# Updates in Diagnosis and Management of Marginal Zone Lymphomas: From biology to Novel Therapeutics

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Marginal zone lymphomas (MZL) are a heterogeneous group of indolent B-cell non-Hodgkin lymphomas originating from memory B-cells in the marginal zone of secondary lymphoid follicles. MZL represents the second most common subtype of indolent NHL, accounting for approximately 5–15% of all NHL cases, and comprises three distinct subtypes: extranodal MZL (EMZL/MALT lymphoma, 50–70%), splenic MZL (SMZL, ~20%), and nodal MZL (NMZL, ~10%). Despite their generally indolent course, MZL presents significant clinical challenges due to heterogeneous presentations, diagnostic complexities, and limited disease-specific treatment data. This educational session will provide a comprehensive overview of recent advances in understanding the biology, diagnosis, and treatment of MZL.

## Etiopathogenesis and Molecular Biology

Chronic inflammation induced by infectious agents or autoimmune diseases plays a central role in MZL pathogenesis. *Helicobacter pylori* is closely associated with gastric EMZL, while hepatitis C virus has been linked to SMZL and various EMZL sites. Other implicated pathogens include *Chlamydia psittaci* (ocular adnexa), *Campylobacter jejuni* (small intestine), and *Borrelia burgdorferi* (cutaneous). Autoimmune conditions such as Sjögren's syndrome and Hashimoto's thyroiditis are associated with salivary gland and thyroid MALT lymphomas, respectively.

Key molecular alterations include NF-κB pathway activation through characteristic translocations in MALT lymphomas: t(11;18)/BIRC3-MALT1, t(14;18)/IGH-MALT1, and t(1;14)/BCL10-IGH. SMZL and NMZL are characterized by NOTCH pathway activation (NOTCH2 mutations in 10–25% of SMZL, ~25% of NMZL) and KLF2 mutations (20–40% of SMZL). Chromatin remodeling genes including KMT2D, CREBBP, and EP300 are frequently mutated across subtypes.

## Diagnostic Challenges and Prognostication

MZL diagnosis relies on histopathology, immunophenotyping, and molecular techniques. Cells typically express CD19, CD20, and CD79a while lacking CD5, CD10, and cyclin D1. Key diagnostic challenges include differentiating MZL from lymphoplasmacytic lymphoma, where the MYD88 L265P mutation (present in 95–97% of LPL but rare in MZL) can aid distinction, though it is not absolute.

Several prognostic indices are available: MALT-IPI (age ≥70, stage III/IV, elevated LDH), HPLL score for SMZL, and the unified MZL-IPI introduced at Lugano 2023. Progression of disease within 24 months (POD24) has emerged as a powerful predictor of poor outcomes, identifying patients who may benefit from novel therapeutic approaches.

## Treatment of Localized Disease

For localized disease, treatment is site-specific. In *H. pylori*-positive gastric MALT, eradication therapy induces complete remission in 70–80% of stage I cases with excellent long-term outcomes. For *H. pylori*-negative or non-gastric EMZL, involved-site radiotherapy (24–30 Gy) achieves CR rates exceeding 90–95%. Recent data support ultra-low-dose radiotherapy (2 × 2 Gy) for orbital adnexal lymphoma with minimal toxicity. For HCV-positive SMZL, direct-acting antivirals achieve sustained virologic response with durable lymphoma regressions in approximately 45% of patients.

## Treatment of Advanced-Stage Disease

For advanced, symptomatic disease, rituximab-based therapies are standard. Bendamustine-rituximab demonstrates an ORR of ~93% and CR of ~81% in EMZL, with 5-year PFS of ~80%. Lenalidomide-rituximab ($R^2$) offers an effective chemotherapy-free option with ORR of 93%, CR of 70%, and 5-year OS of 96%.

**Relapsed/Refractory Disease and Novel Therapeutics**

BTK inhibitors have transformed the R/R setting. Zanubrutinib is now the preferred agent based on the MAGNOLIA trial, demonstrating an ORR of 68%, CR of 26%, with favorable safety profile including low rates of atrial fibrillation (3%). Molecular correlatives identified MYD88 and TNFAIP3 mutations as favorable predictors, while KMT2D mutations predict inferior outcomes.

Emerging therapies include CAR-T cell therapy (axicabtagene ciloleucel showed ORR 77% in ZUMA-5), CD20×CD3 bispecific antibodies (mosunetuzumab, epcoritamab, glofitamab), non-covalent BTK inhibitors (pirtobrutinib), and antibody-drug conjugates. These novel approaches offer promise for multiply relapsed patients.

**Conclusions**

This session will synthesize current evidence and provide practical guidance for MZL management. Key unmet needs include MZL-specific clinical trials, understanding of transformation biology, and development of novel targeted therapies. With the expanding therapeutic armamentarium, the treatment paradigm is shifting toward targeted, immune-based strategies, offering improved outcomes for patients with this heterogeneous disease.