Ibrutinib shows prolonged progression-free survival in symptomatic, previously treated patients with MYD88 mutated Waldenstrom's Macroglobulinemia: Long-term Follow-up of Pivotal Trial (NCT01614821).

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Background

Activating mutations in MYD88 mutations are present in ≥ 95% of WM patients and trigger malignant cell survival through activation of BTK and HCK, both targeted by ibrutinib (Figure 1; Yang *et al.*, Blood 2013; Blood 2016). CXCR4 mutations are found in 30-40% of WM patients and confer *in vitro* resistance to ibrutinib (Cao *et al.*, Leukemia 2014; Rocarro *et al.*, Blood 2014; Xu *et al.*, BJH 2016). Given these findings, we investigated the clinical activity of ibrutinib in previously treated WM patients (Treon *et al.*, NEJM 2015). The initial findings showed that ibrutinib was highly active in previously treated WM patients, and provided support for first ever FDA and EMA drug approval in WM.

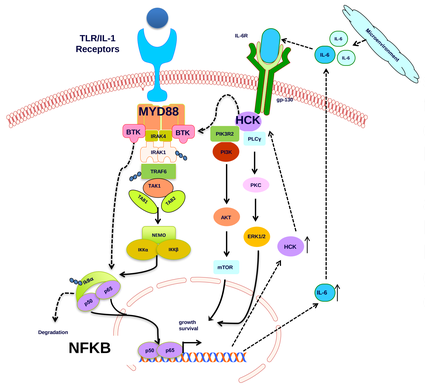


Figure 1. Mutated MYD88 related signaling in WM. Mutated MYD88 transactivates NFKB through divergent pathways that include IRAK1/IRAK4 and BTK. Mutated MYD88 also triggers transcription and activation of the SRC family member HCK. Activated HCK can then trigger BTK, AKT, and ERK1/2 mediated pro-growth and survival signaling in WM cells.

Patients and Methods

Sixty-three symptomatic WM patients who received at least one prior therapy were enrolled, with the following baseline characteristics: median age 63 (range 44-86 yrs); intermediate/high WMIPSS score (78%), median serum IgM 3,520 (range 724-8,390 mg/dL); median hemoglobin level 10.5 (range 8.2-13.8 g/dL); median serum B_2M level 3.9 (1.3-14.2 mg/L); adenopathy >1.5 cm (59%); splenomegaly >15 cm (11%), and median bone marrow disease involvement 60% (range 3-95%). The median number of prior therapies was 2 (range 1-9), and 40% of patients were refractory to their previous therapy. MYD88 and CXCR4 genotyping was performed for 63 and 62 patients, respectively. Ibrutinib was initiated at 420 mg a day, and dose de-escalation for toxicity permitted. Ibrutinib was administered until progression or intolerance, and patients could consent to continue follow-up for response assessment after active protocol follow-up (>40 months) on commercially sourced ibrutinib. Responses were determined using international Workshop for WM (IWWM)-3 criteria (Anderson *et al.*, JNCCN 2012). The study was investigator sponsored and supported by Pharmacyclics LLC, an AbbVie Company.

Results

The median time on ibrutinib was 47 months (range 0.5-64 months), and median on study follow-up was 50 (range 0.5-64 months). Improvements in categorical responses occurred with prolonged treatment, with overall (minor response or better) and major (partial response or better) response rates of 90.4% and 77.7%, respectively. Response rates were not impacted by number of previous treatment regimens (1-3 vs. ≥3) or disease status (relapsed vs. refractory). Eighteen (29%) 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 rose from 10.5 to 14.2 g/dL (p<0.0001). The impact of MYD88 and CXCR4 mutation status on responses, and time to at least minor and major response attainment are shown in **Table 1.**

Table 1. Response rates and kinetics to ibrutinib therapy based on MYD88 and CXCR4 Mutation Status.

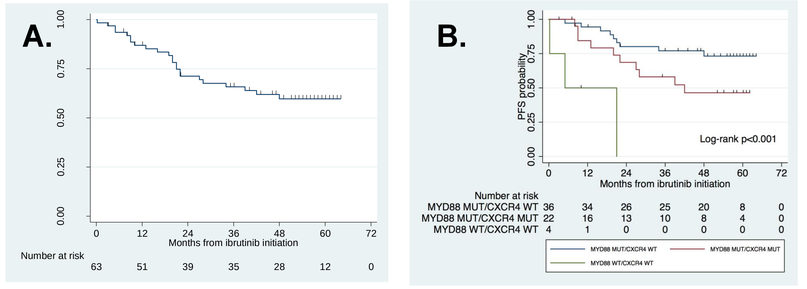
	All Patients (n=63)	$MYD88^{MUT}CXCR4^{WT}$ (n=36)	$MYD88^{MUT}CXCR4^{Mut}$ (n=22)	$MYD88^{WT}CXCR4^{WT}$ (n=4)	P-value
Overall Responses (%)	90.4	100	86.4	50.0	<0.001
Major Responses (%)	77.7	97.2	63.6	0	<0.001
VGPR (%)	27.0	44.4	9.1	0	<0.001
Median Time to Minor Response or better (months)	1.0 (range 1.0-22.5)	1.0 (range 1.0-15)	1.0 (range 1.0-22.5)	1.0	0.10
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 a MYD88 mutation, but no CXCR4 mutation determination. This patient had stable disease. One patient at initial reporting (Treon et al, NEJM 2015) was thought to have MYD88 wild-type disease, and was subsequently found to have MYD88 and CXCR4 mutated disease upon genotyping of CD19-selected WM cells.

Figure 2 shows the Kaplan Meier curves for progression free survival (PFS) for all study participants (A), and by MYD88 and CXCR4 mutation status (B). With a median study follow-up of 50 months, the 5-year PFS for all patients was 60% (95% CI 46-71%). For patients with $MYD88^{Mut}CXCR4^{WT}$, the median PFS was not reached (5-year PFS was 73%; 95% CI 55-85%). For patients with $MYD88^{Mut}CXCR4^{Mut}$, the median PFS was 42 months (5-year PFS 46%; 95% CI 23-67%), and for those with $MYD88^{WT}$ disease it was 5 months (Log-rank p<0.001 for 3-way comparison).

Results

Figure 2. Progression-free survival for all study participants (A), and by MYD88 and CXCR4 mutation status (B) following ibrutinib therapy of previously-treated WM patients.



The 5-year overall survival (OS) for all patients was 87% (95% CI 73-94%), and 93% (95% CI 75-98%) and 80% (95% CI 49-93%) for $MYD88^{Mut}CXCR4^{WT}$ and $MYD88^{Mut}CXCR4^{Mut}$ patients, respectively (Log-rank p=0.41). 5-year OS could not be estimated for $MYD88^{WT}$ patients.

Adverse events associated with ibrutinib therapy.

Adverse events (Grade ≥2) in ≥5% of patients during active follow-up were: neutropenia (22%); thrombocytopenia (14%), pneumonia (9%); GERD (8%); hypertension (8%); anemia (6%); and skin infection (5%). Seven patients (11%) had atrial arrhythmia [Grade 1 (n=1); Grade 2 (n=5); Grade 3 (n=1)], and 6 continued ibrutinib following medical management of 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). Two others had disease transformation, both with prior nucleoside analogue exposure. One heavily pre-treated patient with 5q- cytogenetic findings pre-ibrutinib treatment developed acute leukemia while in a major response on ibrutinib for WM.

Conclusions

The findings confirm that ibrutinib is highly active and produces long-term responses in symptomatic patients with relapsed and refractory WM. Prolonged ibrutinib therapy is associated with improvements in categorical responses, including attainment of VGPR. Response activity, time to major response, and PFS are impacted by MYD88 and CXCR4 mutation status in this patient population.