W37: Impact of Ibrutinib Dose Intensity on Patient Outcomes in Previously Treated Waldenström Macroglobulinemia

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Introduction: The Bruton tyrosine kinase (BTK) inhibitor ibrutinib recently became the first approved therapy for patients with symptomatic Waldenström macroglobulinemia (WM). Temporary interruption of therapy is recommended to manage treatment-related toxicities and when patients undergo invasive procedures. However, the impact of interrupted therapy with ibrutinib has not been evaluated in patients with WM. We therefore examined the clinical implications of dose intensity in previously treated WM patients treated with ibrutinib in the multicenter phase 2 trial supporting regulatory approval.

Methods: Patient charts were retrospectively analyzed and pertinent clinical data were collected surrounding ibrutinib drug holds. Treatment adherence to ibrutinib was documented during the clinical trial, and was measured by overall dose intensity ($DI_{overall}$). DI was defined as the proportion of administered versus planned doses from initiation of therapy until last dose received. Response was assessed based on current criteria. Time to events was estimated using the Kaplan-Meier method and comparisons between groups were made using the log-rank test.

Results: Sixty-three patients with WM were enrolled and began therapy with ibrutinib 420 mg once daily. Fifty patients (79%) held ibrutinib at least once, and there were 102 drug-hold events in total. The median drug hold length was 6 days (range, 2-50 days). An increase in serum IgM level was observed on 63 occasions at the next response assessment after a drug hold. The median increase in serum IgM level was 50% (range, 4-555%), and 37 increases (59%) met criteria for progressive disease (PD). Following the reinitiation of ibrutinib, the median time to a response of stable disease (SD) or better was 125 days (95% CI 109-186 days) for patients who met PD criteria, and was significantly longer for patients with the $MYD88^{MUT}$ $CXCR4^{WHIM}$ versus $MYD88^{MUT}$ $CXCR4^{WT}$ tumor genotype (207 vs. 101 days; $p<0.0001$). The mean $DI_{overall}$ was 97% after a median 3.9 years of ibrutinib therapy. Eighteen patients (29%) had a $DI_{overall}$ below the mean (low DI), and 45 patients (71%) had a $DI_{overall}$ above the mean (high DI). Patients with low $DI_{overall}$ versus high $DI_{overall}$ had no difference in age at ibrutinib initiation, sex, number of prior therapies, beta-2-microglobulin, serum IgM,

hemoglobin level, bone marrow involvement, adenopathy, splenomegaly, and *MYD88* and *CXCR4* mutational status (p>0.05 for all comparisons). Overall PFS was significantly shorter in patients with low $DI_{overall}$ versus high $DI_{overall}$ (median, 22 months vs. not reached [NR]; p=0.008). The mean $DI_{overall}$ for patients with $MYD88^{MUT}$ $CXCR4^{WT}$ (n=37), $MYD88^{MUT}$ $CXCR4^{WHIM}$ (n=21), and $MYD88^{WT}$ $CXCR4^{WT}$ (n=5) tumor genotype was 99%, 95%, and 99%, respectively. A subgroup analysis demonstrated a significant difference in PFS for $MYD88^{MUT}$ $CXCR4^{WHIM}$ patients with low $DI_{overall}$ versus high $DI_{overall}$ (median, 9.4 months vs. NR; p=0.0003), whereas no difference was observed in $MYD88^{MUT}$ $CXCR4^{WT}$ and $MYD88^{WT}$ $CXCR4^{WT}$ patients (p>0.05 for both comparisons). Twenty-five patients missed ³8 consecutive days of ibrutinib therapy. Among patients who held ibrutinib, those who missed doses for ³8 consecutive days experienced a shorter PFS compared to patients who missed <8 consecutive days (median, 35 months vs. NR; p=0.005). This was observed for patients with both the $MYD88^{MUT}$ $CXCR4^{WT}$ (median, 48 months vs. NR; p=0.01) and $MYD88^{MUT}$ $CXCR4^{WHIM}$ (median, 22 months vs. NR; p=0.03) tumor genotype. No patients with $MYD88^{WT}$ $CXCR4^{WT}$ held ibrutinib for ³8 consecutive days.

Conclusion: Temporary interruption of ibrutinib therapy is associated with transient increases in serum IgM level which appear to persist longer for patients with the $MYD88^{MUT}$ $CXCR4^{WHIM}$ tumor genotype. Patients with DI higher than 97% had longer PFS, and holding ibrutinib >1 week during the entire treatment duration was associated with increased PFS events. These findings suggest ibrutinib holds should be minimized and ibrutinib restarted as soon as clinically indicated to achieve optimal patient outcomes.