Waldenstrom's Macroglobulinemia

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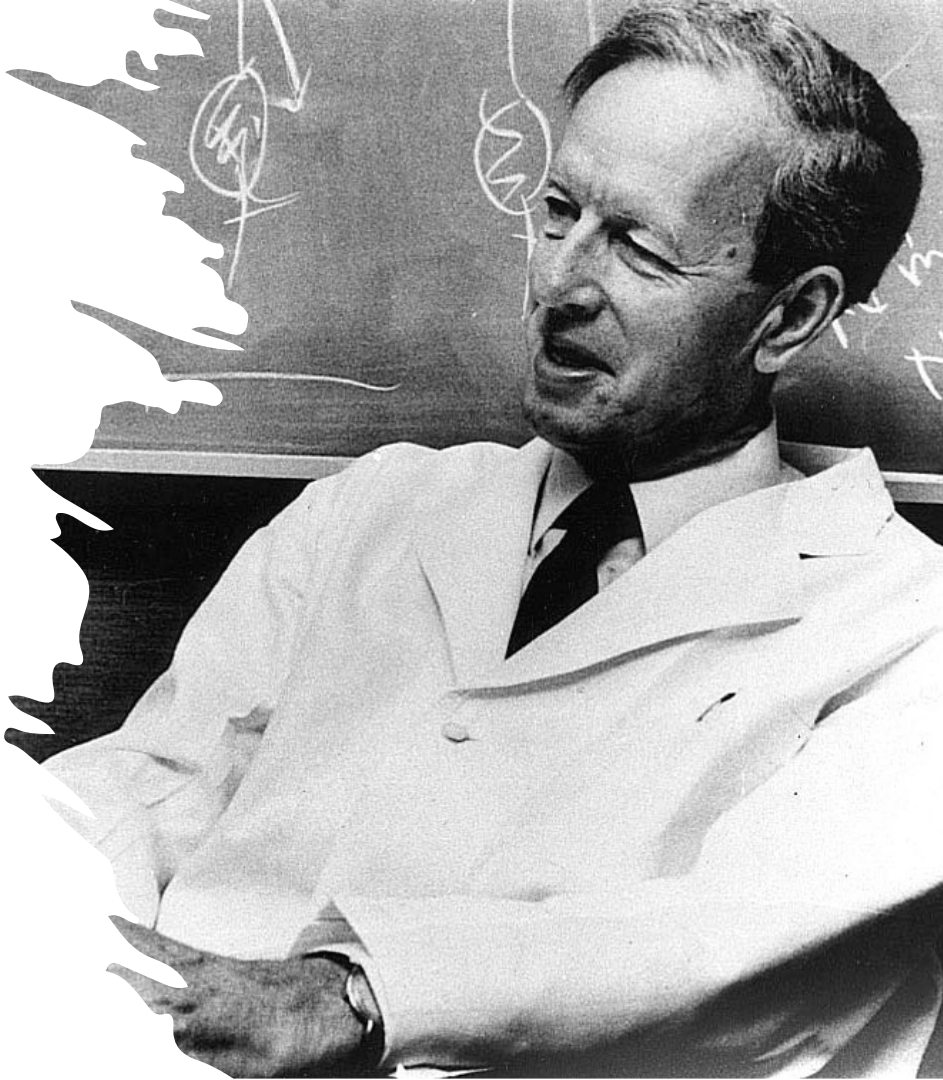
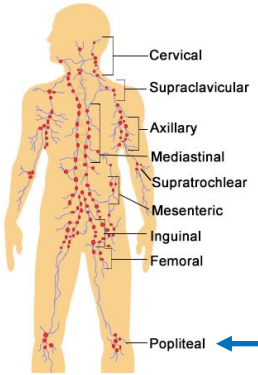


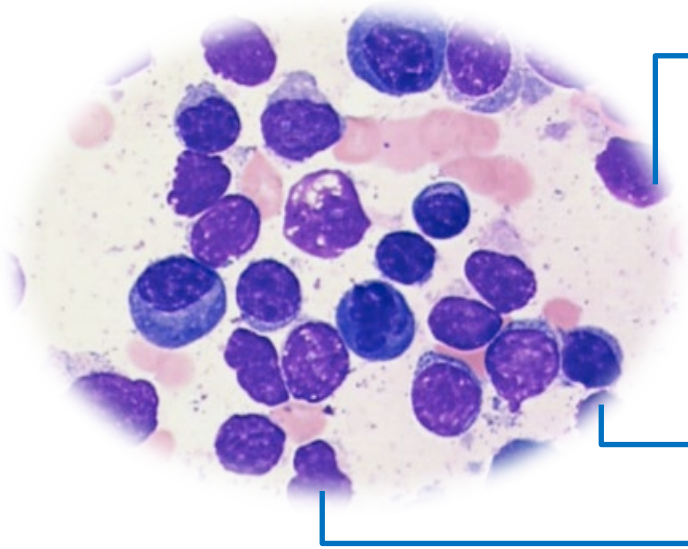
Manifestations of WM Disease

Bing Neel Syndrome



≤20% at diagnosis;
50–60% at relapse

Bone Marrow
↓ Hb>>> ↓ PLT> ↓ WBC



Hyperviscosity Syndrome:
Epistaxis, Headaches,
Impaired vision
>6,000 mg/dL or >4.0 CP

Cold Agglutinemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (22%)
Amyloidosis (10–15%)

Hepcidin
↓ Fe Anemia

Treon S., *Hematol Oncol*. 2013; 31:76-80.

NCCN Guidelines for Initiation of Therapy in WM

- Hb ≤10 g/dL on basis of disease
- PLT <100,000 mm^3 on basis of disease
- Symptomatic hyperviscosity
- Moderate/severe peripheral neuropathy
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloid
- IGM level per se is not an indication to treat per NCCN (but…)

Kyle RA, et al. *Semin Oncol*. 2003;30(2):116-120. Anderson, et al. *J Natl Compr Canc Netw*. 2012 Oct 1;10(10):1211-9.

Primary Treatment of WM with Chemoimmunotherapy

Regimen	ORR	CR	Median PFS (mo)
Rituximab x 4	25-30%	0-5%	13
Rituximab x 8	40-45%	0-5%	16-22
Rituximab/cyclophosphamide	70-80%	5-15%	30-36
Rituximab/nucleoside analogues	70-90%	5-15%	36-62
Rituximab/Proteasome Inhibitor	70-90%	5-15%	42-66
Rituximab/bendamustine	90%	5-15%	69

Reviewed in Dimopoulos, et al. *Blood.* 2014;124(9):1404-11; Treon, et al. *Blood.* 2015;126:721-732; Rummel, et al. *Lancet Oncol.* 2016;17:57-66

WM–Centric Toxicities with Commonly Used Therapies

Agent	WM Toxicities
Rituximab	• **IgM flare (40%-60%)**→Hyperviscosity crisis, Aggravation of IgM-related PN, CAGG, Cryos. • Hypogammaglobulinemia→ infections, IVIG • Intolerance (10%-15%)
Fludarabine	• Hypogammaglobulinemia→ infections, IVIG • **Transformation, AML/MDS (15%)**
Bendamustine	• Prolonger neutropenia, thrombocytopenia (especially after fludarabine) • **AML/MDS (5%-8%)**
Bortezomib	• **Grade 2+3 peripheral neuropathy (60%-70%);** High discontinuation (20%-60%)

Treon, et al. *Blood.* 2015;126:721-732. Treon, et al. *J Clin Oncol*. 2020;38:1198-1208.

MYD88 Directed Pro-survival Signaling in WM

The NEW ENGLAND JOURNAL of MEDICINE

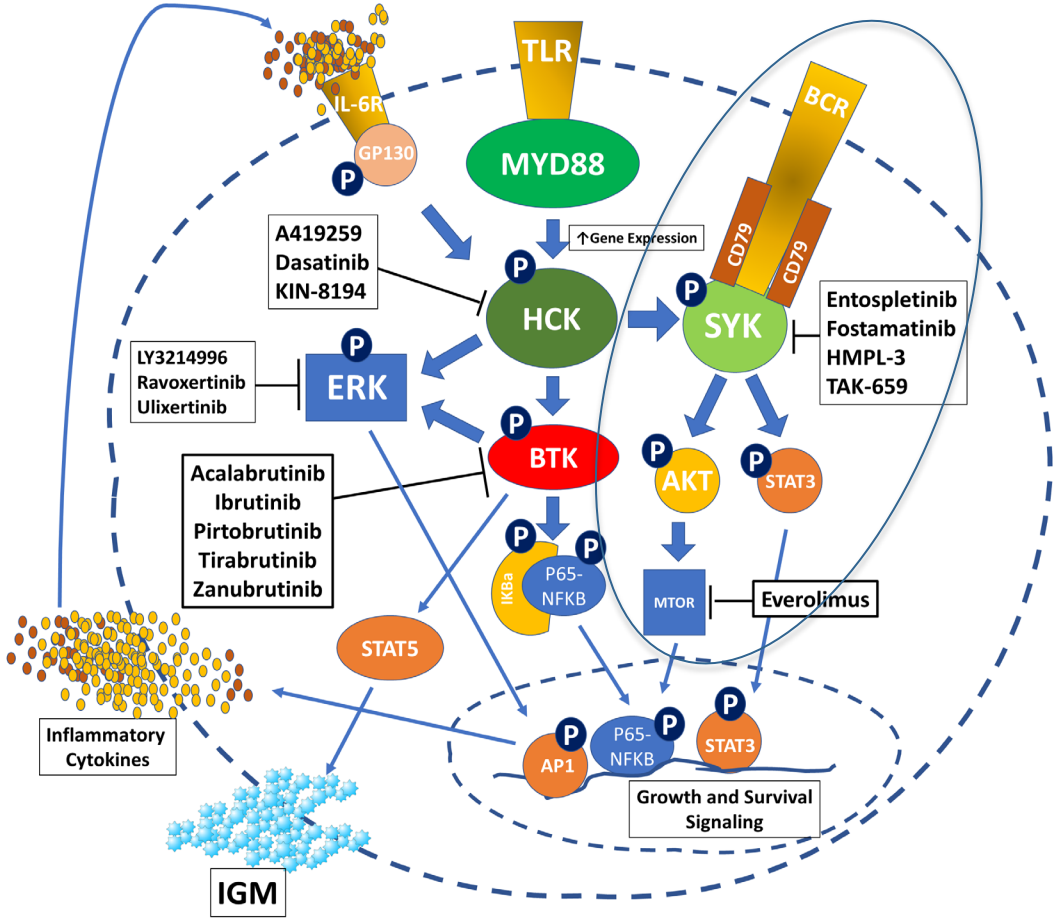
ORIGINAL ARTICLE

MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

MYD88 mutations occur in 95-97% WM Patients

Treon, et al. N Engl J Med. 2012;367(9):826-833.
Yang, et al. Blood. 2013;122(7):1222-1232.
Hodge, et al. Blood. 2014;123(7):1055-1058.
Yang, et al. Blood. 2016;127(25):3237-3252.
Chen, et al. Blood. 2018;131(18):2047-2059.
Liu, et al. Blood Adv. 2020;4(1):141-153.
Munshi, et al. Blood Cancer J. 2020;10:12.
Munshi, et al. Blood Adv. 2022.



CXCR4 Receptor (WHIM-like) Mutations Are Common in WM

Plenary Paper

LYMPHOID NEOPLASIA

The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

Zachary R. Hunter,[1,2] Lian Xu,[1] Guang Yang,[1] Yangsheng Zhou,[1] Xia Liu,[1] Yang Cao,[1] Robert J. Manning,[1] Christina Tripsas,[1] Christopher J. Patterson,[1] Patricia Sheehy,[1] and Steven P. Treon[1,3]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Department of Pathology and Laboratory Medicine, Boston University School of Graduate Medical Sciences, Boston, MA; and [3]Harvard Medical School, Boston, MA

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

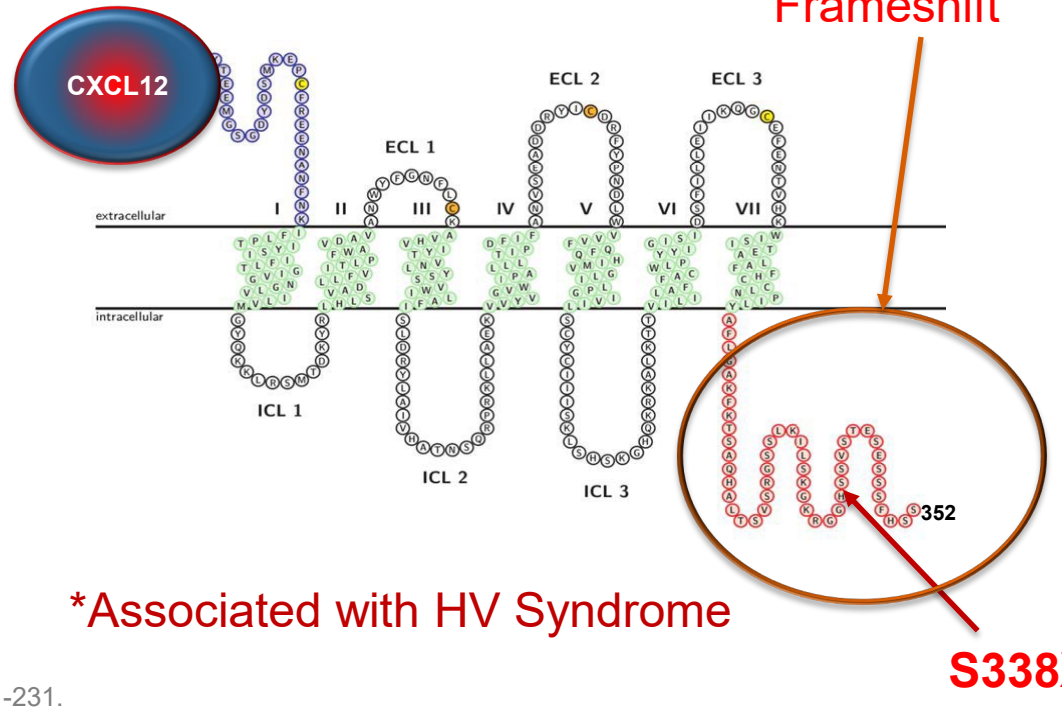
Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenström macroglobulinemia

Steven P. Treon,[1,2] Yang Cao,[1,2] Lian Xu,[1,2] Guang Yang,[1,2] Xia Liu,[1,2] and Zachary R. Hunter[1,3]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Department of Medicine, Harvard Medical School, Boston, MA; and [3]Department of Pathology, Boston University School of Graduate Medical Sciences, Boston, MA

30-40% of WM patients have CXCR4 mutations

CXCR4 mutations
Non-sense (S338X)*
Frameshift



*Associated with HV Syndrome

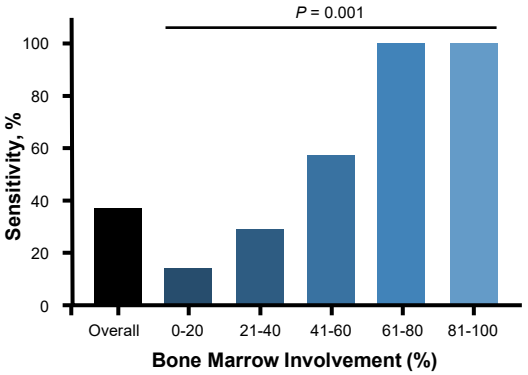
S338X

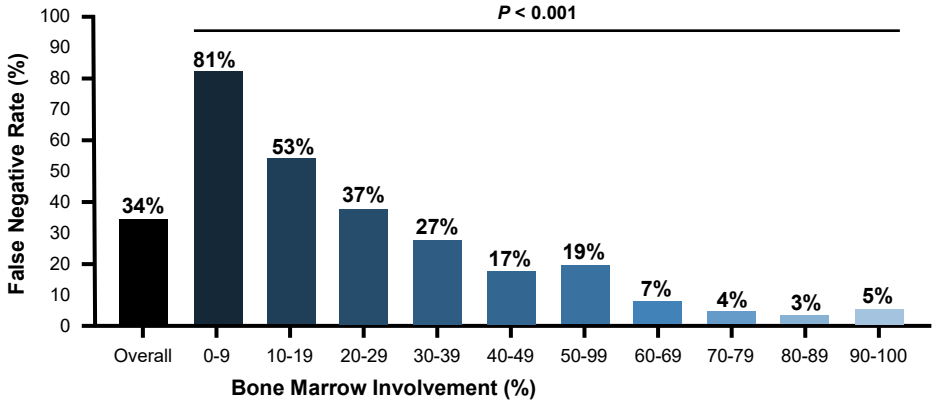
Adapted from Kahler et al. *AIMS Biophysics.* 2016, 3(2): 211-231.

Hunter et al *Blood*. 2014;123(11):1637-1646.; Treon et al, *Blood.* 2014;123(18):2791-2796; Poulain, et al. *Clin Cancer Res*. 2016;22(6):1480-1488.

Challenges of MYD88 and CXCR4 Detection in WM

	MYD88 L265P	
	AS-PCR	NGS
True Positive –no.	391	295
True Negative – no.	23	23
False Positive – no.	0	0
False Negative – no.	0	132
Concordance (κ) – &	Ref.	68 (0.19)
Sensitivity (95% CI) – %	Ref.	66 (61–71)
Specificity (95% CI) – %	Ref.	100 (83–100)
PPV (95% CI) – %	Ref.	100 (98–100)
NPV (95% CI) – %	Ref.	15 (10–22)





Sensitivity for mutated CXCR4 detection was 37% by NGS and unselected BM. Low BM involvement and clonality impacted detection.

Kofides A, et al. *Hemasphere*. 2021;5(8):e624. Gustine JN, et al. *Br J Haematol*. 2021;194(4):730-733.

Ibrutinib monotherapy in previously-treated WM: Pivotal Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D, Christina K. Tripsas, M.A., Kirsten Meid, M.P.H., Diane Warren, B.S., Gaurav Varma, M.S.P.H., Rebecca Green, B.S., Kimon V. Argyropoulos, M.D., Guang Yang, Ph.D., Yang Cao, M.D., Lian Xu, M.S., Christopher J. Patterson, M.S., Scott Rodig, M.D., Ph.D., James L. Zehnder, M.D., Jon C. Aster, M.D., Ph.D., Nancy Lee Harris, M.D., Sandra Kanan, M.S., Irene Ghobrial, M.D., Jorge J. Castillo, M.D., Jacob P. Laubach, M.D., Zachary R. Hunter, Ph.D., Zeena Salman, B.A., Jianling Li, M.S., Mei Cheng, Ph.D., Fong Clow, Sc.D., Thorsten Graef, M.D., M. Lia Palomba, M.D., and Ranjana H. Advani, M.D.

N=63	Median	Range
Age (yrs)	63	44-86
Prior therapies	2	1-9
Refractory to prior therapy	25 (40%)	N/A
Hemoglobin (mg/dL)	10.5	8.2-13.8
Serum IgM (mg/dL)	3,520	724-8,390
B_2M (mg/dL)	3.9	1.3-14.2
BM Involvement (%)	60	3-95
Adenopathy >1.5 cm	37 (59%)	N/A
Splenomegaly >15 cm	7 (11%)	N/A

Treon et al, NEJM 2015

Ibrutinib Activity in Previously Treated WM: *Update of the Pivotal Trial (median f/u 59 mos)*

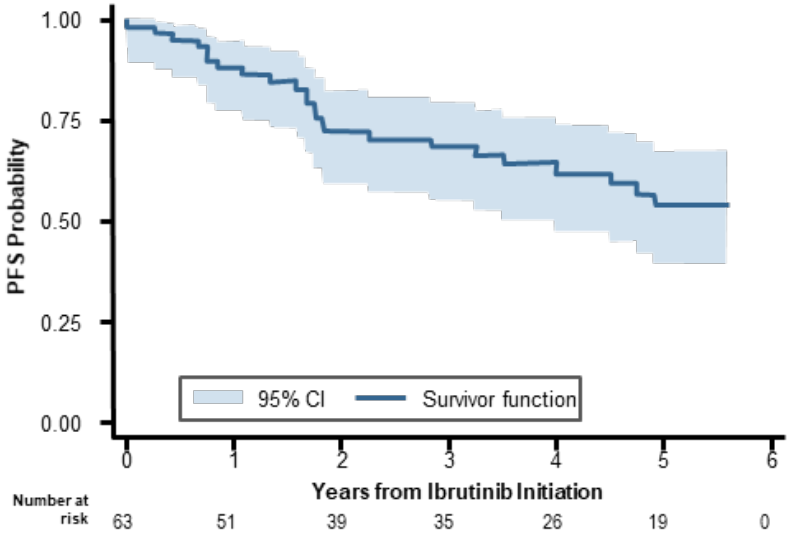
	All Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	MYD88^{WT} CXCR4^{WT}	P-value
N	63	36	22	4	N/A
Overall Response Rate-no. (%)	90.5%	100%	86.4%	50%	<0.01
Major Response Rate-no. (%)	**79.4%**	**97.2%**	**68.2%**	**0%**	**<0.0001**
Categorical responses					
Minor responses-no. (%)	11.1%	2.8%	18.2%	50%	<0.01
Partial responses-no. (%)	49.2%	50%	59.1%	0%	0.03
Very good partial responses-no. (%)	**30.2%**	**47.2%**	**9.1%**	**0%**	**<0.01**
Median time to response (months)					
Minor response (≥Minor response)	0.9	0.9	0.9	0.9	0.38
Major response (≥Partial response)	**1.8**	**1.8**	**4.7**	**N/A**	**0.02**

***One patient had MYD88 mutation, but no CXCR4 determination and had SD.**

Treon, et al. *N Engl J Med*. 2015;372(15):1430-1440.; Updated in Treon, et al. *J Clin Oncol*. 2021;39(6):565-575.

Ibrutinib Activity in Previously Treated WM:
Updated PFS of the Pivotal Trial (median f/u 59 mos)

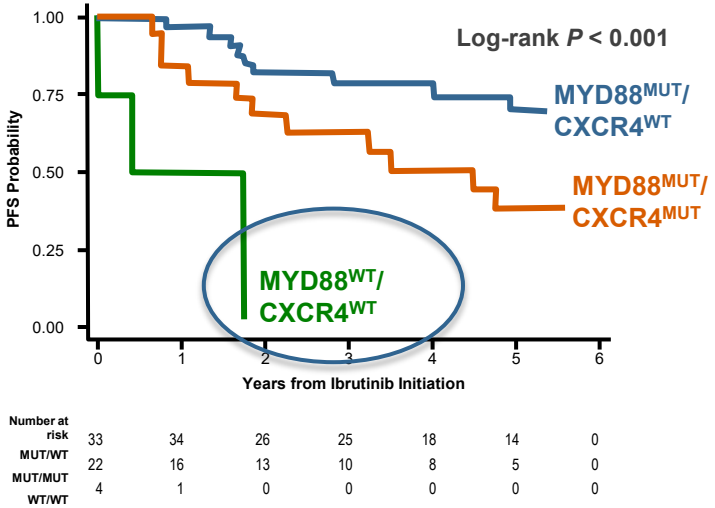
All patients



5-year PFS: 54%

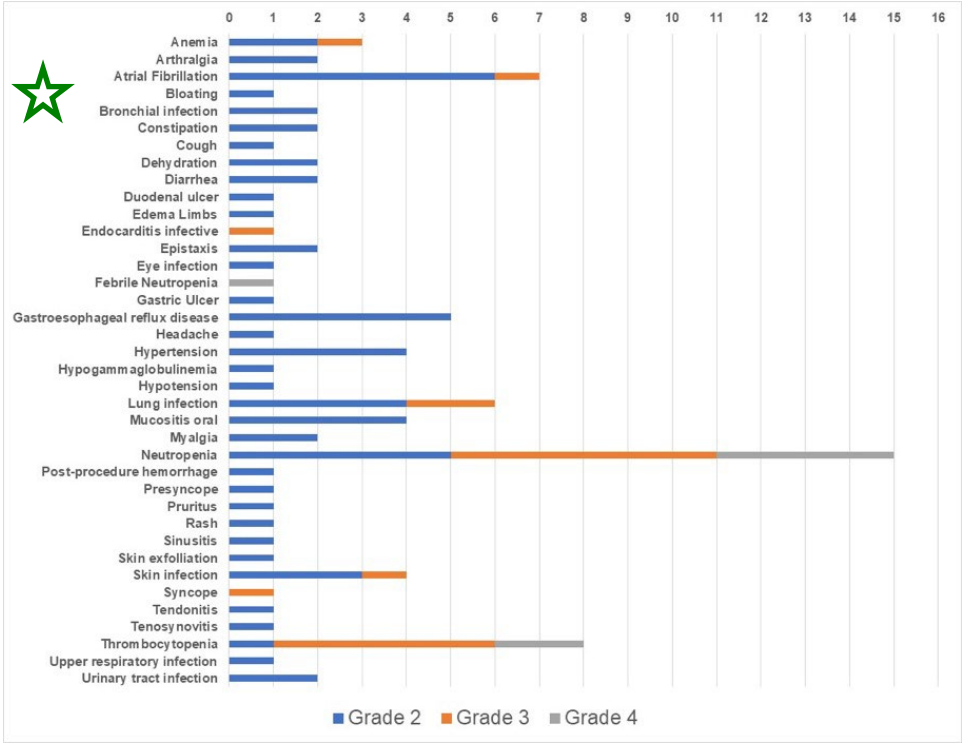
5-year OS: 87%

MYD88 and CXCR4 Mutation Status



Treon, et al. *N Engl J Med*. 2015;372(15):1430-1440.; Updated in Treon, et al. *J Clin Oncol*. 2021;39(6):565-575.

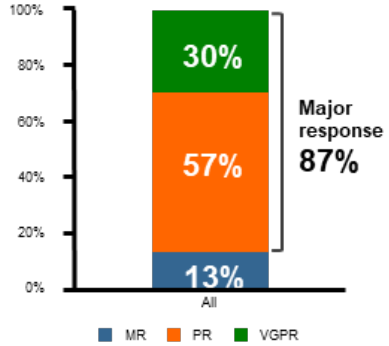
Ibrutinib Activity in Previously Treated WM:
Long Term Toxicity Findings (grade ≥2) of the Pivotal Trial

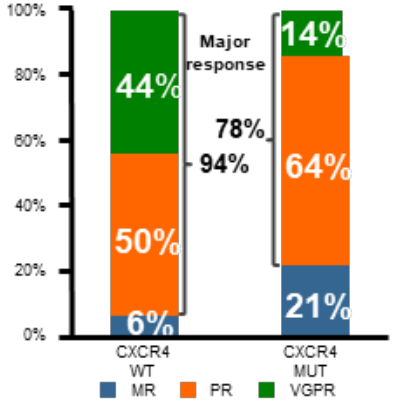


☆ Increased since original report; 8 patients (12.7%) with Afib, including grade 1; 7 continued ibrutinib with medical management.

Treon, et al. *N Engl J Med*. 2015;372(15):1430-1440.; Updated in Treon, et al. *J Clin Oncol*. 2021;39(6):565-575.

Update of Ibrutinib Monotherapy: Treatment-Naïve WM Patients





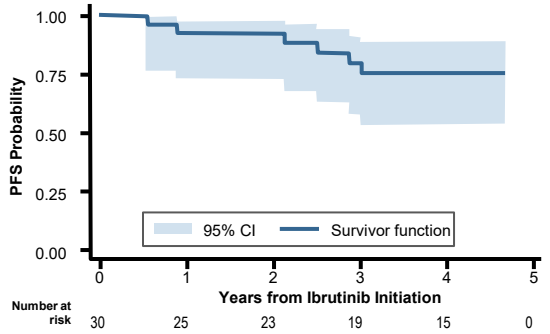
Median time to Response

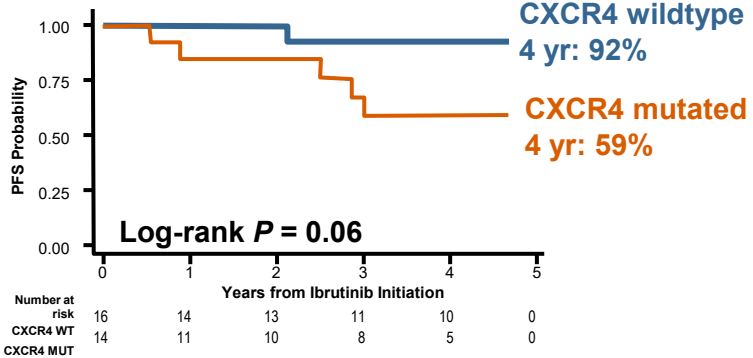
	CXCR4^{WT}	CXCR4^{MUT}
Time to Minor Response (mos).[1]	0.9	1.7
Time to Major Response (mos).[2]	1.8	7.3

1. p=0.07; 2. p=0.01

All patients were MYD88 mutated.

Median f/u: 50 months





Treon SP, et al. *J Clin Oncol*. 2018;36(27):2755-2761. Castillo, et al. *Leukemia. 2022;*36**:**532–539.

Clinical Impact of Drug Holds in WM Patients Receiving Ibrutinib as Primary Therapy

IgM rebound (>25% over nadir and >500 mg/dL)

- 6/16 (37.5%)
- In 5 of these 6 patients, serum IgM returned to pre-hold levels or better following re-start of therapy at a median of 4.6 months (range 3.4-11.2 months).
- One patient's serum IgM level remained elevated after self-holding drug for 15 days and met criteria for progression.

Decreased hemoglobin (>0.5 g/dL)

- 8/16 (50%) experienced a decline in hemoglobin that exceeded 0.5 g/dL, including 5 with a decrease of 1.0 g/dL or more.
- The median time to recovery of the hemoglobin for these patients was 3.7 months (range 3.4-6.1 months).

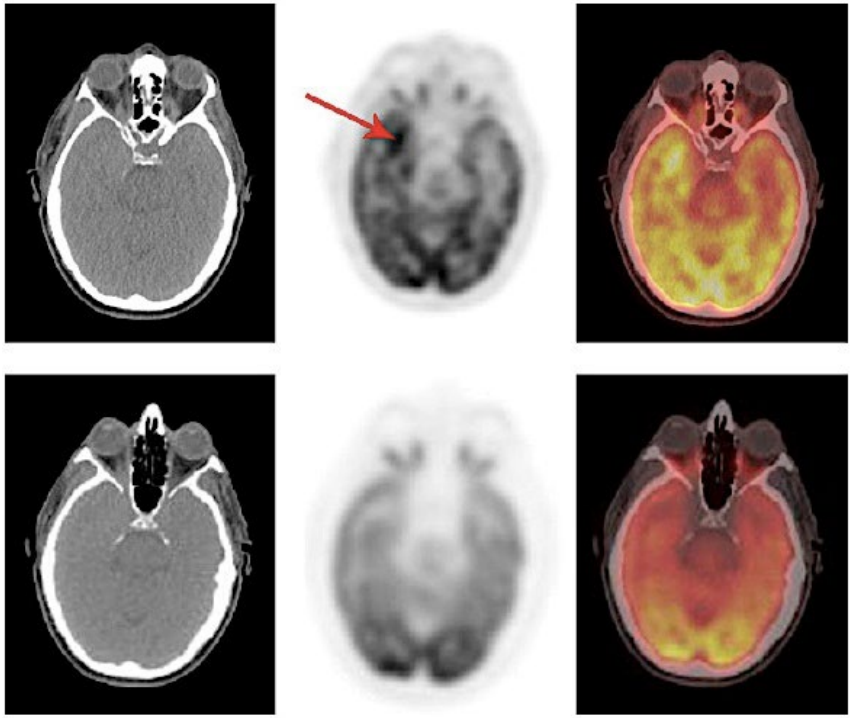
Bottom line: Avoid drug holds when possible

Treon SP, et al. *J Clin Oncol*. 2018;36(27):2755-2761.

Ibrutinib induced response in a WM patient with Bing Neel Syndrome

Pre-treatment

Post-treatment



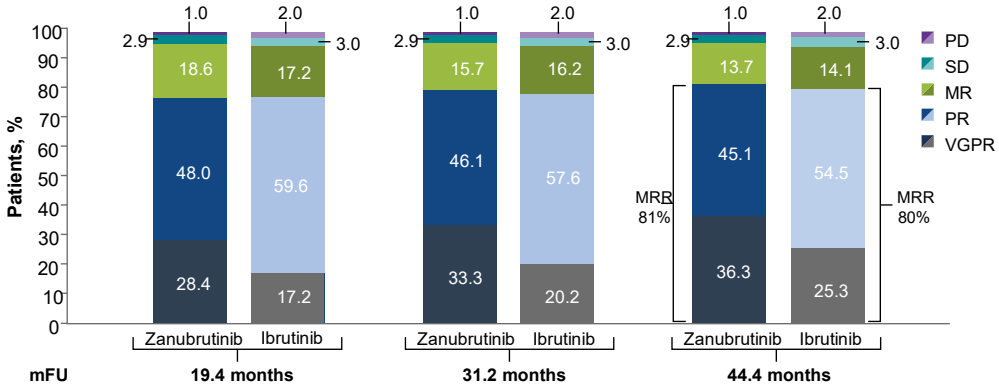
560 mg po once a day

Study Day	Time post-dose (h)	Ibrutinib (nM)		
		CSF	Plasma	%CSF/Plasma
Day 1	0	BLQ	BLQ	NA
	2	34	1133	3·0
1 Month	3	16	463	3·5
4 Months	2·5	7	318	2·2

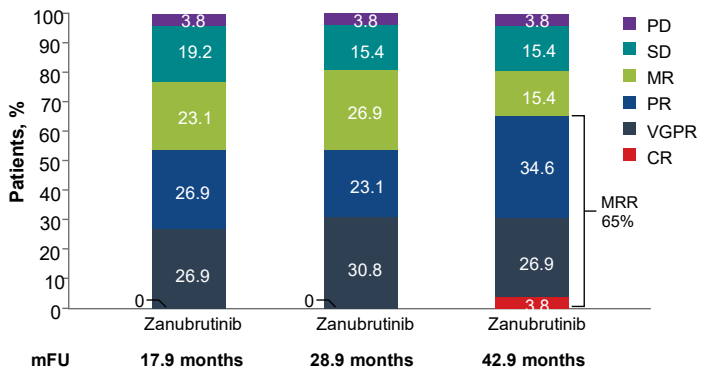
Mason et al, BJH 2016; ;179(2):339-341

ASPEN: Randomized Study of Zanubrutinib vs Ibrutinib Best Overall Response and PFS by Investigator Over Time

Responses Over Time in Patients With *MYD88*^{MUT}



Responses Over Time Observed in *MYD88*^{WT}



- At 44.4 months event free rates for PFS were 78.3% and 69.7% for zanubrutinib and ibrutinib, respectively. For OS, 87.5% and 85.2%, respectively.

- At 42.9 months event-free rates for PFS and OS were 53.8% and 83.9%, respectively.

Data cutoff: October 31, 2021.
CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; mFU, median follow-up; MR, major response; MRR, major response rate; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild type.

Dimopoulos MA et al, 11th International Workshop on WM, Madrid Spain, 2022

ASPEN STUDY Adverse Events of Interest (Cohort 1)

AEs,[a] n (%)	Any grade		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Infection	78 (79.6)	80 (79.2)	**27 (27.6)**	22 (21.8)
Bleeding	61 (62.2)	56 (55.4)	10 (10.2)	9 (8.9)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Hypertension*	**25 (25.5)**	15 (14.9)	**20 (20.4)***	10 (9.9)
Atrial fibrillation/ flutter*	**23 (23.5)***	8 (7.9)	**8 (8.2)***	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia*[b]	20 (20.4)	**35 (34.7)***	10 (10.2)	**24 (23.8)***
Thrombocytopenia	17 (17.3)	17 (16.8)	6 (6.1)	11 (10.9)
Second primary malignancy/ nonskin cancers	17 (17.3)/ 6 (6.1)	17 (16.8)/ 6 (5.9)	3 (3.1)/ 3 (3.1)	6 (5.9)/ 4 (4.0)

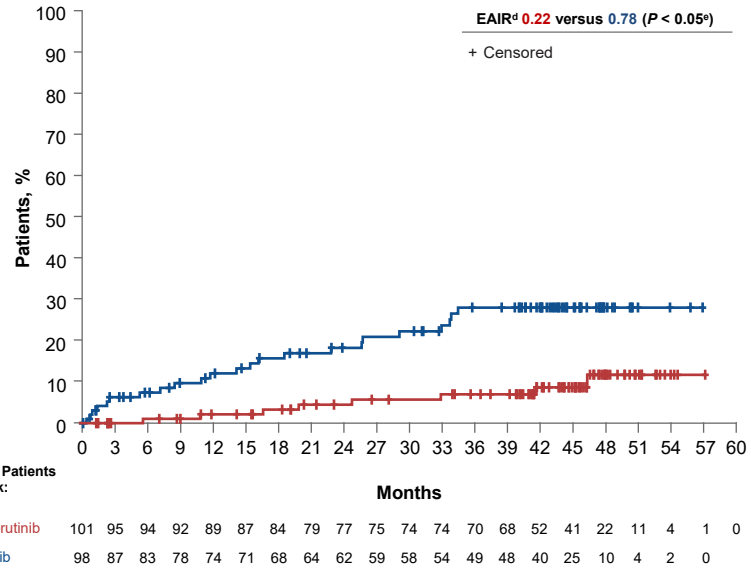
Bol
Data cutoff: October 31, 2021.
*Descriptive purposes only, 1-sided $P < 0.025$ in rate difference in all grades and/or grade ≥3. [a]Grouped terms. [b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.
AE, adverse event.

ASPEN: Cardiovascular Disorders

Cardiovascular AEs

Cardiovascular Disorders, n (%)	ASPEN cohort 1 WM		Pooled analysis B-cell malignancies	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (N=422)	Zanubrutinib (N=1550)
Median treatment duration, months	42.23	43.37	19.96	26.64
Any Cardiovascular AE				
Atrial fibrillation/flutter*	23 (23.5)	8 (7.9)	60 (14.2)	60 (3.9)
Ventricular arrhythmia (VA)[a] Grade ≥2	1 (1.0)	0	6 (1.4)	11 (0.7)
Symptomatic idiopathic VA[b]	1 (1.0)	0	6 (1.4)*	5 (0.3)*
Hypertension[c,*]	25 (25.5)	15 (14.9)	85 (20.1)	225 (14.5)
Any Cardiovascular Medical History				
Atrial fibrillation/flutter	8 (8.2)	10 (9.9)	26 (6.2)	101 (6.5)
Ventricular arrhythmia[a]	0	1 (1.0)	1 (0.2)	14 (0.9)
Hypertension[c]	45 (45.9)	39 (38.6)	206 (48.8)	669 (43.2)

Atrial Fibrillation/Flutter



[a]Ventricular arrhythmia including ventricular tachyarrhythmia (SMQ narrow), ventricular arrhythmias and cardiac arrest (High Level Term MedDRA version 24.0). [b]Symptomatic idiopathic ventricular arrhythmia is defined as a ventricular arrhythmia occurring in structurally normal hearts in the absence of myocardial scarring and active infections and were grade ≥2 per CTCAE. [c]Including hypertension (SMQ narrow). [d]EAIR, as incidence per 100 person-month. [e]Descriptive 2-sided *P* value. **P* <0.05 for EAIR difference between treatments.
AE, adverse event; EAIR, exposure-adjusted incidence rates; SMQ, Standardized MedDRA (Medical Dictionary for Regulatory Activities) queries; VA, ventricular arrhythmia.

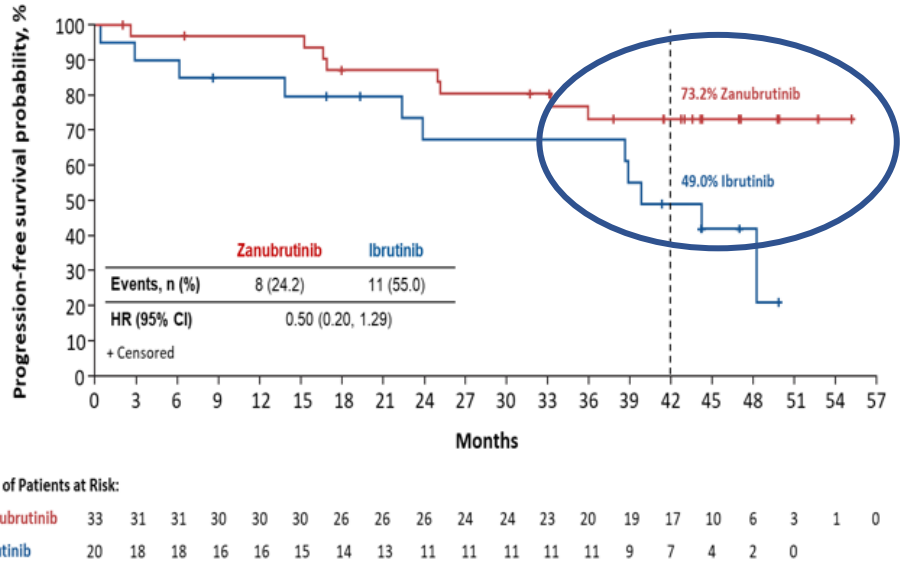
Response and PFS in Patients With *MYD88*^{MUT} by *CXCR4*^{MUT} Status

Response Assessment by *CXCR4* Status[a]

Response	*CXCR4*^{MUT} Ibrutinib (n=20)	*CXCR4*^{MUT} Zanubrutinib (n=33)	*CXCR4*^{WT} Ibrutinib (n=72)	*CXCR4*^{WT} Zanubrutinib (n=65)
VGPR or better, n (%)	2 (10.0)	**7 (21.2)**	22 (30.6)	**29 (44.6)**
Major response, n (%)	13 (65.0)	**26 (78.8)**	61 (84.7)	54 (83.1)
Overall response, n (%)	19 (95.0)	30 (90.9)	68 (94.4)	63 (96.9)
Time to MR, median (months)	6.6	3.4	2.8	2.8
Time to VGPR, median (months)	31.3	11.1	11.3	6.5

Bold blue text indicates >10% difference between arms.

PFS in Patients With *MYD88*^{MUT}*CXCR4*^{MUT}



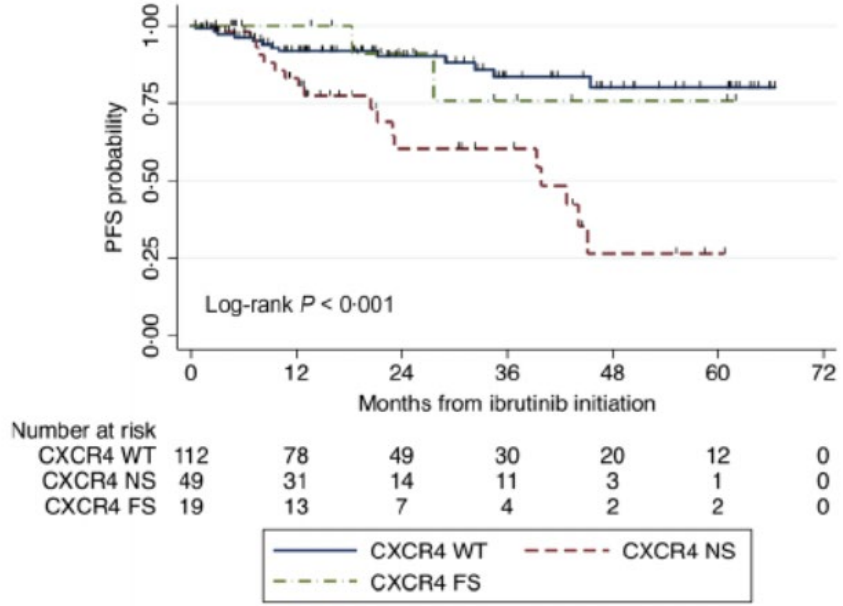
[a]*CXCR4* mutation determined by NGS. Ninety-two ibrutinib patients and 98 zanubrutinib patients had NGS results available.
Data cutoff: October 31, 2021.
CI, confidence Interval; *CXCR4*, C-X-C chemokine receptor type 4 gene; HR, hazard ratio; MR, major response; MUT, mutant; PFS, progression-free survival; VGPR, very good partial response.

CXCR4 Nonsense variants with high clonality impact ibrutinib PFS outcomes

CXCR4 NS vs. FS Mutations

	Total	*CXCR4*^{WT}	*CXCR4*^{NS}	*CXCR4*^{FS}	*P*-value
All patients					
Very good partial response	44 (25%)	36 (33%)	3 (6%)	5 (26%)	<0·001
Partial response	90 (51%)	56 (52%)	24 (49%)	10 (53%)	
Minor response	31 (18%)	13 (12%)	16 (33%)	2 (11%)	
No response	11 (6%)	3 (3%)	6 (12%)	2 (11%)	
Major response (≥partial)	134 (76%)	92 (85%)	27 (55%)	15 (79%)	<0·001
Previously treated					
Very good partial response	33 (26%)	28 (36%)	2 (6%)	3 (21%)	0·002
Partial response	61 (49%)	37 (44%)	15 (45%)	19 (64%)	
Minor response	23 (18%)	11 (14%)	11 (33%)	1 (7%)	
No response	8 (6·4)	2 (3%)	5 (15%)	1 (7%)	
Major response (≥partial)	94 (75%)	65 (83%)	17 (51%)	12 (86%)	0·001
Previously untreated					
Very good partial response	11 (20%)	8 (24%)	1 (6%)	2 (40%)	0·28
Partial response	30 (55%)	20 (59%)	9 (56%)	1 (20%)	
Minor response	10 (18%)	4 (12%)	5 (31%)	1 (20%)	
No response	4 (7%)	2 (6%)	1 (6%)	1 (20%)	
Major response (≥partial)	41 (75%)	28 (82%)	10 (63%)	3 (60%)	0·24

CXCR4^{WT}, *CXCR4* wild type; *CXCR4*^{NS}, *CXCR4* nonsense mutation; *CXCR4*^{FS}, *CXCR4* frame-shift mutation.



N=180; Previously treated 125 (69%)

Castillo et al, BJH 2019; Gustine et al, Blood Adv 2019

ASPEN: Responses by CXCR4 mutation subtypes

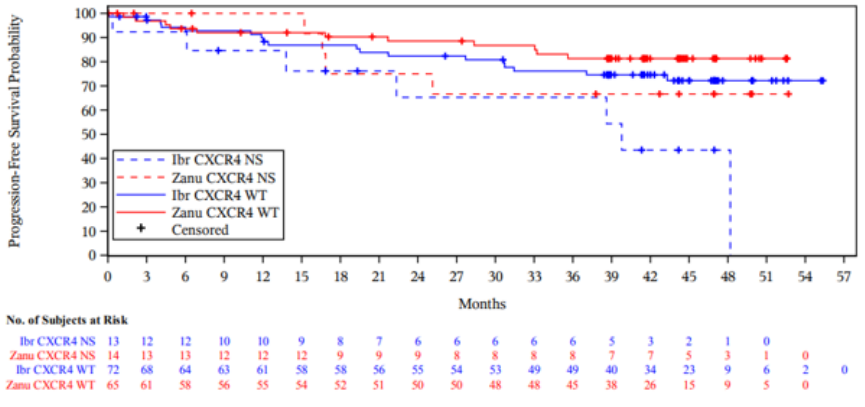
	Patients with *MYD88*^{MUT} treated with ibrutinib			Patients with *MYD88*^{MUT} treated with zanubrutinib		
	CXCR4^{WT} (n=72)	*CXCR4*^{FS} (n=7)	*CXCR4*^{NS} (n=13)	*CXCR4*^{WT} (n=65)	*CXCR4*^{FS} (n=19)	*CXCR4*^{NS} (n=14)
VGPR or better, n (%)	22 (30.6)	**0 (0.0)**	**2 (15.4)**	29 (44.6)	**5 (26.3)**	**2 (14.3)**
Major response, n (%)	61 (84.7)	6 (85.7)	**7 (53.8)**	54 (83.1)	14 (73.7)	12 (85.7)
Time to VGPR or better Median (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)
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)	2.8 (0.9, 28.5)	2.9 (1.8, 49.8)	4.1 (1.0, 38.7)
PFS						
Events, n (%) [c]	18 (25.0%)	4 (57.1%)	7 (53.8%)	11 (16.9%)	4 (21.0%)	4 (28.5%)
P value[b]		0.185	**0.017**		0.473	0.598

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

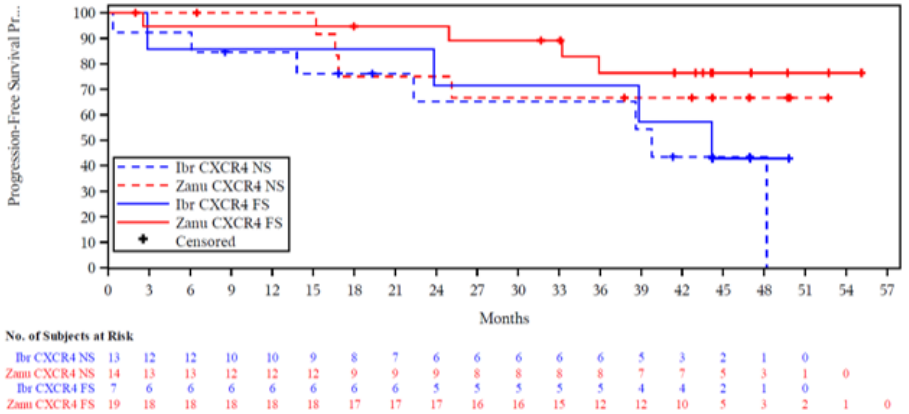
Data cutoff: October 31, 2021. [a]Mutation determined by NGS; NGS results were available for 92 patients in the ibrutinib arm and 98 patients in the zanubrutinib arm. [b] P values were estimated using a Cox regression model with *CXCR4* (WT, FS, NS), *TP53* (WT, MUT), and *TERT* (WT, MUT) mutational statuses as covariates. WT is the reference group. [c] Include the number of progressive disease or death

ASPEN: PFS by CXCR4 mutation subtypes

PFS in *CXCR4*^{NS} vs *CXCR4*^{WT}



PFS in *CXCR4*^{NS} vs *CXCR4*^{FS}



- Patients with *CXCR4*^{NS} had more inferior PFS than CXCR4^{WT} by ibrutinib compared to zanubrutinib
- Both CXCR4^{NS} and CXCR4^{FS} show similar PFS trend, and Zanubrutinib demonstrated a more favorable PFS than ibrutinib in CXCR4^{NS}, and CXCR4^{FS} patients

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.

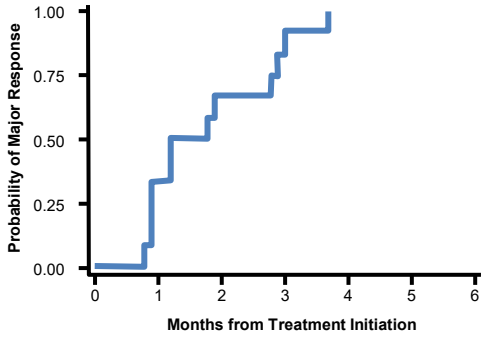
Phase I Trial of CXCR4 antagonist Ulocuplumab and Ibrutinib in CXCR4-mutated Patients with Symptomatic WM

Baseline

	Median
Age (yr)	61.5
sIgM (mg/dL)	5241
BM Involved	65%
Hb (g/dL)	9.1
Prior Rx	0 (0-2)
Sx HV	42%

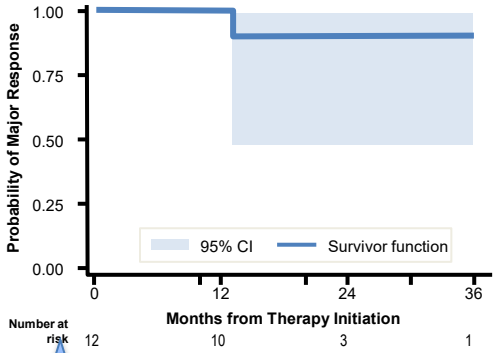
Median follow-up : 22.4 mos.

Median Time to Major Response



1.2 (95% CI 0.9-2.8) months

Median Time to PFS

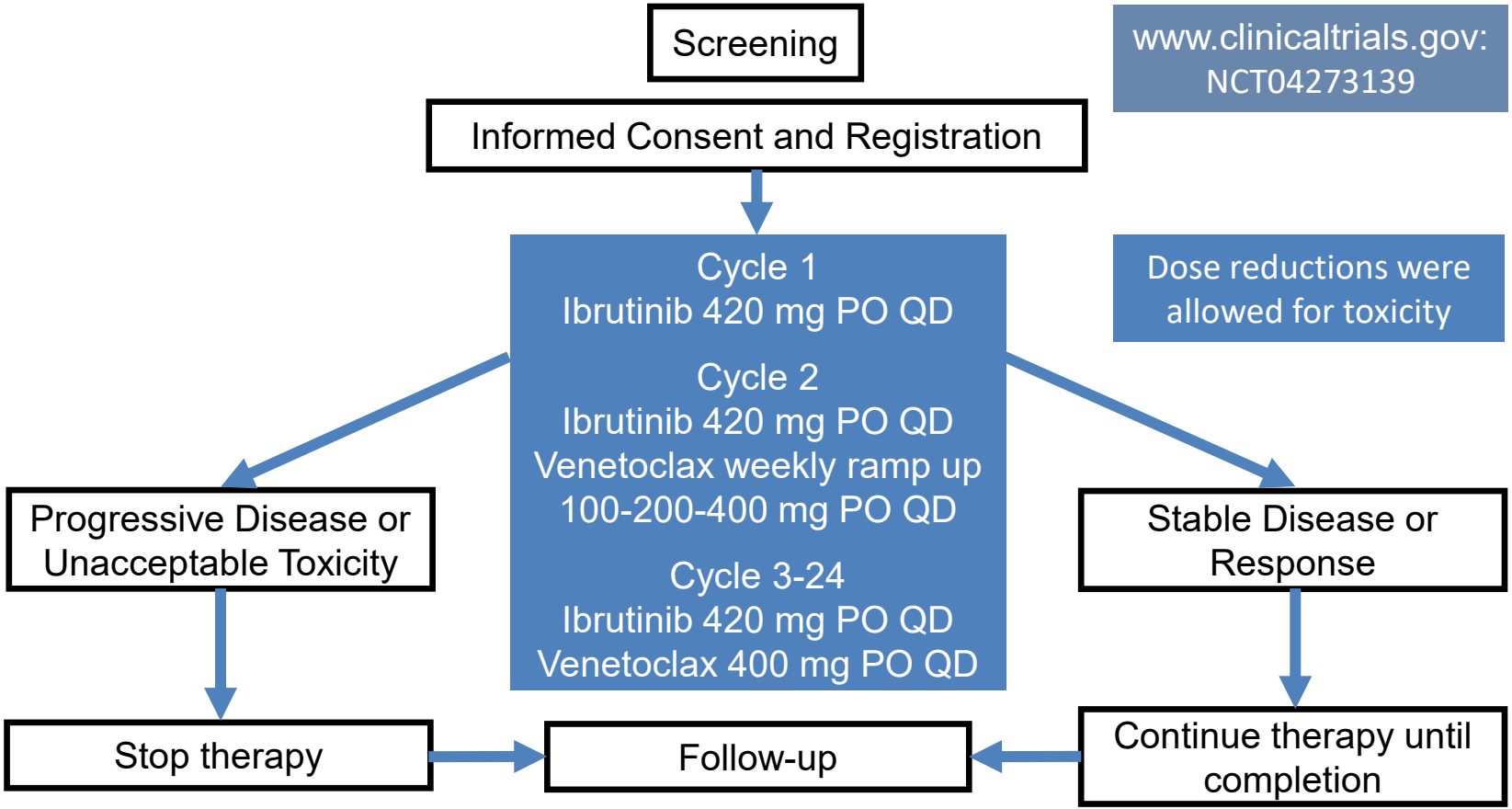


2-year 90% estimated

Major RR: 100%
VGPR: 33%

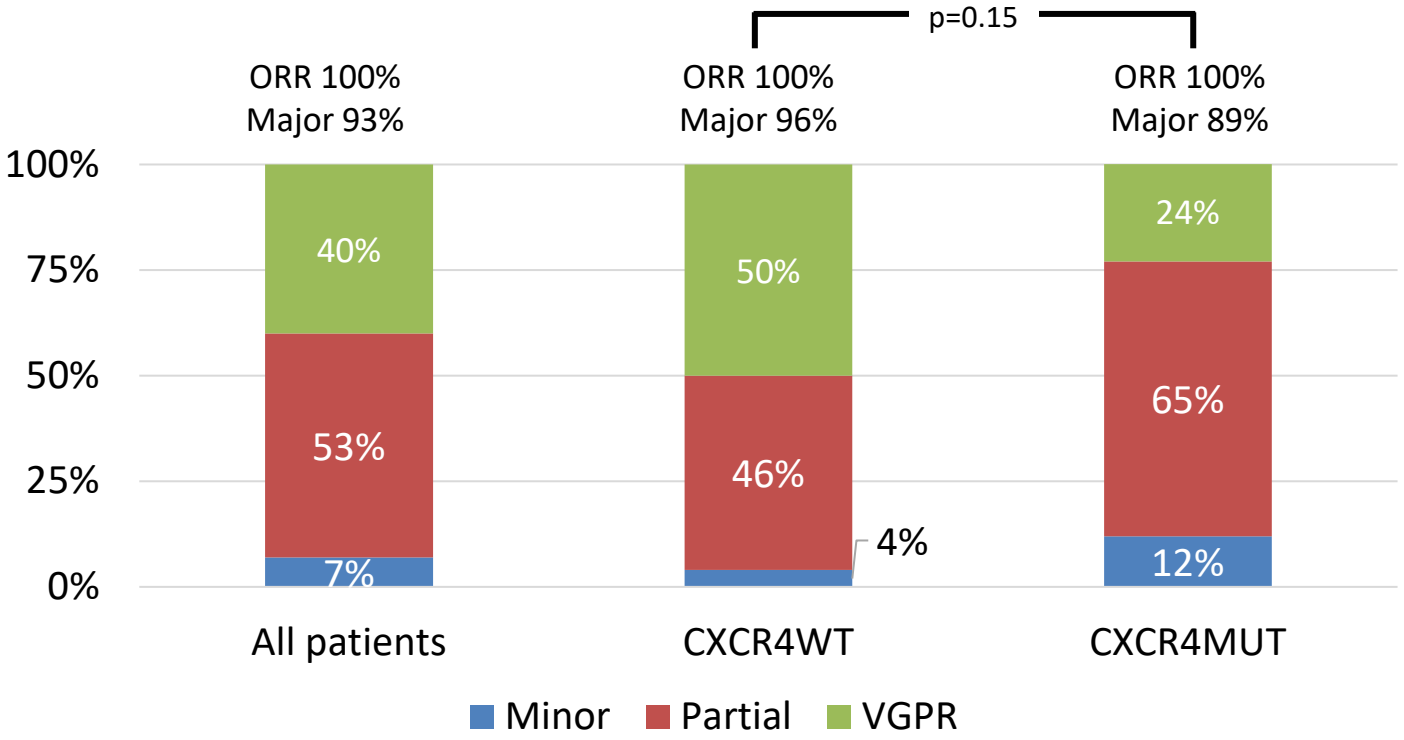
Treon S, et al. *Blood*. 2021; 138 (17): 1535–1539.

Ibrutinib and Venetoclax (IVEN) in Treatment Naïve WM



Castillo et al, ASH 2022

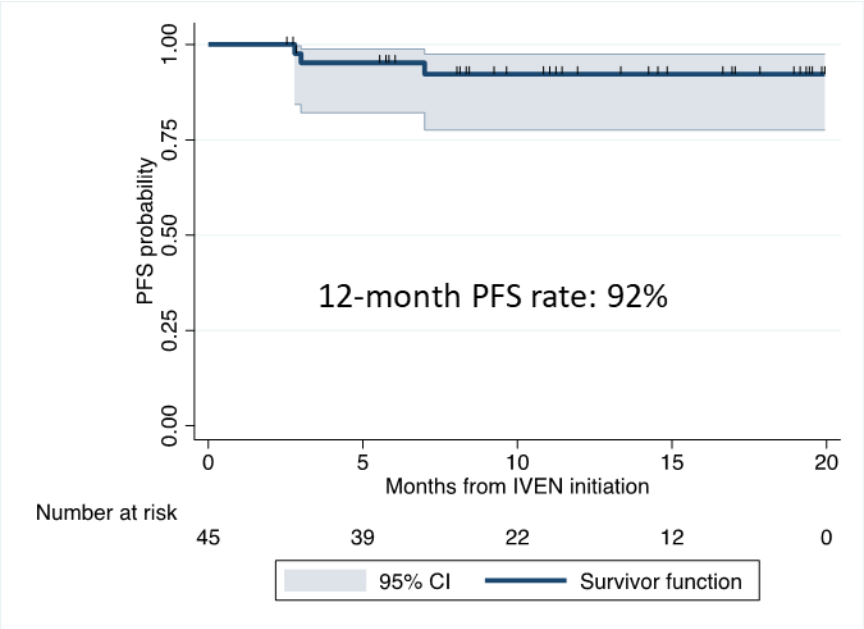
IVEN: Response to therapy

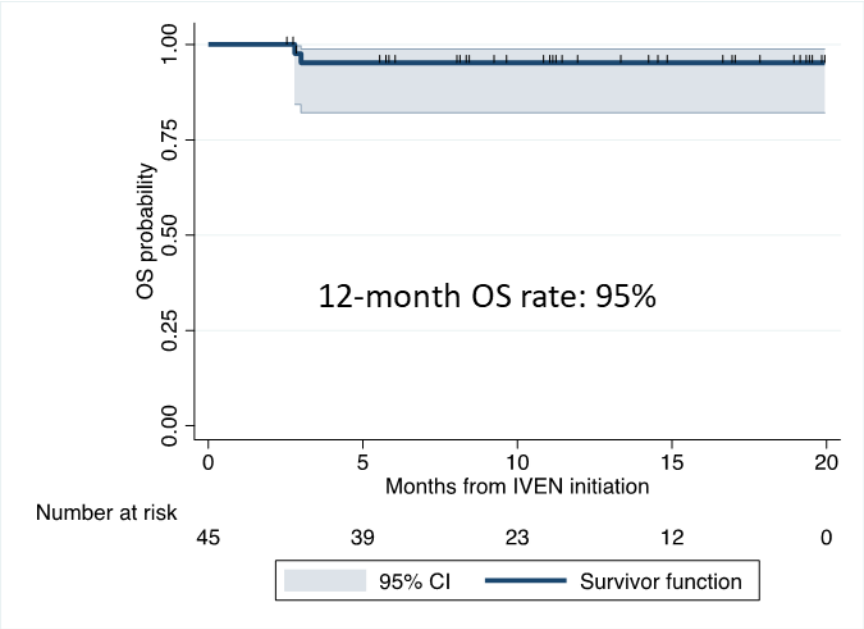


Castillo et al, ASH 2022

IVEN: Survival analysis

Median follow-up: 11 months





Castillo et al, ASH 2022

Safety

Adverse events observed in ≥3 patients and of clinical importance

n=45

Adverse events	Grade 2	Grade 3	Grade 4	Grade 5	Total
Anemia	1	2			3
Atrial fibrillation	1	2	1		4
Diarrhea	8	1			9
Reflux	10				10
Mucositis	7	2			9
Nausea	5				5
Neutropenia	1	10	3		14
Hyperphosphatemia	8				8
Muscle/joint pain	14	2			16
Skin rash	6				6
Ventricular arrhythmia	1		1	2	4
Laboratory TLS		2			2

TLS: tumor lysis syndrome

Castillo et al, ASH 2022

So how do we position BTK-inhibitors relative to Bendamustine-R in treatment naïve patients?

Bendamustine Rituximab versus Ibrutinib as Primary Therapy for Waldenström Macroglobulinemia: An International Collaborative Study

Jithma P. Abeykoon[1], Shaji Kumar[1], Jorge J. Castillo[2], Shirley D'sa[3], Efstathios Kastritis[4], Eric Durot[5], Encarl Uppal[3], Morel Pierre[6], Jonas Paludo[1], Reema Tawfiq[1], Shayna R Sarosiek[7], Olabisi Ogunbiyi[8], Pascale Cornillet-Lefebvre[9], Robert A. Kyle[1], Alain Delmer[10], Morie A. Gertz[1], Meletios A Dimopoulos[11], Steve P. Treon[2], Stephen M. Ansell[1], and Prashant Kapoor[1]

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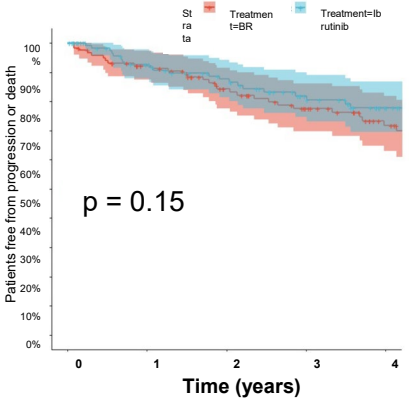
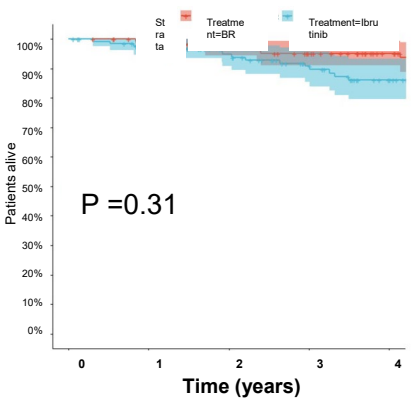
[3]University College London Hospital Foundation Trust, London, United Kingdom, [4]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Alexandra General Hospital, 80 Vas. Sofias Avenue, 11528, Athens, Greece.
[5]Department of Hematology, University Hospital of Reims and UFR Médecine, Reims. [6]Service Hématologie Clinique et Thérapies Cellulaires, CHU Amiens, Amiens, France, [7]Department of Hematology and Oncology, Boston University School of Medicine, Boston Medical Center, Boston, MA.
[8]Translational Psychiatry Research Group, Research Department of Mental Health Neuroscience, Division of Psychiatry, Faculty of Brain Sciences, University College London, United Kingdom.
[9]Laboratoire d'hématologie, Hôpital Robert Debré, Reims, France, [10]HU de Reims, Hôpital Robert-Debré, Université Reims Champagne-Ardenne, Reims, France.
[11]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Alexandra General Hospital, 80 Vas. Sofias Avenue, 11528, Athens, Greece.

Variable	BR	Ibrutinib	p-value
Follow up, median, 95%CI, y	4.5 (3.7-4.9)	4.5 (4-4.7)	0.7
Age, median, range, y	68 (40-86)	68 (39-86)	0.9
IPSS%			0.63
Low	11	17	
Intermediate	33	33	
High	56	48	
Cycles, median (range)	6 (1-6) >4 cycles, 77%	42 (0.3-98)	
Overall response rate, %	94	94	0.91
Major response rate, %	92	83	0.05
Complete response, %	20	2	**<0.001**
≥VGPR, %	50	33	**0.009**

Progression-free survival



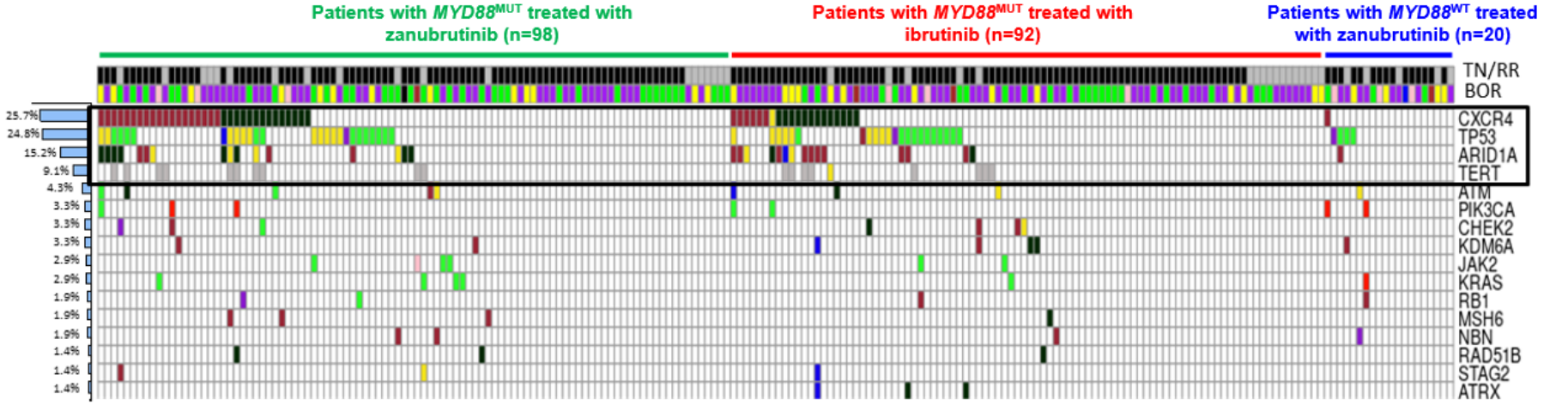
Overall survival



- Bivariate analysis of age matched patients who received either Benda-R or Ibrutinib (N=246)
- 77% of Benda-R patients received 6 cycles
- MYD88 WT patients excluded
- Median Follow-Up: 4.2 years

Abeykoon et al, Eur. Hematol. Assoc. June 2022
Updated IWWM-11, 2022.

High Rate of TP53^{MUT}, TERT^{MUT} were found in ASPEN Study[a] and more often detected in Patients with MYD88^{MUT} or CXCR4^{MUT}



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

Bold text indicates >10% difference between MUT and WT in 210 NGS evaluable WM pts. [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; MR, major response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; *TERT*, telomerase reverse transcriptase gene; TN, treatment-naïve; *TP53*, tumor protein P53 gene.

TP53 Mutations in ASPEN Study

	N=	Total $TP53^{Mut}$	Treatment Naïve $TP53^{Mut}$	Previously Treated $TP53^{Mut}$	p= (TN vs prev. treated)
$MYD88^{Mut}$	190	48/190 (25.2%)	6/190 (3.2%)	42/190 (22.1%)	<0.00001
$MYD88^{WT}$	20	4/20 (20%)	1/20 (5%)	3/20 (15%)	NS

Tam C et al, 11th International Workshop on WM, Madrid Spain, 2022

DNA Binding Domain TP53 mutations identified by NGS

N=265; 13/265 (4.9%); 9/265 Validated (3.4%); 6/265 (2.3%) Somatic.

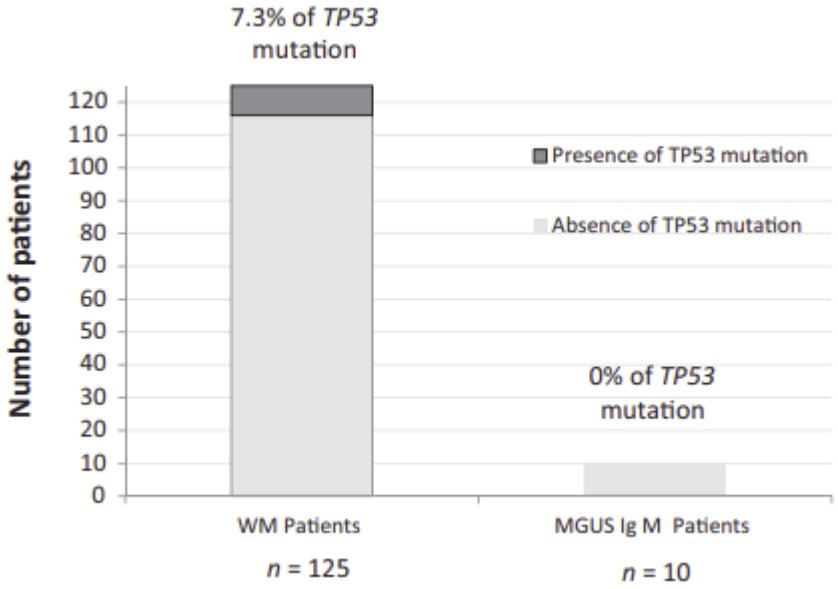
Patient	Nucleotide change	Amino acid change	Variant allele fraction (%)	Total number of reads	Sanger sequencing	
					$CD19^+$ BM	$CD19^-$ PB
WM1	574 C>T; 916 C>T	Q192; R306	15·0; 39·8	878; 379	Present	WT
WM2	833 C>G	P278R	4·9	509	Present	WT
WM3	584 T>C	I195T	11·1	878	Present	WT
WM4	488 A>G	Y163C	8·5	118	Present	WT
WM5	586 C>T	R196	56·1	239	Present	WT
WM6	722 C>T	S241F	46·6	476	Present	WT
WM7	289 G>C	V97L	41·2	182	Present	Present
WM8	847_847insGGG	282_283insG	32·3	690	Present	Present
WM9	704 A>G	N235S	44·4	563	Present	Present
WM10	659 T>C	Y220C	31·2	955	WT	WT
WM11	701 A>G	Y234C	8·5	791	WT	WT
WM12	745 A>G	R249G	3·2	568	WT	WT
WM13	843 C>A	D281E	5·1	431	WT	WT

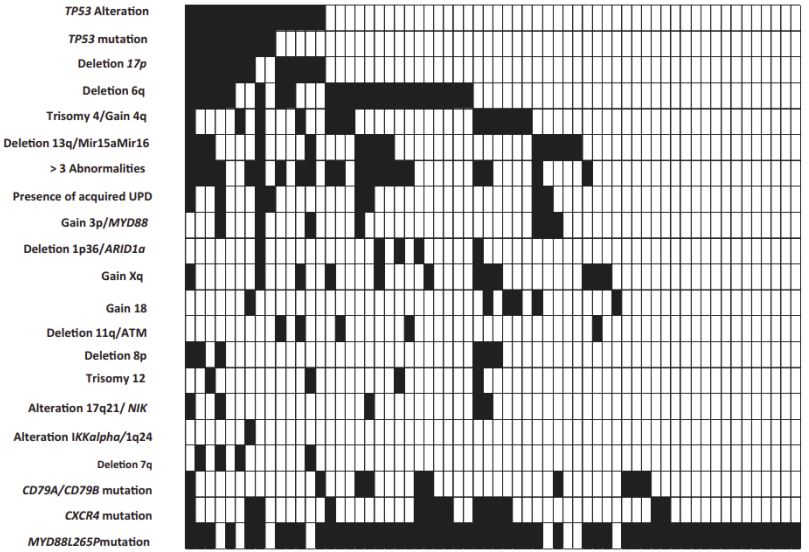
BM, bone marrow; PB, peripheral blood; WT, wild type.

All 6 validated were MYD88 and CXCR4 mutated.
4/6 CXCR4 mutated were NS.

Gustine et al, BJH 2018.

TP53 Mutations in Waldenstrom's Macroglobulinemia





Poulain et al, CCR 2017

blood

Regular Article

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CLINICAL TRIALS AND OBSERVATIONS

A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study

Constantine S. Tam,[1-4] Stephen Opat,[5,6] Shirley D'Sa,[7] Wojciech Jurczak,[8] Hui-Peng Lee,[9] Gavin Cull,[10,11] Roger G. Owen,[12] Paula Marlton,[13,14] Björn E. Wahlin,[15] Ramón García Sanz,[16] Helen McCarthy,[17] Stephen Mulligan,[18] Alessandra Tedeschi,[19] Jorge J. Castillo,[20,21] Jaroslaw Cyz,[22,23] Carlos Fernández de Larrea,[24] David Belada,[25] Edward Libby,[26] Jeffrey V. Matous,[27] Marina Motta,[28] Tanya Siddiqi,[29] Monica Tani,[30] Marek Trneny,[31] Monique C. Minnema,[32] Christian Buske,[33] Veronique Leblond,[34] Judith Trotman,[35,36] Wai Y. Chan,[37] Jingjing Schneider,[37] Sunhee Ro,[37] Aileen Cohen,[37] Jane Huang,[37] and Meletios Dimopoulos,[38] for the ASPEN Investigators

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]St Vincent's Hospital, Fitzroy, VIC, Australia; [3]Department of Medicine, University of Melbourne, Parkville, VIC, Australia; [4]Royal Melbourne Hospital, Parkville, VIC, Australia; [5]Monash Health, Clayton, VIC, Australia; [6]Clinical Haematology Unit, Monash University, Clayton, VIC, Australia; [7]University College London Hospital Foundation Trust, London, United Kingdom; [8]Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland; [9]Flinders Medical Centre, Adelaide, SA, Australia; [10]Sir Charles Gairdner Hospital, Perth, WA, Australia; [11]Department of Lymphoma/Myeloma, University of Western Australia, Perth, WA, Australia; [12]St James's University Hospital, Leeds, United Kingdom; [13]Department of Haematology, Princess Alexandra Hospital, Brisbane, QLD, Australia; [14]School of Medicine, University of Queensland, Brisbane, QLD, Australia; [15]Unit of Hematology, Department of Medicine, Karolinska Universitetssjukhuset-Karolinska Institutet, Stockholm, Sweden; [16]Hospital Universitario de Salamanca, Salamanca, Spain; [17]Royal Bournemouth and Christchurch Hospital, Bournemouth, United Kingdom; [18]Royal North Shore Hospital, Sydney, NSW, Australia; [19]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [20]Bing Center for Waldenstrom Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [21]Department of Medicine, Harvard Medical School, Boston, MA; [22]Sapital Uniwersytecki No 2 im Dr Jana Biziela, Bydgoszcz, Poland; [23]Department of Hematology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland; [24]Amyloidosis and Myeloma Unit, Department of Hematology, Hospital Clinic of Barcelona, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain; [25]Fourth Department of Internal Medicine - Haematology, Charles University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; [26]Department of Medicine, University of Washington and the Seattle Cancer Care Alliance, Seattle, WA; [27]Colorado Blood Cancer Institute, Denver, CO; [28]ASST Spedali Civili di Brescia, Lombardia, Italy; [29]City of Hope National Medical Center, Duarte, CA; [30]Ospedale Civile S Maria delle Croci, Azienda Unita Sanitaria Locale (AUSL), Ravenna, Italy; [31]First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [32]University Medical Center Utrecht, Utrecht, The Netherlands; [33]Comprehensive Cancer Center Ulm-Universitätsklinikum Ulm, Ulm, Germany; [34]Service d'Hématologie Clinique, Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [35]Haematology Department, University of Sydney, Concord, NSW, Australia; [36]Department of Haematology, Concord Repatriation General Hospital, Sydney, Concord, NSW, Australia; [37]BeiGene USA, Inc, San Mateo, CA; and [38]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece

KEY POINTS

- Although not statistically significant, a higher rate of CR/VGPR was observed for zanubrutinib vs ibrutinib (28% vs 19%, respectively).
- The incidence and severity of most BTK-associated toxicities (including atrial fibrillation) were lower with zanubrutinib than ibrutinib.

Bruton tyrosine kinase (BTK) inhibition is an effective treatment approach for patients with Waldenström macroglobulinemia (WM). The phase 3 ASPEN study compared the efficacy and safety of ibrutinib, a first-generation BTK inhibitor, with zanubrutinib, a novel highly selective BTK inhibitor, in patients with WM. Patients with *MYD88*^{L265P} disease were randomly assigned 1:1 to treatment with ibrutinib or zanubrutinib. The primary end point was the proportion of patients achieving a complete response (CR) or a very good partial response (VGPR) by independent review. Key secondary end points included major response rate (MRR), progression-free survival (PFS), duration of response (DOR), disease burden, and safety. A total of 201 patients were randomized, and 199 received ≥1 dose of study treatment. No patient achieved a CR. Twenty-nine (28%) zanubrutinib patients and 19 (19%) ibrutinib patients achieved a VGPR, a nonstatistically significant difference ($P = .09$). MRRs were 77% and 78%, respectively. Median DOR and PFS were not reached; 84% and 85% of ibrutinib and zanubrutinib patients were progression free at 18 months. Atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, and pneumonia, as well as adverse events leading to treatment discontinuation, were less common among zanubrutinib recipients. Incidence of neutropenia was higher with zanubrutinib, although grade ≥3 infection rates were similar in both arms (1.2 and 1.1 events per 100 person-months). These results demonstrate that zanubrutinib and ibrutinib are highly effective in the treatment of WM, but zanubrutinib treatment was associated with a trend toward better response quality and less toxicity, particularly cardiovascular toxicity. (*Blood*. 2020;136(18): 2038-2050)

Prior therapy, n (%)	Ibrutinib (n=81)	Zanubrutinib (n=83)
Number of prior systemic regimens		
1	46 (57)	47 (57)
2	15 (19)	15 (18)
3	13 (16)	14 (17)
4	2 (2)	4 (5)
5	3 (4)	0
≥6	2 (3)	3 (4)
Anti-CD20 (rituximab, ofatumumab)	74 (91)	75 (90)
Alkylating agents (cyclophosphamide, chlorambucil, bendamustine, ifosamide, lomustine, melphalan, cisplatin)	66 (82)	73 (88)
Glucocorticoids (dexamethasone, prednisone, prednisolone, methylprednisone, methylprednisolone, hydrocortisone)	50 (62)	60 (72)
Nucleoside analogues (fludarabine, cladribine, cytarabine, gemcitabine,)	18 (22)	20 (24)
Vinca alkaloids (vincristine, vinblastine, vinorelbine)	18 (22)	23 (28)
Proteasome inhibitors (bortezomib, ixazomib)	10 (12)	10 (12)
Anthracyclines (doxorubicin, epirubicin)	9 (11)	9 (11)
Kinase inhibitors (idelalisib, everolimus)	3 (4)	2 (2)
Immunomodulators (lenalidomide, thalidomide)	1 (1)	1 (1)
Topoisomerase inhibitors (etoposide)	1 (1)	2 (2)
Multi-agent regimens, including anti-CD20	0	1 (1)
Others (interferon, bleomycin, belimumab, methotrexate)	0	4 (5)

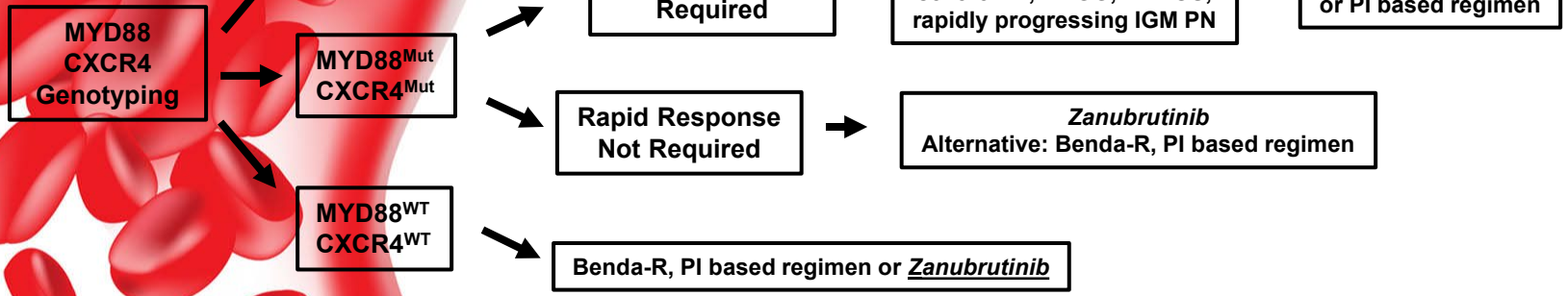
Outcomes in ASPEN Study for TP53 Wild-Type vs. TP53 Mutated Patients

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.

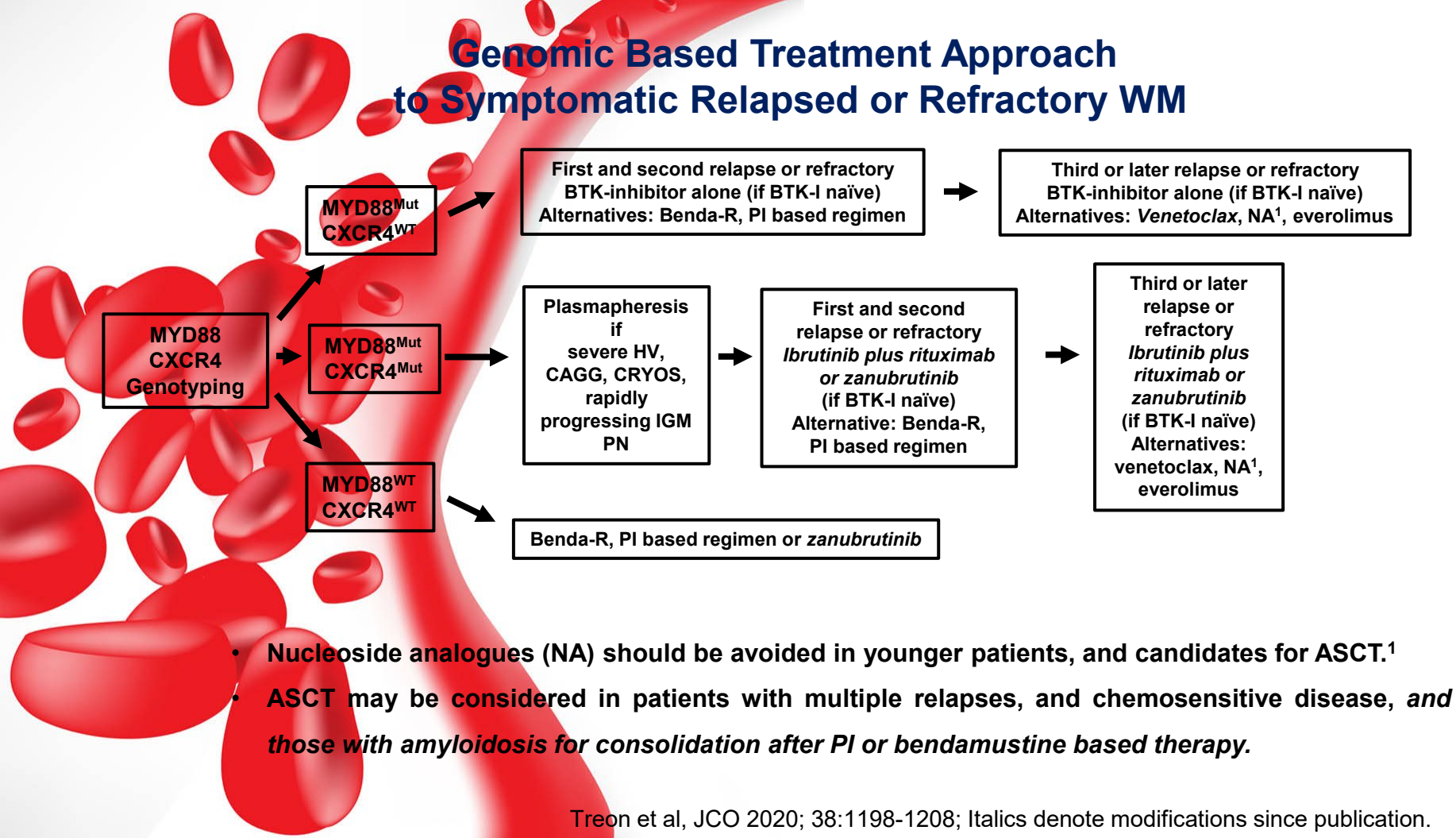
Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM



- Rituximab should be held for serum IgM ≥4,000 mg/dL
- Benda-R for bulky adenopathy or extramedullary disease.
- PI or *bendamustine* based regimen for symptomatic amyloidosis, and possible ASCT as consolidation.
- Rituximab alone, or with ibrutinib if MYD88^{Mut} or bendamustine for IgM PN depending on severity and pace of progression.
- Maintenance rituximab may be considered *in >65 year patients responding to rituximab based regimens or those with < major response.*

Treon et al, JCO 2020; 38:1198-1208; Italics denote modifications since publication.

Genomic Based Treatment Approach to Symptomatic Relapsed or Refractory WM



- Nucleoside analogues (NA) should be avoided in younger patients, and candidates for ASCT.[1]
- ASCT may be considered in patients with multiple relapses, and chemosensitive disease, *and those with amyloidosis for consolidation after PI or bendamustine based therapy.*

Treon et al, JCO 2020; 38:1198-1208; Italics denote modifications since publication.

Conclusions

- Activating MYD88 mutations are found in 95-97% of WM patients and drive multiple growth and survival pathways that include BTK and IRAK1/IRAK4 canonical NFKB signaling.
- CXCR4 mutations are found in 40% of WM patients and drive resistance to BTK-inhibitors, particularly nonsense variants. CXCR4 antagonists may overcome resistance to ibrutinib in $CXCR4^{Mut}$ patients.
- Zanubrutinib shows more favorable activity in CXCR4 mutated, and MYD88 WT patients, and much less Afib.
- TP53 is far more common among previously treated vs. TN patients, and impacts outcomes with BTK-inhibitors. **Should BTK-inhibitors be moved to the frontline before TP53 mutations set in?**