Treatment Advances in Waldenstrom's Macroglobulinemia

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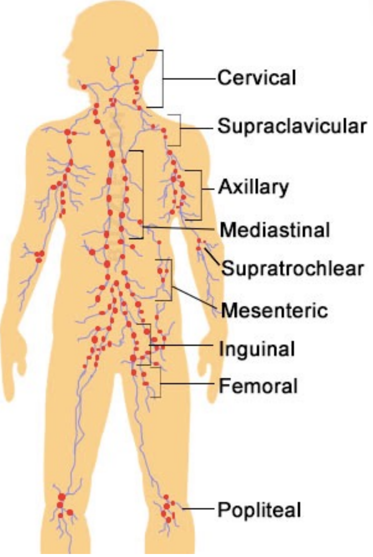
Manifestations of WM Disease

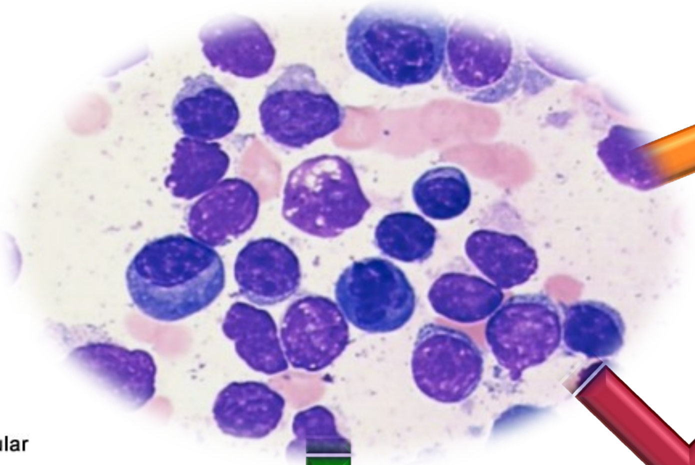
Bing Neel Syndrome



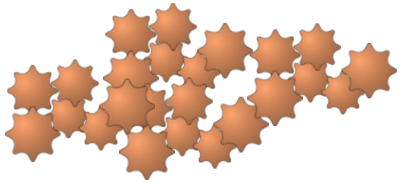
≤20% at diagnosis; 50-60% at relapse

Bone Marrow

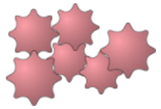
↓Hb>>> ↓PLT> ↓WBC



Hepcidin
↓Fe Anemia



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%)

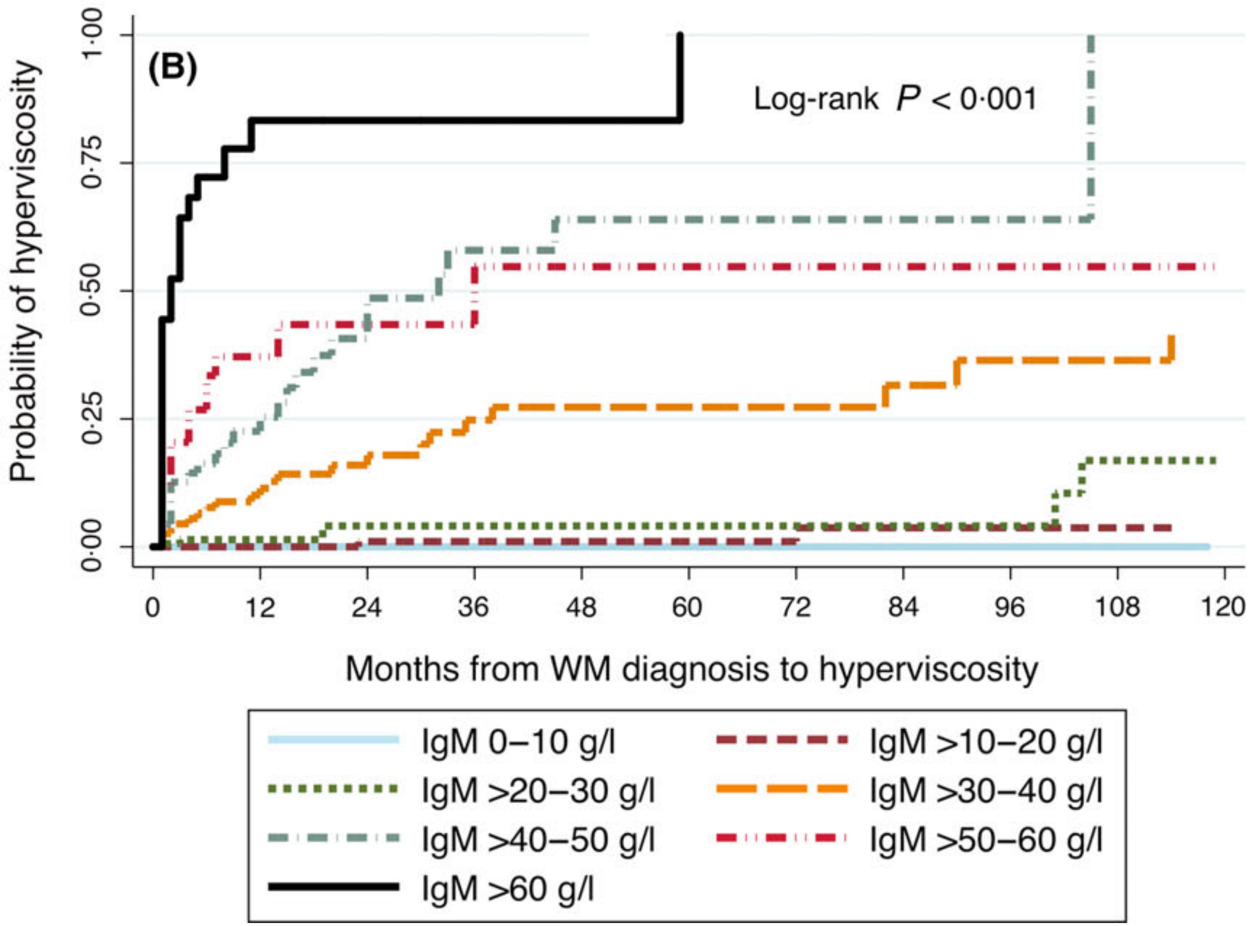
Treon S., *Hematol Oncol*. 2013; 31:76-80.

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.

Serum IGM as a Predictor of Symptomatic Hyperviscosity



Probability of symptomatic hyperviscosity is 370-fold higher for patients with serum IgM >6000 mg/dL

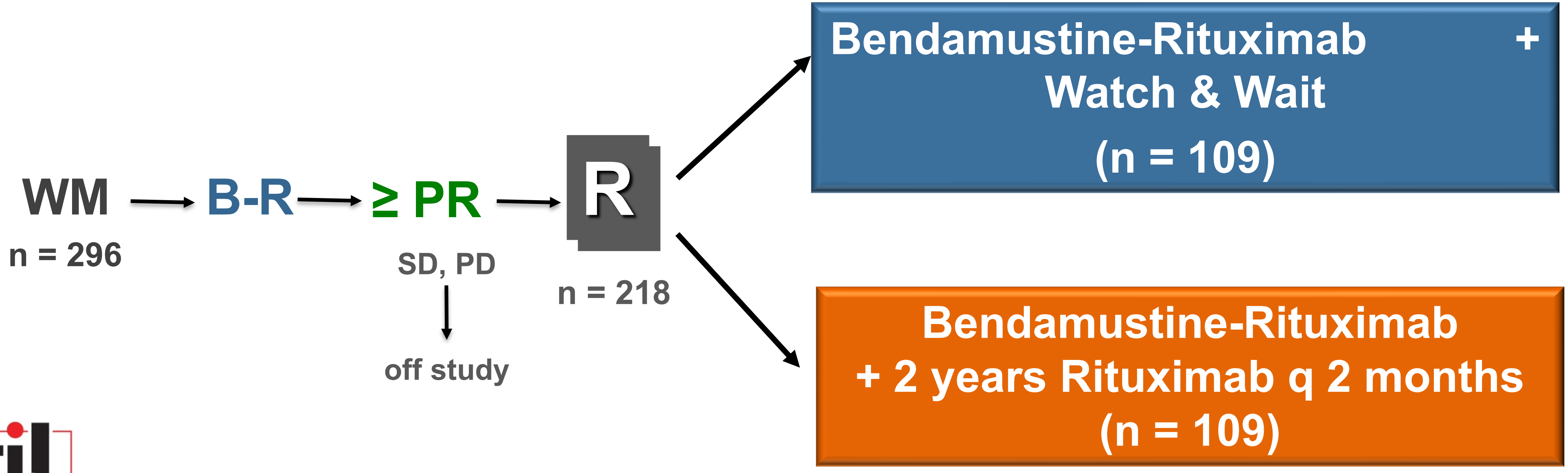
Gustine, et al. *Br J Haematol*. 2017;177(5):717-725.

Primary Therapy of WM with Rituximab

Regimen	ORR	CR	Median PFS (mo)
Rituximab x 4	25-30%	0-5%	13
Rituximab x 8	40-45%	0-5%	16-22
Rituximab/thalidomide	70%	5%	30
Rituximab/cyclophosphamide (i.e. CHOP-R, CVP-R, CPR, CDR)	70-80%	5-15%	30-36
Rituximab/nucleoside analogues (i.e. FR, FCR, CDA-R)	70-90%	5-15%	36-62
Rituximab/Proteasome Inhibitor (i.e. BDR, VR, CaRD)	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

BR + Watch & Wait vs BR + 2 years Rituximab
StiL NHL 7-2008 MAINTAIN Trial



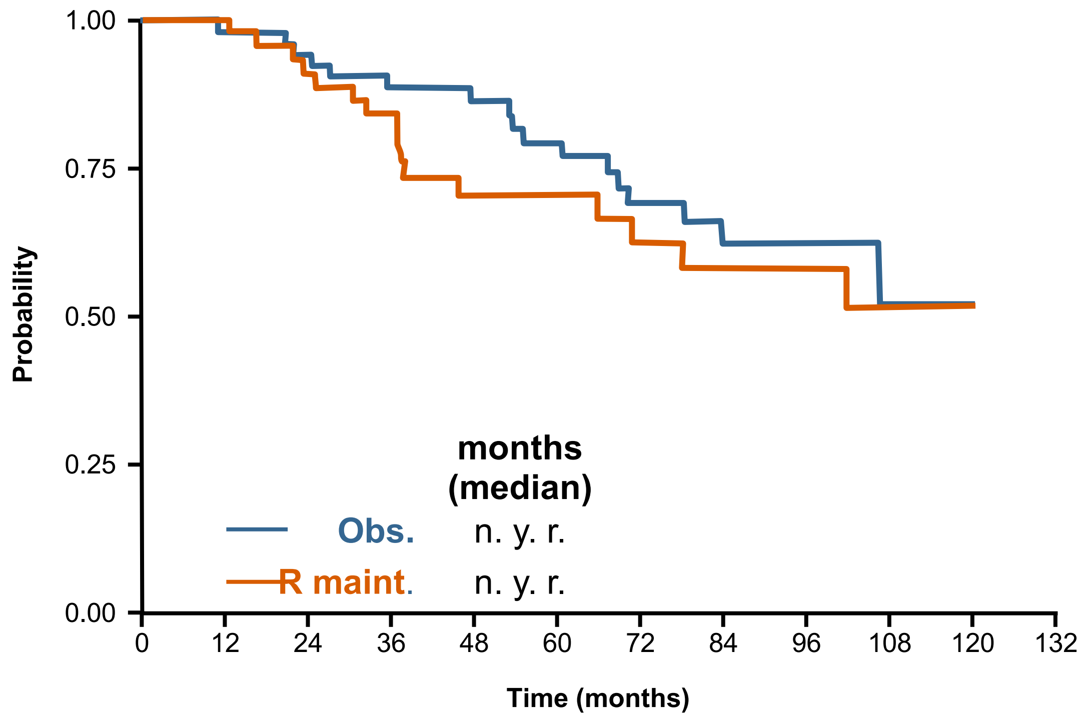
StiL
Studiengruppe indolente Lymphome

Rummel, et al. *Blood*. 2019;134 (Supplement_1): 343

PFS (Patient Age)
StiL NHL 7-2008 MAINTAIN Trial

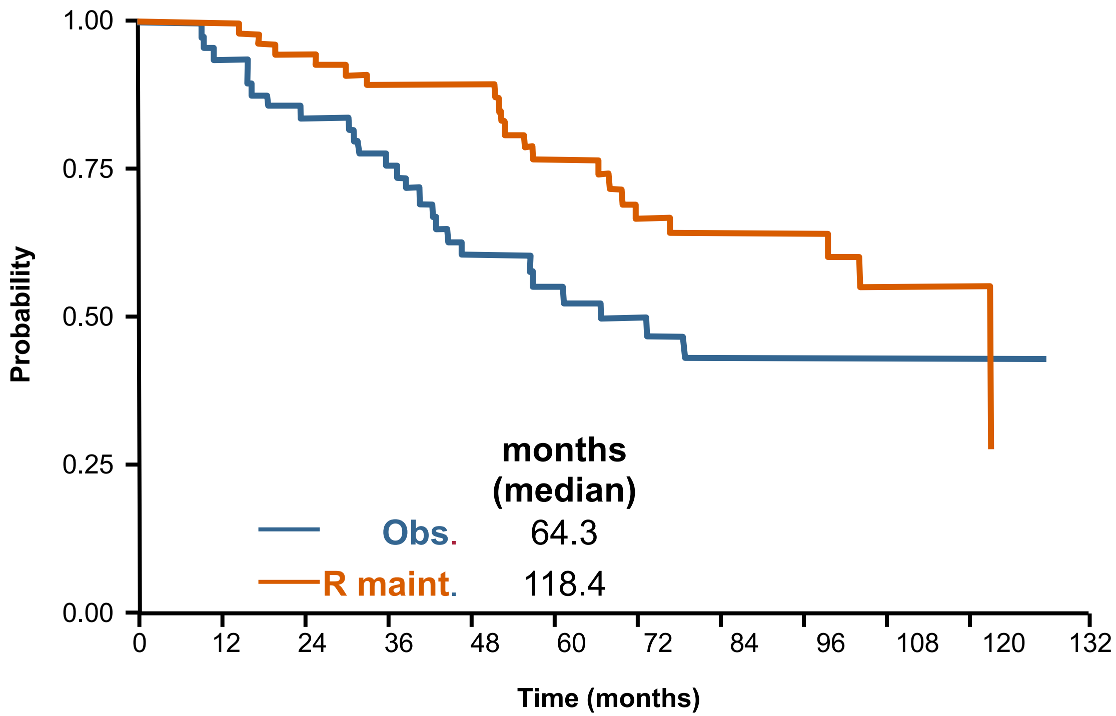
Patients Younger Than 65 years

HR, 0.75 (95% CI, 0.38 – 1.51); *P* = 0.4177



Patients Older Than 65 years

HR, 1.86 (95% CI, 1.03 – 3.38); *P* = 0.0355



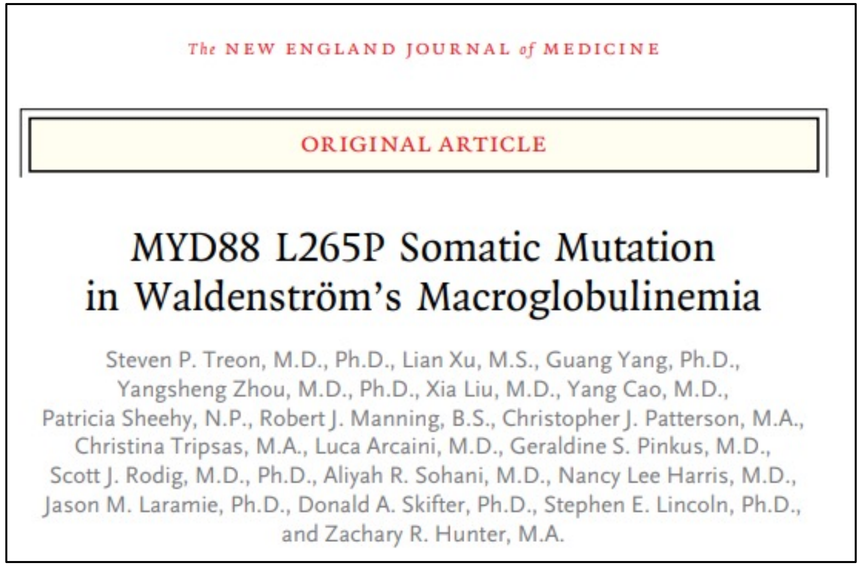
Rummel, et al. *Blood*. 2019;134 (Supplement_1): 343.

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

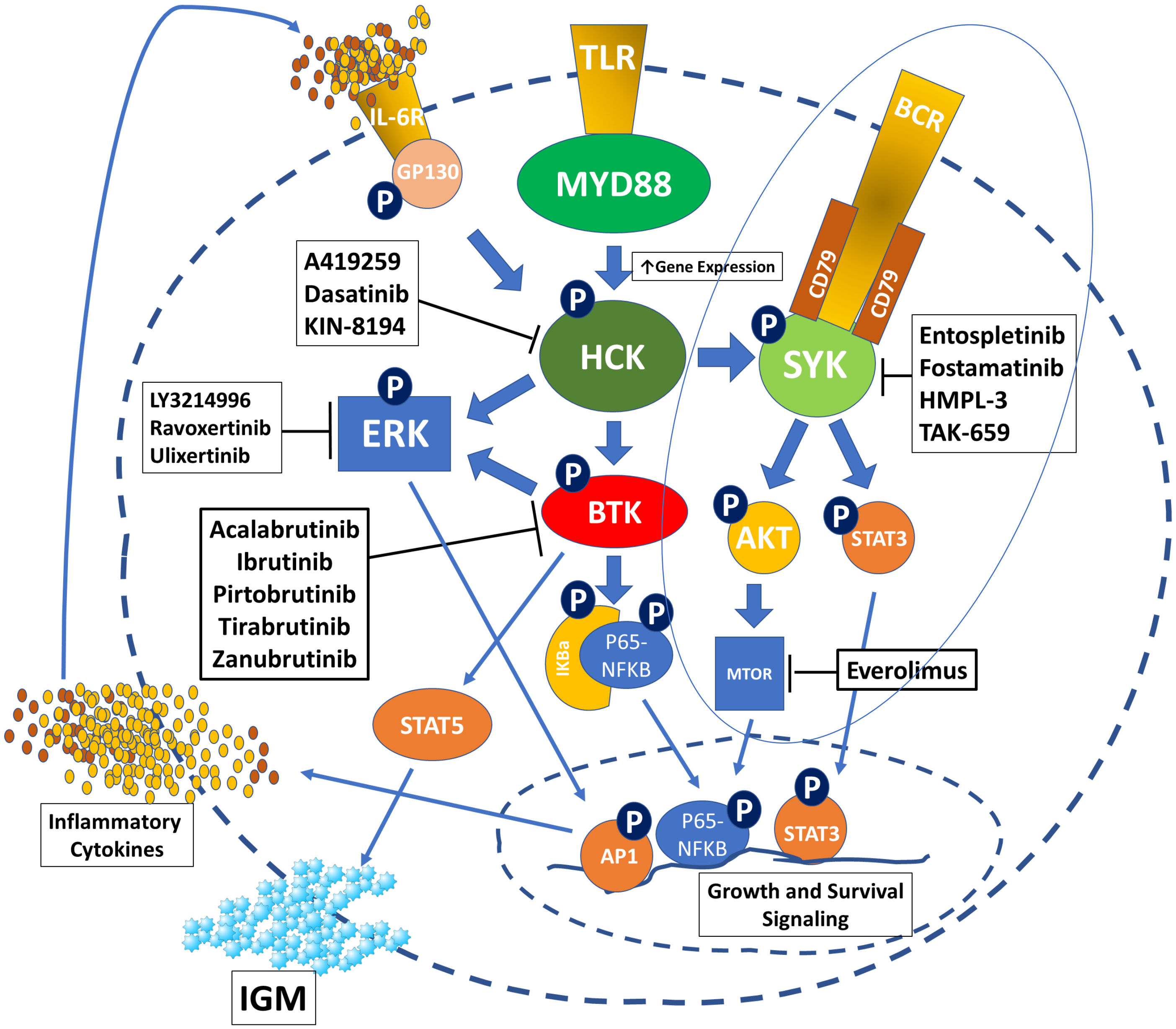

The NEW ENGLAND JOURNAL of MEDICINE

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

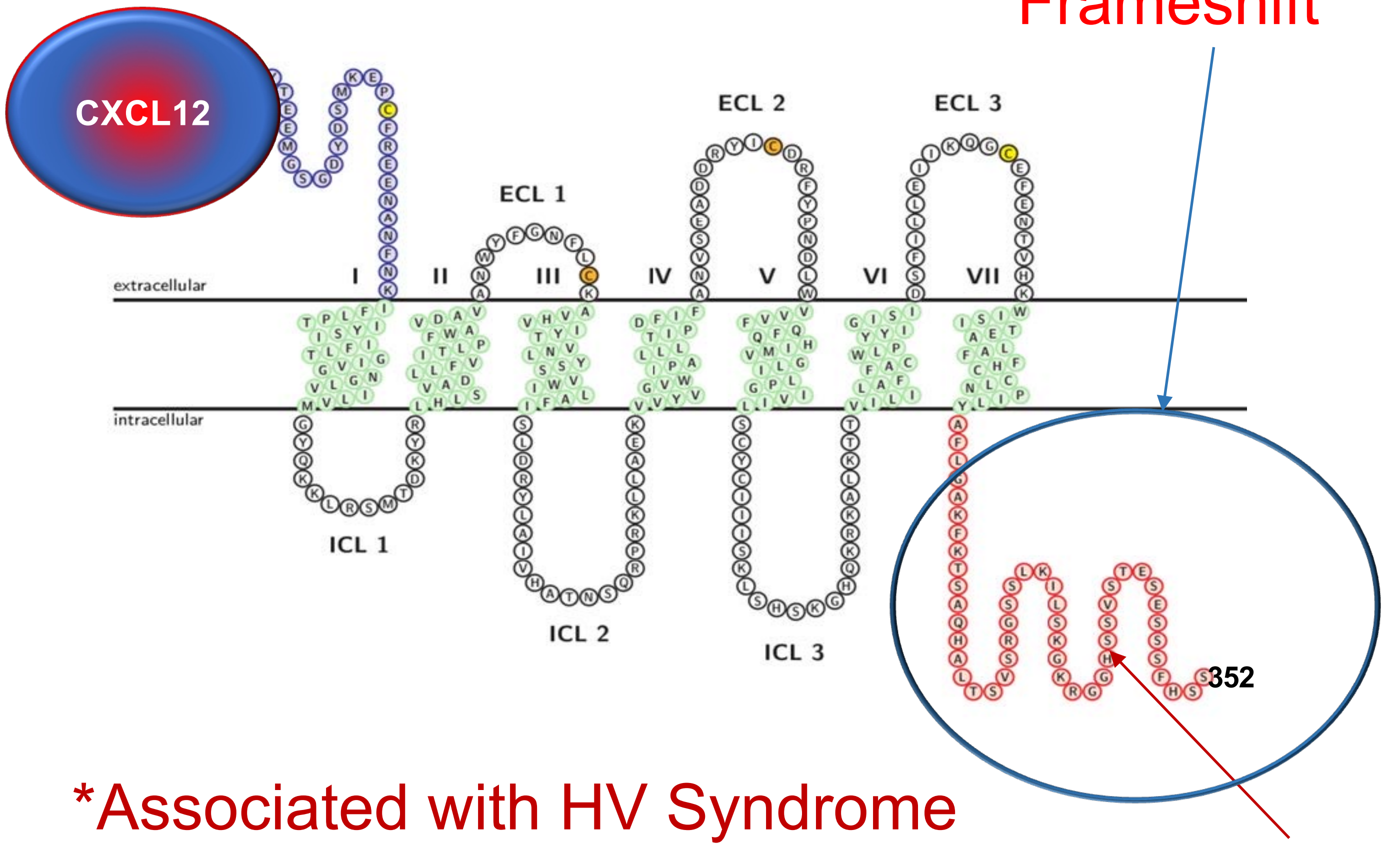
Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenström macroglobulinemia

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.

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)*

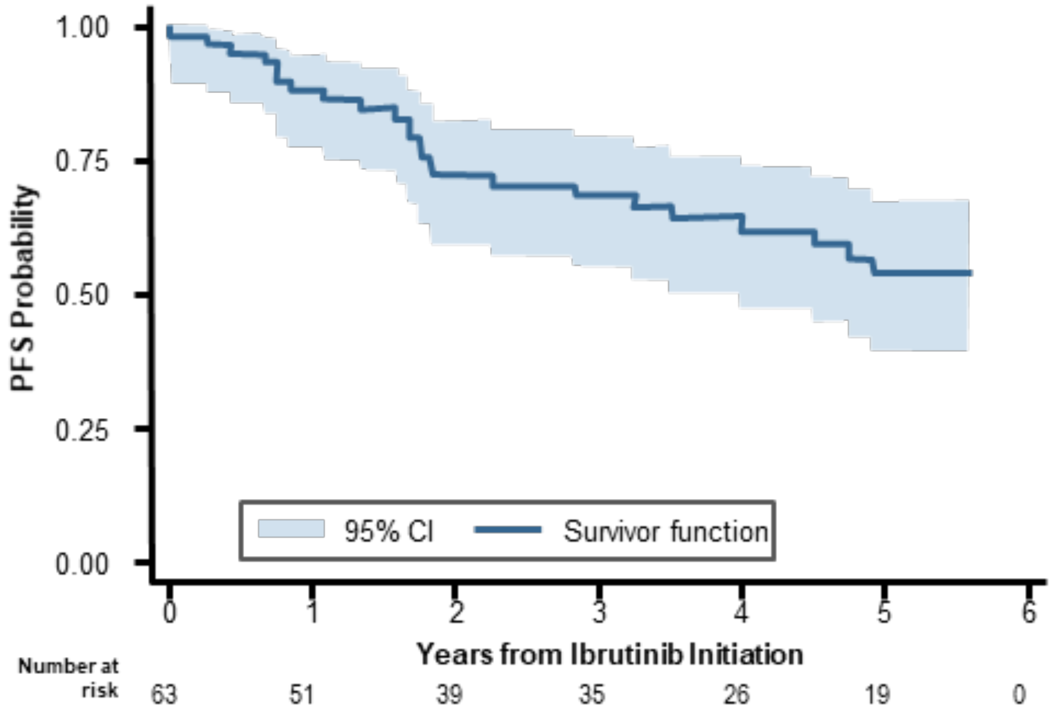
	All Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	MYD88^{WT} CXCR4^{WT}	P-value
N	63	36	22	4	N/A
Overall Response Rate-no. (%)	90.5%	100%	86.4%	50%	<0.01
Major Response Rate-no. (%)	**79.4%**	**97.2%**	**68.2%**	**0%**	**<0.0001**
Categorical responses					
Minor responses-no. (%)	11.1%	2.8%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

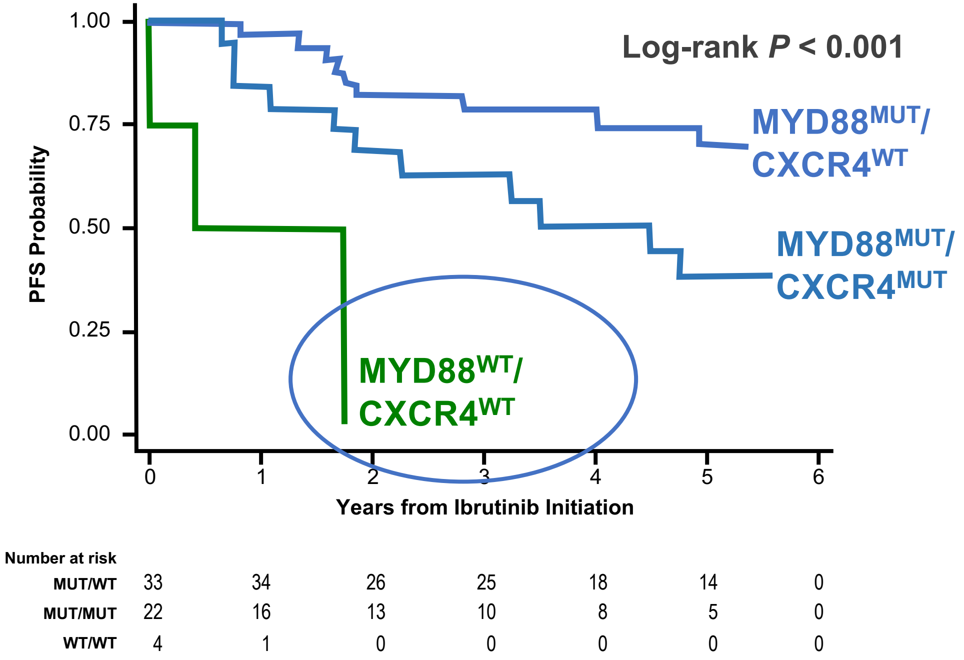
All patients



5-year PFS: 54%

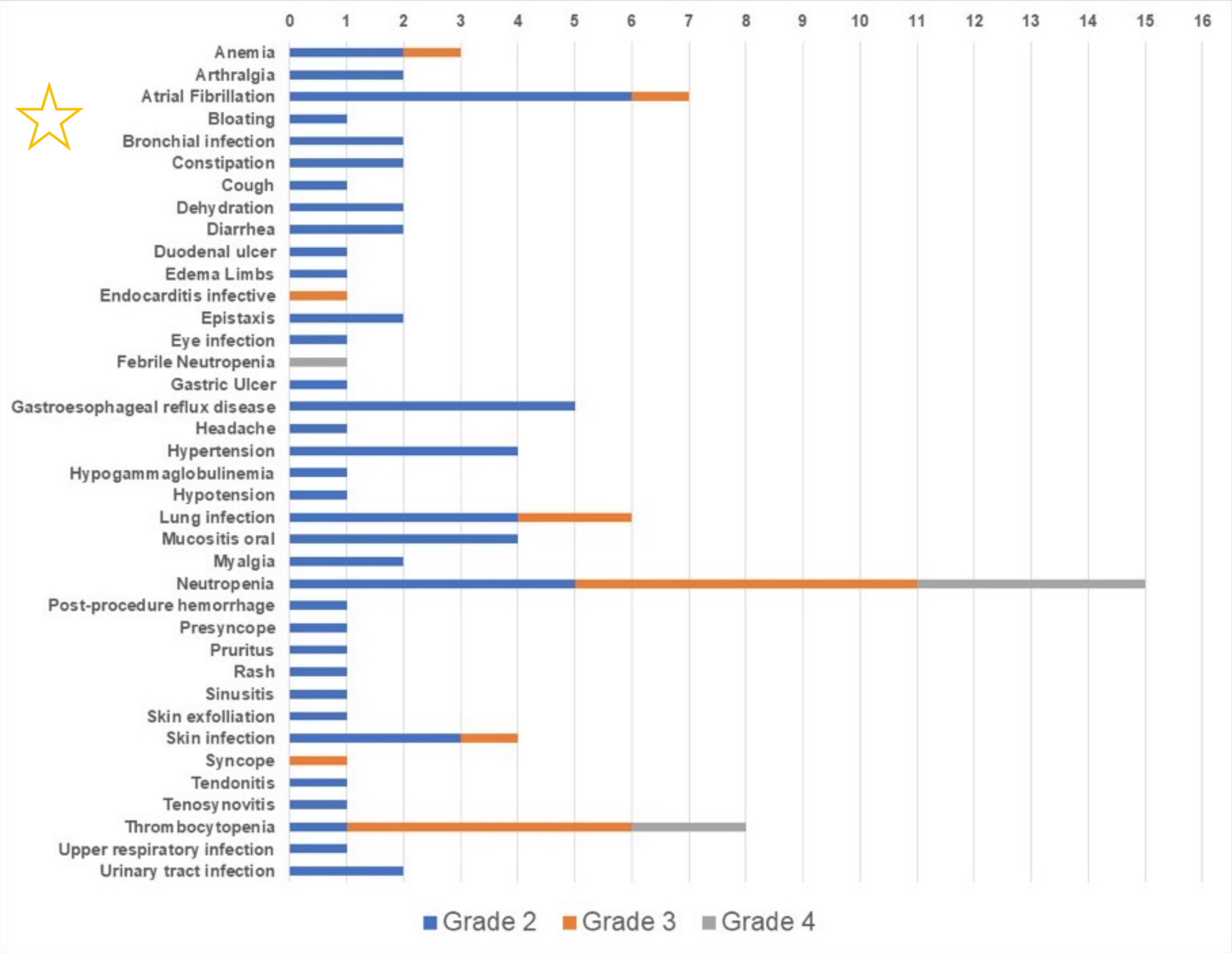
5-year OS: 87%

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.

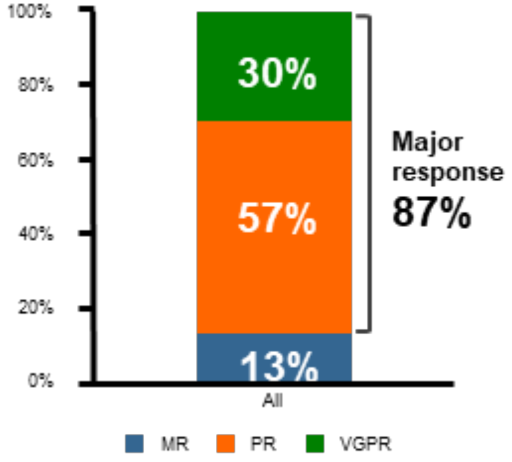
Ibrutinib Activity in Previously Treated WM:
Long Term Toxicity Findings (grade ≥2) of the Pivotal Trial

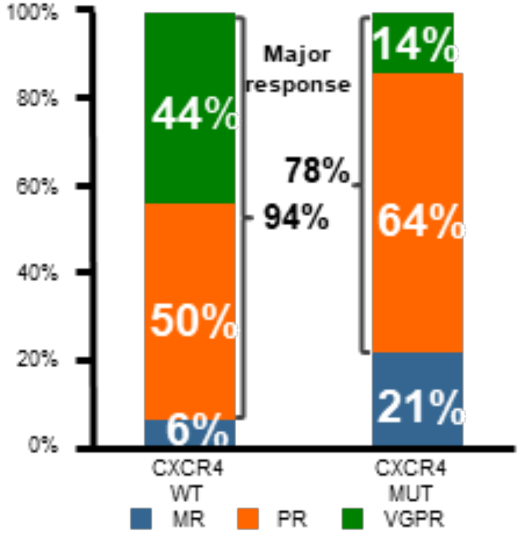


☆ Increased since original report; 8 patients (12.7%) with Afib, including grade 1; 7 continued ibrutinib with medical management.

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



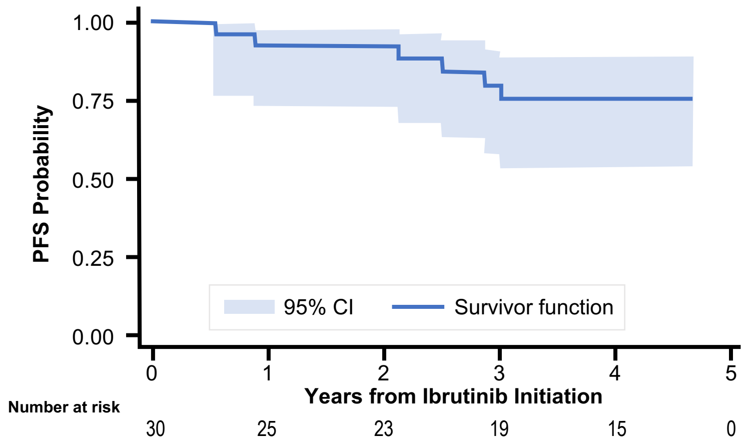


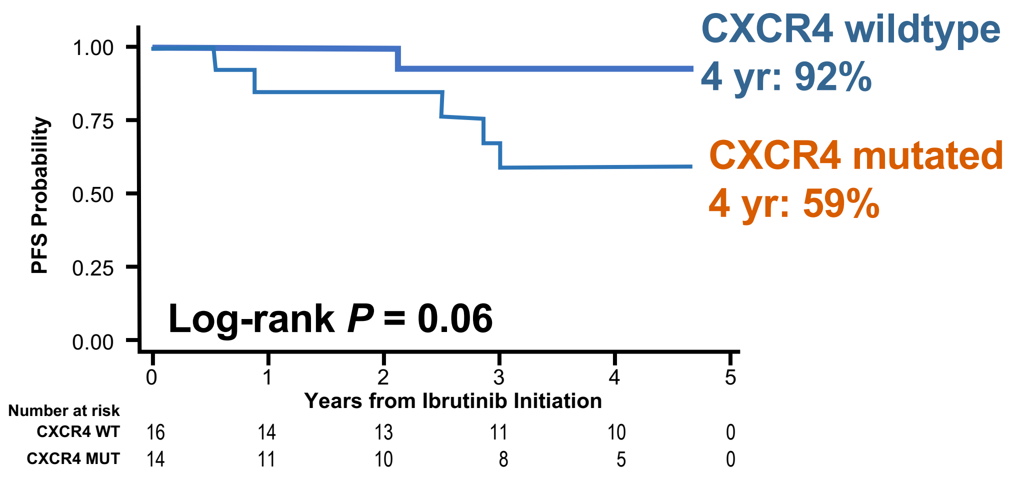
Median time to Response

	$CXCR4^{WT}$	$CXCR4^{MUT}$
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

Median f/u: 50 months





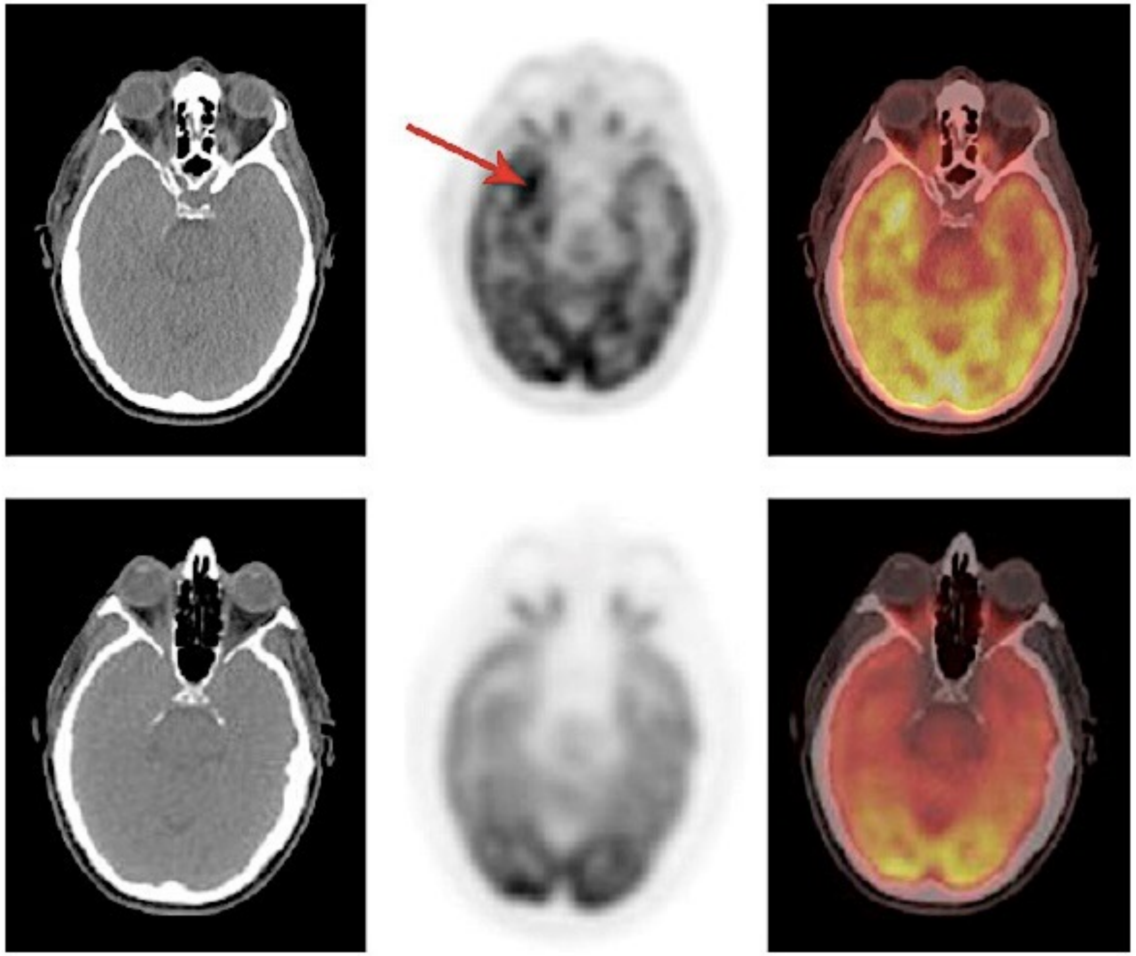
All patients were MYD88 mutated.

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

Ibrutinib induced response in a WM patient with Bing Neel Syndrome

Pre-treatment

Post-treatment

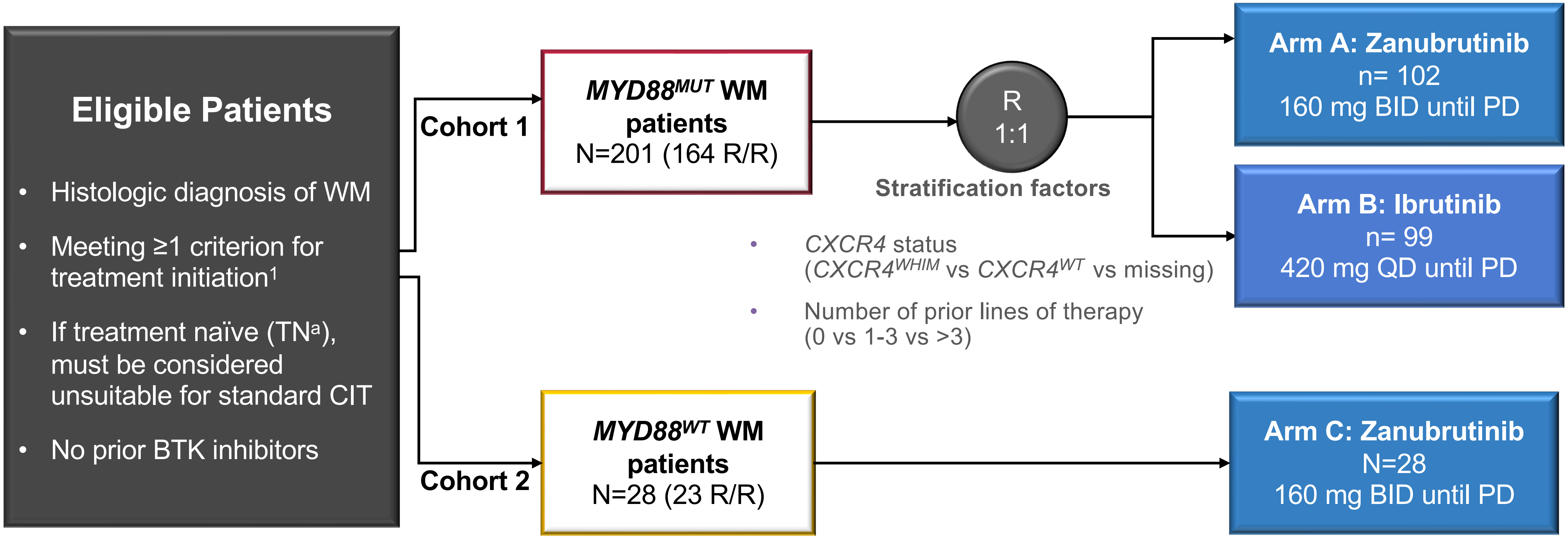


560 mg po once a day

		Ibrutinib (nM)		
Study Day	Time post-dose (h)	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

Zanubrutinib vs Ibrutinib in WM
Phase 3 ASPEN



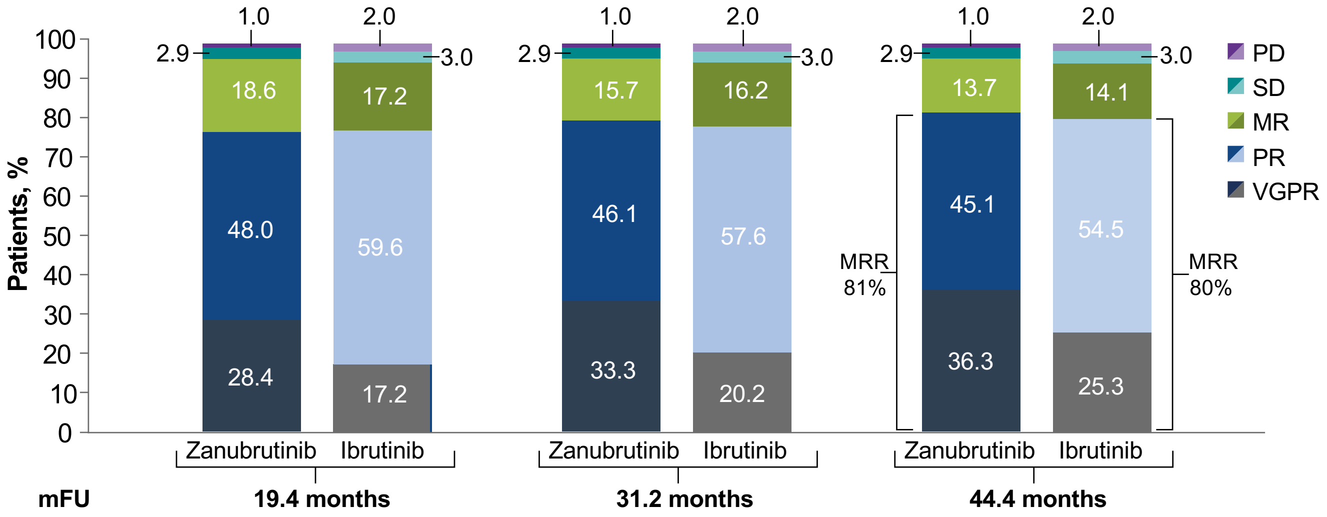
BID, twice daily; BTK, Bruton tyrosine kinase; CIT, chemoimmunotherapy; CXCR4, C-X-C Motif Chemokine Receptor 4; MYD88^{MUT}, myeloid differentiation primary response gene 88 mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström Macroglobulinemia; WT, wild-type.

[a]Up to 20% of the overall population

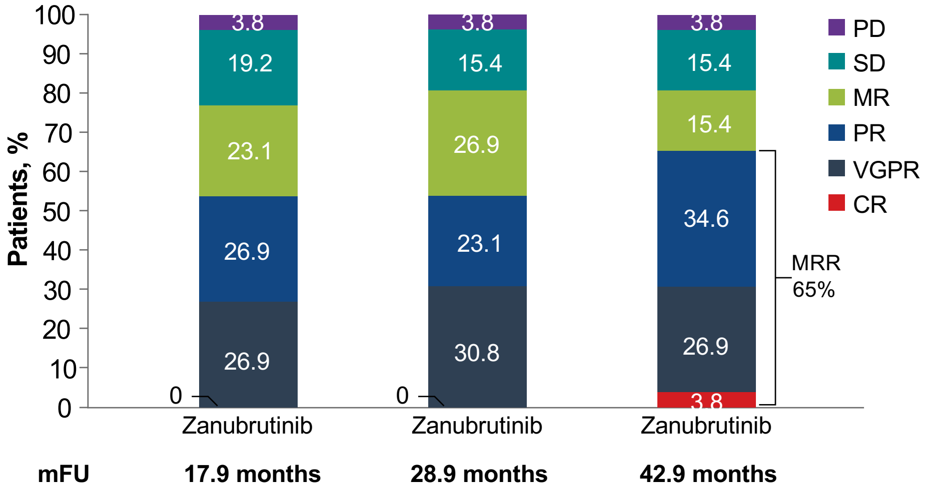
ClinicalTrials.gov Identifier: NCT03053440

ASPEN: Best Overall Response and PFS by Investigator Assessment

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)

Bold blue text indicates rate of AEs with ≥10% (all grades) or ≥5% (grade ≥3) difference between arms.
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.

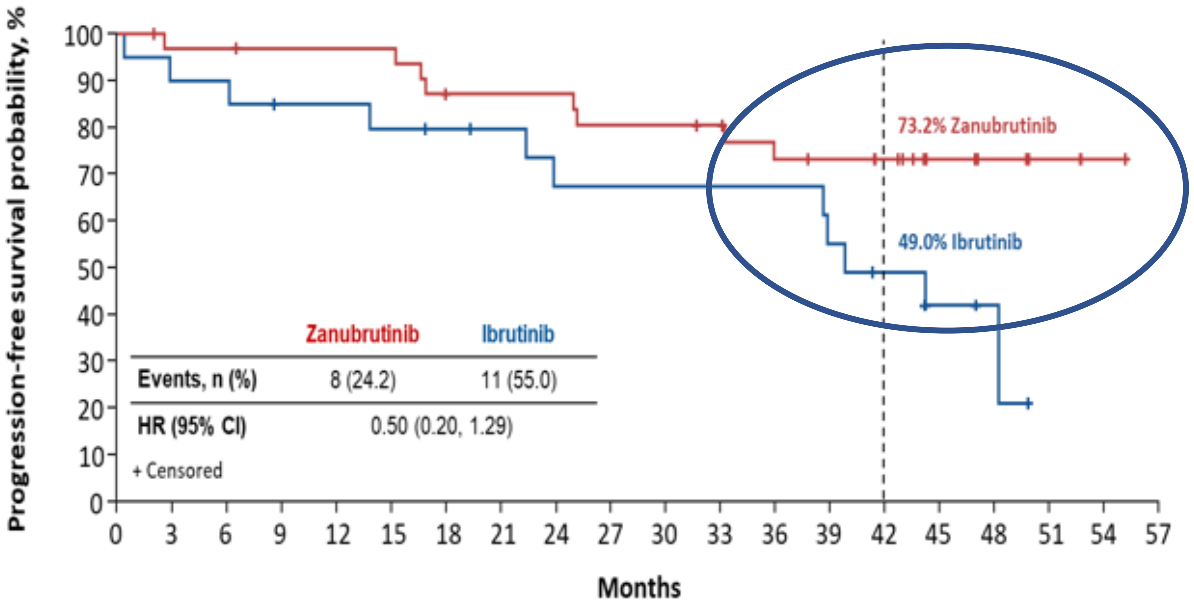
Response and PFS in Patients With *MYD88*^{MUT} by *CXCR4*^{MUT} Status

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}



No. of Patients at Risk:

Zanubrutinib	33	31	31	30	30	30	26	26	26	24	24	23	20	19	17	10	6	3	1	0
Ibrutinib	20	18	18	16	16	15	14	13	11	11	11	11	11	9	7	4	2	0		

[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.

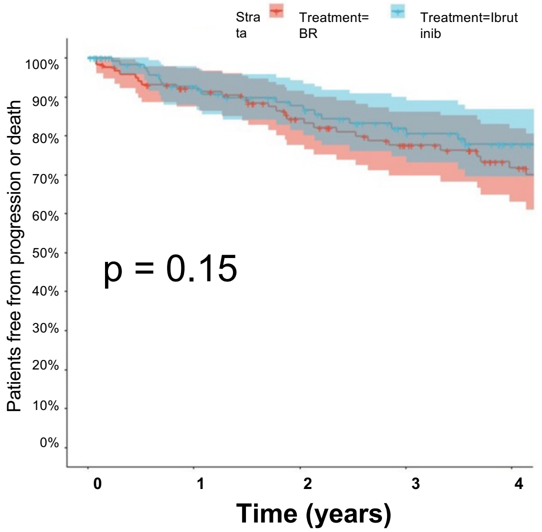
So how do we position BTK-inhibitors relative to Bendamustine-R in treatment naïve patients?

Bendamustine Rituximab v. Ibrutinib as Primary Therapy for WM: An International Collaborative Study

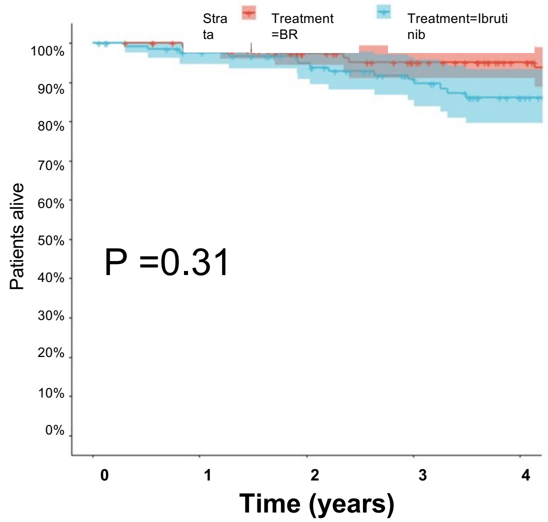
CONQUER CANCER®
THE ASCO FOUNDATION
MERIT AWARD RECIPIENT

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.

TP53 Mutations in ASPEN Study

	N=	Total $TP53^{Mut}$	Treatment Naïve $TP53^{Mut}$	Previously Treated $TP53^{Mut}$	p= (TN vs prev. treated)
All Patients	210	52/210 (24.8%)	7/41 (17.1%)	46/169 (27.2%)	NS
$MYD88^{Mut}$	190	48/190 (25.2%)	6/36 (16.6%)	42/154 (27.3%)	NS
$MYD88^{WT}$	20	5/20 (25%)	1/5 (20%)	4/15 (26.7%)	NS

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CLINICAL TRIALS AND OBSERVATIONS

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

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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)

Most previously treated patients received alkylators

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)

So how do we manage BTK-inhibitor resistant disease?

original reports

Venetoclax in Previously Treated Waldenström Macroglobulinemia

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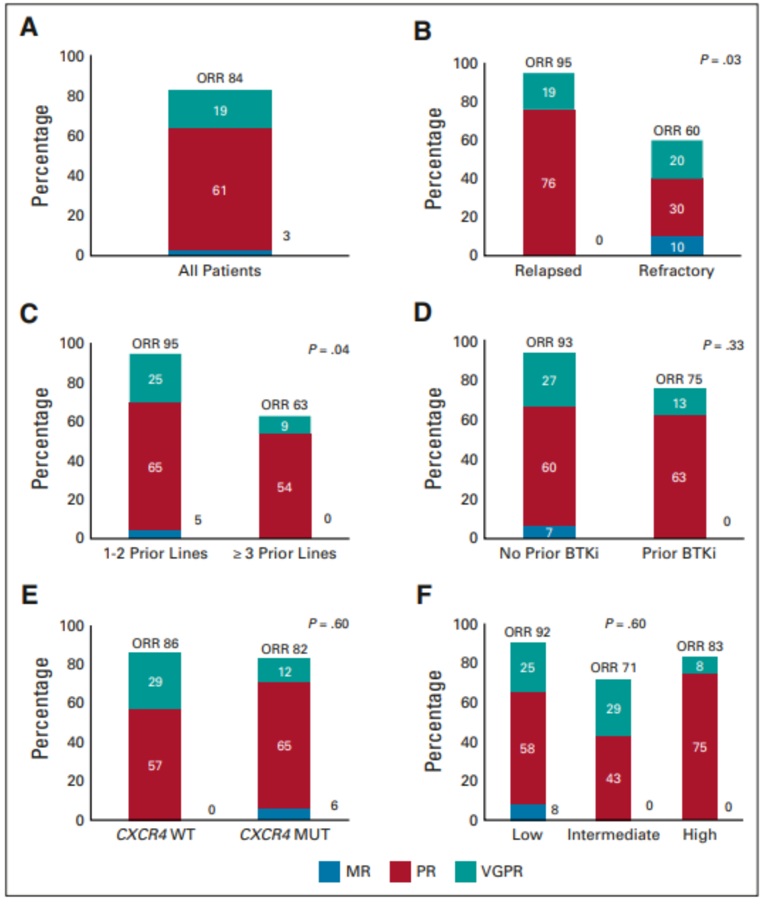
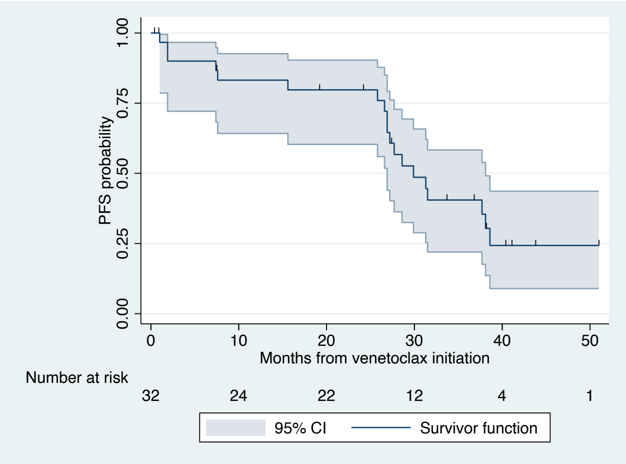
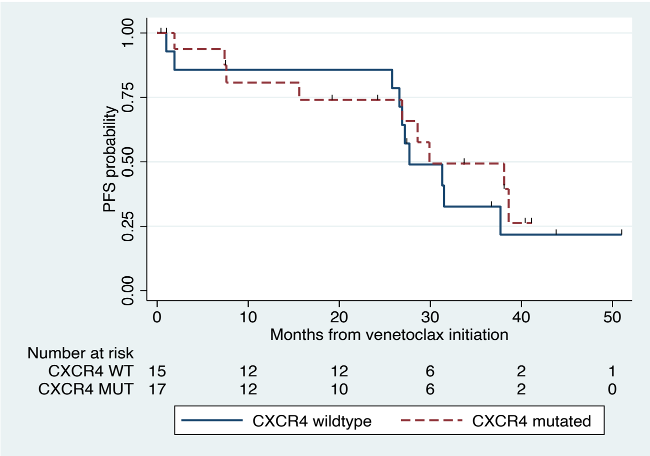
Journal of Clinical Oncology



ORR: 84%; Major RR: 81%

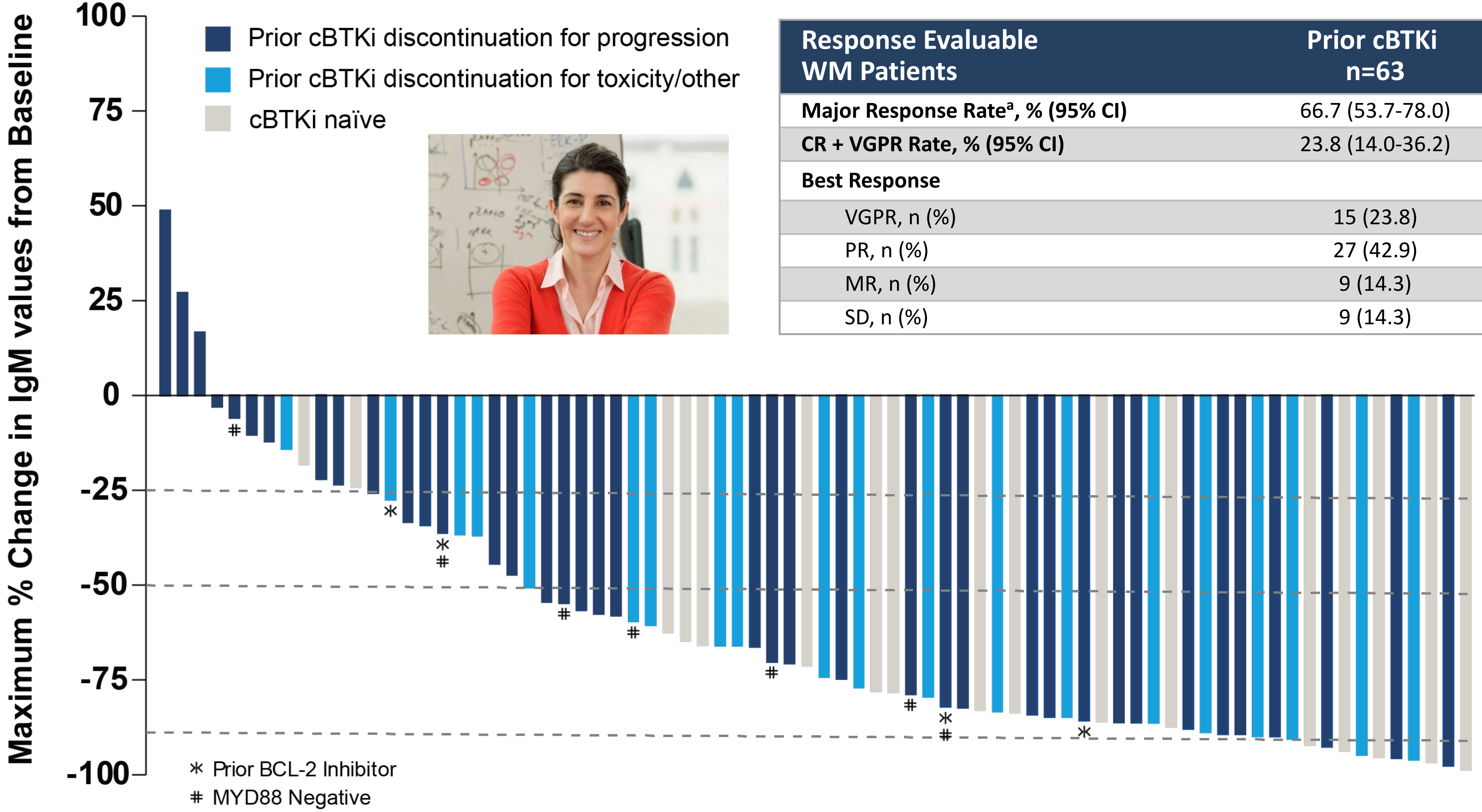




Median f/u: 33 mos; Median PFS: 30 mos.
Not impacted by CXCR4 mutation status.
Grade $\geq$3 neutropenia: 45%

Castillo et al, JCO 2021

Pirtobrutinib Efficacy in WM Patients

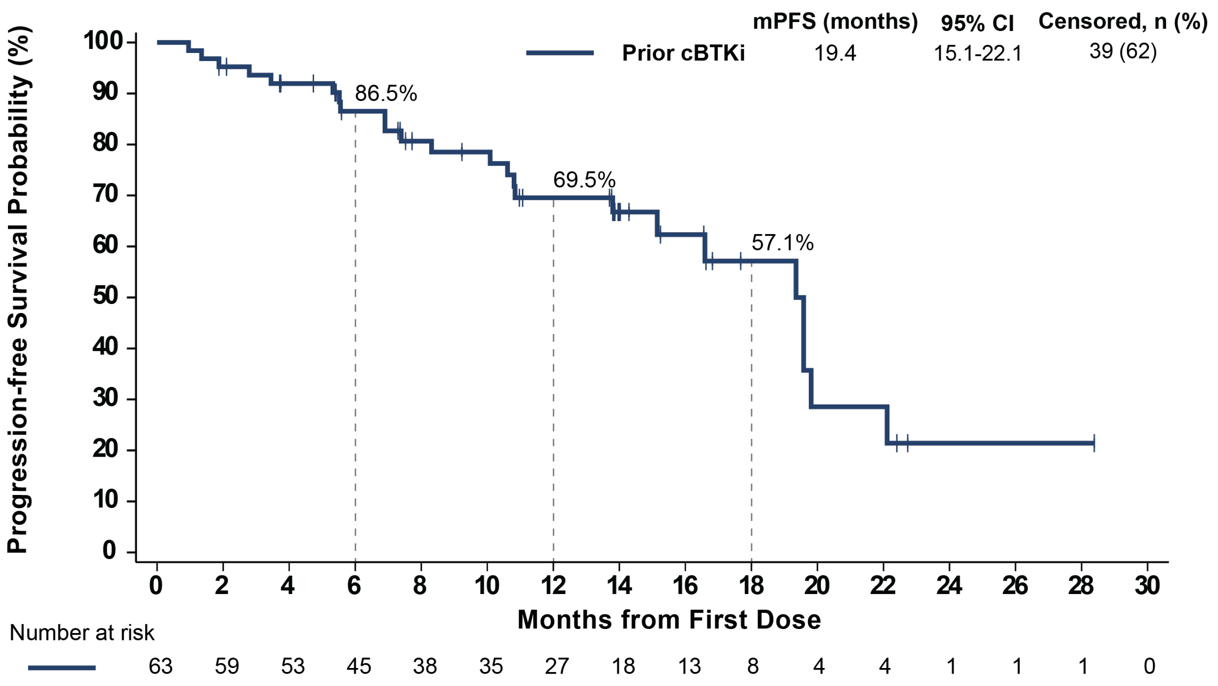


Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], % (95% CI)	66.7 (53.7-78.0)	88.2 (63.6-98.5)
CR + VGPR Rate, % (95% CI)	23.8 (14.0-36.2)	29.4 (10.3-56.0)
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)	0 (0)
SD, n (%)	9 (14.3)	2 (11.8)

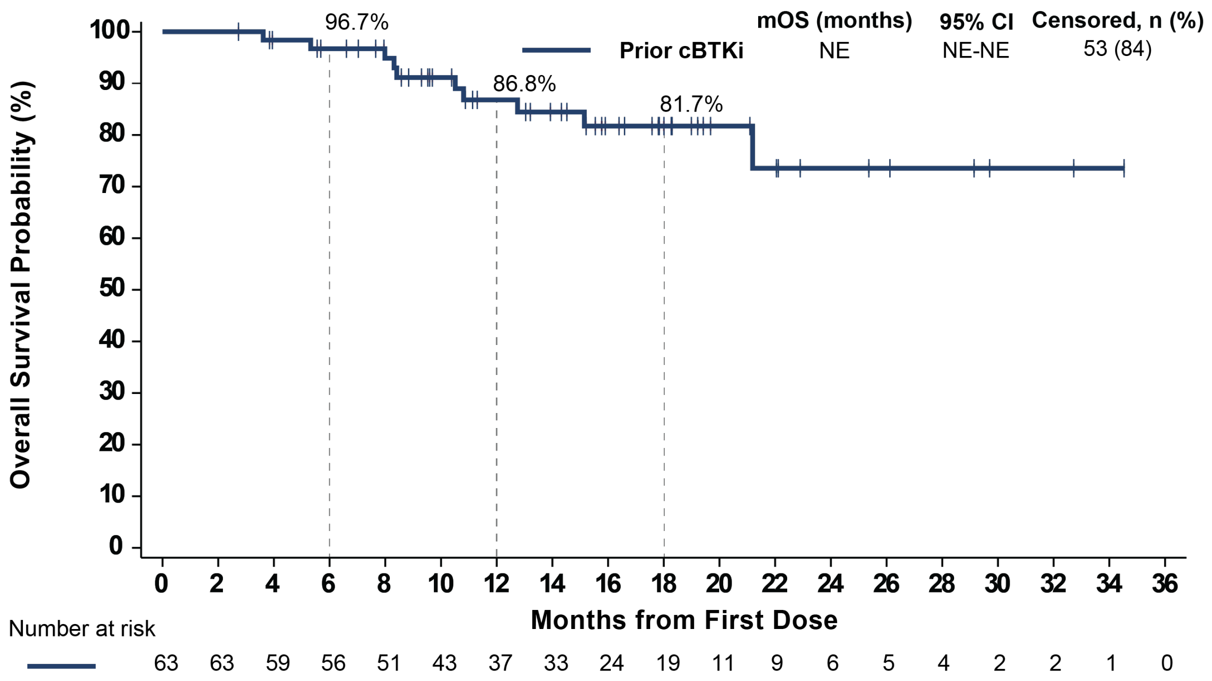
Data cutoff date of 29 July 2022. Data for 4 patients are not shown in the waterfall plot due to missing IgM values at baseline or response assessment. Response as assessed by investigator based on Modified IWWM6 (Owen's) criteria. Under modified IWWM6 criteria, a PR is upgraded to VGPR if corresponding IgM is in normal range or has at least 90% reduction from baseline. [a]Major response includes subjects with a best response of CR, VGPR, or PR. Total % may be different than the sum of the individual components due to rounding.

Progression-Free Survival and Overall Survival **in** Prior cBTKi Patients

Progression-Free Survival



Overall Survival



- The median follow-up for PFS and OS in patients who received prior cBTKi was 14 and 16 months, respectively
- 55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib

Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.

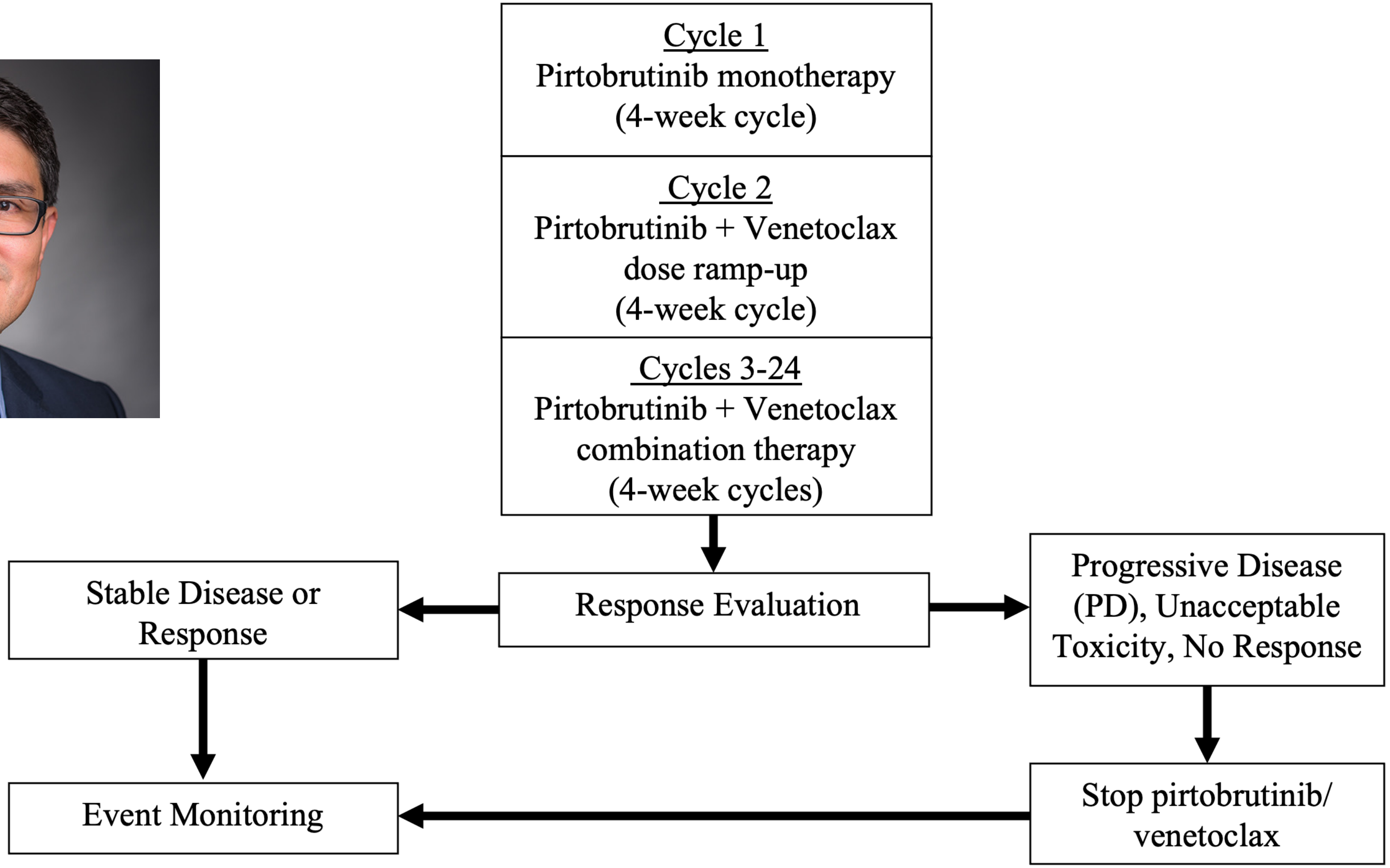
Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and WM safety profiles are generally consistent[h]

Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]WM safety population data can be found via QR code. Constipation is more commonly seen as a TEAE in the WM population than in all patients.

Schema for Pirtobrutinib and Venetoclax Study in Relapsed/Refractory WM



Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM

MYD88 CXCR4 Genotyping

- $MYD88^{Mut}$ $CXCR4^{WT}$ → BTK-inhibitor (monotherapy)
  Alternatives: Benda-R, PI based regimen
- $MYD88^{Mut}$ $CXCR4^{Mut}$
  - → Rapid Response Required → Plasmapheresis for severe HV, CAGG, CRYOS, rapidly progressing IGM PN → Benda-R or PI based regimen
  - → Rapid Response Not Required → *Zanubrutinib*
    Alternative: Benda-R, PI based regimen
- $MYD88^{WT}$ $CXCR4^{WT}$ → Benda-R, PI based regimen or ***Zanubrutinib***

- **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

MYD88 CXCR4 Genotyping

$MYD88^{Mut}$ $CXCR4^{WT}$ →
- First and second relapse or refractory: BTK-inhibitor alone (if BTK-I naïve). Alternatives: Benda-R, PI based regimen
- → Third or later relapse or refractory: BTK-inhibitor alone (if BTK-I naïve). Alternatives: *Venetoclax*, NA[1], everolimus

$MYD88^{Mut}$ $CXCR4^{Mut}$ →
- Plasmapheresis if severe HV, CAGG, CRYOS, rapidly progressing IGM PN
- → First and second relapse or refractory: *Ibrutinib plus rituximab or zanubrutinib* (if BTK-I naïve). Alternative: Benda-R, PI based regimen
- → Third or later relapse or refractory: *Ibrutinib plus rituximab or zanubrutinib* (if BTK-I naïve). Alternatives: venetoclax, NA[1], everolimus

$MYD88^{WT}$ $CXCR4^{WT}$ →
- Benda-R, PI based regimen or *zanubrutinib*

- **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.