, but the latency protein vFLIP has emerged as an attractive target for the treatment of KSHV-associated diseases due to its roles in autophagy and apoptosis.

Cesarman's research group is working to identify small-molecule inhibitors of vFLIP for use in cancer treatment. Other viruses also express latent-phase proteins that play a role in carcinogenesis; latent-phase proteins expressed by Epstein-Barr virus (EBV) are involved in oncogenic processes in lymphoma. Pharmacologic screens have identified DNA methylation as a key regulator in this process, and preclinical experiments aimed at inducing latency followed by T-cell killing are showing promise as an antilymphoma treatment. Future studies will further investigate the potential for targeting the latency switch for treating EBV-positive cancers. Humans also carry endogenous viruses in their genomes that may play a role in oncogenesis. In an effort to characterize the endogenous retrovirome in lymphoma, Cesarman's team is sequencing EBV-positive lymphomas and exploring their gene expression profiles to gain insight into their roles in the disease process. Viruses, both exogenous and endogenous, play an important role in lymphoma biology and continue to present exciting new avenues for drug development.

To wrap up the session, Nicholas Chiorazzi, MD, professor at the Institute of Molecular Medicine, Feinstein Institutes for Medical Research; Kanti R. Rai, MD, professor of molecular

medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, and professor of medicine at the Feinstein Institutes for Medical Research, highlighted the role of autoimmune B cells on chronic lymphocytic leukemia (CLL) disease biology and how these mechanisms might be investigated in MZL. Chiorazzi provided an overview of the research leading to the understanding that CLL is a disease of autoreactive B cells and that signaling through the B-cell receptor (BCR) is important to the development and evolution of the disease. In experiments to characterize the reactivity of the CLL B cells, bacterial strains were able to trigger reactivity with patient-derived CLL antibodies. Biochemical experiments suggest that a nonprotein bacterial antigen is responsible for this reactivity. Experiments with commercial antigen arrays and phage-display experiments have identified several antigens that are able to react with CLL antibodies and may be useful in guiding the development of new treatments. To perform these types of experiments in MZL, Chiorazzi suggests selecting BCRs from patients across the 3 major disease categories, expressing them as the patient's isotype, and screening for natural antigens while considering the cell of origin and with the maturational pathways that marginal zone B cells follow. Tissue and protein arrays are available for these types of experiments and may lead to novel insights into MZL biology.

#### Session IV: Developmental Therapeutics

Alberto J. Arribas, PhD, of the Institute of Oncology Research, spoke about the deregulated pathways and potential vulnerabilities that can be exploited for drug development in MZL. Across the 3 MZL subtypes, several molecular pathways are commonly regulated, including chromatin remodeling, NOTCH, B-cell

receptor, and NF- $\kappa$ B signaling. Outside of these commonalities, each subtype has its distinct profile of signaling pathway dysregulation. Arribas provided an overview of different promising therapeutic approaches targeting these various pathways in lymphoma, including Bruton tyrosine kinase inhibitors (BTKis) with and without anti-IL16 agents (under investigation in MZL and BTKi-resistant MZL); PI3K with and without STAT inhibitors, epigenetic drugs, and miRNA mimics (in MZL and PI3K inhibitor [PI3Ki]-resistant MZL); chimeric antigen receptor (CAR) T-cell therapy (in BTKi- and PI3Ki-resistant MZL); demethylating agents (in splenic MZL); bispecific T-cell engagers (in aggressive lymphoma); antibody-drug conjugates (in DLBCL and indolent lymphoma); immune checkpoint modulators including antibodies to CD47 (in refractory MZL and indolent lymphomas); IRAK4 inhibition with BTKi and PI3Ki (in *MYD88*-mutated disease); mTOR inhibition (in BTKi-, PI3Ki-, and Bcl-2 inhibitor-resistant MZL); Bcl-2 inhibition (in lymphoma); and CXCR4 inhibition (in MZL). Arribas concluded that BTK and PI3K remain interesting targets in MZL, though there is a need for approaches to overcome resistance, that multiple novel therapies are on the horizon, and that novel targeted therapies have potential applications in relapsed and refractory disease.

José Ángel Martínez Climent, MD, PhD, principal investigator of Lymphomas Group, Hemato-Oncology Program, Universidad de Navarra, presented the development and research applications of mouse models of MZL. The importance of the *MYD88* mutation to B-cell lymphoma pathogenesis is well established, but Martínez-Climent noted that it is not known how the *MYD88* mutation drives lymphomas with different clinical, histopathological, and immunological features. To investigate this question, Martínez-Climent's research

group crossed a murine line carrying MYD88<sup>L252P</sup> with mice with genetic lesions in BCL2, BCR, P53, and BLIMP1. Comparison of the mice resulting from these crosses with data from patients with LPL and MALT lymphomas showed similarities in immunoglobulin secretion, indicating the mouse models recapitulate relevant disease characteristics. These models have provided useful information about MZL disease processes. In one case, Martinez-Climent's research team had noticed that B cells and T cells colocalize with CD40 lymphocytes in biopsy samples, so to gain further insight, they performed single-cell RNA sequencing using murine-derived cells. The resulting data indicated that along with an increase in the number of B lymphocytes, T-cell accumulation increased with disease progression and sustained clonal B-cell survival. Functional assays using murine-derived tumor cells confirmed the importance of the B-cell and T-cell interactions for lymphoma cell survival. Blocking CD40 signaling decreased the viability of B cells in vitro and in mouse models, indicating the potential for disrupting this interaction as a therapeutic strategy. Other mouse models of MYD88/CD79B-mutated-DLBCL have also provided useful molecular information about the tumor microenvironment. Martinez-Climent concluded that these mouse models serve as a proof of concept for advancing precision immunotherapy in B-cell lymphomas according to genetic and immunological characteristics.

Anastasios Stathis, MD, director of the Phase I Program, Oncology Institute of Southern Switzerland, and faculty member of Biomedical Sciences, Università della Svizzera italiana, closed the session with a review of ongoing phase 1 studies. From 2017 to 2023, 15 drugs have been approved by the FDA for the treatment of non-Hodgkin lymphoma, but the trials for these drugs enrolled low numbers of

patients with MZL, if they enrolled any at all. Data from the Cancer Therapy Evaluation Program at the National Cancer Institute indicate that results from phase 1 trials show an overall rate of grade 5 adverse events of 1.81% and an overall response rate of 25.1%, including 43.2% in lymphoma.<sup>4</sup> A systematic review of lymphoma also found an overall response rate higher than 30% in the majority of studies.<sup>5</sup> Drug approvals in MZL have been limited and based on data from small trials. FDA-approved therapies for MZL include zanubrutinib (overall response rate, 68.2% [extranodal MZL, 64%; nodal, 76%; splenic, 66.7%]; complete response (CR), 25.8%) and lenalidomide (progression-free survival [PFS] not significant in the MZL cohort).<sup>6,7</sup> A total of 26 phase I trials are ongoing in lymphoma, though none are specific to MZL, including 16 phase 1 and 10 phase 1/2 trials. Twenty of these trials are assessing monotherapies, and 6 are evaluating combination treatments. Among the trials assessing small molecules are those targeted toward BTK, Bcl-2, PKC $\beta$ , MALT1, and IKZF1/3. Combination trials are assessing PI3K $\delta$  plus BTK, Bcl-2 plus lenalidomide and rituximab, CDK9 plus Bcl-2, anti-CD32 plus rituximab, anti-CD47 plus rituximab, and vaccine plus lenalidomide and rituximab. A small number of BTK-degrading compounds are also showing promise, but more research is needed to understand safety and dosing. In the future, Stathis expects to see more patients with MZL in phase 1 trials (and expansion cohorts) and would like to see patients with relapsed disease in trials to test new drugs, opportunities to test new drugs once safety data emerge from other studies, incorporation of molecular testing and liquid biopsies, and international efforts toward MZL trials.

## Session V: Epidemiology Prognosis and Transformation

To open the second day of the workshop, James R. Cerhan, MD, PhD, professor of epidemiology at the Mayo Clinic College of Medicine and Science, Ralph S. and Beverly Caulkins Professor of Cancer Research, coleader of the Genetic Epidemiology and Risk Assessment Program in the Mayo Clinic Comprehensive Cancer Center, codirector of the Biorepositories Program in the Mayo Clinic Center for Individualized Medicine, and associate director of the Mayo Clinic Cancer Registry, provided an update on the epidemiology of MZL. The incidence of MZL has been increasing since 2001; it increases with age and is higher in men for most subtypes, and in most cases, it is highest in patients who are White than in those in other demographics. The incidences of stomach and salivary gland MZL appear to be decreasing, while skin and lung MZL are increasing, especially in women and patients younger than 50 years old. Five-year survival rates continue to increase and are highest for extranodal MZL at 96%, followed by splenic (85%) and nodal (85%) disease. Established risk factors include infections, autoimmune disease, solid organ transplantation, family history, and certain genetic loci. Potential risk factors include smoking, alcohol use, sun exposure, hair dye, and some occupations. MZL does not appear to cluster with any other non-Hodgkin lymphoma subtypes. New risk factors have been evaluated since the last MZL workshop; updated data did not link lymphoma to glyphosate use, body mass index did not impact risk in adults or young adults, physical activity lowered risk for MZL, and low-dose aspirin was protective against MZL. Emerging data will expand understanding of the epidemiologic patterns of this disease and its subtypes. Cause-of-death analysis studies are aiding in the further understanding of MZL.<sup>20</sup>

Next, Luca Arcaini, MD, professor of hematology at the University of Pavia,



James R. Cerhan, MD, PhD

### Q / Is MZL becoming more common in the US?

**Cerhan** / When we look at the Surveillance, Epidemiology, and End Results Program (SEER) data in the US from 2001 to 2021, that's what we reported at the [MZL Workshop] meeting. The number of newly diagnosed cases is going up, but after accounting for the age of the population and size, the age-adjusted incidence for MZL is fairly stable, maybe a slight increase, but nothing statistically significant. When we think of MZL, this was also true for nodal and extranodal subtypes. In contrast, we see about a 1% per year increase in the incidence [of MZL], and most of that is occurring in women. We are seeing a little bit of an increase, but nothing dramatic.

### Q / Your presentation highlighted differences in MZL incidence across different demographic groups. What are the potential underlying factors contributing to these disparities, and how can we address them?

**Cerhan** / The incidence of MZL increases strongly with age. It's similar in men and women, and, overall, it's higher in patients who are non-Hispanic White relative to [those who are] African American, Hispanic, or Asian and Pacific Islander. This pattern for age and race/ethnicity holds for the main MZL subtypes. However, nodal MZL is more common in men, splenic is more common in women, and [the incidence is] similar for extranodal. We don't understand this variation, but some of the leading risk factors for MZL are infections, including hepatitis C and having a history of autoimmune disease. We know both these risk factors are more common in patients who are White compared with other racial and ethnic groups and have been increasing in the US population. Additionally, autoimmune diseases are much more common in women than men. This might explain some of the increase in splenic MZL, particularly in non-Hispanic White women.

### Q / There has been much media attention on an increasing incidence of cancers diagnosed before the age of 50 years. Are we seeing this in MZL?

**Cerhan** / Looking at the US SEER data, we do not see any significant increase in the incidence in the under-age 50 group with the MZL subtypes. However, we are seeing a statistically significant increase in extranodal MZL, no change in nodal,

and perhaps a small decline in the incidence of splenic, which contrasts with what we're seeing overall. This is now just in the under-50 [group], the increase in MZL; extranodal MZL was much greater in women, particularly for the extranodal sites of the skin and perhaps the lung. We don't understand the reasons for these patterns yet.

### Q / What about US survival rates for patients with MZL?

**Cerhan** / The most recent relative US survival rates and relative survival accounts for competing risk of dying as you age are quite high currently in the US, at 92%. They're a bit lower for nodal and splenic at 85% and a bit higher for extranodal at 96%, interestingly. Unlike the patterns we see for incidence, these survival rates are quite similar for men and women and by race and ethnicity, and they've been slowly getting better since 2001, but they are quite high.

### Q / Do patients with MZL mainly die of their lymphoma or with their lymphoma?

**Cerhan** / Keeping in mind that overall survival is quite high, patients with MZL are a bit more likely to die of nonlymphoma causes than dying of their lymphoma. This distinction gets even stronger as you go into older age groups. One interesting recent finding is that newly diagnosed patients with MZL who have a relapse, a progression, or need treatment within 2 years of their diagnosis are subsequently more likely to die of their lymphoma while those patients who go 2 years without any of these events may be dying of other causes, not due to their lymphoma.

### Q / How do MZL risk factors cluster with other non-Hodgkin lymphoma subtypes, and what are the implications of this finding for our understanding of MZL pathogenesis?

**Cerhan** / MZL is very similar to the other common lymphoma subtypes in that they share some of the risk factors, but they also tend to have some distinct associations. Family history, for example, is an established risk factor as it is for all other lymphoma subtypes, and they have the same strength of risk. From a genetics perspective, it looks like MZL is more strongly correlated with some subtypes, like chronic lymphocytic leukemia and diffuse large B-cell lymphoma, compared with, say, follicular lymphoma.

Infectious agents tend to be unique to MZL or certain MZL subtypes. A *Helicobacter pylori* infection and gastric MZL are often called MALT lymphoma. However, I can counter that right away with the hepatitis C virus, which is the most very strongly associated with MZL, but we see it in multiple other lymphoma subtypes as well. Autoimmune disease is a driver of

MZL. Again, we do see this shared with some other lymphoma subtypes, particularly diffuse large B-cell lymphoma. Studying these patterns provides us with some insights into etiology, and what's coalescing around factors related to MZL looks like factors related to the immunologic status of the host. Immune suppression along with antigenic stimulation, be that an infectious agent or an autoimmune disease, seems to be particularly important for MZL.

**Q / What are the most pressing research questions in MZL epidemiology that must be addressed to further improve our understanding of this disease?**

**Cerhan /** In terms of causes of MZL, some newer risk factors require additional study, including smoking, alcohol use, sun exposure, and physical activity in certain occupations, as we have better tools to identify pathogens. This should be pursued, particularly for extranodal MZL. There could be some new findings there. In terms of outcomes after MZL diagnosis, it is important to be able to predict at diagnosis which treatments will fail patients early, that [is], an event within 24 months of their diagnosis, because then we could identify patients up front who need to have different treatments [because they] are not going to do well on their current standard. These are the patients you want to get on clinical trials as well as study their biology. We need to identify new treatment targets for those

patients. However, for patients who go the 24 months without a relapse or progression and subsequently go on to die of other causes, you can reassure them and manage them with a low touch. You don't need to be aggressive with them because they're going to live out their life expectancy.

**Q / Where do you see this field headed?**

**Cerhan /** The integration of MZL epidemiology with MZL biology and immunology is going to accelerate, and that is going to give us some new mechanistic insights into how genetics and the environment impact the development of MZL. Hopefully, the reason to do that is to identify opportunities for prevention. The other big area that I see this field going [toward] is it is going to become more global, and studying populations with contrasting risk factors may help us identify new causes and new ways to prevent the disease.

**Q / Is there anything you would like to add?**

**Cerhan /** I want to acknowledge the Lymphoma Research Foundation for sponsoring the [MZL] workshop. It can bring [together] researchers from very different perspectives and give a deep dive into this disease, and now [we] have it published in *ONCOLOGY*.

discussed the features of transformed MZL (tMZL). MZL can undergo transformation to large B-cell lymphoma, DLBCL, and high-grade large B-cell lymphoma after diagnosis; the identification of tMZL requires histologic assessment. The features of tMZL include a rise in lactate dehydrogenase (LDH) level, hypercalcemia, a sudden decline in performance status, rapid localized nodal growth, new/unexpected extranodal sites of disease, and the presence of new B symptoms. The histology of tMZL is generally straightforward, though some cases show borderline features. Transformation to DLBCL is indicated by the presence of confluent sheets of blasts, but it can be difficult to identify blasts, and the "sheet of blasts" is not clearly defined. tMZL is generally

related to a complex karyotype and mutations in *NOTCH3*, *TP53*, and *TBL1XR1*. Of note, Arcaini remarked that a subset of DLBCLs diagnosed as de novo may be tMZL. Current research limitations in tMZL include heterogeneous data quality and series with incomplete or missing data and short follow-up times, which translates to heterogeneous data in incidence rates, risk factors, and outcomes. Estimates of the incidence of transformation are around 3% to 15% at 5 years and 5% to 18% at 10 years; rates seem to vary by disease subtype.<sup>8-11</sup> tMZL is tied to increased mortality and poor survival regardless of subtype.<sup>8,12,13</sup> Risk factors for transformation at diagnosis and in MZL include unique clinical characteristics, lab values, and biological features. Limited

data are available to predict prognosis, but the progression of disease at 24 months (POD24) seems to have some applicability here. Limited information is available to guide treatment selection for tMZL; rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and anthracycline are treatment options for patients with and without previously untreated MZL, respectively, and CAR T-cell therapy is an emerging treatment option. Acknowledging the need for better definitions in this space, Arcaini introduced a retrospective study that is underway to assess clinical and molecular characteristics, pathology, and outcomes in MZL to fill the knowledge gaps.

Juan Alderuccio, MD, associate professor of medicine, Division of

Hematology, University of Miami, followed with a discussion of prognostic models in MZL. Patients with MZL are generally known to have good survival; in an analysis of data from the University of Miami, rates of median PFS were highest at 10.6 years in extranodal MZL, followed by nodal (4.8 years) and splenic (3.9 years) MZL, and median OS was not reached. Several useful measures can help assess prognosis in MZL. Key prognostic factors include monoclonal paraprotein, which is correlated with PFS after frontline therapy in MZL, in patients with extranodal disease, and in patients treated with rituximab and immunotherapy and is also tied to the risk for transformation. The MALT-International Prognostic Index (IPI) model considers age 70 years or older, Ann Arbor stage III/IV, and elevated LDH to predict risk (low, intermediate, or high) for EFS in patients with extranodal MZL and other MZL subtypes.<sup>8,14,15</sup> An analysis of data from patients with extranodal MZL at the University of Miami identified multiple mucosal sites (MMS) as a factor correlated with survival in MZL. The Revised MALT-IPI, which includes MMS, categorizes patients into low (score 0), low-medium (score 1), medium-high (score 2), and high-risk (score 3 or higher) groups. The Revised MALT-IPI score was tracked with the rate of POD24 and transformation events. In splenic MZL, 2 prognostic scores are useful: the Italian Lymphoma Intergroup risk score, which considers hemoglobin level more than 12 g/dL, LDH level higher than normal, and albumin level more than 3.5 g/dL; and the HPLL model, which considers hemoglobin concentration, platelet count, elevated LDH, and the presence of extrahilar lymphadenopathy. For assessing MZL as a single entity in patients in need of systemic therapy, the MZL-IPI score includes LDH, absolute lymphocyte count, hemoglobin, platelets, and nodal

MZL or disseminated MZL. The MZL-IPI score categorizes patients into low-, intermediate-, and high-risk groups and is correlated with PFS and OS in patients with MZL.<sup>16</sup> Alderuccio also noted that POD24 and failure to achieve CR after frontline therapy are 2 separate factors linked to outcomes in MZL that may have some applications to determining prognosis. Future research will inform the utility of these models in the context of emerging therapies.

### **Session VI: Assessment Criteria, Response Evaluation, and Surrogate End Points**

To kick off this session, Alderuccio returned with an overview of the clinical utility of PET/CT imaging. The use of PET/CT imaging to characterize MZL has been controversial due to the variability in 18fluodeoxyglucose (FDG) avidity across the different subtypes and the risk of high tissue avidity obscuring critical information; however, modern technology may be overcoming these hurdles. In an analysis of data from the University of Miami, researchers sought to identify cases of MZL with FDG-avid disease. Across 187 locations in 152 patients, FDG-avid disease was detectable in 78.1% and was detectable across a variety of tumor locations. FDG avidity increased with increasing tumor size, with tumors smaller than 0.5 cm being non-FDG-avid. In patients with multiple mucosal sites, over 80% of patients showed FDG avidity across all disease locations. Not much data exist to describe the role of PET/CT in nodal MZL, and PET/CT showed low sensitivity for detecting bone marrow involvement in MZL. The value of measuring metabolic tumor volume is not clear for MZL and is a subject for future studies. CXCR4 tracers can aid in the detection of MZL via PET/CT but are limited by high rates of splenic tracer uptake and retention. Alderuccio concluded that PET/CT should be included in the staging workup

for patients with MZL, but it is important to correlate the findings with other disease information, especially in locations with the potential for obfuscation. Future studies should further characterize the role of PET/CT in response assessment and as part of screening for clinical trials.

Catherine Thieblemont, MD, PhD, head of the Hemato-Oncology Department at the Hôpital Saint-Louis, Paris, France, followed with a discussion of the clinical utility of minimal residual disease (MRD). Defined as the presence of residual cancer cells after treatment in patients with clinically undetectable disease, MRD may be helpful in identifying appropriate treatment and adapting treatment approaches in MZL. Thieblemont discussed how the identification of MRD in patients can be performed using imaging, biological approaches, or a combination of the 2. Of note, in splenic disease, MRD is particularly challenging to implement because it may not exhibit any blood involvement. The role of imaging-detected MRD in MZL is an active area of research; clinical trials are assessing the roles of PET in prognosis and response assessment in MZL, and CT-identified MRD has been used to help guide de-escalation of treatment. Biologic evaluation of MRD (including assessments via measurement of IgH rearrangements and multicolor flow cytometry) has also been used in clinical trials and has been linked to outcomes including response, PFS, OS, and POD24 positivity. The addition of MRD can also improve efficacy assessments by providing more information about how a patient's disease is responding to treatment.<sup>17</sup> With the emergence of new therapies that lead to deeper responses, MRD may be a useful parameter to compare efficacy between similar treatments. MRD may also have applications as a surrogate end point, with additional data presented in the next session. Thieblemont

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Juan Alderuccio, MD

**Q / In your analysis of extranodal MZL, you mentioned the PFS rate of 10.6 years. What are the implications of this long PFS for treatment strategies and patient counseling?**

**Alderuccio /** When we performed this analysis, we included 411 patients with extranodal MZL. What is important to mention is that the majority of these patients received treatment, and a large proportion had localized disease treated with radiation therapy—approximately 60% of the patients. This long PFS of more than 10 years underscores that in patients with localized extranodal MZL, radiation therapy was associated with good outcomes. That is still, when it is possible, the preferred treatment strategy in this setting. It also shows that regardless of whether the patient receives radiation therapy or [another] type of therapy, the disease cause is indolent. With the current therapies, patients are able to have long-term [PFS].

Regarding treatment selection, it is important to evaluate the potential toxicity of the therapies, as most of these patients have an indolent disease cause. It is important to consider quality of life and other metrics for treatment selection. For the future development of clinical trials, this needs to be highly considered, because with such a long PFS, quality of life is a major metric that needs to be considered in drug development in MZL.

**Q / How do you weigh the MALT-IPI score in treatment decisions for patients with extranodal MZL, and how does that influence your initial choice of therapy?**

**Alderuccio /** The MALT-IPI is a prognosis model that was used in the only randomized phase 3 clinical trial in extranodal MZL, IELSG-19 [NCT00210353].<sup>1</sup> Patients received single-agent rituximab [Rituxan] or chlorambucil or chlorambucil plus rituximab. This model was constructed based on 3 variables—age greater than 70 years, advanced-stage disease, and elevated lactate dehydrogenase levels. In clinical practice, the MALT-IPI helps to restratify patients. Unfortunately, we do not decide on treatments based on the MALT-IPI.

Currently, we do not perform treatment selection based on any prognosis model, overall, in lymphoma. The only

exception is in patients with large B-cell lymphoma.... In the phase 3 POLARIX trial [NCT03274492], patients with an IPI score of more than 2 were enrolled in the study and received POLA-R-CHP [polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone].<sup>2</sup> Besides that specific example, in the other lymphomas, specifically MZL, we do not [consider prognosis model use] in treatment selection.

**Q / In your presentation, you emphasize the importance of POD24 and achieving a CR in MZL. How do you incorporate those factors into your assessment of treatment responses and prognosis?**

**Alderuccio /** That is an important point—achieving a CR after frontline therapy was associated with better survival, but also with a lower risk of high-grade transformation to large B-cell lymphoma, an event that has been associated with shorter survival.... We did a retrospective study in 237 patients treated with bendamustine [Bendeka] rituximab, and we observed that the CR rate was very high, and there were [almost] no cases of progression of disease within 24 months.<sup>3</sup> In patients with advanced-stage extranodal MZL, bendamustine rituximab was the regimen that has been associated with higher complete responses and lower incidence of POD24.

A caveat to mention about POD24 in MZL is a concept that was extrapolated from follicular lymphoma, where it was defined as progression of disease within 24 months after immunochemotherapy with R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone] and most recently with bendamustine rituximab. It is an alkylating agent plus an anti-CD20. In MZL, single-agent rituximab is still commonly used, especially in splenic marginal zone lymphoma. That is something to mention—most of the studies that evaluate outcomes of patients with POD24 include in these analyses or immunochemotherapy or simulation rituximab in the evaluation.

**Q / Looking at the other part of your presentation of PET and CT imaging, what are the limitations of that in this disease and how do you address the challenges in your practice?**

**Alderuccio /** The limitation of PET/CT in extranodal MZL is that there are some specific areas that have low FDG avidity, such as the stomach and ocular adnexa. The reason for that is the lesions are usually small and also are located

in an area with high physiologic background FDG avidity. For example, the ocular adnexa is close to the brain, which is highly FDG avid, so these lesions cannot be seen well on the PET/CT. The stomach itself and all the gastrointestinal tract is highly FDG avid. Small lesions are difficult to differentiate from the physiologic background.

In clinical practice, if that lesion is located in, for example, the ocular adnexa, we usually perform PET/CT and also an MRI of the eye that will better define those areas. For the gastrointestinal tract, especially in the stomach, we usually perform upper endoscopies that also help us to see the stomach and take biopsies to subsequently assess the response.

One strategy that we have been performing at our institution with patients at the time of diagnosis is that we perform PET/CT and a CT with contrast, or MRI, depending on the disease location. If the disease is FDG avid at the time of response assessment, we perform PET/CT, and if at baseline before therapy the PET/CT was negative, then we do it all with CT with contrast, or with MRI.

**Q / Are you able to expand on how FDG avidity works with PET/CT and correlates with disease activity and the prognosis in different MZL subtypes?**

**Alderuccio /** In the form of an important marker of prognosis is metabolic tumor volume. What it does is the metabolic activity of disease burden is calculated based on a specific threshold. All the areas that are above that threshold are added for a single volume. That has been associated with prognosis in diffuse MZL and in follicular lymphoma.

The issue in MZL is, first, we do not know what the appropriate threshold is. Second, in extranodal MZL, there is a significant number of patients [who] have localized disease, so this metric is not going to be very useful. Also, single and small lesions are difficult to differentiate from normal tissue. Another problem that we have in MZL is specifically splenic MZL, which commonly affects the bone marrow. It is difficult to incorporate the bone marrow in the tumor volume. All these problems prevent the use of metabolic tumor volume in MZL at the present time.

There is no strong correlation between metabolic tumor volume or FDG avidity and the prognosis. In indolent lymphoma, overall, we usually perform PET/CT, and any area that has a significantly higher FDG avidity than the rest of the lesions, we usually try to obtain a tissue sample of that area to rule out transformation to large B-cell lymphoma. Usually, the treatment is different and is commonly based on an anthracycline-based therapy.

**Q / Where do you see this field headed?**

**Alderuccio /** Compared with follicular lymphoma and large B-cell lymphoma, MZL is behind in drug development. Usually, most of the data about treatment are extrapolated or have been obtained from follicular lymphoma, where, for example, the phase 3 BRIGHT trial [NCT00877006] or the phase 3 StiL NHL 1-2003 trial [NCT00991211] enrolls both diseases, follicular lymphoma and MZL, or the study cohort was largely composed of follicular lymphoma.<sup>4,5</sup> The field needs to move now to focus [more] on [MZL-based] studies, and ideally in the different groups. For example, bendamustine rituximab has been associated with good outcomes in extranodal MZL in the [phase 2 BRISMA/IELSG36 trial (NCT02853370)].<sup>6</sup>

In this clinical trial, the use of bendamustine rituximab in patients with splenic MZL was associated with a higher incidence of infections compared with what was previously observed in extranodal MZL. Also, the disease biology is different, and eventually, the response assessment needs to be performed differently [compared] with what we do in other types of lymphomas. After we focus these studies on these clinical trials by subgroup, we will [better learn] about the response and the toxicity of these regimens in these specific subgroups. The caveat for this is that MZL is a rare subtype, so [it will require] critical national efforts in order to accrue patients in an appropriate period of time.

**Q / Is there anything else that you wanted to discuss today?**

**Alderuccio /** It is important to highlight the need for potentially specific changes from the Lugano classification, adapting for MZL, because the disease is usually localized and in extranodal MZL [is] in small lesions. In splenic MZL, the Lugano classification may not fit well for staging and response assessment because usually the bone marrow is affected, and the sensitivity of the PET/CT to detect bone marrow involvement in MZL is low compared with the sensitivity of the PET/CT for bone marrow involvement in large B-cell lymphoma and Hodgkin lymphoma. Ideally, the field needs to develop an appropriate staging and response assessment system for MZL.



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concluded that MRD can improve clinical assessments in routine practice and has the potential to accelerate the rate at which useful information is obtained from clinical trials. Future research will validate the use of MRD and explore its role in aiding treatment decisions in MZL.

Next, Côme Bommier, MD, of Hôpitaux de Paris and Mayo Clinic, discussed the clinical utility of early surrogate end points. A challenge facing drug development in MZL is the many years required to assess outcomes in clinical trials. In an effort to accelerate the assessment of potential therapies to spare time and resources, surrogate end points are being investigated that more rapidly provide sufficient information about treatment efficacy without sparing patient safety. Only 1 study has shown positive results for a surrogate end point assessed in MZL: the study assessed early CR as a surrogate end point in the phase 3 IELSG19 trial (NCT00210353).<sup>18</sup> CR was chosen based on data indicating that more patients who were treated with double therapy had a higher rate of and spent more time in CR than those treated with single therapy. CR at 24 months (CR24) and time to CR censored at 24 months were compared

with POD24, and results indicated that time to CR and CR24 captured 95% of the information describing 8-year PFS. Using this surrogate end point, the researchers were able to obtain a single measurement at 2 years that provided a strong prediction of 8-year PFS. Bommier concluded that more phase 3 trials are needed in MZL, and further research is needed to fully understand the role of CR24 in MZL.

**Session VII: Clinical Trials**

To kick off the discussion of clinical trials, Izidore S. Lossos, MD, professor of medicine, chief of the Lymphoma Section at the Division of Hematology, endowed director of the Lymphoma Program, and head of Lymphoma Site Disease Group at the University of Miami Sylvester Comprehensive Cancer Center, provided an overview of the clinical trials in North America (Table). Lossos began with an overview of research needs in MZL treatment, for which there is no established standardized approach. Patients have lengthy survival and some do not require treatment, but the criteria for treatment initiation are based on those for FL and are not applicable to many patients with extranodal and splenic

MZL. Only 1 randomized trial has been performed in the rituximab era in patients with extranodal MZL, so treatment guidelines are based on large institutional experiences.

Treatment for nodal disease is similar to that for FL, and first-line rituximab is generally used to treat splenic disease. Past trials assessing up-front chemotherapy showed variable responses, and trials in relapsed/refractory MZL showed objective response rates in the 60% to 70% range and variable CR rates, but some potentially useful therapies have been taken out of circulation. Current clinical gaps include the fact that MZL remains incurable for most patients, there are few trials specifically targeting MZL, the role of PET is not understood, inclusion and response criteria are needed, and more efficient treatments are required. No trials are currently recruiting for newly diagnosed MZL, 5 are recruiting to assess treatments in newly diagnosed FL/MZL/low-grade non-Hodgkin lymphoma, 1 is recruiting for recurrent MZL, and 2 are recruiting for FL/MZL/low-grade non-Hodgkin lymphoma. Recruitment has been completed for 2 trials in newly

**TABLE. Clinical trials testing chemoimmunotherapy in MZL**

	DESIGN	INDUCTION	MAINTENANCE	N	STAGE III-IV	EMZL	NMZL	SMZL	3-y PFS
<b>CISL</b> (NCT01213095) <sup>19</sup>	Phase 2	R-CVP x6-8	R every 8w, x 12	47	100%	67%	33%	0%	81%
<b>PLRG</b> (NCT00801281) <sup>20</sup>	Phase 3	R-CVP x6-8 or R-CHOP x6-8	R every 8w, x 12	92	94%	NA	NA	NA	82% <sup>a</sup>
<b>GALLIUM</b> (NCT01332968) <sup>21</sup>	Phase 3	BR x6 or R-CVP x8 or R-CHOP x6	R every 8w, x 12	99	93%	24%	36%	39%	80% <sup>a</sup>
<b>IELSG38</b> (NCT01808599) <sup>22</sup>	Phase 2	R-Clb x22wk	R every 8w, x 12	61	100%	100%	0%	0%	84%

BR, bendamustine plus rituximab; EMZL, extranodal marginal zone lymphoma; MZL, marginal zone lymphoma; NMZL, nodal marginal zone B-cell lymphoma; PFS, progression-free survival; R, rituximab; R-Clb, rituximab plus chlorambucil; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; SMZL, splenic marginal zone lymphoma.

<sup>a</sup> No difference per chemotherapy arm



**Andrew D. Zelenetz, MD, PhD**, Medical Director of Quality Informatics at Memorial Sloan Kettering Cancer Center

### **Q / What are the most significant recent advancements in the treatment of MZL, and how have these impacted treatment outcomes?**

**Zelenetz /** When we talk about advances in MZL, one of the things we suffer from is there tends to be a lack of focus on MZL as a separate entity. The reason for this is if you take MZL in its entirety it only represents 5% to 6% of all non-Hodgkin lymphomas. It's a relatively rare entity. What makes it even more complicated is we have 3 subtypes of MZL, including extranodal, splenic, and nodal marginal zone lymphoma, that have different clinical behaviors and somewhat different molecular lesions. Some are difficult to quantitatively measure, like [in] splenic MZL, how big should a spleen be? When it shrinks how do we know that someone's in remission?

The rarity and the complexity of the disease have made it less attractive for pharmaceutical companies to focus their attention on MZL. What often happens is that MZL gets folded in with the much more common follicular lymphoma. Both are slow-growing, indolent B-cell lymphomas, and there is an MZL cohort. When the study results are published, usually, the [results for] patients with MZL are a little bit too small to report by themselves, and you don't know what that new treatment did in MZL. This is a real problem that we have.

### **Q / What are some emerging treatment options in the?**

**Zelenetz /** Some of the small molecules have proven to have efficacy in MZL. One of the first was the PI3K inhibitors, the PI3K $\delta$  inhibitors, [which,] unfortunately, as a class, are now dead, but these were particularly good drugs for MZL, and there was substantial activity. What followed that was a study of a [BTK] inhibitor and in a phase 2 study dedicated to MZL, it was demonstrated that there was activity, and it became incorporated as one of the go-to treatments for the management of MZL.<sup>1</sup>

Subsequently, additional studies have been done with other BTK inhibitors, including zanubrutinib [Brukinsa], which has FDA approval for the treatment of MZL.<sup>2</sup> This represents a bit of a bright light where we did introduce a new drug for the treatment of MZL in a specific area. We've seen [that] the other big area of interest in the development of drugs for lymphoma has been in immunotherapy, and there's been a big push for CD19-directed CAR T cells; a number have been approved for

the treatment of diffuse large B-cell lymphoma and follicular lymphoma.

The early results, particularly with axicabtagene ciloleucel [Yescarta], suggested that maybe MZL didn't respond as well. This was an issue of small numbers with limited follow-up, and when you looked at the initial curves in the low-grade lymphoma study, it looked like the MZL [cohort] wasn't doing as well, but in fact, with longer follow-up, with more patients, the outcomes have improved. We also have seen promising results with lisocabtagene maraleucel in MZL, but because of the size of the population and where we are, we haven't gotten the approval for these agents for the treatment of MZL. This is an area a missed opportunity.

Another big missed opportunity in the other exciting area of immunotherapy that's emerging in the B-cell lymphomas is the bispecific antibodies. We've seen agents approved for DLBCL and follicular lymphoma. It's been very difficult to even get any of the sponsors interested in doing an MZL study. There's some exploratory information. There's the inclusion of a few patients in early phase 1 or phase 1b studies that suggest that there's activity, but getting the pharmaceutical companies to commit to a full evaluation of these drugs in MZL has been frustrating.

### **Q / What are the challenges to managing adverse effects?**

**Zelenetz /** Each of these new classes of drugs has its own adverse effect [AE] profile. What happened to the PI3K inhibitor is the FDA felt that the way they were being developed, they were more risk than benefit, which is why they put the kibosh on the class, though it is not impossible to change the development strategy. We did this for one of these agents and showed that you could have a favorable safety vs toxicity profile.

For the drugs that we're actively developing and actively using, like rituximab monotherapy, which is still a mainstay; BTK inhibitors; the investigational use of CAR T cells; and bispecific antibodies, we're not seeing unique toxicities associated with these agents, with an exception. What we're seeing, in large measure, is an AE profile similar to other B-cell malignancies. Sometimes, MZL can have a significant leukemic phase, so there can be a lot of circulating lymphoma cells, and in that setting, particularly with bispecific antibodies and CAR T cells, there can be an exacerbation of cytokine release syndrome.

These toxicities can be mitigated by a variety of strategies, such as reducing the disease burden before going into treatment. That's a frequent approach with CAR T cells to use some bridging treatment to do some cytoreduction. We know that cytoreduction, if we left it alone, would be transient, but that is one way of doing it. With the bispecific antibodies

[we] do what we call step-up dosing, where we use a small amount of the drug and then increase the drug over time. These are ways that we can mitigate this overstimulation of T cells that contribute to the cytokine release syndrome, but again, these are challenges that we can see in other settings with B-cell lymphomas and MZL, fortunately, does not represent a uniquely difficult area with respect to AE profile of drugs.

**Q / How can clinicians stay updated on the rapidly evolving field of MZL treatment?**

**Zelenetz /** This is a problem in lymphoma. If you look at the American Cancer Society chart, lymphoma is either fifth or sixth, depending on a man or a woman [for the most common cancers]. That sounds like, “Oh, that’s pretty common.” If you break it down, and then you would have the list, MZL wouldn’t be fifth or sixth, it would be 30th or 50th. That’s true for each of the lymphomas. As an aggregate, yes, they’re relatively common, but as individual diseases, they become less and less. When the practicing oncologist is looking to augment their knowledge and education, the first thing they’re doing is not thinking about the lymphoma session at [the American Society of Clinical Oncology Annual Meeting]; they have to go to see the breast cancer session or the lung cancer or colon cancer session. When they look at the new visits in their clinic, those are the patients who are coming in the door much more frequently.

What clinicians need to do is they need to have resources where they can find dedicated information. Places like the Lymphoma Research Foundation [and] the Leukemia & Lymphoma Society have on their websites information that is for patients, but also for treating physicians to bring them up to date. The other place that gets the most traffic is the B cell guidelines from the NCCN [National Comprehensive Cancer Network]. These are not only used widely in the United States, but they’re also used widely around the world since these lymphomas are not a

dime a dozen. If we look at the total number of doctors who treat lymphoma, and we looked at the total number of patients, the reality is that the average person, not the lymphoma specialist, but the average person sees maybe 1 or 2 lymphomas every year or 2, not very frequently, and so it’s more important to have a real-time place to go, and that’s really where the NCCN guidelines help physicians, because those are updated a minimum of once a year, usually twice a year.

The lymphoma guidelines tend to be updated sometimes 3 times a year based on the most current data. This is where there’s a smaller trial that may not make it to FDA approval of a drug, but may allow us to recommend a drug for the treatment of MZL.

**Q / How would you like to see the field evolve?**

**Zelenetz /** I’d like to see pharmaceutical companies appreciate the fact that MZLs are biologically distinct and be more open to having clinical trials dedicated to MZL so that we can understand the efficacy of these drugs. We can come up with interesting ideas [of combining different treatments], and this has a great theoretical potential for treatment of MZL, [but] is it going to work? I need access to the drugs. That is an important aspect of what we do, is to try to convince pharmaceutical companies to appreciate some of these rare orphan diseases that may not make billions of dollars selling a drug for MZL, but that doesn’t mean that these are not important areas, and it’s an opportunity where they have drugs that may have very important positive impacts on the outcome of patients with MZL.

**References**

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2. FDA grants accelerated approval to zanubrutinib for marginal zone lymphoma. FDA. September 16, 2021. Accessed January 9, 2025. <https://shorturl.at/hG4f8>

diagnosed MZL and 1 trial in relapsed MZL. Historically, MZL enrollment in clinical trials has been low due to restrictive inclusion criteria—based Lugano recommendations and the lower incidence of MZL. Lossos noted that specific staging and response assessment criteria are needed for most extranodal MZL sites, and he proposed new criteria for assessing treatment response and for the inclusion of patients with

MZL in clinical trials. Lossos concluded by highlighting 3 ongoing phase 2 clinical trials in patients with MZL at the University of Miami.

Christian Buske, MD, medical director at the Comprehensive Cancer Center and the Institute of Experimental Cancer Research at Ulm University, Germany, and attending physician and professor of medicine at the Medical Department for Internal Medicine III,

Hematology/Oncology, Ulm University Hospital, followed with an overview of European MZL clinical trials. Buske began by introducing the phase 3 GALLIUM study (NCT01332968), an open-label, randomized trial assessing obinutuzumab vs rituximab in a population including adults with previously untreated CD20-positive MZL.<sup>19</sup> The trial had an unacceptable rate of adverse effects, supporting

the push toward chemotherapy-free treatment approaches in MZL. Several ongoing studies are assessing chemotherapy-free treatments including BTK inhibitors (phase 2 IELSG47/MALIBU), PI3K inhibitors (phase 2 COUP-1 [NCT03474744]), checkpoint inhibitors (phase 2 POLE-1), and anti-CD20 antibodies (phase 2 OLYMP-1 [NCT0322865]). Planned studies include the phase 3 IELSG48, MAGNOLIA, and MARSUN studies and the phase 2 EPOS-1 study. Buske

closed the discussion by sharing 2 academic projects. The first was related to the need for real-world data; the MZL registry is a prospective and academically funded web-based registry that is actively recruiting all adult MZL patients. Second, Buske described an ongoing international retrospective study that aims to identify clinically relevant subgroups of patients with nodal MZL. Patient data and tissue samples from more than 50 international sites are being collected and analyzed.

## Future Road Map Toward Progress in MZL: A Roundtable Discussion and Workshop Summary

In the final session of the workshop, Habermann and Rossi led a roundtable discussion of the progress made on the objectives set in the 2019 meeting. The group discussed remaining concerns and unanswered questions, divided into 6 major subtopics, and set short- and long-term goals for addressing the lingering issues.



**Emanuele Zucca, MD**, Consultant and Head of the Lymphoma Unit at the Institute of Southern Switzerland

### Q / What are the 3 types of MZL?

**Zucca** / MZLs are a very [complex] condition; there are at least 3 different diseases.... It is not straightforward to speak about MZLs as a simple thing. To add a fourth layer of clinical complexity, [for] many patients, when they present with advanced-stage disease, identification of the original type of MZL is not easy. When the patient [presents] with a big spleen, lymph nodes, [or] leukemic lymphocytosis, [they are] at that stage [where it is] nearly impossible to say this was primarily [the] splenic, extranodal, or the nodal subtype. This is something not so rare in everyday clinical practice.

As a clinician, once we have a diagnosis, we should try to understand whether a patient needs therapy. This is because, in general, particularly [on the] extranodal MZL side, several anatomic cells or splenic MZL do not necessarily need to be treated from the beginning. They may have a very indirect natural cause of the disease for several years with no treatment requirement. The first issue is to understand when therapy is required, and [while] this need of therapy is well defined for endurance settings like chronic lymphocytic leukemia or follicular lymphoma, this is not so evident or well defined in MZLs. To add again [to that] complexity, we have different types of MZLs that might not behave in the same way. Nodular MZLs are usually treated as follicular lymphomas, and therefore, the indication to treat primarily nodal MZL can be assumed to be the same for follicular lymphoma.

We have, for example, the French group criteria standardly

used for MZL that can be adopted for the nodal MZL subtype. This is not the same for splenic. We may or may not have well-defined criteria, but also in splenic, there are some criteria for starting therapy, which may be cytopenia, for example, or bulky splenomegaly, which is produced in local symptoms. Asymptomatic disease is the reason to start therapy in extranodal lymphomas as well.

### Q / What is the current standing of liquid biopsy in MZL?

**Zucca** / There has been...some good evidence that we can do liquid biopsy in MZL and that liquid biopsy can mirror the biology of the tissue, but again, the frequency of liquid biopsy is different in the different subtypes. For example, nearly all splenic MZLs and most nodal MZLs have shown the possibility to be properly managed and followed up using [circulating tumor] DNA, but only [in] a significantly smaller portion of patients with extranodal MZL was [it] successful. To be followed with liquid biopsy, this is a work in progress, but at present, there is no clear evidence for minimal residual disease [MRD] determination and assessment. We have 1 ongoing study on splenic MZL and a recently completed trial with [all subtypes of] MZL using, in both [studies], treatment with rituximab plus a [Bcr tyrosine kinase] inhibitor, where a subset of patients had MRD evaluation. We do not have the data yet, but we hope to offer some explanation or further insight when these data are mature enough.

### Q / What else do you want to highlight?

**Zucca** / We need some attention to the potential pathways which nowadays discover MZL but never explore it. There's the potential [for this to be done], but it will require several months, if not a year [to be done properly].

## Biology and Pathology

Concerns and unanswered questions in biology and pathology include understanding differences in the MZL subtypes, the tumor microenvironment, molecular clusters, and immunology related to MZL. Solutions proposed for these knowledge gaps include performing further research to define MZL disease subtypes, exploring the MZL tumor microenvironment, taking an unbiased approach to characterize extranodal disease, and investigating the switch to antigenic stimulation in MZL in the short term. In the long term, participants seek to establish MZL-specific biologic correlates for pathology and diagnostic uses, identify ways to differentiate MZL from LPL and define the source and precursors for MZL.

## Epidemiology Transformation

In epidemiology and transformation, current unmet needs include the lack of understanding of the epidemiology of nodal disease, extranodal subsets, and splenic MZL; the lack of consensus around the pathologic diagnosis of transformation; and the need to identify transformation risk, natural history, and underlying biological mechanisms. Aims for the immediate future include efforts to define risk factors for each MZL subtype, harmonize the classification of disease subtypes, and understand the risks and biology related to transformation. In the longer term, the group aims to define the predictors and markers of MZL transformation.

## Assessment Criteria, Response Evaluation, and Surrogate End Points in MZL

Persistent issues in disease assessment include the need for improved assessment criteria, response criteria, and end points specific to MZL. Tasks to address these issues in the near future include developing new response criteria including specific response criteria for splenic MZL, understanding the role of MRD and PET and other staging modalities, and identifying the role of end points including minor response, CR, and potential surrogate end points in MZL. In the long term, the participants prioritized the development of novel genomic and radiologic assessments of response.



Davide Rossi, MD

### Q / What is the significance of the MZL Workshop hosted by the Lymphoma Research Foundation?

**Rossi /** The MZL Workshop is an invaluable initiative by the Lymphoma Research Foundation. MZL is a relatively rare subtype of non-Hodgkin lymphoma, and workshops like this create a dedicated space for researchers, clinicians, and patient advocates to focus specifically on advancing our understanding of MZL. It's significant because it fosters collaboration, shares the latest research findings, and ultimately aligns the entire community on strategies to improve patient outcomes.

### Q / How does the MZL Workshop contribute to advancing research and improving outcomes for patients with MZL?

**Rossi /** The workshop serves as a catalyst for innovation and collaboration. By bringing together experts from around the world, it encourages the sharing of novel research findings and clinical trial updates. This accelerates the development of new therapeutic approaches. Additionally, it's an opportunity to discuss challenges in diagnosis, treatment, and patient care, which helps refine clinical guidelines and improve the standard of care for MZL patients. Most importantly, the patient-focused aspect of the workshop ensures that the research priorities remain aligned with what truly matters to those living with MZL.

### Q / Looking at the updates and advancements made in MZL over the years, what is something you think has impacted the field?

**Rossi /** One of the most impactful advancements has been the introduction of targeted therapies, such as Bruton's tyrosine kinase (BTK) inhibitors. These have revolutionized how we approach treatment for MZL, offering more effective and less toxic options than traditional chemotherapy. The growing understanding of the molecular and genetic underpinnings of MZL has also been transformative, enabling more precise and personalized treatment strategies. I'd also highlight the role of collaborative research networks like the International Extranodal Lymphoma Study Group, which has significantly expanded the pool of data available for study in what is a rare lymphoma subtype.

### Q / Where do you hope to see the field advance?

**Rossi /** I hope to see continued progress in precision medicine, particularly with biomarkers that can predict response to specific therapies. This would help diagnostics and tailor treatments even more effectively. Another promising area for growth is T-cell redirecting therapies, which have shown remarkable success in treating other types of lymphoma but have yet to establish a clear role within the MZL treatment landscape. Lastly, I'd love to see more global collaboration to expand clinical trial access and ensure equitable care for all patients, regardless of where they live.

### MZL Targeted Pathways

There also remains a need to improve the field's knowledge of targetable pathways for MZL treatment, as drug development is not keeping up with what is known about MZL biology.

Immediate solutions to this issue are to push to identify new targetable pathways; optimize the applications of CAR T-cell therapy; generate preclinical data; and, in the long term, implement new trials with targeted therapies in the relapsed/refractory setting. The participants emphasized the importance of working with policy makers toward these goals.

### Concerns and unanswered questions

- Druggable pathways and preclinical data are limited (MYD88, BRAF,

NOTCH, CREBBP, NFkB, p53, FAS [cutaneous]).

- Tumor targets are poorly understood: which drugs and which targets?

### Immediate action solutions (1-5 years)

- Identify new pathways and targets.
- Target microenvironment.
- Develop new preclinical data.
- Prognostic models integrated with plasmacytic differentiation, histology, genetics, and clinical data are needed.

### Long-term solutions (more than 5 years)

- Implement new trials that are targeted therapies in the relapsed/refractory setting.

### Etiology and Natural History of MZL Subtypes

The etiology and natural history of MZL subtypes remain inconsistently defined, and there appear to be geographic differences influencing disease biology. To resolve the inconsistencies, the participants set aims to further define the MZL subtypes and select patients within those subsets for treatment or clinical trial enrollment and to define cure in MZL subtypes. An overarching goal is to determine how many different diseases are present within the MZL umbrella.

### Concerns and unanswered questions

- The etiology and natural history of MZL subtypes are not uniformly defined.
- There appear to be geographic differences.
- The microbiome needs to be further studied.

### Immediate action solutions (1-5 years)

- Further define MZL lymphoma subtypes with larger data sets.
- Define which patients in each disease subset need treatment.
- The role of infectious agents needs further exploration.
- Define cure in the MZL subtypes.
- Define appropriate patients for clinical trials in MZL subtypes.

### Long-term solutions (more than 5 years)

- Determine how many diseases MZL represents.
- Further understanding relationships of MZL disease with age.

### Treatment of MZL

Finally, many challenges persist with treating MZL. Treatment patterns are not standardized and may vary widely. Clinical trials typically do not discriminate between patients with MZL and other indolent lymphomas and often do not predefine MZL subtypes, and it is not clear whether local control vs long-term control should be the treatment priority. In the short term, initiatives to address these issues include further research into the MZL subtypes; defining new clinical trial strategies, including those with a focus on MZL; and pursuing orphan disease designation for MZL subtypes. In the long term, participants agreed it would be important to define standards of care for each of the MZL subtypes and to develop curative approaches tailored to each subtype.

### Concerns and unanswered questions

- The treatment patterns vary and could be further standardized in MZL.
- Clinical trials routinely include groups of indolent FLs and MZL, and not patients with MZL only.
- MZL subtypes (extranodal, splenic, nodal) are not predefined in clinical trials.
- A major treatment issue is local control vs long-term control.
- Orphan definition needs to be pursued.

### Immediate action solutions (1-5 years)

- Further define areas of research for all subtypes of MZL.
- Define new clinical trial strategies.
- Clinical trials should be designed for MZL in certain study designs.
- Trials should define individual subsets.
- Orphan disease designation for individual subsets.

### Long-term solutions (more than 5 years)

- Define standards of care for each of the subtypes to benchmark new therapeutic approaches.
- Develop curative approaches to all subtypes of MZL.
- Work with pharmaceutical companies on strategies for different groups of patients (elderly, eligible...).
- The science is further ahead of treatment.



Julie M. Vose, MD, MBA

**Q / What is the significance of the MZL Workshop hosted by the Lymphoma Research Foundation?**

**Vose /** MZL is a fairly rare type of lymphoma. It's always good to get experts together to talk about new research, treatments, and discoveries. This is an opportunity to do that, which is difficult with such a rare lymphoma. The Lymphoma Research Foundation is great to be able to get experts together and talk about some advancements in this area, so we appreciate that opportunity.

**Q / How does the MZL Workshop contribute to advancing research and improving outcomes for patients with MZL?**

**Vose /** Since it is such a rare lymphoma, it's difficult to do clinical trials for MZL, and [patients] often are included with other types of indolent cell-growing lymphomas. It's important to get different experts together to be able to collaborate, put their data together, and analyze some of these clinical trials through new research and treatments for MZL, and just try to put all of our heads together and make sure that we can understand the data and formulate new clinical trials. With such rare types of diseases, this type of workshop is important for advancing the treatments and research into MZL.

**Q / Looking at the updates and advancements made in MZL over the years, what is something you think has impacted the field?**

**Vose /** We've had the opportunity to use monoclonal antibodies and chemotherapy in MZL for a number of years, but the biggest area of research is understanding the genomics and the biology of MZL. Also, using some of our newer therapies, such as Bruton tyrosine kinase inhibitors, either alone or in combination, for MZL, has been one of the biggest opportunities that we've had, and that's all through research that's been done to understand the biology of lymphoma. There are great opportunities to use our science to help patients.

**Q / Where do you hope to see the field advance in the future?**

**Vose /** The biggest advancements have been in understanding biology and using some of these newer treatments to try to see if we can improve the outcome for patients with MZL. Since it is such a rare disease, we do need to work collaboratively and work on clinical trials together with a lot of different centers to try to pool our data. That's important, and that's how meetings like this bring us together to formulate new ideas and to put groups together to do clinical trials.

**Q / Is there anything else you'd like to add?**

**Vose /** This is just a good example of how the Lymphoma Research Foundation helps scientists and clinicians get together and formulate ideas [and] work together in clinical trials and research, and is an important body for helping us take the next step to cure our patients with lymphoma.

**Summary**

The 2024 MZL Scientific Workshop brought together a cohort of experts to discuss recent advancements in MZL biology, diagnosis, characterization, and treatment. This forum provided a platform for the discussion of the state of the field and allowed MZL experts to reflect on recent learnings, identify gaps in knowledge, and develop priorities and strategies to continue to propel the field's understanding of MZL. Exciting progress has been made since 2019, but continuing efforts are needed to understand and characterize MZL, especially the disease subtypes, to inform diagnosis, assessment, clinical trial design, and ultimately treatment.

**Acknowledgements**

This meeting, in addition to several projects presented, was supported by grants from the Lymphoma Research Foundation. The steering committee expresses appreciation to the attendees, ADC Therapeutics, and the Foundation staff who participated in

fruitful discussion and made this year's meeting possible. Each presenter whose work is included herein reviewed and approved the summary of that work. ■

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