ASPEN Biomarker Analysis: Response to Bruton Tyrosine Kinase Inhibitor (BTKi) Treatment in Patients with Waldenström Macroglobulinemia (WM) Harboring *CXCR4*, *TP53,* and *TERT* Mutations

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Background: *MYD88*, *CXCR4,* and *ARID1A* are the most frequently mutated genes in WM (*Blood* 2014;123[11]:1637-1646), and the mutational status of *MYD88* and *CXCR4* impacts BTKi ibrutinib efficacy in WM (*N Engl J Med* 2015;372(15):1430-1440; *Blood* 2020;136(18):2038-2050). ASPEN is a randomized, phase 3 study comparing zanubrutinib with ibrutinib in patients with *MYD88*^{MUT} WM; patients with *MYD88*^{WT} WM received zanubrutinib.

Aims: To evaluate low frequency genetic alterations in patients with WM and their association with efficacy of ibrutinib and zanubrutinib (separately and pooled) in different subpopulations.

Methods: 190 patients with *MYD88*^{MUT} (98 zanubrutinib; 92 ibrutinib) and 20 patients with *MYD88*^{WT} (all zanubrutinib) had evaluable NGS results. NGS was performed on pretreatment bone marrow aspirates

using a 152-gene panel with 0.25% sensitivity. Correlation between genetic alterations and treatment responses was analyzed by multivariate analyses.

Results: *CXCR4* (25.7%), *TP53* (24.8%), *ARID1A* (15.2%), and *TERT* (9.1%) were the most frequently mutated genes identified. *TP53*^{MUT} rates were similar between patients with *MYD88*^{MUT} and *MYD88*^{WT}. *TERT*^{MUT} was detected only in patients with *MYD88*^{MUT} (10% [19/190] mutation rate). *ARID1A*^{MUT} and *TERT*^{MUT} were associated with a higher rate of *CXCR4*^{MUT} and were more often detected in patients with *MYD88*^{MUT}.

In the pooled analysis of patients with *MYD88*^{MUT} WM, patients with *CXCR4*^{MUT}, *TP53*^{MUT}, and *TERT*^{MUT} trended toward a lower very good partial response (VGPR) + complete response (CR) rate and a less favorable progression-free survival (PFS) than patients with the respective WT alleles (HR=1.32, 2.15, and 1.79, respectively) (Figure 1). The median time to response (VGPR+CR) also appeared longer in patients with mutant alleles.

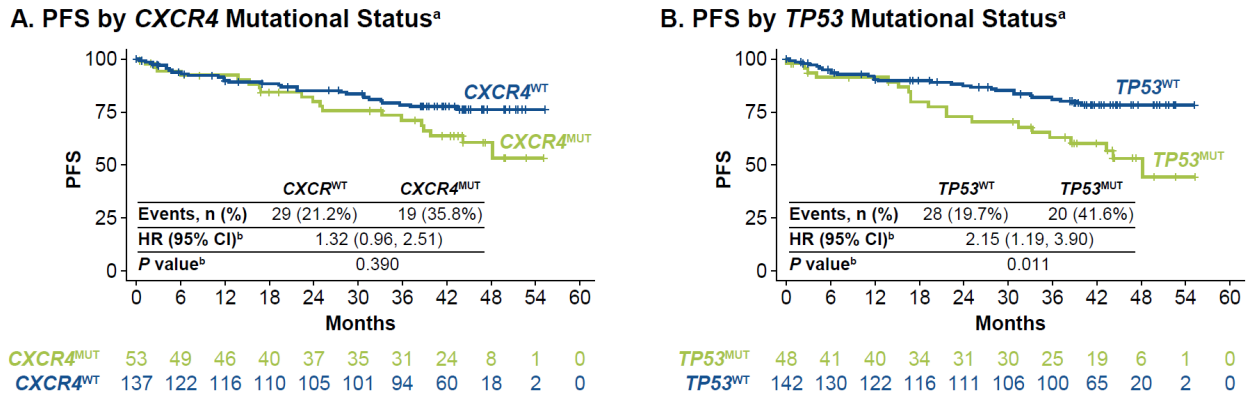
As shown in Table 1, among *CXCR4*^{MUT} subgroups, a lower major response rate (MRR) was observed in patients with *CXCR4*nonsense (*CXCR4*^{NS}; 53.8%; *P* = 0.135) compared with *CXCR4*frameshift (*CXCR4*^{FS}; 85.7%; *P* = 0.958) and *CXCR4*^{WT} (84.7%) receiving ibrutinib, whereas comparable MRR was observed across all subpopulations receiving zanubrutinib (85.7%, 73.7%, and 83.1%, respectively). The median PFS (months) in patients receiving ibrutinib by *CXCR4*^{NS}, *CXCR4*^{FS}, and *CXCR4*^{WT} mutational statuses was 39.8, 44.2, and not reached (NR), respectively, and NR in all subpopulations receiving zanubrutinib.

The VGPR+CR rate (13.6% vs 30.0%; *P*=0.202) and MRR (63.6% vs 85.7%; *P*=0.040) were lower in patients with *TP53*^{MUT} than *TP53*^{WT} with ibrutinib; VGPR+CR rate (34.6% vs 37.5%; *P*=0.636) and MRR (80.8% vs 81.9%; *P*=0.978) were similar between *TP53*^{MUT} and *TP53*^{WT} subgroups with zanubrutinib.

Among the 20 patients with *MYD88*^{WT}, 4 had *TP53*^{MUT}, with a lower MRR (50%), and none achieved VGPR or CR, compared with *TP53*^{WT} (63% MRR and 25% VGPR+CR).

Conclusion: In addition to *CXCR4*^{MUT} and *ARID1A*^{MUT}, *TP53*^{MUT} and *TERT*^{MUT} were detected at a high rate in the ASPEN study. *CXCR4*^{MUT}, *TP53*^{MUT}, and *TERT*^{MUT} were correlated with inferior response to BTKi therapy, and more patients with *CXCR4*^{MUT} were present in the zanubrutinib arm. Consistent with more potent inhibition of BTK, zanubrutinib demonstrated deeper responses in patients with *CXCR4*^{MUT} or *TP53*^{MUT} WM compared with ibrutinib, with more favorable response regardless of the mutational status.

Figure 1. Progression-Free Survivals in patients with *MYD88*^{MUT} WM by (A) *CXCR4* and (B) *TP53* Mutational Status



Data cutoff: October 31, 2021.

[a]Pooled analysis of patients with *MYD88*^{MUT} WM from cohort 1 including 98 treated by zanubrutinib and 92 treated by ibrutinib.

[b]HR and *P* values were estimated using a Cox regression model with *CXCR4 (*WT, FS, NS*), TP53 (*WT, MUT*),* and *TERT (*WT, MUT*)* mutational statuses as covariates. WT is the reference group.

FS, frameshift; HR, hazard ratio; NS, nonsense; PFS, progression-free survival; WT, wild type.

Table 1. Response Assessment by *CXCR4* and *TP53* Mutational Statuses in Patients With *MYD88*^{MUT} WM[a]

Patients with MYD88^{MUT} treated with ibrutinib					
	***CXCR4*^{WT} (n=72)**	***CXCR4*^{FS} (n=7)**	***CXCR4*^{NS} (n=13)**	***TP53*^{WT} (n=70)**	***TP53*^{MUT} (n=22)**
VGPR or better, n (%)[b]	22 (30.6)	0	2 (15.4)	21 (30.0)	3 (13.6)
OR (95% CI)	-	0.14 (0.00,3.23)	0.64 (0.13,3.08)	-	0.44 (0.12,1.55)
P value	-	*0.223*	*0.579*	-	*0.202*
Major response, n (%)[b]	61 (84.7)	6 (85.7)	7 (53.8)	60 (85.7)	14 (63.6)
OR (95% CI)	-	1.06 (0.10, 10.36)	0.33 (0.07,1.41)	-	0.29 (0.09,0.95)
P value	-	*0.958*	*0.135*	-	***0.040***
Time to VGPR or better Median (min, max), months	11.3 (2.0, 49.9)	-	31.3 (16.6, 46.0)	11.4 (2.0, 49.9)	24.9 (5.6, 46.9)
Time to major response Median (min, max), months	2.8 (0.9, 49.8)	7.0 (2.8, 41.5)	2.9 (1.2, 13.6)	2.9 (0.9, 49.8)	3.0 (1.0, 13.8)
PFS					
Events, n (%)	18 (25.0%)	4 (57.1%)	7 (53.8%)	18 (25.7%)	11 (50.0%)
Median, months[c]	NE	44.2	39.8	NE	44.2
HR (95% CI)[d]	-	2.08 (0.70,6.16)	3.39 (1.23,9.31)	-	2.36 (1.10,5.09)
P value[d]		*0.185*	***0.017***		***0.027***
Patients with MYD88^{MUT} treated with zanubrutinib					
	***CXCR4*^{WT} (n=65)**	***CXCR4*^{FS} (n=19)**	***CXCR4*^{NS} (n=14)**	***TP53*^{WT} (n=72)**	***TP53*^{MUT} (n=26)**
VGPR or better, n (%)[b]	29 (44.6)	5 (26.3)	2 (14.3)	27 (37.5)	9 (34.6)
OR (95% CI)	-	0.51 (0.16,1.66)	0.24 (0.04,1.26)	-	1.27 (0.46,3.52)
P value	-	*0.269*	*0.093*	-	*0.636*
Major response, n (%)[b]	54 (83.1)	14 (73.7)	12 (85.7)	59 (81.9)	21 (80.8)
OR (95% CI)	-	0.66 (0.18,2.36)	1.52 (0.25,9.01)	-	1.01 (0.29,3.47)
P value	-	*0.524*	*0.639*	-	*0.978*
Time to VGPR or better Median (min, max), months	6.5 (1.9, 42.0)	11.1 (2.8, 26.0)	10.3 (9.4, 11.1)	6.5 (1.9, 42.0)	11.1 (3.0, 26.0)
Time to major response Median (min, max), months	2.8 (0.9, 28.5)	2.9 (1.8, 49.8)	4.1 (1.0, 38.7)	2.8 (0.9, 49.8)	2.8 (1.0, 5.6)
PFS					
Events, n (%)	11 (16.9%)	4 (21.0%)	4 (28.5%)	10 (13.8%)	9 (34.6%)
Median, months[c]	NE	NE	NE	NE	NE
HR (95% CI)[d]	-	0.62 (0.17, 2.25)	0.67 (0.15,2.88)	-	2.20 (0.81, 5.98)
P value[d]		*0.473*	*0.598*		*0.120*

Data cutoff: October 31, 2021.

[a]Mutation determined by NGS; NGS results were available for 92 patients in the ibrutinib arm and 98 patients in the zanubrutinib arm.

[b]OR and *P* values were estimated using a logistic regression model with *CXCR4* (WT, FS, NS), *TP53* (WT, MUT), and *TERT* (WT, MUT) mutational statuses as covariates. WT is the reference group.

[c]Median PFS was estimated by Kaplan-Meier method.

[d]HR and *P* values were estimated using a Cox regression model with *CXCR4* (WT, FS, NS), *TP53* (WT, MUT), and *TERT* (WT, MUT) mutational statuses as covariates. WT is the reference group.

FS, frameshift; HR, hazard ratio; NE, not estimable; NGS, next-generation sequencing; NS, nonsense; OR, odds ratio; PFS, progression-free survival; VGPR, very good partial response; WM, Waldenström macroglobulinemia; WT, wild type.

Bold red text highlights *P* value <0.05.