**WM, from a Molecular signature to a Molecular-based therapeutic armamentarium**

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**Background.** Waldenström macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized by bone marrow infiltration of lymphoplasmacytic cells along with production of an IgM monoclonal protein in the serum. It can be associated with various complications related to tumor infiltration or to the serum monoclonal component. This definition has evolved in recent year with the groundbreaking discovery of a driver mutation, an essential new biomarker tool for diagnosis. Biological markers have now become essential for the diagnosis of WM, for prognosis determination, monitoring of response to therapy and progression, and possibly even in the decision of the optimal treatment.

**Methods.** Review of the literature including most recent appearance in international meetings of WM, from diagnosis to therapeutic.

**Results.** In recent years, genomic characterization of WM has led to the identification of the L265P mutation on MYD88, now considered an essential new biomarker tool for diagnosis. Interestingly, other mutations were identified, potentially mutually exclusive, certainly second hits, including CXCR4, CD79 and TP53 with a variety of consequence to the tumour cells, from mechanism of chemoresistance to BCR agents, to pathway deregulation and to prognosis impact, respectively for the 3 examples provided.

**Conclusion.** Overall, there has been tremendous progress made in recent years in the understanding of the molecular profile and alterations of WM, that will eventually impact the treatment options, the treatment paradigm, and the understanding of the failures from the past and certainly how and where we can improve to prolong the survival of patients with WM, along with improving their quality of life with living longer with WM.