Treatment Landscape of Waldenström's Macroglobulinemia

HARVARD MEDICAL SCHOOL

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Disclosures – Steven Treon

Research Support/P.I.	Janssen, Pharmacyclics, BMS
Consultant	Janssen, Pharmacyclics, Beigene, BMS

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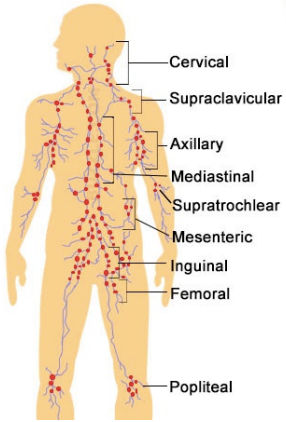
Manifestations of WM Disease

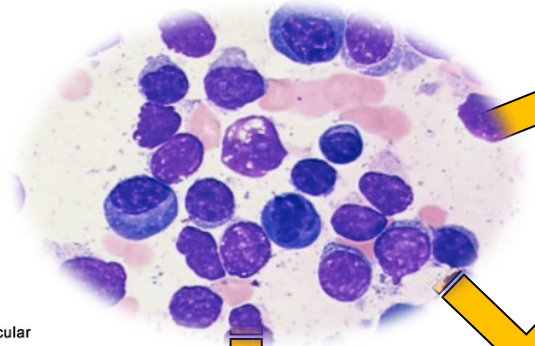
Bing Neel Syndrome

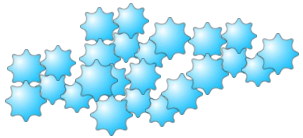


≤20% at diagnosis;
50-60% at relapse.

Bone Marrow

↓Hb>>> ↓PLT> ↓WBC





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

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

Hepcidin
↓Fe Anemia

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

NCCN Guidelines for Initiation of Therapy in WM

- Hb ≤10 g/dL on basis of disease
- PLT <100,000 mm^3 on basis of disease
- Symptomatic hyperviscosity
- Moderate/severe peripheral neuropathy
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloid.

Kyle RA, et al. Semin Oncol. 2003;30(2):116-120; Anderson et al, JNCCN 2012; 10(10):1211-9.

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

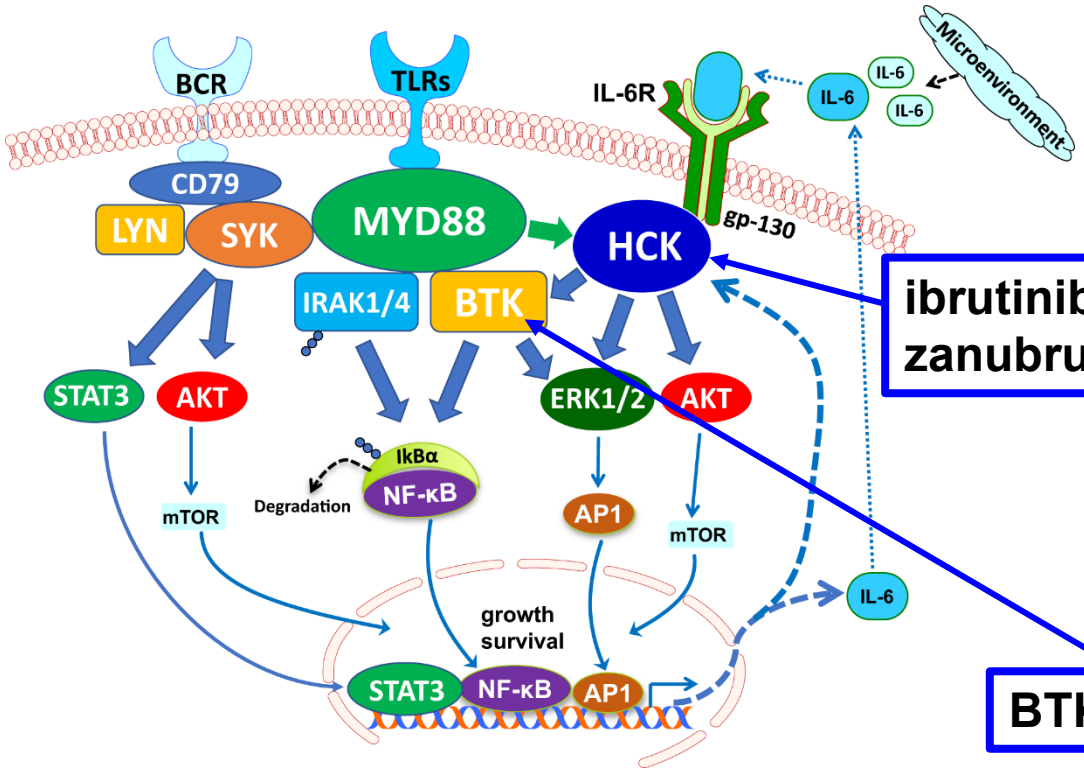
Reviewed in Dimopoulos et al, Blood 2014; 124(9):1404-11; Treon et al, Blood 2015 126:721-732; Rummel et al, ASH 2019

WM–centric toxicities with commonly used therapies

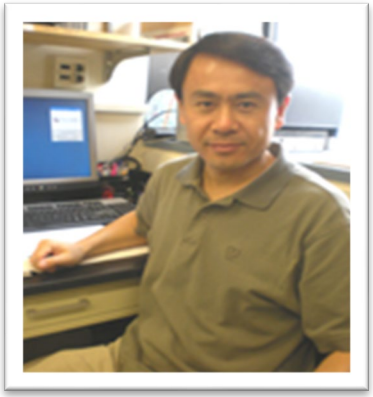
Agent	WM Toxicities
Rituximab	• **IgM flare (40-60%)->** Hyperviscosity crisis, Aggravation of IgM related PN, CAGG, Cryos. • Hypogammaglobulinemia-> infections, IVIG • Intolerance (10-15%)
Fludarabine	• Hypogammaglobulinemia-> infections, IVIG • **Transformation, AML/MDS (15%)**
Bendamustine	• Prolonged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

Personal communication

Pro-Survival Signaling by Mutated MYD88 in Waldenström's Macroglobulinemia



ibrutinib
zanubrutinib



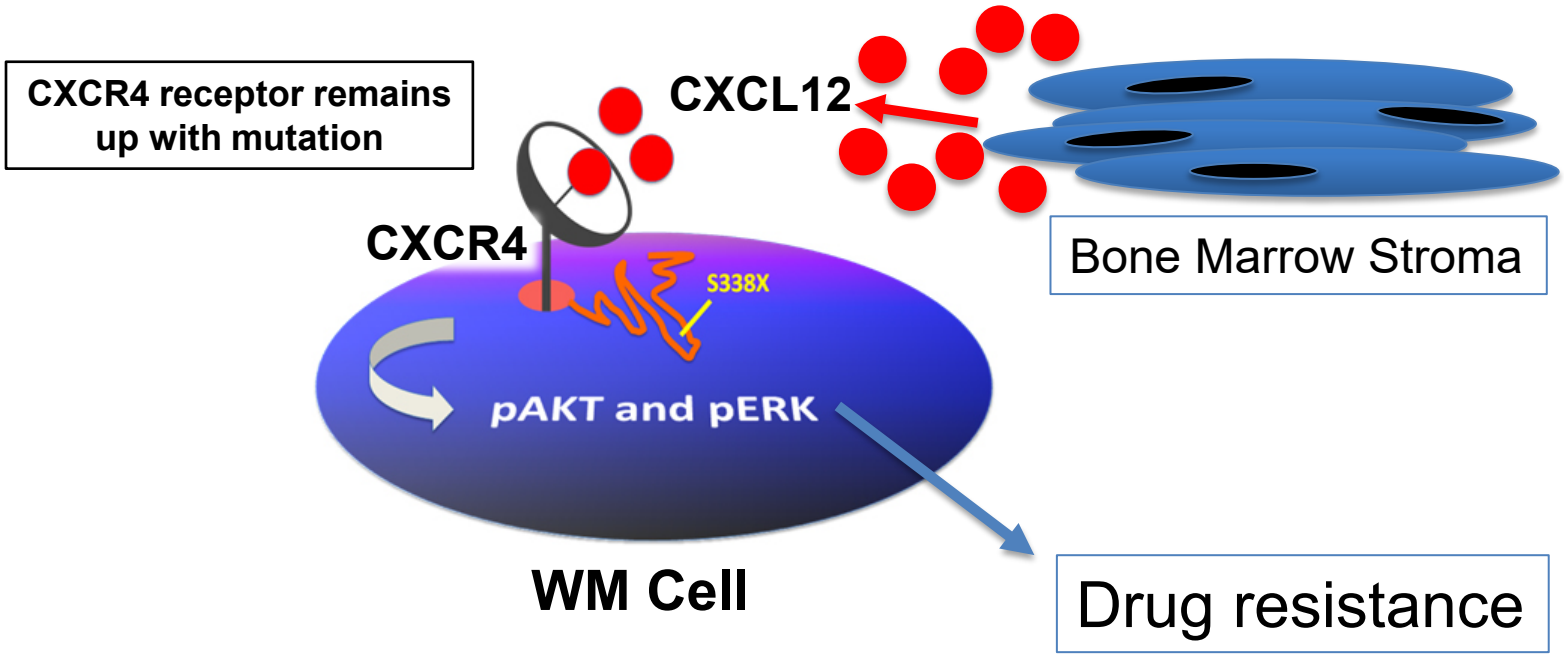
Yang et al, Blood 2013 122(7):1222-32;
Yang et al, Blood 2016 127(25):3237-52
Munshi and Yang et al, BCJ 2020

BTK-inhibitors

95-97% of WM patients have mutations in MYD88

Mutated CXCR4 permits ongoing pro-survival signaling by CXCL12

30-40% of WM patients have mutations in CXCR4



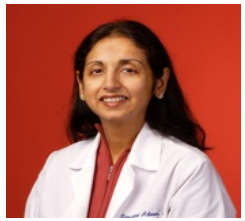
Cao et al, Br J Haematol. 2015 Mar;168(5):701-7; Roccarro et al, Blood. 2014 Jun 26;123(26):4120-31

Multicenter study of Ibrutinib in Relapsed/Refractory WM (>1 prior therapy)

DANA-FARBER CANCER INSTITUTE

Opened May 2012

S Treon PI



R Advani

L Palomba

Screening

Registration

420 mg po qD Ibrutinib

Progressive Disease (PD) or Unacceptable Toxicity

Stop Ibrutinib

Event Monitoring

Stable Disease or Response Continue

Event Monitoring

✔ **MYD88, CXCR4 Mutation Status**

ClinicalTrials.gov Identifier: NCT01614821

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

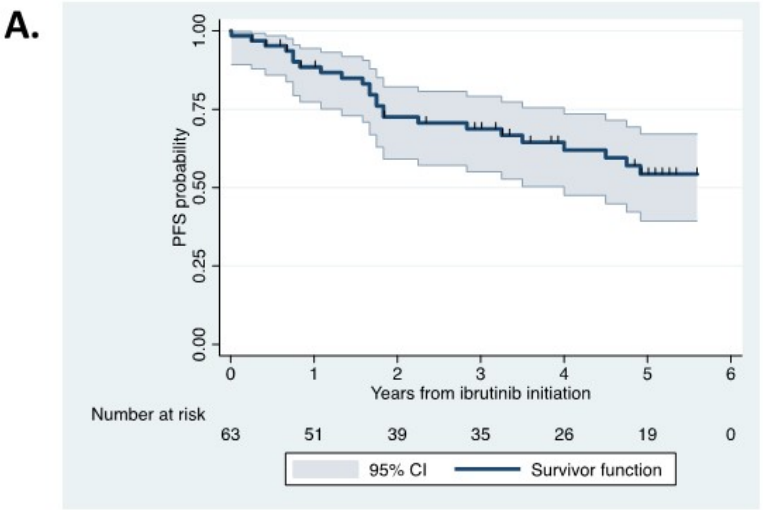
	All Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	MYD88^{WT} CXCR4^{WT}	P-value
N=	63	36	22	4	N/A
Overall Response Rate-no. (%)	90.5%	100%	86.4%	50%	<0.01
Major Response Rate-no. (%)	**79.4%**	**97.2%**	**68.2%**	**0%**	**<0.0001**
Categorical responses					
Minor responses-no. (%)	11.1%	2.8%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

Updated from Treon et al, NEJM 2015

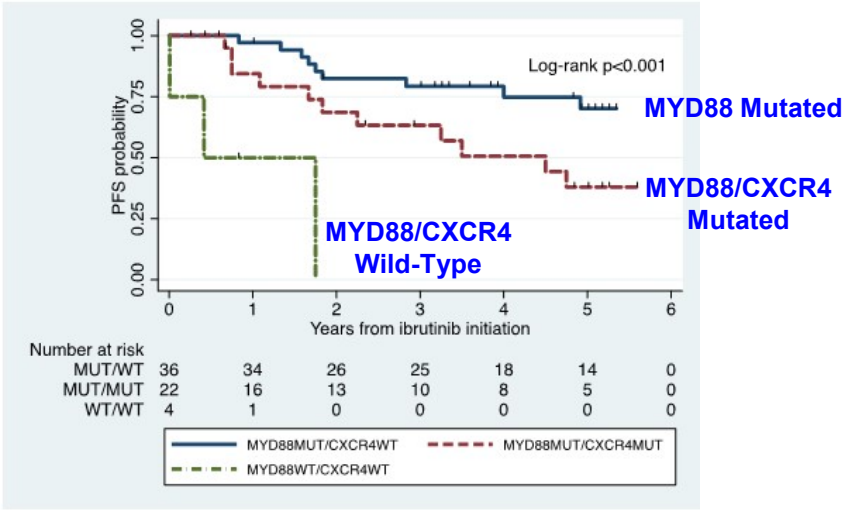
Ibrutinib in Previously Treated WM: Updated PFS

All patients



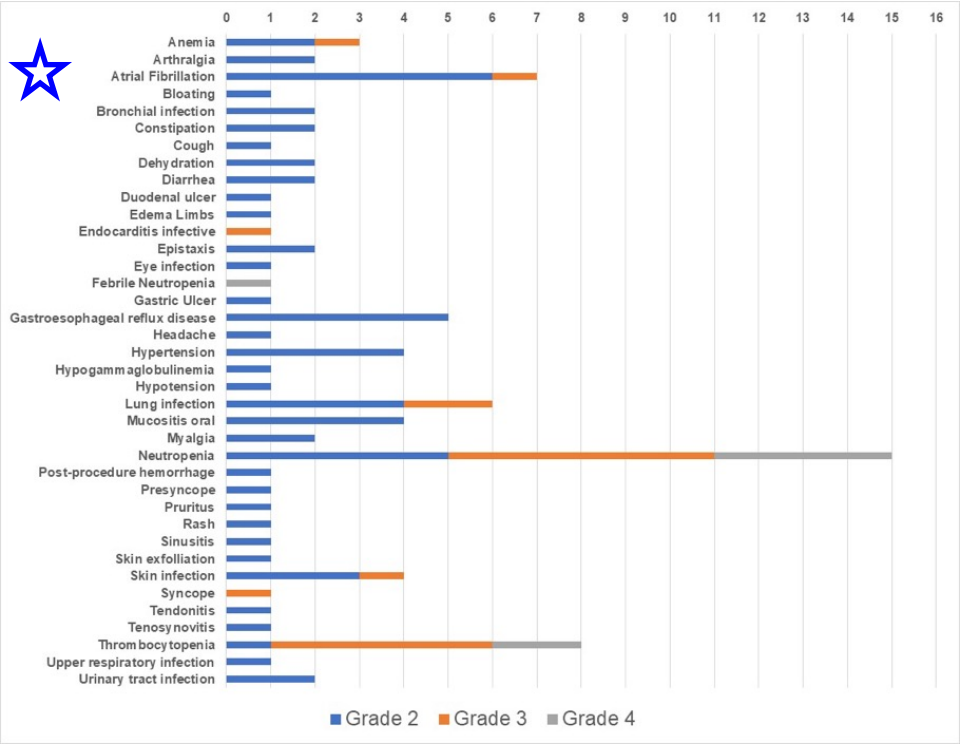
5 year PFS: 54%
5 year OS: 87%

MYD88 and CXCR4 Mutation Status



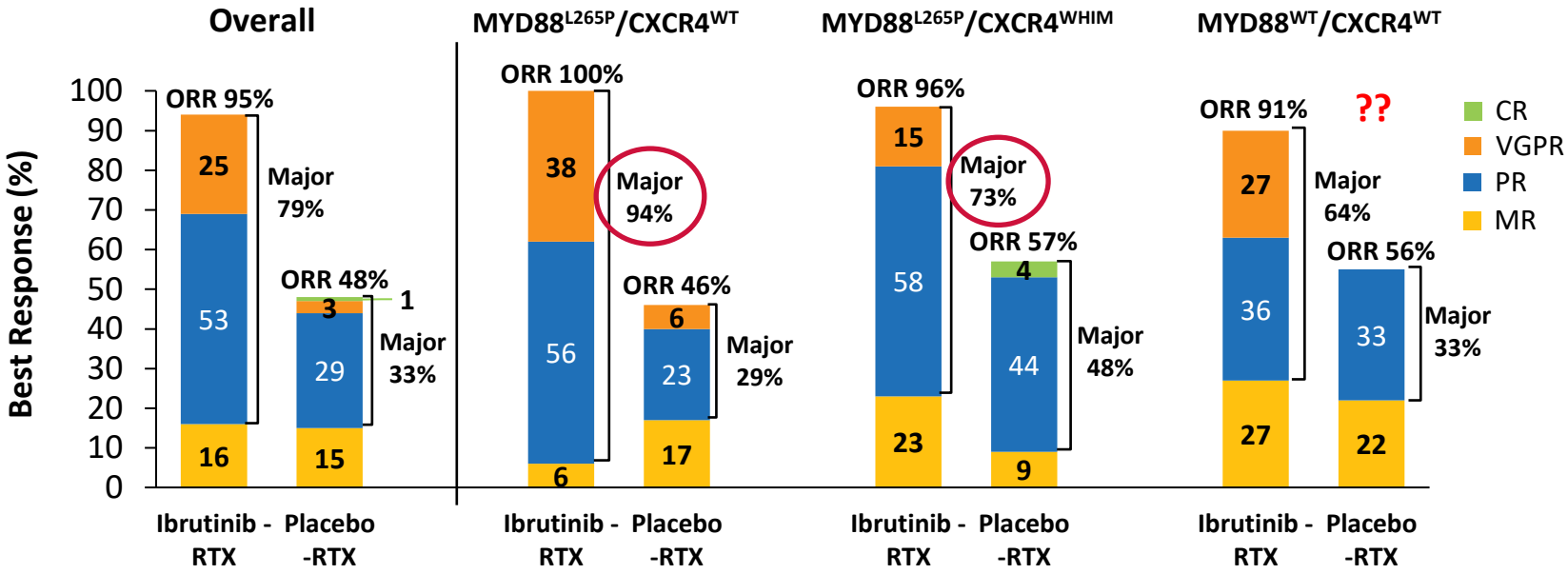
Updated from Treon et al, NEJM 2015

Long Term Toxicity Findings (grade ≥2)



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

Responses in Innovate AB Study: Update

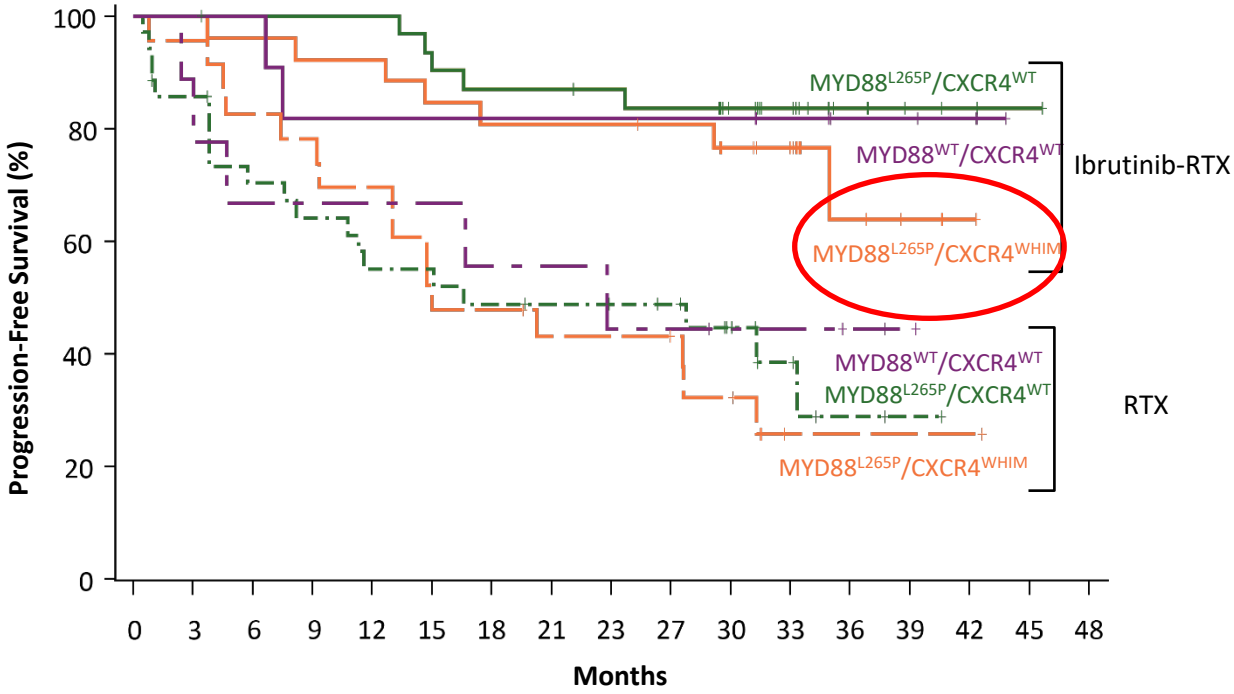


[a]Following modified 6th IWWM Response Criteria (NCCN 2014); required two consecutive assessments.

Median time to ≥PR, months (range)	2 (1–28)	6 (2–26)	2 (1–28)	5 (2–17)	3 (1–19)	11 (4–18)	6 (1–17)	6 (5–26)
Median time to ≥MR, months (range)	1 (1–18)	3 (1–24)	1 (1–18)	3 (1–24)	1 (1–11)	3 (1–8)	2 (1-17)	3 (2–17)

Buske et al., ASH 2018; abstract 149 (oral presentation)

Progression-Free Survival Benefit: Impact of MYD88/CXCR4 Genotype



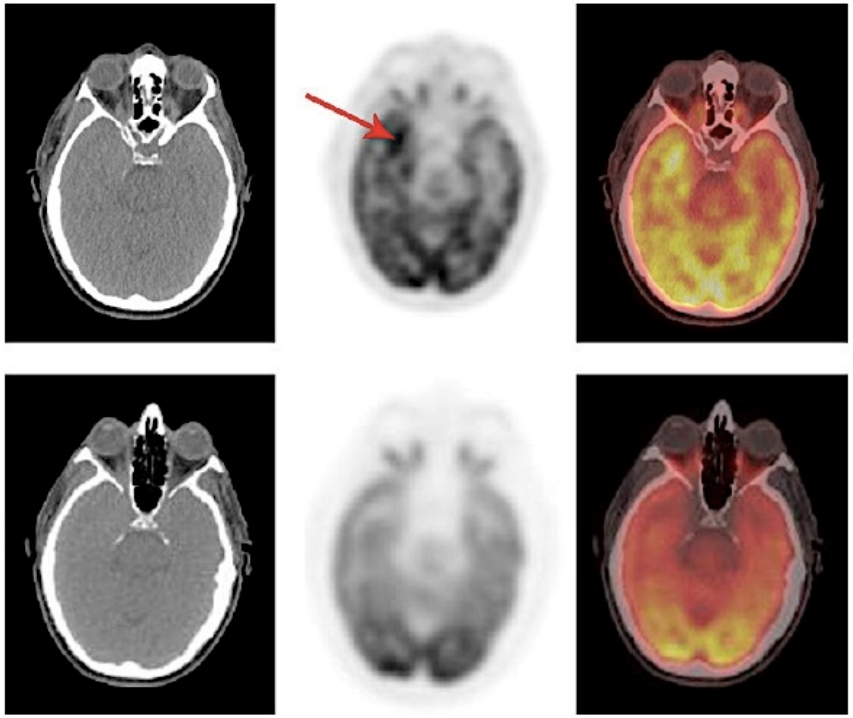
- **Improved PFS with ibrutinib**
- **36-month PFS rates**
  - **MYD88^{L265P}/CXCR4^{WT}: 84% vs 29%**
  - **MYD88^{L265P}/CXCR4^{WHIM}: 64% vs 26%**
  - **MYD88^{WT}/CXCR4^{WT}: 82% vs 44%**

Buske et al., ASH 2018; abstract 149 (oral presentation)

Ibrutinib induced response in a WM patient with Bing Neel Syndrome

Pre-treatment

Post-treatment

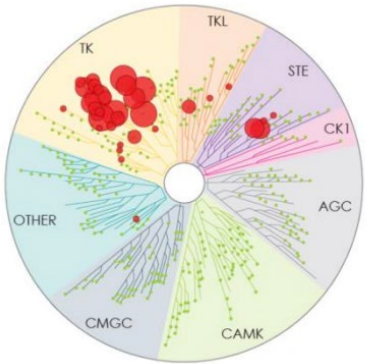


560 mg po one a day

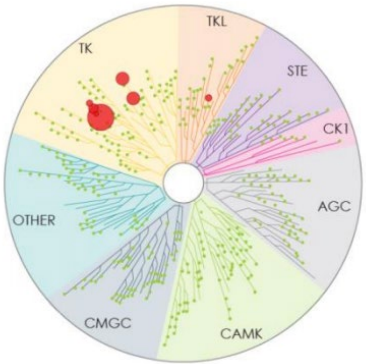
Study Day	Time post-dose (h)	Ibrutinib (nM)		
		CSF	Plasma	%CSF/Plasma
Day 1	0	BLQ	BLQ	NA
	2	34	1133	3·0
1 Month	3	16	463	3·5
4 Months	2·5	7	318	2·2

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

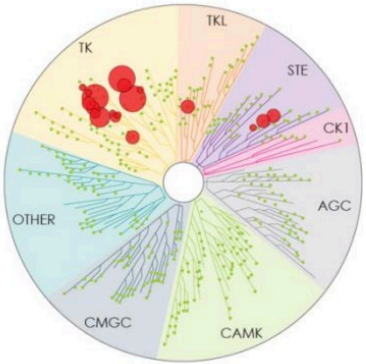
Covalent BTK-inhibitors in WM (Cys481)



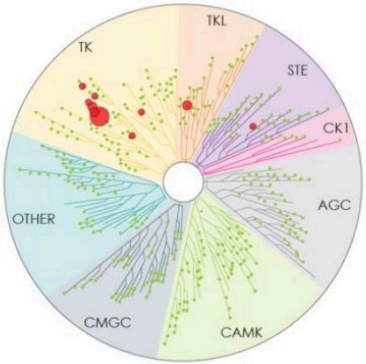
Ibrutinib



Acalabrutinib



Zanubrutinib



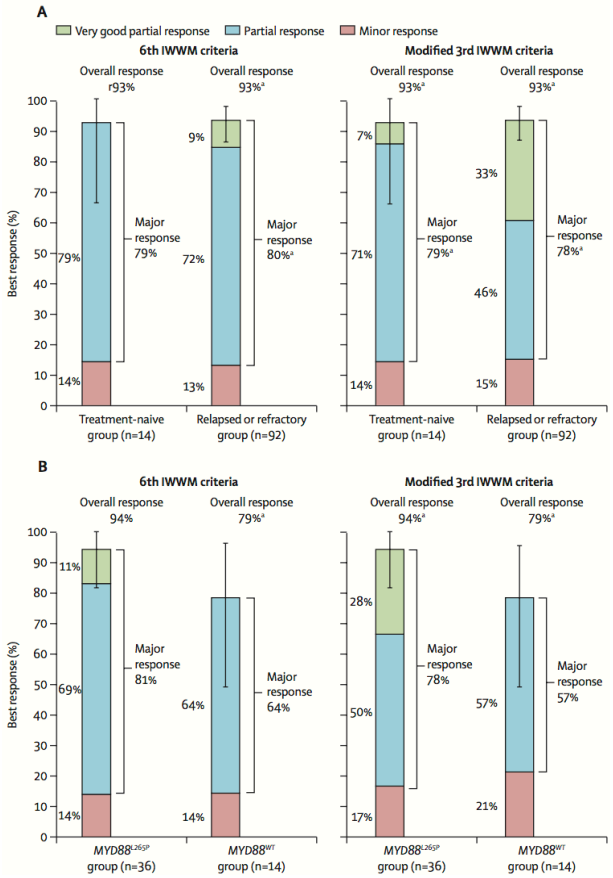
Tirabrutinib

	IC_{50}/EC_{50} (nM)				
	acalabrutinib	ibrutinib	spebrutinib	zanubrutinib	tirabrutinib
BTK	5.1 ± 1.0	1.5 ± 0.2	2.3 ± 0.5	0.5 ± 0.0	5.6 ± 1.0
TEC	126 ± 11	10 ± 12	16 ± 4	44 ± 19	77 ± 7
ITK	>1000	4.9 ± 1.2	24 ± 2	50 ± 5	>1000
TXK	368 ± 141	2.0 ± 0.3	9.1 ± 2.7	2.2 ± 0.6	116 ± 35
BMX	46 ± 12	0.8 ± 0.1	1.6 ± 0.4	1.4 ± 0.4	4.3 ± 0.4
EGFR	>1000	5.3 ± 1.3	199 ± 35	21 ± 1	>1000
ERBB2	~1000	6.4 ± 1.8	>1000	88 ± 26	>1000
ERBB4	16 ± 5	3.4 ± 1.4	49 ± 12	6.9 ± 0.6	991 ± 274
BLK	>1000	0.1 ± 0.0	131 ± 27	2.5 ± 0.4	1133 ± 767
JAK3	>1000	32 ± 15	5.4 ± 1.1	1377 ± 218	>1000
hPBMC	2.9 ± 0.2	0.6 ± 0.0	7.4 ± 0.7	0.9 ± 0.3	6.2 ± 1.9
hWB	9.2 ± 4.4	5.8 ± 3.0	140 ± 85	2.4 ± 0.4	not assessed

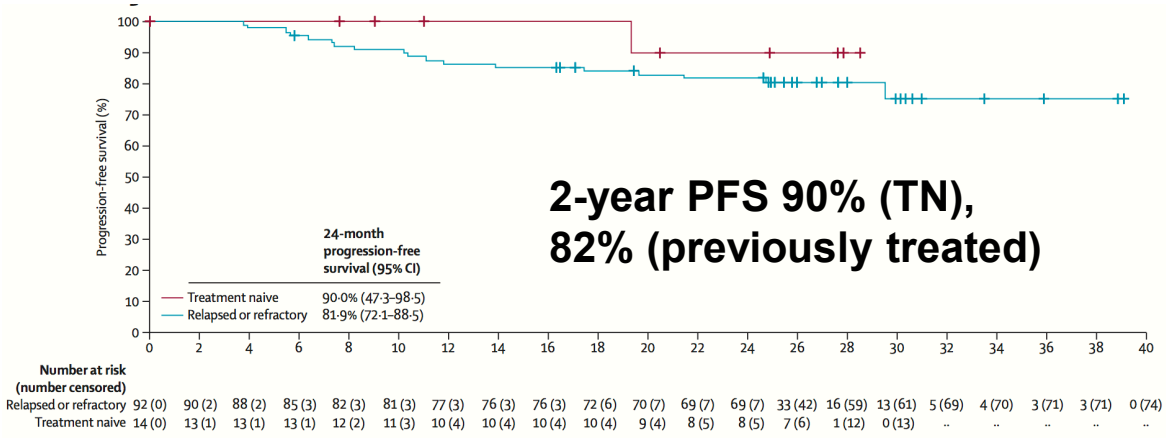
BLK, B lymphocyte kinase; BMX, bone marrow tyrosine kinase gene in chromosome X; ERBB2, erb-b2 receptor tyrosine kinase; ERBB4, erb-b4 receptor tyrosine kinase; ITK, interleukin-2-inducible T-cell kinase; JAK3, Janus kinase 3; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TXK, T and X cell expressed kinase.

Kaptein et al, ASH 2018; Abstract 1871.

Acalabrutinib in Treatment Naïve and Previously Treated WM



100 mg po BID ☆



2-year PFS 90% (TN), 82% (previously treated)

Median follow-up: 27.4 months

Owen et al., Lancet Hematology 2020

Acalabrutinib in Treatment Naïve and Previously Treated WM

	Grade 1–2	Grade 3	Grade 4
Headache	41 (39%)	0	0
Diarrhoea	33 (31%)	2 (2%)	0
Contusion	31 (29%)	0	0
Dizziness	27 (25%)	0	0
Fatigue	22 (21%)	2 (2%)	0
Nausea	22 (21%)	2 (2%)	0
Upper respiratory tract infection	23 (22%)	0	0
Constipation	22 (21%)	0	0
Arthralgia	20 (19%)	1 (1%)	0
Back pain	18 (17%)	1 (1%)	0
Cough	18 (17%)	0	0
Lower respiratory tract infection	13 (12%)	5 (5%)	0
Neutropenia	1 (1%)	6 (6%)	11 (10%)
Pyrexia	17 (16%)	1 (1%)	0
Vomiting	17 (16%)	1 (1%)	0
Decreased appetite	14 (13%)	2 (2%)	0
Rash	16 (15%)	0	0
Pain in extremity	12 (11%)	1 (1%)	0
Epistaxis	11 (10%)	1 (1%)	0
Sinusitis	12 (11%)	0	0
Skin lesion	12 (11%)	0	0
Dyspepsia	11 (10%)	0	0
Dyspnoea	10 (9%)	1 (1%)	0
Erythema	11 (10%)	0	0
Increased tendency to bruise	11 (10%)	0	0

Afib: 5%

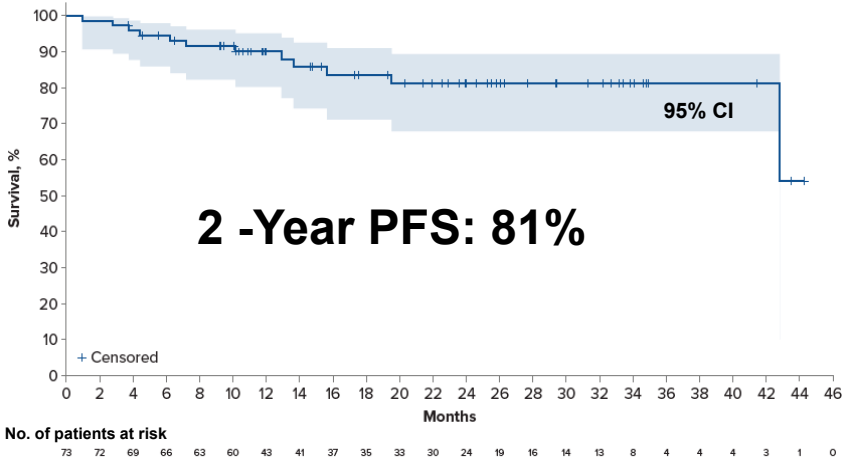
No atrial brillation event led to acalabrutinib withholding or discontinuation.

Median follow-up: 27.4 months

Zanubrutinib in WM: Phase 2 data in TN and previously treated pts.

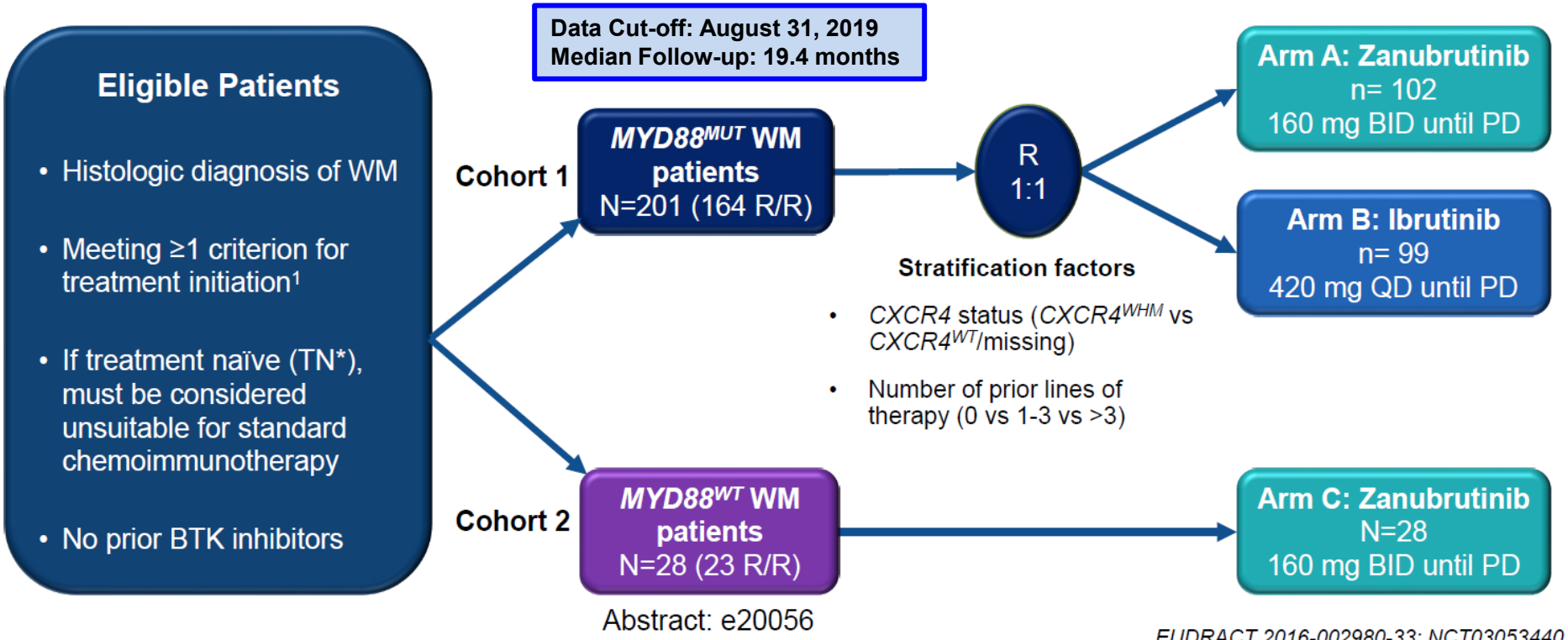
Best Response in WM	zanubrutinib		
	Overall	TN	RR
Evaluable for efficacy, n	73	24	49
Median Follow-up	23.9 mo	12.3 mo	24.8 mo
Response Criteria	Mod. 6th IWWM (IgM decreases only, and not extramedullary disease)		
Median Prior Lines of Therapy		0	2 (1-8)
ORR	92%	96%	90%
MRR	82%	87%	78%
CR/VGPR[1]	42%	29%	49%
PR	40%	58%	31%

Progression Free Survival (PFS)



Trotman et al, EHA 2019

ASPEN Study Design: Zanubrutinib vs Ibrutinib in *MYD88*^{MUT} WM



BID, twice daily; BTK, Bruton tyrosine kinase; 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.
*Up to 20% of the overall population.

1. Dimopoulos MA, et al. *Blood*. 2014;124:1404-1411.

Tam et al, ASCO 2020

ASPEN Study Objectives

Primary Objective

- To compare the efficacy of zanubrutinib vs ibrutinib
  - Primary endpoint was CR + VGPR rate in patients with activating mutations (*MYD88*^{MUT}) WM

Secondary Objectives

- To further compare the efficacy, clinical benefit, and anti-lymphoma effects of zanubrutinib vs ibrutinib
- To evaluate safety and tolerability of zanubrutinib versus ibrutinib as measured by the incidence, timing, and severity of TEAEs according to NCI-CTCAE (version 4.03)

Exploratory Objectives

- To characterize the PK of zanubrutinib in patients with WM
- To compare QoL by EORTC QLQ-C30 and EQ-5D

AE, adverse event; EORTC QLQ-C30, EORTC Quality of Life Questionnaire - Core Questionnaire; EQ-5D, EuroQoL-5D; MYD88^{MUT}, myeloid differentiation primary response gene 88 mutant; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PK, pharmacokinetics; QoL, quality of life; TEAE, treatment-emergent AE.

ASPEN: Demographics and Disease Characteristics

Characteristics, n (%)	Overall ITT	
	Ibrutinib (n = 99)	Zanubrutinib (n =102)
Age, years median (range)	70.0 (38, 90)	70.0 (45, 87)
> 65 years	**70 (70.7)**	61 (59.8)
> 75 years	22 (22.2)	**34 (33.3)**
Gender, n (%)		
Male	65 (65.7)	69 (67.6)
Female	34 (34.3)	33 (32.4)
Prior Lines of Therapy, n (%)		
0	18 (18.2)	19 (18.6)
1-3	74 (74.7)	76 (74.5)
>3	7 (7.1)	7 (6.9)
Genotype by central lab*, n (%)		
MYD88^{L265P}/*CXCR4*^{WT}	90 (90.9)	91 (89.2)
MYD88^{L265P}/*CXCR4*^{WHIM}	8 (8.1)	11 (10.8)
IPSS WM[1]		
Low	13 (13.1)	17 (16.7)
Intermediate	42 (42.4)	38 (37.3)
High	44 (44.4)	47 (46.1)
Hemoglobin ≤ 110 g/L	53 (53.5)	**67 (65.7)**

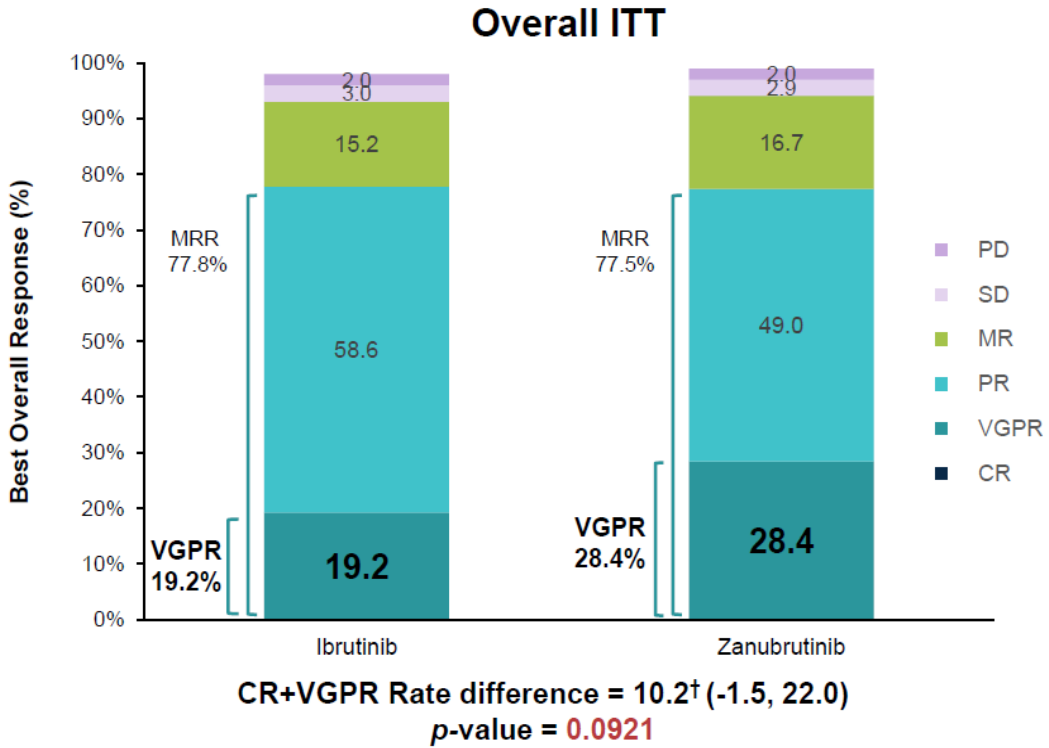
CXCR4, C-X-C Motif Chemokine Receptor 4; ITT, intention-to-treat; IPSS WM, International Prognostic Scoring System for Waldenström macroglobulinemia; MYD88, myeloid differentiation primary response gene 88; NGS, next-generation sequencing.

*"Wildtype-blocking PCR" for *MYD88* and Sanger sequencing for *CXCR4* using bone marrow aspirates. One patient had local NGS testing results of *MYD88 L265P/ CXCR4* Unknown.

1. Morel et al, *Blood*. 2009;113:4163-4170.

ASPEN: Efficacy – Response by IRC (Data cutoff: 31 August 2019)

- Superiority in CR+VGPR rate compared to ibrutinib in relapsed/refractory population (primary study hypothesis) was not significant*



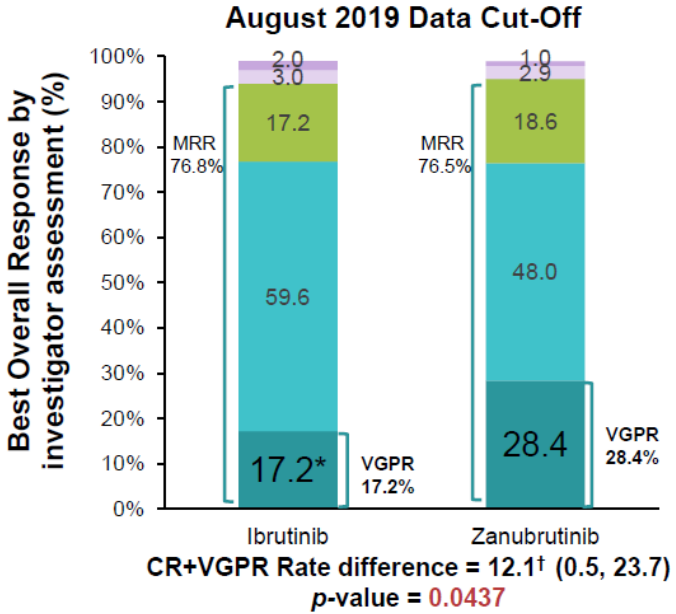
CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MRR, major response rate; MR, minor response; ; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good PR.
Overall concordance between Independent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

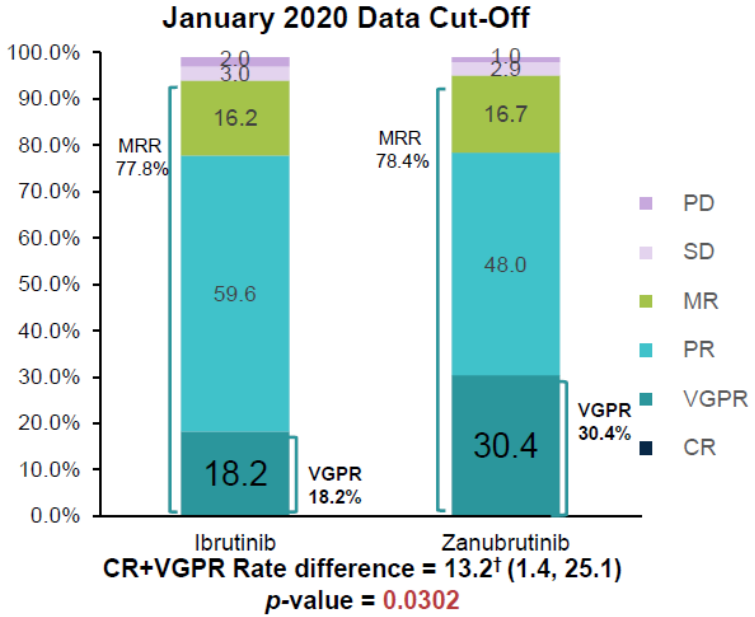
Tam et al, ASCO 2020

ASPEN: Secondary Efficacy Endpoints

Assessment of Response According to Investigator and IgM Analysis

Investigator-Assessed Response





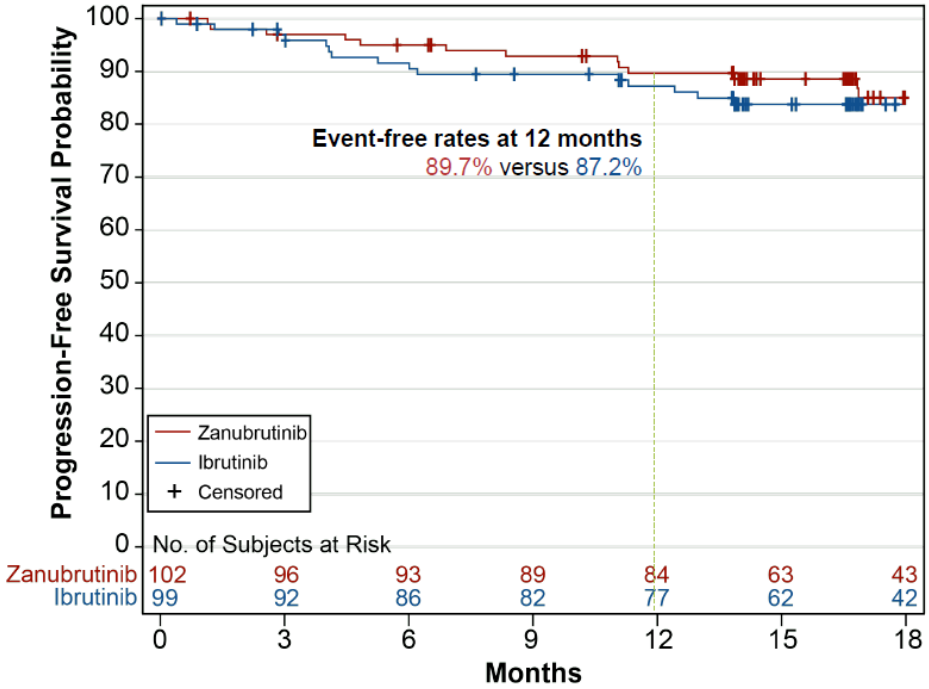
IgM Reduction

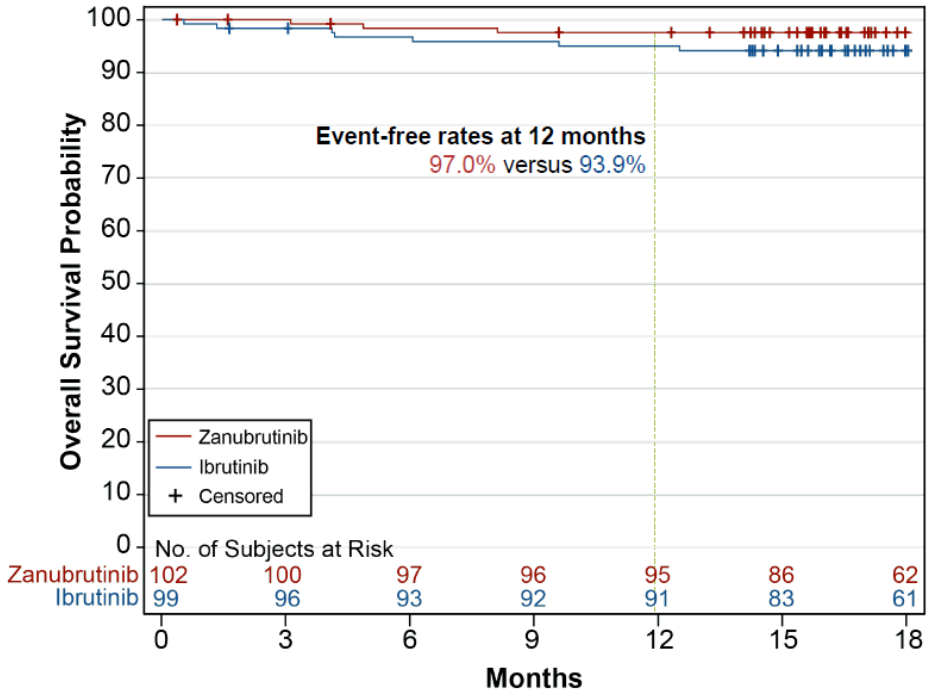
- Area-under-the-curve (AUC) for IgM reduction over time was significantly greater for zanubrutinib vs ibrutinib (p=0.037)

CR, complete response; EMD, extramedullary disease; IgM, Immunoglobulin M; IRC, independent review committee; MRR, major response rate; MR, minor response; ; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SPEP, serum protein electrophoresis; VGPR, very good PR.
*Excluded two patients with VGPR by IRC: MR (EMD present) and PR (IgM assessment by local SPEP M-protein)
†Adjusted for stratification factors and age group. *P* value is for descriptive purpose only.

Tam et al, ASCO 2020

ASPEN: Progression-Free and Overall Survival in ITT population





IRC, independent review committee; VGPR, very good partial response.
Disease progression determined by IRC.

Tam et al, ASCO 2020

ASPEN: AE Categories of Interest (BTKi Class AEs)

AE *Categories*, n (%) (pooled terms)	All Grades		Grade ≥ 3	
	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Ibrutinib (n = 98)	Zanubrutinib (n = 101)
Atrial fibrillation/ flutter†	**15 (15.3)**	2 (2.0)	4 (4.1)	0 (0.0)
Diarrhea (PT)	**31 (31.6)**	21 (20.8)	1 (1.0)	3 (3.0)
Hemorrhage	**58 (59.2)**	49 (48.5)	8 (8.2)	6 (5.9)
Major hemorrhage[a]	9 (9.2)	6 (5.9)	8 (8.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)	**12 (12.2)**	6 (5.9)
Neutropenia[b]†	13 (13.3)	**30 (29.7)**	8 (8.2)	**20 (19.8)**
Infection	66 (67.3)	67 (66.3)	19 (19.4)	18 (17.8)
Second Malignancy	11 (11.2)	12 (11.9)	1 (1.0)	2 (2.0)

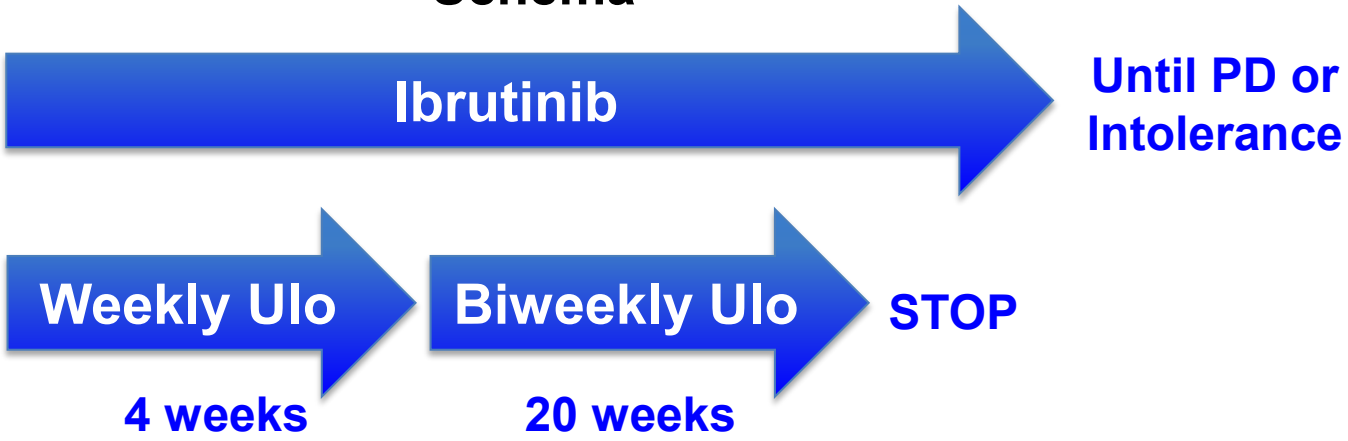
Higher AE rate in bold blue with ≥ 10% difference in any grade or ≥ 5% difference in grade 3 or above.
No tumor lysis syndrome was reported. Opportunistic infection ibrutinib (n=2), zanubrutinib (n=1).
AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.
[a]Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.
[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
† Descriptive two-sided *P*-value < 0.05.

Tam et al, ASCO 2020

Strategies to Enhance BTK Inhibitors

Phase I/II Trial of Ulocuplumab and Ibrutinib in CXCR4 mutated patients with symptomatic WM

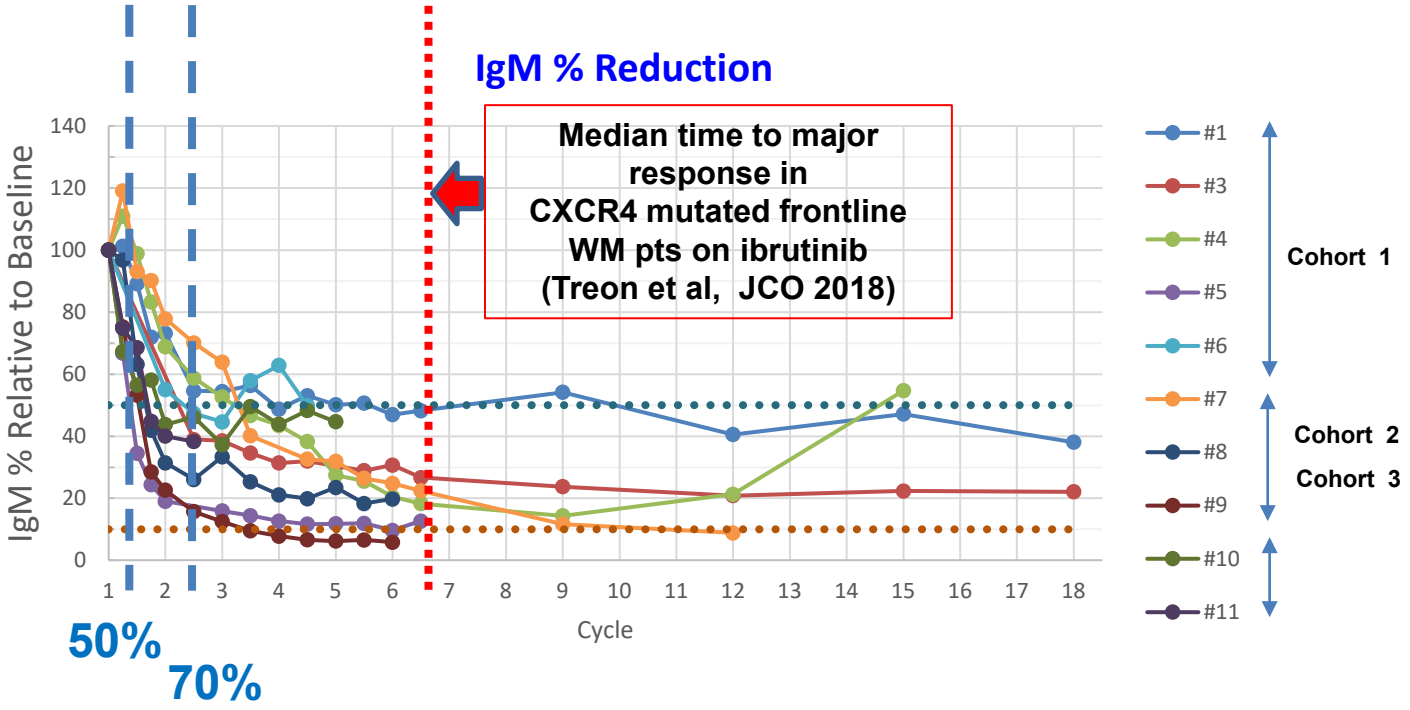
Schema



Dose Level	Ibrutinib	Ulocuplumab Cycle 1	Ulocuplumab Cycles 2-6
Level 1 –Starting dose	420mg PO DQ	400 mg weekly	800 mg every other week
Level 2	420mg PO DQ	800 mg weekly	1200 mg every other week
Level 3	420mg PO DQ	800 mg weekly	1600 mg every other week

ClinicalTrials.gov Identifier: NCT03225716

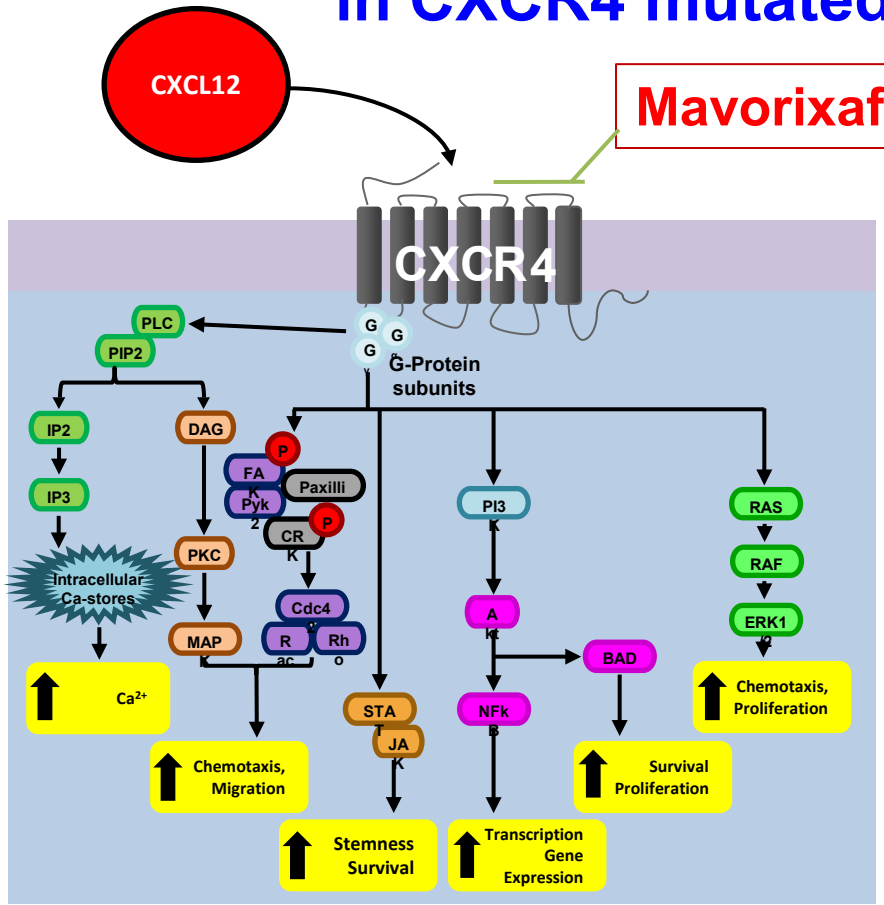
Responses to Ibrutinib and CXCR4 Inhibitor Ulucuplomab in Symptomatic CXCR4 mutated WM patients

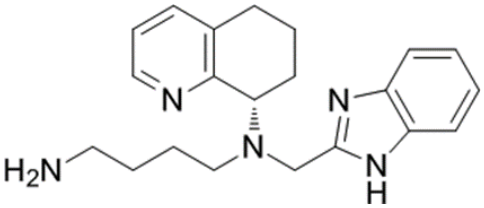


Median prior therapies: 0 (range 0-1)

DFCI Unpublished Data

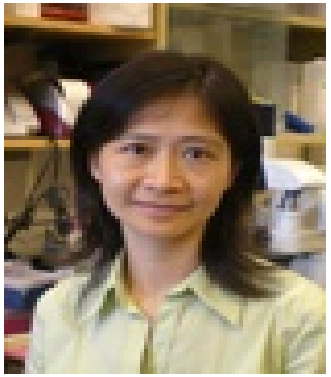
Mavorixafor in combination with ibrutinib in CXCR4 mutated WM



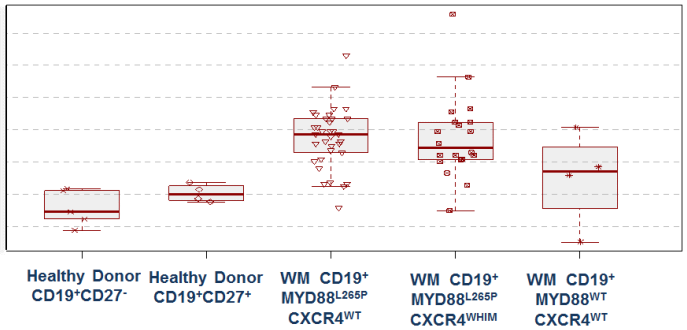


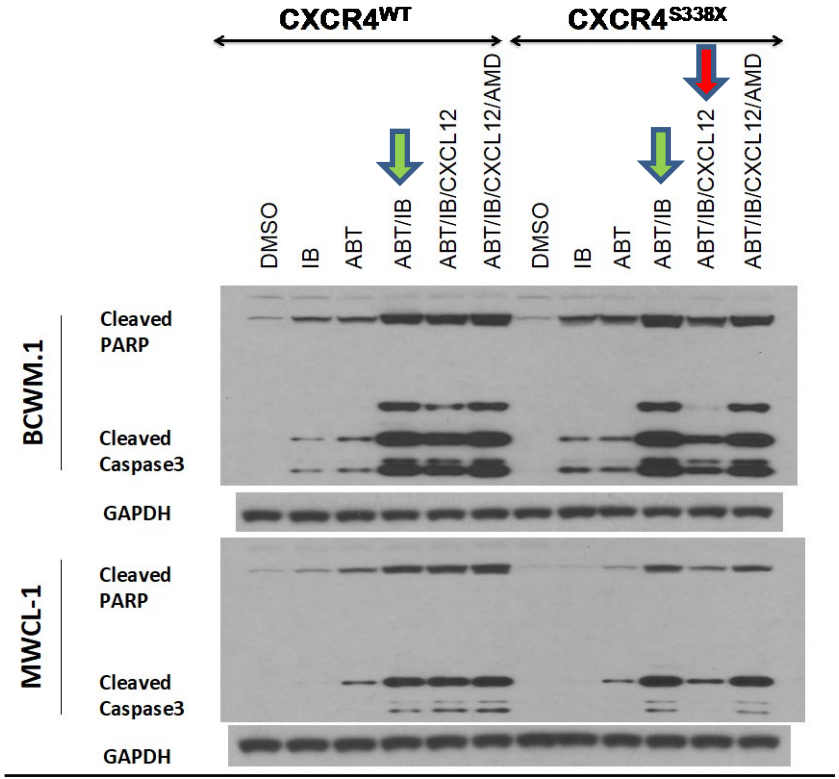
- Non-competitive, allosteric, small molecule antagonist of CXCR4
- Orally Bioavailable; mean $t_{1/2}$ of ~23 hours
- High volume of distribution

Venetoclax (ABT-199) augments ibrutinib induced apoptosis

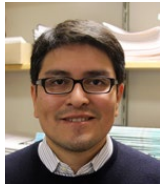


Higher BCL2 levels in MYD88 mutated WM





Cao et al, BJH 2015; 168(5): 701–7



J. Castillo

Phase II Study of Venetoclax in Previously Treated WM

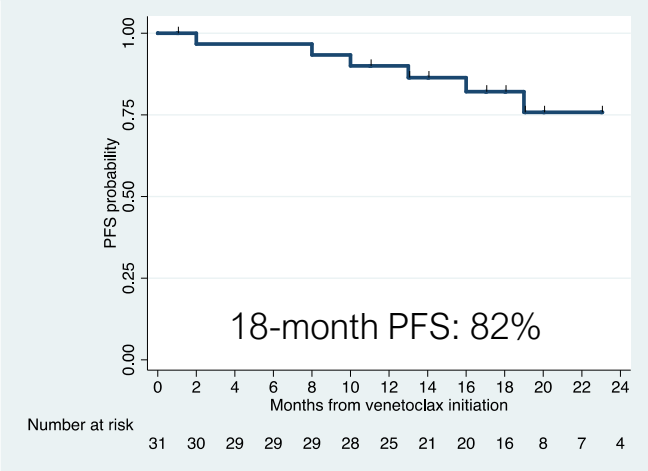
Multicenter Study: Cornell (John Allan, Rick Furman); City of Hope (Tanya Siddiqi)

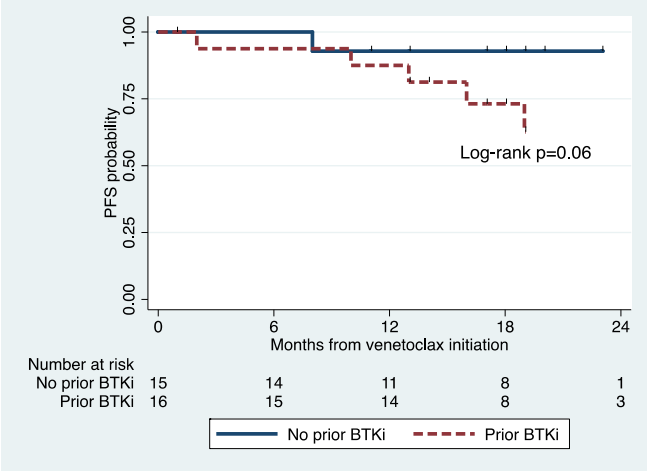
	All patients	Prior BTK inhibitor		CXCR4 mutations	
Response	n=31	No (n=15)	Yes (n=16)	No (n=14)	Yes (n=17)
Overall (≥Minor)	27 (90%)	14 (93%)	13 (81%)	13 (93%)	14 (82%)
Major (≥Partial)	25 (83%)	13 (87%)	12 (75%)	12 (86%)	13 (76%)
Very good partial	6 (20%)	5 (33%)	1 (6%)	4 (29%)	2 (12%)
Partial	19 (63%)	8 (54%)	11 (69%)	8 (54%)	11 (69%)
Minor	2 (7%)	1 (6%)	1 (6%)	1 (6%)	1 (6%)
Time to response	1.9 months	1.1 months	3.8 months	1.3 months	2.1 months

BM involvement
At baseline, median 40% (4-95%).
At best response, median 3% (0-50%).

Castillo et al, 17th IMW 2019

Phase II Study of Venetoclax in Previously Treated WM





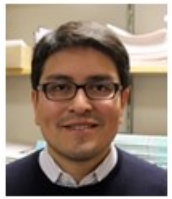
Median 18 months. Range 1-30 months.

Castillo et al, 17th IMW 2019

Ibrutinib and Venetoclax in Treatment Naïve WM

24 months

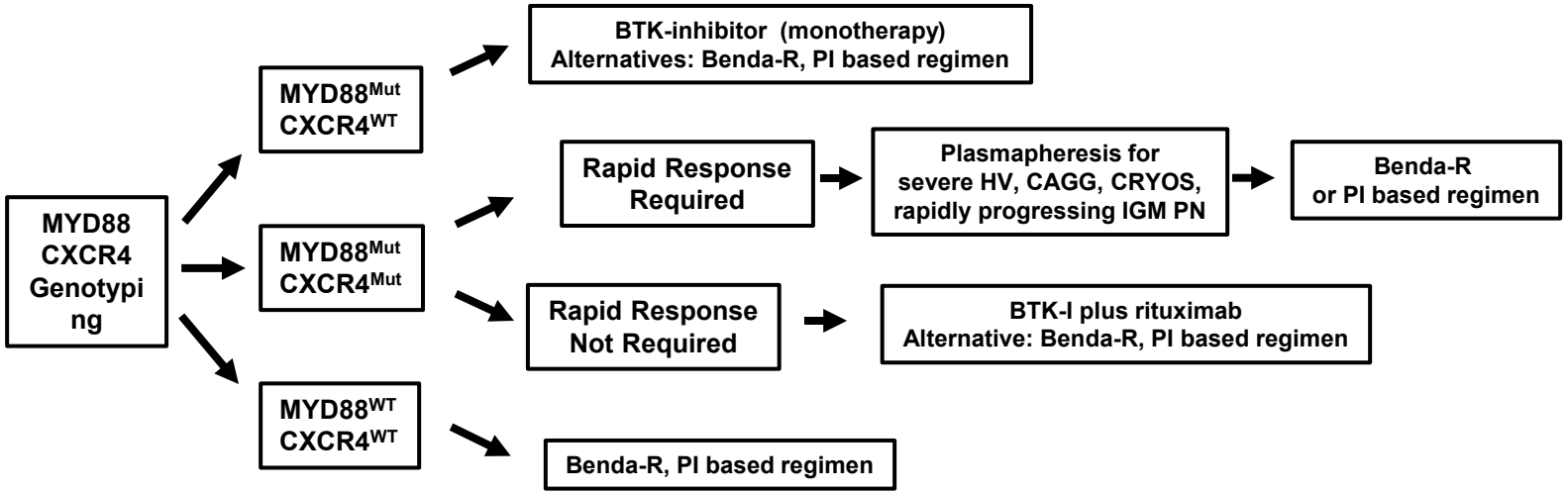
Ibrutinib 420 mg/day x 4 weeks	Ibrutinib 420 mg/day Add Venetoclax 100 mg/day week 5 200 mg/day week 6 400 mg/day weeks 7,8	Ibrutinib 420 mg/day And Venetoclax 400 mg/day	Observation
4 weeks	4 weeks	22 months	Follow to PD or off study



Jorge Castillo, PI (DFCI)

Personal communication

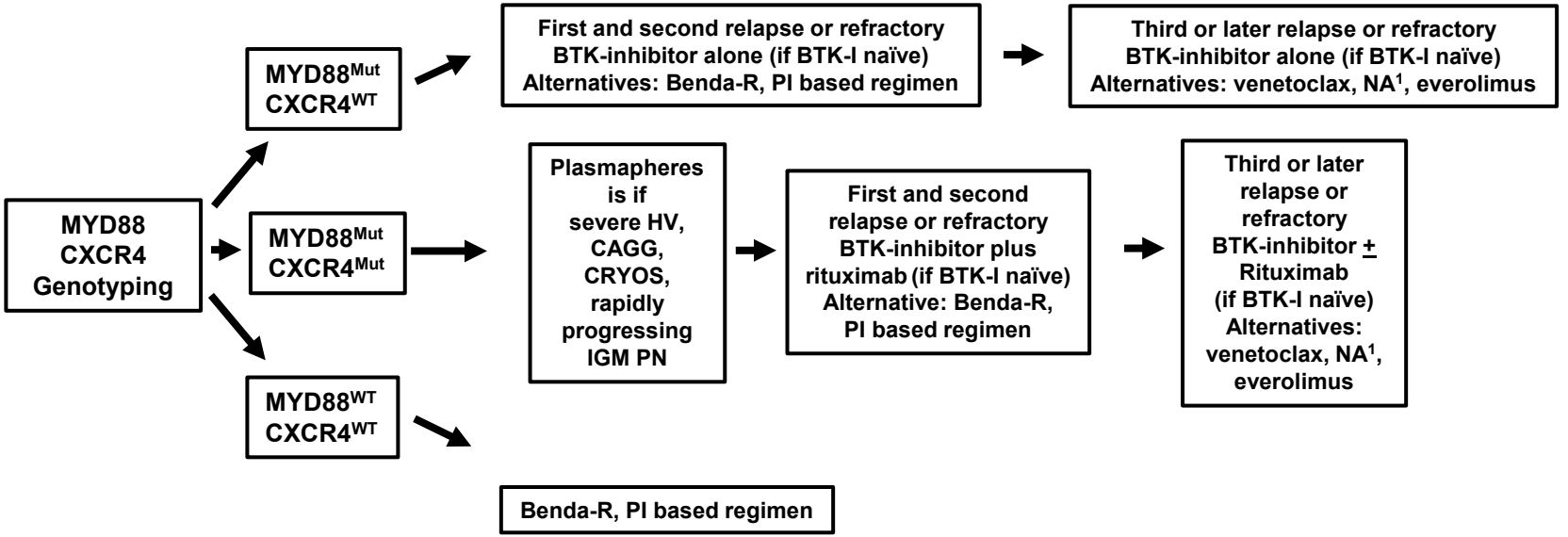
Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM



- Rituximab should be held for serum IgM ≥4,000 mg/dL
- Benda-R for bulky adenopathy or extramedullary disease.
- PI 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 patients responding to rituximab based regimens.

Treon et al, JCO 2020

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.

Treon et al, JCO 2020