# Abstract

## Novel Therapies for Waldenstrom's Macroglobulinemia

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There have been significant advances in the understanding of the pathogenesis and molecular alterations that occur in WM. Genomic and proteomic analysis studies have led to the discovery of dysregulated signaling pathways in WM. In addition, the understanding of the role of the bone marrow microenvironment in WM, specifically the role of mast cells, stromal cells, and cytokines that regulate proliferation and survival such as BlyS and APRIL have led to the development of novel agents that, not only target WM cells, but also their bone marrow milieu. Based on these, many targeted therapeutic agents and monoclonal antibodies have been tested in the preclinical setting and in early phase I and II studies in WM. A new paradigm shift has evolved in WM utilizing novel therapeutic agents targeting the WM clone and its bone marrow microenvironment. Novel agents tested in clinical trials in WM include the immunomodulatory agents thalidomide and its analogue lenalidomide, the proteasome inhibitor bortezomib and its combination with rituximab, the anti-CD52 antibody alemtuzumab-1H (Campath), antisense Bcl-2 inhibitor G3139 (Oblimersen sodium), sildenafil citrate, the tyrosine kinase inhibitor imatinib mesylate (Gleevec) that targets the WM cells and the mast cells in the bone marrow microenvironment through CD117 signaling, TACI-Ig Atacicept (TACI bind to BlyS and APRIL), the irreversible proteasome inhibitor PR-171, the Akt inhibitor perifosine, and the mTOR inhibitor RAD001. Agents being tested in the preclinical setting for future clinical trials in WM include the PKC inhibitor enzastaurin, anti-CD70 antibody SGN-70, the proteasome inhibitor NPI-0052, CXCR4 inhibitor AMD3100, Triterpenoids such as CDDO and CDDO-Im, statins such as simvastatin, and natural compounds such as resveratrol. The current challenge is to identify combinations of agents that act synergistically against WM cells and their microenvironment in order to carry out clinical trials that achieve high remission rates and prolonged survival in patients with WM.