Novel therapeutic agents in Waldenstrom Macroglobulinemia

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Waldenstrom macroglobulinemia (WM) is a distinct low-grade B cell lymphoma characterized by the presence of lymphoplasmacytic cells in bone marrow and a serum monoclonal immunoglobulin (Ig) M protein. To date, there are no FDA-approved therapeutic agents for the specific treatment of WM. Most treatment options were originally derived from other lymphoproliferative diseases, including multiple myeloma and chronic lymphocytic leukemia. Therefore, there is a need for the development of novel therapeutic agents that are based on the activity of these agents in WM preclinically and clinically. To date, we have tested multiple agents in the preclinical setting, including small targeted molecules such as the Akt inhibitor perifosine (KRX-0401; Keryx Biopharmaceuticals); mammalian target of rapamycin (mTOR) inhibitor everolimus (RAD001; Novartis Pharmaceuticals Inc); PKC inhibitor enzastaurin (Eli Lilly and Company); proteasome inhibitors, including bortezomib (Millennium Inc), salinosporamide A (NPI-0052; Nereus Inc), and carfilzomib (PR-171; Proteolix Inc); histone deacetylase inhibitor LBH589 (Novartis Pharmaceuticals Inc); pan tyrosine kinase inhibitor TKI258 (Novartis Pharmaceuticals Inc); pan-PKC inhibitor midostaurin (PKC412; Novartis Pharmaceuticals Inc); PI3K/mTOR inhibitor BEZ235 (Novartis Pharmaceuticals Inc), Src inhibitor AZD0530 (Astra Zeneca Inc); and CXCR4 inhibitor plerixafor (AMD3100; Genzyme Inc). In clinical trials, we have recently completed a phase II clinical trial of single agent perifosine in relapsed or relapsed/refractory WM, a phase II clinical trial of single-agent everolimus in relapsed or relapsed/refractory WM, and a phase II clinical trial of the combination of bortezomib and rituximab in relapsed or relapsed/refractory WM. Ongoing studies include first-line therapy with weekly bortezomib and rituximab as well as the phase II trial of enzastaurin in relapsed/refractory WM. Upcoming studies include the use of everolimus in combination with rituximab or in combination with bortezomib and rituximab, as well as the single-agent study of LBH589 in relapsed/refractory WM.