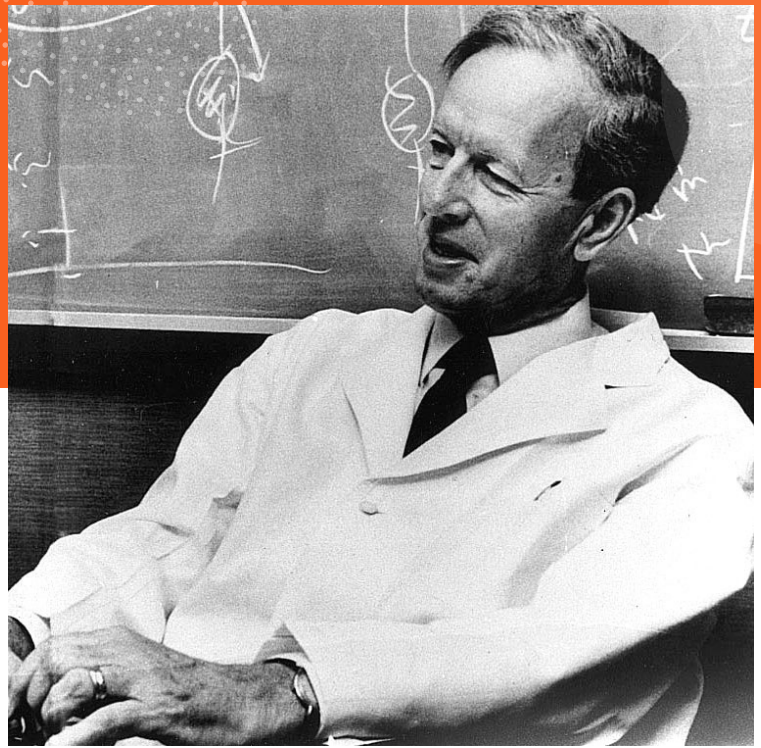
Updates in Waldenstrom's Macroglobulinemia



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Disclosures

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Abbvie/Pharmacyclics
Beigene
BMS
Eli Lilly
Janssen Pharmaceuticals
X4 Pharmaceuticals
IP assigned to DFCI for MYD88, CXCR4, and IRAK and HCK and other inhibitors.

“Big” Questions in WM

- Chemoimmunotherapy vs. BTK-inhibitors
- Which BTK-inhibitor and for which patient
- Role of genomics in treatment decision making
- How to manage intolerant or progressing patients on BTK-Inhibitors

MYD88 Directed Pro-survival Signaling in WM

The NEW ENGLAND JOURNAL of MEDICINE

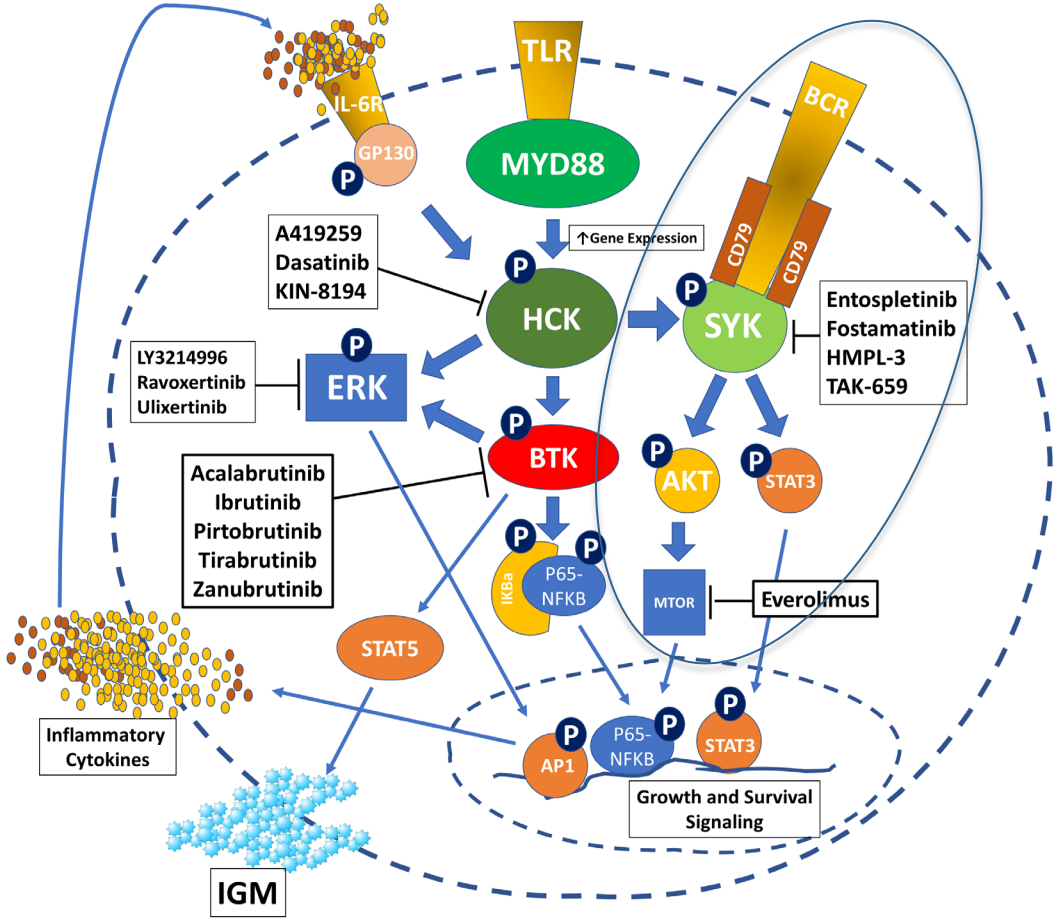
ORIGINAL ARTICLE

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

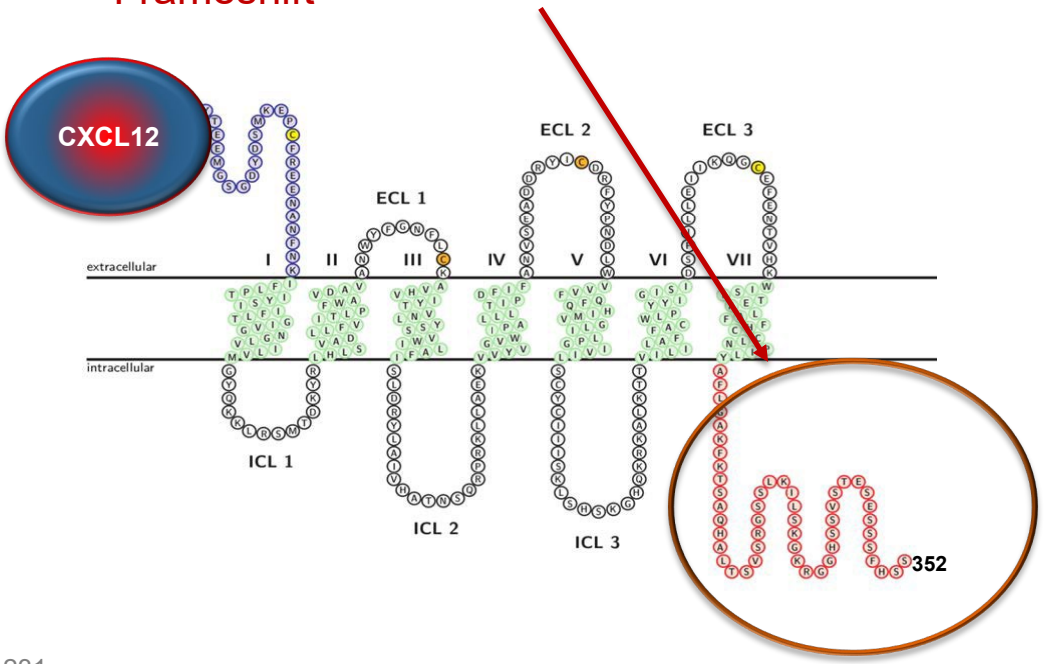
Steven P. Treon,[1,2] Yang Cao,[1,2] Lian Xu,[1,2] Guang Yang,[1,2] Xia Liu,[1,2] and Zachary R. Hunter[1,3]

[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) - HV Syndrome; ↓ BTK-I Response
- Frameshift



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.

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)*

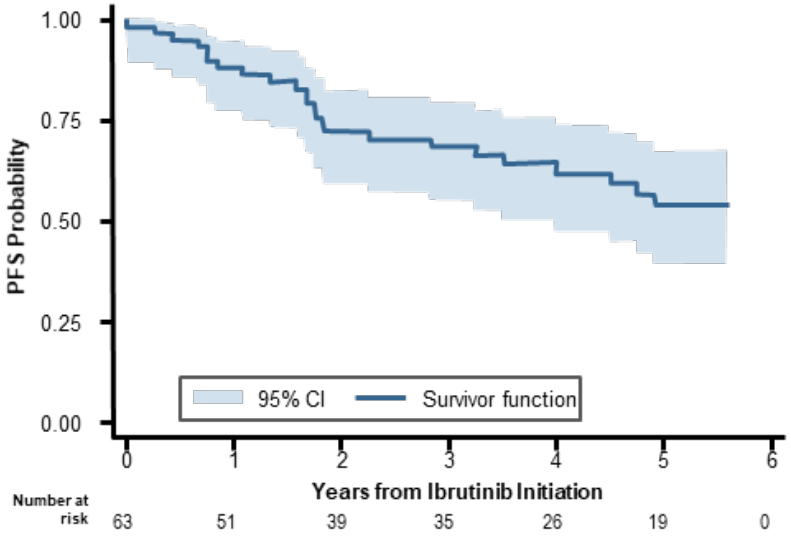
	All Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	MYD88^{WT} CXCR4^{WT}	P-value
N	63	36	22	4	N/A
Overall Response Rate-no. (%)	90.5%	100%	86.4%	50%	<0.01
Major Response Rate-no. (%)	**79.4%**	**97.2%**	**68.2%**	**0%**	**<0.0001**
Categorical responses					
Minor responses-no. (%)	11.1%	2.8%	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)

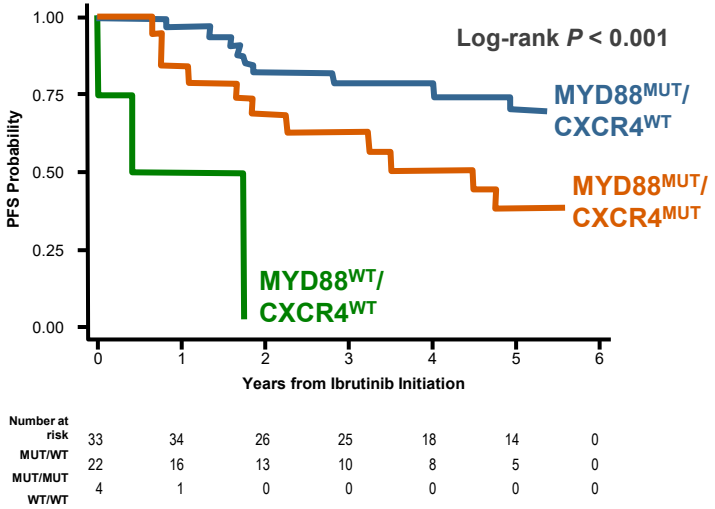
All patients



5-year PFS: 54%

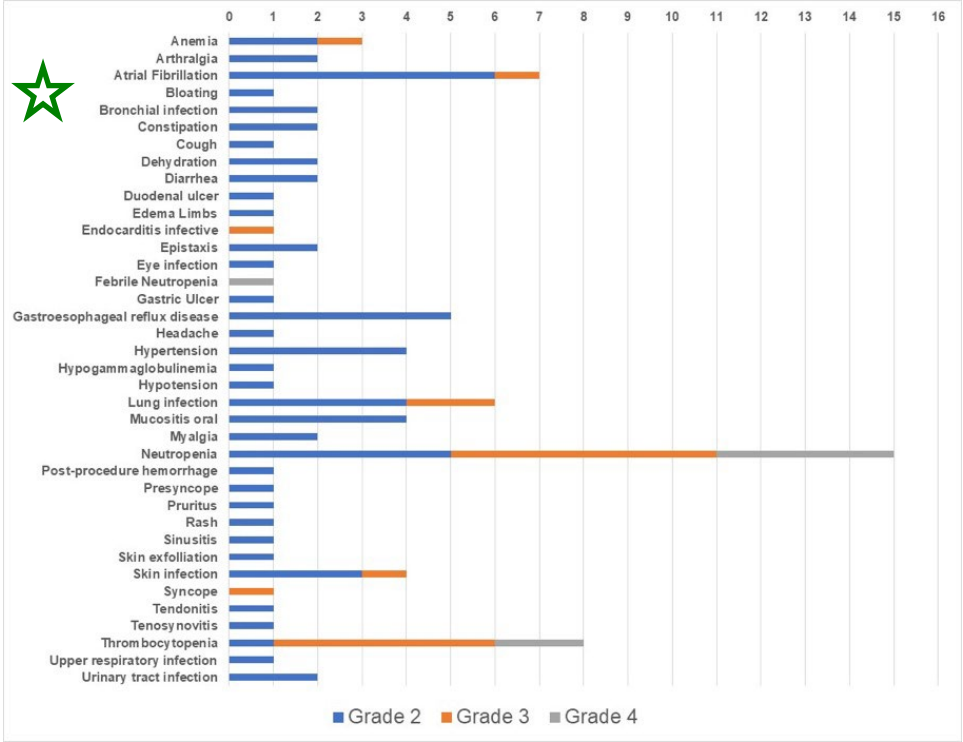
5-year OS: 87%

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

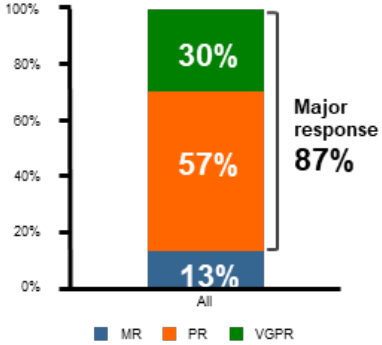


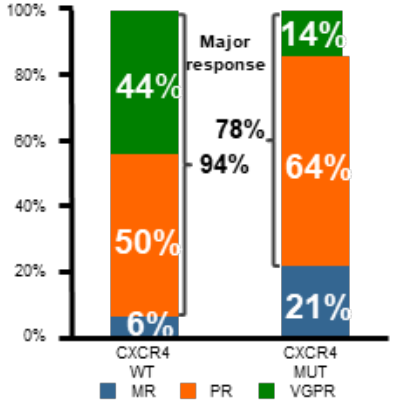
☆ Increased since original report; 8 patients (12.7%) with Afib, including grade 1; 7 continued ibrutinib with medical management.

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 in Treatment-Naïve WM Patients

All patients were MYD88 mutated.



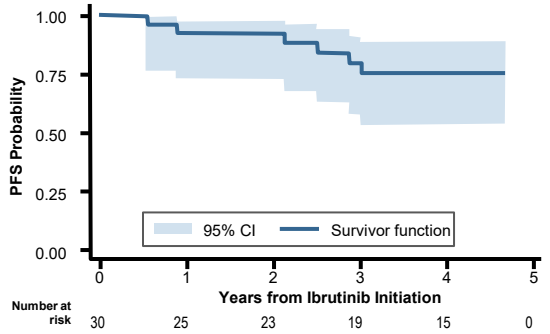


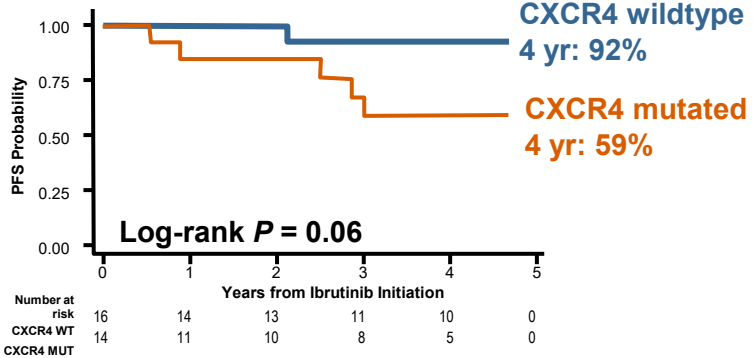
Median time to Response

	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

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)

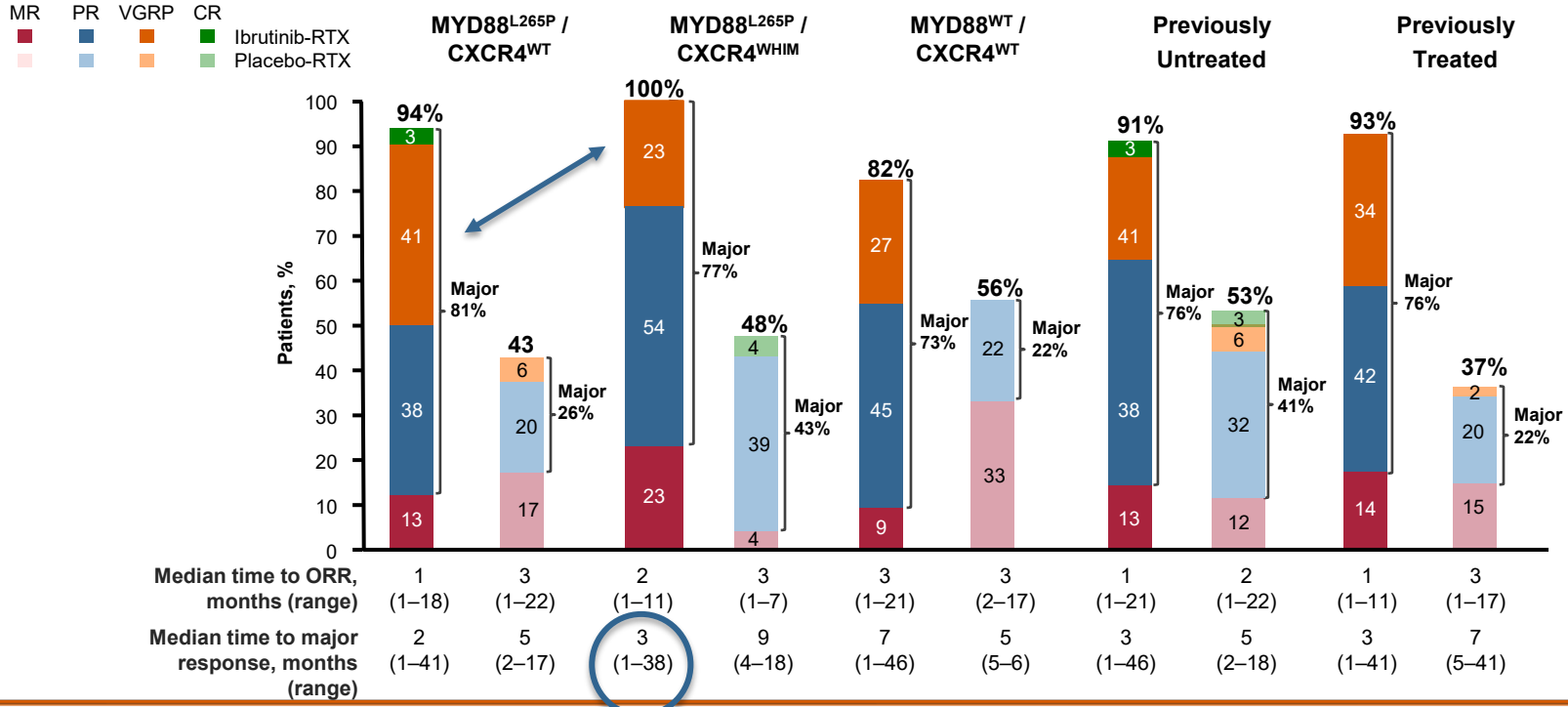
- 6/16 (37.5%)
- In 5 of these 6 patients, serum IgM returned to pre-hold levels or better following re-start of therapy at a median of 4.6 months (range 3.4-11.2 months).
- One patient's serum IgM level remained elevated after self-holding drug for 15 days, and met criteria for progression.

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

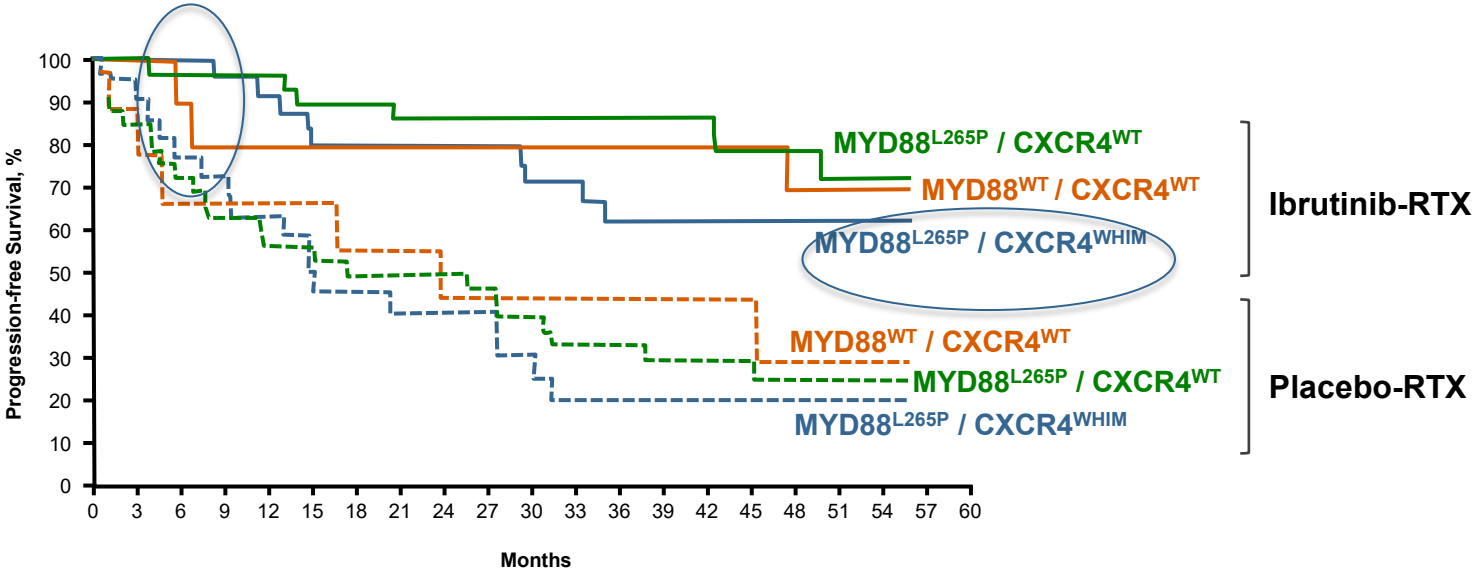
iNNOVATE: Response Rates by Genotype and Prior Treatment Status



Higher response rates with ibrutinib-RTX were independent of genotype or prior treatment status

Garcia Sanz, et al. EHA Abstract EP782.

iNNOVATE: PFS by Genotype

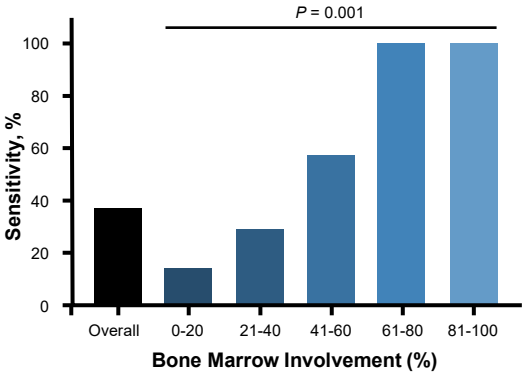


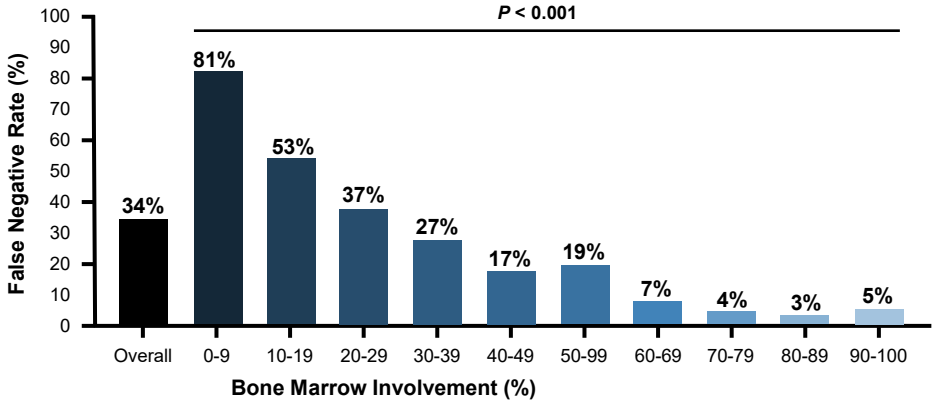
54-month PFS	Ibrutinib-RTX	Placebo-RTX
MYD88^{Mut}/CXCR4^{WT}	72%	25%
MYD88^{Mut}/CXCR4^{Mut}	63%	21%
MYD88^{WT}/CXCR4^{WT}	70%	30%

Garcia Sanz, et al. EHA Abstract EP782.

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)





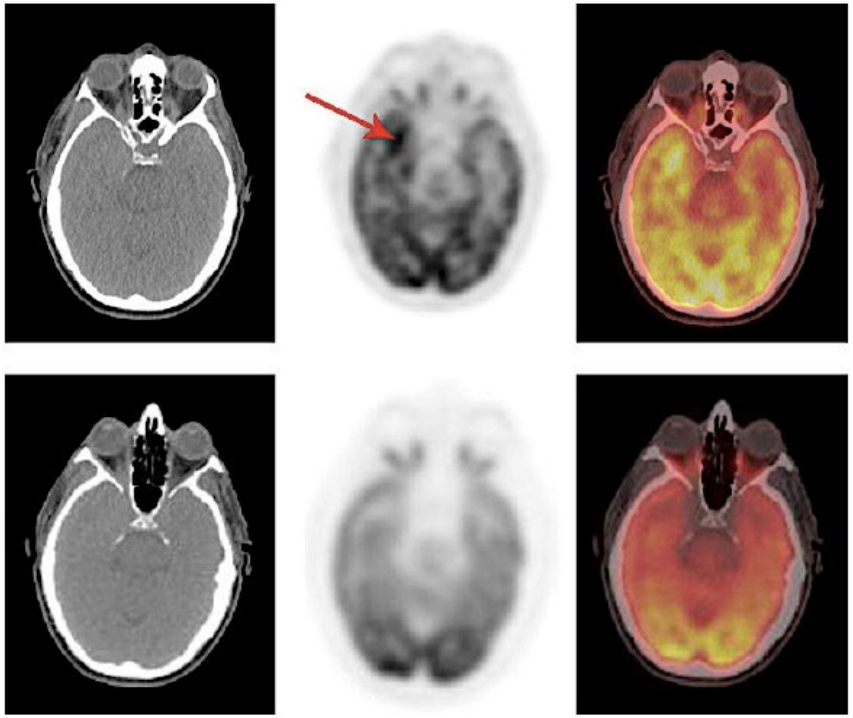
Sensitivity for mutated CXCR4 detection was 37% by NGS and unselected BM. Low BM involvement and clonality impacted detection.

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

Ibrutinib 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

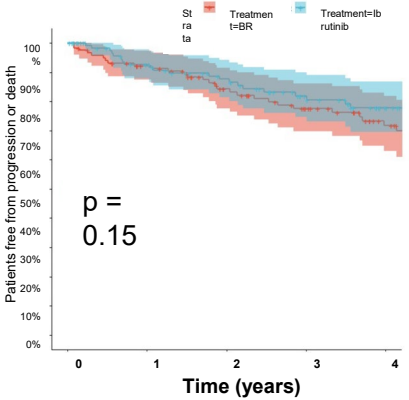
Bendamustine Rituximab versus Ibrutinib as Primary Therapy for Waldenström Macroglobulinemia: An International Collaborative Study

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]

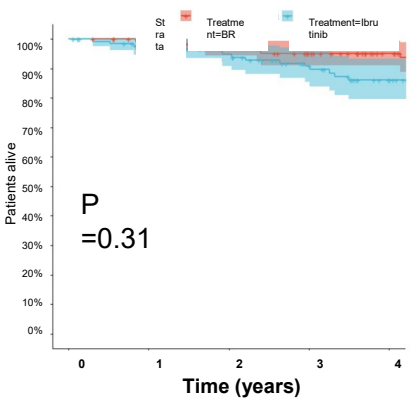
[1]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, [2]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA.
[3]University College London Hospital Foundation Trust, London, United Kingdom, [4]Department of 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

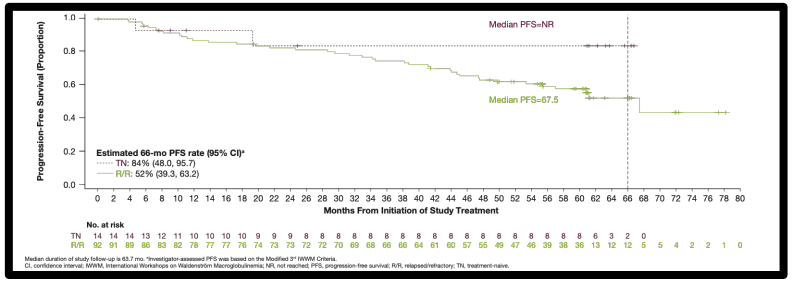
Abeykoon et al, Eur. Hematol. Assoc. June 2022

Response to Acalabrutinib in WM

Characteristic	Modified 3rd IWWM Criteria TN (n=14)	Modified 3rd IWWM Criteria R/R (n=92)	6th IWWM Criteria TN (n=14)	6th IWWM Criteria R/R (n=92)
ORR (≥ MR)	13 (93)	87 (95)	13 (93)	87 (95)
95% CI	(66–100)	(88–98)	(66–100)	(88–98)
MRR (≥ PR)	11 (79)	75 (82)	11 (79)	77 (84)
95% CI	(49–95)	(72–89)	(49–95)	(75–91)
Best response				
CR	0	2 (2)	0	4 (4)
VGPR	1 (7)	38 (41)	1 (7)	21 (23)
PR	10 (71)	35 (38)	10 (71)	52 (57)
MR	2 (14)	12 (13)	2 (14)	10 (11)
SD	0	4 (4)	0	5 (5)
Time to initial response, median (range), mo	1.0 (0.9–7.4)	1.0 (0.9–39.6)	1.0 (0.9–7.4)	1.8 (0.9–36.6)

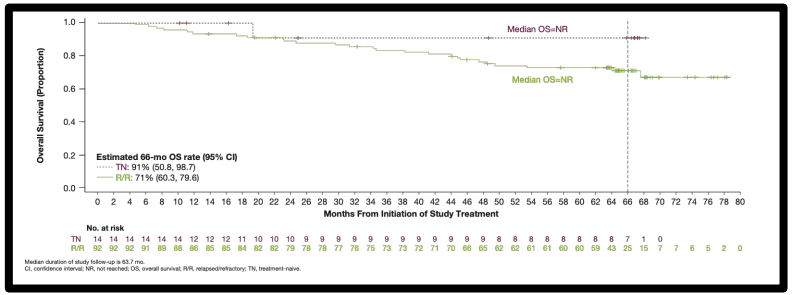
Data are n (%) unless otherwise specified.
CI, confidence interval; CR, complete response; IWWM, International Workshops on Waldenström Macroglobulinemia; MRR, major response rate; MR, minor response; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; VGPR, very good partial response.

PFS



Median duration of study follow-up is 63.7 mo. *Investigator-assessed PFS was based on the Modified 3rd IWWM Criteria.
CI, confidence interval; IWWM, International Workshops on Waldenström Macroglobulinemia; NR, not reached; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naive.

OS



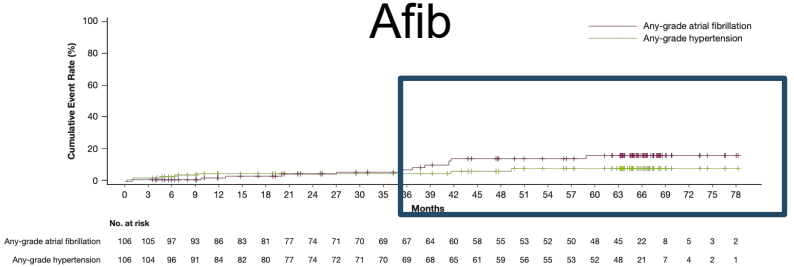
Median duration of study follow-up is 63.7 mo.
CI, confidence interval; NR, not reached; OS, overall survival; R/R, relapsed/refractory; TN, treatment-naive.

Toxicity to Acalabrutinib in WM

ECI, n (%)	TN (n=14) Any Grade	TN (n=14) Grade 3–4	R/R (n=92) Any Grade	R/R (n=92) Grade 3–4
Cardiac events	3 (21)	2 (14)	13 (14)	6 (7)
Atrial fibrillation/flutter	1 (7)	0	11 (12)	2 (2)
Bleeding	10 (71)	0	56 (61)	6 (7)
Major bleeding[a]	0	0	9 (10)	6 (7)
Hypertension	0	0	7 (8)	4 (4)
Infections	8 (57)	2 (14)	79 (86)	30 (33)
SPMs	1 (7)	0	17 (18)	7 (8)
SPMs excluding non-melanoma skin	1 (7)	0	11 (12)	6 (7)

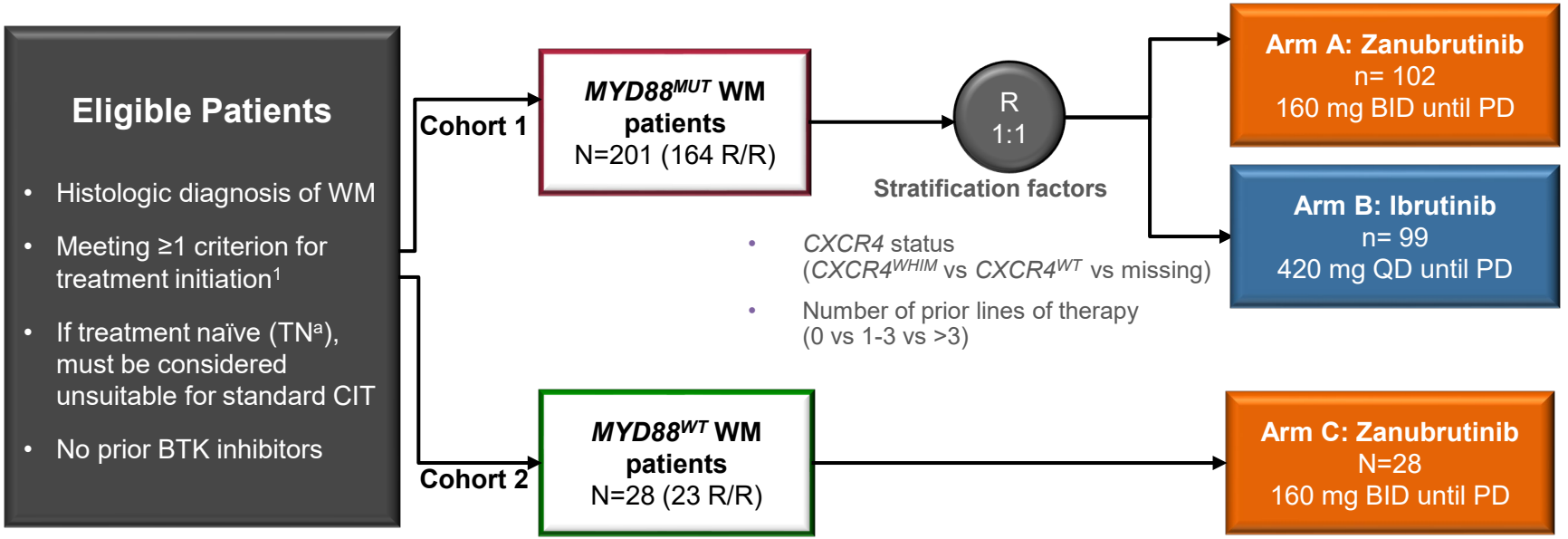
[a]Major bleeding events were defined as any bleeding event that was grade ≥3, serious, or any central nervous system bleeding (any grade or seriousness).
ECI, event of clinical interest; R/R, relapsed/refractory; SPMs, second primary malignancies; TN, treatment-naive.

Afib



Owen et al, EHA 2022

Zanubrutinib vs Ibrutinib in WM
Phase 3 ASPEN

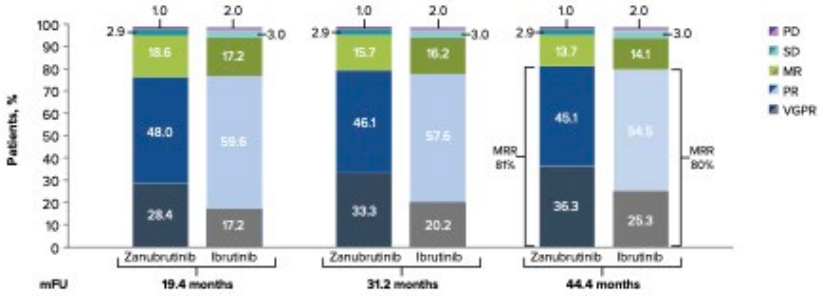


BID, twice daily; BTK, Bruton tyrosine kinase; CIT, chemoimmunotherapy; CXCR4, C-X-C Motif Chemokine Receptor 4; MYD88MUT, myeloid differentiation primary response gene 88 mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström Macroglobulinemia; WT, wild-type.

[a]Up to 20% of the overall population

ClinicalTrials.gov Identifier: NCT03053440

MYD88^{Mut}



MYD88^{WT}

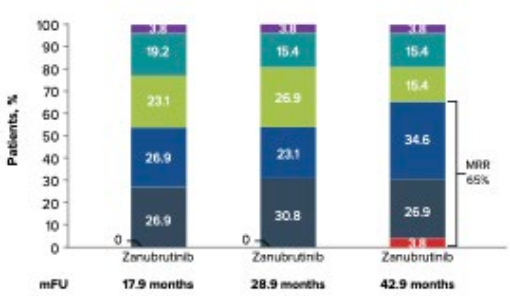
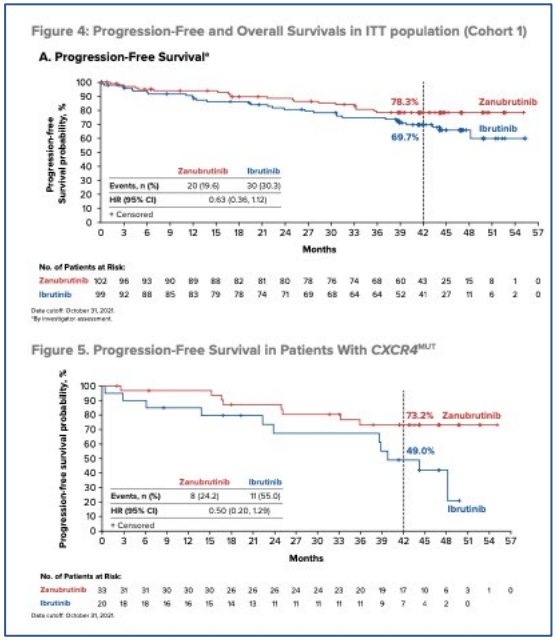
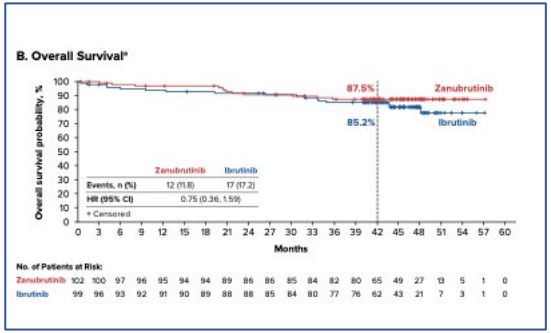


Table 2: Response Assessment by *CXCR4* Status[a]

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

Bold text indicates >10% difference between arms. Data cutoff: October 31, 2021.
[a]*CXCR4* mutation determined by NGS. Ninety-two ibrutinib patients and 98 zanubrutinib patients had NGS results available.

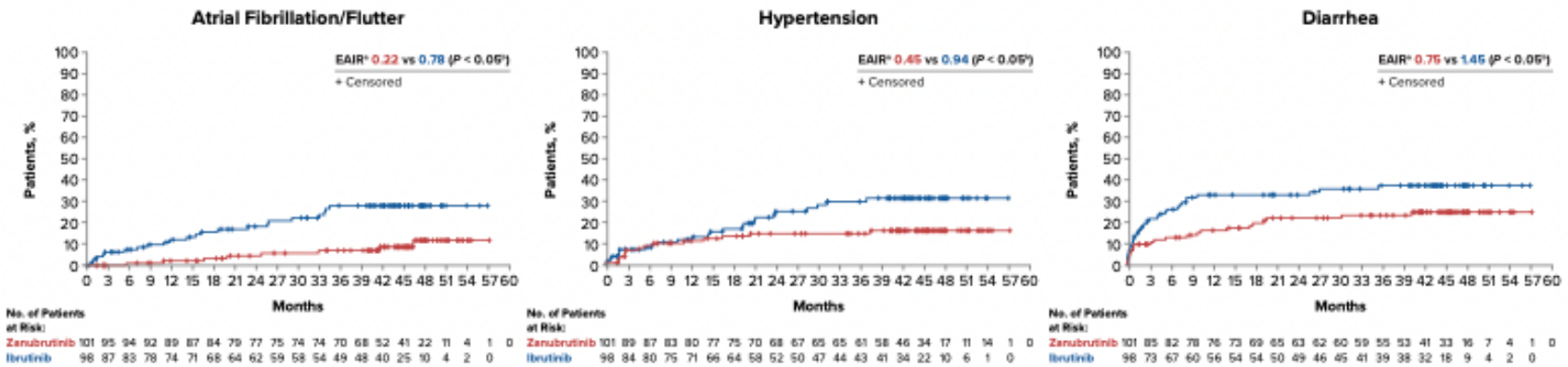




Dimopoulos et al, EHA 2022

Adverse Events

AEs,* n (%)	All grades		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)



Dimopoulos et al, EHA 2022

Dose Reductions Related to Adverse Effects in Ibrutinib Treated WM Patients

- **95/358 (25%) required at least 1 dose reduction for intolerance**

  -Median time to 1st dose reduction 7.3 (0.5-75 months)

  -26/95 (27%) continued to be symptomatic after dose-reduction

  -10/26 of dose-reduced patients required second dose-reduction at a median of 23 (3-75 months)

  -Median age 71 vs 66 years for dose reduced patients

- **Hematological responses were maintained or improved in 73% and 21% of dose reduced patients with 1 year of follow-up (N=48).**

N=385

Sarosiek ,et al. *Blood.* 2021;138 (Supplement 1): 3529.

Zanubrutinib in Previously Treated B-Cell Malignancies Intolerant to Ibrutinib/Acalabrutinib

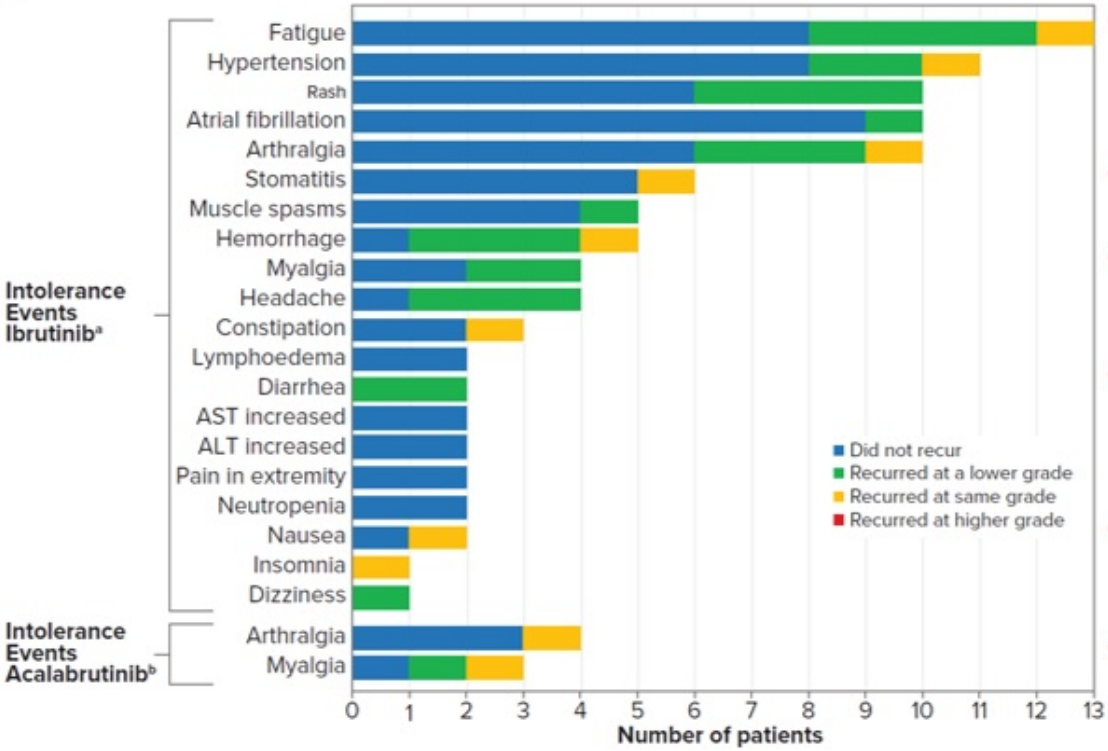
Characteristics	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=10)	Total (N=67)
Indication, n (%)			
CLL	38 (66.7)	5 (50.0)	43 (64.2)
WM	9 (15.8)	2 (20.0)	11 (16.4)
SLL	6 (10.5)	1 (10.0	7 (10.4)
MCL	2 (3.5)	1 (10.0)	3 (4.5)
MZL	2 (3.5)	1 (10.0)	3 (4.5)
Age, median (range), year	71.0 (49-91)	73.5 (65-83)	71.0 (49-91)
Male, n (%)	30 (52.6)	6 (60.0)	36 (53.7)
ECOG PS 0, n (%)	33 (57.9)	4 (40.0)	37 (55.2)
No. of prior therapy regimens, median (range)	1.0 (1-12)	2.5 (1-5)	1.0 (1-12)
Prior BTKi, n (%)	57 (100)	10 (100)	67 (100)
Ibrutinib monotherapy	49 (86.0)	6 (60.0)[a]	55 (82.1)
Ibrutinib combination therapy	9 (15.8)[b]	0	9 (13.4)
Acalabrutinib monotherapy	0	10 (100)	10 (14.9)
Time on prior BTKi,[c] median (range), months	10.61 (1.1-73.7)	3.33 (0.5-26.9)	—
On-study zanubrutinib dosing regimen			
160 mg bid	35 (61.4)	7 (70.0)	42 (62.7)
320 mg qd	22 (38.6)	3 (30.0)	25 (37.3)

Data Cutoff: 8 September 2021

a. Six patients had both prior ibrutinib and acalabrutinib therapies. b. One patient received ibrutinib combination therapy followed by ibrutinib monotherapy. c. Cumulative ibrutinib exposure for cohort 1 and acalabrutinib for cohort 2.

Shadman M, et al. EHA 2021. Abstract EP642.

Recurrence of Ibrutinib and Acalabrutinib Intolerance Events on Zanubrutinib

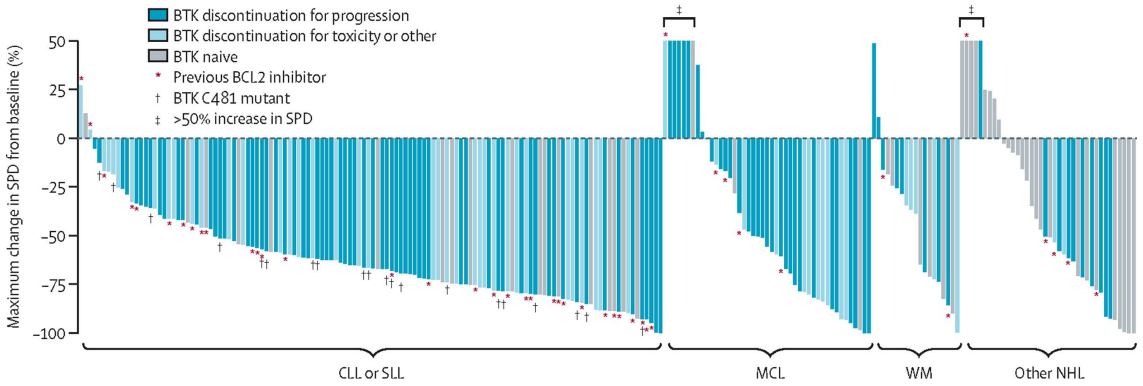


- 34/57 (59.6%) of patients who took ibrutinib and 7/10 (70.0%) of patients who took acalabrutinib did not have recurrence of any intolerance event
- No ibrutinib or acalabrutinib intolerance events recurred at a higher severity
- 81/115 (70.4%) ibrutinib intolerance events and 15/18 (83.3%) acalabrutinib intolerance events did not recur
- 25/38 (65.8%) grade 3 ibrutinib intolerance events and 3/4 (75.0%) grade 3 acalabrutinib intolerance events did not recur while on zanubrutinib
- All grade 4 intolerance events (neutropenia [n=2], ALT increase [n=1], AST increase [n=1]) did not recur on zanubrutinib
- 1 patient (1.5%) discontinued zanubrutinib due to recurrence of a prior intolerant event (myalgia; acalabrutinib)

[a]18 ibrutinib intolerance events (arthritis, bone pain, bronchitis, embolism, heart rate irregular, malaise, pericardial effusion, pleural effusion, pneumonia, psoriasis, pyrexia, sinusitis, subcutaneous abscess, supraventricular tachycardia, transaminases increased, ventricular extrasystoles, vertigo, and vomiting) occurred in 1 patient and did not recur on zanubrutinib. [b]11 acalabrutinib intolerance events (abdominal pain, asthenia, atrial fibrillation, dyspepsia, fatigue, groin pain, headache, insomnia, malaise, pain in extremity, and rash) occurred in 1 patient and did not recur on zanubrutinib (not shown here).
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Shadman et al, ASH 2021

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a Phase 1/2 study



WM	Prior Therapies	N=	Evaluable	ORR	Major RR
All	3 (2-4)	26	19	68%	47%
Prior BTK	3 (3-4)	18	13	69%	38%

Median on treatment time: 3.2 (0.1-10.9 mos.)
PD (n=7); AEs (n=0); Withdrawal (n=1);
18 remain on treatment.

Mato et al, Lancet 2021

What BTK-inhibitor do you choose and for which WM patient?

	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib*
Convenience/Compliance	+		**	
Need for deeper IGM response (i.e. IgM demyelinating PN, Cold Agglutinin Disease, Cryoglobulinemia)			+	
Bing Neel Syndrome	+			
History of Arrythmia or Bleeding			+	
Neutropenic or Pancytopenic	+			
MYD88 wild-type (alternative to BR, Bort DR)			+	
CXCR4-mutated (alternative to BR, Bort DR)	Add Rituximab		+	
Intolerant to ibrutinib	+/dose reduction	***	+	
Acquired resistance to covalent BTK-inhibitor				+

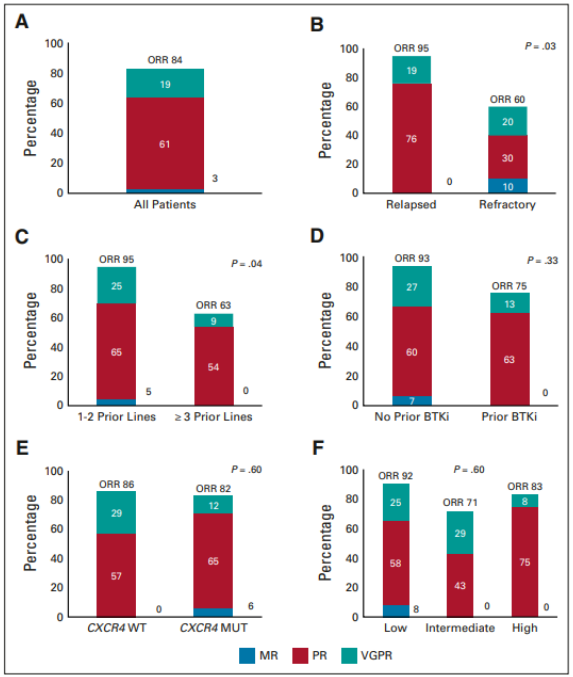
*Investigational product. Activity shown in WM patients with intolerance or acquired resistance to covalent BTK-inhibitors (Mato et al, Lancet 2021)
**Approved for once or twice daily administration; limited data for once daily administration in WM (Trotman et al, Blood 2020.
***Data in CLL patients for switchover (Awan et al, Blood Adv 2019)

original reports

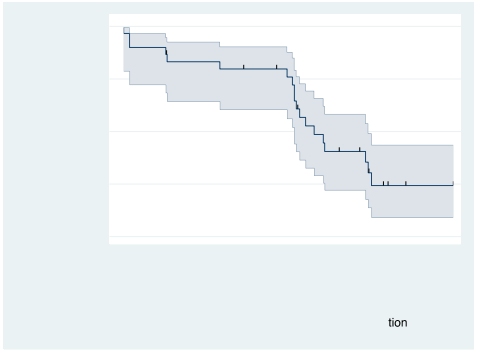
Venetoclax in Previously Treated Waldenström Macroglobulinemia

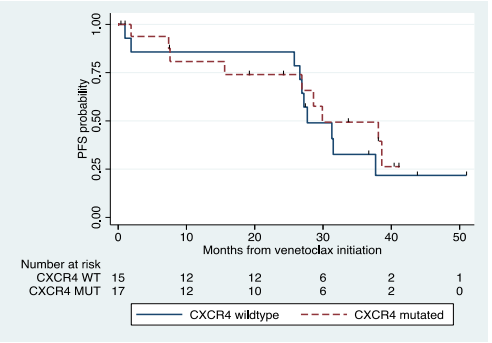
Journal of Clinical Oncology®

Jorge J. Castillo, MD[1,2]; John N. Allan, MD[3]; Tanya Siddiqi, MD[4]; Ranjana H. Advani, MD[5]; Kirsten Meid, MPH[1]; Carly Leventoff, BA[1]; Timothy P. White, BA[1]; Catherine A. Flynn, NP[1]; Shayna Sarosiek, MD[1,2]; Andrew R. Branagan, MD[2,6]; Maria G. Demos, BA[1]; Maria L. Guerrera, MD[1]; Amanda Kofides, BA[1]; Xia Liu, BA[1]; Manit Munshi, BA[1]; Nicholas Tsakmaklis, BA[1]; Lian Xu, BA[1]; Guang Yang, BA[1]; Christopher J. Patterson, BA[1]; Zachary R. Hunter, PhD[1,2]; Matthew S. Davids, MD[2,7]; Richard R. Furman, MD[3]; and Steven P. Treon, MD, PhD[1,2]



ORR: 84%; Major RR: 81%



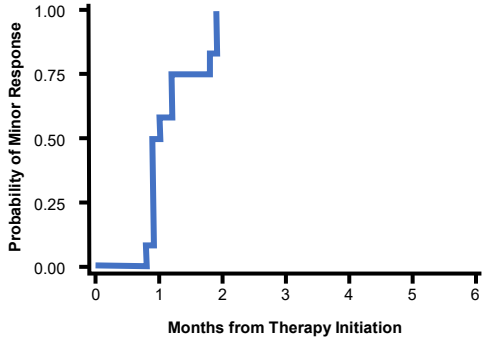


Median f/u: 33 mos; Median PFS: 30 mos.
Not impacted by CXCR4 mutation status.
Grade ≥3 neutropenia: 45%

Castillo et al, JCO 2021

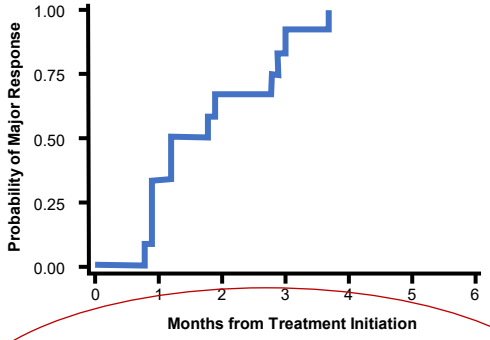
Phase I/II Trial of CXCR4 antagonist Ulocuplumab and Ibrutinib in CXCR4-mutated Patients with Symptomatic WM

Median Time to Minor Response



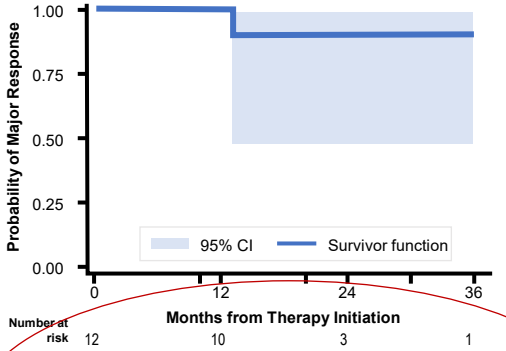
0.9 (95% CI 0.9-1.8) months

Median Time to Major Response



1.2 (95% CI 0.9-2.8) months

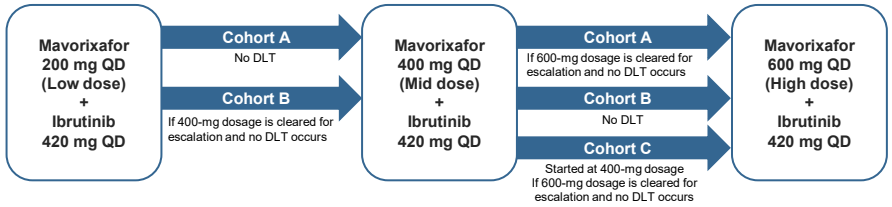
Median Time to PFS



2-year 90% estimated

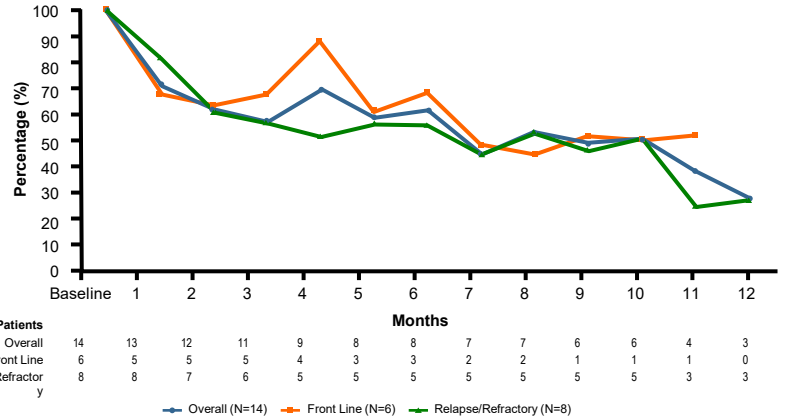
Treon S, et al. *Blood*. 2021; 138 (17): 1535–1539.

Mavorixafor and Ibrutinib in WM



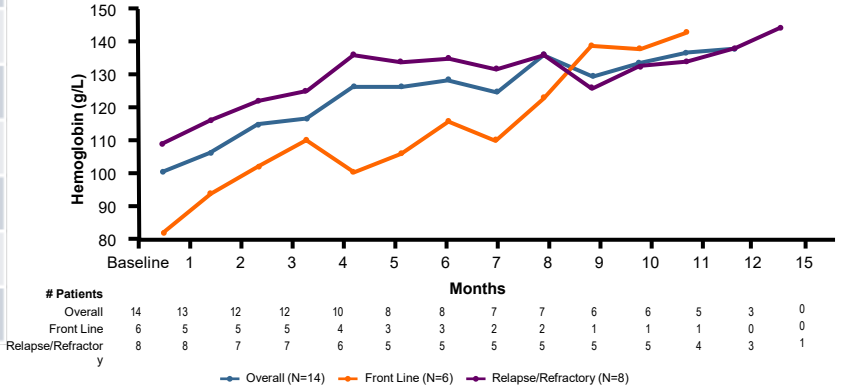
Participant	Age, y	Duration of Treatment in Study, wk	AE	Drug Discontinued	Serious	Grade	Outcome	Investigator-Determined Causality
1	76	63.3	Hypertension	No	No	3	Recovered	Possibly combination therapy
2	71	22.1	Atrial fibrillation	No	Yes	3	Recovered	Possibly ibrutinib
			Atrial fibrillation	No	Yes	3	Recovered	Possibly combination therapy
			Cryptococcal pneumonia	No	Yes	3	Recovered	Probably combination therapy
			Cryptococcal brain abscess	No	Yes	3	Recovered	Probably combination therapy
3	81	3.9	Pneumonia	Yes	Yes	5	Fatal	Possibly combination therapy
			Sepsis	Yes	Yes	5	Fatal	Possibly combination therapy

Median IgM Levels Normalized to Baseline



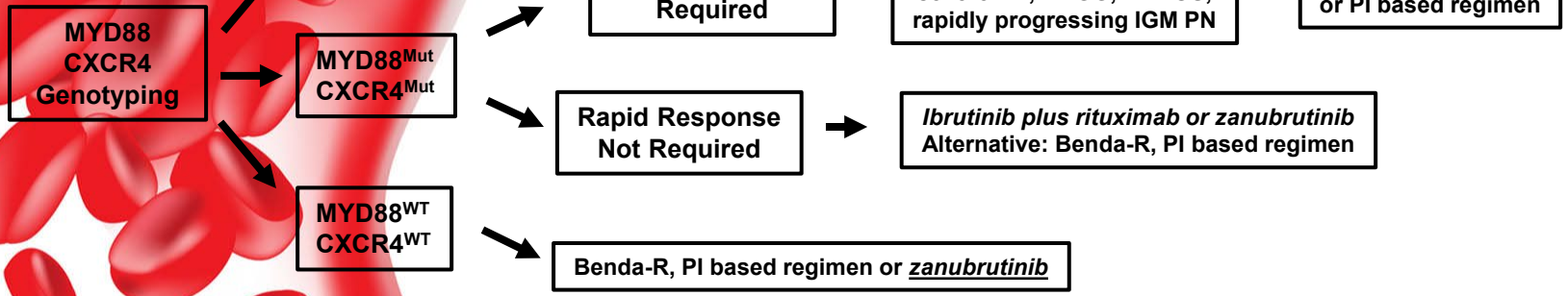
All Patients (N=14) Front Line (N=6) Relapse/Refractory (N=8)

Median Change from Baseline in Hgb



Treon S, et al. *Blood*. 2021;138 (Supplement 1): 1362.

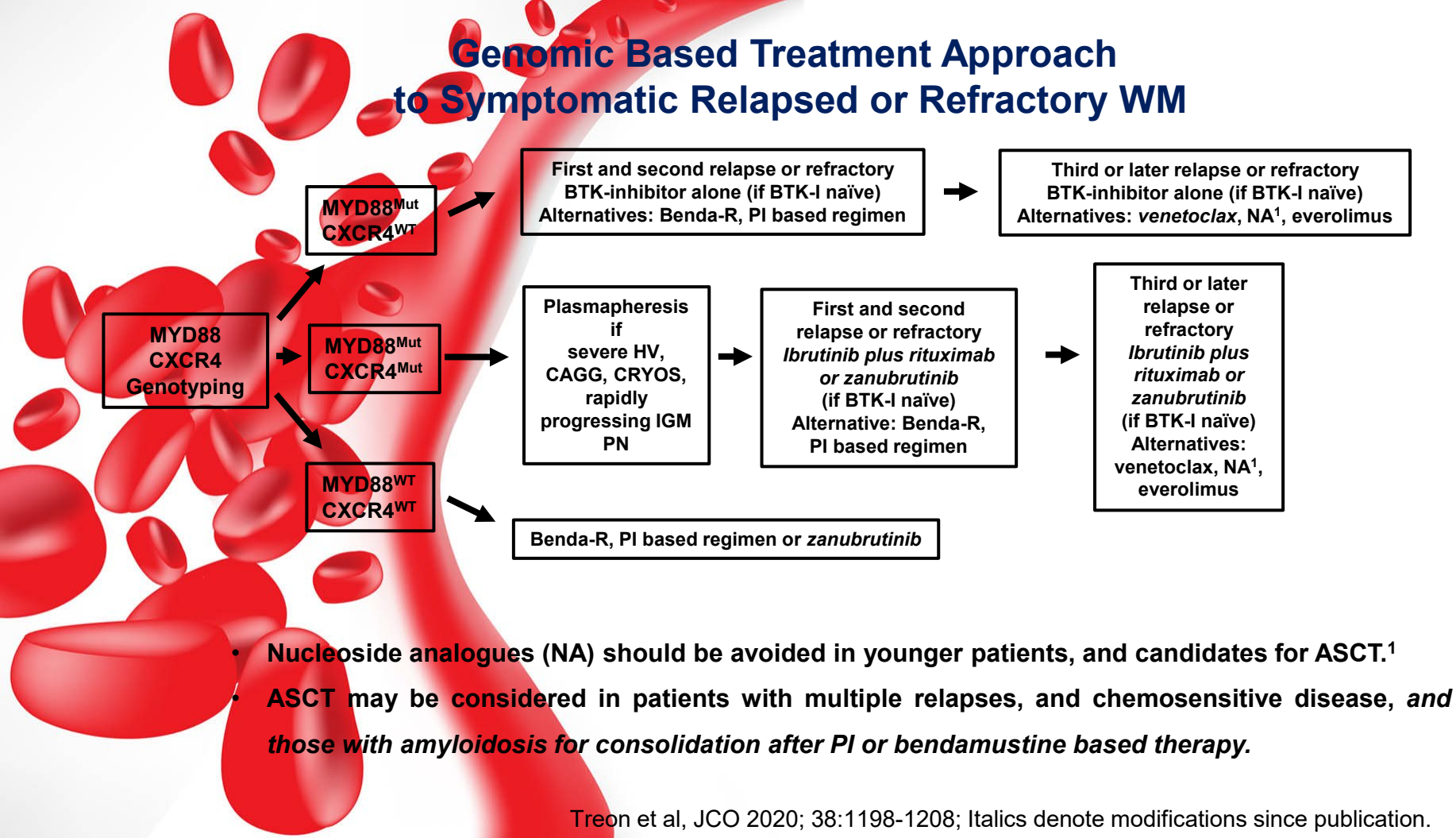
Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM



- 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 MYD88Mut 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

- **Chemoimmunotherapy vs. BTK-inhibitors**

  Benda-R and Ibrutinib show similar levels of efficacy. Genomics and patient specific morbidities should be factored into treatment decision making.

- **Which BTK-inhibitor and for which patient**

  -Ibrutinib, Acalabrutinib and Zanubrutinib are highly active in WM. Those at risk for Afib and $MYD88^{WT}$ disease should receive zanubrutinib.

  -Those with cytopenias should be considered for ibrutinib.

  -$CXCR4^{Mut}$ patients can be considered for either ibrutinib and rituximab or zanubrutinib.

- **Role of genomics in treatment decision making**

  MYD88 and CXCR4 mutation status is important. AS-PCR should be used for MYD88 detection.

- **How to manage intolerant or progressing patients on BTK-Inhibitors**

  Both dose reduction of ibrutinib and switchover to another covalent BTK-inhibitor is reasonable.