Phase II Study of Venetoclax in Previously Treated Waldenström Macroglobulinemia

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Background

- Venetoclax is an oral BCL2 antagonist approved for the treatment of chronic lymphocytic leukemia.
- However, the role of venetoclax in Waldenstrom macroglobulinemia (WM) is unknown
- Immunophenotypic and genomic sequencing studies have shown that BCL2 is highly expressed and activated in WM cells (Chng Blood 2006; Hunter Blood 2016).
- In a study of patients with non-Hodgkin lymphoma, venetoclax showed efficacy in 4 patients with WM (Davids J Clin Oncol 2017).
- We initiated a phase II study to evaluate the safety and efficacy of venetoclax monotherapy in previously treated patients with WM (NCT02677324).

Methods

- The study was approved by the Institutional Review Board at each participating institution, and all patients had provided informed consent prior to treatment initiation.
- Venetoclax was given in the outpatient setting and followed a ramp-up of 200 mg daily days 1-7, 400 mg daily days 8-14, then 800 mg daily thereafter, for maximum of 2 years.
- Patients were closely monitored for tumor lysis syndrome (TLS) during the first 24 hours of each dose escalation.
- Toxicity was graded per CTCAE v.4.03.
- Response was assessed based on IWWM-6 criteria.
- Primary outcome was overall response rate.
- Sample size of 30 patients was estimated based on H0=40% versus H1=70% with alpha=0.05 and power=80%.

Selected inclusion criteria

- Clinicopathological diagnosis of WM
- Serum IgM >2 x ULN
- Previously treated
- Age ≥18 years
- Good performance
- Normal organ and marrow function

Selected exclusion criteria

- Serious medical condition
- Concurrent anti-cancer agent
- Known CNS lymphoma
- Active HIV, HBV, HCV infection
- Lactating or pregnant women

Results

Table 1. Patients' baseline characteristics

Characteristic	Number (%)
Age, years	66 (39-80)
Male sex	17 (57%)
Previous treatments	2 (1-10)
Prior BTK inhibitors	15 (50%)
MYD88 L265P	30 (100%)
CXCR4 mutations	16 (53%)
Serum IgM level (mg/dl)	3,543 (642-7,970)
Hemoglobin level (g/dl)	10.6 (6.4-13.5)
Platelet count (K/ul)	222 (7-445)
Lymphadenopathy	9 (30%)
Splenomegaly	6 (20%)

Figure 1. Best response to venetoclax in 30 patients with WM

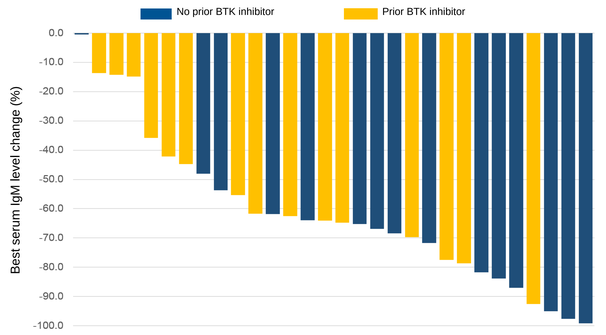

Table 2. Categorical responses to venetoclax in 30 patients with WM

Response	Number (%)
Overall (≥Minor)	26 (87%)
Major (≥Partial)	22 (74%)
Very good	5 (17%)
Partial	17 (57%)
Minor	4 (13%)
Stable	4 (13%)

Patients with refractory disease had lower major response rate than patients with relapsed disease (57% vs. 95%; p=0.01).

Major response rate was not statistically different based on prior BTKi exposure or CXCR4 mutational status.

However, VGPR rate was lower in patients with previous BTKi exposure (7% vs. 27%; p=0.10), and those with CXCR4 mutations (6% vs. 29%; p=0.10).

Median time to response (TTR) was 9 weeks and was slower in patients with prior BTKi exposure than in patients without (19 vs. 6 weeks; p=0.02).

TTR was not impacted by relapsed vs. refractory disease or CXCR4 mutations.

Figure 2. Bone marrow response to venetoclax in 30 patients with WM

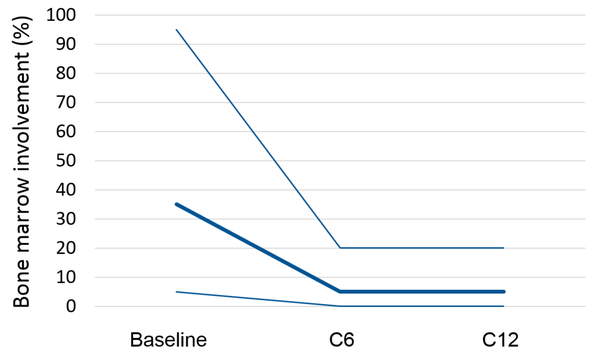

Table 3. Adverse events to venetoclax in 30 patients with WM

Adverse Event, N (%)	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Neutropenia	2 (7)	4 (14)	6 (21)	3 (10)	15 (52)
Anemia	1 (3)	5 (17)	2 (7)	0	8 (28)
URI	2 (7)	0	1 (3)	0	3 (10)
Nausea	9 (31)	4 (14)	0	0	13 (48)
Headache	2 (7)	3 (10)	0	0	5 (17)
diarrhea	4 (14)	1 (3)	0	0	5 (17)
Chills	2 (7)	1 (3)	0	0	3 (10)
Constipation	2 (7)	1 (3)	0	0	3 (10)
Mucositis oral	2 (7)	1 (3)	0	0	3 (10)
Muscle Cramps	1 (3)	1 (3)	0	0	2 (7)

There was only 1 episode of laboratory TLS.
There were no deaths and no IgM flares.

Conclusion

Our interim results show that venetoclax provides a safe and effective treatment option for patients with symptomatic, previously treated WM, including those previously exposed to BTKi.

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