Waldenstrom's Macroglobulinemia

New Orleans Summer Cancer Meeting
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Educational Objectives

1. Discuss the criteria for diagnosis and initiation of therapy for patients with Waldenström's macroglobulinemia

2. Assess the safety and efficacy of current and emerging therapies for patients with Waldenström's macroglobulinemia

3. Integrate current guidelines, available clinical trial data, and real-world finding into individualized strategies for treatment selection, sequencing, and monitoring of Waldenström's macroglobulinemia

Introduction

- Waldenström's macroglobulinemia (WM) is an indolent non-Hodgkin lymphoma (NHL) characterized by:[1]
  - Bone marrow infiltration with lymphoplasmacytic cells
  - IgM monoclonal gammopathy
- Incidence: 3 cases per million people in the United States[2]
- Accounts for 1.9% of cases of NHL[3]
  - Median age at diagnosis: 62 - 73 years
  - Two times more common in men than women

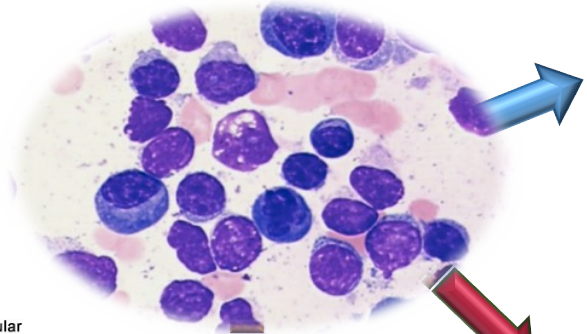
1. Owen RG, et al. *Semin Oncol*. 2003;30:110-115. 2. Sekhar J, et al. *Leuk Lymphoma.* 2012;53:1625-1626. 3. Wang H, et al. *Cancer*. 2012;118:3793-3800.

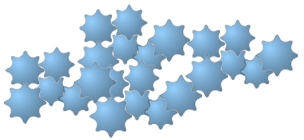
Manifestations of WM Disease

Bing Neel Syndrome

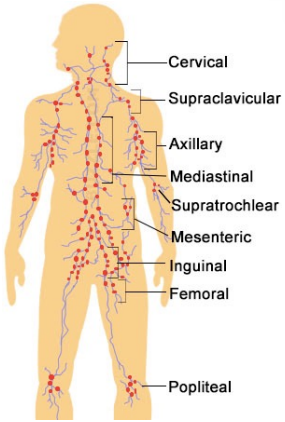
Bone Marrow

↓Hb>>> ↓PLT> ↓WBC

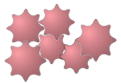




Hyperviscosity Syndrome:
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP



Hepcidin
↓Fe Anemia



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

≤20% at diagnosis; 50-60% at relapse

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

Current WM Diagnostic Criteria

- **International Workshop Criteria[1]**
  - IgM monoclonal gammopathy of any concentration
  - Bone marrow infiltration by small lymphocytes, plasmacytoid cells, and plasma cells
  - Diffuse, interstitial, or nodular pattern of bone marrow infiltration
  - CD19+, CD20+, sIgM+
  - CD5, CD10, CD23 expressed in some cases

- **WHO Criteria[2]**
  - Lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration

1. Owen RG. *Semin Oncol.* 2003;30-196-200; 2 Swerdlow SH, et al. *Blood*. 2016;127(20):2375-2390.

Initial Treatment Options for WM Prior to the Introduction of BTK Inhibitors

Rituximab monotherapy

Nucleoside analogues

- Fludarabine/cyclophosphamide/rituximab (FCR)
- Fludarabine/rituximab (FR)
- Cladribine, Dex, Rituximab

Alkylating agents

- R-CHOP or R-CVP
- Rituximab/cyclophosphamide/dexamethasone (RCD)
- Bendamustine plus rituximab (BR)

Proteasome inhibitors

- Bortezomib/rituximab/dexamethasone (BRD)
- Carfilzomib/rituximab/dexamethasone (CaRD)
- Ixazomib/dexamethasone/rituximab (IDR)

Olszewski AJ, et al. *Blood*. 2015;126:882.=

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

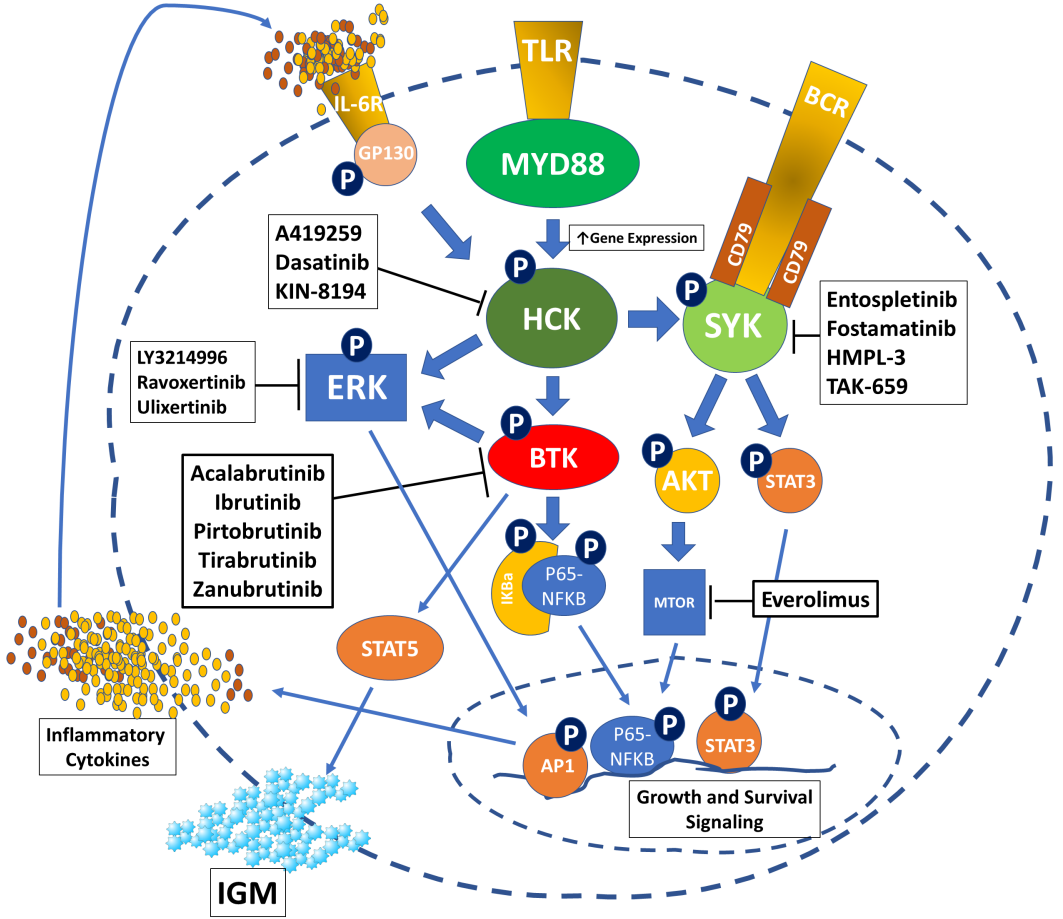
WM–Centric Toxicities with Commonly Used Therapies

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

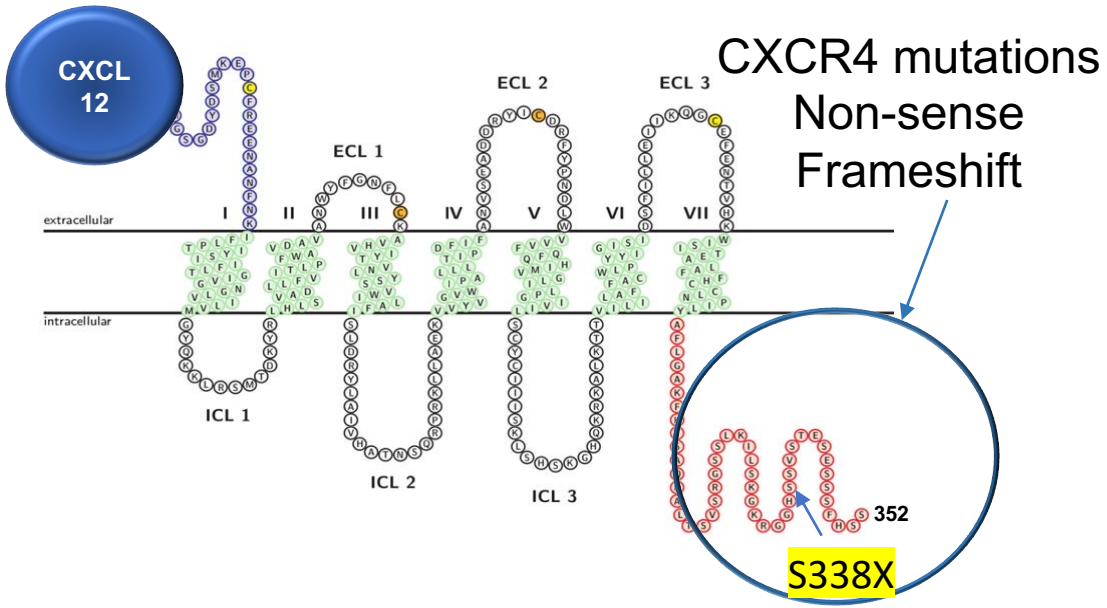
MYD88 mutations occur in 95-97% WM Patients



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

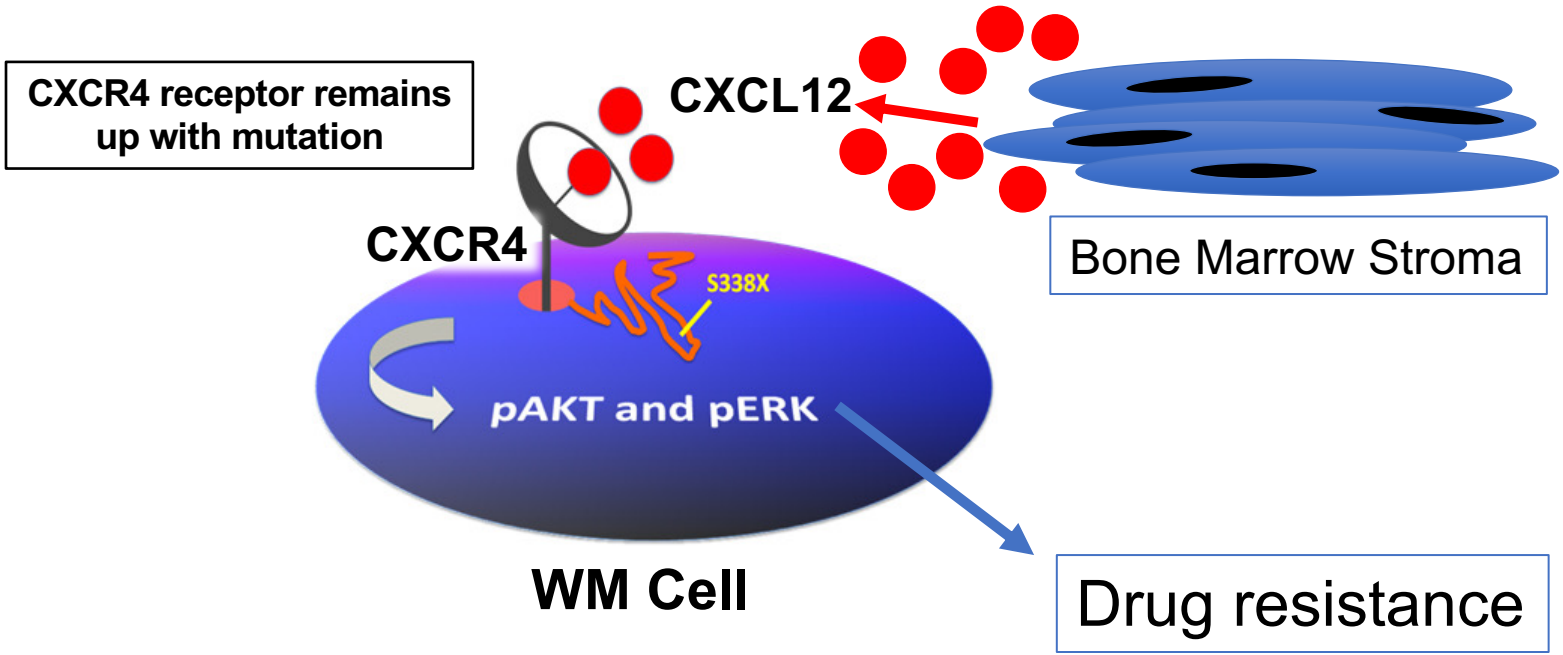
30-40% of WM patients have CXCR4 mutations



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.

Mutated CXCR4 permits ongoing pro-survival signaling by CXCL12



30-40% of WM patients have mutations in CXCR4

Cao et al, Br J Haematol. 2015 Mar;168(5):701-7; Roccarro et al, Blood. 2014 Jun 26;123(26):4120-31

MYD88 and CXCR4 Mutations

Clinical Presentation

S338X

Clinical Characteristics	$MYD88^{L265P}$ $CXCR4^{WT}$	$MYD88^{L265P}$ $CXCR4^{WHIM/FS}$	$MYD88^{L265P}$ $CXCR4^{WHIM/NS}$	$MYD88^{WT}$ $CXCR4^{WT}$
IgM	↑↑	↑↑	↑↑↑↑	↑
BM infiltration	↑↑↑	↑↑	↑↑↑↑	↑
Sensitivity to BTK inhibitors	↑↑↑	↑↑	↑	↓
Incidence, %	~60	27-40	27-40	< 10

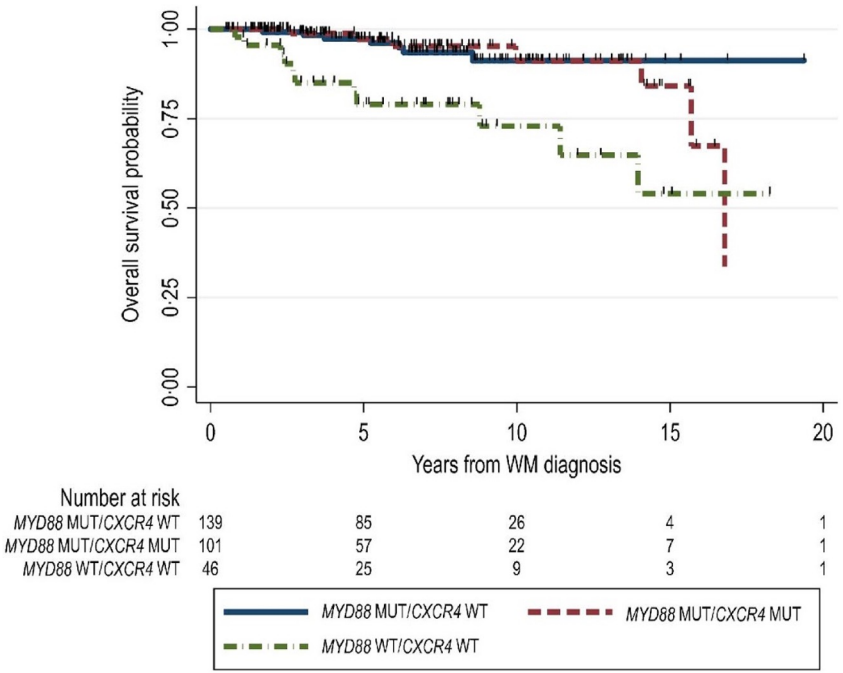
Patients with MYD88 and Nonsense CXCR4 mutations (S338X) show high IGM levels, symptomatic hyperviscosity, and shorter time to initial treatment.

BTK; Bruton's tyrosine kinase

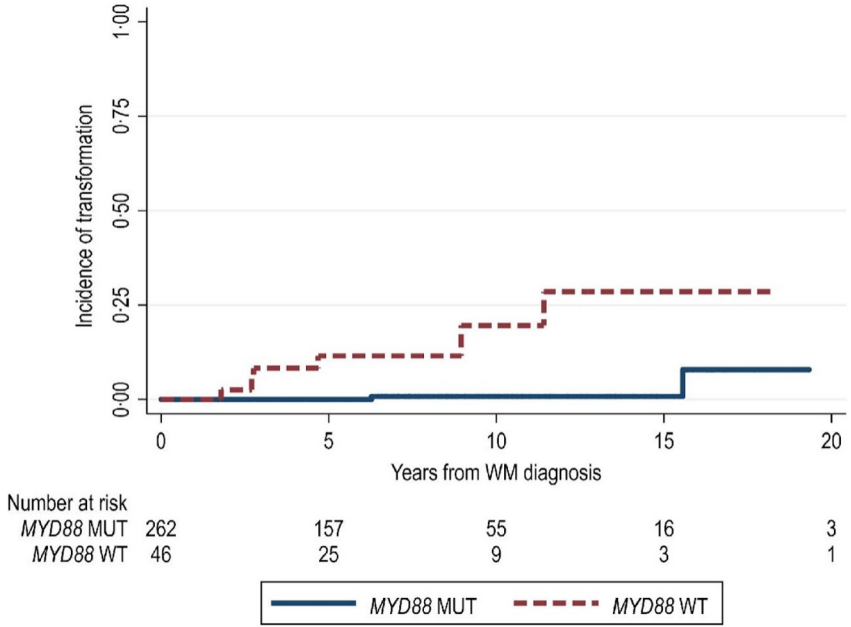
Treon et al, Blood 2014; Schmidt et al, BJH 2015; Abeykoon J, et al. *Cancer Manage and Res*. 2017;9:73-83; Wang et al, Neoplasia 2021.

Prognostic Implications of MYD88 and CXCR4 Mutations

Overall Survival



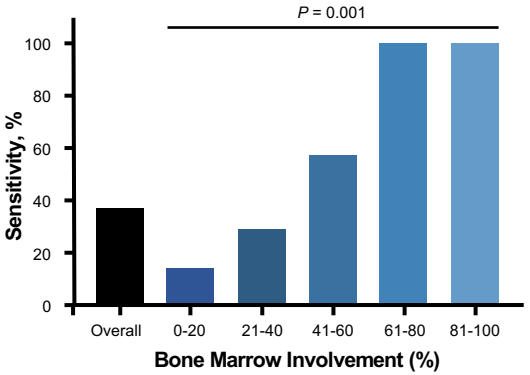
Transformation

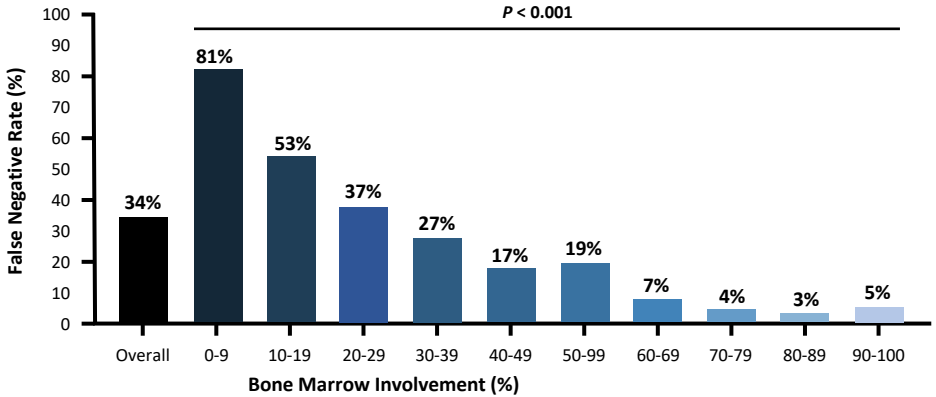


Figures from Treon SP, et al. *Br J Haematol.* 2018;180(3):374-380.

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

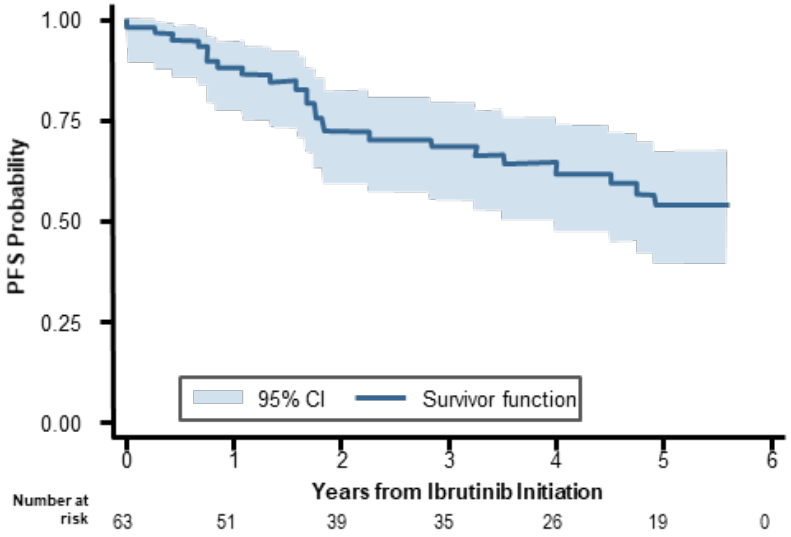
	All Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	MYD88^{WT} CXCR4^{WT}	P-value
N	63	36	22	4	N/A
Overall Response Rate-no. (%)	90.5%	100%	86.4%	50%	<0.01
Major Response Rate-no. (%)	**79.4%**	**97.2%**	**68.2%**	**0%**	**<0.0001**
Categorical responses					
Minor responses-no. (%)	11.1%	2.8%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

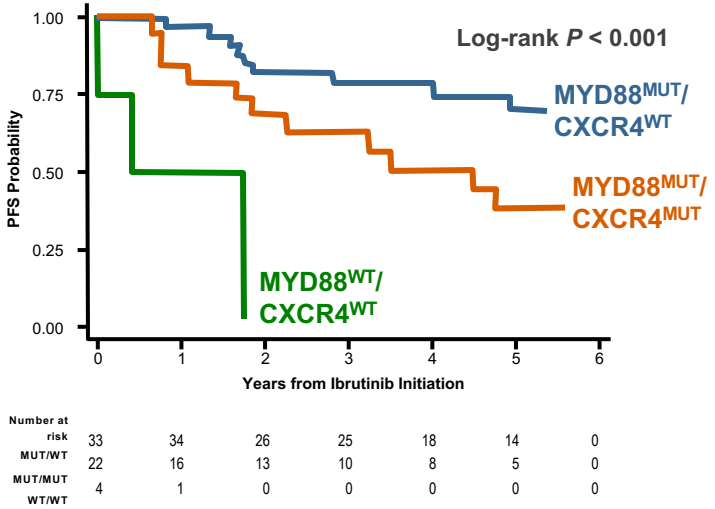
All patients



5-year PFS: 54%

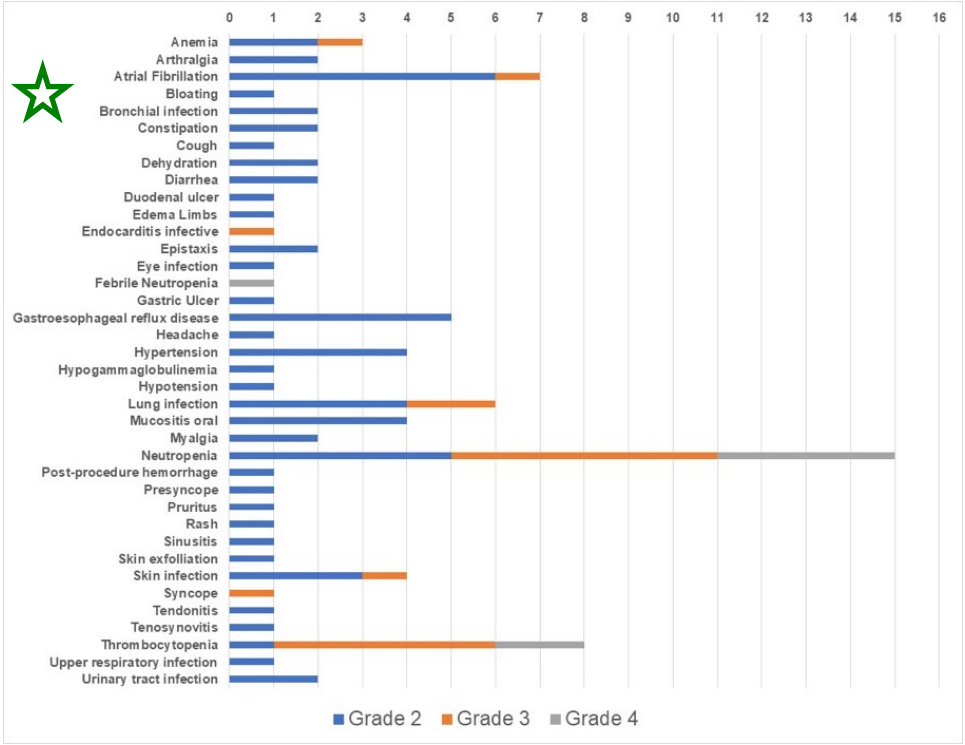
5-year OS: 87%

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.

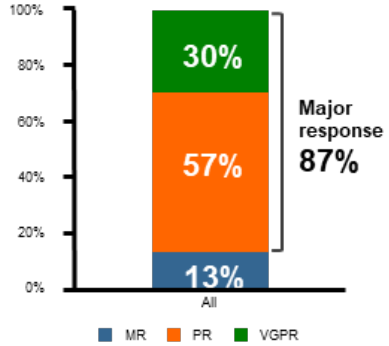
Ibrutinib Activity in Previously Treated WM:
Long Term Toxicity Findings (grade ≥2) of the Pivotal Trial

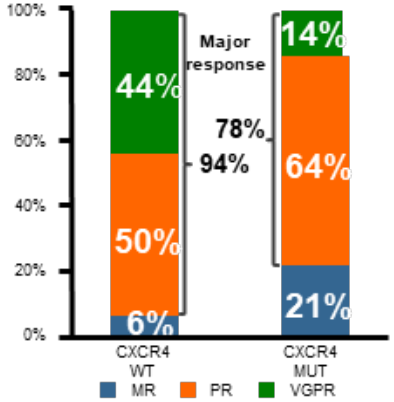


☆ Increased since original report; 8 patients (12.7%) with Afib, including grade 1; 7 continued ibrutinib with medical management.

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





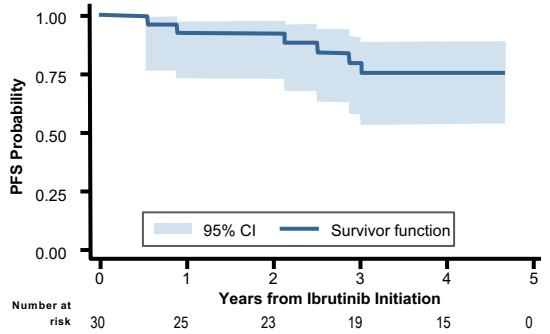
Median time to Response

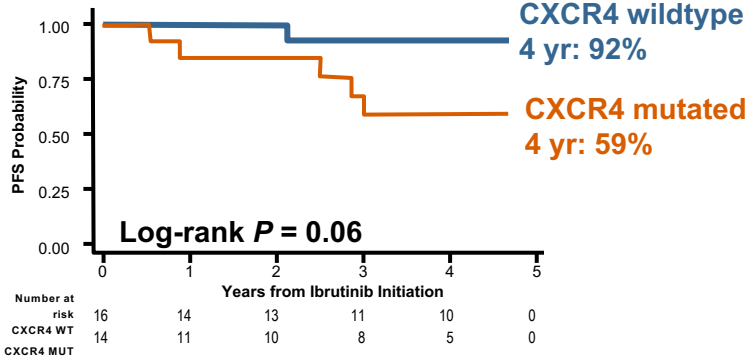
	CXCR4^{WT}	CXCR4^{MUT}
Time to Minor Response (mos).[1]	0.9	1.7
Time to Major Response (mos).[2]	1.8	7.3

1. p=0.07; 2. p=0.01

All patients were MYD88 mutated.

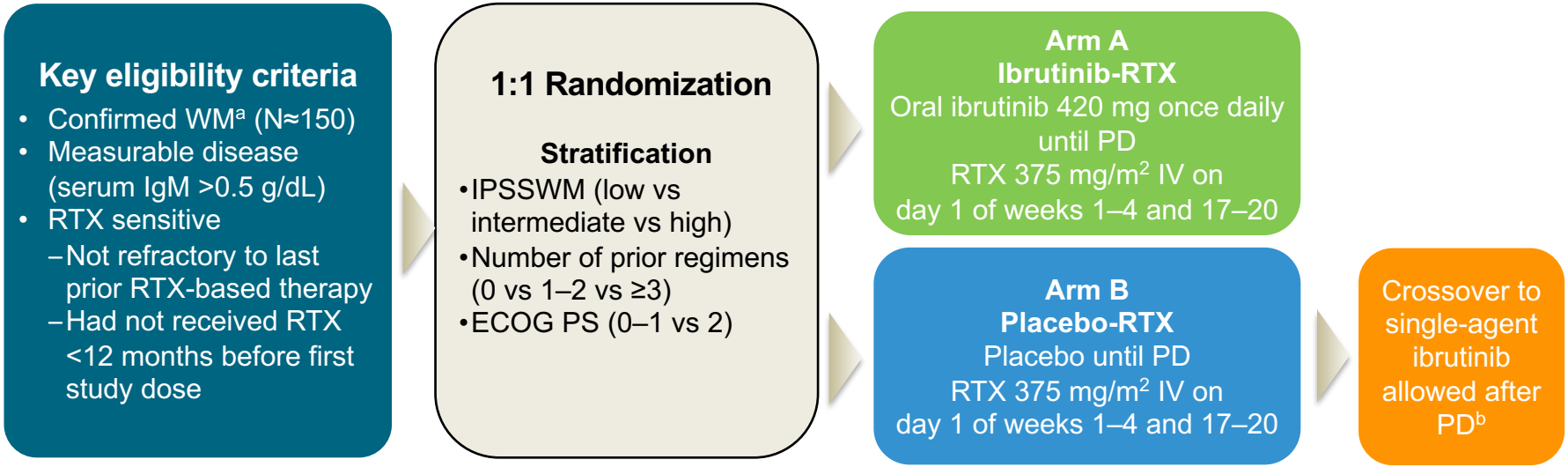
Median f/u: 50 months





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

iNNOVATE (PCYC-1127) study design

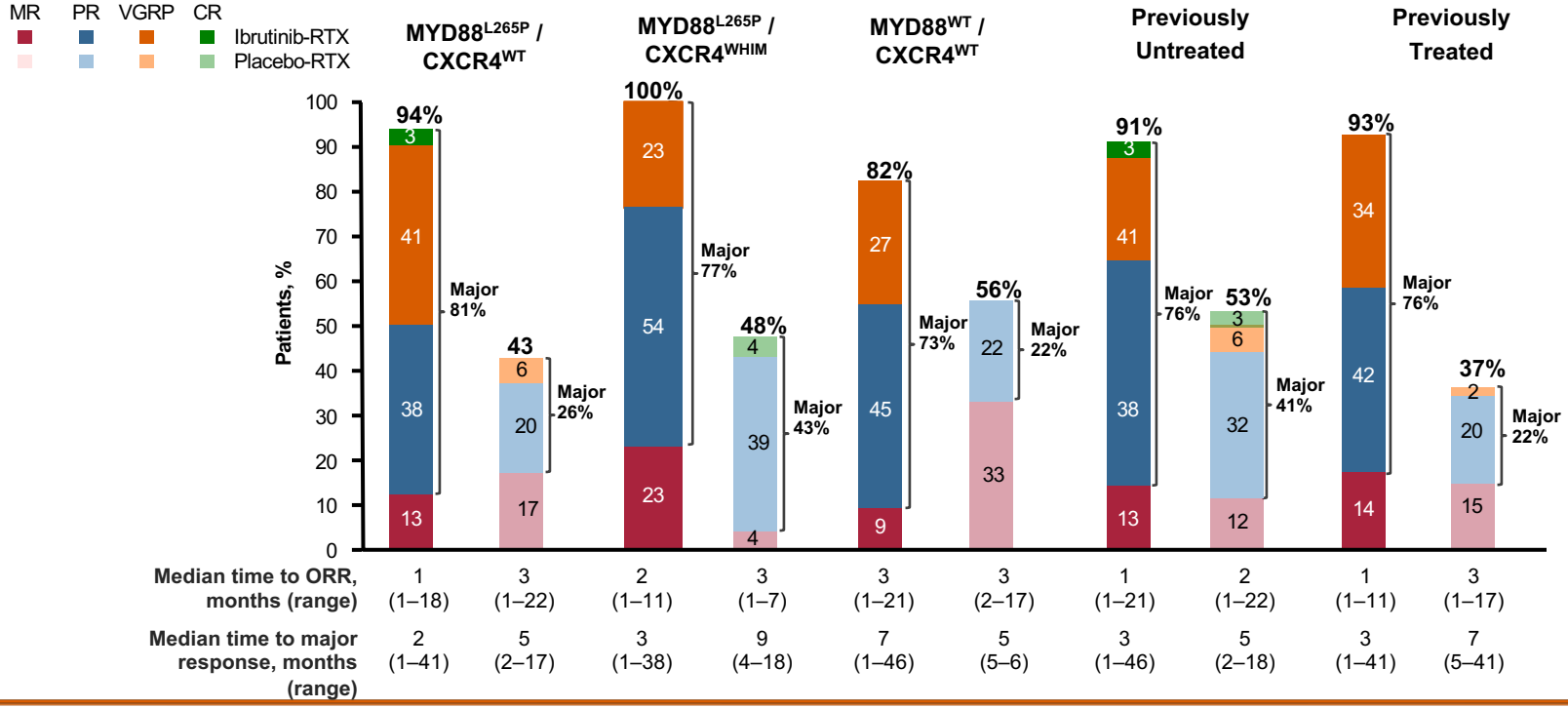


- **Endpoints:** PFS and response rates by IRC, OS, Hgb improvement, TTNT, safety
- At study closure, patients without PD could continue ibrutinib in an extension program

Hgb, hemoglobin; IPSSWM, International Prognosis Scoring System for Waldenström's Macroglobulinemia; IRC, independent review committee; TTNT, time to next treatment.
[a]Treatment-naive patients were allowed to enroll following a protocol amendment (November 2015); therefore, their enrollment started later than relapsed patients.
[b]Patients in the placebo-RTX arm could receive next-line single-agent ibrutinib in crossover following IRC-confirmed PD.
iNNOVATE Study; ClinicalTrials.gov ID: NCT02165397

Buske et al., J Clin Oncol 2022; 40(1): 52-62

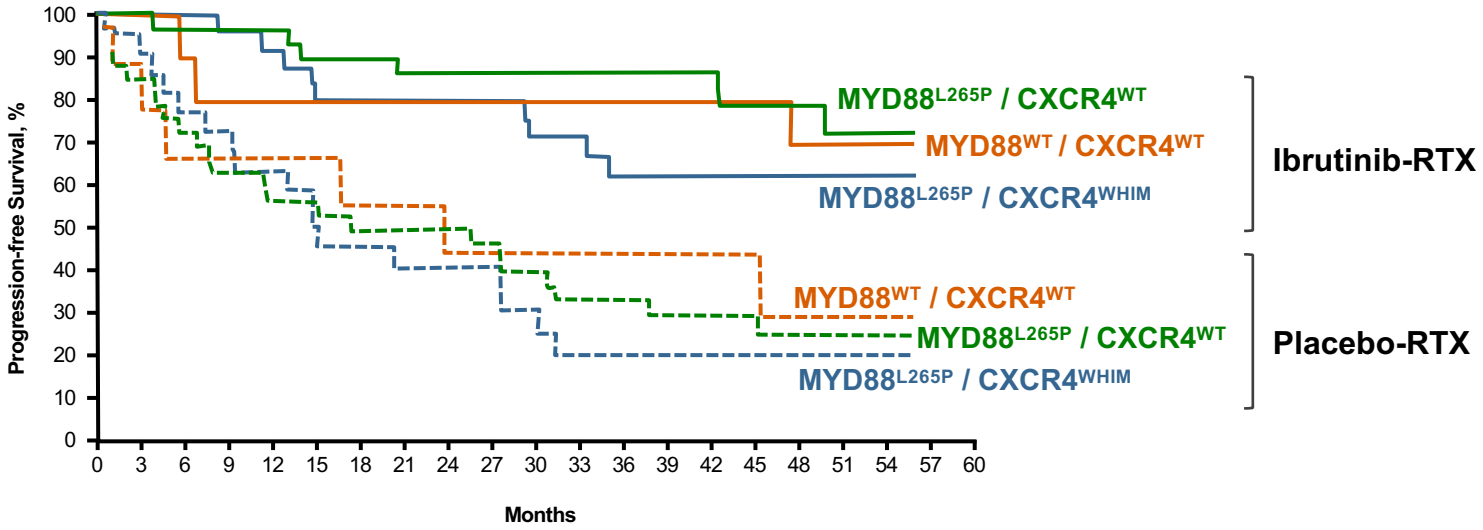
iNNOVATE: Response Rates by Genotype and Prior Treatment Status



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



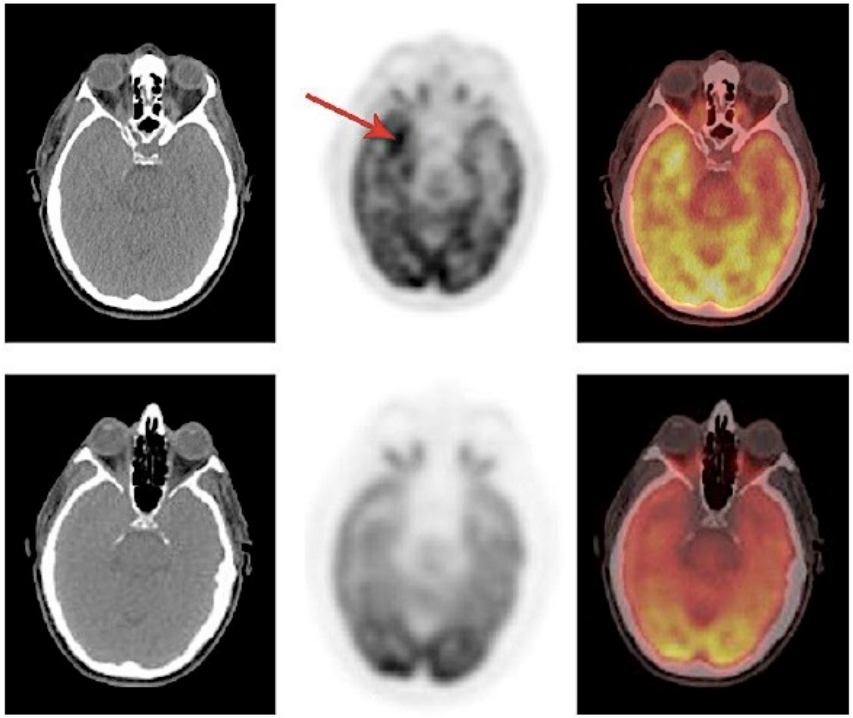
54-month PFS	Ibrutinib-RTX	Placebo-RTX
MYD88^{Mut}/CXCR4^{WT}	72%	25%
MYD88^{Mut}/CXCR4^{Mut}	63%	21%
MYD88^{WT}/CXCR4^{WT}	70%	30%

Garcia Sanz, et al. EHA Abstract EP782.

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

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

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

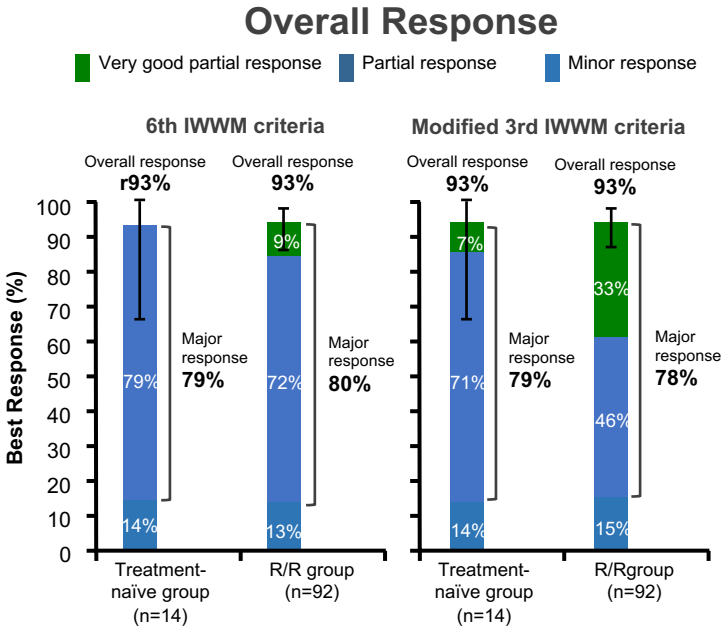
- 6/16 (37.5%)
- In 5 of these 6 patients, serum IgM returned to pre-hold levels or better following re-start of therapy at a median of 4.6 months (range 3.4-11.2 months).
- One patient's serum IgM level remained elevated after self-holding drug for 15 days, and met criteria for progression.

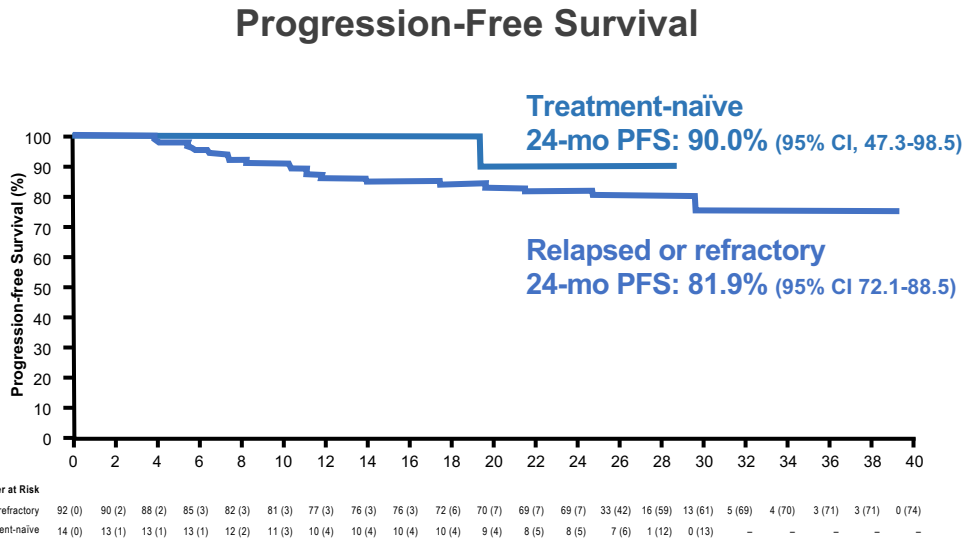
Decreased hemoglobin (>0.5 g/dL)

- 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

Acalabrutinib Phase 2 WM Study: Efficacy





- Median duration of follow-up was 27.4 months
- Median duration of response has not been reached
  - 24-month duration of response for treatment-naïve patients (90%) and relapsed/refractory patients (82%)
- Overall survival was 92% in treatment-naive patients and 89% in relapsed/refractory patients

Owen RG, et al. *Lancet Haematol.* 2020;7:e112–21.

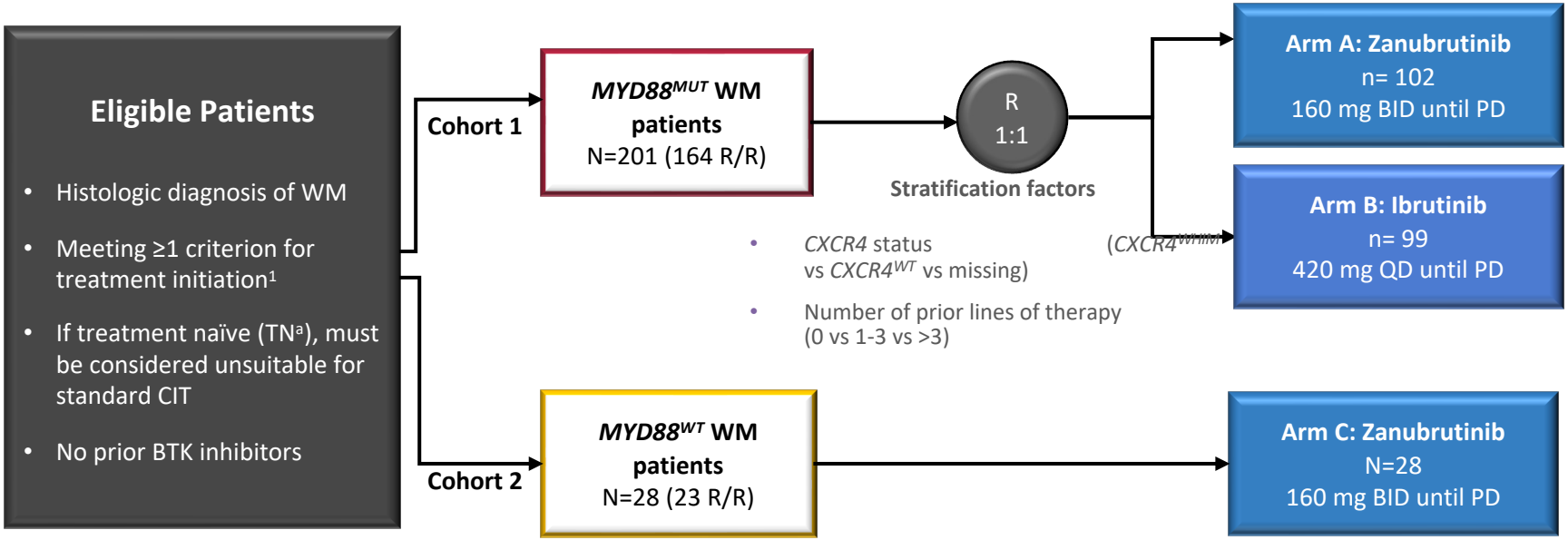
Acalabrutinib Phase 2 WM Study: Safety and Tolerability

Most Frequent AEs, n (%)	Grade 1-2	Grade 3	Grade 4
Headache	41 (39)	0	0
Diarrhea	33 (31)	2 (2)	0
Contusion	31 (29)	0	0
Dizziness	27 (25)	0	0
URTI	23 (22)	0	0
Fatigue	22 (21)	2 (2)	0
Nausea	22 (21)	2 (2)	0
Constipation	22 (21)	0	0
Arthralgia	20 (19)	1 (1)	0
Back pain	18 (17)	1 (1)	0
Cough	18 (17)	0	0
Pyrexia	17 (16)	1 (1)	0
Vomiting	17 (16)	1 (1)	0
Rash	16 (15)	0	0

- Atrial fibrillation occurred in 5% (5/106) of patients
  - All events were grade 1-2 except for one (1%) grade 3 event
- Hypertension occurred in 5% (5/106) of patients
- 28% (30/106) of patients discontinued acalabrutinib during the study period
  - AEs led to discontinuation in 7% (7/106) of patients

Owen RG, et al. *Lancet Haematol* 2020;7:e112–21.

Zanubrutinib vs Ibrutinib in WM *Phase 3 ASPEN*

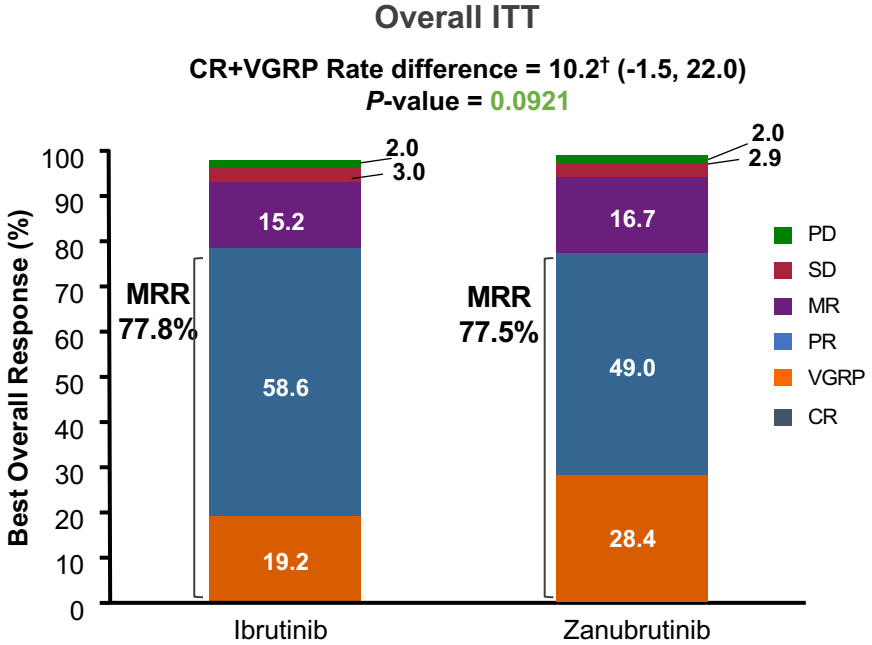


BID, twice daily; BTK, Bruton tyrosine kinase; CIT, chemoimmunotherapy; CXCR4, C-X-C Motif Chemokine Receptor 4; MYD88^{MUT}, myeloid differentiation primary response gene 88 mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström Macroglobulinemia;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

[a]Up to 20% of the overall population

ClinicalTrials.gov Identifier: NCT03053440

Zanubrutinib vs Ibrutinib in WM
ASPEN Cohort 1: Efficacy, Response by IRC

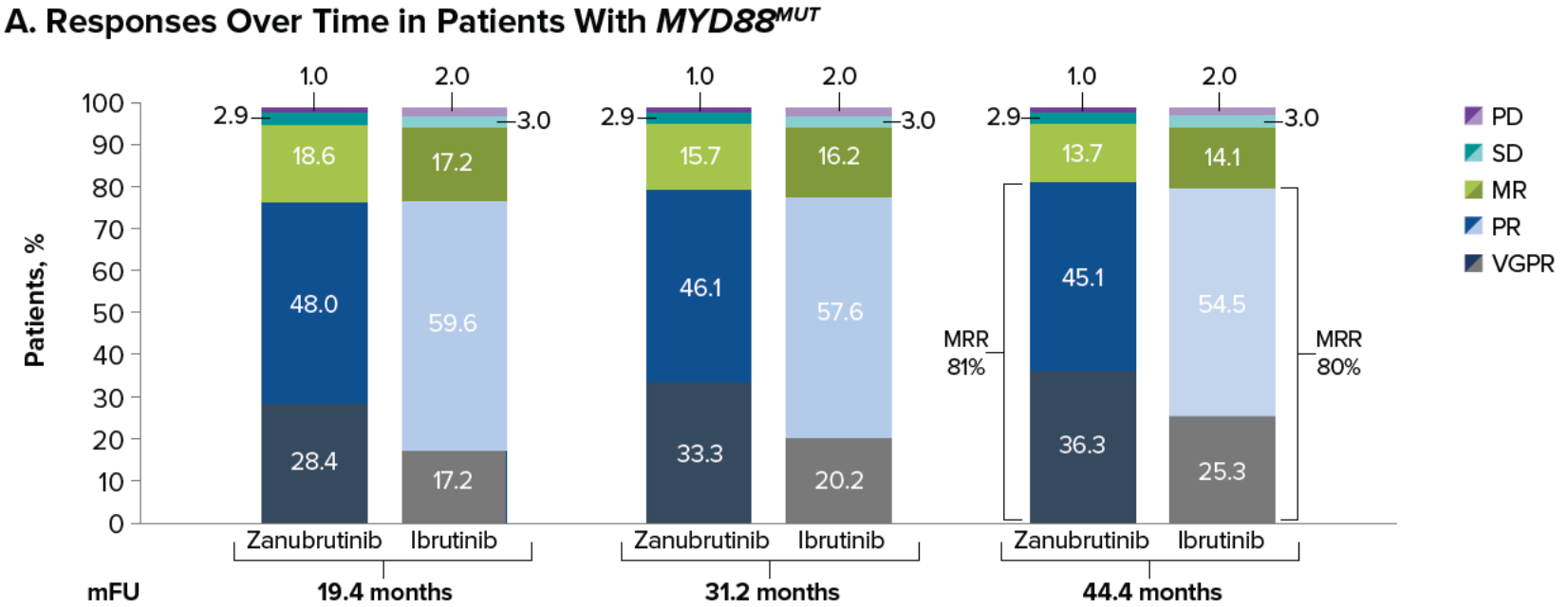


- Data cutoff: August 31, 2019
- Superiority in CR+VGPR rate compared to ibrutinib in relapsed/refractory population (primary study hypothesis) was not significant* (p-value 0.1160)

CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MRR, major response rate; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.
Overall concordance between Independent review and investigators = 94%
*All other *P* values are for descriptive purposes only. †Adjusted for stratification factors and age group.

Tam CS et al. *J Clin Oncol*. 2020;38(15 Suppl):8007.

Zanubrutinib vs Ibrutinib in WM *ASPEN*
Cohort 1: Long Term Follow-up



Data cutoff: October 31, 2021

1. Tam et al. *ASCO* 2022;Abstract 7521.

Zanubrutinib vs Ibrutinib in WM

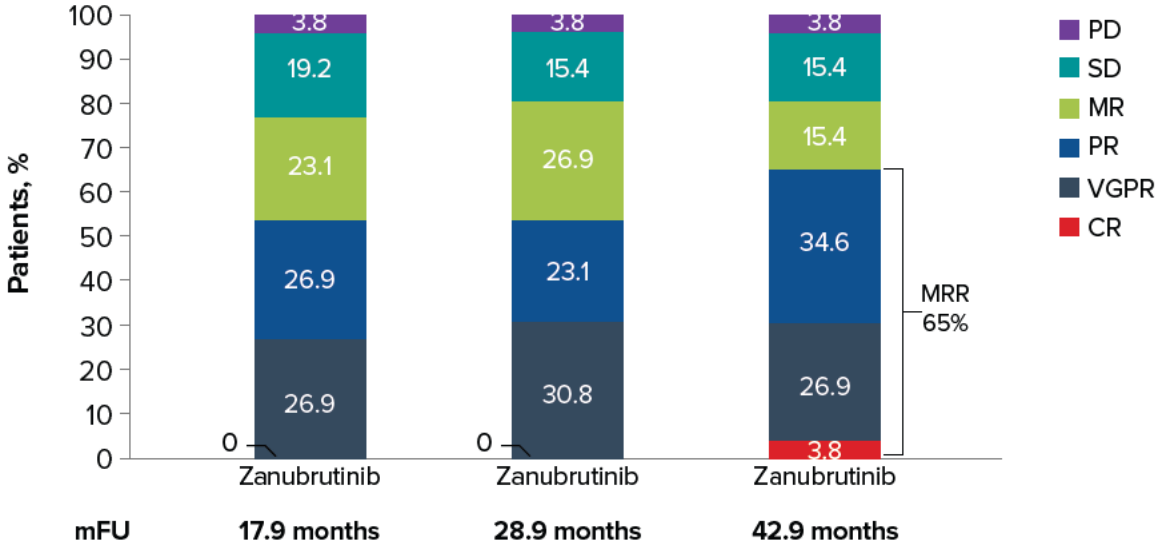
ASPEN Cohort 1: Response by Genotype

	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

1. Tam et al. *ASCO* 2022;Abstract 7521.

Zanubrutinib vs Ibrutinib in WM *ASPEN Cohort 2: Long Term Follow-up*

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



Data cutoff: October 31, 2021

1. Tam et al. *ASCO* 2022;Abstract 7521.

N=28

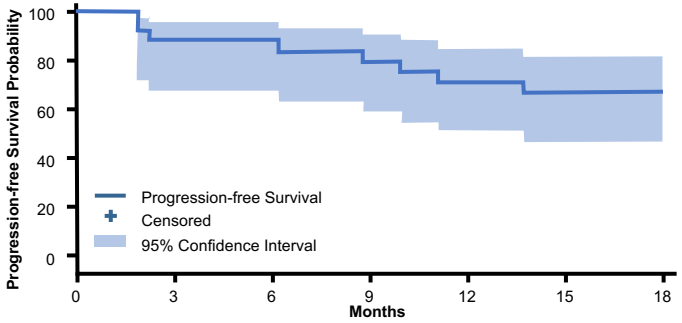
REGULAR ARTICLE

blood advances

Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial

Meletios Dimopoulos,[1] Ramon Garcia Sanz,[2] Hui-Peng Lee,[3] Marek Trneny,[4] Marzia Varettoni,[5] Stephen Opat,[6,7] Shirley D'Sa,[8] Roger G. Owen,[9] Gavin Cull,[10,11] Stephen Mulligan,[12] Jaroslaw Czyz,[13,14] Jorge J. Castillo,[15,16] Marina Motta,[17] Tanya Siddiqi,[18] Mercedes Gironella Mesa,[19] Miquel Granell Gorrochategui,[20] Dipti Talaulikar,[21] Pier Luigi Zinzani,[22,23] Elham Askari,[24] Sebastian Grosicki,[25] Albert Oriol,[26] Simon Rule,[27] Janusz Kloczko,[28] Alessandra Tedeschi,[29] Christian Buske,[30] Veronique Leblond,[31] Judith Trotman,[32,33] Wai Y. Chan,[34] Jan Michel,[35] Jingjing Schneider,[34] Ziwen Tan,[36] Aileen Cohen,[34] Jane Huang,[34] and Constantine S. Tam,[37-40] for the ASPEN investigators

	N	%
ORR	23	81%
Major (PR or better)	13	50%
VGPR	7	27%



Baseline demographic and disease characteristics

Characteristic	Treatment-Naïve (n = 5)	Relapsed/refractory (n = 23)	Overall (N = 28)
Bone marrow involvement, n (%)	4 (80)	22 (96)	26 (93)
Median percent tumor cells (min, max)	13 (0, 70)	25 (0, 90)	23 (0, 90)

Zanubrutinib vs Ibrutinib in WM

ASPEN Cohort 1: AEs of Special Interest (BTKi Class)

AEs,[a] 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)

Bold 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]AE categories (grouped terms) of preferred terms by Medical Dictionary for Regulatory Activities v24.0. [b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.

1. Tam et al. *ASCO* 2022;Abstract 7521.

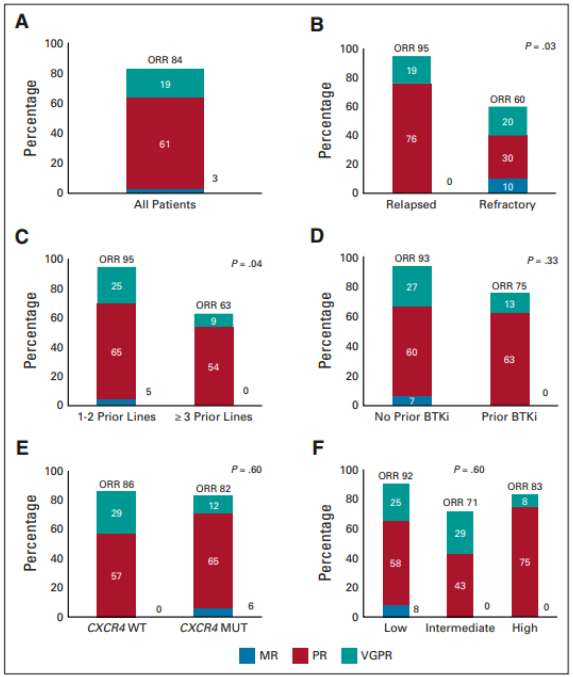
Emerging Treatment Options

- Novel Covalent BTK-inhibitor Combinations
- CXCR4 inhibitors
- Non-covalent BTK inhibitors
- BCL2 inhibitors
- Antibody drug conjugates (Loncastuximab)
- Bispecific antibodies (CD19, CD20, BCMA)
- CAR T cell Immunotherapy

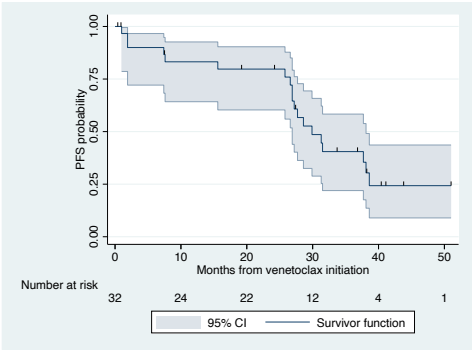
Venetoclax in Previously Treated Waldenström Macroglobulinemia

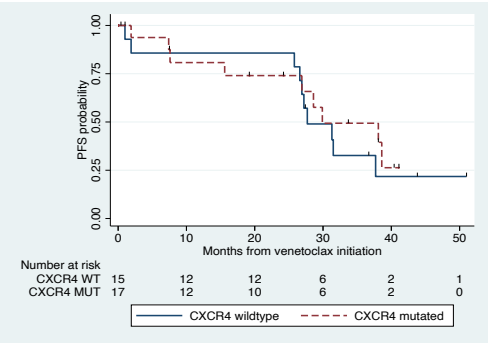
Journal of Clinical Oncology®

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%



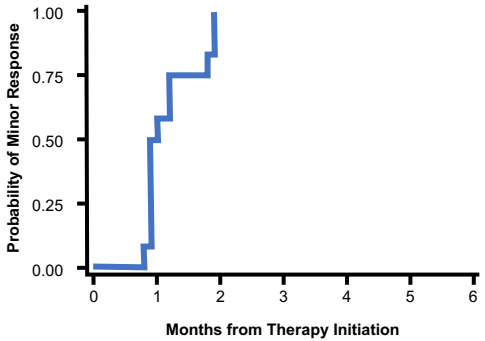


Median f/u: 33 mos; Median PFS: 30 mos.
Not impacted by CXCR4 mutation status.
Grade ≥3 neutropenia: 45%

Castillo et al, JCO 2021

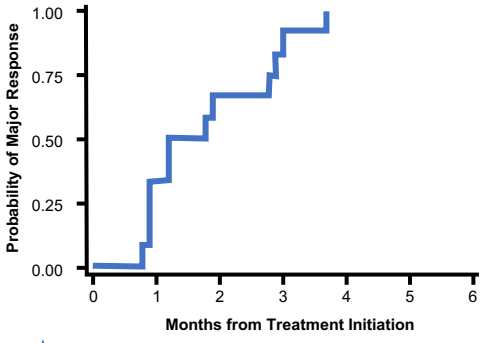
Phase I Trial of CXCR4 antagonist Ulocuplumab and Ibrutinib in CXCR4-mutated Patients with Symptomatic WM

Median Time to Minor Response



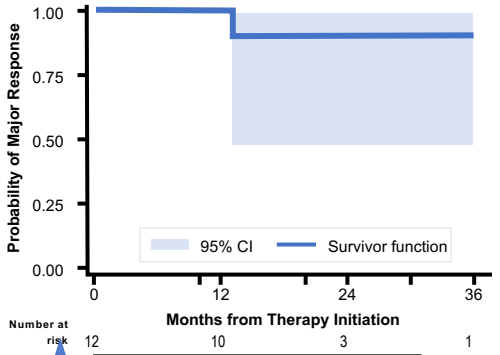
0.9 (95% CI 0.9-1.8) months

Median Time to Major Response



1.2 (95% CI 0.9-2.8) months

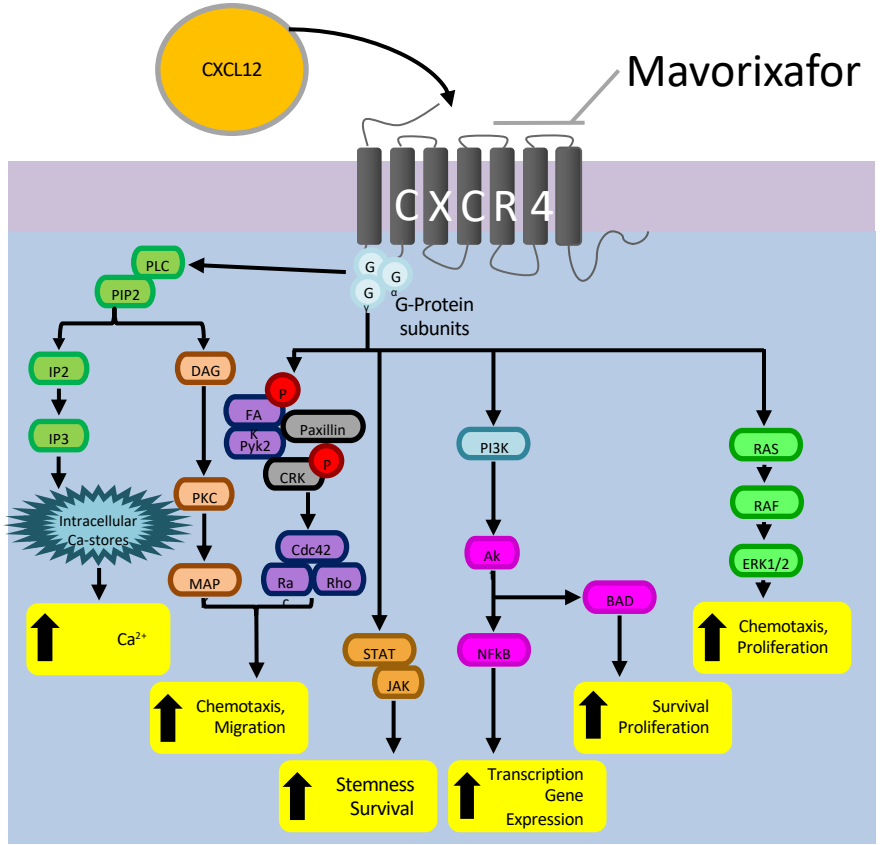
Median Time to PFS

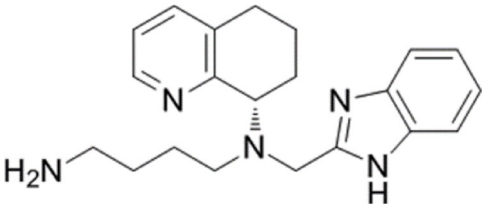


2-year 90% estimated

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

Mavorixafor in combination with ibrutinib in CXCR4 mutated WM

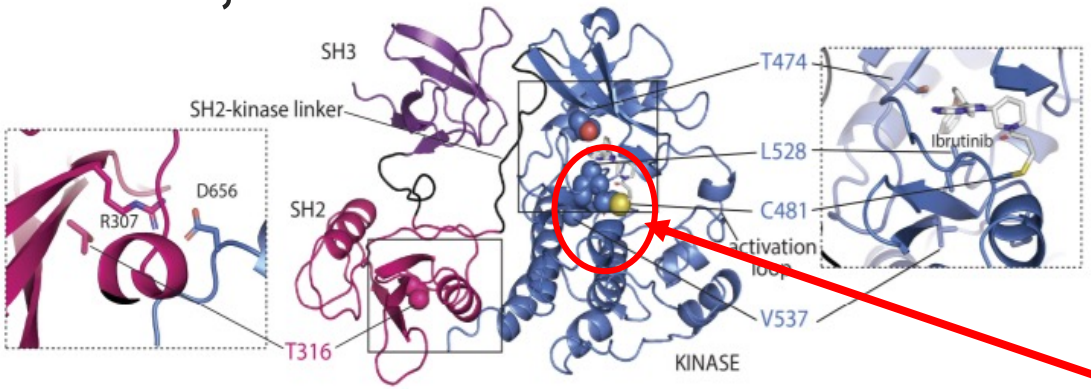




- Non-competitive, allosteric, small molecule antagonist of CXCR4
- Orally Bioavailable; mean $t_{1/2}$ of ~23 hours
- High volume of distribution

ClinicalTrials.gov:NCT04274738

BTK^{Cys481} is the Key Target of Covalent BTK-inhibitors Ibrutinib, Zanubrutinib and Acalabrutinib

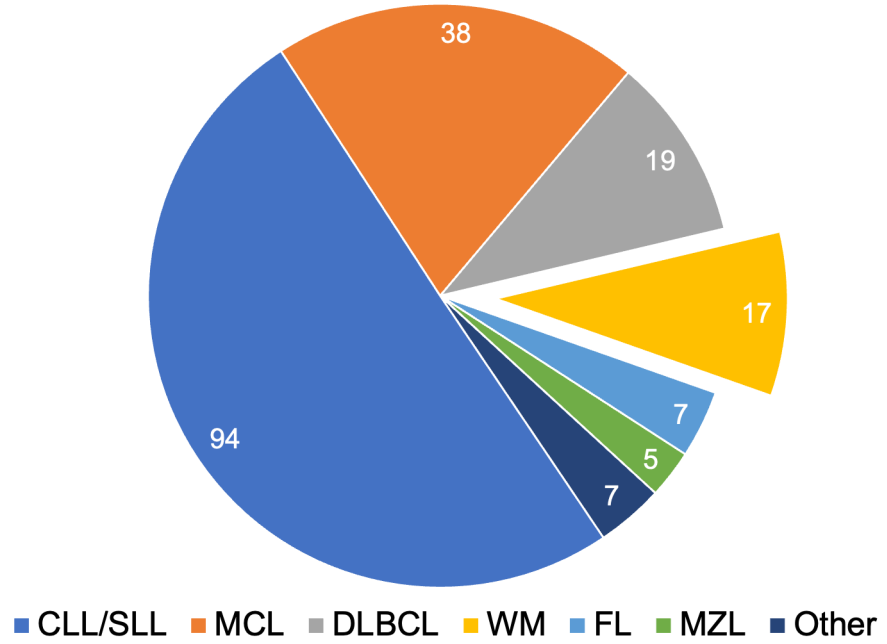


Position	316	474	481	528	537
Native residue	Threonine (T)	Threonine (T)	Cysteine (C)	Leucine (L)	Valine (V)
Reported Ibrutinib resistance mutations	Alanine (A)	Isoleucine (I) Serine (S)	Arginine (R) Serine (S) Tyrosine (Y) Phenylalanine (F)	Tryptophan (W)	Isoleucine (I)

Pirtobrutinib (LOXO-305) is a non-covalent BTK-inhibitor that targets BTK (G473-K483)

Kueffer LE, Joseph RE, Andreotti AH. *Front Cell Dev Biol*. 2021;9:655489.

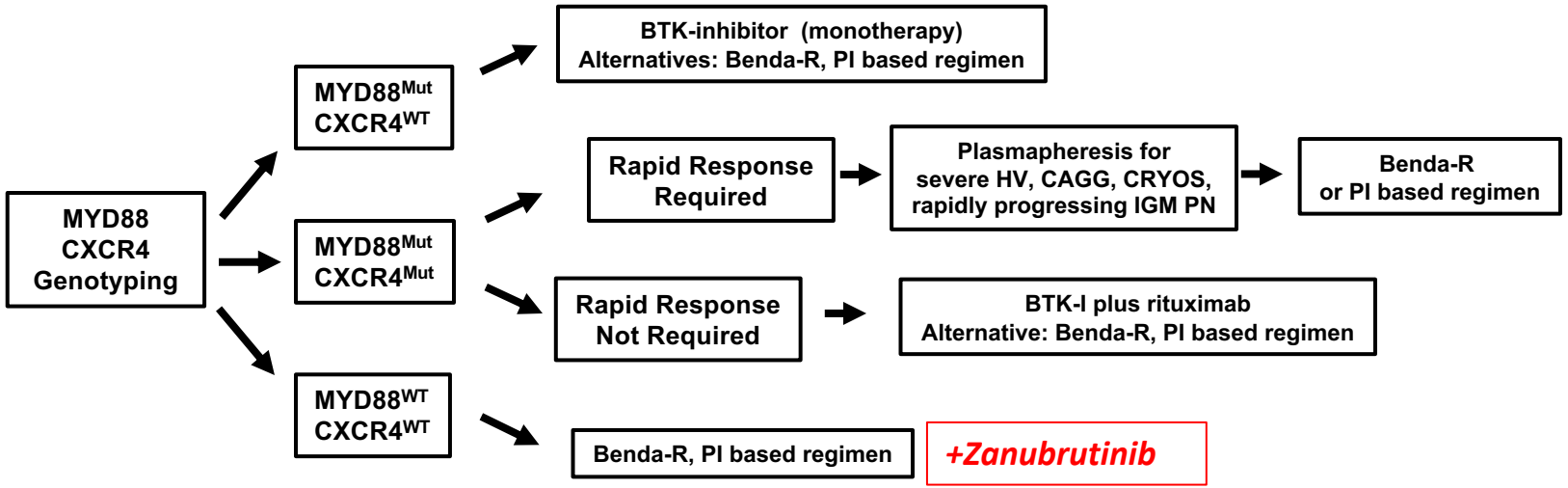
Non-covalent BTK-inhibitor Pirtobrutinib in Previously Treated NHLs: Results from the Phase 1/2 BRUIN Study



- 15 evaluable for efficacy
- 60% previously exposed to covalent BTK inhibitors
- ORR 60%
  - 1 VPGR
  - 4 PR
  - 4 MR

Wang M, et al. ASH 2020: Abstract 117.

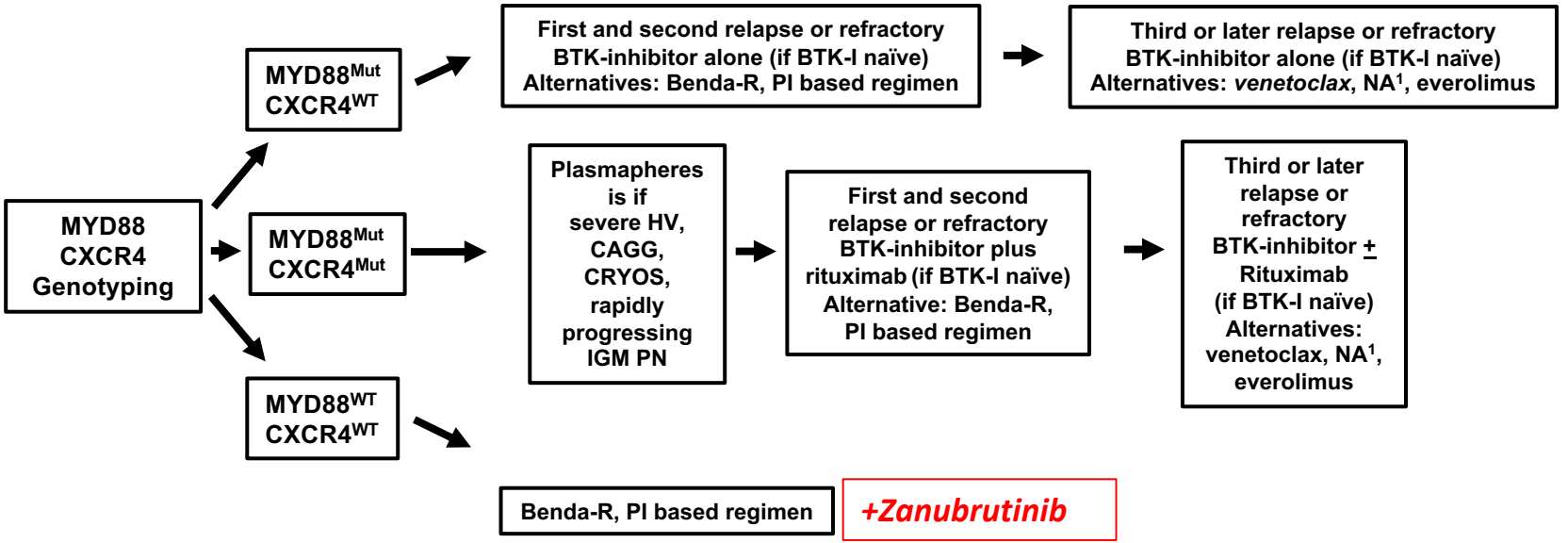
Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM



- **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

- Waldenström's macroglobulinemia is an uncommon subtype of NHL characterized by bone marrow infiltration and increased monoclonal IgM
- Highly recurring mutations in MYD88 and CXCR4 are present in WM and impact disease presentation, prognosis, and/or treatment outcome
- Treatment selection for WM relies on a number of patient characteristics, including disease stage, prior therapies, comorbidities, disease burden, and mutation status
- Novel targeted therapies are under investigation for WM include combination therapies with covalent BTK inhibitors, non-covalent BTK inhibitors, ADCs, BCL-2 and CXCR4 inhibitors.

Thank you!!

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