Prospective Phase II Study of Ixazomib, Dexamethasone and Rituximab in Previously Untreated Patients with Waldenström Macroglobulinemia

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Introduction

Waldenström 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 (Treon et al. J Clin Oncol 2009). 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 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) for a total of 12 cycles. Rituximab was held for the first two cycles of therapy to minimize risk of an 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.

Table 1. Baseline characteristics

Characteristics	Median or number	Range or %
Age at WM diagnosis (years)	62.5	46-81
Age at enrollment (years)	65	46-82
Male sex	21/26	81%
Serum IgM (mg/dl)	4,528	653-7,650
Serum IgA (mg/dl)	61.5	8-140
Serum IgG (mg/dl)	609	160-4677
Hemoglobin (g/dl)	10.2	6.9-13.2
Platelet count (K/ul)	211.5	77-420
Beta-2-microglobulin (mg/l)	4.0	1.8-10.8
Low IPSSWM score	5/26	19%
Intermediate IPSSWM score	11/26	42%
High IPSSWM score	10/26	38%
Adenopathy	12/26	46%
Splenomegaly	3/26	12%
Bone marrow involvement (%)	55%	5-95%
MYD88 L265P mutation	26/26	100%
CXCR4 mutation	15/26	58%

Figure 1. Categorical response

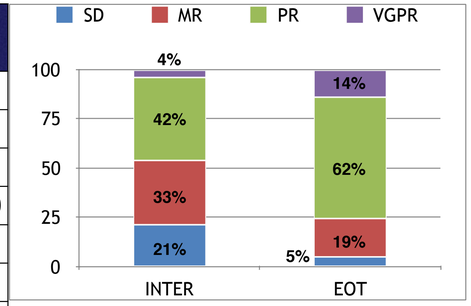

Figure 2. Serum IgM response

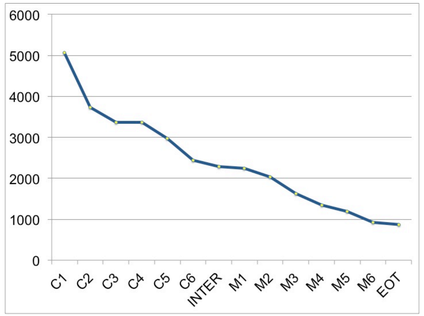

Figure 3. Hemoglobin response

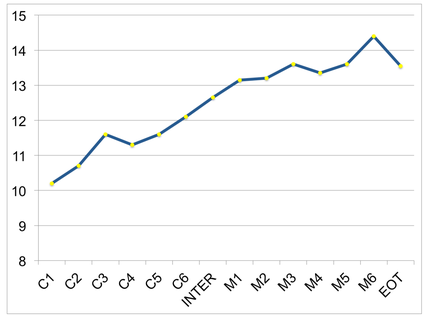

Figure 4. PFS estimate

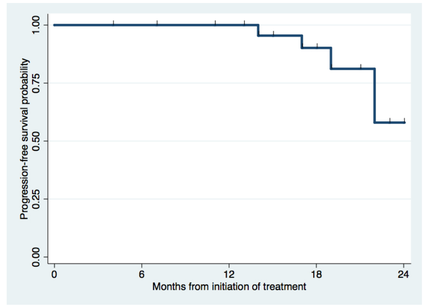

Figure 5. Time to response based on CXCR4 mutations

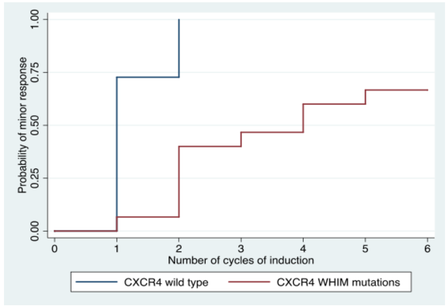

Table 2. Selected adverse events

	All grades	Gr 2	Gr 3
Infusion rxs	10	5	
Neuropathy	6		1
Rash	7	2	
Hyperglycemia	5	1	
Vomiting	4	1	

Conclusion

Our study shows that the combination of IDR is highly effective in symptomatic untreated WM patients with an ORR of 95% and 18-month PFS rate of 90%. IDR was well-tolerated, and represents a novel, neuropathy-sparing proteasome inhibitor regimen for the treatment of WM. CXCR4 mutations impact the time to response but not the depth of response to IDR.

Disclosures:
Castillo: Pharmacyclics: Consultancy, Research; Millennium: Research Funding; Abbvie: Research Funding; Janssen: Consultancy, Research
Treon: Pharmacyclics: Consultancy, Research