## Integrating Signaling inhibitors into WM therapy

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Next generation sequencing technology has led to the discovery of novel signaling pathways that are critical for Waldenstrom Macroglobulinemia (WM). Specifically, MYD88 and CXCR4 mutations have given new insights into the mechanisms of progression and drug resistance that occur in patients with this unique entity. These pathways are also critical in activating downstream signaling pathways including IRAK, PI3K/Akt/mTOR and NF-kB pathways among others. In addition, the interaction of Waldenstrom cells with the bone marrow niche leads to activation of many cytokines and chemokines that regulate proliferation, adhesion and cell trafficking of B cells. Moreover, miRNA profiling has shown that specific miRNAs such as miR-155 can play a critical role in the pathogenesis and molecular/signaling regulation of these cells. Based on these significant advances in understanding the molecular alterations in these cells, several preclinical and clinical studies have shown promising results in patients with WM. These include proteasome inhibitors such as bortezomib, carfilzomib and oprozomib, BTK inhibitors such as Ibrutinib, PI3K/Akt/mTOR inhibitors such as everolimus and new generations of PI3K inhibitors, CXCR4 inhibitors and HDAC inhibitors such as panobinostat. Together, these studies have improved the response and progression-free survival of patients with WM and have paved the way for well-designed combinations of therapy that can induce deep remissions.