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CLINICAL TRIALS AND OBSERVATIONS

*Comment on Luminari et al, page 798*

# POD24 in MZL: a means to an end or an end point in itself?

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**In this issue of *Blood*, Luminari et al demonstrate that patients with marginal zone lymphoma (MZL) who experience early progression (progression of disease at 24 months [POD24]) have poor survival.[1] Overall survival after POD24 was 53% at 3 years, a stark contrast to the 95% 5-year survival rate from diagnosis in patients without early progression. These results extend the seminal study in follicular lymphoma (FL) from the National LymphoCare Study by Casulo et al[2] to include indolent nonfollicular B-cell lymphomas (INFLs).**

Outcomes in FL and INFLs have improved greatly in the rituximab era, and 10-year survival estimates range from 60% to 80%, depending on subtype.[3,4] Although progression of a malignancy is never desirable, periods of remission, progression, and retreatment are expected in the disease course of indolent lymphomas. Despite a rapid increase in therapy options in the last decade, there remains a subset of patients who will transform to a more aggressive subtype or become refractory to available therapies; early identification of these patients is of great clinical interest. Prognostic indices at diagnosis are readily available for both MZL[5] and FL[6]; however, the initial diagnostic variables become less relevant as patients move through their disease course. Dynamic assessment of prognosis based on updated information is critical to provide accurate risk assessment and optimal disease management.

The data from the NF10 registry presented by Luminari and colleagues provide important information for dynamic assessment of prognosis in MZL by identifying a high-risk population consisting of the 18% of patients who experienced early progression. Poor outcomes after POD24 were observed across marginal zone subtypes, with 3-year survival rates after early progression ranging from 33% for disseminated MZL to 71% for extranodal MZL, although the sample size limits firm subtype-specific conclusions. Just as vital, patients in the NF10 study who did not suffer early progression from initial systemic therapy had excellent outcomes, with 5-year survival rates from diagnosis ranging from 93% to 98% among the various marginal zone subtypes. These results confirm previous results in FL. Moreover, previous studies have shown that survival for patients without early progression in FL[7] and INFL[3] is similar to that of the background population over the next 5 to 10 years. These data provide powerful tools for the re-assessment of prognosis for clinicians as well as important reassurance for patients at their 2-year follow-up visits.

There are some important caveats that need to be considered. Indolent lymphomas are heterogeneous in their presentation and initial management. The POD24 analysis by Luminari et al was limited to patients who required immediate therapy, which made up only 24% of the NF10 INFL cohort. Similarly, the NLCS study in FL was based on the most aggressively treated patients. Using a 24-month cutoff may not be optimal for less aggressive management approaches.[3,7] Statistically, use of a dichotomous end point like POD24 always involves a loss of information, and the prognostic impact of early events may vary based on the timing of the event.[8] The role of early transformation versus early indolent progression or relapse events is also in need of further evaluation,[9] as is the impact of maintenance therapy on early event-related prognosis. The utility of early events will require periodic reassessment as the management strategy and therapy options for patients with FL and INFL continue to evolve. However, from a research standpoint, the use of these end points can facilitate more rapid identification of high-risk patients in correlative studies of FL and INFL. Clinical and/or biologic features of these high-risk patients can then be used to generate predictive models at diagnosis to help aid clinical risk prediction and first-line therapy selection.

Finally, for the treating physician, it is important to remember that early progression end points such as POD24 are ways of identifying high-risk patients after they have been exposed to initial therapy. They are not meant to be therapy goals at the time of initial management for the individual patient. Therapy selection should still be made to maximize outcomes over the life of the patient, not to maximize achieving these surrogate outcomes.

*Conflict-of-interest disclosure: M.J.M. has received research funding from Celgene and Nanostring and serves on an advisory board for Morphosys.* ■

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DOI 10.1182/blood.2019002305

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**LYMPHOID NEOPLASIA**

*Comment on Mottok et al, page 802*

# PMBL: flying under the immune radar

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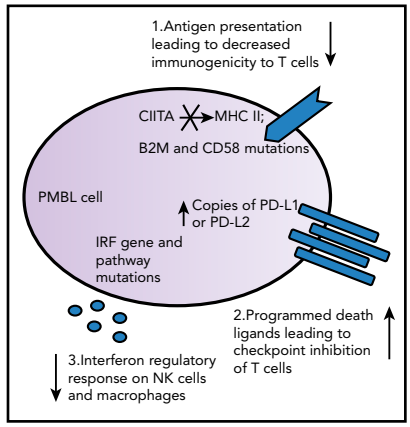
**In this issue of *Blood*, Mottok et al present a large case series of well defined primary mediastinal B-cell lymphoma (PMBL) that includes whole genome sequencing of all 94 cases and molecular confirmation of diagnosis in 73 cases.[1,2] The resulting mutation and copy number data are correlated with gene expression signatures, which confirm previous correlations using smaller data sets as well as extend the description of mechanisms of immune evasion and driver mutations. Altogether, this highly annotated and large PMBL case series should provide a rich and definitive data set for genetic research in this disease.**

PMBL is an unusual, somewhat enigmatic lymphoma that combines some clinical, cytogenetic, and gene expression profile features of classical Hodgkin lymphoma with the most common aggressive non-Hodgkin B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL).[3,4] PMBL is thought to arise from mutations accumulated in thymic B cells and is 1 of only 2 lymphomas, along with nodular sclerosis Hodgkin lymphoma, that are more common in women than men. Other typical clinical features include location in the anterior mediastinum, local tissue invasion, and relatively young patient age at diagnosis. Some data suggest that a more dose-intense treatment regimen than that usually administered for DLBCL may benefit patients with PMBL.[5] However, a precise pathologic diagnosis on which to base informative clinical trials can be difficult because PMBL exhibits morphologic and immunophenotypic profiles that overlap with other types of lymphomas and also because morphologically similar DLBCL can occur in the mediastinum whereas PMBL-like tumors can be found at other locations in the body.[2,4,6]

The study by Mottok et al advances the work on immune evasion in PMBL via (1) structural aberrations and mutations involving *CIITA*, the master transcriptional regulator of major histocompatibility complex class II gene transcription (a system that is responsible for antigen presentation[7]) and (2) copy number alterations and rearrangements of the programmed death-ligand 1 (*PDL1* and protein CD274) and *PDL2* (also known as *PDCD1LG2* and protein CD273) genes at 9p24.1 that are responsible for T-cell–mediated immune responses (see figure).[8] The Mottok study adds detail to the abnormalities in *CIITA* and *PDL*, as well as other immune-related genes, in terms of mutation and copy number information. In addition, mutations in the interferon regulatory factor (*IRF*) genes, including a hotspot in the B-cell immune response gene *IRF4*, and mutations in *IRF* downstream targets were detected in 52% of the cases. Altogether, this multipronged genetic approach, which affects antigen presentation as well as responses from T cells, natural killer cells, and macrophages (see figure) creates an immune-privileged phenotype for PMBL that allows it to fly under the detection radar and represents a blend of various strategies used by other B-cell–derived lymphomas (reviewed in Scott and Gascoyne[9]).

Among driver mutations, Janus kinase-signal transducer and activator of transcription (JAK-STAT) and nuclear factor-κB (NF-κB) signaling pathway genes,




Schematic diagram summarizing immune escape mechanisms of PMBL. PMBL tumors can harbor multiple genetic alterations, including mutations, indels, and copy number alterations, which enable them to evade tumor immunosurveillance. These general approaches to immune evasion firstly include alterations in antigen presentation such as rearrangements, indels, and mutations of the *CIITA* gene, which encodes the master transactivator of the major histocompatibility complex (MHC) class II molecules; mutations in the gene encoding the invariant chain CD58, also known as the lymphocyte adhesion molecule LFA-3, that in the wild-type state, strengthens the adhesion between the antigen-presenting cell (in this case, the PMBL cell) and reactive T cells; and mutations in the gene encoding β-2 microglobulin (B2M), which in the wild-type state, normally stabilizes the MHC class I molecules to activate $CD8^+$ T cells. Secondly, T-cell activation is affected by amplification of the genes encoding programmed death-ligand 1 (PD-L1) and PD-L2, which bind the inhibitory checkpoint molecule programmed cell death protein 1 (PD-1) on antigen-specific T cells. Thirdly, natural killer (NK) cells and macrophages are affected by mutations in the interferon regulatory response cytokines and downstream genes which, in the wild-type state, upregulate antigen presentation via MHC.

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