Combination Therapy with Rituximab and Fludarabine is highly active in Waldenstrom's macroglobulinemia.

Steven P Treon, MD PhD 1, Parveen Wasi, MD 2, Christos A Emmanouilides, MD PhD 3, Stanley R Frankel, MD 4, Eva Kimby, MD PhD 5, Andrew Lister, MD 6, Pierre Morel, MD 7, Abigail Kelliher 8, Andrew Branagan 1, Frederick Preffer, PhD 8 and Kenneth C Anderson, MD 1. 1Medical Oncology, Dana Farber Cancer Institute, Boston, MA, United States, 02115; 2Hematology Oncology, McMaster University Medical Center, Hamilton, ON, Canada; 3Hematology Oncology, UCLA Medical Center, Los Angeles, CA, United States; 4Hematology Oncology, Greenebaum Cancer Center, Baltimore, MD, United States; 5Hematology, Karolinska Institutet, Stockholm, Sweden, SE-141; 6Medical Oncology, St BartSt Bartholomew's Hospital and Cancer Research, London, United Kingdom, EC1A 7BE; 7Clinical Hematology, Centre Hospitalier Schaffner, Lens, France, 62300 and 8Pathology, Massachusetts General Hospital, Boston, MA, United States, 02114.

Rituximab and fludarabine as single agents are active in Waldenstrom's macroglobulinemia (WM) with an overall response rate (ORR) of 30-70%. In this study, we examined these agents in combination in WM patients who had received < 2 prior therapies, and who had not previously been treated with any nucleoside analogue or rituximab, utilizing the following schema:

Weeks 1-4; rituximab (375 mg/m2) q week
Weeks 5, 9, 13; fludarabine (25 mg/m2/day) x 5 days
Weeks 17, 18; rituximab (375 mg/m2) q week
Weeks 19, 23, 27; fludarabine (25 mg/m2/day) x 5 days
Week 30, 31; rituximab (375 mg/m2) q week

Patients were evaluated at week 12, and if they demonstrated stable disease (SD) or better were eligible for further therapy and were evaluable for response. Dose modifications, and delay in fludarabine administration, along with use of G-CSF were permitted based on hematological toxicities. 23 WM patients have been enrolled with a median age of 61 (range 52-75 yrs), and median prior therapies of 1 (range 0-2). At present, 15 patients are off protocol therapy including 1 patient who experienced complications after an abrupt surge in her serum IgM and viscosity levels following 4 infusions of rituximab. Two patients (1 PR, 1 SD) died while off protocol therapy, and their cause of deaths were reported by their treating clinicians as unrelated to protocol therapy or disease. Delays in therapy due to neutropenia were common, and 44.4% of patients experienced Grade ¾ neutropenia, which clinically was not significant in most patients. However, protocol therapy was truncated after the 4^{th} (n=2) and 5^{th} (n=1) courses of fludarabine for 3 patients who had persistent neutropenia and/or thrombocytopenia despite delays in therapy and/or use of G-CSF support. 12/14 (85.7%) of evaluable patients responded (1 CR, 8 PR, 3 MR) with response durations ranging from 3-11+ months. The preliminary results of this study therefore suggest that rituximab in combination with fludarabine appears to result in higher ORR than those reported with either agent alone, with acceptable toxicity. The impact on response duration remains to be defined.