ASPEN Biomarker Analysis: Response to BTK Inhibitor Treatment in Patients With Waldenström Macroglobulinemia Harboring *CXCR4*, *TP53*, and *TERT* Mutations

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DISCLOSURES

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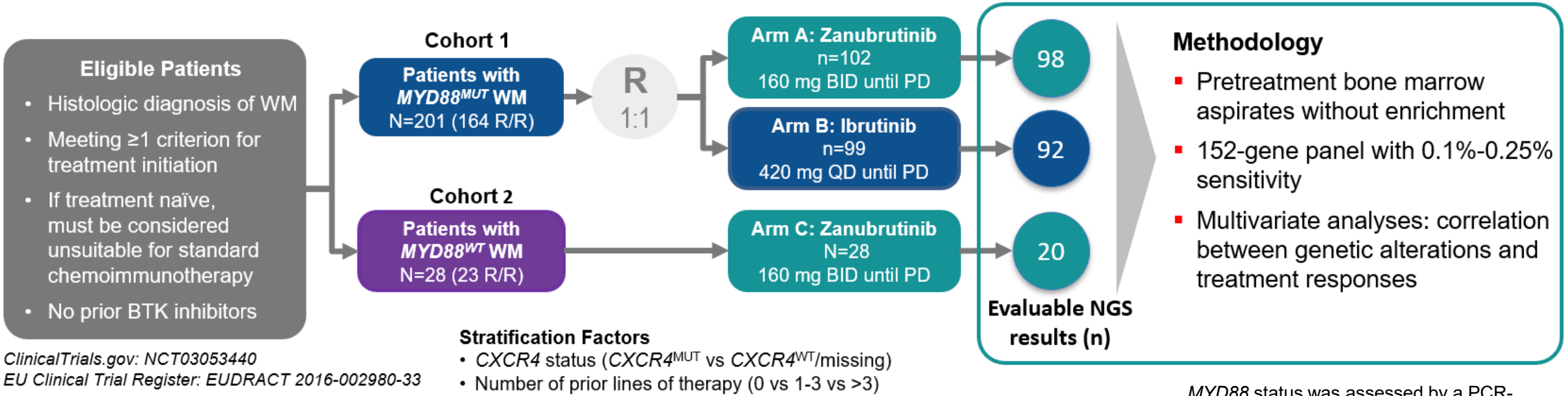
INTRODUCTION

- *MYD88*^{L265P}, *CXCR4*^{WHIM}, and *ARID1A* are the most frequently mutated genes in patients with WM[1]
  - *MYD88*^{L265P} activating mutation triggers tumor-cell growth through BTK protein[2]
  - *CXCR4*^{WHIM} mutations promote cell survival signaling and confer ibrutinib resistance[3]
- Mutation status of *MYD88* and *CXCR4* impacts the efficacy of BTK inhibitors in patients with WM[4-6]
  - Prognosis is worse for patients with *MYD88*^{WT} WM than those with *MYD88*^{L265P} [4,5]
  - Prognosis is worse for patients with *CXCR4*^{MUT} than those with CXCR4^{WT} in BTK inhibitor–treated WM (NS worse than FS)[6]
- The aim of this biomarker study is to evaluate low-frequency genetic alterations in patients with WM treated on the ASPEN phase 3 study and their association with efficacy of ibrutinib and zanubrutinib (separately and pooled) in different subpopulations

ARID1A, AT-rich interactive domain-containing protein 1A gene; BTK, Bruton tyrosine kinase; *CXCR4*, C-X-C chemokine receptor type 4 gene; FS, frameshift; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; NS, nonsense; WHIM; warts, hypogammaglobulinemia, infections, myelokathexis; WM, Waldenström macroglobulinemia; WT, wild type.

1. Hunter ZR, et al. *Blood* 2014;123:1637-1646; 2. Yang G, et al. *Blood* 2013;122:1222-1232. 3. Cao Y, et al. *Leukemia* 2015;29:169-76. 4. Treon SP, et al. *Blood* 2014;123:2791-2796. 5. Treon SP, et al. *N Engl J Med* 2015;372:1430-1440; 6. Castillo JJ, et al. *Br J Haematol* 2019;187:356-363.

ASPEN is an Open-Label, Multicenter, Randomized Phase 3 Study of Zanubrutinib vs Ibrutinib in Patients With WM



ClinicalTrials.gov: NCT03053440
EU Clinical Trial Register: EUDRACT 2016-002980-33

Stratification Factors
- *CXCR4* status (*CXCR4*^{MUT} vs *CXCR4*^{WT}/missing)
- Number of prior lines of therapy (0 vs 1-3 vs >3)

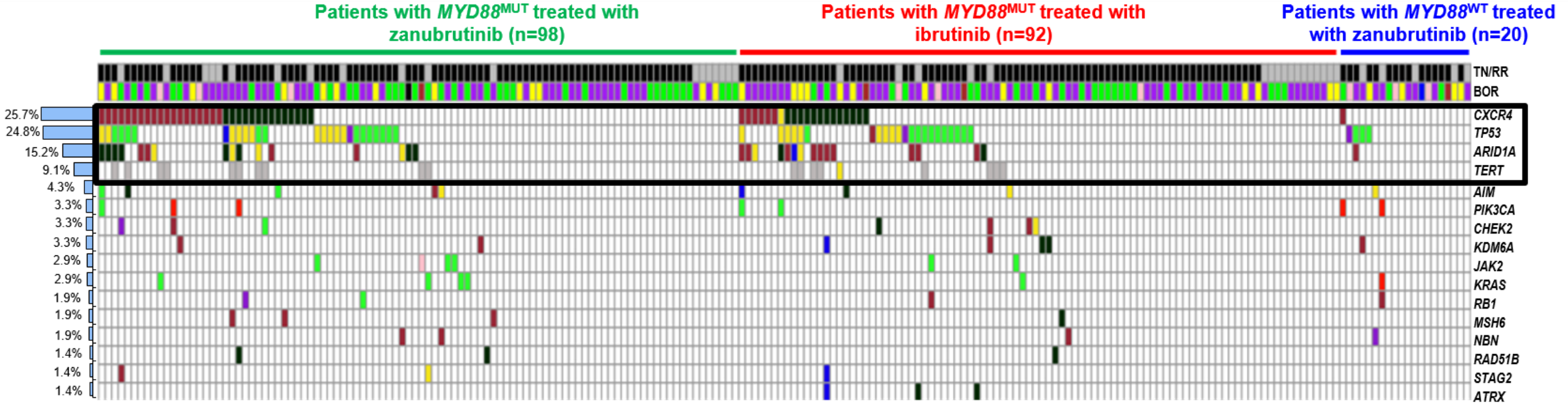
Clinical efficacy endpoints include
- Response rates (CR+VGPR, major responses)
- Time to response
- PFS assessed according to response criteria in the NCCN® WM guidelines and modified Owen criteria[1] by investigator

MYD88 status was assessed by a PCR-based assay, with 0.2%-0.5% LOD which was used for patients' enrollment. *CXCR4* status was evaluated by sanger sequencing with 10%-15% sensitivity for stratification factors and tested by 152-gene NGS panel with 0.1%-0.25% sensitivity for biomarker analysis.

BID, twice a day; BTK, Bruton tyrosine kinase; CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; LOD, limit of detection; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PCR, polymerase chain reaction; PD, progressive disease; PFS, progression-free survival; QD, once a day; R/R, relapsed/refractory; VGPR, very good partial response; WT, wild type; WM, Waldenström macroglobulinemia.

1. Owen et al. *Br J Haematol* 2013;160(2):171-176

High Rates of *TP53*^{MUT} and *TERT*^{MUT} Were Found in ASPEN Study[a] and More Often Detected in Patients With *MYD88*^{MUT} or *CXCR4*^{MUT}



In zanubrutinib-treated vs ibrutinib-treated *MYD88*^{MUT} cohorts, the *CXCR4*^{NS} rate is 14.2% (14/98) vs 14.1% (13/92), and the *CXCR4*^{FS} rate is 19.4% (19/98) vs 7.6%(7/92), respectively

Mutation rate, % (n)	*MYD88*^{WT} (n=20)	*MYD88*^{MUT} (n=190)	*CXCR4*^{WT} (n=156)	*CXCR4*^{MUT} (n=54)	CXCR4^{FS} (n=27)	CXCR4^{NS} (n=27)
TP53	4 (20%)	48 (25.3%)	33 (21.2%) *	**19 (35.2%)** *	8 (29.6%)	**11 (40.7%)** *
TERT	0	**19 (10%)**	6 (3.9%) *	**13 (24.1%)** *	**4 (14.8%)** *	**9 (33.3%)** *
ARID1A	1 (5%)	**31 (16.3%)**	9 (5.8%) *	**23 (42.6%)** *	**11 (40.7%)** *	**12 (44.4%)** *

TN/RR status: TN, RR

BOR_INV (31Oct2021): CR, VGPR, PR, MR, SD, PD, Discontinuation before 1st assessment

Mutation type: not detected, missense, nonsense, splice site, multiple alterations, amplification, deletion, frameshift, promoter, fusion

Bold text indicates >10% difference between MUT and WT in 210 NGS-evaluable patients with WM. *P value <0.05, based on Fisher's exact test, WT is the reference group

[a]Including 190 patients with *MYD88*^{MUT} (98 treated by zanubrutinib, and 92 treated by ibrutinib) and 20 patients with *MDY88*^{WT} (all zanubrutinib), *MYD88* status was assessed by a PCR-based assay which was used for patients' enrollment. *CXCR4* status was evaluated by NGS.

BOR, best overall response; CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; FS, frameshift; INV, investigator; MR, minor response; *MYD88*, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing; NS, nonsense; PD, progressive disease; PR, partial response; RR, relapsed/refractory; SD, stable disease; VGPR, very good partial response; *TERT*, telomerase reverse transcriptase gene; TN, treatment naïve; *TP53*, tumor protein P53 gene; WM, Waldenström macroglobulinemia; WT, wild type.

In Patients With *MYD88*^{MUT} WM[a], Those With *CXCR4*^{MUT}, *TP53*^{MUT}, *TERT*^{MUT} Trended Toward an Inferior Response to BTK Inhibitors[a]

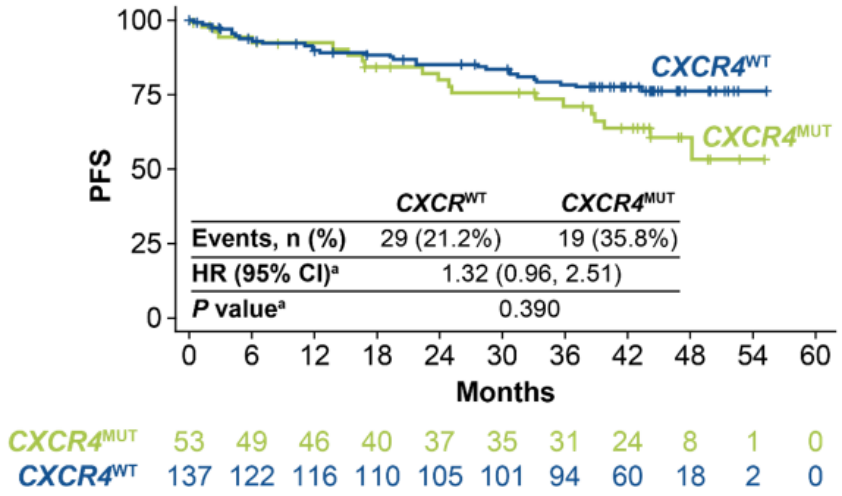
Response	*CXCR4*^{WT} (n=137)	*CXCR4*^{MUT} (n=53)	*TP53*^{WT} (n=142)	*TP53*^{MUT} (n=48)	*TERT*^{WT} (n=171)	*TERT*^{MUT} (n=19)
VGPR or better, n (%)	51 (37.2)*	**9 (17.0)***	48 (33.8)	12 (25.0)	58 (33.9)	**2 (10.5)**
Major Response, n (%)	115 (83.9)	**39 (73.6)**	119 (83.8)	**35 (72.9)**	143 (83.6)	**11 (57.9)**
Median time to VGPR or better (min, max), months	8.4 (1.9, 50.0)	11.1 (2.8, 46.0)	9.3 (1.9, 50.0)	11.1 (3.0, 46.9)	9.3 (1.9, 50.0)	34.1 (22.2, 46.0)
Median time to Major Response (min, max), months	2.8 (0.9, 49.8)	4.6 (1.0, 49.8)	2.9 (0.9, 49.8)	2.9 (1.0, 13.8)	2.8 (0.9, 49.8)	5.6 (1.8, 22.2)

- Responses in patients with *CXCR4*^{MUT}, *TP53*^{MUT}, and *TERT*^{MUT} trended toward **lower VGPR+CR rate or Major Response rate** and **longer median time to response** than patients with the respective WT alleles
- Responses in patients with *ARID1A*^{MUT} show less difference (<10%) regarding VGPR+CR rate or MRR than those with *ARID1A*^{WT}, suggesting limited clinical impact

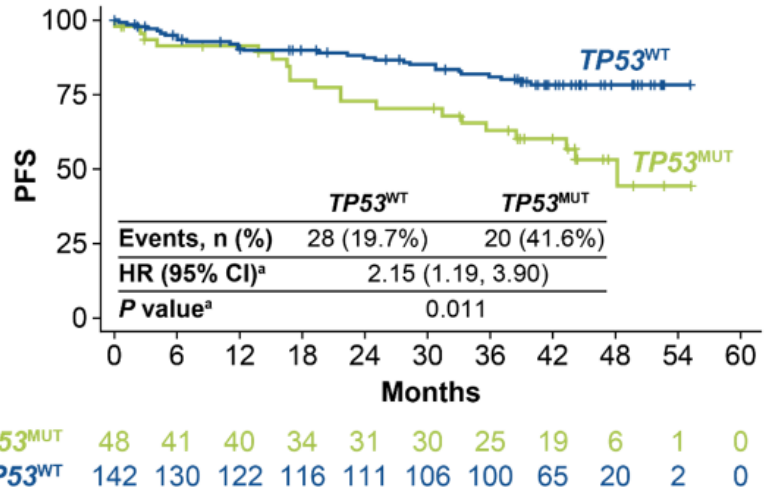
Data cutoff: October 31, 2021.
Bold text indicates >10% difference between MUT and WT.
**P* value <0.05, based on a logistic regression model with *CXCR4* (WT, MUT), *TERT* (WT, MUT), and *TP53* (WT, MUT) mutational status as covariates. WT is the reference group.
[a]*MYD88* status was assessed by PCR-based assay, with a total of 190 patients with *MYD88*^{MUT} WM.
ARID1A, AT-rich interactive domain-containing protein 1A gene; C-X-C chemokine receptor type 4 gene; CR, complete response; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; PCR, polymerase chain reaction; *TERT*, telomerase reverse transcriptase gene; *TP53*, tumor protein P53 gene; VGPR, very good partial response; WM, Waldenström macroglobulinemia; WT, wild type.

PFS in Patients With *CXCR4*^{MUT}, *TP53*^{MUT}, and *TERT*^{MUT} Trended Toward Less Favorable Outcome Than Patients With the Respective WT Alleles

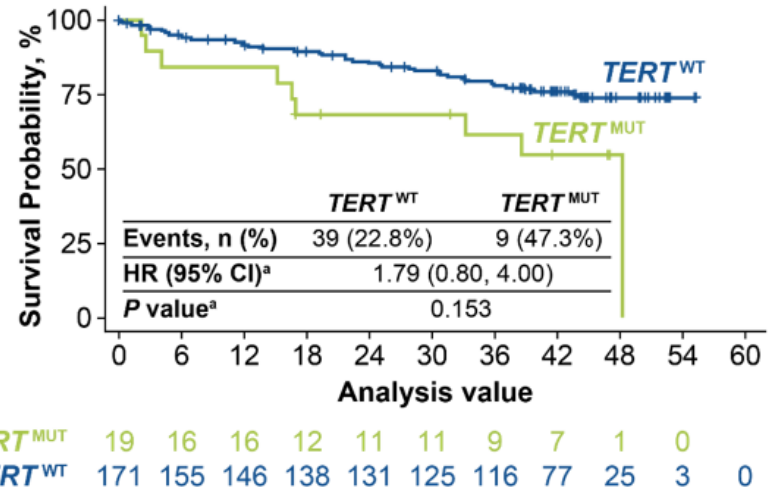
PFS by *CXCR4* Mutational Status



PFS by *TP53* Mutational Status



PFS by *TERT* Mutational Status



Data cutoff: October 31, 2021.
Pooled analysis of patients with *MYD88*^{MUT} WM from cohort 1 including 98 treated by zanubrutinib and 92 treated by ibrutinib.
[a]HR and *P* values were estimated using a Cox regression model with *CXCR4* (WT, MUT), *TP53* (WT, MUT), and *TERT* (WT, MUT) mutational statuses as covariates. WT is the reference group.
CXCR4, C-X-C chemokine receptor type 4 gene; HR, hazard ratio; MUT, mutant; PFS, progression-free survival; *TERT*, telomerase reverse transcriptase gene; *TP53*, tumor protein P53 gene; WM, Waldenström macroglobulinemia; WT, wild type.

Zanubrutinib Showed Deeper, Faster Responses and Favorable PFS vs Ibrutinib in WM With *CXCR4*^{NS} and *CXCR4*^{FS} Mutations[a]

	Patients with *MYD88*^{MUT} treated with ibrutinib			Patients with *MYD88*^{MUT} treated with zanubrutinib		
	CXCR4^{WT} **(n=72)**	***CXCR4***^{FS} **(n=7)**	***CXCR4***^{NS} **(n=13)**	***CXCR4***^{WT} **(n=65)**	***CXCR4***^{FS} **(n=19)**	***CXCR4***^{NS} **(n=14)**
VGPR or better, n (%)	22 (30.6)	**0**	**2 (15.4)**	29 (44.6)	**5 (26.3)**	**2 (14.3)**
Major Response, n (%)	61 (84.7)	6 (85.7)	**7 (53.8)**	54 (83.1)	14 (73.7)	12 (85.7)
Median time to VGPR or better (min, max), months	11.3 (2.0, 49.9)	-	31.3 (16.6, 46.0)	6.5 (1.9, 42.0)	11.1 (2.8, 26.0)	10.3 (9.4, 11.1)
Median time to Major Response (min, max), months	2.8 (0.9, 49.8)	7.0 (2.8, 41.5)	2.9 (1.2, 13.6)	2.8 (0.9, 28.5)	2.9 (1.8, 49.8)	4.1 (1.0, 38.7)
PFS						
Event-free rate at 42 months, %	74.6	**57.1**	**43.5**	81.3	76.4	**66.7**
P value[b]	-	0.185	**0.017**	-	0.473	0.598

- Compared to ibrutinib, zanubrutinib demonstrated a more favorable VGPR+CR rate in *CXCR4*^{FS} (*P* value[c] = 0.06) and major response rate in *CXCR4*^{NS} (*P* value[c] = 0.09)

Data cutoff: October 31, 2021.

Bold text indicates >10% difference between FS and WT or between NS and WT. **Bold red text** highlights *P* value < 0.05.

[a]Mutation determined by NGS and available for 92 patients in the ibrutinib arm and 98 patients in the zanubrutinib arm. [b]Estimated using a Cox regression model with *CXCR4* (WT, FS, NS), *TERT* (WT, MUT), and *TP53* (WT, MUT) mutational status as covariates. WT is the reference group. [c]Estimated using a logistic regression model with treatment group, *TERT* (WT, MUT) and *TP53* (WT, MUT) mutational status as covariates within the respective subgroups. *CXCR4*, C-X-C chemokine receptor type 4 gene; CR, complete response; FS, frameshift; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing; NS, nonsense; PFS, progression-free survival; *TERT*, telomerase reverse transcriptase gene; *TP53*, tumor protein P53 gene; VGPR, very good partial response; WM, Waldenström macroglobulinemia; WT, wild type.

Zanubrutinib Showed Deeper, Faster Responses and Favorable PFS vs Ibrutinib in WM With *TP53*^{MUT,a}

Response	Patients with *MYD88*^{MUT} treated with ibrutinib		Patients with *MYD88*^{MUT} treated with zanubrutinib	
	TP53^{WT} (n=70)	*TP53*^{MUT} (n=22)	*TP53*^{WT} (n=72)	*TP53*^{MUT} (n=26)
VGPR or better, n (%)	21 (30.0)	**3 (13.6)**†	27 (37.5)	9 (34.6)†
Major Response, n (%)	60 (85.7)*	**14 (63.6)***	59 (81.9)	21 (80.8)
Median time to VGPR or better (min, max), months	11.4 (2.0, 49.9)	24.9 (5.6, 46.9)	6.5 (1.9, 42.0)	11.1 (3.0, 26.0)
Median time to Major Response (min, max), months	2.9 (0.9, 49.8)	3.0 (1.0, 13.8)	2.8 (0.9, 49.8)	2.8 (1.0, 5.6)
PFS				
Event-free rate at 42 months, %	72.1	**57.9**	84.6	**62.0**
P value[b]	-	**0.027**	-	0.120

- Compared to ibrutinib, zanubrutinib demonstrated a more favorable VGPR+CR rate (*P* value[c] < 0.05) and major response rate (*P* value[c] = 0.11) in *TP53*^{MUT}

Data cutoff: October 31, 2021.
Bold text indicates >10% difference between MUT and WT. **Bold red** text highlights P value < 0.05.
**P* value <0.05, based on a logistic regression model with CXCR4 (WT, FS, NS), TP53 (WT, MUT), and TERT (WT, MUT) statuses as covariates. WT is the reference group.
[a]Mutation determined by NGS and available for 92 patients in the ibrutinib arm and 98 patients in the zanubrutinib arm. [b]Estimated using a Cox regression model with CXCR4 (WT, FS, NS), TP53 (WT, MUT), and *TERT* (WT, MUT) mutational status as covariates. WT is the reference group. [c]Estimated using a logistic regression model with treatment group, *TERT* (WT, MUT) and *CXCR4* (WT, FS, NS) mutational status as covariates within the respective subgroups(† P value <0.05).
MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing; PFS, progression-free survival; *TP53*, tumor protein P53 gene; VGPR, very good partial response; WT, wild type.

TERT$^{MUT, a}$ May be a New Risk Factor for BTKi therapy

Response	Patients with *MYD88*^{MUT} treated with ibrutinib		Patients with *MYD88*^{MUT} treated with zanubrutinib	
	TERT^{WT} (n=83)	*TERT*^{MUT} (n=9)	*TERT*^{WT} (n=88)	*TERT*^{MUT} (n=10)
VGPR or better, n (%)	23 (27.7)	**1 (11.1)**	35 (39.8)	**1 (10.0)**
Major Response, n (%)	70 (84.3)*	**4 (44.4)***	73 (83.0)	**7 (70.0)**
Median time to VGPR or better (min, max), months	11.4 (2.0, 49.9)	46.0 (46.0, 46.0)	6.7 (1.9, 42.0)	22.2 (22.2, 22.2)
Median time to Major Response (min, max), months	2.8 (0.9, 49.8)	10.3 (2.9, 13.8)	2.8 (0.9, 49.8)	3.7 (1.8, 22.2)
PFS				
Event-free rate at 42 m, %	68.4	74.0	83.4	**37.5**
P value[b]		0.304		**0.001**

Data cutoff: October 31, 2021.
Bold text indicates >10% difference between MUT and WT. **Bold red** text highlights P value < 0.05.
**P* value <0.05, based on a logistic regression model with CXCR4 (WT, FS, NS), TP53 (WT, MUT), and *TERT* (WT, MUT) statuses as covariates. WT is the reference group.
[a]Mutation determined by NGS and available for 92 patients in the ibrutinib arm and 98 patients in the zanubrutinib arm. [b]Estimated using a Cox regression model with CXCR4 (WT, FS, NS), TP53 (WT, MUT), and *TERT* (WT, MUT) mutational status as covariates. WT is the reference group.
MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing; PFS, progression-free survival; *TERT*, telomerase reverse transcriptase gene; VGPR, very good partial response; WT, wild type.

CONCLUSIONS

- The ASPEN study detected high mutational rates of *TP53* and *TERT* in addition to *CXCR4* and *ARID1A* in patients with *MYD88*^{MUT} WM
- Patients with *CXCR4*^{NS} showed reduced VGPR, MRR and PFS than those with *CXCR4*^{WT} in the ibrutinib arm; for zanubrutinib, only VGPR rate was reduced.
- Patients with *TP53*^{MUT} had reduced VGPR, MRR and PFS in the ibrutinib arm; no significant differences currently exist in the zanubrutinib arm. The VGPR rate for *TP53*^{MUT} was significantly higher in zanubrutinib than ibrutinib arm.
- *TERT*^{MUT} may be a novel risk factor for patients receiving BTK inhibitor therapy.

ARID1A, AT-rich interactive domain-containing protein 1A gene; BTK, Bruton tyrosine kinase; *CXCR4*, C-X-C chemokine receptor type 4 gene; FS, frameshift; MRR, major response rate; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; NS, non-sense; PFS, progression-free survival; *TERT*, telomerase reverse transcriptase gene; *TP53*, tumor protein P53 gene; VGPR, very good partial response; WT, wild type; WM, Waldenström macroglobulinemia.

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