# Long-Term Follow-up of Previously Treated Patients Who Received Ibrutinib for Symptomatic Waldenström's Macroglobulinemia: Update of Pivotal Clinical Trial

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## Background

MYD88 mutations are present in 95% of WM patients and trigger malignant cell growth through Bruton's Tyrosine Kinase and Hematopoietic Cell Kinase, both targets of ibrutinib. CXCR4 mutations are found in 30-40% of previously treated WM patients and confer *in vitro* resistance to ibrutinib. We therefore performed a prospective study that examined the activity of ibrutinib in previously treated WM patients (Treon et al, NEJM 2015). The findings showed that ibrutinib was highly active in previously treated WM patients and supported the first ever FDA and EMA drug approval for the treatment of WM. Herein, we provide a long-term follow-up of this study. Sixty-three symptomatic WM patients who received at least one prior therapy were enrolled.

## Patients and Methods

We conducted a prospective, single-arm phase II study evaluating ibrutinib in symptomatic relapsed/refractory WM patients. All patients had a clinicopathological diagnosis of WM, and met criteria for treatment initiation based current international guidelines (Owen BJH 2013; Kyle Semin Oncol 2003). Ibrutinib at a daily dose of 420 mg was administered orally until disease progression or unacceptable toxicity. Dose reduction was permitted. *MYD88* and *CXCR4* mutation status were determined by allele-specific polymerase chain reaction (AS-PCR) and Sanger sequencing methods, as previously described (Xu Blood 2013; BJH 2015). **Data cutoff was July 15, 2017.**

## Results

**Table 1**. Baseline clinical characteristics.

| Characteristic | Patients (N=63) |
|---|---|
| Age, years | 63 (44-86) |
| Male sex | 48 (76%) |
| IPSSWM score | |
| Low | 14 (22%) |
| Intermediate | 27 (43%) |
| High | 22 (35%) |
| Serum IgM level, mg/dl | 3,520 (724-8,390) |
| Hemoglobin level, g/dl | 10.5 (8.2-13.8) |
| Serum β2-microglobulin, mg/l | 3.9 (1.3-14.2) |
| Adenopathy ≥1.5 cm | 37 (59%) |
| Splenomegaly ≥15 cm | 7 (11%) |
| Bone marrow involvement, % | 60 (3-95) |
| Prior Therapies | 2 (1-9) |
| Refractory to Last Therapy | 25 (40%) |
| MYD88 Mutation (n=63) | 58 (92%) |
| CXCR4 Mutation (n=62) | 21 (34%) |

## Results

Patients received protocol administered ibrutinib for 40 months, and transitioned to commercial supply thereafter. Ibrutinib was administered until progression or intolerance. The median time on ibrutinib was 46.6 (range 0.5-60 months). Improvements in categorical responses occurred with prolonged treatment. The overall and major (>PR) response rates were 90.4% and 77.7%, respectively, and were not impacted by prior lines of therapy or relapsed or refractory status. Seventeen (27%) patients achieved a VGPR. No complete responses were observed. At best response, median serum IgM level declined from 3,520 to 821 mg/dL (p<0.0001). At baseline 46/63 (73%) patients had a serum IgM >3,000 mg/dL versus 4/63 (6%) patients at best response (p<0.0001). At best response, median bone marrow involvement declined from 60% to 20% (p<0.0001), and the median hemoglobin level increased from 10.5 to 14.2 g/dL (p<0.0001)..

**Table 2.** The impact of MYD88 and CXCR4 mutation status on responses and time to at least minor (overall) and PR or better (major) responses.

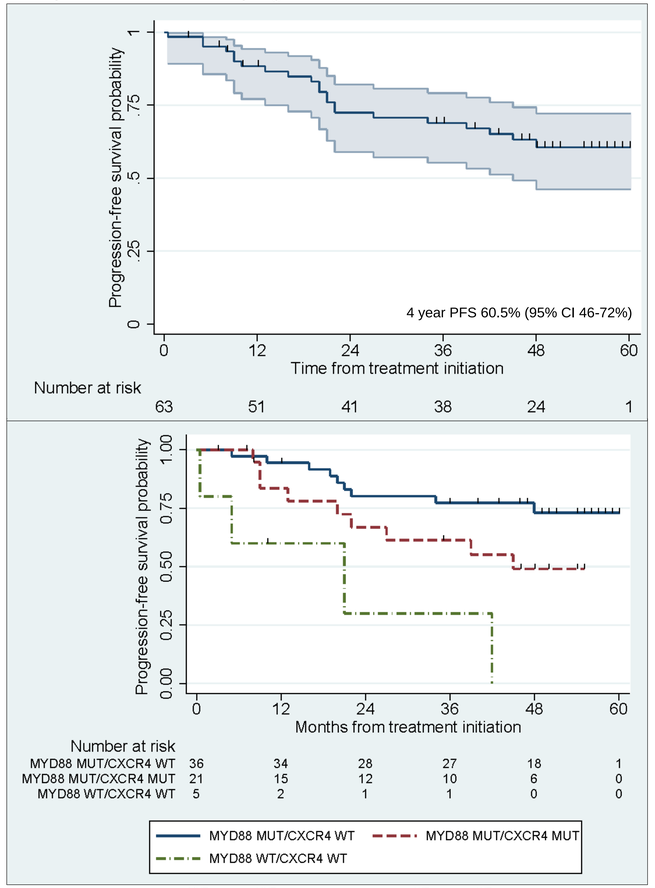
| | All patients (n=63) | $MYD88^{MUT}$ $CXCR4^{WT}$ (n=36) | $MYD88^{MUT}$ $CXCR4^{MUT}$ (n=21) | $MYD88^{WT}$ $CXCR4^{WT}$ (n=5) | P-Value |
|---|---|---|---|---|---|
| Overall Responses (%) | 90.4 | 100 | 85.7 | 60 | 0.0038 |
| Major Responses (%) | 77.7 | 97.2 | 66.6 | 0 | <0.001 |
| VGPR (%) | 27 | 41.6 | 9.5 | 0 | 0.0114 |
| Median Time to Minor Response or better (months) | 1.0 (range 1.0-22.5) | 1.0 (range 1.0-15) | 1.0 (range 1.0-22.5) | 1.0 (range 1.0-18) | 0.1 |
| Median Time to Major Response (months) | 2.0 (range 1.0-49) | 2.0 (range 1.0-49) | 6.0 (range 1.0-40) | N/a | 0.05 |

*One patient had MYD88 mutation, but no CXCR4 mutation determination; this patient had stable disease.

Adverse events (Grade >2) that were at least possibly related to protocol therapy in >5% of patients during protocol therapy were as follows: anemia (n=4); atrial fibrillation (n=6); GERD (n=5); hypertension (n=5); neutropenia (n=14); oral mucositis (n=4) pneumonia (n=6); skin infection (n=3); thrombocytopenia (n=9). Seven patients (11%) had atrial arrhythmia [Grade 1 (n=1); Grade 2 (n=5); Grade 3 (n=1)] on ibrutinib. Six of the seven patients continued ibrutinib with medical management for their atrial arrhythmia. Four patients came off protocol therapy for toxicity: atrial fibrillation (n=1); infection not related to drug therapy (n=1), procedure related hematoma (n=1), and thrombocytopenia (n=1). The findings from the long-term follow-up of this pivotal study confirm that ibrutinib is highly active in symptomatic patients with relapsed and refractory WM, and produces durable responses.

## Results

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




By comparison, median PFS for $MYD88^{MUT}CXCR4^{MUT}$ is 45 months, $MYD88^{WT}CXCR4^{WT}$ was is 21 months, and median PFS for $MYD88^{MUT}CXCR4^{WT}$ has not been reached (Log-rank p=0.0093 for 3 way comparison).

## Conclusion

Prolonged ibrutinib therapy is associated with improvements in categorical responses, including attainment of VGPR. Ibrutinib response activity and PFS are impacted by MYD88 and CXCR4 mutation status in this patient population.

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