# The Role of Serum Immunoglobulin Free Light Chain In Response and Progression In Waldenstrom Macroglobulinemia

Xavier Leleu, MD, PhD[1], Wanling Xie, MS[2*], Meghan Rourke[3*], Ranjit Banwait[3*], Renee Leduc[4*], Nitin Roper[4*], Edie Weller[4*] and Irene Ghobrial, MD[3]

[1]Service des Maladies du Sang, Hopital Huriez, CHRU, Lille, France; [2]Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA; [3]Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [4]Dana-Farber Cancer Institute, Boston, MA

**Introduction:** Waldenstrom macroglobulinemia (WM) is a low grade B cell lymphoma characterized by the secretion of IgM protein in the serum. The IgM level lacks sensitivity due to its prolonged half-life. The serum free light chain (sFLC) assay has shown significant clinical application in plasma cell dyscrasias, specifically in multiple myeloma, and is used to monitor response to therapy. In this study, we sought to examine the role of sFLC in the response and progression of patients with WM.

**Methods:** This study was performed using serum collected from a homogeneous cohort of patients diagnosed with WM and uniformly treated on a phase 2 trial using the combination of bortezomib with rituximab, previously untreated (N=26) or relapsed and or refractory to prior therapy (N=37). Patients eligible for this analysis must have measurable sFLC levels at baseline. A total of 48 patients were included. FLC response is defined as achievement of normal iFLC value or 50% decrease from baseline in the iFLC level during therapy and follow-up. Concordance between FLC and IgM response rate was evaluated using Kappa statistics. Correlation was evaluated using Spearman correlation coefficient. Time to progression was estimated using Kaplan-Meier methodology. We also did landmark analysis to compare overall response rate and time to progression by FLC or IgM response status at 2 months after therapy initiation; Fisher Exact test or Log-rank test were used.

**Results:** The median iFLC value was 103.50mg/L (range 22.5-3540), the median kappa over lambda ratio was 13.45 (0.01-665), and the median serum IgM value by nephlometry was 3995 mg/dL (537-10,800). Overall, as per M spike response criteria, 29 (60%, 90% CI: 48%, 72%) patients responded, e.g. had partial response or better, and 19 patients failed to obtain response. Using serum IgM protein measurement by nephlometry during therapy and follow up post-therapy, 35 (73%, 90% CI: 60%, 83%) patients responded with a PR or better (>50% decrease), with 3 (6%) having normalization of their serum IgM. In comparison, iFLC response during treatment and follow up occurred in 38 (79%, 90% CI: 67%, 88%): with 2(4%) having normalization of value, 21(44%) having 50%

reduction and 15(31%) having both. The time to iFLC response and IgM response among patients who achieved response by both criteria was calculated (N=33). The median time to iFLC response was 2.1 months (range 0.9-28.7months), while the median time to IgM response was 3.0 months (0.9-14.7) (p=0.07). The median time to progression per the protocol was 18.9 months (95% CI:10.5-NR). The Kappa concordance between iFLC 25% increase and M spike progression was 0.63 (95% CI: 0.41-0.84). This showed a better concordance compared to using the iFLC >50% definition (kappa=0.58, 95% CI: 0.35, 0.81), indicating that progression using iFLC>25% would be a better definition for patients with WM. The median time to progression by iFLC>25% increase was 13.7 months (95% CI:10.9-19.4) and the median time to IgM >25% increase was 14.6 months (95% CI: 9.5-19.1), showing a more rapid detection of progression by iFLC compared to M spike and IgM measurements. We next examined whether attaining a response using iFLC can be a predictor of overall response to therapy. Seventeen patients (35%) achieved an iFLC response at 2 months after therapy initiation. Patients with early iFLC response were more likely to have intermediate/high ISS-WM stage, elevated B2M or low Hemoglobin<11.5 gm/dL (p<0.05). Early iFLC response was related to overall IgM response during therapy and follow up (p=0.02). In multivariable models when adjusting for ISS stage, B2M or Hgb, there was no significant association between FLC early response and TTP either by protocol, FLC or IgM criteria. However, there was trend that early response was related to prolonged TTP especially when adjusting for hgb risk factors (HRs ranges from 0.63~0.80, p>0.3 for various TTP endpoints.

**Conclusion:** iFLC may be a useful marker of tumor measurement that correlates well with IgM and M spike measurements. The time to iFLC response was shorter by 1 month compared to IgM or M spike measurement. The median time to progression by iFLC was shorter by 1 month compared to IgM. There was a trend that early response was related to prolonged TTP when adjusting for other risk factors.