confirmation, PET/CT is useful to identify sites in which a tissue biopsy is more likely to be diagnostically informative.[4,5]

The article by Falchi et al[1] in this issue updates the MDACC experience and reports data on the largest cohort thus far published of CLL or RS patients (n = 332) with FDG/PET evaluation and concurrent available lymph node histology. This single-institution study aims to correlate FDG/PET with histology, clinical features, and survival. Although an $SUV_{max} \geq 5$ is validated as a meaningful cutoff to identify the optimal site to detect RS, an $SUV_{max} \geq 10$ had the best discriminatory power to predict survival. Not unexpectedly, patients with higher SUV_{max} were more likely to present with poor prognostic features such as 17p deletion or ZAP-70 positivity. Moreover, in multivariate analysis, $SUV_{max} \geq 10$ was independently associated with a shorter overall survival.[1]

Worthy of note is the attempt to correlate FDG/PET findings with lymph node histology. To that purpose, cases were classified as having: histologically indolent CLL; histologically aggressive CLL (HA-CLL) (see figure); or RS.[1] Not surprising, but still important, information is that fine-needle aspiration proved to be inadequate for detecting disease transformation. Interestingly, patients with HA-CLL and RS shared similar FDG/PET patterns and traits of disease aggressiveness (eg, constitutional symptoms, high lactate dehydrogenase [LDH] values) but patients with HA-CLL had a better survival (median: 17.6 vs 7.7 months). These observations are in keeping with those previously reported by Montserrat's group,[6] which identified patients with aggressive disease and a survival intermediate between CLL and RS under the term of "accelerated CLL."

It is worth mentioning, however, that criteria for defining CLL histological subgroups have not been agreed upon nor validated. CLL guidelines, for example, only recognize RS as a form of CLL transformation.[7,8] On the other hand, in the study under consideration, an $SUV_{max} \geq 10$ but not histology was retained as a prognostic variable in controlled survival analysis, which is an interesting finding warranting additional investigation. That in CLL, because it occurs in other indolent lymphoid malignancies,[9] there is a continuous spectrum of lesions from typical to fully transformed cases should not be surprising and fits with our current understanding of CLL pathogenesis.[10] With this in mind, the different FDG/PET patterns observed in CLL are most likely a mere reflection of different, but unfrozen, phases of CLL biology.

Where do we stand today in using FDG/PET to benefit CLL patients? FDG/PET is important for detecting disease transformation, a not infrequent phenomenon that in the case of RS can be estimated to occur in around 10% of patients. Disease transformation, which is frequently overlooked, has an extremely poor prognosis and requires aggressive therapy.[5,9] There are some clinical hints to suspect disease transformation, including the development of general symptoms, enlarging lymphadenopathy, and increasing LDH. A positive FDG/PET not only supports the possibility of transformation but points to the site where a biopsy is more likely to be informative. On the other hand, the available studies do not justify using FDG/PET routinely in the prognostic evaluation or response to therapy assessment in patients with untransformed CLL.

The MDACC group study sets the stage for other prospective studies to further elucidate the role of FDG/PET in the management of CLL. Meanwhile, outside of clinical trials, FDG/PET has an important role in supporting the possibility of disease transformation and guiding tissue biopsy.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Treon et al, page 2791

Waldenström macroglobulinemia: genetics dictates clinical course

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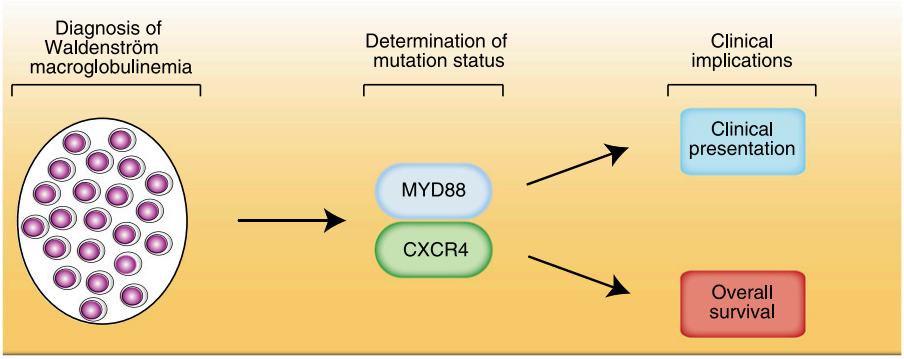
In this issue of *Blood*, Treon and colleagues provide strong evidence that mutations in *MYD88* and *CXCR4* dictate clinical presentation and survival in Waldenström macroglobulinemia (WM).[1]

WM is a rare malignancy of immunoglobulin M–secreting B cells.[2] Recent work identified recurrent somatically acquired activating mutations in *MYD88* as well as in *CXCR4* in WM patient samples.[3,4] In more than 90% of WM patient samples, the *MYD88* L265P mutation is detectable. This aberration, which is also found in other



Determination of the *MYD88* and *CXCR4* mutation status in WM has clinical implications.

lymphoma subtypes such as the activated B cell–like subtype of diffuse large B-cell lymphoma (ABC DLBCL) or mucosa-associated lymphoid tissue lymphoma, leads to constitutive activation of the oncogenic nuclear factor-κB signaling pathway.[5–7] CXCR4 is a chemokine receptor that promotes survival of WM cells.[4] Different mutations affecting the C terminus of *CXCR4* can be identified in roughly 30% of WM patients.[4] Although these analyses provided important insights into the molecular pathogenesis of WM, it remained unclear if these genetic aberrations impact clinical presentation or survival of affected patients.

In this issue, Treon et al investigate the clinical implications of *MYD88* and *CXCR4* mutations in WM.[1] Virtually all patients harboring mutations in *CXCR4* also exhibited mutated *MYD88*. Patient samples harboring *CXCR4* mutations were further distinguished based on the mutation pattern (nonsense vs frameshift mutations). Interestingly, the mutation status of *CXCR4* and *MYD88* was associated with significant differences in clinical presentation and outcome (see figure).[1] Patients with mutated *MYD88* and *CXCR4* nonsense mutations exhibited bone marrow infiltration significantly more frequently, had higher serum immunoglobulin M levels, and presented with symptomatic disease, including hyperviscosity, syndrome more frequently. In contrast, patients with mutated *MYD88* and *CXCR4* frameshift or nonsense mutations presented less frequently with adenopathy. Finally, patients that were wild type for both *MYD88* and *CXCR4* were characterized by adverse survival compared with patients with mutated *MYD88* alone or patients that harbored both mutations. Taken together, these results suggest that the *MYD88* and *CXCR4* mutation status determines clinical presentation and outcome of patients diagnosed with WM (see figure).[1]

From a clinical standpoint, the results by Treon et al can potentially be highly relevant for WM treatment. A better understanding which oncogenic pathways are activated and used in WM is a prerequisite for the optimal utilization of novel therapeutic agents. To this end, the determination of the *MYD88* and *CXCR4* mutation status might help us identify novel subgroups of WM that differ with respect to clinical presentation and prognosis. Additionally, these subgroups might benefit differentially to novel therapeutic strategies. Bruton's tyrosine kinase, which interacts with *MYD88*, is a promising target for the treatment of WM, and encouraging results were obtained by using the Bruton's tyrosine kinase inhibitor ibrutinib in relapsed and refractory WM.[8] Similarly, interleukin-1 receptor–associated kinase inhibitors that are being developed for clinical use hold promise for the treatment of WM because *MYD88* coordinates the assembly of a signaling complex consisting of different members of the interleukin-1 receptor–associated kinase family.[5,6] Finally, the use of CXCR4 inhibitors such as plerixafor might be promising in WM patients with mutated *CXCR4*. Importantly, large and well-designed clinical trials with accompanying scientific programs are required to investigate if specific subtypes of WM respond preferentially to novel compounds. This approach will pave the way to more specific and less toxic treatment regimens for patients with WM.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● MYELOID NEOPLASIA

Comment on Goodwin et al, page 2838

Hallway gossip between Ras and PI3K pathways

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In this issue of *Blood*, Goodwin et al investigate the pathogenesis of juvenile myelomonocytic leukemia (JMML), demonstrating that mutant Shp2 induces granulocyte macrophage–colony-stimulating factor (GM-CSF) hypersensitivity and that the p110δ subunit of phosphatidylinositol 3-kinase (PI3K) further promotes this dysregulation.[1]