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Proceedings of the 2019 Lymphoma Research Foundation Marginal Zone Lymphoma Scientific Workshop:

A LYMPHOMA RESEARCH FOUNDATION WHITE PAPER

JANUARY 2021

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Introduction

In April of 2019, the Lymphoma Research Foundation (LRF) gathered international experts in the field of marginal zone lymphoma (MZL) in New York City for the inaugural International Scientific Workshop on Marginal Zone Lymphoma.

MZL is an uncommon non-Hodgkin lymphoma with a typically indolent clinical course. The management of MZL is complicated by an incomplete understanding of the molecular etiology and natural history of the multiple presentations of MZL. Despite recent efforts to develop targeted chemotherapies and immunotherapies in lymphoma, MZL has long been a neglected area of lymphoma research, particularly in the United States.

Recently developed agents with activity in MZL -- such as the BTK inhibitor, ibrutinib -- have provided novel treatment options, but the questions of when and how much to treat MZL remain open. Clinicians treating MZL also remain unsure how to define treatment response and disease progression, which complicates the design of clinical trials.

At this two-day scientific workshop, MZL experts from North America and Europe discussed the current state of MZL treatment and research and highlighted new lines of inquiry intended to move the MZL field forward, in terms of both understanding the core biology of the disease and treating the disease most effectively. The need for greater collaboration and larger, pooled datasets emerged as a central theme, with widespread support from researchers on both sides of the Atlantic, as well as from representatives from industry.

The following is a summary of the workshop proceedings, presenting the key findings of each speaker, on topics including the biology and pathology of MZL, the epidemiology and natural history of MZL, MZL transformation, MZL assessment and response criteria, MZL treatment, and MZL clinical trials.

Biology and Pathology of Marginal Zone Lymphomas (MZL)

Session Chair: Eric D. Hsi, MD, Cleveland Clinic

At present, differences among the various subtypes of MZL are not well understood. By better understanding the biology of the normal marginal zone B-cell, the understanding of the abnormalities associated with MZL will become clearer. In the near future, MZL researchers intend to further define the biology of extranodal, nodal, and splenic MZL and to definitively describe the localized cell of origin and the microenvironment required to support the growth of MZL tumors. Over the long term, investigators hope to identify biological correlates of MZL pathology that can function as biomarkers within the context of clinical laboratory diagnosis.

Andrea Cerutti, MD, PhD (ICREA, Catalan Research Institute for Advanced Studies, Barcelona, Spain) discussed the "Immunology of the Marginal Zone B-Cell." As described by Dr. Cerutti, the biology and function of the splenic marginal zone B-cell remains poorly understood, particularly in humans. Importantly, splenic marginal zone B-cells bridge the gap between early innate immune responses and late adaptive immune responses. Within the spleen, marginal zone B-cells interact with antigen-bearing myeloid cells to initiate adaptive immune responses such as the production of antigen-specific IgM and IgG responses. In carrying out this function, splenic marginal zone B-cells play an important protective role in infection, particularly related to sepsis. However, marginal zone B-cells are extremely flexible and versatile cells. MZL cells play a role in antigen presentation to follicular helper T-cells and initiation of classical germinal center reactions. In terms of their immunoglobulin gene repertoire, marginal zone B-cells are quite similar to plasma cells in the spleen that express IgM in a clonal fashion, which suggests that marginal zone B-cells are sustained via stimulation with a specific unknown antigen. Marginal zone B-cells are further sustained in their local microenvironment by a variety of supporting cells, including cytokine-secreting cells such as group 3 innate lymphoid cells (ILC3s), which produce copious amounts of the cytokine BAFF and induce IgM, IgG, and IgA production in marginal zone B-cells. Marginal reticular cells (MRCs) and splenic neutrophils are also important to the marginal zone B-cell microenvironment; notably, the distribution of splenic neutrophils is strongly influenced by the gut microbiota [1].

Anne J. Novak, PhD (Mayo Clinic) Anne J. Novak, PhD (Mayo Clinic) presented on the topic of "Genomic, Transcriptomic, and Immune Profiling of MZL." The central aims of Dr. Novak's work include further defining the molecular pathology of low-grade MZL, with the goal of improving treatment decisions, as well as defining the immune signature of MZL and relating this signature to early clinical failure in MZL. Early results from Dr. Novak's efforts to define the gene expression profile of MZL indicate that rare low-grade MZL subtypes cluster in an intercalating pattern with more common MZL subtypes, which suggests that MZL subtypes share certain RNA expression signatures, and that these signatures may not be location/subtype-specific. Transcriptomic and genomic clustering analysis revealed four distinct MZL clusters, defined as MZL-1, MZL-2, MZL-3, and MZL-4. Notably, the MZL-2 cluster was significantly associated with early clinical failure as defined by event-free survival at 24 months; in pathway analysis, the MZL-2 cluster was found to be enriched for genes related to the NOTCH and NF-kB signaling pathways, suggestive of a strongly pro-proliferative phenotype. Pathway analysis further revealed enrichment of the BCR pathway in the MZL-1 cluster, enrichment of plasma-cell like genes and the IgM secretory pathway in the MZL-3 cluster, and enrichment of the MYC/export pathway in the MZL-4 cluster. Immune profiling analysis using a machine learning deconvolution technique with whole transcriptome data revealed that the MZL-1 microenvironment is strongly B-cell enriched, whereas the MZL-2 microenvironment is strongly infiltrating immune cell enriched.

On the subject of extranodal MZL, **Andrew Wotherspoon, (Royal Marsden NHS Foundation Trust)** reviewed the "Pathology and Diagnosis of EMZL." Dr. Wotherspoon described the biology of MALT lymphoma, emphasizing that contact with foreign antigens and mucosal permeability are likely important factors in the development of MALT lymphomas, particularly those arising in the stomach.[2] In terms of

immunophenotype, CD43 is known to be aberrantly expressed in 50 percent of MALT lymphomas; when present, CD43 can be useful as a marker for diagnosis. Although MALT lymphomas are typically restricted to their site of origin, they may present with more disseminated disease. When MALT lymphomas disseminate, they typically spread to other extranodal sites.[3] While local-regional lymph nodes may be involved, disseminated lymph node involvement is rare and bone marrow infiltration is less frequent than in other indolent/low grade B cell lymphomas (present in 2-20 percent of cases). There is an association between *Helicobacter pylori (H.pylori)* infection and development of gastric MALT lymphoma; however, various studies conflict on the prevalence of *H. pylori* infection in gastric MALT lymphoma, suggesting that there may be a geographic or genetic influence.[4] Over time, the prevalence of *H. pylori* in gastric MALT lymphoma has decreased, creating additional challenges for gastric MALT lymphoma diagnosis and management. In addition to *H. pylori*, other chronic, low-grade infections have also been known to be associated with MALT lymphoma, including hepatitis C virus (HCV), *Chlamydophila psittaci* (previously *Chlamydia*) in the conjunctiva and ocular adnexa, *Borrelia burgdorferi* in the skin, and *Achromobacter xylosoxidans* in the lung. Autoimmune disorders such as Hashimoto thyroiditis and Sjögren disease of the salivary gland may precipitate development of MALT lymphoma. Transformation of extranodal MZL, resulting in a sheet of large cells, is associated with inferior prognosis and may be driven by TP53 mutations, loss of p16 protein, or rearrangements in MYC.[5]

A further presentation on extranodal MZL was given by **Ming-Qing Du, MD, PhD (University of Cambridge)** on the specific topic of "MALT Lymphoma: Deregulated Cellular Signaling." Dr. Du highlighted the critical signals required to support growth of marginal zone B-cells, including BAFF, CD40, TLR, BCR, and NOTCH receptor signaling. In the context of MALT lymphoma transformation, B-cells typically acquire genetic changes that enhance these pathways' signals that are triggered by physiologically relevant stimuli. Often, these pathways are activated in the context of an inflammatory response. It has been proposed that chronic inflammation produced by infectious or autoimmune processes provides the immuno-signaling milieu that sustains the survival of the cells comprising a low-grade MALT lymphoma. Notably, the surface immunoglobulin molecules comprising BCRs on gastric MALT lymphoma B-cells do not recognize *H. pylori* antigens, but are instead polyreactive to auto-antigens, likely reflected by biased usage of IGHV3-7 and IGHV1-69 genes by gastric MALT lymphoma B-cells. Salivary gland, ocular adnexal, and thyroid MALT lymphoma are believed to display BCRs with similarly self-polyreactive properties, also owing to biased immunoglobulin hypervariable gene usage. There is a significant association between BCR and acquired somatic genetic changes in marginal zone lymphoma of several sites, arguing for their oncogenic cooperation in the lymphoma development.[6]

Eric D. Hsi, MD (Cleveland Clinic) gave a presentation describing the "Pathology of Nodal and Splenic MZL." Dr. Hsi characterized nodal MZL as a clinicopathologic diagnosis representing 1.5-1.8 percent of all lymphoid neoplasms. From a histopathology perspective, nodal MZL represents the proliferation of a small lymphocyte population with features of marginal zone centrocyte-like B-cells, or, more infrequently, of monocytoid B-cells. The immunophenotype of nodal MZL is not specific, but cells typically express CD19 and CD20, and lack CD10, BCL6, LMO2, HGAL, and CD5. Immunoglobulin superfamily receptor 1 (IRTA1) is expressed in some MZL cells and is a positive marker for MZL.[7]) The contribution of large cells and the definition of transformation from nodal MZL to diffuse large B-cell lymphoma is not well characterized. Whereas up to 60 percent of patients present with greater than 20 percent large cells, these patients experience no worse outcomes than patients with fewer large cells. However, those with greater than 50 percent large cells experience inferior survival.[8] Turning to splenic MZL (SMZL), Dr. Hsi described a rare disorder, comprising fewer than two percent of all lymphoid neoplasms, in a disorder that is sometimes associated with HCV infection. Splenomegaly, bone marrow involvement, and blood involvement are common in SMZL. In terms of its immunophenotype, SMZL cells typically express CD20 and BCL2; a

minority may variably express CD5 and IgD. CD10 and cyclin D1 are not expressed.[9] Although myeloid cell nuclear differentiation antigen (MNDA) is present on nearly all SMZL cells, this marker is nonspecific, appearing also in other small B-cell lymphomas. Recurrent mutations in SMZL include KLF2, NOTCH2, and other NOTCH and NF-kB pathway activating mutations; however, these mutations need not always be present (no mutations are highly recurrent in NMZL).[10] Thus, SMZL requires immunophenotypic characterization for accurate diagnosis, incorporating known markers for CLL/SLL, MCL, and FL in the spleen, and known markers for HCL, MCL, and LPL in the blood and bone marrow. Diagnosis of splenic diffuse red pulp lymphoma and distinguishing it from SMZL may require evaluation of the spleen histopathology.[11]

Davide Rossi, MD, PhD (Institute of Oncology Research), reviewed splenic marginal zone lymphoma (SMZL) and nodal marginal zone lymphoma (NMZL) pathogenesis. Dr. Rossi described the limited understanding of SMZL and NMZL molecular pathogenesis prior to the genomic era. In the current genomic era, however, it is now understood that NOTCH pathway genes are frequently mutated in SMZL, in addition to other marginal zone differentiation-associated genes, in as many as 60 percent of patients.[12] A common mutation in SMZL occurs in the KLF2 transcription factor, leading to activation of NF-kB signaling[13] Further evidence for the importance of NF-kB signaling in the molecular pathogenesis of SMZL comes from the observation that the non-canonical NF-kB pathway frequently undergoes mutation in SMZL, including hits to TRAF3, MAP3K14, and BIRC3. Importantly, non-canonical NF-kB pathway activation enabled through these common mutations can empower a cell to evade ibrutinib- and BTK-mediated inhibition of NF-kB activation that is stimulated through canonical, antigen-dependent BCR signaling, and can in fact lead to an SMZL cell gaining antigen independence. In NMZL, like in SMZL, mutations in NOTCH2 and KLF2 are common in NMZL. However, unlike in SMZL, in NMZL, mutations in MLL2 and PTPRD are enriched as well. Because the PTPRD mutation does not occur in SMZL, the occurrence of this mutation effectively distinguishes NMZL from SMZL; when present, it is associated with upregulation of cell-cycle genes and a pro-proliferative phenotype.[14] Seeking to further refine the classification of SMZL subtypes, Dr. Rossi described the IELSG46 study (NCT03288415), which is a retrospective, observational, training-validation cohort study incorporating both SMZL clinical data and tumor biological samples. Using data from the IELSG46 study, Dr. Rossi highlighted 3 molecular clusters in SMZL, described as MC1, MC2, and MC3. MC1, the largest cluster, featured mutations in NOTCH and non-canonical NF-kB pathway genes like NOTCH2, NOTCH1, and KLF2. MC2, a much smaller cluster, featured mutations in epigenetic genes such as KMT2D, EP300, and CREBBP, among other genes. The smallest cluster, MC3, featured mutations leading to enrichment in the DNA damage response pathway, including TP53, ATM, and MYD88. Notably, the SMZL molecular clusters had underlying biological differences leading to different relative survival, with 10-year relative survival ranging from 78.9 percent in MC1 to 88.7 percent in MC2.[15] Taken together, Dr. Rossi suggested that these findings indicate "non-canonical NF-kB mutations should be investigated as a biomarker of resistance to ibrutinib in MZL," and that NOTCH2 and KLF2 mutations "identify SMZL cases with the greatest loss of survival expectancy when treated conventionally."

Epidemiology, Transformation and MZL Signature in DLBCL

Session Chair: Margaret A. Shipp, MD, Dana-Farber Cancer Institute

At present, the epidemiology and natural history of extranodal, nodal, and splenic MZL remain poorly understood, and the factors which contribute most strongly to MZL transformation risk are not known. In the immediate future, investigators hope to further define risk factors for each subset of MZL and to better understand the core biology and etiology of MZL transformation. Over the longer term, MZL investigators seek to identify the key biological changes that define the transition from MZL to diffuse large B-cell lymphoma (DLBCL); once these key biological changes are identified, investigators can then incorporate predictive biomarkers into MZL diagnosis and treatment programs.

James R, Cerhan, MD, PhD (Mayo Clinic) reviewed MZL epidemiology, describing the disease's incidence and survival statistics. According to the American Cancer Society, in 2016, there were an estimated 7,460 newly diagnoses patients with MZL, which comprised 7 percent of all non-Hodgkin lymphomas.[16] Based on data from the SEER 18 database from 2001-2015, nodal MZL represented 30.6 percent of all MZL cases, with an incidence of rate of 5.96 per 1,000,000 person-years, whereas extranodal MZL represents 69.4 percent of all MZL cases, with an incidence of 11.77 per 1,00,000 person-years. The incidence of MZL was highest among white individuals (20.0 per 1,000,000 person-years), followed by Hispanic individuals (17.1 per 1,000,000 person-years), black individuals (14.8 per 1,000,000 person-years), and Asians or Pacific islanders (14.8 per 1,000,000 person-years). Defying this trend were ocular MALT (highest incidence in Asians and Pacific islanders) and salivary gland MZL (highest incidence in Hispanics). Incidence generally increases with age and is slightly higher in males for most MZL subtypes. The 5-year relative survival for MZL was 88.9 percent (81.6 percent for nodal MZL and 93.1 percent for extranodal MZL)[17] Turning to the analytic epidemiology of MZL, The genetic, lifestyle, occupational, and environmental risk factors for the disease. Family history of lymphoma is a salient risk factor for MZL, particularly a history of NHL, CLL, HL, or, most significantly, DLBCL. Genetic and environmental risk factors for extranodal MZL include infectious agents such as *Helicobacter pylori, Borrelia burgdorferi*, and *Chlamydia psittaci*, as well as autoimmune disorders such as Sjögren syndrome and Hashimoto thyroiditis. Preliminary data suggest a significant risk factor for nodal MZL is having the occupation of metal worker (odds ratio 3.6), whereas significant risk factors for splenic MZL include asthmatic status (odds ratio 2.3) and use of hair dye (odds ratio 6.5).[18] HCV infection is an additional risk factor for MZL, including both nodal MZL and splenic MZL. Solid organ transplantation is a further risk factor for MZL, particularly extranodal MZL.[19]

Izidore S. Lossos, MD (University of Miami Health System), presented on "MZL Transformation to High-Grade Lymphoma." Dr. Lossos described high-grade lymphoma transformation (HGT) as a detrimental event in the natural history of MZL, one associated with poor outcome and shortened overall survival. Dr. Lossos stated that HGT, defined as a histological demonstration of an increase in the proportion of large cells diffusely infiltrating affected tissue, occurs with an annual incidence of 1.1 per 100 patients, plateauing at 12 to 15 years.[20] MZL patients who present with multiple mucosal sites (MMS), which occurs in 11 percent of patients in the Miami MZL Cohort, are at greater risk of HGT and therefore of shortened overall survival.[21] According to data from the Miami MZL Cohort, most untreated patients with HGT and MZL at diagnosis or following active surveillance are capable of achieving complete remission rates as high as 91 percent when using standard frontline DLBCL therapy, but previously treated patients achieve less robust complete response rates (52.6 percent).[20] According to Dr. Lossos, monitoring the patient response to initial therapy may be key to improving progression-free survival and overall survival in MZL patients, particularly those at risk of HGT. Currently, the pathogenesis and biology of HGT remain poorly understood. To advance treatment and understanding, clinicians must be educated to perform biopsies at the time of relapse so that HGT may be diagnosed. As well, investigators must determine the value of PET-CT in MZL HGT, and identify optimal therapeutic approaches. Because there are few planned therapeutic trials designed specifically to

target MZL patients, collaborative efforts are needed to address HGT knowledge gaps in MZL.

To conclude the session, **Margaret A. Shipp, MD (Dana-Farber Cancer Institute)** presented on the characterization of marginal zone lymphoma in diffuse large B-cell lymphoma (DLBCL).The Shipp group, in collaboration with the Getz group at the Broad Institute, conducted a study to characterize the genomic profile of primary DLBCL, with the intention of defining DLBCL genetic substructure. For the study cohort, the group selected 304 patients with newly diagnosed DLBCLs and subjected them to whole exome sequencing. After further algorithmic analysis, the investigators identified 98 significantly mutated candidate cancer genes,[22] of which demonstrated significant spatial clustering, meaning the mutations co-localized in 3D space within a protein, even if the mutations were not near each other in terms of genetic sequence. Signature analysis revealed that mutations related to aging processes and to the activity of the B-cell mutator enzyme AID were predominant in the sampled cohort. Because mutations, copy number variations, and chromosomal rearrangements all contribute to the genetic substructure of DLBCL, Dr. Shipp and colleagues performed a technique called non-negative matrix factorization to identify genetically distinct subsets of DLBCL. The clustering algorithm identified five distinct DLBCL subsets with coordinate genetic signatures, termed Clusters 1 (C1) through Cluster 5 (C5). Importantly, all three types of genetic alterations factored significantly in generating these clusters. The C1 cluster, described as "favorable risk ABC-DLBCLs of putative extrafollicular origin," possessed many mutations typically associated with MZL, including alterations of multiple NOTCH2 and NF-kB pathway components. The C1 cluster was also highly enriched for BCL6 translocations, which have been associated with MZL transformation. Additionally, C1 DLBCLs exhibited multiple genetic bases of immune evasion, of note given the described infectious and inflammatory bases of marginal zone lymphoma.[22] Among the genetically defined DLBCL clusters, C1 tumors had the lowest rate of AID mutations suggesting an extrafollicular rather than a germinal center origin. Thus, Dr. Shipp proposed that the C1 DLBCL genetic cluster may represent either occultly transformed MZLs or *de novo* transformation of extrafollicular B-cell precursors with highly similar genetic features.

MZL Assessment Criteria and Response Evaluation

Session Chair: Morton Coleman, MD, Weill Cornell Medicine

At present, specific assessment criteria for the evaluation of response in MZL are lacking; instead, the assessment and response criteria for MZL are the same as those used for follicular lymphoma (FL). In the near term, MZL investigators intend to define specific assessment and response criteria, with a greater emphasis on MZL site specificity. To this end, investigators will further define the role of positron emission tomography (PET) and other staging modalities in the assessment of MZL. Over the longer term, MZL investigators hope to develop molecular and genomic approaches that can be employed to assess response and relapse in MZL, to homogenize response assessment criteria, and to better define precise criteria for initiation of therapy.

Catherine Thieblemont, MD, PhD (Hôpital Saint-Louis, Université Diderot, Paris) presented on assessment criteria and the International Prognostic Index (IPI) in MZL. Dr. Thieblemont noted that, at present, several classifications are used for treatment response assessment in MZL, and that based on these criteria, such as the Lugano criteria, it is only truly feasible to assess response in nodal MZL, and not in extranodal disease. Dr. Thieblemont suggested that it is not a settled matter whether CT-scan response assessment is well suited to MZL, which is primarily an extranodal disease, and that splenic MZL and gastric MZL, or MZL from other extranodal sites prove difficult to assess based on CT-scan criteria. Dr. Thieblemont called for the various response assessment criteria for these diseases, such as the Lugano and Matutes classifications[23,24] for splenic MZL or gastric MALT lymphoma,[25] to be homogenized, so as to facilitate better comparison of the results between different clinical trials.[26,27] Turning to a discussion of endpoint criteria in MZL, Dr. Thieblemont described theoretical endpoints of interest, those that are currently validated by the FDA and EMA, and those that are currently used in clinical trials and in routine practice.[28,29,30] Dr. Thieblemont described a wide range of endpoints that are of theoretical interest, including patient-centered measures such as quality of life but also including overall response rate, complete response rate, progression free survival, event free survival, duration of response, time to next treatment, overall survival, specific overall survival, histological transformation. However, the endpoints currently validated by the FDA for use in phase 2 clinical trials are the overall response rate and complete response rate,[26] which may not fully capture patient outcomes in MZL. Dr. Thieblemont concluded her presentation by discussing surrogate endpoints for tracking MZL treatment response, which are endpoints that can be measured more quickly, at lower cost, and/or less invasively than the true endpoints of interest.[31] Surrogate endpoints in MZL include CT, PET-CT, minimal residual disease (MRD), and progression of disease within 2 years (POD24). Dr. Thieblemont suggested that specific prognostic scores may provide better treatment decision information in MZL; however, the value of PET-CT and MRD criteria in MZL treatment assessment requires further characterization.

Lale Kostakoglu, MD, MPH (Icahn School of Medicine at Mount Sinai) presented on "PET/CT in Marginal Zone Lymphoma." Dr. Kostakoglu opened her discussion by noting that the value of PET in routine evaluation of MALT remains unestablished[32] and highlighted the difficulty of using fluorodeoxyglucose (FDG) PET in the staging of MZL: The sensitivity of FDG-PET is highly variable in the disease, ranging from 50 to 80 percent in various studies.[33] As well, FDG avidity in MZL is highly histopathologic subtype dependent. However, FDG PET remains useful because CT-based staging is of limited utility in the evaluation of extranodal disease.[34] FDG PET is useful in staging MZL to confirm localized disease and ensure effective radiotherapy.[35] In particular, gastric and ocular MALT possess low FDG avidity.[36,37,38] In histologically transformed (HT) MZL, FDG PET is necessary to confirm HT and PET-based Lugano Response Criteria are also used for HT MZL.[39] Dr. Kostakoglu also noted that quantitative PET is still exploratory, but many groups are currently investigating use of this technique.[40,41] During the discussion following the session, various discussants proposed that site-specific imaging is required to monitor response in MZL (for example, MRI in ocular adnexal MALT).

MZL Treatment I: MZL Targeted Pathways and Radiotherapy

Session Chair: Anas Younes, MD, Memorial Sloan Kettering Cancer Center

At present, only limited pre-clinical data on druggable targets in MZL are available. In the near term, MZL investigators seek to identify new druggable pathways and develop supporting pre-clinical data. Once new druggable targets have been elucidated, over the long term, MZL investigators intend to conduct new clinical trials, with a particular emphasis on the relapsed/refractory disease setting. Radiotherapy remains effective for local control in many MZL cases; however, it remains unclear what the ideal dosing schedule for radiotherapy should be in patients with MZL.

Anas Younes, MD (Memorial Sloan Kettering Cancer Center) led the session with a presentation on MZL molecular pathways and targets. Dr. Younes described the involvement of multiple signaling pathways in MZL, including the BCR, NOTCH, and TLR pathways, which converge on the NF-kB transcription factor and its target genes.[6,42] Druggable targets in these pathways include Syk, BTK, MALT1, IRAK4, p50/p65, BCL2, and the PI3K/AKT/mTOR cascade.[43] Among the single agents active in relapsed/refractory MZL, the PI3K inhibitor copanlisib demonstrates the highest response rate, at 69 percent,[44] followed by lenalidomide at 61 percent, the BTK inhibitor ibrutinib at 48 percent , the proteasome inhibitor bortezomib at 48 percent, the PI3K inhibitor idelalisib at 47 percent, the anti-CD20 monoclonal antibody rituximab at 45 percent, and the mTOR inhibitor everolimus at 20 percent.[26, 43] Dr. Younes noted that the first phase 1 clinical trial of a MALT1 inhibitor in patients with non-Hodgkin lymphoma, the JNJ67856633LYM1001 trial, has just begun enrolling patients. Dr. Younes concluded his presentation by noting that clinicians now have the tools to intercept several signaling pathways crucial to the molecular pathology of MZL; in the future, Dr. Younes would like to see greater use of multi-agent combination therapies that either target multiple nodes in the same pathway or that target multiple distinct signaling pathways.

Francesco Bertoni, MD (Institute of Oncology Research) described druggable pathways and pre-clinical data in MZL treatment. Dr. Bertoni highlighted the history of antibiotic therapies demonstrating anti-tumor activity in MALT lymphomas, including antibiotic therapy for *H. pylori* in the stomach, antibiotic therapy for *C. psittaci* in the ocular adnexa, and antibiotic therapy for *B. burgdorferi* in the skin.[45] In light of this history, Dr. Bertoni argued that infections and eradication therapies still represent important fields of therapeutic inquiry in the treatment of MZL. Turning to molecular targets of MZL therapies, Dr. Bertoni highlighted the utility of drugs targeting PI3K (idelalisib,[46] parsaclisib,[47] and copanlisib[44]), BTK (ibrutinib[26]), CD20 (rituximab),[48] and BCL2 (venetoclax).[49] However, Dr. Bertoni stressed that development of combination therapies is necessary, either targeting the same pathway multiple times, or targeting different pathways. Supporting this notion, Dr. Bertoni highlighted the finding that a combination of copanlisib and venetoclax was highly active in cultured MZL cells, benefitting 16 of 17 tested cell lines (94%)[50]; a phase 1 trial (NCT03886649) of this combination in patients with relapsed or refractory B-cell non-Hodgkin lymphoma is currently in pre-recruitment. Additional molecular targets that remain to be fully investigated in the further development of anti-MZL therapeutic agents include NIK, MALT1, MYD88, IRAK4, IRAK1, the TLRs, and the NOTCH pathway, as well as protein machinery involved in DNA methylation and chromatin remodeling. Dr. Bertoni concluded his presentation by stressing that future investigations of MZL therapies will benefit from further dividing MZL into clear subtypes based on specific biologic features.

Peter Martin, MD (Weill Cornell Medicine) presented on the topic of standard systemic therapy in MZL. Dr. Martin described the current NCCN guidelines for MZL treatment, and detailed the FDA-approved treatments currently available for MZL and MZL-related conditions, including: chlorambucil, cyclophosphamide, and doxorubicin for malignant lymphoma (pre-MZL); fludarabine for low-grade NHL that has failed or relapsed after prior therapy (pre-MZL); rituximab for relapsed or refractory CD20-positive B-cell NHL[51]; ibritumomab tiuxetan for relapsed or refractory, low-grade or follicular B-cell NHL (pre-MZL); bendamustine for indolent B-cell NHL that has progressed within six months of treatment with rituximab[52]; as well

as ibrutinib and lenalidomide for relapsed or refractory MZL.[53] Drugs that have been approved by the FDA, but not for the specific indication of MZL (despite inclusion of MZL in registrational trials), include obinutuzumab, idelalisib, copanlisib, and duvelisib. A further class of drugs that demonstrate activity in MZL and are approved for treatment of other B-cell NHLs includes ritixumab with hyaluronidiase, ofatumumab, acalabrutinib, venetoclax, and bortezomib. Dr. Martin noted a trend towards using rituximab with scheduled maintenance dosing[54] and suggested that including rituximab maintenance therapy may improve MZL complete response rates and provide longer remission durations.[55] After laying out the current treatment landscape, Dr. Martin highlighted current questions that remain under active investigation, questions such as the optimal dosing of rituximab, the efficacy of newer anti-CD20 antibodies and novel agents, and whether there is an optimal chemotherapy backbone to co-administer with anti-CD20 agents. Dr. Martin further questioned whether it is proper to group all MZL subtypes together in clinical trials assessing the efficacy of these agents. Dr. Martin argued that such lumping together of MZL may be appropriate for assessing clinical activity, but differences in prognostic scores and the resultant stratification, as well as differences in staging and response criteria, complicate the analysis of such studies.

Thomas Habermann, MD (Mayo Clinic), concluded the session with a presentation on radiotherapeutic treatment of MZL. Dr. Habermann highlighted the importance of radiotherapy in managing various MZL subtypes, including extranodal MALT lymphoma. Radiotherapy-mediated local control in extranodal MZL results in long-term favorable survival rates, particularly in gastric, ocular, and thyroid MALT lymphomas.[56,57,58,59,60,61,62] At this time, there is not a universally accepted dosing schedule established for radiotherapy use in MALT lymphoma. Radiation doses used in the management of MALT lymphoma range from 24 to 30 Gy. Whereas National Comprehensive Cancer Network (NCCN) guidelines suggest 20 x 1.5 Gy or 15 x 12 Gy dosing schedules, recent randomized trials support the use of a 12 x 2 Gy dosing schedule. Notably, whereas four 9-megavolt photon beams are advisable in most MALT lymphomas, in the case of conjunctival or cutaneous disease, 4-12 megavolt electron beams may be equally effective while resulting in less associated toxicity. Treatment-associated toxicities with radiotherapy in the management of MALT lymphoma include anorexia, malaise, nausea, and dyspepsia in gastric MALT; chronic dry mouth in salivary gland MALT; radiation pneumonitis secondary to fibrosis in pulmonary MALT; and secondary malignancies in MALT lymphomas of all types. In a study of early-stage MZL patients (n = 490) treated with radiotherapy with curative intent, relapse occurred in 60 (24 percent) of patients, ten in the treated field; transformation was observed in 1.6 percent of these patients.[61]

MZL Treatment II: Disease Etiology and Natural History

Session Chair: Thomas M. Habermann, MD, Mayo Clinic, Rochester

At present, the etiology and natural history of MZL subtypes are not uniformly defined. In the immediate future, MZL investigators will further define MZL subtypes by employing larger data sets with a specific focus on MZL. Over the long term, MZL investigators hope to further define and subcategorize exactly how many specific and distinct MZL disease states there are — disease states that are currently defined simply as MZL.

Catherine Thieblemont, MD, PhD (APHP, Hôpital Saint-Louis, Université Diderot, Paris) presented on the topic of nodal and splenic MZL. As described by Dr. Thieblemont, nodal and splenic MZL constitute a heterogeneous group of diseases, despite sharing characteristics such as being rare, indolent B-cell lymphomas that tend to be asymptomatic for several years.[63] Importantly, there is no current standard management practice for patients with these diseases.[64,65] Watchful waiting is commonly practiced; however, it remains unclear when the appropriate time to initiate therapy and whether therapy should be localized or systemic. Local therapy consists of splenectomy in SMZL and localized radiotherapy in nodal MZL. Systemic therapy options for splenic MZL include rituximab, either alone or with maintenance therapy, and antiviral therapy in cases associated with comorbid HCV infection.[11] In SMZL, systemic therapy options include R-bendamustine and R-CHOP (in case of transformation).[66] Notably, some novel agents are presently being evaluated for safety and efficacy in the context of MZL; however, most of these new agents appear to be too toxic for regular clinical use in indolent disease. Promising exceptions to this trend include the BTK inhibitor ibrutinib[26] and perhaps some of the novel PI3K inhibitors.[67] Dr. Thieblemont suggested that therapeutic modality selection can be improved through careful patient-specific profiling and analysis of data from clinical trials organized around specific MZL subtypes. Currently, possible criteria for initiating therapy in splenic MZL may include symptomatic splenomegaly, anemia, and thrombocytopenia. For nodal MZL, criteria for initiating therapy are the same as those used in follicular lymphoma, informed by high tumor burden criteria and GELF criteria.

Andrés J. M. Ferreri, MD (San Raffaele Scientific Institute), presented on ocular adnexal MALT lymphoma. Ocular adnexal MALT comprises 24 percent of all MALT cases, and has a relatively favorable prognosis profile; patients typically experience a five-year overall survival of 96 percent.[68] Notably, there are differences in terms of patient characteristics and prognosis depending on the form of ocular adnexal MALT encountered (i.e. conjunctival vs other ocular adnexal MALT), as well as upon patient geographic location. High-grade transformation (HGT) is a form of ocular adnexal MALT with a particularly poor prognosis, occurring only rarely. HGT ocular adnexal MALT is associated with a suboptimal response, elevated LDH levels, and extensive nodal disease in four or more sites. When identified at presentation, HGT ocular adnexal MALT has a better prognosis than when HGT is identified at relapse.[69] Turning to the topic of therapeutic decision making in ocular adnexal MALT, Dr. Ferreri emphasized the importance of avoiding overtreatment in these patients, which can be complicated by the disease's varied presentation in a heterogeneous patient population.[70] Following surgical biopsy, a watchful waiting approach may be warranted, especially among elderly patients, those who underwent a complete surgical resection, and those with asymptomatic and indolent lesions.[71] In the presence of *Chlamydia psittaci* infection, which is frequently associated with the disease, antibiotic therapy (e.g. doxycycline) is warranted[72]; however, persistent forms of C. psittaci are resistant to antibiotics.[73] Notably, macrolide antibiotics may produce an anti-lymphoproliferative effect, and these drugs are now being tested alone and in combination with other therapies, such as lenalidomide, in clinical trials.[74] In patients infected with HCV, antiviral therapy is indicated. Anecdotal evidence of cases of ocular adnexal MZL treated with antiviral therapy exist in the literature, and Dr. Ferreri mentioned that a prospective trial of HCV-clearing antiviral therapy in ocular adnexal MZL is ongoing in Italy. In cases of residual ocular adnexal MZL that are negative for infection, radiotherapy may be indicated for low-stage disease, whereas systemic drug therapy may be indicated for advanced-stage disease.

David J. Straus, MD (Memorial Sloan Kettering Cancer Center) presented on the topic of bronchial-associated lymphoid tissue (BALT) lymphomas. According to Dr. Straus, BALT lymphoma is a primary lymphoma of the lung that comprises 3.6 percent of all extranodal lymphomas and 0.4 percent of all non-Hodgkin lymphomas. BALT lymphoma is associated with comorbid chronic lung infection and concomitant chronic inflammation that induces the bronchial lymphoid hyperplasia prerequisite to the development of frank BALT lymphoma. Patients with BALT lymphoma tend to be older (>60 years old) and female, and most patients are asymptomatic (previously termed "pseudolymphoma of the lung") or present with non-specific symptoms such as cough or labored breathing. In rare cases, BALT lymphoma may transform into a more aggressive lymphoma presentation.[75] Turning to a description of the BALT lymphoma experience at MSKCC, Dr. Straus described a consecutive case series of 127 patients newly diagnosed with lymphoma from 1995 to 2017. The MSKCC experience suggests BALT lymphoma has a long disease course, often even without treatment with an expectant approach. As such, Dr. Straus stressed that clinicians must exercise careful judgment to avoid the risk of over-treatment in patients with BALT lymphoma.

Continuing on the theme of MALT, **Thomas M. Habermann, MD (Mayo Clinic)** presented on the treatment, etiology, and natural history of MALT at salivary, dural, and other sites. Dr. Habermann highlighted the IELSG41 study of extranodal MZL of the salivary glands, using the study to illustrate that autoimmune disease is frequently comorbid with salivary gland MZL, occurring in 41 percent of the 248 patients included in IELSG41.[76] Of those patients who had autoimmune disease, Sjögren disease was particularly common, occurring in 83% of those with autoimmune disease; upon multivariate analysis, patients with salivary gland MZL who also had Sjögren disease were shown experience better overall and progression-free survival relative to those without Sjögren disease. Salivary gland MZL disease was most often localized (59 percent), but local regional presentation was also relatively common (17 percent). In terms of treatment, 57 percent of IELSG41 patients were given local therapy, consisting of radiotherapy and surgical intervention, whereas 37 percent were given systemic therapy (47 percent rituximab), and 6 percent were observed. Those patients who received rituximab were significantly more likely to experience lengthened overall survival. Notably, female salivary gland MZL patients are more common than male patients (3:1 ratio). In a rare variant, dural MALT lymphoma, Dr. Habermann described a plasmacytic presentation with potential for direct CNS infiltration as well as leptomeningeal involvement. Based on experiences at the MSKCC and University of Miami, in which 3-year overall survival rates for marginal zone dural lymphoma patients were 100 percent, marginal zone dural lymphoma appears to be an indolent disease, associated with long survival.[77]

Turning to MALT of other sites, Dr. Habermann described extranodal MALT of the thyroid, which represents 1-5 percent of all thyroid malignancies, and 2 percent of all extranodal lymphomas. The disease is typically managed by localized radiotherapy and surgical intervention, either with or without adjuvant chemoradiotherapy.[78,79] Dr. Habermann also described MALT of the small bowel, colon, and rectum, noting that MALT lymphomas represent as many as a third of all small bowel non-Hodgkin lymphomas.[80,81,82,83] Typically, colorectal MALT lymphoma is managed surgically, in as many as half of all patients. Other treatment strategies, in order of their prevalence in a 51-patient retrospective analysis, include radiotherapy, chemotherapy, combination therapy, and observation. Outcomes with colorectal MALT demonstrate a 5-year overall and progression-free survival rates of 94 percent and 92 percent, respectively. MALT of the bladder is managed with local treatment strategies.[84] An emerging strategy in breast extranodal marginal zone lymphoma patients who relapse after radiation therapy is single agent rituximab.[62]

Cynthia M. Magro, MD (Weill Cornell Medicine), described cutaneous marginal zone lymphoma. Dr. Magro reviewed the classic presentation of cutaneous MZL, including its clinical features as well as its phenotypic and cytogenetic profile. Typically, patients with marginal zone lymphoma have a plaque or nodule presentation, usually with multiple lesions (72 percent), but sometimes with solitary lesions (28

percent). These lesions most commonly occur on the upper trunk and extremities. Recurrence is relatively common, occurring in as many as 40 percent of cases. However, death resulting from recurrent disease is rare, warranting the classification of cutaneous MZL as an indolent lymphoma. Cutaneous MZL lymphomas are typically derived from post-germinal center B-cells, and the neoplastic lymphocytes are typically small, round, and monocytoid or centrocytic in terms of their morphology. Phenotypically, the cells are kappa / lambda immunoglobulin light-chain restricted and frequently IgG4-positive, CD20-positive, CD79-positive, BCL6-negative, and CD10-negative. Dr. Magro went on to describe unusual variants of cutaneous MZL, including epidermotropic and blastic presentations of the disease. Epidermotropic MZL represents an uncommon manifestation, hallmarked by a disseminated skin rash reminiscent of pityriasis rosea, that is responsive to rituximab. Blastic transformed disease, typically treated with local excision without subsequent recurrence, has an indolent clinical course similar to primary cutaneous marginal zone lymphomas, but may take an aggressive course with poor outcomes. Notably, expression of CD5 and CD23 are phenotypically associated with development of blastic MZL.

Emanuele Zucca, MD (Oncology Institute of Southern Switzerland, Bellinzona/University of Bern/International Extranodal Lymphoma Study Group, Bellinzona), presented on gastric MALT. During his talk, Dr. Zucca highlighted a number of controversial issues in the management of gastric MZL, such as: the establishment of diagnostic criteria, response evaluation criteria, and a staging system; the role of PET in diagnosis and staging; the role of antibiotic therapy in *H. pylori* negative cases of gastric MALT; and best practices for managing residual disease. On the topic of diagnostic criteria, Dr. Zucca noted the utility of the Wotherspoon criteria in combination with B-cell clonality analysis, which together can distinguish gastric MZL from chronic gastritis.[85] Although clonality is suggestive of MALT lymphoma, a demonstration of monoclonality by PCR analysis of rearranged immunoglobulin genes is not a perquisite for diagnosis of gastric MALT lymphoma, meaning that some gastric MALT may in fact be pseudoclonal. Importantly, gastric MALT lymphomas are at least initially antigen-driven in their growth, as evidenced by their histological features, the presence of somatic hypermutation in immunoglobulin genes, and association with chronic *H. pylori gastritis*.[86] Dr. Zucca noted that gastric MALT lymphoma that is associated with *H. pylori* infection is, perhaps surprisingly, often relatively indolent relative to *H. pylori*-negative gastric MALT.[87] However, Dr. Zucca suggested that antibiotic treatment may be responsible for the relative indolence of *H. pylori*-associated disease.[88] Tumor progression models for gastric MALT lymphoma suggest that loss of antigen dependence, t(11;18) translocation, and BCR-independent NF-kB activation are hallmarks of full-blown gastric MALT lymphoma.[89] Notably, *H. pylori* eradication therapy may offer clinical benefit even to *H. pylori*-negative gastric MALT lymphoma patients, particularly those lacking the t(11;18) translocation; this unexpected benefit may result from false negative *H. pylori* diagnostic testing, from the involvement of other microorganisms susceptible to antibiotic therapy, or from the involvement of other unknown mechanisms. In any case, according to published reports, as many as 15-20% of *H. pylori*-negative gastric MALT lymphoma patients respond to anti-*H. pylori* treatment.[90] For gastric MALT lymphoma patients who fail antibiotic therapy, chemotherapy, immunotherapy (i.e. rituximab) and radiotherapy offer curative potential.

MZL Clinical Trials: Summary of Ongoing Investigator-Initiated Trials

Session Chair: Emanuele Zucca, MD, Oncology Institute of Southern Switzerland, University of Bern/IELSG

At present, treatment patterns for MZL are neither well standardized nor well defined according to site-specific criteria. In the near future, MZL investigators seek to further define areas of research for all subtypes of MZL, which will enable the development of new clinical trial strategies. Over the long-term, MZL investigators hope new trials will enable clinicians to better define standards of care for each of the subtypes of MZL, and to develop new curative therapeutic approaches.

A summary of ongoing U.S. studies was provided by **Michael E. Williams, MD (University of Virginia, Charlottesville**). Dr. Williams described studies of checkpoint inhibitor-based therapies (e.g. pembrolizumab), cellular therapies (e.g. CD20 CAR-T cells), radiotherapeutics, and novel agent-based therapies (e.g. pevondistat, selinexor, and venetoclax) that are actively recruiting patients as of April 2019. Dr. Williams then highlighted current gaps and opportunities in the design of MZL clinical trials, noting that there are few MZL-focused clinical trials, particularly based in the United States, where there is no current cooperative group trial. Because the incidence of each subtype of MZL is relatively low, individual subtypes of MZL are rare, necessitating broad-based, multicenter, collaborative trial design. Future trial designs will take greater advantage of newly identified biomarkers, and, with regulatory support, incorporate novel endpoints into study design, particularly endpoints that incorporate patient quality of life measures. As well, future trial designs have the opportunity to improve outcomes via the use of highly targeted agents rather than traditional cytotoxic chemotherapeutic regimens.

A summary of ongoing European studies was provided by **Christian Buske, MD (University Hospital of Ulm)**. Dr. Buske described the NF10 study program by the Fondazione Italiana Linfomi (FIL), which investigates indolent non-follicular lymphoma. The NF10 study was conceived to provide a prospective collection of real-world data that would allow for more accurate and definitive prognosis in indolent non-follicular lymphoma. Enrolled patients will be followed for up to 5 years, at several centers in Europe, South America, and Asia. Dr. Buske then described a second source of real-world data, the German MZL lymphoma registry, which is a prospective, academically funded web-based registry for patients with MZL that has been ongoing since May 2015, at a total of 91 German clinical centers. The inclusion criteria for the German MZL registry specify that reference pathology is required. The German MZL registry has been enrolling approximately 100 to 120 patients per year.[91]

Turning to a description of European-led clinical trials, Dr. Buske summarized the IELSG-19 study, which demonstrated that chlorambucil plus rituximab produces better event-free survival and progression-free survival outcomes relative to chlorambucil or rituximab alone in patients with MALT lymphoma, either de novo or relapsed after previous localized therapy.[92]

The GALLIUM study evaluated the clinical performance of immunochemotherapy with obinutuzumab or rituximab in patients with previously untreated MZL. The investigators found that patients in the obinutuzumab arm experienced similar rates of progression-free survival at 3 years compared to the Rituximab arm. Because there was greater toxicity associated with both obinutuzumab/bendamustine and rituximab/bendamustine further intensification of immunochemotherapy may result in overtreatment in MZL patients, suggesting that chemotherapy-free approaches may be more viable.[93]

One such chemotherapy-free approach may be single-agent ibrutinib, which has been tested in patients with relapsed/refractory MZL (NCT01980628). Included patients received ibrutinib until disease progression or unacceptable toxicity. The clinical efficacy as judged by objective response rate was 48%, and ibrutinib was found to be effective across all included MZL subgroups. This trial resulted in ibrutinib receiving the first FDA approval (on an accelerated basis) for the specific treatment of MZL in patients who require systemic therapy and who previously received anti-CD20 therapy.[26]

Based on the promising results observed with ibrutinib single-agent therapy in MZL, the ongoing MALI-BU-IELSG47 study was conceived as a

phase 2 trial to investigate the clinical performance of ibrutinib plus rituximab combination therapy in untreated MZL, including extranodal MZL, splenic MZL, and nodal MZL. The primary endpoints of the MALIBU study will be complete response at 12 months and progression-free survival at 5 years.

Dr. Buske next discussed trials involving copanlisib in patients with relapsed or refractory indolent B-cell lymphoma, beginning with the phase 2 CHRONOS-1 study. Patients enrolled in the CHRONOS-1 study had indolent B-cell lymphoma (FL, MZL, SLL, and LPL/WM) and had failed at least two lines of prior therapy. These patients received single-agent copanlisib therapy until either disease progression or development of unacceptable toxicity. At 2 years of follow up, patients with MZL who received copanlisib experienced an objective response rate of 78.3% (n = 18). In terms of safety, Dr. Buske suggested that copanlisib was relatively well tolerated, compared with other agents with similar mechanisms of action, although there were reports of treatment-related adverse events such as hyperglycemia and hypertension.[94]

Following up on the success of the CHRONOS-1 study, the COUP-1 single-arm phase 2 study was designed to evaluate the clinical performance of copanlisib and rituximab combination therapy in treatment-naïve and relapsed confirmed MZL patients with nodal, extranodal, or splenic disease who are ineligible for local therapy. The COUP-1 study, which is a German and Austrian collaboration through the German Lymphoma Alliance, is scheduled to begin by October of 2019.

The German Lymphoma Alliance has also planned the POLE-1 trial, a single-arm phase 2 German and Italian collaborative study designed to evaluate the clinical performance of pembrolizumab in treatment-naïve and relapsed confirmed MZL patients with nodal, extranodal, or splenic disease who are ineligible for local therapy. The POLE-1 trial is currently scheduled to begin in February 2020.

Using a similar design to the COUP-1 and POLE-1 trials, the German Lymphoma Alliance's OLYMP-1 trial is a single-arm phase 2 study taking place in Germany that is designed to evaluate the clinical performance of obinutuzumab as a single agent in treatment -naïve MZL patients with nodal, extranodal, or splenic disease who are ineligible for local therapy. The OLYMP-1 study has been activated and is presently ongoing.

Dr. Buske concluded his presentation by describing studies currently in the IELSG MZL study pipeline. IELSG38, which investigated the clinical performance of chlorambucil in combination with subcutaneous rituximab in patients with MALT lymphoma, has completed its enrollment phase, and follow up and analysis is now ongoing. The IELSG48 randomized phase 3 study is planned to compare the clinical performance of rituximab single-agent therapy with that of rituximab-plus-acalabrutinib combination therapy in patients with splenic MZL in the first-line setting. The primary endpoint of the IELSG48 trial will be progression-free survival at 3 years. Lastly, the IELSG49 study is a run-in pilot study of the investigational anti-CD19 agent MOR208 in combination with acalabrutinib in patients with relapsed or refractory MZL who have failed previous systemic therapy. The primary endpoint of the IELSG 49 study will be complete response rate, defined according to the international Revised Response Criteria for Malignant Lymphoma.

Discussion and Goals

At the conclusion of the workshop, a discussion session took place that focused on currently unmet needs in the field of MZL, with an emphasis on identifying opportunities for large-scale study designs that leverage the opportunities for collaboration that can be facilitated by the LRF. These unmet needs were focused in six key thematic areas: biology and pathology; epidemiology and transformation; assessment criteria, response evaluation, and surrogate endpoints; targeted pathways for MZL; etiology and natural history; and MZL treatment. The following chart summarizes the chief conclusions to arise from the discussion section.

Session	Concerns/ Unaswered Questions	Immediate Action Solutions (1-5 Years)	Long-Term Solutions (More than 5 Years)
Biology and Pathology	-Biologic differences in the subtypes of marginal zone lymphoma are not well understood -The microenvironment is not well defined -Molecular Clusters: how to move forward? -The immunology is not well understood	-Further define the biology of extranodal, nodal and splenic marginal zone lymphomas -Further define the microenvironment -Define the switch to antigenic stimulation in MZL	-Establish biologic correlates that can be translated and applied to the clinical laboratory for the pathology and diagnosis of MZL -Differentiate MZL from lymphoplasmacytic lymphoma -Define the source of MZL
Epidemiology/Transformation	-The broad epidemiology of nodal, multiple extranodal subsets, and splenic MZL are not well understood -Transformation risk, natural history, and biology of MZL require further characterization	-Further define risk factors for developing each subset of MZL -Further understand the biology of transformation in MZL -Further understand the genetic risks for transformation	-Define the predictors and markers of MZL transformation to diffuse large B-cell lymphoma that can be incorporated into treatment programs -Define role of gluphostase in the development of MZL
Assessment Criteria, Response Evaluation, and surrogate endpoints in MZL	-Assessment and response criteria are those utilized in other lymphoma subtypes that usual present with nodal involvement, and few extranodal involvement and need to be further defined. -Disease specific endpoints are required that are specific to MZL	-Develop new response criteria -Further understand PET and other staging modalities -Develop response criteria for splenic marginal zone lymphoma for clinical trials -Define the role of minor response in MZL subtypes -Define CR in MZL subtypes -Define surrogate endpoints in MZL subtypes	-Develop novel genomic approaches to assess response and relapse -Develop MRD criteria

Session	Concerns/ Unaswered Questions	Immediate Action Solutions (1-5 Years)	Long-Term Solutions (More than 5 Years)
Marginal zone lymphoma targeted pathways	Drugable pathways and pre-clinical data are limited -Which drugs and which targets?	-Identify new pathways -Develop new pre-clinical data	-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 are not uniformly defined. -There appear to be geographic differences.	-Further define MZL lymphoma subtypes with larger data sets -Define which patients in each disease subset that need treatment -Define cure in the MZL subtypes -Define appropriate patients for clinical trials in MZL subtypes	-Determine how many diseases MZL represent
Treatment of MZL	-The treatment patterns vary and are not well standardized in MZL -Clinical trials routinely include the group of indolent with follicular lymphomas and MZL, and not MZL patients only. -MZL subtypes (EMZL, SMZL, NMZL) are not predefined in clinical trials -Treatment issue: local control versus long-term control -Orphan definition	-Further define areas of research for all subtypes of MZL -Define new clinical trial strategies -Clinical trials should be designed for MZL only. -Trials should define individual subsets -Orphan disease designation for individual subsets	-Define standards of care for each of the subtypes to benchmark new therapeutic approaches -Develop curative approaches to all subtypes of MZL

Summary

The MZL 2019 Scientific Workshop provided a collegial, collaborative environment for international experts in the field of MZL to discuss the current state of knowledge of the disease, with a goal of defining future directions that are necessary to move the field forward. Recent advances in targeted chemotherapy and immunotherapy have provided more treatment options for MZL, however, it remains unclear when patients with MZL should receive treatment, and how much treatment they should receive, particularly given the heterogeneous clinical presentation of MZL at different anatomic sites and given the relatively indolent clinical course of the disease. To ensure that MZL treatments do not cause more toxicity than they resolve, the international community of MZL researchers must form collaborations that further the understanding of the core biology and natural history of MZL, identify biomarkers correlative of disease progression and response, and further define the efficacy of different treatment options in specific anatomical sites and subtypes of MZL, which will allow clinicians to provide the optimal approaches to patients with the multifaceted disease of marginal zone lymphoma.

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Workshop Agenda

Day One: April 17, 2019

12:30 pm **Welcome and Opening Remarks**

12:45 pm **Biology and Pathology of Marginal Zone Lymphomas (MZL)**
Session Chair: Eric D. Hsi, MD, ***Cleveland Clinic***

Immunology of the Marginal Zone B-Cell
Andrea Cerutti, MD, PhD, *Icahn School of Medicine at Mount Sinai/ICREA*

Genomic, Transcriptomic, and Immune Profiling of MZL
Anne J. Novak, PhD, *Mayo Clinic, Rochester*

Panel Discussion

Extranodal MZLs

Pathology and Diagnosis of EMZL
Andrew Wotherspoon, MD, *Royal Marsden NHS Foundation Trust*

MALT Lymphoma: Deregulated Cellular Signalling
Ming-Qing Du, MD, PhD, *University of Cambridge*

Splenic and Nodal MZL

Pathology of Nodal and Splenic MZL
Eric D. Hsi, MD, *Cleveland Clinic*

Splenic and Nodal MZL: Pathogenesis
Davide Rossi, MD, PhD, IOSI, *Institute of Oncology Research*

Panel Discussion

3:15 pm **Break**

3:30 pm **Epidemiology, Transformation and MZL Signature in DLBCL**
Session Chair: Margaret A. Shipp, MD, ***Dana-Farber Cancer Institute***

MZL Epidemiology
James R. Cerhan, MD, PhD, *Mayo Clinic, Rochester*

MZL Transformation to Higher-Grade Lymphoma
Izidore S. Lossos, MD, *University of Miami Health System*

MZL in DLBCL
Margaret A. Shipp, MD, *Dana-Farber Cancer Institute*

Panel Discussion

5:00 pm **MZL Assessment Criteria and Response Evaluation**
Session Chair: Morton Coleman, MD, ***Weill Cornell Medicine***

Assessment Criteria/IPI
Catherine Thieblemont, MD, PhD, *CHU Paris-GH St-Louis Lariboisière F.Widal – Hôpital Saint-Louis*

Imaging/ Response Evaluation
Lale Kostakoglu, MD, MPH, *Icahn School of Medicine at Mount Sinai*

Panel Discussion

6:00 pm **New York Lymphoma Rounds and Workshop Dinner**
Workshop attendees attended a special session of Lymphoma Rounds, LRF's national CME program, which provides a forum for healthcare professionals to meet and address issues specific to the diagnosis and treatment of lymphoma patients. This evening's program featured Marginal Zone lymphoma cases.

7:30 am **MZL Treatment I**

Session Chair: Anas Younes, MD, *Memorial Sloan Kettering Cancer Center*

MZL Molecular Pathways and Targets
Anas Younes, MD, *Memorial Sloan Kettering Cancer Center*

MZL Treatment: Druggable Pathways and Pre-clinical Data
Francesco Bertoni, MD, *Institute of Oncology Research*

Standard Systemic Treatment
Peter Martin, MD, *Weill Cornell Medicine*

Radiation
Thomas Habermann, MD, *Mayo Clinic, Rochester*

Panel Discussion

9:00 am **Break**

9:15 am **MZL Treatment II: Disease Etiology and Natural History**

Session Chair: Thomas M. Habermann, MD, *Mayo Clinic, Rochester*

Nodal and Splenic
Catherine Thieblemont, MD, PhD
CHU Paris-GH St-Louis Lariboisière F.Widal - Hôpital Saint-Louis

MALT

Ocular Adnexa
Andrés J. M. Ferreri, MD, *San Raffaele Scientific Institute*

Bronchial-Associated Lymphoid Tissue (BALT) Lymphomas
David J. Straus, MD, *Memorial Sloan Kettering Cancer Center*

Salivary, Dural and Other Sites
Thomas M. Habermann, MD, *Mayo Clinic, Rochester*

Cutaneous Marginal Zone Lymphoma
Cynthia M. Magro, MD, *Weill Cornell Medicine*

Gastric Marginal Zone Lymphoma
Emanuele Zucca, MD, *Oncology Institute of Southern Switzerland, University of Bern/ IELSG, Director of the Operation Office*

Panel Discussion

12:00 pm **Lunch/ MZL Clinical Trials I: Summary of Ongoing Industry-Published Trials**

Session Co-Chairs: Michael E. Williams, MD, *University of Virginia* and Emanuele Zucca, MD, *Oncology Institute of Southern Switzerland, University of Bern/IELSG*

AstraZeneca – Kathleen Reed, *Hematology Medical Science Liaison*

BeiGene – William Reed, MD, *Senior Medical Director, Hematology*

Genentech – Michael Wei, MD, PhD, *Medical Director, Product Development, Oncology*

Kite, a Gilead Company – Mauro Avanzi, MD, PhD, *Director, Clinical Development*

Verastem – Kirk Taylor, MD, Senior Vice President, *Medical Affairs Strategy and Operations*

1:15 pm **MZL Clinical Trials II: Summary of Ongoing Investigator-Initiated Trials**

Session Chair: Emanuele Zucca, MD, *Oncology Institute of Southern Switzerland, University of Bern/IELSG*

U.S. Studies Summary
Michael E. Williams, MD, *University of Virginia*

European Studies Summary
Christian Buske, MD, *University Hospital of Ulm*

Panel Discussion

2:45 pm **Workshop Summary and Panel Discussion**

MZL Scientific Workshop Co-chairs and Steering Committee Members

4:00 pm **MZL Scientific Workshop Adjourns**

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