

New Monoclonal Antibodies for the Treatment of Waldenstrom's Macroglobulinemia and Chronic Lymphocytic Leukemia. John C. Byrd M.D. Division of Hematology-Oncology, Department of Medicine, The Ohio State University, Columbus, Ohio 43210, USA

The use of the chimeric anti-CD20 antibody rituximab in Waldenstrom's macroglobulinemia (WM) and chronic lymphocytic leukemia (CLL) has produced promising results when administered as a single agent. Studies are now ongoing in WM with rituximab in combination with fludarabine or cladribine based therapies. Other studies have demonstrated that release of TNF- α can generate survival signals in tumor cells through stimulation of the NF κ B pathway and is associated with infusion toxicity of rituximab and Campath-1H. TNF- α also diminishes erythrocyte progenitor proliferation and likely contributes to the pathogenesis of anemia in lymphoproliferative disorders such as WM and CLL. These observations provide justification for developing antibody-based combination therapies that eliminate intrinsic survival signals generated by TNF- α . Based upon these data, we have initiated a combination trial combining etanercept and rituximab for patients with previously treated WM and CLL. Other antibodies recently approved for use in CLL such as Campath-1H are currently under clinical evaluation in chemotherapy and rituximab refractory WM. Antibodies targeting HLA-DR, an antigen expressed on virtually all WM and CLL cells are in clinical trials at the present time. Pre-clinical studies from our laboratory and others have demonstrated that this antibody induces apoptosis through a caspase independent manner through release of apoptosis inducing factor. Pre-clinical combination studies with other agents active in the treatment of WM are currently ongoing. Hu1D10 is the first fully humanized HLA-DR β -chain directed monoclonal antibody to enter the clinic. Our group and others have demonstrated that Hu1D10 is expressed in a subset of WM and CLL patients. A phase I clinical trial of Hu1D10 in WM and CLL is currently ongoing based upon these data. In addition, other high affinity class II antibodies are currently being considered for development in WM, CLL and other diseases. Application of antibody therapy to WM and CLL offers promise to potentially improve outcome concurrent with diminishment of toxicity observed with chemotherapy regimens utilized in the treatment of this disease.