

Treatment Landscape of Waldenström's Macroglobulinemia



Steve Treon MD, PhD, FACP, FRCP
Professor of Medicine
Bing Center for Waldenström's Macroglobulinemia
Dana Farber Cancer Institute
Harvard Medical School

Disclosures – Steven Treon

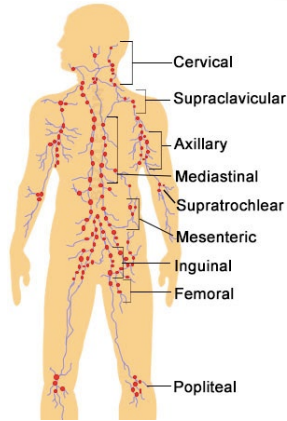
Research Support/P.I.	Janssen, Pharmacyclics, BMS
Consultant	Janssen, Pharmacyclics, Beigene, BMS

This presentation may contain unregistered products or indications of investigational drugs, please check the drug compendium or consult the company

Manifestations of WM Disease



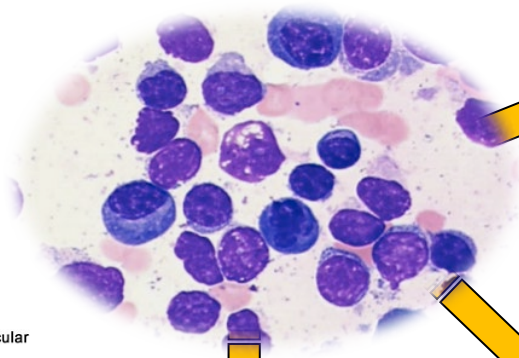
Bing Neel Syndrome



≤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 Agglutininemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (22%)
Amyloidosis (10-15%)



Hepcidin
↓Fe Anemia

NCCN Guidelines for Initiation of Therapy in WM

- Hb \leq 10 g/dL on basis of disease
- PLT $<$ 100,000 mm³ on basis of disease
- Symptomatic hyperviscosity
- Moderate/severe peripheral neuropathy
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloid.

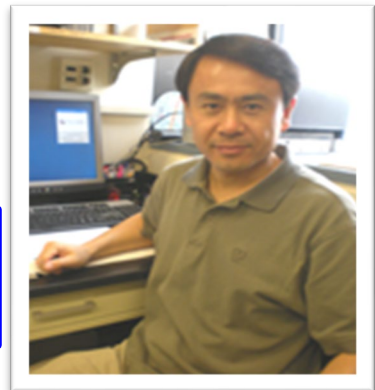
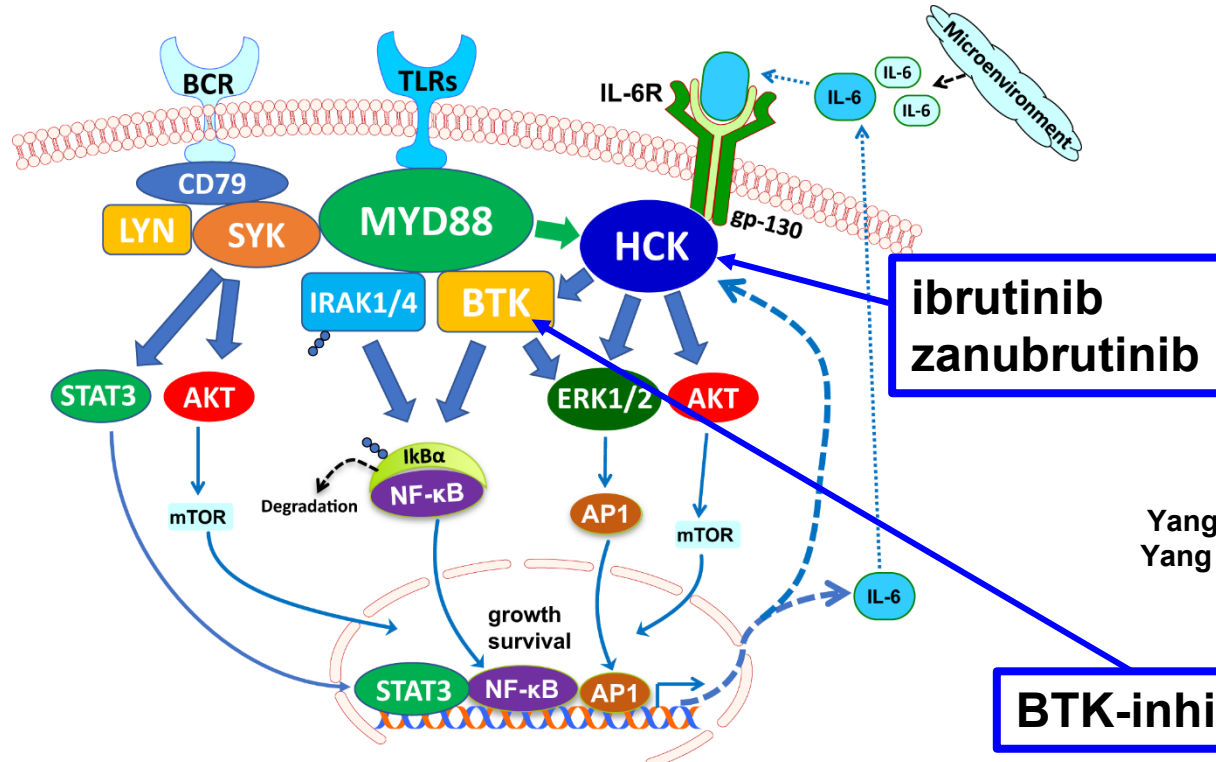
Primary Therapy of WM with Rituximab

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

WM–centric toxicities with commonly used therapies

Agent	WM Toxicities
Rituximab	<ul style="list-style-type: none">• IgM flare (40-60%)-> Hyperviscosity crisis, Aggravation of IgM related PN, CAGG, Cryos.• Hypogammaglobulinemia-> infections, IVIG• Intolerance (10-15%)
Fludarabine	<ul style="list-style-type: none">• Hypogammaglobulinemia-> infections, IVIG• Transformation, AML/MDS (15%)
Bendamustine	<ul style="list-style-type: none">• Prolonged neutropenia, thrombocytopenia (especially after fludarabine)• AML/MDS (5-8%)
Bortezomib	<ul style="list-style-type: none">• Grade 2+3 Peripheral neuropathy (60-70%); High discontinuation (20-60%)

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



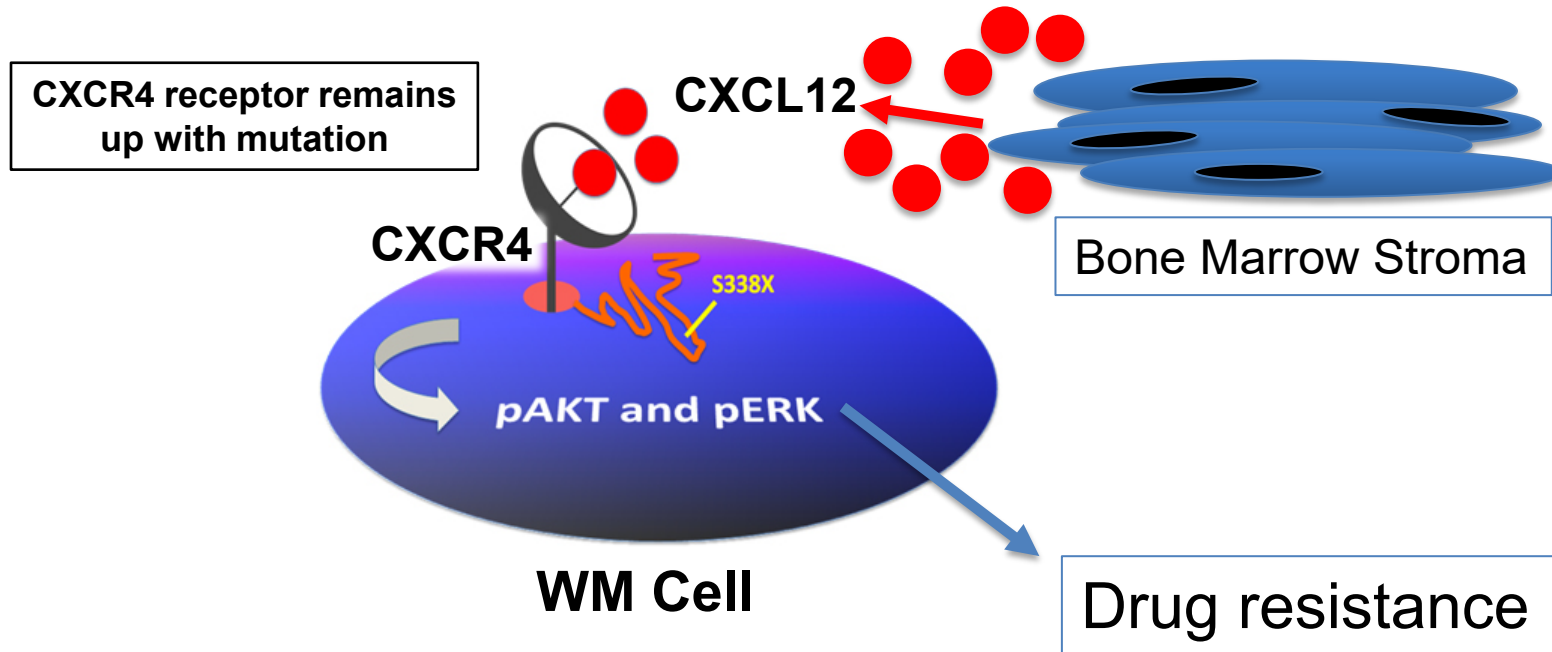
Yang et al, Blood 2013 122(7):1222-32;
 Yang et al, Blood 2016 127(25):3237-52
 Munshi and Yang et al, BCJ 2020

BTK-inhibitors

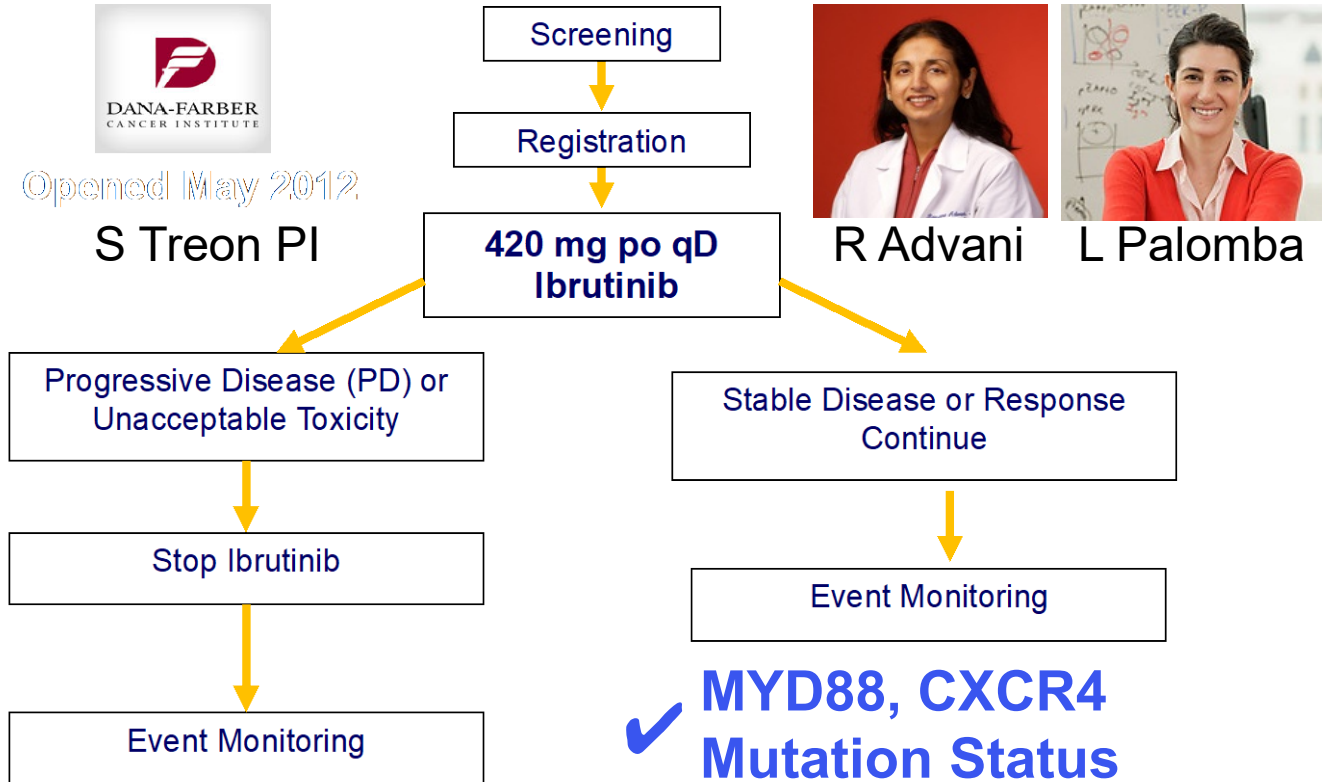
95-97% of WM patients have mutations in MYD88

Mutated CXCR4 permits ongoing pro-survival signaling by CXCL12

30-40% of WM patients have mutations in CXCR4



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



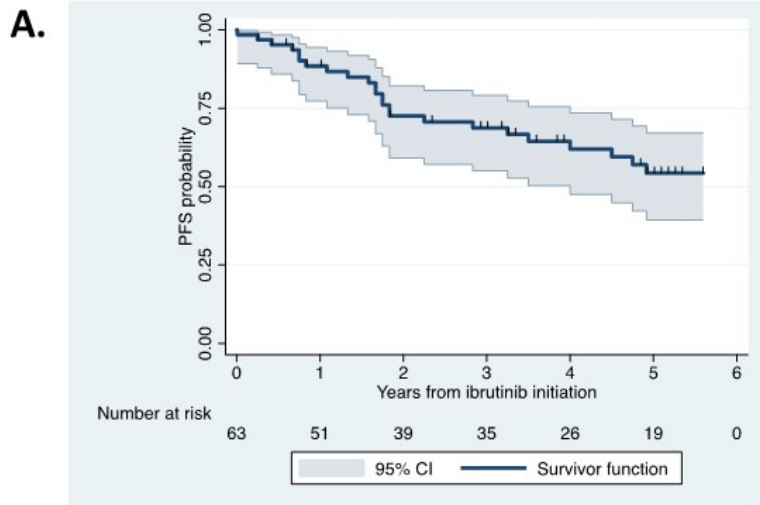
Ibrutinib Activity in Previously Treated WM: Update of the Pivotal Trial (median f/u 59 mos)

	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.

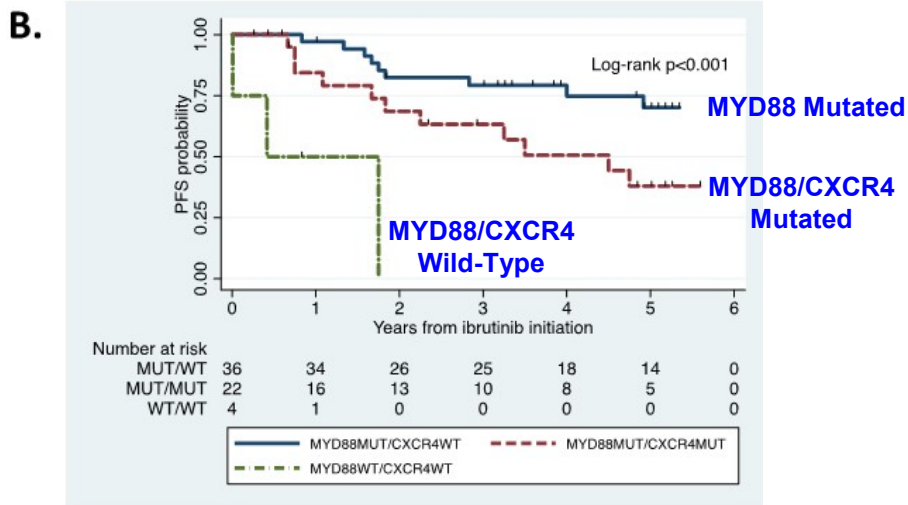
Ibrutinib in Previously Treated WM: Updated PFS

All patients



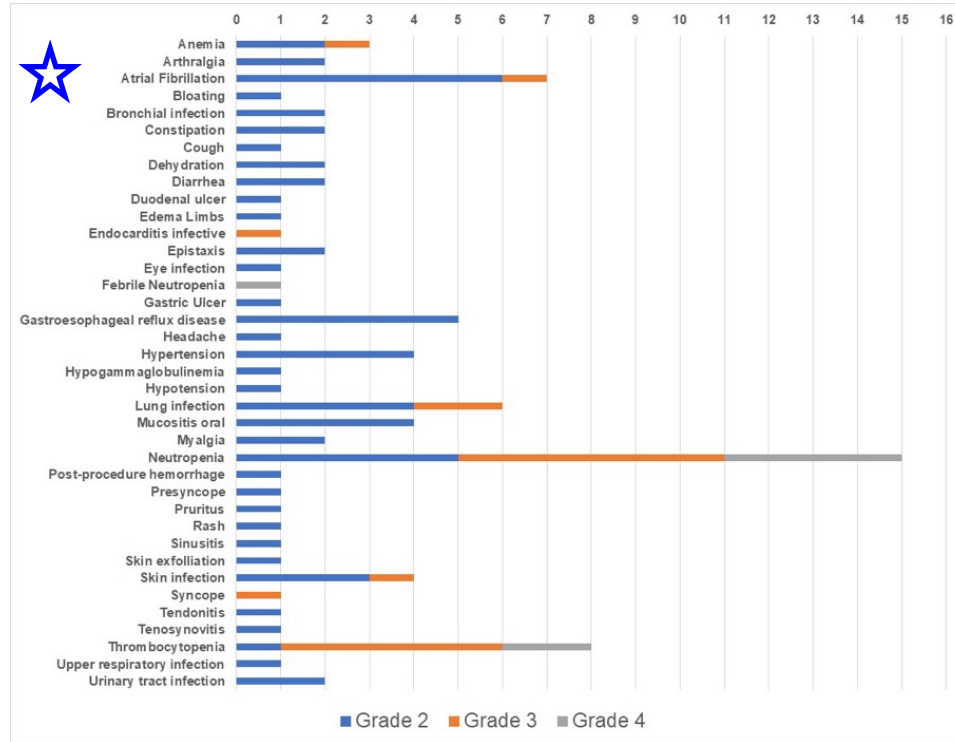
5 year PFS: 54%
5 year OS: 87%

MYD88 and CXCR4 Mutation Status



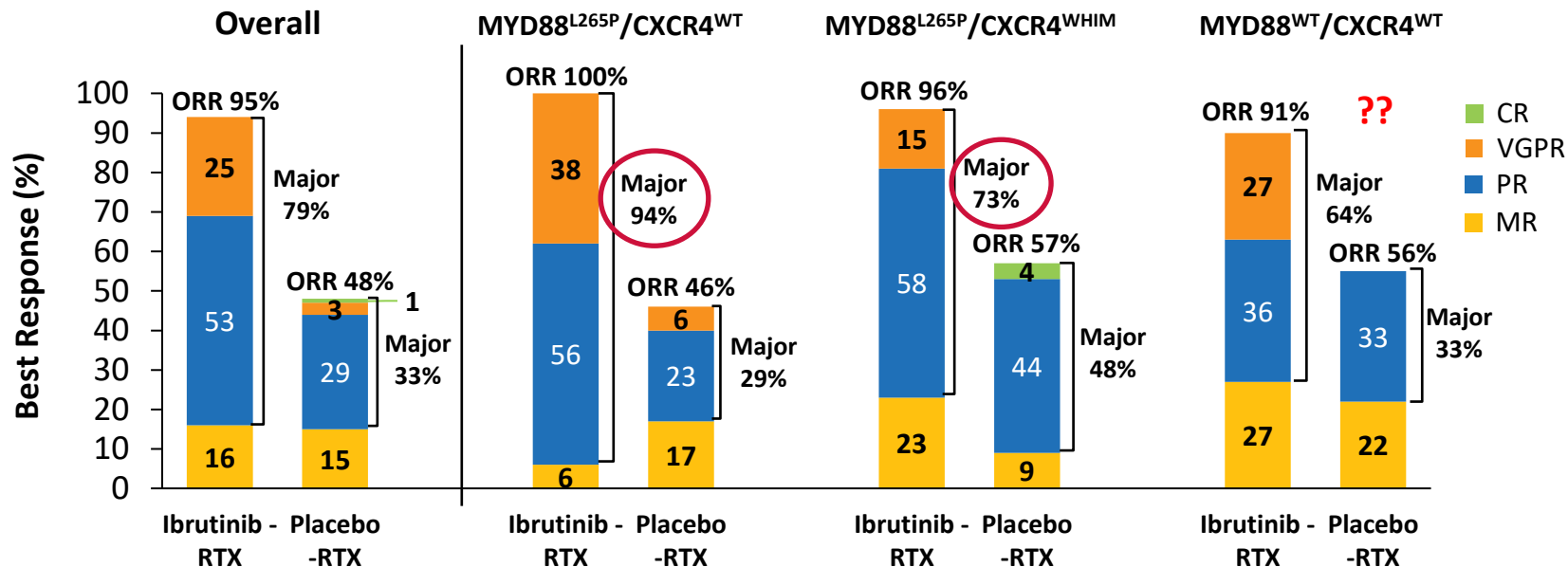
Updated from Treon et al, NEJM 2015

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.

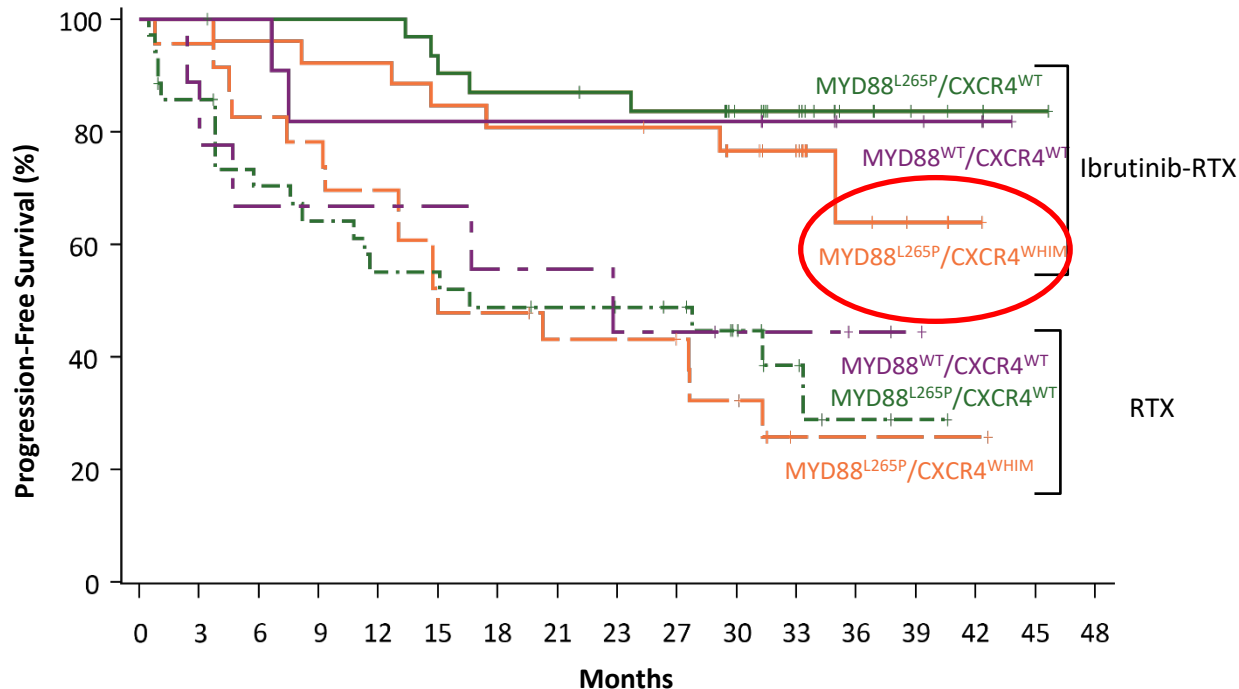
Responses in Innovate AB Study: Update



*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)

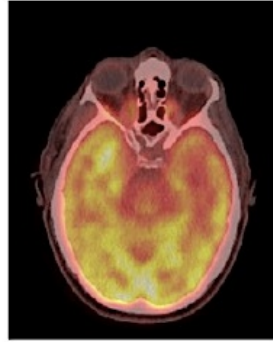
Progression-Free Survival Benefit: Impact of MYD88/CXCR4 Genotype



- 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%

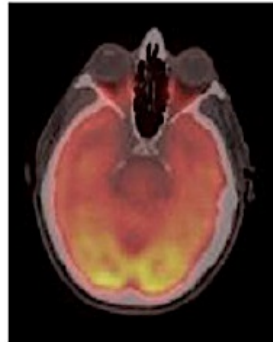
Ibrutinib induced response in a WM patient with Bing Neel Syndrome

Pre-treatment



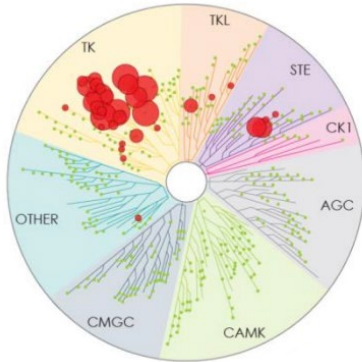
560 mg po one a day

Post-treatment

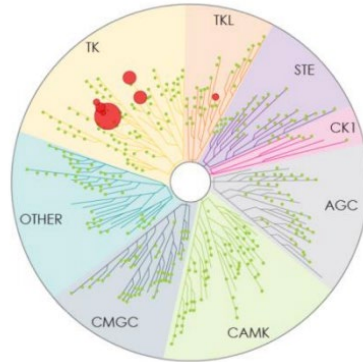


Study Day	Time post-dose (h)	Ibrutinib (nM)		
		CSF	Plasma	%CSF/Plasma
Day 1	0	BLQ	BLQ	NA
	2	34	1133	3.0
1 Month	3	16	463	3.5
4 Months	2.5	7	318	2.2

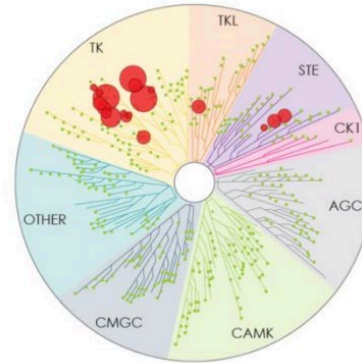
Covalent BTK-inhibitors in WM (Cys481)



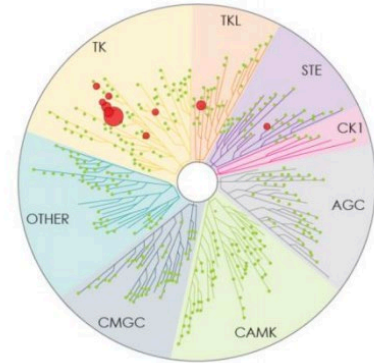
Ibrutinib



Acalabrutinib



Zanubrutinib



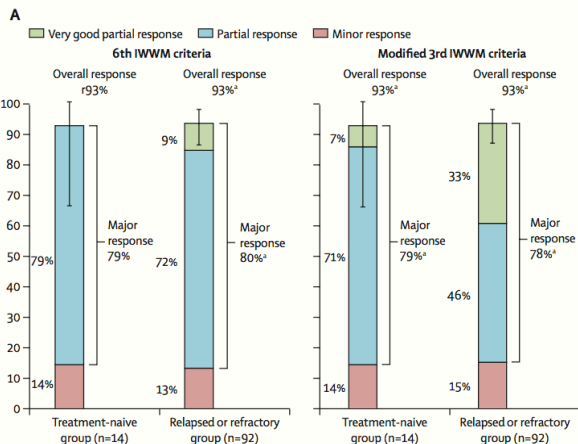
Tirabrutinib

	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
TXX	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
hPBMK	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

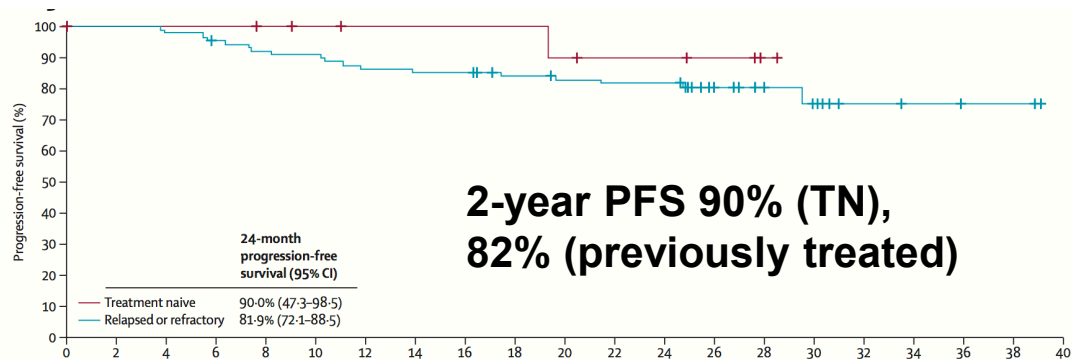
BLK, B lymphocyte kinase; BMX, bone marrow tyrosine kinase gene in chromosome X; ERBB2, erb-b2 receptor tyrosine kinase; ERBB4, erb-b4 receptor tyrosine kinase; ITK, interleukin-2-inducible T-cell kinase; JAK3, Janus kinase 3; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TXX, T and X cell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

Kaptein et al, ASH 2018; Abstract 1871.

Acalabrutinib in Treatment Naïve and Previously Treated WM

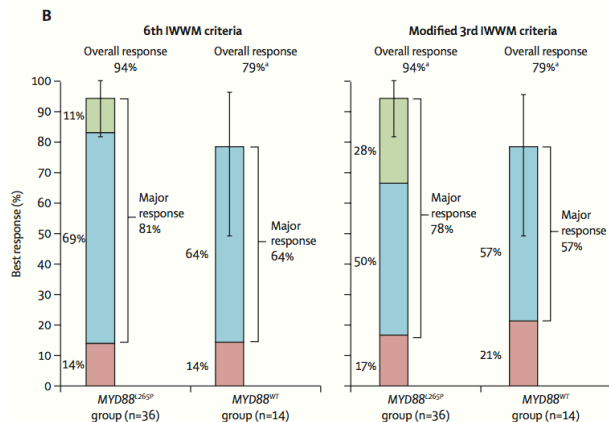


100 mg po BID 



Number at risk (number censored)

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40
Relapsed or refractory	92 (0)	88 (2)	85 (3)	82 (3)	81 (3)	77 (3)	76 (3)	76 (3)	72 (6)	70 (7)	69 (7)	69 (7)	33 (42)	16 (59)	13 (61)	5 (69)	4 (70)	3 (71)	3 (71)	0 (74)	
Treatment naïve	14 (0)	13 (1)	13 (1)	13 (1)	12 (2)	11 (3)	10 (4)	10 (4)	10 (4)	9 (4)	8 (5)	8 (5)	7 (6)	1 (12)	0 (13)						



Median follow-up: 27.4 months

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

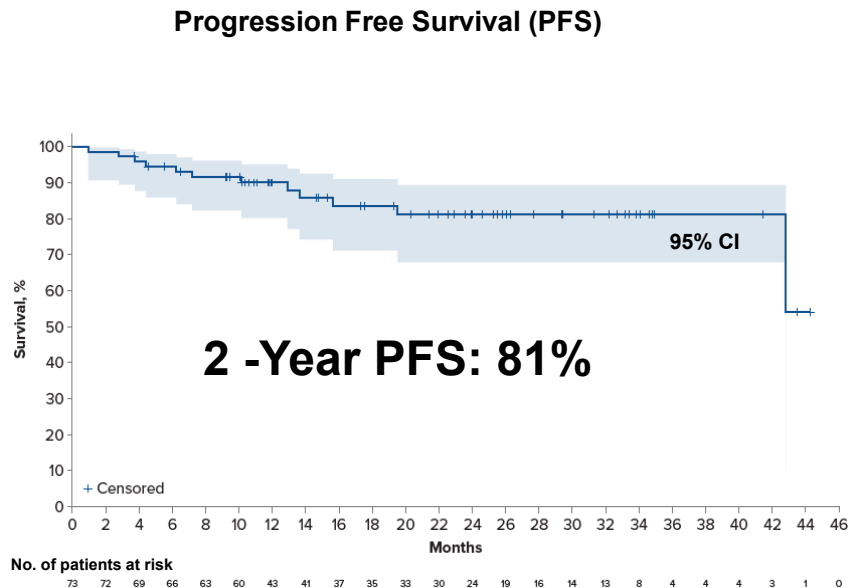
Afib: 5%

No atrial brillation event led to acalabrutinib withholding or discontinuation.

Median follow-up: 27.4 months

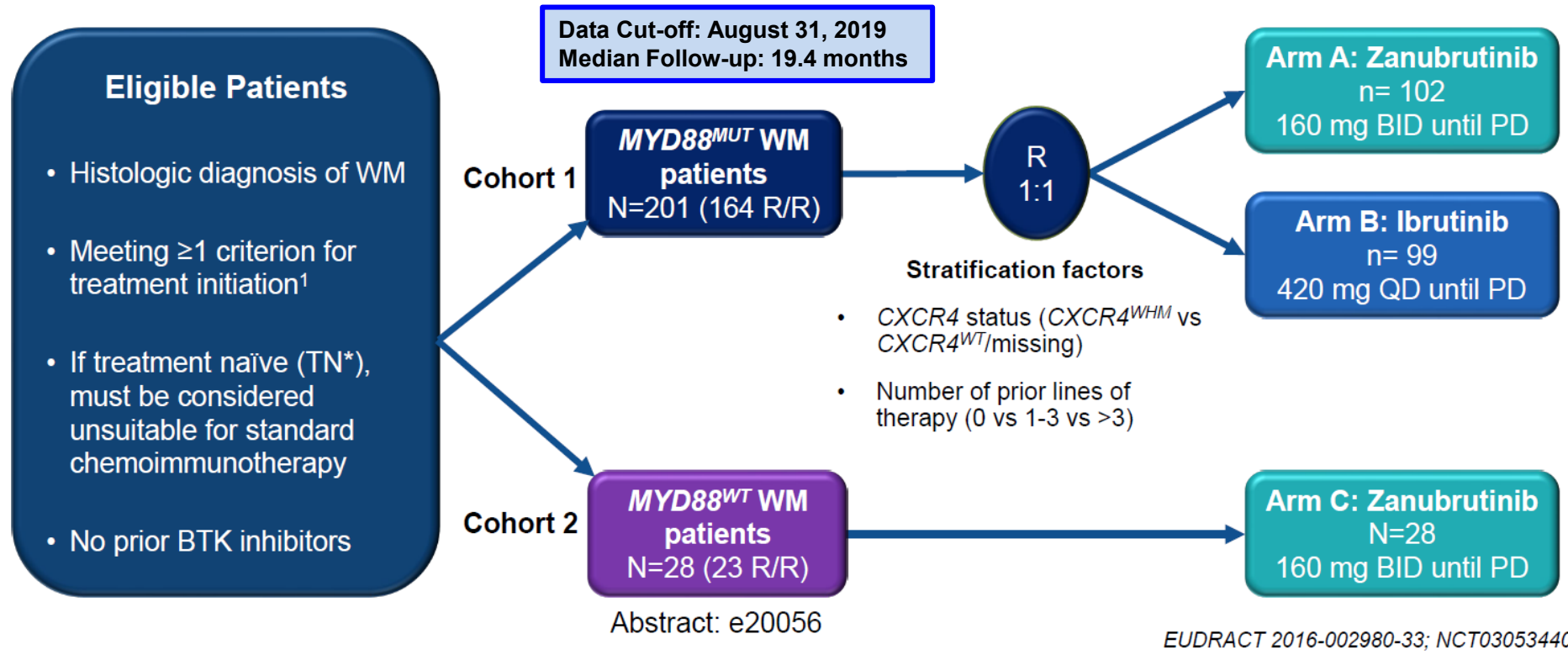
Zanubrutinib in WM: Phase 2 data in TN and previously treated pts.

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. 6 th 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%



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.

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

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)
	70 (70.7)	61 (59.8)
	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 (%)		
<i>MYD88</i> ^{L265P} / <i>CXCR4</i> ^{WT}	90 (90.9)	91 (89.2)
<i>MYD88</i> ^{L265P} / <i>CXCR4</i> ^{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)

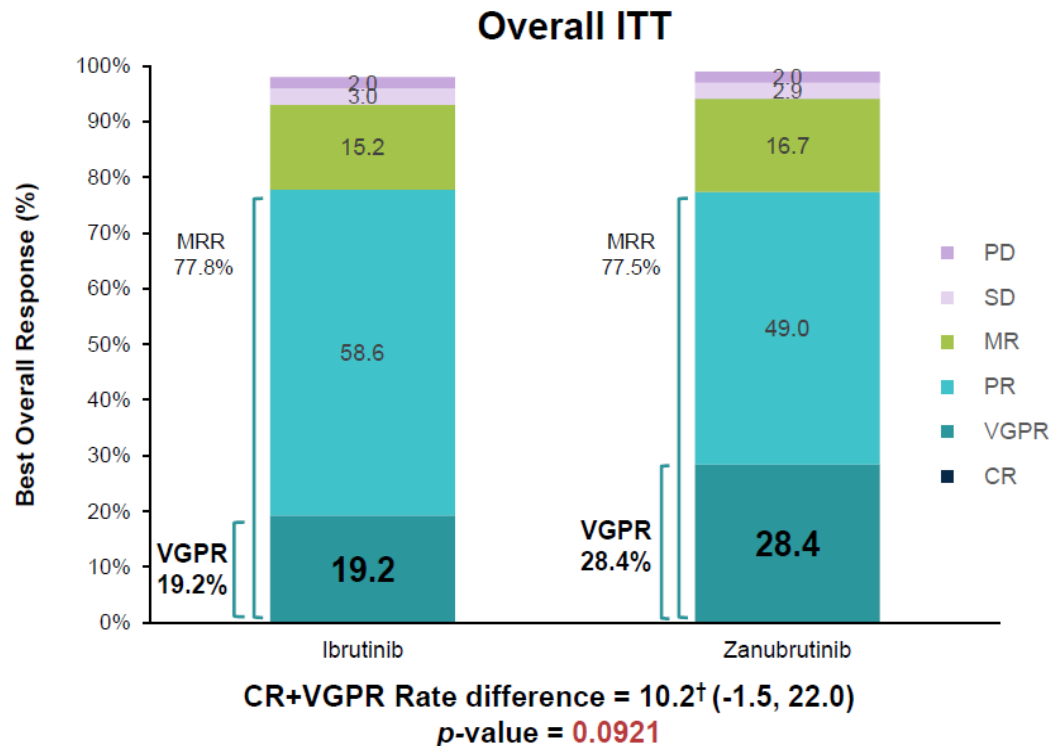
CXCR4, C-X-C Motif Chemokine Receptor 4; ITT, intention-to-treat; IPSS WM, International Prognostic Scoring System for Waldenström macroglobulinemia; *MYD88*, myeloid differentiation primary response gene 88; NGS, next-generation sequencing.

*"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.

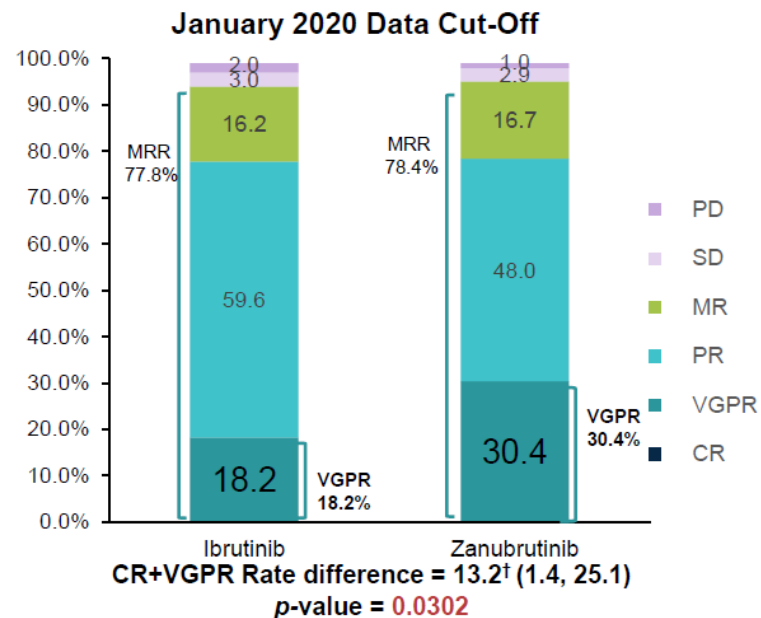
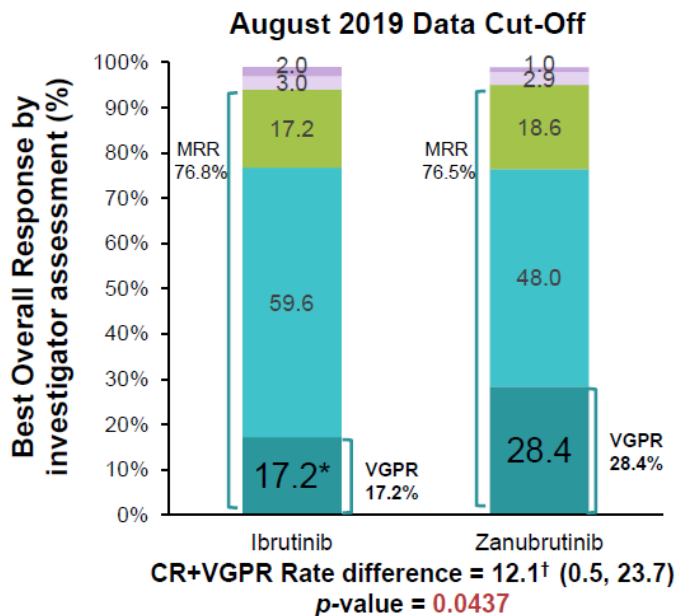
Overall concordance between Independent review and investigators = 94%

* All other *P* values are for descriptive purposes only. †Adjusted for stratification factors and age group.

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 ($p=0.037$)

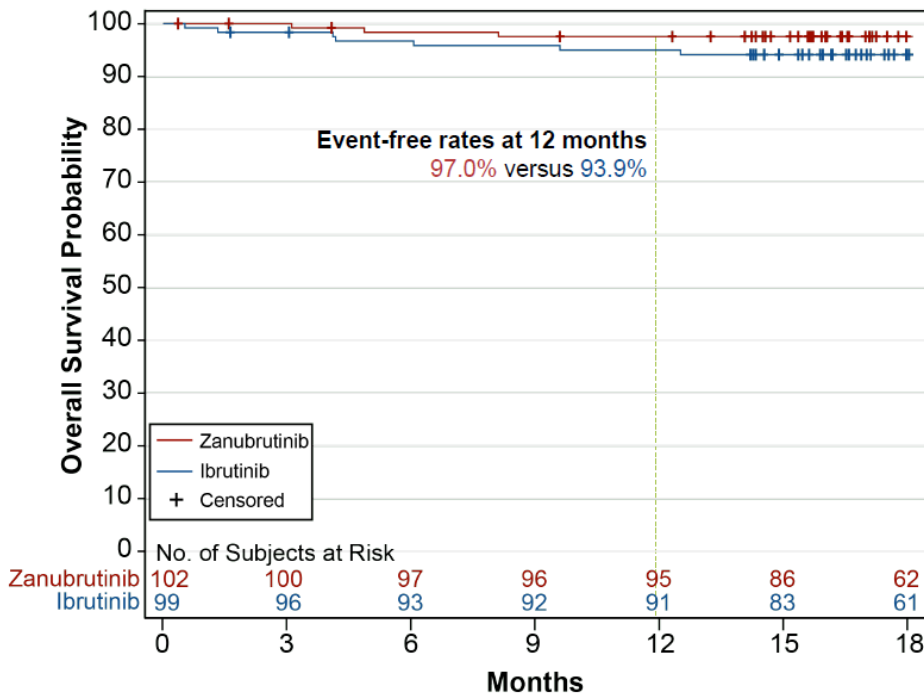
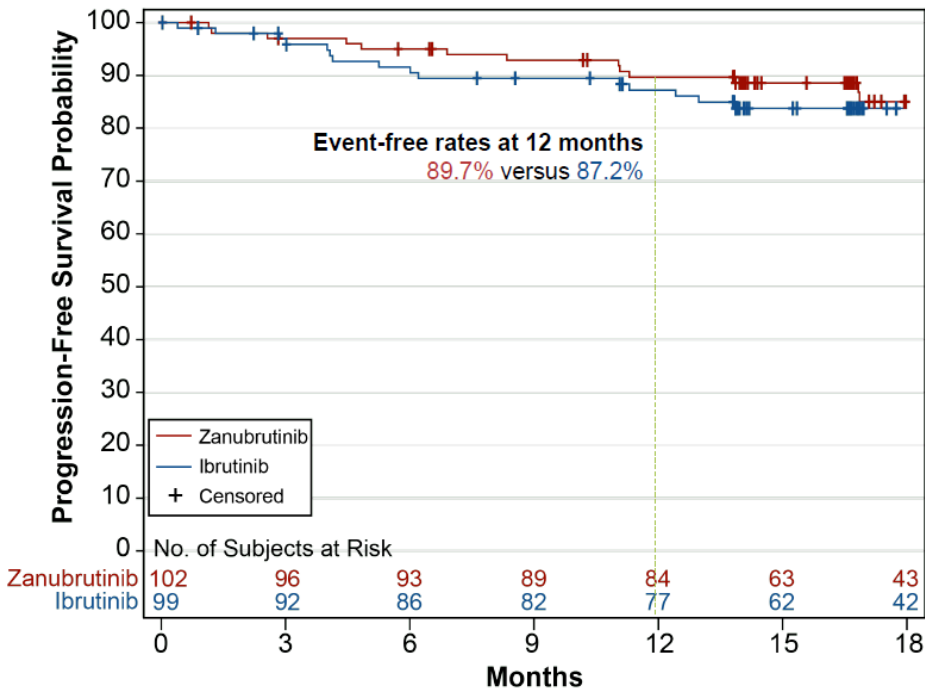
CR, complete response; EMD, extramedullary disease; IgM, Immunoglobulin M; IRC, independent review committee; MRR, major response rate; MR, minor response; ; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SPEP, serum protein electrophoresis; VGPR, very 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.

^aDefined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.

^bIncluding PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.

[†] Descriptive two-sided P-value < 0.05.

Strategies to Enhance BTK Inhibitors



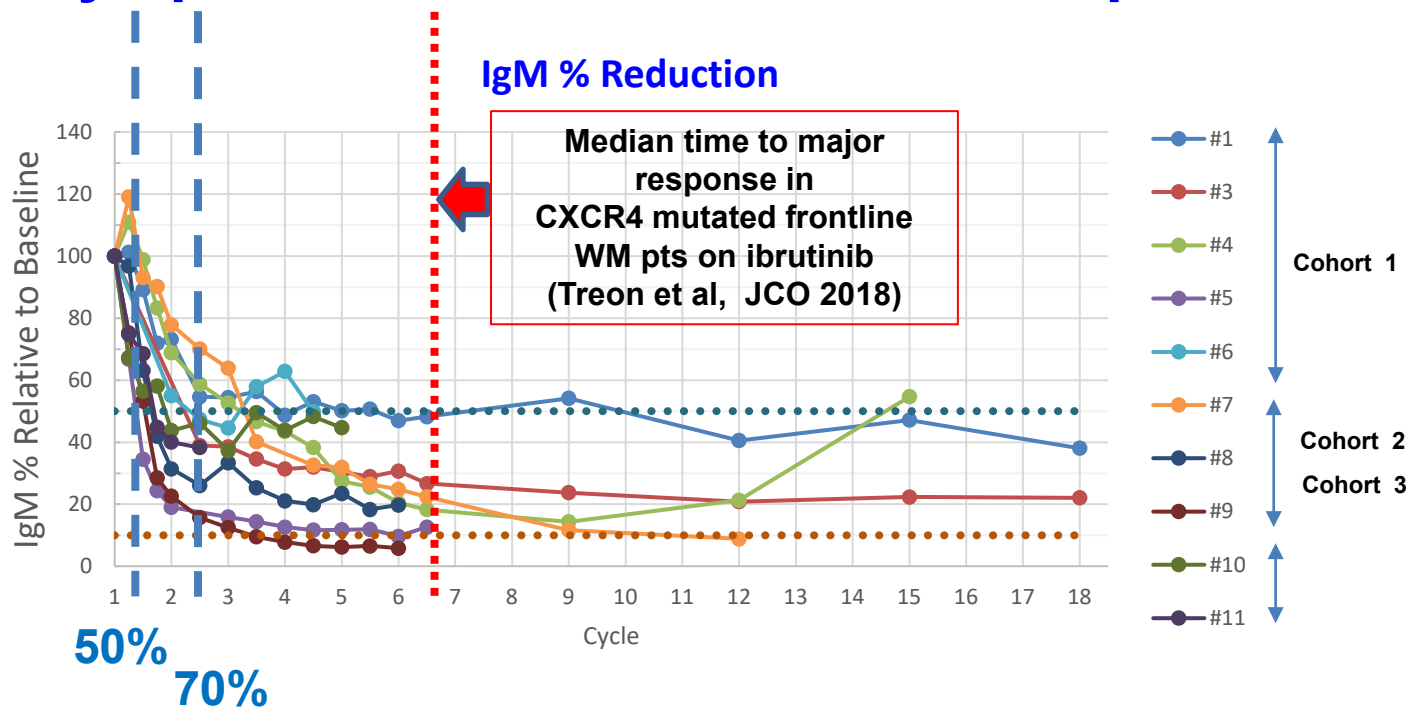
Phase I/II Trial of Ulocuplumab and Ibrutinib in CXCR4 mutated patients with symptomatic WM

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

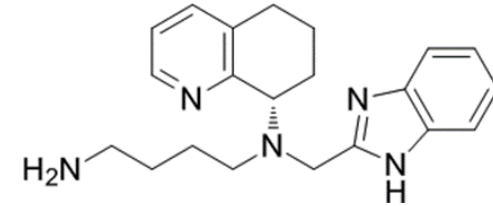
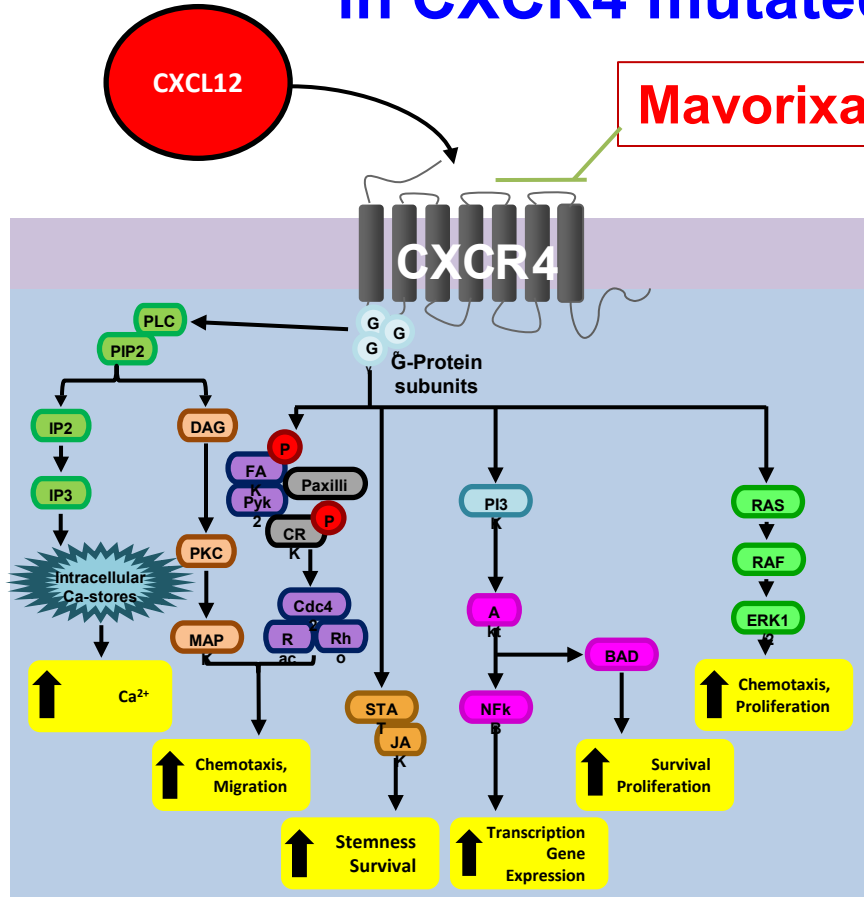
Responses to Ibrutinib and CXCR4 Inhibitor Ulucuplomab in Symptomatic CXCR4 mutated WM patients



Median prior therapies: 0 (range 0-1)

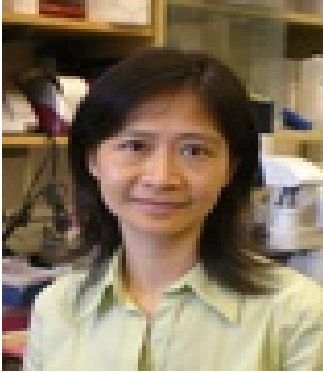
DFCI Unpublished Data

Mavorixafor in combination with ibrutinib in CXCR4 mutated WM

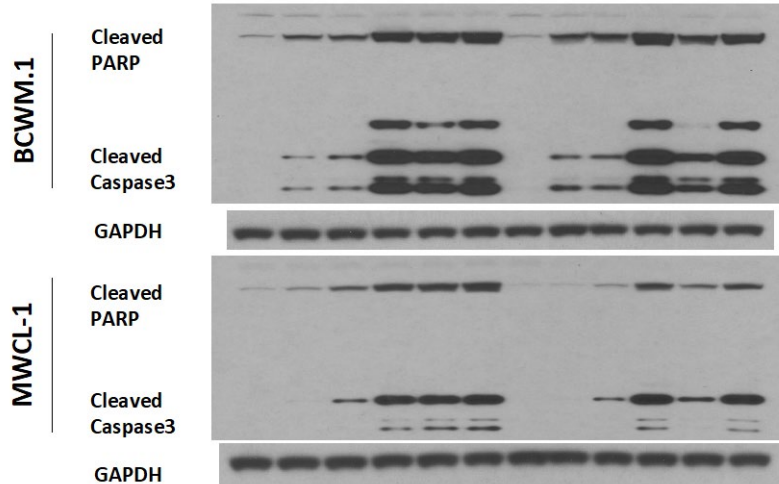
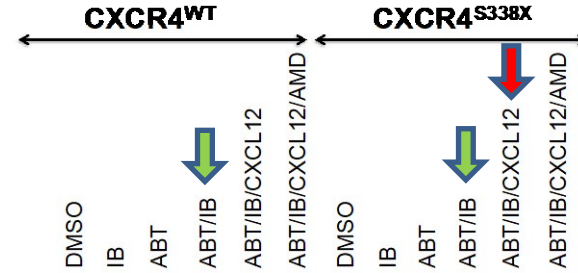
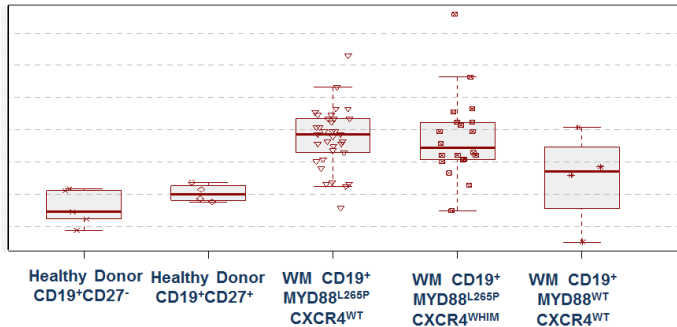


- Non-competitive, allosteric, small molecule antagonist of CXCR4
- Orally Bioavailable; mean $t_{1/2}$ of ~23 hours
- High volume of distribution

Venetoclax (ABT-199) augments ibrutinib induced apoptosis



Higher BCL2 levels in MYD88 mutated WM





J. Castillo

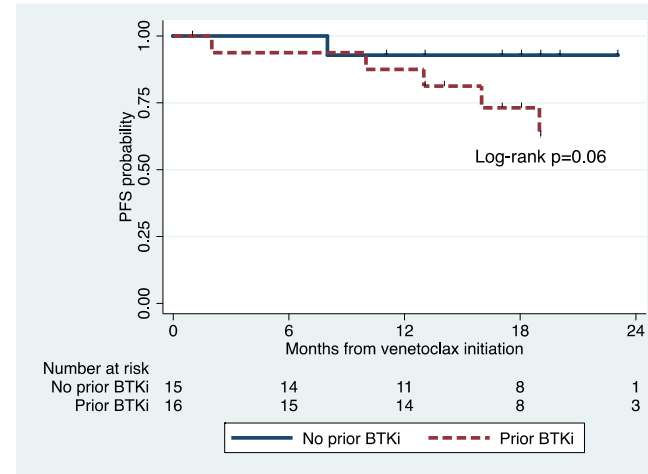
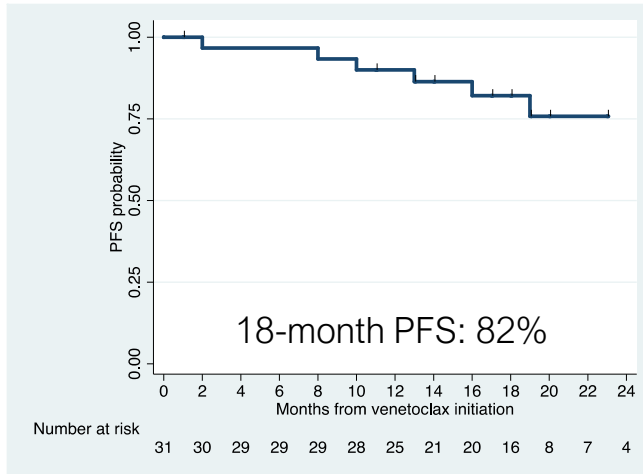
Phase II Study of Venetoclax in Previously Treated WM

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

Response	All patients	Prior BTK inhibitor		CXCR4 mutations	
	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%).

Phase II Study of Venetoclax in Previously Treated WM

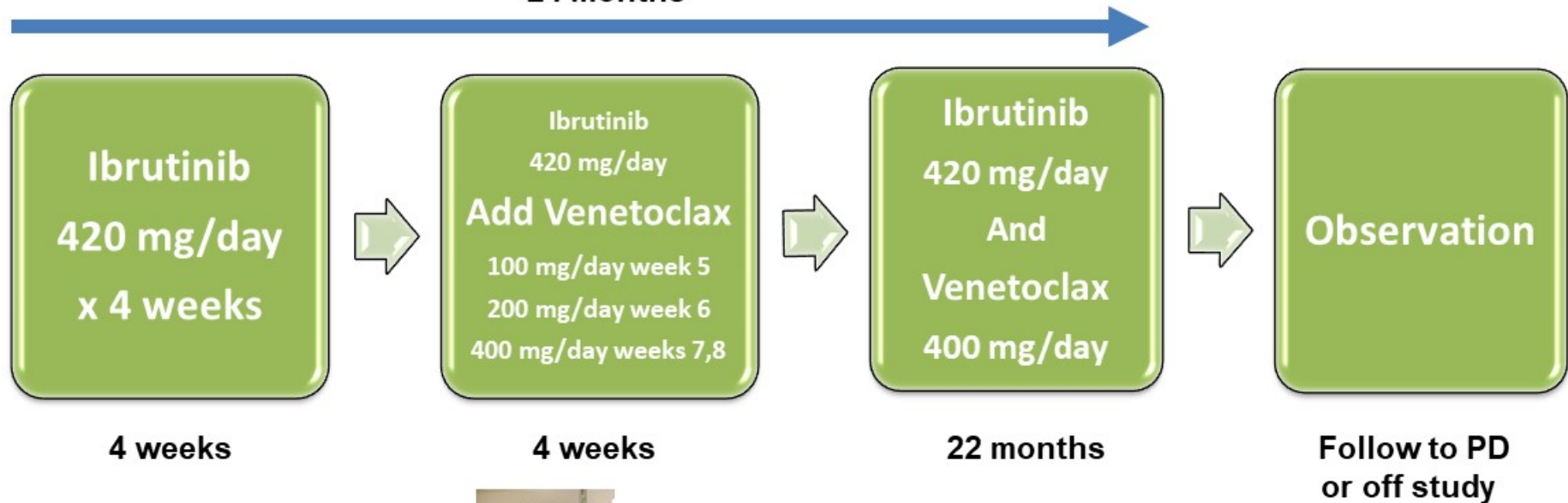


Median 18 months. Range 1-30 months.

Castillo et al, 17th IMW 2019

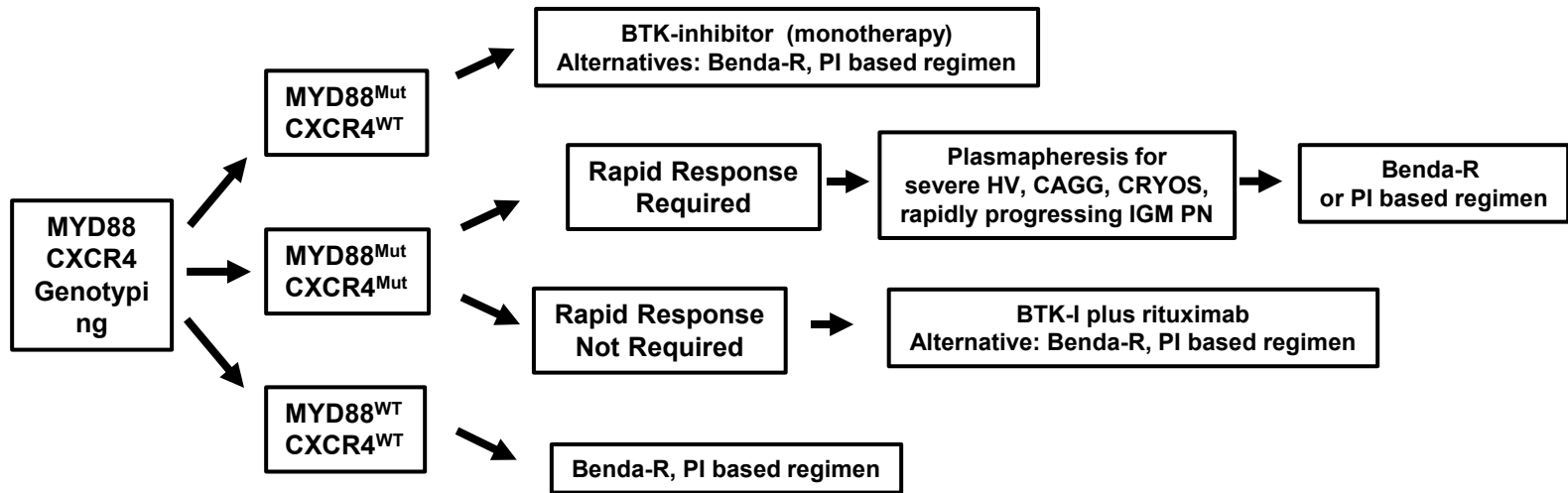
Ibrutinib and Venetoclax in Treatment Naïve WM

24 months



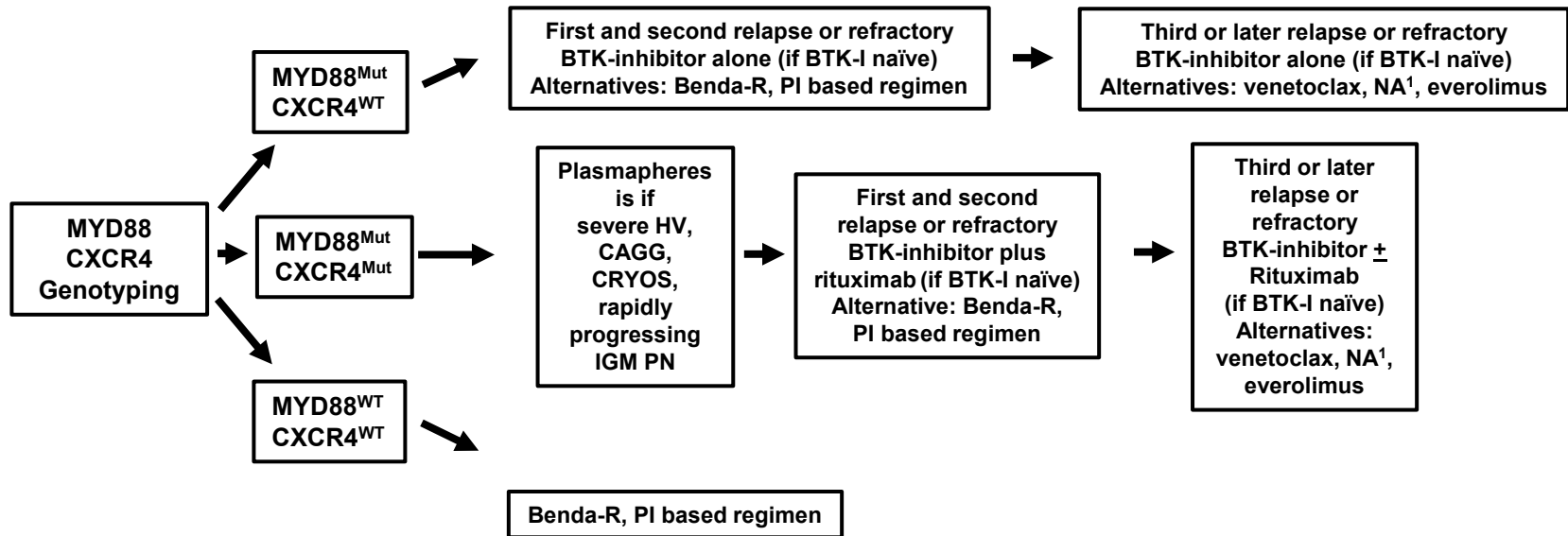
Jorge Castillo, PI (DFCI)

Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM



- Rituximab should be held for serum IgM $\geq 4,000$ 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.

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.