Ixazomib, dexamethasone and rituximab (IDR) as primary therapy for symptomatic Waldenström's Macroglobulinemia

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Introduction: Waldenström's macroglobulinemia (WM) is an incurable B-cell lymphoma characterized by the accumulation of IgM-secreting lymphoplasmacytic cells in the bone marrow and other organs. Bortezomib in combination with rituximab and dexamethasone (BDR) is highly active as primary therapy in WM, though treatment-related neuropathy is common with BDR in WM, and often leads to premature treatment discontinuation. Ixazomib is an orally administered proteasome inhibitor with limited neuropathy that is active in myeloma, but has not been previously evaluated in WM.

Methods: Symptomatic, previously untreated patients with a clinicopathological diagnosis of WM were included in this prospective, single-arm phase II study evaluating ixazomib 4 mg PO on days 1, 8 and 15 + dexamethasone 20 mg PO/IV on days 1, 8 and 15 + rituximab 375 mg/m2 IV on day 1 (IDR) were administered for six 4-week cycles (induction) followed by six 8-week cycles (maintenance). Rituximab was held for the first two cycles of therapy to minimize risk of IgM flare. Zoster prophylaxis and proton pump inhibitors were administered throughout IDR therapy. The study was approved by the institutional review board at the Dana-Farber Cancer Institute, and registered under Clinicaltrials.gov ID NCT02400437.

Results: Twenty-six WM patients were enrolled and were exposed to IDR therapy. The median age at WM diagnosis was 63 (range 46-81 years) and the median age at initiation of therapy was 65 (range 46-82 years). Baseline median hemoglobin was 10.2 (range 6.9-13.2 g/dL), median serum IgM level was 5,068 (range 653-7,650 mg/dL), 46% of patients had lymphadenopathy and 12% had splenomegaly. The median bone marrow involvement was 55% (range 5-95%). The MYD88 L265P gene mutation was identified in all cases. CXCR4 gene mutations were identified in 15 patients (58%) of patients, of whom 10 (67%) had nonsense, and 5 (33%) frameshift mutations. Sixteen patients have completed the induction phase of therapy at this time. Following induction therapy, the median serum IgM level decreased to 2,316 (range 287-5,820 mg/dL), median hemoglobin increased to 13.1 (range 10.4-14.6 g/dL), and median bone marrow involvement decreased to 23% (range 0-76%). P-value <0.001 for all comparisons against baseline. The median time to response was 8 weeks. The median time to response in CXCR4 mutant patients was 12 weeks versus 8 weeks in wild-type CXCR4 patients (log-rank p=0.03). Using consensus response criteria, the overall response rate was 88% (VGPR 6%, PR 44%, MR 38%) with a major response rate of 50%. Major responses (VGPR + PR) were observed in 47% of patients with CXCR4 mutations versus 64% in those who were wild-type CXCR4 (p=0.32). Four patients have been taken off study; 2 for lack of response, 1 due to lack of clinical benefit with persistent failure to thrive while in PR, and 1 for progressive neuropathy while in PR although in part due to worsening of diabetic neuropathy. No other grade 3 or 4 adverse events were reported.

Conclusion: These preliminary data suggest that the combination of IDR is an active, well-tolerated, neuropathy-sparing regimen in symptomatic untreated WM patients.