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FEBRUARY 2025 | Vol 39 • No 1

Insights, Knowledge Gaps, and Priorities in

Marginal Zone Lymphoma Research

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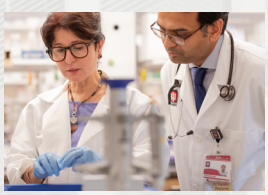

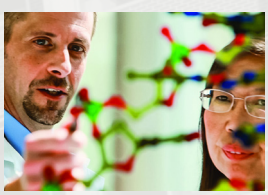

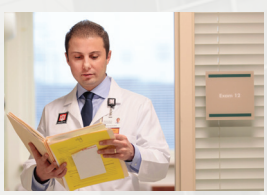

2020s

Lead site for promising first-in-human clinical trial for patients with relapsed multiple myeloma.
– Attaya Suvannasankha, MD

IU Simon Cancer Center earned Comprehensive Cancer Center status, the NCI's highest designation, and became a National Comprehensive Cancer Network member.

IU Health Medical Center and IU Simon Comprehensive Cancer Center mapped pancreatic cancer tumor neighborhoods, one of the country's highest-volume pancreatic cancer programs.
– Ashiq Masood, MD

Launched a first-of-its-kind personalized therapy study of Black women with breast cancer to improve treatment outcomes through genetic and ctDNA data.

– Tarah Ballinger MD and Bryan P. Schneider, MD

Completed the most extensive mapping of healthy breast cells to enhance the understanding of breast cancer development across genetic ancestries.

Initiated new clinical trial for targeted therapy drug for treatment-resistant testicular cancer patients.
– Nabil Adra, MD

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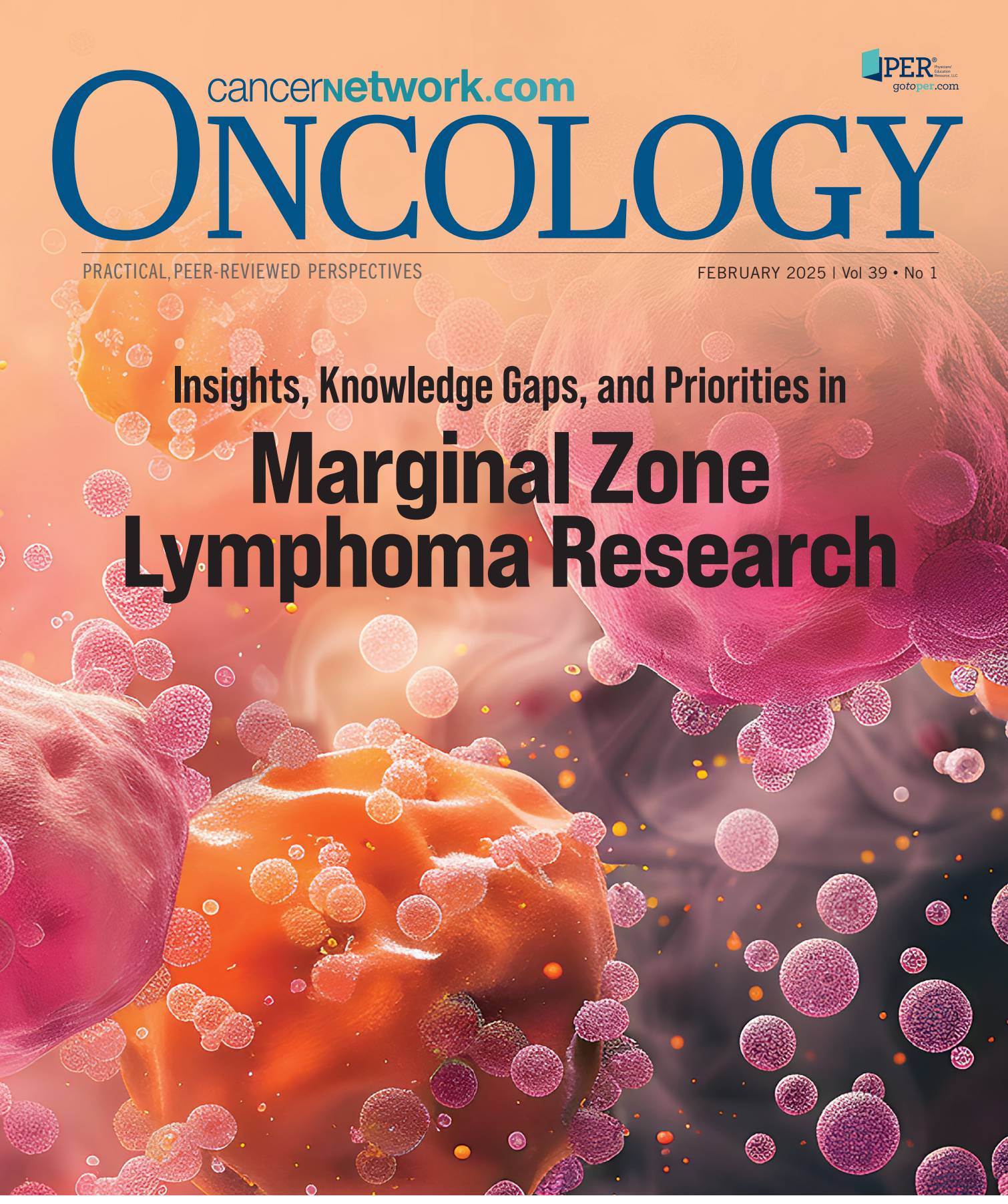

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The Potential for Improved Processes, Outcomes, and Economics of Health Care

Rapid Reporter
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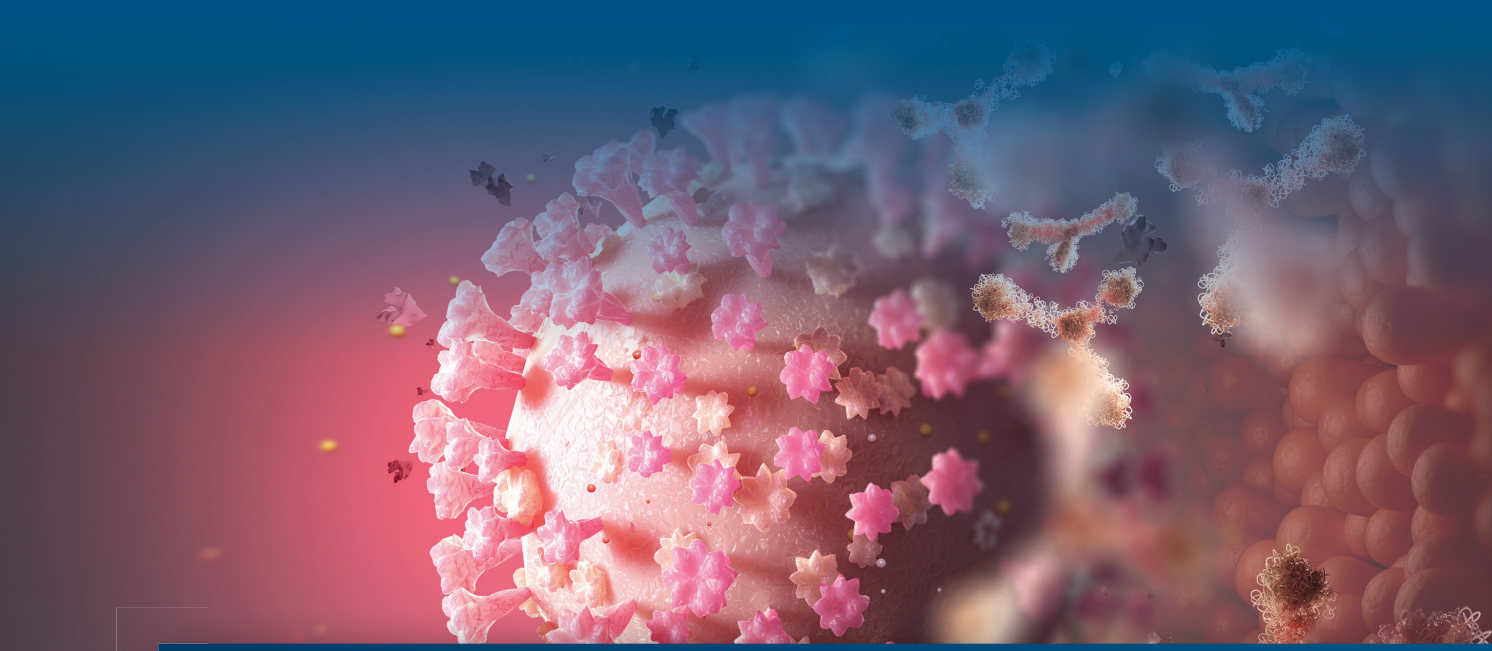

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Our Board Members Have Been Busy!

Take a look to see what they've been up to.

Matthew Matasar, MD, MS
Cancer Survivorship Editorial Advisory Board Member
During the 66th American Society of Hematology Annual Meeting and Exposition, Matasar presented findings on odronextamab monotherapy for patients with diffuse large B-cell lymphoma as part of the phase 1 ELM-1 study (NCT02290951). During the conference, Matasar spoke with CancerNetwork® regarding the trial. You can view the full video here: cancernetwork.com/view/odronextamab-demonstrates-safety-in-treating-dlbcl-population

John L. Marshall, MD
Gastrointestinal Cancer Editorial Advisory Board Member
Marshall has been recognized as one of the Top Doctors in 2025 by Castle Connelly. This is the sixth time he has been given this award, with the first being in 2016. Congratulations to Dr Marshall on this wonderful recognition.

Correction Issued: The December 1, 2024, CME article entitled "3 Things You Should Know About Hemolytic Anemias" was published with an error. As of the date of publication, rilzabrutinib remains under review for approval in immune thrombocytopenia. This error has been addressed as of January 16, 2025, and content has been adjusted as follows:

The text has been updated to: Rilzabrutinib may inhibit the production of autoimmune antibodies.[17]

TO VIEW THE FULL CORRECTED ARTICLE, VISIT
cancernetwork.com/view/3-things-you-should-know-about-hemolytic-anemias

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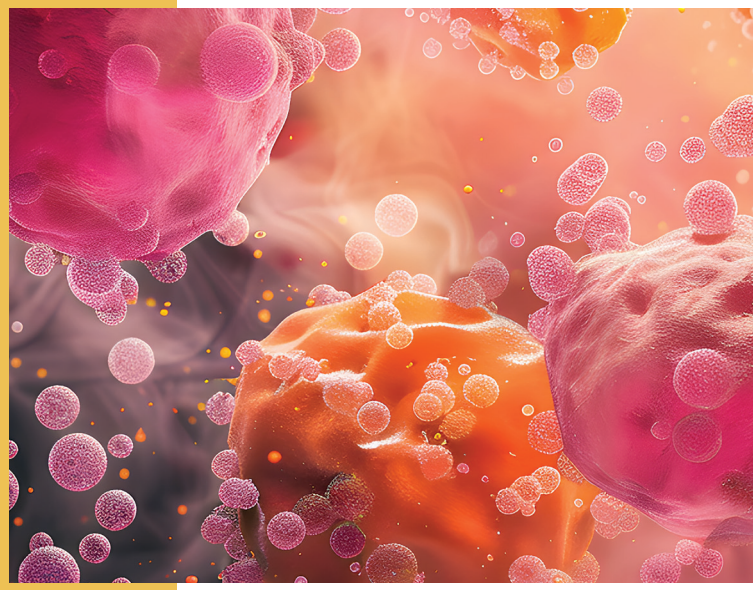

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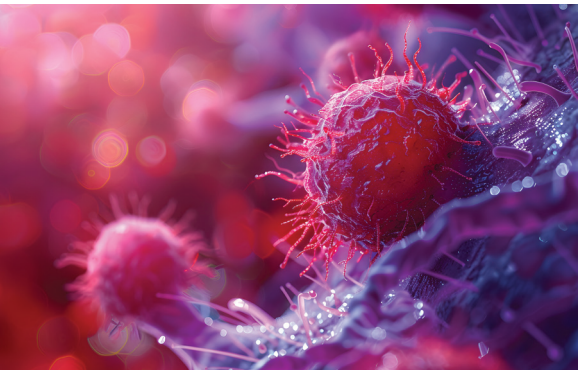
ONCOLOGY and its website, CancerNetwork.com, provide oncologists with the practical, timely, clinical information they need to deliver the highest level of care to their patients. Expert authors and peer review ensure the quality of *ONCOLOGY* and CancerNetwork.com's articles and features. Focused discussions capture key clinical take-aways for application in today's time-constrained practice environment.

MZL Expert Insights
Summit Sponsored by the Lymphoma Research Foundation

Marginal zone lymphoma (MZL) is a rare type of non-Hodgkin lymphoma that has several different subtypes and potential clinical presentations. The 3 subtypes—extranodal, nodal, and splenic—are typically indolent in nature at the time of diagnosis but can sometimes progress to a faster-growing clinical pattern or transform into a diffuse large B-cell lymphoma. With the rarity of this type of lymphoma, it is often difficult to gather clinical or research information to help the patients we treat. The Lymphoma Research Foundation is extremely helpful in supporting expert workshops in the research and treatment of rare types of lymphoma, such as MZL. This support has led to a working group that includes basic and translational/clinical researchers from North America and Europe who meet regularly and share their research. This collaboration and exchange supports the research in these rare lymphomas such as MZL.

The 2024 MZL Virtual Scientific Workshop included many physicians and researchers who discussed many aspects of MZL such as hematopathology, molecular diagnosis, potential causative agents, and treatments. The workshops always start with an introduction and history of the lymphoma type, including biology, pathology, epidemiology, treatments, and pathways to target novel treatments. *ONCOLOGY* is working with the Lymphoma Research Foundation to publish the report from the 2024 MZL Workshop so that all hematology/oncology physicians who care for these patients may benefit from this knowledge. Physicians from around the world participated in discussing hematopathology, molecular diagnosis, possible pathogenic agent associations, and standard and novel treatments.



Julie M. Vose, MD, MBA,
Payne Distinguished Chair in Hematology/Oncology Chief, Division of Hematology/Oncology University of Nebraska Medical Center

Despite understanding more about the molecular findings and diagnosis for MZL, in some recurrent cases, treatments remain difficult. Future clinical trials will need to subclassify patients with MZL in their own category and not categorize them with follicular lymphoma, which often happens. Molecular analysis of individual cases may lend itself to more personalized treatment options for patients with MZL.

Collaborations such as this one allow physicians and researchers from around the world to share knowledge and add a great deal of understanding about this uncommon type of lymphoma. The Lymphoma Research Foundation should be congratulated for their ongoing support of this and other similar workshops adding to the scientific knowledge of rare lymphoma subtypes. ■

For the 2L treatment of adult patients with aRCC

Explore the use of LENVIMA® + everolimus

Discover more about LENVIMA at **LENVIMAHCP.com**

Not an actual patient.

2L=second line; aRCC=advanced renal cell carcinoma.

INDICATION

LENVIMA is indicated, in combination with everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hypertension. In DTC (differentiated thyroid cancer), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC (renal cell carcinoma), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥100 mmHg. In HCC (hepatocellular carcinoma), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

Cardiac Dysfunction. Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Please see Selected Safety Information throughout and accompanying Brief Summary of full Prescribing Information.

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

Arterial Thromboembolic Events. Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

Hepatotoxicity. Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients; 2% of patients discontinued LENVIMA due to hepatic encephalopathy, and 1% discontinued due to hepatic failure.

Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Renal Failure or Impairment. Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus–treated patients (10% grade 3).

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

Proteinuria. In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3). Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria ≥2+ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Diarrhea. Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus–treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Fistula Formation and Gastrointestinal Perforation. Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

QT Interval Prolongation. In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

Hypocalcemia. In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus–treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Across clinical studies of 1823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events, of any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus–treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

Hemorrhagic Events (cont'd). Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Impairment of Thyroid Stimulating Hormone Suppression/ Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus–treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in HCC and 60% of LENVIMA + everolimus–treated patients in RCC.

Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease, or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.

Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for 30 days after the last dose.

Adverse Reactions

In RCC, the most common adverse reactions (≥30%) observed in LENVIMA + everolimus–treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 89% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients.

Use in Specific Populations

Because of the potential for serious adverse reactions in breastfed children, advise women to discontinue breastfeeding during treatment and for 1 week after the last dose. LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC (endometrial carcinoma) and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC and severe renal impairment. There is no recommended dose for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end-stage renal disease.

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with DTC, RCC, or EC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or EC and severe hepatic impairment.

For more information about LENVIMA, please see accompanying Brief Summary of full Prescribing Information.

Printed in USA/October 2024 LENV-US11120

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

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

Marginal Zone Lymphoma Workshop Cochairs

Thomas Habermann, MD
Professor of Medicine, Mayo Clinic Rochester, MN, Member of the Lymphoma Research Foundation's esteemed Scientific Advisory Board

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Deputy Head of the Division of Hematology of the Oncology Institute of Southern Switzerland IOSI,
Head of the Laboratory of Experimental Hematology at the Institute of Oncology Research IOR in Bellinzona, Switzerland

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 comprises 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 (1-5 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

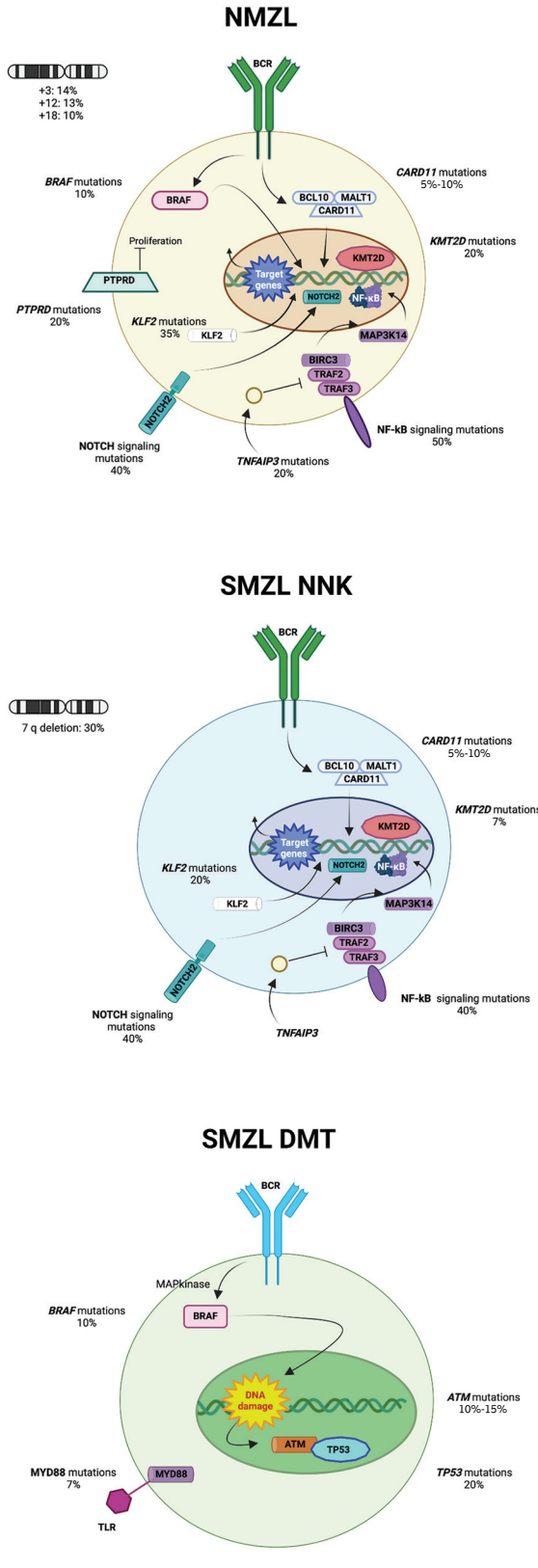
To kick off the workshop, Davide Rossi, MD, PhD, deputy head of the Division of Hematology of the Oncology Institute of Southern Switzerland and head of the Laboratory of Experimental Hematology at the Institute of Oncology Research in Bellinzona, Switzerland, provided an overview of the research advancements 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 Mayo Clinic, Rochester, Minnesota, 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/Waldenström 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, λ 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%-97% of cases).[1] 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,



NMZL, nodal marginal zone B-cell lymphoma; SMZL, splenic marginal zone lymphoma.

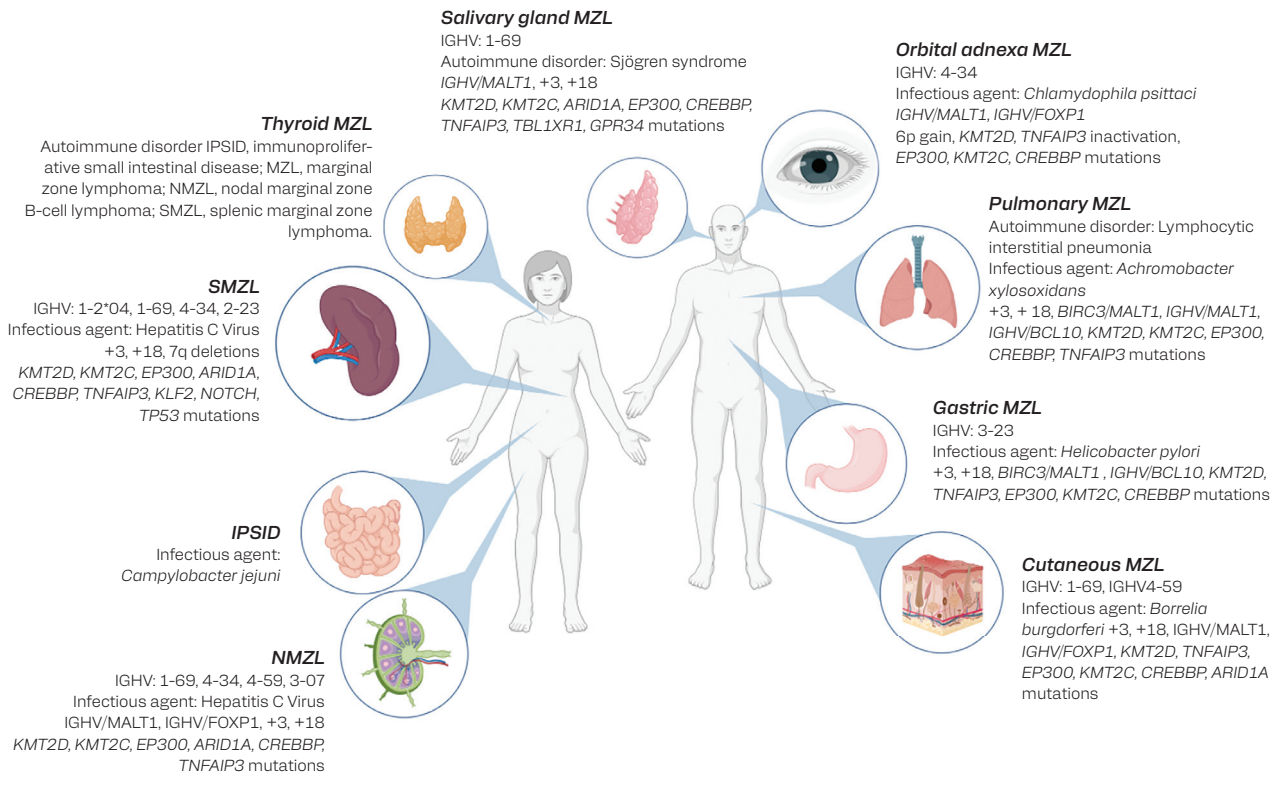
FIGURE 1. Key Molecular Alterations in NMZL and SMZL With NNK and DMT Genotypes
This is a schematic representation of the genes and pathways that are molecularly deregulated. The prevalence of these alterations is indicated alongside each gene or pathway, providing an overview of frequency and relevance.

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. Anatomical Representation of Various MZL Subtypes. This figure illustrates the anatomical distribution, molecular characteristics, and associated triggers of various subtypes of MZL.



IPSID, immunoproliferative small intestinal disease; MZL, marginal zone lymphoma; NMZL, nodal marginal zone B-cell lymphoma; SMZL, splenic marginal zone lymphoma.

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).[2] 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.

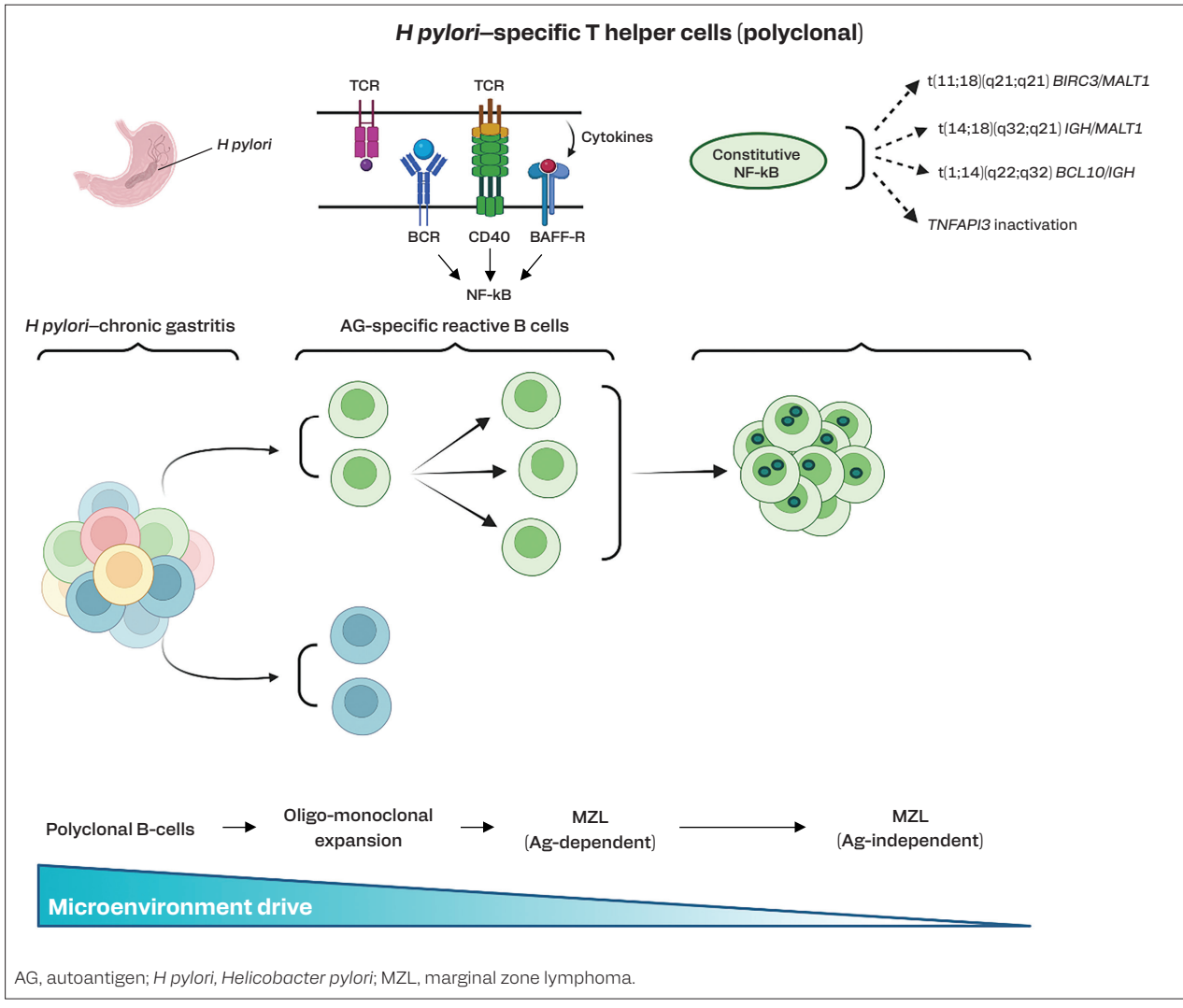
In addition, maybe the detection of sheets of blasts by the hematopathologist when diagnosing MZL may be linked to more aggressive behavior. Yet the books are still not closed [on] how to define these sheets of blasts. It's suggested that the monotonous proliferation of large cells that are more than 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 intratumoral 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*, *Chlamydophila 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,



AG, autoantigen; *H pylori*, *Helicobacter pylori*; MZL, marginal zone lymphoma.

FIGURE 3. Overview of the Pathogenetic 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 NewYork-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.[3] 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 λ 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-kB 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 Martinez-Climent noted that it is not known how the *MYD88* mutation drives lymphomas with different clinical, histopathological, and immunological features. To investigate this question, Martinez-Climent's research

group crossed a murine line carrying MYD88^{L252P} 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.[4] A systematic review of lymphoma also found an overall response rate higher than 30% in the majority of studies.[5] 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).[6,7] 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, PKCβ, MALT1, and IKZF1/3. Combination trials are assessing PI3Kδ 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.[8]

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 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.[8-11] tMZL is tied to increased mortality and poor survival regardless of subtype.[8,12,13] 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.[9-15,16] 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.[17] 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 18fludeoxyglucose (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.[17] 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 excellent outcomes of these patients with localized extranodal MZL treated with radiation therapy. Thus when it is possible, this remains the preferred treatment strategy in this setting. Furthermore, prognosis was overall good regardless of whether the patient receives radiation therapy or [another] type of systemic therapy, underscoring the disease behavior is largely 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 course. 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 developed from the only randomized phase 3 clinical trial in extranodal MZL, IELSG-19 [NCT00210353].[1] 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 risk-stratify 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 demonstrating an IPI score of 2 or more received POLA-R-CHP [polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone].[2] 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 across multiple studies.... Importantly, we conducted a retrospective study in 237 patients treated with bendamustine [Bendeka] rituximab, and we observed that the CR rate was 81% and there were very few cases of progression of disease within 24 months.[3] In patients with advanced-stage extranodal MZL, bendamustine plus rituximab seems to be the regimen that has been associated with higher complete response, longer PFS, and lower incidence of POD24.

A caveat to mention about POD24 in MZL is a concept that was extrapolated from the LymphoCare study in follicular lymphoma, where it was defined as [POD24] after immunochemotherapy with R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone] and most recently with bendamustine rituximab.[3] It is an alkylating agent plus an anti-CD20. In MZL, single-agent rituximab is still commonly used, especially in splenic marginal zone lymphoma, and studies confirming shorter survival in MZL also included patients treated with this agent. Thus, this is an important caveat to consider when selecting second-line and beyond therapies in relapsed/refractory MZL.[4]

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 this is thise 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 and all the gastrointestinal tract are normally highly

FDG avid. Small lesions are difficult to differentiate from the physiologic background giving the erroneous conception that MZL is a nonFDG avid disease.

In clinical practice, if the lesion is located in, for example, the ocular adnexa, we usually perform an MRI of the eye that will better define those areas. For the gastrointestinal tract, especially in the stomach, we usually perform upper endoscopies with random biopsiesthat also help us to see the stomach and take biopsies to subsequently assess the response using the GELA histological grading system.[5]

At our institution, conducting staging PET/CT and CT with contrast, or MRI, depending on the disease location. In those patients with baseline FDG avid disease, we select PET/CT for response assessment. However, in patients with no baseline FDG-avid disease, then we conduct response assessment with CT, 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 / Metabolic tumor volume is an important biomarker associated with survival in lymphoma that accurately reflects the overall FDG-avid tumor burden. Metabolic tumor volume is calculated by setting a specific SUV threshold, commonly 41% of SUVmax or SUV of 4 or more, and the volumes of individual lesions are then added to derive the total tumor volume.

The challenge in extranodal MZL is that a significant number of patients will have small areas of disease located in organs with high FDG-avidity. This characteristic will make it difficult to calculate tumor volumes accurately. Furthermore, the role of metabolic tumor volume in patients with localized disease remains poorly understood. Another challenge is in splenic MZL where the bone marrow is regularly involved and remains problematic the inclusion of this tissue in tumor volume calculations.

Another PET/CT metric is SUVmax. However, the correlation between pretreatment FDG-avidity and prognosis in lymphoma remains unclear with some studies demonstrating worse outcomes in those with high pretreatment SUVmax in follicular lymphoma. In clinical practice, PET/CT also aids in the selection of areas with significantly higher SUVmax for tissue biopsy to rule out transformation to aggressive lymphoma. This event is highly relevant and informs treatment selection as transformation to large B-cell lymphoma requires an anthracycline-based regimen.

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 treatment data have originated in studies enrolling patients with follicular lymphoma and MZL. For example, the phase 3 BRIGHT trial [NCT00877006] and the phase 3 StiL NHL 1-2003 trial [NCT00991211] enrolled both histologies diseases, but study cohorts were largely composed of follicular lymphoma and MZL patients were evaluated as a single group.[6,7] The field needs to move now to focus on [MZL-based] studies, and ideally in the different subtypes. For example, different toxicities have been reported with bendamustine rituximab in extranodal MZL and splenic MZL. The [phase 2 BRISMA/IELSG36 trial (NCT02853370)].6 evaluated the safety and efficacy of this regimen in splenic MZL, reporting a higher incidence of infections compared to prior reports in extranodal MZL. Finally, fixed-duration programs are highly desired in indolent diseases such as MZL.

Also, the disease biology and clinical presentation are unique for each MZL subtype, underscoring the need for MZL-specific staging and response assessment criteria in practice and clinical trials. Finally, MZL is a rare disease, and multicenter efforts are needed to quickly complete accruing goals in clinical trials testing novel agents that may impact practice.

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

Alderuccio / It is important to highlight the need to consider modifications in the current Lugano classification towards MZL-specific criteria for staging and response assessment. For example, patients with extranodal disease <1.0 cm on scans do not present measurable disease by the current classification being a common scenario in extranodal MZL. Similarly, patients with splenic MZL may present a spleen <13 cm but symptoms and/or cytopenias and have diffuse FDG-avidity of the spleen. Based on the current classification, these patients may not be eligible for clinical trials.

Finally, I would like to mention again the need to incorporate quality-of-life metrics as clinical trial endpoints and the development of fixed-duration therapies for a disease largely characterized by indolent behavior.

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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).[18] 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
CISL (NCT01213095)[19]	Phase 2	R-CVP x6-8	R every 8w, x 12	47	100%	67%	33%	0%	81%
PLRG (NCT00801281)[20]	Phase 3	R-CVP x6-8 or R-CHOP x6-8	R every 8w, x 12	92	94%	NA	NA	NA	82%[a]
GALLIUM (NCT01332968)[21]	Phase 3	BR x6 or R-CVP x8 or R-CHOP x6	R every 8w, x 12	99	93%	24%	36%	39%	80%[a]
IELSG38 (NCT01808599)[22]	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; NA, not available; 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.

[a] 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 space?

Zelenetz / Some of the small molecules have proven to have efficacy in MZL. One of the first was the PI3K inhibitors, the PI3Kδ 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.[1]

Subsequently, additional studies have been done with other BTK inhibitors, including zanubrutinib [Brukinsa], which has FDA approval for the treatment of MZL.[2] 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 of 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.

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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.[19] 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 [NCT03322865]). 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 [Bruton 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 (older, 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.

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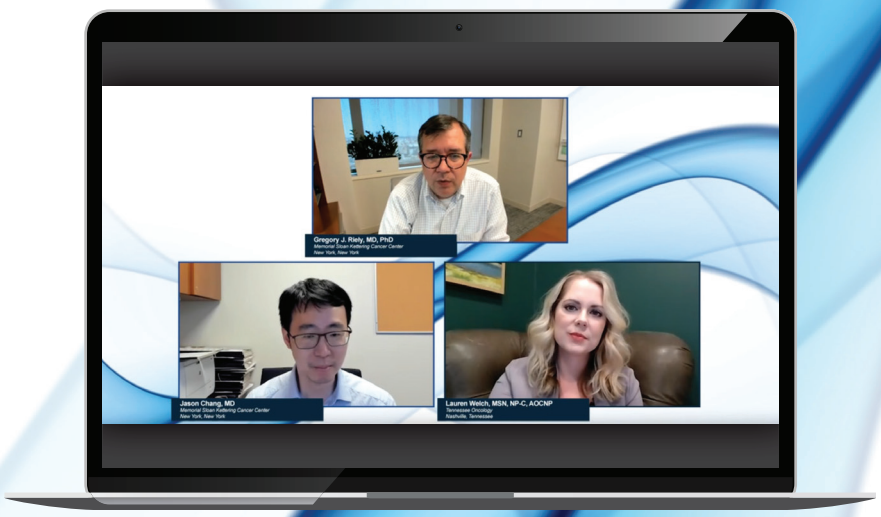

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3 Things You Should Know About Identifying and Treating Epithelioid Sarcoma

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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:
- Differentiate epithelioid sarcoma from other malignant and nonmalignant lesions by identifying key characteristics and the clinical presentation
- Implement a multidisciplinary management approach for epithelioid sarcoma including the roles of surgical oncology, pathology, radiation therapy, and medical oncology to optimize patient outcomes through coordinated care and individualized treatment planning.

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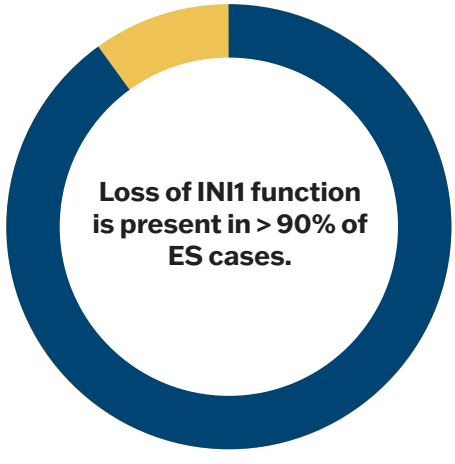
Epithelioid sarcoma (ES) is a rare form of soft tissue sarcoma (STS) that accounts for fewer than 1% of STS cases.[1] The disease is known for being difficult to diagnose and treat and for being associated with high rates of local recurrence (34%-77%) and metastasis (≈40%).[2] As such, it is important to have up-to-date and accurate information about ES. Here are 3 things you should know about identifying and treating ES.

1 ES is often misdiagnosed, but it has distinctive features that can aid in identification.

The incidence of ES in the United States is approximately 5 cases per million individuals.[3] Classic, or distal-type, ES usually presents as a painless, flesh-colored mass on the distal aspect of an extremity and sometimes with overlying ulceration, bleeding, or necrosis.[1,2] Proximal-type ES also appears as a painless lesion, but it can be located on the proximal extremity, trunk, or pelvis.[4] Thus, ES shares many presenting features with various soft tissue lesions, benign or malignant. It is therefore not surprising that it is often initially misdiagnosed.[5]

Given the ambiguous clinical features of ES, the diagnosis often hinges on microscopic appearance and genetic analysis. The distinctive mutation in ES is a loss of INI1 function, which is present in over 90% of tumors regardless of subtype.[6] Other molecular features of ES include the presence of vimentin, cytokeratin, and epithelial membrane antigen, although these are nonspecific markers.

As with all suspected cases of STS, it is recommended that possible ES lesions be evaluated by collaborating members of a multidisciplinary team who are experienced in the management of sarcomas.[7] Such a team will often include a medical oncologist, orthopedic surgeon, pathologist, radiation oncologist, and other supporting health care providers. A team approach helps to ensure that the diagnosis and treatment plan are both timely and accurate.



2 ES treatment follows guidelines, but it is individualized based on disease characteristics.

As with many other types of cancer, treatment for ES follows some general evidence-based guidelines. However, the treatment plan is developed individually by a multidisciplinary team and influenced by aspects of the disease and patient factors.

Wide surgical excision of the tumor with neoadjuvant or adjuvant radiation treatment of the tumor bed is the primary treatment of choice in most cases of ES.[2,7,8] Depending on the location and extent of local tumor invasion, limb-sparing surgery may or may not be feasible, with amputation being the alternative.[7,8] Perioperative radiation treatment effectively reduces rates of local recurrence, and it is recommended in all but the lowest stages of ES.[7,8]

Disease that recurs, metastasizes, or is diagnosed at an advanced stage is often treated with some form of systemic therapy (eg, traditional chemotherapy or targeted medication).[7] In addition to disease factors, individual patient characteristics must be considered, and shared decision-making is encouraged. Age, comorbidities, personal goals, and lifestyle factors all have the potential to tip the scales of treatment decisions.

3 Systemic treatment for ES is reserved for advanced cases, but it has improved with the addition of targeted therapy.

The use of systemic treatment for STS has traditionally been controversial, and it is reserved for advanced cases.[7,8] Indeed, NCCN guidelines only recommend systemic treatment when the primary tumor is unresectable, the disease is metastatic at diagnosis, or recurrence has occurred following primary treatment.[7] The prognosis for patients who qualify for systemic treatment is generally poor, with a median life expectancy of 8 months for metastatic ES.[2]

Historically, systemic treatment for advanced cases of ES has not been particularly promising. Two retrospective, single-arm cohort studies on traditional chemotherapy (specifically, anthracycline, gemcitabine, and/or ifosfamide-based regimens) for the treatment of ES did not demonstrate favorable outcomes. The overall response rates in both studies were around 15%, and progression-free survival ranged from 43.3 to 66.3 weeks.[9,10] Moreover, the results of 1 of these studies found that 50% of the patients experienced an adverse event during treatment.[9]

Mechanistic insight into the root cause of ES has led to the development of a promising targeted treatment, however. As mentioned above, over 90% of ES tumors demonstrate a loss of INI1 function.[6] INI1 is a tumor suppressor that inhibits the EZH2 enzyme, indirectly stimulating the transcription of tumor suppressor genes.[11] Tazemetostat is a novel EZH2 inhibitor that was developed to treat ES. In 2020,

Targeted treatment is now recommended for advanced ES.

the medication received accelerated approval and orphan drug status from the FDA for treating advanced ES based on results of a phase 2 clinical trial.[12] The study enrolled 62 patients; investigators found an objective response rate of 15%, with 26% of patients having disease control at 32 weeks of follow-up.[12] This has led to NCCN guidelines listing tazemetostat as the preferred treatment for recurrent, metastatic, or locally advanced and unresectable ES.[7] Additionally, tazemetostat is still being investigated in combination with doxorubicin as a first-line systemic therapy for advanced ES.[13]

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1 In the management of epithelioid sarcoma (ES), targeting EZH2 addresses which of the following features present in most cases leading to uncontrolled tumor growth?

A. Increased expression of INI1/SMARCB1 resulting in upregulation of EZH2
B. Increased expression of INI1/SMARCB1 resulting in downregulation of EZH2
C. Loss of INI1/SMARCB1 resulting in upregulation of EZH2
D. Loss INI1/SMARCB1 resulting in downregulation of EZH2

2 Your 21-year-old male patient is referred to you after an initial consult with an orthopedic surgeon who performed a core needle biopsy on a firm, nonmobile mass on his forearm that gradually increased in size over the past 18 months. MRI showed heterogeneous necrosis indicative of malignancy, but CT scans of the chest, abdomen, pelvis are negative for metastatic disease. Immunohistochemistry staining of the tumor is positive for CD34, cytokeratin, EMA, and vimentin, and negative for CD31, S-100, and INI1, confirming the diagnosis of ES. According to current data and guideline recommendations, what is the next best step in the management of this patient's ES at this time?

A. Doxorubicin
B. Gemcitabine plus docetaxel
C. Larotrectinib, 100 mg, orally twice daily
D. Tazemetostat, 800 mg, orally twice daily
E. Tazemetostat, 800 mg, orally twice daily plus doxorubicin

The Potential for Improved Processes, Outcomes, and Economics of Health Care

Nora Janjan, MD, MPSA, MBA

Inefficiencies in medicine are rampant in clinical care. Mounting regulations and demands from both public and private health insurance carriers fuel much of the inefficiency in health care. This includes 629 discrete regulatory requirements across 9 domains. The primary drivers of these 341 hospital- and 288 physician-related requirements are the Centers for Medicare & Medicaid Services, the Office of Inspector General, the Office for Civil Rights, and the Office of the National Coordinator for Health Information Technology.[1] In parallel with the burgeoning number of government bureaucrats responsible for writing and overseeing these regulations, medicine has had to expand its administrative staff. The average-sized hospital dedicates 59 full-time equivalent employees (FTEs) to regulatory compliance, over a quarter of which are doctors and nurses. Over two-thirds of FTEs associated with regulatory compliance are involved with conditions of participation and billing/coverage verification, which represents 63% of the total average annual cost of regulatory burdens. The pace of changes in regulations makes compliance challenging. Fraud and abuse laws are outdated and have not evolved to support new models of care.

Technology and Physician Burnout

The average hospital spends over a million dollars annually to meet administrative requirements and upgrades to information technology. Quality reporting requirements are often duplicative and have inefficient reporting processes, especially for practices involved in value-based purchasing models. Among other factors, this increase in the regulatory burden for medicine has significantly contributed to the continued rise in health care costs. Currently, health care dedicates over $39 billion per year to comply with the administrative aspects of regulations. Despite the injection of technologies that should eliminate many of these inefficiencies, physicians and other caregivers are struggling with burnout, especially in this post–COVID-19 era of medicine. Now artificial intelligence is hoped to relieve the predictable physician shortage and the weighty documentation tasks of physicians and other health care professionals. The advancements in medical outcomes have resulted from scientific breakthroughs—not bureaucrats.

Increasing Costs Relating to Health Care

The cost of American health care is borne by every taxpayer and through individuals directly paying for health insurance and out-of-pocket care. Among the ways the average taxpayer currently underwrites American health care are the following: (1) Medicare taxes; (2) income taxes that fund Medicaid, the Children's Health Insurance Program (CHIP), the Affordable Care Act (ACA) subsidies, and other health care programs and entities; (3) an individual's share of payment to a health care plan; (4) the increased cost of products to underwrite an employer's cost for health care insurance benefits to its employees; (5) costs of supplemental health insurance coverage; and (6) out-of-pocket costs.

When someone retires, they continue to

pay income taxes on their Social Security income and pay Medicare premiums. Supplemental health insurance is often recommended to cover the approximate 30% of health care expenses not covered under Medicare. Federal taxes subsidize the ACA and every other public health insurance program. The taxpayer's state taxes also help underwrite Medicaid and local health care entities and services. In all cases, health care plan deductibles and other out-of-pocket health care expenses remain an issue. At every turn, the taxpayer pays and pays. To paraphrase an old song, "Where has all the money gone?"

However, the enormous amount of money invested in our health care systems has not translated into a healthier America. In the US, the 2022 per capita health care expenditures averaged $12,555, which was about $6000 greater than in other high-income countries.[2,3] The total national health care expenditures in 2019, before the pandemic, equaled $3.8 trillion, reaching $4.5 trillion in 2022, consistently representing about 17.5% of the gross domestic product.[3-5] The total national health care expenditures in 2022 were $200 billion greater than health care costs at the height of the pandemic in 2021. Over the past 2 decades, multiple studies have found that 15% to 25% of total health care expenditures are spent on overall administrative costs.[6] Beyond regulatory costs alone, the most prevalant administrative costs are billing and coding, including follow-up of accounts billed to insurance companies, and health care system administration.[7-9] In 2019, nearly $1 trillion was spent on 5 administrative areas that included financial transactions, industry-agnostic corporate functions, industry-specific operational functions, customer and patient services, and administrative clinical support functions.[10] These administrative costs to medical practices, however, do not include the federal and state infrastructure needed to manage governmental health care programs.

Private vs Public Insurance Funding

About 48% of Americans have employer-based private insurance, while 23% are exclusively covered under a public health care plan. Medicaid/CHIP and Medicare were the most common public health care plans in 2022, covering about 21% and 15% of the population in America, respectively. In 2008, 54% of Americans had employer-based health insurance, and only 13% and 11% were insured by Medicaid and Medicare, respectively.[11] Funded by both the federal government and the individual states, Medicaid benefits are administered by the states under federal requirements. Medicaid covers 17% of adults between the ages of 19 and 64 years, 40% of children, and 33% of people with disabilities. Direct purchase health care under the subsidized ACA covered only about 10% of the US population in 2023, costing the US taxpayer $2.0 trillion in federal subsidies.[12] By 2034, the annual amount of federal subsidies for the ACA is projected to nearly double, reaching $3.5 trillion per year or 8.5% of the gross domestic product. In fiscal year 2020, the Department of Health and Human Services (HHS) proposed $1.2 trillion in mandatory funding and $87.1 billion in discretionary budget authority.[12] The post–COVID-19 proposed HHS budget for 2025 included $1.7 trillion in mandatory funding and $130.7 billion in discretionary budget authority, representing a 50% increase over the discretionary funding requested in 2020.[13,14] Simply put, these budgetary increases are unsustainable.

Physicians Feel the Impact of Regulatory Decisions

The increased regulatory load has also impacted the demographics of medical practice. Over the past decade, more than half of all physicians have become health system employees, increasing to nearly 70% of physicians under the age of 45.[15,16] Contributing to this shift in medical practice, physicians are encumbered by student loans and the inordinate costs of establishing and running a credentialed medical practice. Even in the past, the business of medicine was never included in the medical school curriculum. Due to deliberate shifts in reimbursement patterns to effect change, private medical practices have been acquired by health care conglomerates. For politicians in Washington, DC, it is easier to effect changes in health care when interacting with a few large corporate entities rather than thousands of independent private practice physicians. As more physicians become employees, medical societies, which represent physicians, have less influence on health care policy than large health care systems. Despite the dedication of health care professionals during the pandemic and an approximate 20% cumulative inflation rate over the past 4 years, another approximate 2.8% cut in Medicare reimbursement was scheduled for 2025. When adjusted for inflation, Medicare reimbursement has dropped 29% since 2001.[17]

Everyone in medicine is frustrated by the inefficiencies of a broken system restricted by regulations and administrative waste. Although many in medicine will oppose it, the Department of Government Efficiency (DOGE) will address the inefficiencies and unnecessary regulations within the health care system that are ineffective in improving the health care and health of Americans. The economic cost of health care to the nation and the individual taxpayer is enormous and unsustainable. The onerous health care costs and often unnavigable health care system that has developed with burgeoning regulations place massive burdens on our patients and every taxpayer. It will then be up to medicine to respond when inefficiencies within health care programs are eliminated by DOGE. ■

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Continuing Medical Education

Follow-Up VISIT from PER®

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3 Things You Should Know About Adverse Events With Targeted Therapies for DLBCL

RELEASE DATE: February 1, 2025
EXPIRATION DATE: February 1, 2026

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:
- Recognize adverse events associated with the different classes of targeted therapies used in relapsed/refractory DLBCL
- Formulate strategies for the monitoring, identification, and mitigation of toxicities linked to targeted agents in patients with DLBCL

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Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) are adverse events (AEs) of particular concern with bispecific antibodies (BsAbs) and chimeric antigen receptor (CAR) T-cell therapies used in treating diffuse large B-cell lymphoma (DLBCL).[1] Here are 3 things you should know about managing these AEs.

1 CRS and ICANS are AEs of particular concern with bispecific antibody and CAR T-cell therapy.

The hallmark symptom associated with CRS is fever. Hypoxia, hypotension, tachypnea, nausea, headache, fatigue, myalgia, and malaise can also occur, typically after administration of the CAR T-cell product or the first full dose of bispecific antibodies. ICANS can cause delirium, dysgraphia, tremor, lethargy, difficulty concentrating, agitation, confusion, expressive aphasia, apraxia, depressed level of consciousness, encephalopathy, and seizures. CRS and ICANS can result from administration of either CAR T-cell therapy or bispecific antibodies (**Table 1**).[2-5]

2 Guidelines help grade and manage CRS and ICANS.

Several grading systems have been developed for CRS and ICANS. The American Society for Transplantation and Cellular Therapy (ASTCT) created a consensus tool to harmonize the various definitions and grading systems for both AEs (**Table 2**).[6]

3 Antibody-drug conjugates are associated with unique toxicity profiles.

Guidelines for the treatment of DLBCL include several antibody-drug conjugates (ADCs) in various lines of therapy.[7] Each ADC presents a unique toxicity profile. Polatuzumab vedotin (pola) can be coadministered with bendamustine with or without rituximab, a combination that can pose a challenge to patients with preexisting neuropathy. In a single-arm phase 1b/2 trial (NCT02257567), the most common AEs of grade 3 or greater in the pola plus bendamustine and rituximab (pola-BR) and BR only arms were neutropenia (46.2% and 33.3%), anemia (28.2% and 17.9%), thrombocytopenia (41% and 23.1%), and

TABLE 1. Rates of CRS and ICANS in Trials With CAR T-Cell Therapy and Bispecific Antibodies

	CAR T-CELL THERAPY		BISPECIFIC ANTIBODIES	
Drug	**Axi-cel**	**Liso-cel**	**Epcoritamab**	**Glofitamab**
Trial	ALYCANTE[2] (NCT04531046)	TRANSFORM-1[3] (NCT04472598)	EPCORE NHL-1[4] (NCT03625037)	Phase 2[5] (NCT03075696)
CRS				
Any grade, %	93.5	49	51.0	63.0
Grade 3+, %	8.1	1	3.2	3.9
Time to onset (range)	1.5 days (1.0-3.0)	5.0 days (1-63)	15 days (1-23)	13.6 hours[a] (6-52)
Duration (range)	5.0 days (4.0-9.0)	4.0 days (1-16)	2 days	30.5 hours (0.5-317.0)
ICANS				
Any grade, %	51.6	11	6.4	7.8
Grade 3+, %	14.5	4	0.6	2.6
Time to onset, days (range)	6.0 (5.0-8.0)	11.0 (7-17)		
Duration, days (range)	5.0 (3.0-8.0)	4.5 (1-0)		

[a] From cycle 1 day 8 dose

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; liso-cel, lisocabtagene maraleucel.

TABLE 2. ASTCT CRS and ICANS Consensus Grading and Management[6]

ADVERSE EVENT	GRADE 1	GRADE 2	GRADE 3	GRADE 4
CRS				
Fever	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C
		With		
Hypotension	None	Not requiring vasopressors	Requiring vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or		
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, face mask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, or mechanical ventilation)
Management	Symptomatic treatment with antipyretics and IV fluids. Close monitoring.	Administer IV fluids and oxygen. Consider tocilizumab if symptoms persist.	Administer tocilizumab and/or corticosteroids. Intensive care support.	High-dose corticosteroids, tocilizumab, ICU care. Supportive therapy including mechanical ventilation.
ICANS				
ICE score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	None	None	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	None	None	None	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	None	None	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing triad
Management	Monitor closely. Symptomatic treatment.	Frequent neurological assessments. Consider corticosteroids.	Administer corticosteroids. Seizure precautions. ICU monitoring if needed.	High-dose corticosteroids, ICU care, anticonvulsants for seizure control.

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; EEG, electroencephalogram; ICANS, immune effector cell associated neurotoxicity syndrome; ICE, immune effector cell encephalopathy; ICP, intracranial pressure; ICU, intensive care unit; IV, intravenous.

infection (23.1% and 20.5%), respectively.[8] Peripheral neuropathy is an AE of particular concern with pola and was reported in 43.6% of patients. All cases were grade 1 or 2 and were resolved in most patients. Growth factor support for neutropenia and dose reductions or delays are management techniques for AEs due to pola.

Loncastuximab tesirine (lonca) is recommended as a third-line regimen for patients with DLBCL.[7] In the multicenter, single-arm, phase 2 LOTIS-2 trial (NCT03589469) of 145 patients, the most common grade 3 or higher treatment-emergent AEs (TEAEs) were neutropenia (26%), thrombocytopenia (18%), and increased gamma-glutamyl transferase (17%). A total of 39% of patients experienced serious AEs. Eight fatal TEAEs were reported, but none were

attributed to lonca.[9] Management of AEs associated with lonca includes dose delays or reductions and growth factor support. To mitigate these AEs, treatment with lonca is given at a higher dose for the first 2 doses and then the dose is lowered. Prophylaxis with dexamethasone is also used, and patients are advised to avoid sun exposure.

Brentuximab vedotin (BV) has not yet received FDA approval for use in patients with DLBCL; however, the phase 3 ECHELON-3 trial (NCT04404283) demonstrated improved outcomes with BV added to a regimen of lenalidomide and rituximab (BV-R2) vs lenalidomide and rituximab alone (R2).[10] In this trial, in the BV-R2 and R2 arms, grade 3 TEAEs were reported in 88% and 77% of participants, serious TEAEs were reported in 60% and 50% of participants, and grade 5 TEAEs were reported in 12% and 8% of participants, respectively. The most common TEAEs were neutropenia (46% vs 32%), anemia (29% vs 27%), and diarrhea (31% and 23%), respectively. Peripheral neuropathy of any grade was reported in 31% of patients in the BV-R2 arm and 24% of patients in the R2 arm. Grade 3 peripheral neuropathy occurred in 6% and 2% of patients, respectively. AEs were typically managed with dose delays or reductions and growth factor support. ■

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1 In the phase 2 EPCORE NHL-1 study (NCT03625037) that assessed the efficacy and safety of epcoritamab, a CD3 × CD20 T-cell–engaging bispecific antibody, 51% of patients developed CRS. What was the most common time to develop it?

A. After 1 cycle
B. Following the first full dose
C. After receiving 2 cycles
D. After receiving 3 cycles

2 In the phase 3 ECHELON-3 study (NCT04404283), which of the following was the most frequently occurring adverse event observed in patients who received brentuximab-vedotin in combination with lenalidomide-rituximab?

A. Anemia
B. Nausea
C. Neutropenia
D. Peripheral neuropathy

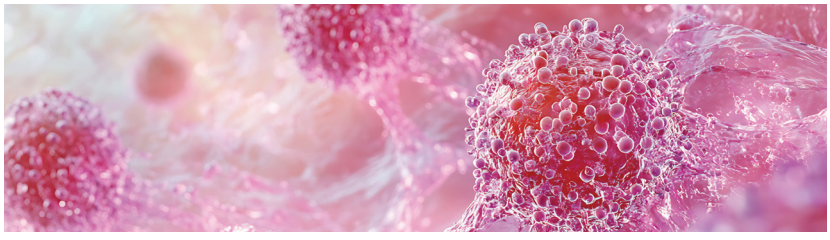
3 You are treating a patient with relapsed DLBCL after a recent CD19-directed CAR T-cell transplant. The patient developed myalgias, fever, tachycardia, and hypotension without hypoxia after the first dose. Upon further evaluation and workup, the patient is diagnosed with grade 2 CRS.
Which of the following treatment approaches would be most appropriate?

A. Monitor the patient carefully, but no other intervention needed.
B. Monitor carefully as outpatient for 8 hours, initiate IV fluids, and provide acetaminophen.
C. Admit to the hospital and provide IV fluids, acetaminophen, and corticosteroids.
D. Admit to the hospital, provide corticosteroids and tocilizumab.

ONCOLOGY CARE

Conference Compendium

ONCOLOGY reviews key trials from the 2024 San Antonio Breast Cancer Symposium. Highlights from the conference included increased efficacy for HER2-low/-ultralow populations, new surgical interventions, and reduced adverse effects.



Fam-Trastuzumab Deruxtecan-nxki Improves Efficacy in Metastatic Breast Cancer

The randomized, open-label phase 3 DESTINY-Breast06 trial (NCT04494425), which evaluated fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) compared with physician's choice of therapy (TPC) in patients with hormone receptor–positive and HER2-low/-ultralow metastatic breast cancer, showed improved progression-free survival (PFS) regardless of type of endocrine resistance and time to progression (TTP) on frontline endocrine therapy with CDK4/6 inhibition.

In the population of patients who had a TTP of less than 6 months, the median PFS was 14.0 months with T-DXd vs 6.5 months with TPC (HR, 0.38; 95% CI, 0.25-0.59). Patients with a TTP between 6 and 12 months had a median PFS of 13.2 months with T-DXd vs 6.9 months with TPC (HR, 0.69; 95% CI, 0.43-1.12). Patients who went more than 12 months before progressing on frontline therapy experienced a median PFS of 12.9 months with T-DXd vs 8.2 months with TPC (HR, 0.67; 95% CI, 0.51-0.88).

Moreover, the median PFS was 12.4 months (95% CI, 10.3-15.2) with T-DXd vs 6.6 months (95% CI, 5.4-7.4) with TPC in patients with primary endocrine resistance (HR, 0.57; 95% CI, 0.42-0.77). Patients with secondary endocrine resistance achieved a median PFS of 13.2 months (95% CI, 12.0-15.5) with T-DXd vs 9.5 months (95% CI, 8.0-11.1) with TPC (HR, 0.68; 95% CI, 0.55-0.84).

The study had previously met its primary end point, demonstrating an improvement in PFS in the HER2-low (HR, 0.62; $P<.0001$) population. A key secondary end point of PFS in the HER2-low/-ultralow population was also met (HR, 0.64; $P<.0001$).

The confirmed objective response rates were 57.8% and 25.7% with T-DXd and TPC, respectively, in patients with primary endocrine resistance, and 57.1% and 34.0%, respectively, in those with secondary endocrine resistance.

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Elacestrant/Abemaciclib Produces Clinical Benefit in Metastatic Breast Cancer

Results from an analysis of the phase 1b segment of the ELECTRA study (NCT05386108) and arm C of the phase 2 ELEVATE study (NCT05563220) showcased the clinical benefit and tolerable safety data of treatment with elacestrant (Orserdu) and abemaciclib (Verzenio) in patients with estrogen receptor–positive/HER2-negative advanced or metastatic breast cancer who had previous exposure to endocrine therapy and CDK4/6 inhibitors.

The pooled data of cohort 3 from ELECTRA and arm C of ELEVATE showed that when elacestrant was given at a daily dose of 345 mg plus abemaciclib at 150 mg twice daily (n=38), the regimen induced an objective response rate of 18%, which included a complete response rate of 5% and a partial response rate of 13%; the stable disease rate was 66% and 16% of patients experienced disease progression. The clinical benefit rate was 84%.

With a median follow-up of 7.5 months at data cutoff, efficacy-evaluable patients from the phase 1b portion of ELECTRA who received the doublet (n=27) experienced a median progression-free survival (PFS) of 8.7 months (95% CI, 6.1-16.6). When broken down further, those who previously received endocrine therapy and CDK4/6 inhibitors (n=24) experienced

a median PFS of 8.7 months (95% CI, 6.1-16.6), those with *ESR1* mutations (n=11) had a median PFS of 8.7 months (95% CI, 2.0-not calculable [NC]), and those without those mutations (n=12) had a median PFS of 7.2 months (95% CI, 1.9-NC). Those who received prior endocrine therapy plus CDK4/6 inhibition for 12 months or longer (n=16) experienced a median PFS of 16.6 months (95% CI, 7.5-NC).

Of note, evaluable patients from arm C of the ELEVATE study (n=26/30) had a median observational time for PFS of 4.6 months at data cutoff, and thus median PFS could not be assessed.

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Surgical Intervention Improves Efficacy in Young Patients With Breast Cancer

Patients with the *BRCA* gene and are 40 years or younger with breast cancer who underwent risk-reducing mastectomy (RRM) and/or risk-reducing salpingo-oophorectomy (RRSO) experienced higher rates of overall survival (OS), disease-free survival (DFS), and breast cancer-free interval (BCFI), according to findings from a retrospective, international cohort study.

At the median follow-up of 8.2 years (IQR, 4.7-12.8), 691 (13.0%) OS, 1928 (36.3%) DFS, and 1753 (33.0%) BCFI events were recorded.

For patients who experienced RRM, there was a notably reduced risk of DFS (adjusted HR [aHR], 0.58; 95% CI, 0.52-0.65) and BCFI (aHR, 0.55; 95% CI, 0.48-0.62) events, irrespective of *BRCA* gene, age at diagnosis, tumor subtype, tumor size, and nodal status. OS events were also noted (aHR, 0.65; 95% CI, 0.53-0.78).

At the time of RRM, the median age was 36.6 years (IQR, 33.0-39.6); the median time from diagnosis to RRM was 0.8 years (IQR, 0.5-2.7); median follow-up after RRM was 5.1 years (IQR, 2.7-8.3). Per the sensitivity analyses, only patients tested for *BRCA* before or at diagnosis were included (aHR, 0.61; 95% CI, 0.42-0.88), as well as those with delayed entry (aHR, 0.54; 95% CI, 0.44-0.66), and when the 3-year landmark analysis was performed (aHR, 0.57; 95% CI, 0.45-0.71).

For patients who experienced RRSO, there was a significant reduction in risk of BCFI (aHR, 0.65; 95% CI, 0.57-0.74) and DFS (aHR, 0.68; 95% CI, 0.61-0.77) events. There was also reduced risk of OS (aHR, 0.58; 95% CI, 0.47-0.70) events in this group, irrespective of age at diagnosis, tumor size, and nodal status. There was significant interaction with regard to tumor subtype (triple-negative breast cancer: aHR, 0.43; 95% CI, 0.32-0.58; hormone receptor–positive breast cancer: aHR, 0.80; 95% CI, 0.61-1.06) and specific to *BRCA* genes (*BRCA1*: aHR, 0.44; 95% CI, 0.34-0.57; *BRCA2*: aHR 0.85; 95% CI, 0.63-1.14).

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Neoadjuvant HER3-DXd Maintains Response Rates With Fewer TRAEs in Breast Cancer

Comparable pathological complete response (pCR) rates and objective response rates (ORR) with more favorable treatment-related adverse effect data were attained by neoadjuvant patritumab deruxtecan (HER3-DXd) with or without letrozole (Femara) compared with multi agent chemotherapy, based on results from the 3-arm, randomized, open-label phase 2 SOLTI VALENTINE trial (NCT05569811).

Data showed that the antibody-drug conjugate (ADC; n = 50) elicited a pCR rate of 4.0% (95% CI, 0.5%-13.7%) and an ORR of 70.0% (95% CI, 55.4%-82.1%). When paired with letrozole (n = 48), the pCR rate was 2.1% (95% CI, 0.1%-11.1%) and the ORR was 81.3% (95% CI, 67.4%-91.1%); 1 patient experienced progressive disease (PD). With standard multiagent chemotherapy (n = 24), the pCR rate was 4.2% (95% CI, 0.1%-21.1%) and the ORR was 70.8% (95% CI, 48.9%-87.4%); 1 patient had PD. In the total population of 122 patients, the pCR rate was 3.3% (95% CI, 0.9%-8.2%) and the ORR was 74.6% (95% CI, 65.9%-82.0%); 2 patients had PD.

Moreover, patritumab deruxtecan demonstrated biological evidence of antitumor activity, with a drop in Ki67, a switch to less proliferative PAM50 subtypes, and a decrease in risk of recurrence. The ADC also led to an increase in CelTIL score that correlated with treatment response.

Additional data showed that in the ADC arms, there was a significant change in CelTIL score from baseline to day 1 of cycle 2 and from baseline to surgery. Mafalda Oliveira, MD, PhD, of Vall d'Hebron Institute of Oncology, Spain, who presented the results, added that a link between CelTIL change from baseline to day 1 of cycle 2 and radiological response was observed. Lastly, there was a shift from high or medium risk of recurrence scores at baseline to low scores at the time of surgery; this was also true for the chemotherapy arm. ■

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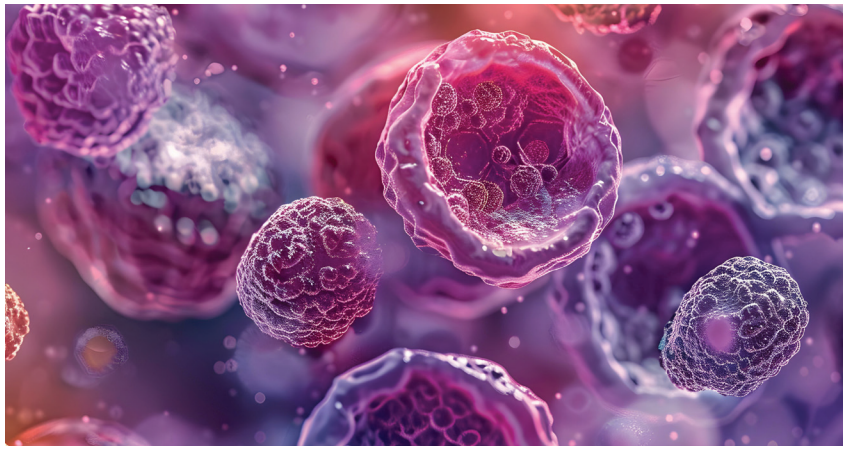
ONCOLOGY reviewed key presentations from the 66th American Society of Hematology Annual Meeting and Exposition. The focal points of the conference include positive results regarding a subcutaneous injection, minimal residual disease rates, and erythropoietin-stimulating agents used in hematologic malignancies.



Subcutaneous Epcoritamab Elicits Deep Responses in Heavily Pretreated CLL

Epcoritamab-bysp (Epkinly) monotherapy demonstrated clinical activity with deep responses in heavily pretreated patients with chronic lymphocytic leukemia (CLL), according to findings from the CLL expansion and optimization cohorts of the phase 1/2 EPCORE CLL-1 trial (NCT04623541).

Results showed that in the expansion cohort, which had a median follow-up of 22.8 months, the overall response rate (ORR) in response-evaluable patients (n=21) was 67% and the complete response (CR) rate was 43%. In those with TP53 aberrations (n=15), these rates were 67% and 33%, respectively; in the *IGHV*-unmutated group (n=16), these were 63% and 44%. In patients who were double-exposed to both Bruton tyrosine kinase and BCL-2 inhibitor (n=19), the ORR was 53% and the CR rate was 37%.

In the cycle 1 optimization (C1 OPT) cohort, which had a median follow-up of 2.9 months among 10 evaluable patients, the ORR was 60% and the CR rate was 10%.

Further efficacy findings showed that in the response-evaluable group of the expansion cohort, the partial response (PR) rate was 24%, the stable disease (SD) rate was 19%, and 5% of patients had progressive disease (PD). In those with TP53 aberrations, these rates were 33%, 13%, and 7%; in those with *IGHV*-unmutated disease, the rates were 19%, 19%, and 0%, respectively. In the double-exposed subgroup, these rates were 16%, 21%, and 5%, respectively.

In the C1 OPT cohort, the PR, SD, and PD rates were 50%, 20%, and 10%, respectively.

TO VIEW THE FULL ARTICLE AND REFERENCES, VISIT cancernetwork.com/ASH24_EPCORE

Overall MRD Negativity Rates Improved With Cilta-Cel vs SOC in MM

Results from the phase 3 CARTITUDE-4 trial (NCT04181827) showed that in patients with lenalidomide (Revlimid)-refractory multiple myeloma who already underwent 1 to 3 lines of therapy, cilta-cabtagene autoleucel (cilta-cel; Carvykti) elicited superior efficacy and response rates compared with standard-of-care (SOC) therapy.

Cilta-cel markedly improved overall minimal residual disease (MRD) negativity rates vs SOC, achieving 89% vs 38% at the 10^{-5} threshold and 86% vs 19% at the 10^{-6} threshold in evaluable patients. With cilta-cel, MRD-negativity onset was rapid, typically taking place within 2 months from the time of infusion. Further, an MRD benefit with cilta-cel was observed across all prespecified subgroups.

At a median follow-up of 33.6 months (range, 0.1-45.0), the secondary end point of overall MRD negativity in the intention-to-treat population with 10^{-5} sensitivity was 62.0% in the cilta-cel arm vs 18.5% in the SOC arm (OR, 7.6; $P<.0001$). In the population evaluable for MRD, the rates were 89.0% vs 37.9% (OR, 13.3; $P<.0001$), respectively. Rapid MRD negativity was observed in 48% of patients treated with cilta-cel by day 56, increasing to 60% by 6 months post-infusion. At the 10^{-6} MRD threshold, cilta-cel maintained superior rates at 57% vs 9% ($P<.0001$).

Cilta-cel improved MRD-negative complete response (CR) rates, with 44% of patients achieving MRD-negative CR or better at 12 months vs 8% with SOC. For these patients, median progression-free survival (PFS) exceeded 3 years, and overall survival (OS) was not reached.

Sustained MRD negativity (≥ 12 months apart) was achieved in 52% of the cilta-cel arm vs 10% of the SOC

arm ($P < .0001$). This corresponds with high rates of PFS and OS at 30 months (93.2% and 97.3% respectively). Among evaluable patients, 75% receiving ciltacel sustained MRD negativity compared with 50% on SOC ($P = .0159$).

TO VIEW THE FULL ARTICLE AND REFERENCES, VISIT
cancernetwork.com/ASH24_CARTITUDE4

ESAs Yield Response in VEXAS Syndrome With or Without MDS

Treatment with erythropoietin-stimulating agents (ESAs) and/or luspatercept (Reblozyl) demonstrated positive clinical efficacy and safety in patients with vacuoles in myeloid progenitors, E1 ubiquitin-activating enzyme, X-linked, autoinflammatory manifestations of the somatic (VEXAS) syndrome with or without myelodysplastic syndrome (MDS), based on results from a multicenter, retrospective study.

At week 16, hematologic improvement-erythroid (HI-E) was 38.8%, overall; 43.7% for no transfusion dependency (NTD); 25.6% for low transfusion dependency (LTD); and 23.0% for high transfusion dependency (HTD). A total of 2 responders, both with high transfusion burden (HTB), relapsed after 6.3 and 9.2 months, respectively. The remaining responders had responses between 4.3 and 96.0 months.

Additionally, baseline low levels of endogenous erythropoietin were associated with higher levels of HI-E. Lower rates and short-term responses to ESA, as well as the ability to identify patients with poorer outcomes, were correlated with red blood count transfusion dependence.

Also, 8 patients (1 with no transfusion dependency, 3 with low transfusion burden, and 4 with HTB) were treated with luspatercept using the approved schedule following ESA failure. Of the 8 patients, 7 had MDS; none had the *SF3B1* mutation. By week 16, 4 of the 8 (50.0%) patients had reached HI-E, 1 patient with NTD and 3 with LTD. No patients with HTB reached HI-E. Additionally, 3 of 4 patients that reached HI-E continued luspatercept and responded after 10, 15, and 16 months, respectively. Luspatercept treatment was discontinued by the last responders after 6 months; other therapeutic interventions were required for severe inflammation.

At week 16, the baseline predictive factor of HI-E response for ESA was age at ESA onset (risk ratio [RR], 1.00; 95% CI, 0.94-1.07), reticulocytes at ESA onset (RR, 0.99; 95% CI, 0.96-1.01), and platelet count at ESA onset (RR, 1.00; 95% CO, 0.99-1.01).

TO VIEW THE FULL ARTICLE AND REFERENCES, VISIT
cancernetwork.com/ASH24_VEXAS

Positive Efficacy and Safety Outcomes Results From Second-Line Liso-Cel in LBCL

According to real-world findings in patients with relapsed or refractory large B-cell lymphoma, treatment in the second line with CD19-directed, 4-1BB chimeric antigen receptor T-cell therapy lisocabtagene maraleucel (liso-cel; Breyanzi) yielded comparable safety and efficacy end points to those of the 2 pivotal trials that informed the FDA's approval.

Results from the observational, post-marketing study using data collected from the Center for International Blood and Marrow Transplant Research Registry were compared against the pivotal phase 3 TRANSFORM (NCT03575351) and phase 2 PILOT (NCT03483103) trials.

At a median follow-up of 6.4 months (95% CI, 6.1-6.5; range, 0.2-14.8) the median progression-free survival (PFS) and overall survival (OS) in the overall second-line cohort (n=156) was not reached (NR; 95% CI, NR-NR). In the TRANSFORM-ineligible cohort the median PFS and OS was NR (95% CI, 5.8-NR) and NR (95% CI, NR-NR), respectively. For the cohort of patients whose eligibility for TRANSFORM was unknown or eligible, the median PFS was NR (95% CI, 6.0-NR) and the median OS was NR (95% CI, NR-NR).

The 6-month PFS rates in the overall, TRANSFORM-ineligible, and TRANSFORM-unknown/eligible cohorts were 61% (95% CI, 52%-69%), 58.5% (95% CI, 48%-68%), and 65% (95% CI, 49%-77%), respectively. The 6-month OS rates in these respective populations were 87% (95% CI, 80%-92%), 85% (95% CI, 76%-91%), and 90% (95% CI, 76%-96%).

Additional efficacy findings illustrated that the objective response rate (ORR) in the second-line cohort was 84% (95% CI, 77%-89%), with a complete response (CR) rate of 70% (95% CI, 62%-77%). The ORRs in the TRANSFORM-ineligible and TRANSFORM-unknown/eligible cohorts were 84% (95% CI, 75%-90%) and 84% (95% CI, 71%-93%), respectively. The respective CRs in these populations were 68% (95% CI, 58%-76%) and 75% (95% CI, 60%-86%). The median duration of response (DOR) was NR in all 3 cohorts, with 6-month DOR rates of 73% (95% CI, 62%-81%), 70% (95% CI, 57%-80%), and 78% (95% CI, 59%-89%) in the second-line, TRANSFORM-ineligible, and TRANSFORM-unknown/eligible cohorts, respectively. ■

TO VIEW THE FULL ARTICLE AND REFERENCES, VISIT
cancernetwork.com/ASH24_TRANSFORM

IMPORTANT SAFETY INFORMATION (cont'd)

Thrombocytopenia and Neutropenia

- New or worsening thrombocytopenia, with platelet count less than 50×10^9/L, was observed in 20% of patients treated with OJJAARA. Eight percent of patients had baseline platelet counts less than 50×10^9/L.
- Severe neutropenia, absolute neutrophil count (ANC) less than 0.5×10^9/L, was observed in 2% of patients treated with OJJAARA.
- Assess complete blood counts (CBC), including platelet and neutrophil counts, before initiating treatment and periodically during treatment as clinically indicated. Interrupt dosing or reduce the dose for thrombocytopenia or neutropenia.

Hepatotoxicity

- Two of the 993 patients with MF who received at least one dose of OJJAARA in clinical trials experienced reversible drug-induced liver injury. Overall, new or worsening elevations of ALT and AST (all grades) occurred in 23% and 24%, respectively, of patients treated with OJJAARA; Grade 3 and 4 transaminase elevations occurred in 1% and 0.5% of patients, respectively. New or worsening elevations of total bilirubin occurred in 16% of patients treated with OJJAARA. All total bilirubin elevations were Grades 1-2. The median time to onset of any grade transaminase elevation was 2 months, with 75% of cases occurring within 4 months.
- Delay starting therapy in patients presenting with uncontrolled acute and chronic liver disease until apparent causes have been investigated and treated as clinically indicated. When initiating OJJAARA, refer to dosing in patients with hepatic impairment.
- Monitor liver tests at baseline, every month for 6 months during treatment, then periodically as clinically indicated. If increases in ALT, AST or bilirubin related to treatment are suspected, modify OJJAARA dosage based upon Table 1 within the Prescribing Information.

Major Adverse Cardiovascular Events (MACE)

- Another JAK inhibitor increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke [compared with those treated with tumor necrosis factor (TNF) blockers] in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated.
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Inform patients receiving OJJAARA of the symptoms of serious cardiovascular events and the steps to take if they occur.

Thrombosis

- Another JAK inhibitor increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated. Evaluate patients with symptoms of thrombosis and treat appropriately.

Malignancies

- Another JAK inhibitor increased the risk of lymphoma and other malignancies excluding nonmelanoma skin cancer (NMSC) (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated. Current or past smokers were at increased risk.
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

Adverse Reactions

- The most common adverse reactions (≥20% in either study) are thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, and nausea.

Organic Anion Transporting Polypeptide (OATP)1B1/B3 Inhibitors

- Momelotinib is an OATP1B1/B3 substrate. Concomitant use with an OATP1B1/B3 inhibitor increases momelotinib maximal concentrations (C_{max}) and area under the concentration-time curve (AUC), which may increase the risk of adverse reactions with OJJAARA. Monitor patients concomitantly receiving an OATP1B1/B3 inhibitor for adverse reactions and consider OJJAARA dose modifications.

Breast Cancer Resistance Protein (BCRP) Substrates

- Momelotinib is a BCRP inhibitor. OJJAARA may increase exposure of BCRP substrates, which may increase the risk of BCRP substrate adverse reactions. When administered concomitantly with OJJAARA, initiate rosuvastatin (BCRP substrate) at 5 mg and do not increase to more than 10 mg once daily. Dose adjustment of other BCRP substrates may also be needed. Follow approved product information recommendations for other BCRP substrates.

Pregnancy

- Available data in pregnant women are insufficient. OJJAARA should only be used during pregnancy if the expected benefits to the mother outweigh the potential risks to the fetus.

Lactation

- It is not known whether OJJAARA is excreted in human milk. Because of the potential for serious adverse reactions in a breastfed child, patients should not breastfeed during treatment with OJJAARA, and for at least 1 week after the last dose of OJJAARA.

Females and Males of Reproductive Potential

- Advise females of reproductive potential who are not pregnant to use highly effective contraception during therapy and for at least 1 week after the last dose of OJJAARA.

Hepatic Impairment

- Momelotinib exposure increased with severe hepatic impairment (Child-Pugh C). The recommended starting dose of OJJAARA in patients with severe hepatic impairment (Child-Pugh C) is 150 mg orally once daily. No dose modification is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B).

Please see Brief Summary of the full Prescribing Information on the following pages.

Reference: 1. OJJAARA (momelotinib). Prescribing Information. GSK; 2023.

PMUS-MMLJRNA240002 August 2024
Produced in USA.

Ojjaara (momelotinib) GSK

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
OJJAARA (momelotinib) tablets, for oral use

The following is a brief summary only; see full prescribing information for complete product information available at www.OJJAARAhcp.com

1 INDICATIONS AND USAGE

OJJAARA is indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Infections

Serious (including fatal) infections (e.g., bacterial and viral, including COVID-19) occurred in 13% of patients treated with OJJAARA. Infections regardless of grade occurred in 38% of patients treated with OJJAARA *[see Adverse Reactions (6.1)]*. Delay starting therapy with OJJAARA until active infections have resolved. Monitor patients receiving OJJAARA for signs and symptoms of infection and initiate appropriate treatment promptly.

Hepatitis B Reactivation

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase (ALT) or aspartate transaminase (AST), have been reported in patients with chronic hepatitis B virus (HBV) infection taking Janus Kinase (JAK) inhibitors, including OJJAARA. The effect of OJJAARA on viral replication in patients with chronic HBV infection is unknown. In patients with HBV infections, check hepatitis B serologies prior to starting OJJAARA. If HBsAg and/or anti-HBc antibody is positive, consider consultation with a hepatologist regarding monitoring for reactivation versus prophylactic hepatitis B therapy. Patients with chronic HBV infection who receive OJJAARA should have their chronic HBV infection treated and monitored according to clinical HBV guidelines.

5.2 Thrombocytopenia and Neutropenia

OJJAARA can cause thrombocytopenia and neutropenia *[see Adverse Reactions (6.1)]*.

New or worsening thrombocytopenia, with platelet count less than 50×10^9/L, was observed in 20% of patients treated with OJJAARA. Eight percent of patients treated with OJJAARA had baseline platelet counts less than 50×10^9/L.

Severe neutropenia, absolute neutrophil count (ANC) less than 0.5×10^9/L, was observed in 2% of patients treated with OJJAARA.

Assess complete blood counts (CBC), including platelet and neutrophil counts, before initiating treatment and periodically during treatment as clinically indicated. Interrupt dosing or reduce the dose for thrombocytopenia or neutropenia *[see Dosage and Administration (2.4) of full prescribing information]*.

5.3 Hepatotoxicity

Two of the 993 patients with MF who received at least one dose of OJJAARA in clinical trials experienced reversible drug-induced liver injury. Overall, new or worsening elevations of ALT and AST (all grades) occurred in 23% and 24%, respectively, of patients treated with OJJAARA; Grade 3 and 4 transaminase elevations occurred in 1% and 0.5% of patients, respectively. New or worsening elevations of total bilirubin occurred in 16% of patients treated with OJJAARA. All total bilirubin elevations were Grades 1-2. The median time to onset of any grade transaminase elevation was 2 months, with 75% of cases occurring within 4 months.

Delay starting therapy in patients presenting with uncontrolled acute and chronic liver disease until apparent causes have been investigated and treated as clinically indicated. When initiating OJJAARA, refer to dosing in patients with hepatic impairment *[see Dosage and Administration (2.3) of full prescribing information]*.

Monitor liver tests at baseline, every month for 6 months during treatment, then periodically as clinically indicated. If increases in ALT, AST or bilirubin related to treatment are suspected, modify OJJAARA dosage based upon Table 1 *[see Dosage and Administration (2.4) of full prescribing information]*.

5.4 Major Adverse Cardiovascular Events (MACE)

Another JAK inhibitor increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke [compared with those treated with tumor necrosis factor (TNF) blockers] in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Inform patients receiving OJJAARA of the symptoms of serious cardiovascular events and the steps to take if they occur.

5.5 Thrombosis

Another JAK inhibitor increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated.

Evaluate patients with symptoms of thrombosis and treat appropriately.

5.6 Malignancies

Another JAK inhibitor increased the risk of lymphoma and other malignancies excluding nonmelanoma skin cancer (NMSC) (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated. Current or past smokers were at increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risk of Infections and Hepatitis B Reactivation *[see Warnings and Precautions (5.1)]*
- Thrombocytopenia and Neutropenia *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions (5.4)]*
- Thrombosis *[see Warnings and Precautions (5.5)]*
- Malignancies *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OJJAARA was evaluated in 215 patients in 2 clinical trials (MOMENTUM and SIMPLIFY-1 anemic subgroup [hemoglobin (Hb) <10 g/dL]) *[see Clinical Studies (14) of full prescribing information]*.

MOMENTUM

Patients in the MOMENTUM trial had been previously treated with a JAK inhibitor and were randomly assigned 2:1 to receive double-blind OJJAARA 200 mg orally once daily (n = 130) or danazol 300 mg orally twice daily (n = 65) for 24 weeks, after which they were eligible to receive open-label OJJAARA in an extended treatment phase. Among patients who received OJJAARA, 72% were exposed for 24 weeks or longer and 52% were exposed for 48 weeks or longer *[see Clinical Studies (14) of full prescribing information]*.

Serious adverse reactions occurred in 35% of patients who received OJJAARA during the randomized treatment period of the MOMENTUM trial; the most common serious adverse reactions (≥2%) included bacterial infection (8%), viral infection (5%), hemorrhage (4%), acute kidney injury (3%), pneumonia (3%), pyrexia (3%), thrombosis (3%), syncope (2%), thrombocytopenia (2%), and renal and urinary tract infection (2%). Fatal adverse reactions occurred in 12% of patients who received OJJAARA; the most common (≥2%) fatal adverse reaction was viral infection (5%).

Permanent discontinuation of OJJAARA due to an adverse reaction occurred in 18% of patients during the randomized treatment period of the MOMENTUM trial. Adverse reactions that resulted in permanent discontinuation (≥2%) included viral infection (2%) and thrombocytopenia (2%). Dosage reduction or treatment interruption due to an adverse reaction occurred in 34% of patients. Adverse reactions requiring dosage reduction and/or treatment interruption (≥2%) included thrombocytopenia (13%), bacterial infection (2%), diarrhea (2%), and neutropenia (2%).

Among the 130 patients treated with OJJAARA during the randomized treatment period of MOMENTUM, the most common adverse reactions (≥20%) were thrombocytopenia, diarrhea, hemorrhage, and fatigue (Table 1).

(continued on next page)

ADVERSE REACTIONS (*cont'd*)

Clinical Trials Experience (*cont'd*)

Table 1: Adverse Reactions Occurring in ≥5% of Patients Receiving OJJAARA during Randomized Treatment in MOMENTUM

Adverse Reaction	OJJAARA n = 130		Danazol[a] n = 65	
	All Grades[b] %	Grade ≥3 %	All Grades %	Grade ≥3 %
Thrombocytopenia[c]	28	22	17	12
Diarrhea[c]	22	0	9	2
Hemorrhage[c]	22	2	18	8
Fatigue[c]	21	2	20	5
Nausea[c]	16	2	9	3
Bacterial infection[c,d]	15	8	18	8
Abdominal pain[c]	13	1	18	3
Viral infection[c,d]	12	5	3	0
Pruritus[c]	11	2	11	0
Elevated liver enzymes[c]	10	2	9	3
Pyrexia[c]	10	2	8	0
Cough[c]	8	0	5	0
Paresthesia[c]	8	1	2	0
Dizziness[c]	8	2	2	0
Vomiting[c]	8	1	0	0
Rash[c]	6	0	11	0
Renal and urinary tract infection[c,d]	6	2	11	5
Arrhythmia[c]	5	1	6	2
Neutropenia	5	5	3	3

[a]Study was not designed to evaluate meaningful comparisons of the incidence of adverse reactions across treatment groups.
[b]Adverse reactions graded using CTCAE v.5.
[c]Grouped term includes other related terms.
[d]Excludes opportunistic infections.

SIMPLIFY-1

Patients in the SIMPLIFY-1 trial were JAK inhibitor naïve and randomly assigned 1:1 to receive double-blind OJJAARA 200 mg orally once daily (n = 215) or ruxolitinib 5 to 20 mg orally twice daily (n = 217). Upon completion of the double-blind treatment phase, all patients were eligible to receive OJJAARA during the open-label phase. The safety of OJJAARA was evaluated in the population of patients with MF who were anemic at study entry. SIMPLIFY-1 enrolled 180 anemic patients who received OJJAARA (n = 85) or ruxolitinib (n = 95). Among these anemic patients who received OJJAARA, 78% were exposed for 24 weeks or longer and 61% were exposed for 48 weeks or longer [*see Clinical Studies (14) of full prescribing information*].

Serious adverse reactions occurred in 28% of the anemic patients who received OJJAARA during the randomized treatment period of the SIMPLIFY-1 trial; the most common serious adverse reactions (≥2%) included bacterial infection (7%), pneumonia (6%), heart failure (4%) arrhythmia (2%), and respiratory failure (2%). A fatal adverse reaction (bacterial infection) occurred in 1 patient who received OJJAARA.

Permanent discontinuation of OJJAARA due to an adverse reaction occurred in 19% of the anemic patients during the randomized treatment period of the SIMPLIFY-1 trial. Adverse reactions that resulted in permanent discontinuation of OJJAARA (≥2%) included bacterial infection (2%), dizziness (2%), fatigue (2%), hypotension (2%), and thrombocytopenia (2%). Dosage reductions or treatment interruptions of OJJAARA due to an adverse reaction occurred in 21% of patients. Adverse reactions requiring dosage reduction and/or treatment interruption (≥2%) were thrombocytopenia (8%), pneumonia (4%), bacterial infection (2%), abdominal pain (2%), elevated liver enzymes (2%), and hypotension (2%).

Among the 85 anemic patients treated with OJJAARA during the randomized treatment period of SIMPLIFY-1, the most common adverse reactions (≥20%) were dizziness, fatigue, bacterial infection, hemorrhage, thrombocytopenia, diarrhea, and nausea (Table 2).

Table 2: Adverse Reactions Occurring in ≥5% of Anemic Patients Receiving OJJAARA during Randomized Treatment in SIMPLIFY-1

Adverse Reactions	OJJAARA n = 85 Baseline Hb <10 g/dL		Ruxolitinib[a] n = 95 Baseline Hb <10 g/dL	
	All Grades[b] %	Grade ≥3 %	All Grades %	Grade ≥3 %
Dizziness[c]	24	1	15	2
Fatigue[c]	22	0	25	1
Bacterial infection[c,d]	21	8	12	2
Hemorrhage[c]	21	1	18	2
Thrombocytopenia[c]	21	11	34	6
Diarrhea[c]	20	1	20	1
Nausea[c]	20	0	3	1
Abdominal pain[c]	18	1	14	1
Cough[c]	14	0	11	0
Hypotension[c]	14	2	0	0
Pain in extremity	12	0	5	0
Pyrexia[c]	12	1	11	0
Rash[c]	12	0	3	0
Renal and urinary tract infection[c,d]	12	1	4	0
Elevated liver enzymes[c]	11	4	9	0
Headache[c]	11	0	16	0
Peripheral edema	11	0	8	0
Arrhythmia[c]	8	2	2	1
Paresthesia[c]	8	0	3	0
Pneumonia[c]	8	8	5	3
Vomiting[c]	8	0	5	0
Back pain	7	1	2	0
Viral infection[c,d]	6	0	13	2
Vitamin B1 deficiency	6	0	7	0

[a]Study was not designed to evaluate meaningful comparisons of the incidence of adverse reactions across treatment groups.
[b]Adverse reactions graded using CTCAE v.4.03.
[c]Grouped term includes other related terms.
[d]Excludes opportunistic infections.

Other Adverse Reactions

Clinically relevant adverse reactions occurring in <5% of anemic patients in the MOMENTUM and SIMPLIFY-1 studies include:
Eye Disorders: Blurred vision.
Infections and Infestations: Fungal infection (excludes opportunistic infections).
Nervous System Disorders: Neuralgia, peripheral neuropathy, peripheral motor neuropathy, polyneuropathy.
Vascular Disorders: Flushing.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on OJJAARA

Organic Anion Transporting Polypeptide (OATP)1B1/B3 Inhibitors

Momelotinib is an OATP1B1/B3 substrate. Concomitant use with an OATP1B1/B3 inhibitor increases momelotinib maximal concentrations (C_{max}) and area under the concentration-time curve (AUC) *[see Clinical Pharmacology (12.3) of full prescribing information]*, which may increase the risk of adverse reactions with OJJAARA. Monitor patients concomitantly receiving an OATP1B1/B3 inhibitor for adverse reactions and consider OJJAARA dose modifications *[see Dosage and Administration (2.4) of full prescribing information]*.

7.2 Effect of OJJAARA on Other Drugs

Breast Cancer Resistance Protein (BCRP) Substrates

Momelotinib is a BCRP inhibitor. OJJAARA may increase exposure of BCRP substrates, which may increase the risk of BCRP substrate adverse reactions [*see Clinical Pharmacology (12.3) of full prescribing information*]. When

(continued on next page)

DRUG INTERACTIONS (*cont'd*)

Effect of OJJAARA on other Drugs (*cont'd*)

administered concomitantly with OJJAARA, initiate rosuvastatin (BCRP substrate) at 5 mg and do not increase to more than 10 mg once daily. Dose adjustment of other BCRP substrates may also be needed. Follow approved product information recommendations for other BCRP substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data on the use of OJJAARA in pregnant women are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage. Based on animal reproduction studies conducted in rats and rabbits, momelotinib may cause embryo-fetal toxicity at exposures lower than the expected exposure in patients receiving 200 mg once daily *(see Data)*. OJJAARA should only be used during pregnancy if the expected benefits to the mother outweigh the potential risks to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: In an embryofetal development study, pregnant rats received momelotinib 2, 6 or 12 mg/kg/day orally, during the period of organogenesis (Gestation Day 6 to 17). Embryo-fetal toxicity (embryonic death, soft tissue anomalies, skeletal variations, and lower mean fetal body weights) was observed at 12 mg/kg (in the presence of maternal toxicity). Skeletal variations were observed (in the absence of maternal toxicity) at 6 mg/kg/day at exposures 3.5 times the exposure at the recommended human dose of 200 mg daily based on combined momelotinib and M21 (a major human metabolite) AUC. No developmental toxicity was observed at 2 mg/kg/day at exposures equivalent to the recommended dose (based on combined momelotinib and M21 AUC).

In an embryofetal developmental study, pregnant rabbits received momelotinib at 7.5, 30 or 60 mg/kg/day orally during the period of organogenesis (Gestation Day 7 to 20). Momelotinib was associated with maternal toxicity at 60 mg/kg/day, which resulted in reduced mean fetal weight, delayed bone ossification, and an abortion at less than the exposure at the recommended dose (based on combined momelotinib and M21 AUC). No developmental toxicity was observed at lower doses tested in rabbits.

In a pre- and post-natal development study, pregnant rats received momelotinib 2, 6 or 12 mg/kg/day orally from organogenesis through lactation (Gestation Day 6 to lactation Day 20). Decreased pup body weights and embryo-lethality were observed in the dams administered 6 and 12 mg/kg/day. Pup survival was significantly reduced in the 12 mg/kg/day group from birth to Day 4 of lactation. Momelotinib exposure in dams at 12 mg/kg and 6 mg/kg were approximately 2 times the exposure at the recommended dose (based on combined momelotinib and M21 AUC). The exposure in dams at the No Observed Adverse Effect Level (NOAEL) dose of 2 mg/kg was less than the exposure at the recommended dose (based on combined momelotinib and M21 AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of momelotinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. It is not known whether OJJAARA is excreted in human milk. Momelotinib was present in rat pups following nursing from treated dams with adverse effects observed in the offspring. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in a breastfed child, patients should not breastfeed during treatment with OJJAARA, and for at least 1 week after the last dose of OJJAARA.

Data

Animal Data: In a pre- and postnatal development study, momelotinib was administered orally to rats during the lactation period; the drug was detected in plasma of nursing pups, which adversely affected pup survival.

8.3 Females and Males of Reproductive Potential

Contraception

Advise females of reproductive potential who are not pregnant to use highly effective contraception during therapy and for at least 1 week after the last dose of OJJAARA.

8.5 Geriatric Use

There were 275 patients aged 65 years and older in the clinical studies for MF *[see Clinical Studies (14) of full prescribing information]*. Of the total number of OJJAARA-treated patients in these studies, 163/216 (75%) were aged 65 years and older, and 63/216 (29%) were aged 75 years and older. No overall differences in safety or effectiveness of OJJAARA have been observed between patients aged 65 years and older and younger adult patients.

8.6 Hepatic Impairment

The recommended starting dose of OJJAARA in patients with severe hepatic impairment (Child-Pugh C) is 150 mg orally once daily *[see Dosage and Administration (2.3) of full prescribing information]*. No dose modification is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B).

Momelotinib is extensively metabolized *[see Clinical Pharmacology (12.3) of full prescribing information]*. Momelotinib exposure increased with severe hepatic impairment (Child-Pugh C). No clinically significant changes in momelotinib exposure were observed in subjects with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B) *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

There is no known antidote for overdose with OJJAARA. If overdose is suspected, the patient should be monitored for signs or symptoms of adverse reactions or effects, and appropriate supportive treatment should be instituted immediately. Further management should be as clinically indicated. Hemodialysis is not expected to enhance the elimination of momelotinib.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA approved patient labeling (Patient Information).

Infections

Inform patients that OJJAARA can increase the risk of infections (including COVID-19) and instruct them to promptly report to their healthcare provider any signs and symptoms of infection *[see Warnings and Precautions (5.1)]*.

Thrombocytopenia and Neutropenia

Inform patients that OJJAARA can cause thrombocytopenia and neutropenia, and of the need to monitor complete blood count, including platelet and neutrophil counts, before and during treatment. Advise patients to observe for and report any bleeding to their healthcare provider *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Inform patients that OJJAARA can cause hepatotoxicity, and of the need to monitor liver blood tests before and during treatment *[see Warnings and Precautions (5.3)]*.

Major Adverse Cardiovascular Events (MACE)

Advise patients that events of MACE including myocardial infarction, stroke, and cardiovascular death have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which OJJAARA is not indicated. Advise patients, especially current or past smokers and patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events and to report them to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Thrombosis

Advise patients that events of deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in clinical studies with another JAK-inhibitor used to treat rheumatoid arthritis, a condition for which OJJAARA is not indicated. Advise patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.5)]*.

Malignancies

Advise patients, especially current or past smokers, that lymphoma and other malignancies (excluding non-melanoma skin cancers (NMSC)) have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which OJJAARA is not indicated *[see Warnings and Precautions (5.6)]*.

Pregnancy

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential who are not pregnant to use highly effective contraception during therapy and for 1 week after the last dose of OJJAARA *[see Use in Specific Populations (8.3)]*.

Lactation

Advise patients not to breastfeed during treatment with OJJAARA and for at least 1 week after the last dose of OJJAARA *[see Use in Specific Populations (8.2)]*.

GSK

GlaxoSmithKline
Durham, NC 27701

OJJ:1BRS 10/23

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Produced in USA.

Ojjaara
(momelotinib)
200 mg • 150 mg • 100 mg tablets

START WITH A TREATMENT APPROVED FOR MF WITH ANEMIA[1]

INDICATION

OJJAARA is indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia.

OJJAARA WAS STUDIED IN JAKi-NAÏVE AND JAKi-EXPERIENCED PATIENTS. EXPLORE THE DATA.

IMPORTANT SAFETY INFORMATION

Risk of Infections

- Serious (including fatal) infections (e.g., bacterial and viral, including COVID-19) occurred in 13% of patients treated with OJJAARA. Infections regardless of grade occurred in 38% of patients. Delay starting therapy until active infections have resolved. Monitor patients for signs and symptoms of infection and initiate appropriate treatment promptly.

Hepatitis B Reactivation

- Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase (ALT) or aspartate transaminase (AST), have been reported in patients with chronic hepatitis B virus (HBV) infection taking Janus Kinase (JAK) inhibitors, including OJJAARA. The effect of OJJAARA on viral replication in patients with chronic HBV infection is unknown. In patients with HBV infections, check hepatitis B serologies prior to starting OJJAARA. If HBsAg and/or anti-HBc antibody is positive, consider consultation with a hepatologist regarding monitoring for reactivation versus prophylactic hepatitis B therapy. Patients with chronic HBV infection who receive OJJAARA should have their chronic HBV infection treated and monitored according to clinical HBV guidelines.

Please see additional Important Safety Information on the following page with accompanying Brief Summary of the full Prescribing Information.