Ibrutinib Monotherapy in Symptomatic, Treatment-Naive patients with Waldenstrom's Macroglobulinemia.

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Background

Whole genome sequencing has revealed activating mutations in MYD88 (95%) and CXCR4 (30-40%) in WM patients (Treon *et al.*, NEJM 2012; Hunter *et al.*, Blood 2013; Xu *et al.*, BJH 2016). MYD88 mutations trigger NF-kB activation via BTK and HCK, both targets of ibrutinib (Yang *et al.*, Blood 2013; Blood 2016). WM cells expressing CXCR4 mutations also show enhanced AKT and ERK activation, and resistance to ibrutinib (Cao *et al.*, Leukemia 2014). Among previously-treated patients, ibrutinib monotherapy produced overall responses in 90%; and major responses in 77% of patients (Treon *et al.*, NEJM 2015), and a median progression-free survival >5 years (Treon et al, ASH 2017). The absence of MYD88 mutations and presence of CXCR4 mutations adversely impacted time to major response, overall, major and VGPR response rates, as well as the median time to progression in previously treated WM patients (Treon *et al.*, ASH 2017). Among rituximab-refractory patients, similar response rates were observed, and the 18-month PFS and OS survival rates were 86% and 97%, respectively (Dimopoulos *et al.*, Lancet Oncol 2017). Patients with CXCR4 mutations showed slower improvements in serum IgM and hemoglobin levels. Herein, we report on the safety and efficacy of the first prospective study of ibrutinib monotherapy in symptomatic, treatment-naïve WM patients, and impact of CXCR4 mutation status on response outcome.

Patients and Methods

Symptomatic, treatment-naive WM patients were eligible. Ibrutinib (420 mg) was administered daily until progression or unacceptable toxicity. Dose reduction was permitted. All patient tumors were genotyped for MYD88 and CXCR4 mutations. Responses were determined using International Workshop for WM (IWWM)-6 criteria (Owen *et al.*, BJH 2013). **Data cutoff was January 22, 2018. The study was investigator sponsored and supported by Pharmacyclics LLC, an AbbVie Company.**

Table 1. Baseline clinical characteristics.

Characteristic	All WM Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	P-value
N=	30	16	14	
Median age (years)	67 (43-83)	67 (43-83)	67 (43-75)	0.94
Sex				
Male	23 (77%)	12 (75%)	11 (79%)	0.99
Female	7 (23%)	4 (25%)	3 (21%)	
IPSSWM score – no. (%)				
Low	5 (17%)	3 (19%)	2 (14%)	0.36
Intermediate	11 (37%)	4 (25%)	7 (50%)	
High	14 (47%)	9 (56%)	5 (36%)	
Serum Immunoglobulins				
Median IgM (mg/dl)	4,370 (844-10,321)	3,928 (858-10,321)	5,295 (844-7,450)	0.31
IgM >3,000 mg/dl	18 (60%)	9 (56%)	9 (64%)	0.65
Median IgA (mg/dl)	62 (11-576)	62 (15-576)	60 (11-132)	0.96
Median IgG (mg/dl)	563 (191-3,251)	606 (278-3,251)	470 (191-1,108)	0.38
Median ANC (ul)	3,370 (1,680-9,900)	3,450 (1,750-9,900)	3,220 (1,680-6,270)	0.38
Hemoglobin level				
Median (g/dl)	10.3 (7.5-14.4)	10.1 (8.6-14.4)	10.6 (7.5-13.5)	0.23
<11 g/dl – no. (%)	20 (67%)	12 (75%)	8 (57%)	0.30
<10 g/dl – no. (%)	10 (33%)	7 (44%)	3 (21%)	0.20
Platelet count				
Median (ul)	247,000 (59,000-491,000)	288,000 (129,000-418,000)	199,000 (59,000-491,000)	0.12
<100,000/ul – no. (%)	2 (7)	0 (0)	2 (14)	0.12
Serum β_2-microglobulin				
Median (mg/l)	3.8 (2.0-7.6)	4.2 (2.3-6.9)	3.4 (2.0-7.6)	0.07
>3 mg/l – no. (%)	22 (73)	13 (81)	9 (64)	0.29
Median BM Disease Involvement	65% (5-95%)	60% (5-95%)	70% (10-90%)	0.60
Extramedullary Disease				
Adenopathy >1.5 cm – no. (%)	10 (33%)	8 (50%)	2 (14%)	0.04
Splenomegaly >15 cm – no. (%)	5 (17%)	4 (25%)	1 (7%)	0.19

Results

Thirty WM patients received ibrutinib. All carried MYD88 mutation, and 14 (47%) CXCR4 mutation. Following ibrutinib, median serum IgM levels declined from 4,370 to 1,513 mg/dL; bone marrow involvement declined from 65% to 20%; and hemoglobin rose from 10.3 to 13.9 g/dL (p<0.0001 for all comparisons). Overall (≥minor) and major (≥partial) responses for all patients were 100% and 83%, respectively. Major (94% vs. 71%) and very good partial (31 vs. 7%) responses were higher, and time to major responses more rapid (1.8 vs. 7.3 months; p=0.01) in wild-type versus mutated CXCR4 patients, respectively. With a median follow-up of 14.6 months, two patients (both CXCR4 mutated) progressed. The 18-month estimated progression-free survival is 92% (95% CI 73-98%). All patients are alive.

Table 2. Response rates and kinetics to ibrutinib therapy.

	All Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	P-value
N=	30	16	14	N/A
Overall Response Rate-no. (%)	30 (100%)	16 (100%)	14 (100%)	1.00
Major Response Rate-no. (%)	25 (83%)	15 (94%)	10 (71%)	0.16
Categorical responses				
Minor responses-no. (%)	5 (17%)	1 (6%)	4 (29%)	0.16
Partial responses-no. (%)	19 (63%)	10 (63%)	9 (64%)	1.00
Very good partial responses-no. (%)	6 (20%)	5 (31%)	1 (7%)	0.18
Median time to response (months)				
Minor response (≥Minor response)	1.0	0.9	1.7	0.07
Major response (≥Partial response)	1.9	1.8	7.3	0.01

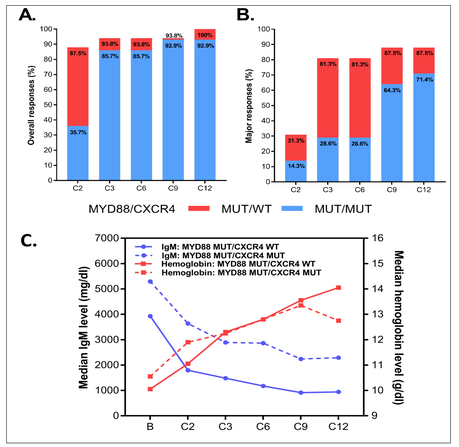

Figure 1. Cumulative overall and major response rates, and changes in serum IgM and hemoglobin levels by treatment cycles stratified by CXCR4 mutation status. Overall (A) and major (B) responses, and serial changes in serum IgM and hemoglobin levels (C) by ibrutinib treatment cycles by CXCR4 mutation status are shown at the denoted cycle. All patients had MYD88 mutated disease.

Results

Figure 2. Kaplan-Meier curve for progression-free survival.

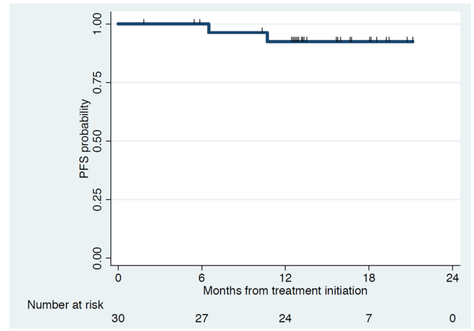

Table 3. Adverse events associated with ibrutinib therapy.

Event or Abnormality	Grade 2	Grade 3	Grade 4	Total Grades 2-4
Alanine transaminase elevation	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Arthralgia	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Aspartate transaminase elevation	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Atrial fibrillation	3 (10%)	0 (0%)	0 (0%)	3 (10%)
Bruising	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Cellulitis	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Diarrhea	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Drug-induced hepatitis	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Foot pain	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Hematoma	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Hypertension	2 (7%)	2 (7%)	0 (0%)	4 (13%)
Mucosal infection	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Neck abscess	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Neutropenia	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Palpitations	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Pneumonia	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Procedural hemorrhage	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Rash: maculopapular	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Rash: vasculitic	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Rectal bleeding	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Thrombocytopenia	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Upper respiratory infection	2 (7%)	0 (0%)	0 (0%)	2 (7%)
Urinary tract infection	2 (7%)	0 (0%)	0 (0%)	2 (7%)

*Listed are adverse events that were deemed by the investigators to be possibly, probably, or definitely associated with the study drug; no related grade 4 toxicities were observed.

Conclusion

Ibrutinib is highly active, produces durable responses, and is safe as primary therapy in symptomatic WM patients. CXCR4 mutation status impacts responses to ibrutinib.