ZANUBRUTINIB DOSING AND MUTATIONAL STATUS IMPACT RESPONSE AND OUTCOMES IN WALDENSTRÖM MACROGLOBULINEMIA

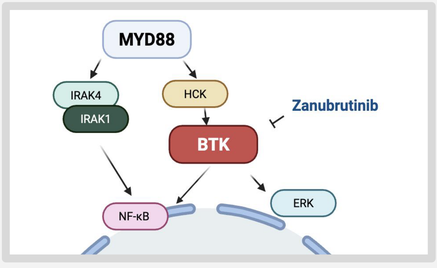
A Guijosa [1,2], N Tsakmaklis [1], M Kobs [1], N Budano [1], J Nguyen [1], A Eurell [1], K Meid [1], ML Guerrera [1,2], ZR Hunter [1,2], SP Treon [1,2], S Sarosiek [1,2], JJ Castillo [1,2]

1. Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute
2. Department of Medicine, Harvard Medical School

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INTRODUCTION

Zanubrutinib is a covalent BTK inhibitor and a standard treatment for Waldenström macroglobulinemia (WM) based on a phase III clinical trial. Off-trial experience with zanubrutinib in WM, however, is limited.

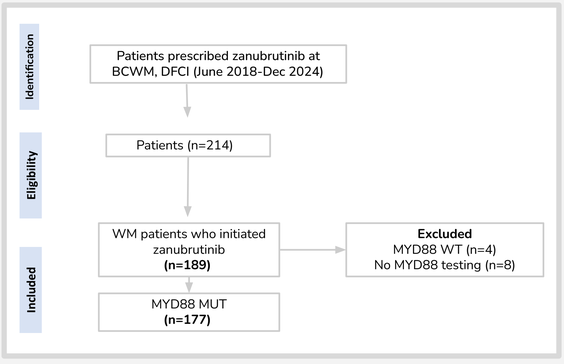


AIM

Assess the impact of zanubrutinib dosing and mutational status on response (VGPR) and progression-free survival (PFS) in a large off-trial cohort.

METHODS

Patients prescribed zanubrutinib at Dana-Farber Cancer Institute's Bing Center for Waldenström Macroglobulinemia (2018–2025) were identified via pharmacy informatics. Diagnosis was confirmed by EMR review (IWWM2); response assessed per IWWM11. Multivariable logistic and Cox models adjusted for age, sex, prior treatment, dose, and mutational status.



RESULTS

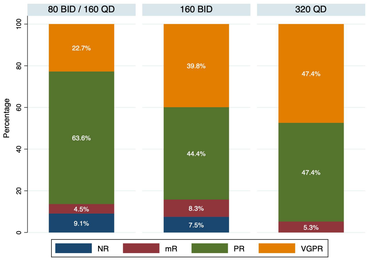
177 patients with MYD88-mutated WM were included.

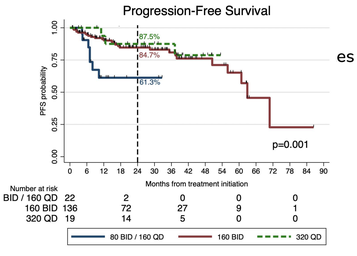
Characteristic		*n* = 177
Age, median (range)		71 (47-96)
Sex, n (%)	*Female*	78 (44.1%)
	Male	99 (55.9%)
Hemoglobin (g/dL), median (range)		10.6 (5.5-16.7)
IgM (mg/dL), median (range)		2770.0 (40-10,952)
Bone marrow involvement (%), median (range) (n=131)		70.0 (3.0-95.0)
MYD88 , n (%)	*WT*	0 (0%)
	MUT	177 (100%)
CXCR4 (n=154), n (%)	*WT*	91 (59.1%)
	MUT	63 (40.9%)
TP53 (n=146), n (%)	*Unaltered*	124 (84.9%)
	Altered	22 (15.1%)
Treatment Status, n (%)	*Untreated*	105 (59.3%)
	Treated	72 (40.7%)
Lines of therapy, median (Range)		1 (0-7)
Transitioned from ibrutinib, n (%)	*No*	137 (77.4%)
	Yes	40 (22.6%)
Initial zanubrutinib dose, n (%)	*80 mg BID / 160 mg QD*	22 (12.4%)
	160 mg BID	136 (76.8%)
	320 mg QD	19 (10.7%)

Zanubrutinib dosing and outcomes

VGPR rates were similar between 160-BID and 320-QD (40% vs. 47%; p=0.53), with comparable 24-month PFS (85% vs. 88%; p=0.70).

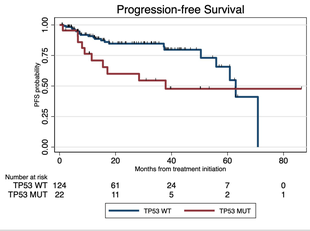
Reduced dosing resulted in lower VGPR (23% vs. 41%; p=0.10) and 24-month PFS rates (61% vs. 85%; p=0.001).





TP53 Mutational Status

TP53 mutations were associated with lower 24-month PFS rates (60% vs. 85%; p=0.039) but did not affect response.



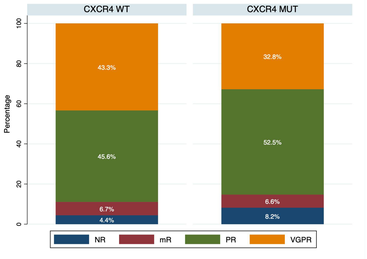
Multivariate analysis

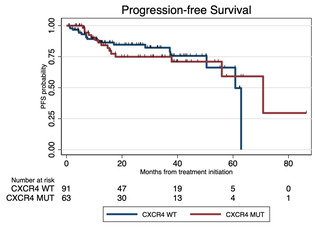
Variable	OR (VGPR)	*p*-value
Age >65	1.52	0.339
Male Sex	0.98	0.952
CXCR4 Mut	0.54	0.123
TP53 Mut	1.48	0.461
Treated (vs. TN)	1.78	0.168
Dosage (half vs. full)	**0.22**	**0.032**

Variable	HR (PFS)	*p*-value
Age >65	1.52	0.506
Male sex	1.17	0.679
CXCR4 Mut	1.07	0.869
TP53 Mut	**2.69**	**0.018**
Treated (vs. TN)	**2.78**	**0.028**
Dosage (half vs. full)	**6.71**	**<0.001**

CXCR4 mutational status

CXCR4 mutations were associated with numerically lower VGPR at best response (33% vs. 43%, p=0.19), shallower IgM reductions (frameshift: −68.6%, nonsense: −79.5%, wild-type: −85.6%; p=0.034), and delayed responses (6-month VGPR rates: 8% vs. 30%; p=0.02; longer median time to VGPR: 14 vs. 7 months; p=0.07), but did not impact PFS.





CONCLUSION

In the largest off-trial zanubrutinib-treated WM cohort, **standard QD and BID dosing showed similar efficacy.**

Reduced dosing and TP53 mutations were associated with worse outcomes while CXCR4 mutations delayed response but did not compromise 2-year PFS.

CONTACT INFORMATION

Alberto Guijosa
alberto_guijosaramirez@dfci.harvard.edu

Jorge J Castillo
jorgej_castillo@dfci.harvard.edu