(200 words)

Clinical Implications of Genomic Profiling

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Introduction: MYD88 L265P and CXCR4 nonsense and frameshift mutations are the most common recurrent somatic mutations in Waldenström macroglobulinemia (WM), with detection rates of 90% and 40%, respectively. These mutations are also prevalent in IgM monoclonal gammopathy of undetermined significance (MGUS) or smoldering WM (SWM).

Main points: Mutational burden in MGUS and SWM are related to bone marrow tumor infiltration and also with the risk of progression to symptomatic WM, particularly in SWM. Due to lower infiltration, digital droplet PCR (ddPCR) can have higher clinical applicability to assess MYD88 and CXCR4 mutations in IgM MGUS and SWM, providing a molecular-based risk classification. In WM, CXCR4 mutations (usually subclonal) can have impact in clinical presentation and also in response to Bruton tyrosine kinase inhibitors (BTKi). The infrequent cases with wild-type MYD88 have lower responses to BTKi and carry a higher risk of transformation.

Conclusion: The development of high-throughput technologies has allowed us to characterize the molecular landscape of MW and the asymptomatic IgM gammopathies. As a result, we can now use these technologies to diagnose, model risk factors for progression, make treatment decisions, potentially track response to treatment, and design clinical trials in this disease.

Disclosures:

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Biography:

Carlos Fernandez de Larrea completed his training in hematology at Hospital Clínic in Barcelona. His doctoral thesis was awarded with the Extraordinary Award of the University of Barcelona (2012). He has been visiting investigator at the Centre for Amyloidosis of Pavia, the National Cancer Institute in Bethesda, as well as at Memorial Sloan Kettering Cancer Center in New York for 18 months, working in CAR-T cells for myeloma. He is currently consultant of the Department of Hematology at Hospital Clínic de Barcelona, research group leader at IDIBAPS and Associate Professor in the

University of Barcelona. He participates actively in clinical trials for multiple myeloma and macroglobulinemia.