Genomic Based Treatment Strategies for Waldenström's Macroglobulinemia

HARVARD MEDICAL SCHOOL

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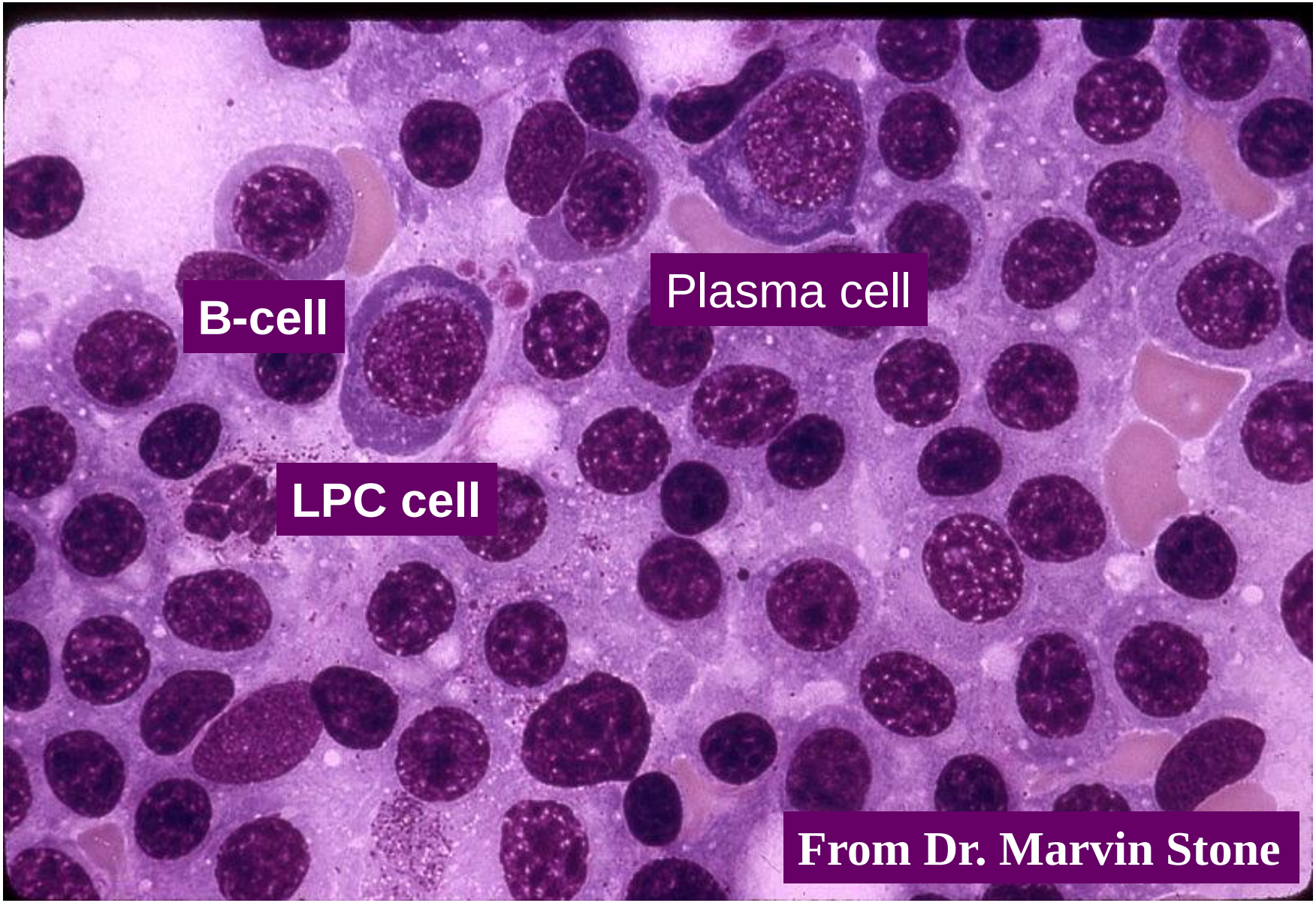
Steven P. Treon, MD, MA, MS, PhD
Professor of Medicine, Harvard Medical School
Director, Bing Center for WM
Chair, WM Clinical Trials Group

WM Treatment Approach



Bone Marrow aspirate of a patient with WM

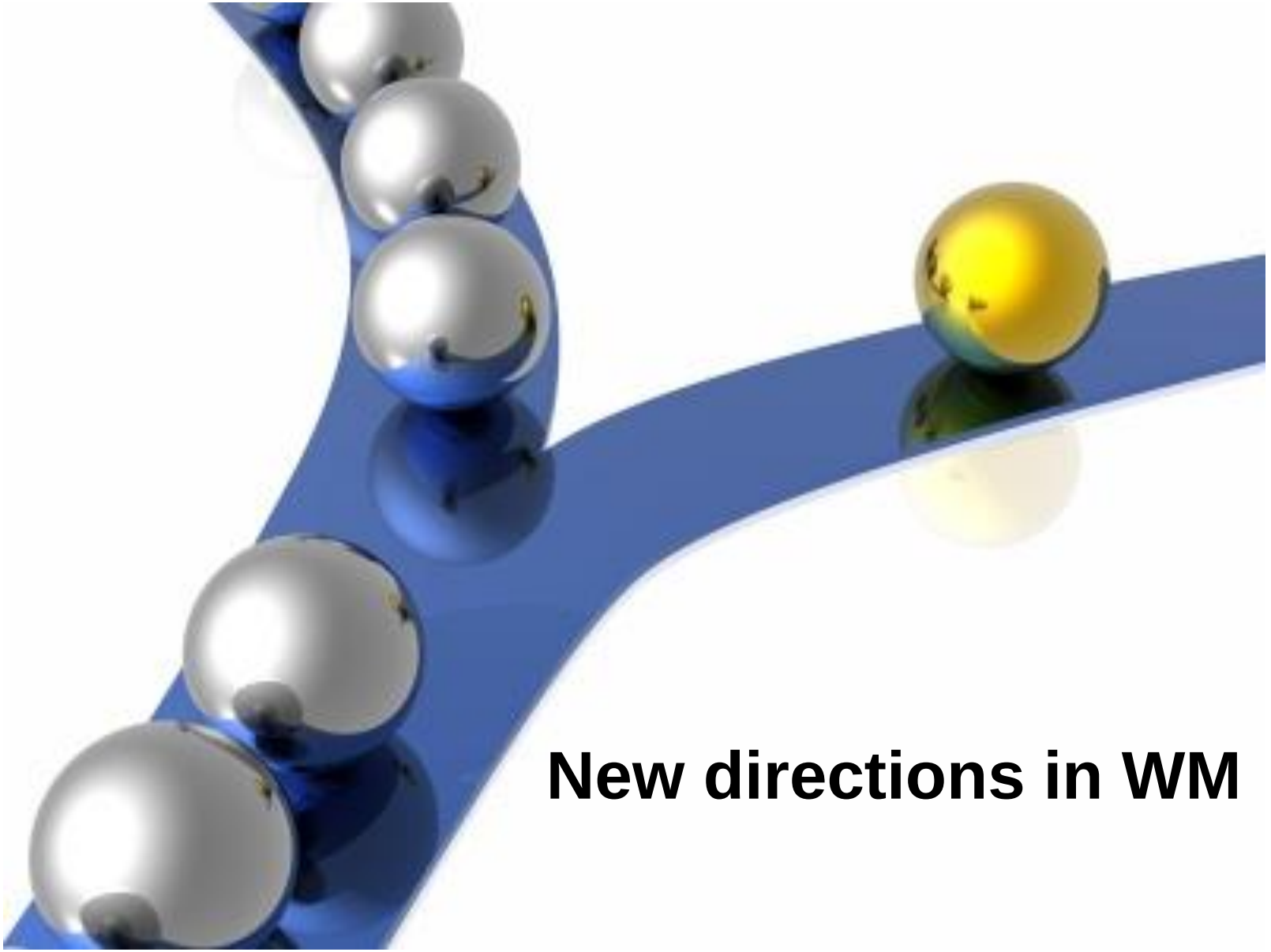
Primary Therapy of WM with Rituximab

Regimen	ORR	VGPR/CR	TTP (mo)
Rituximab x 4	25-30%	0-5%	13
Rituximab x 8	40-45%	5-10%	16-22
Rituximab/thalidomide	70%	10%	30
Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, CDR	70-80%	20-25%	30-36
Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R	70-90%	20-30%	36-62
Rituximab/Proteasome Inhibitor i.e. BDR, VR, CaRD	70-90%	20-40%	42-66
Rituximab/bendamustine	90%	30-40%	69

Reviewed in Dimopoulos et al, Blood 2014; 124(9):1404-11; Treon et al, Blood 2015; How I Treat WM

WM–centric toxicities with commonly used therapies

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



New directions in WM

WHOLE GENOME SEQUENCING IN WM

3,000,000,000 nucleotides

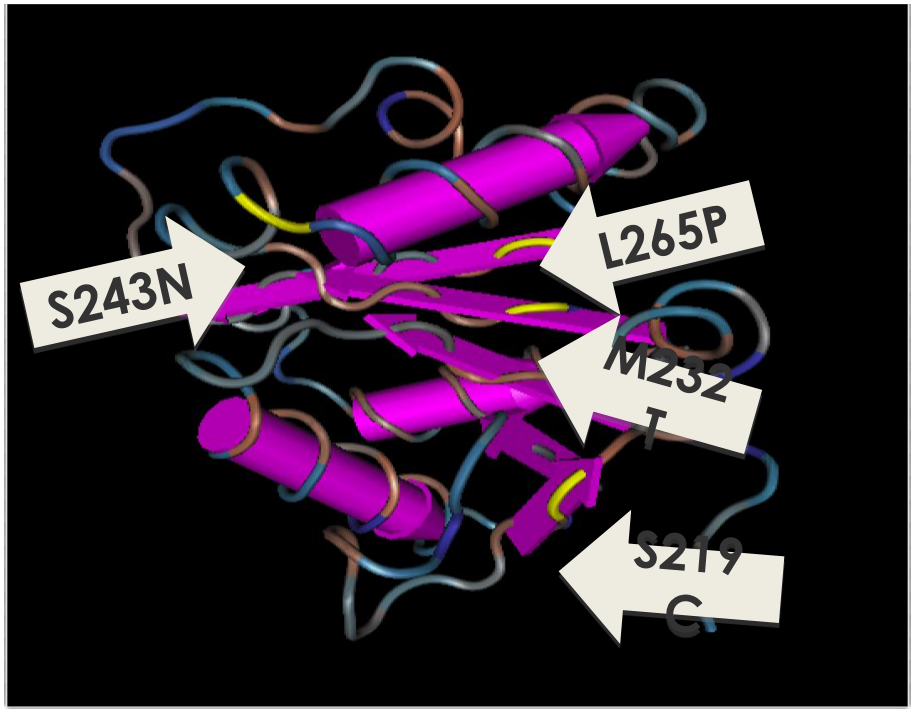
Paired Sequencing from same individuals

NORM

WM

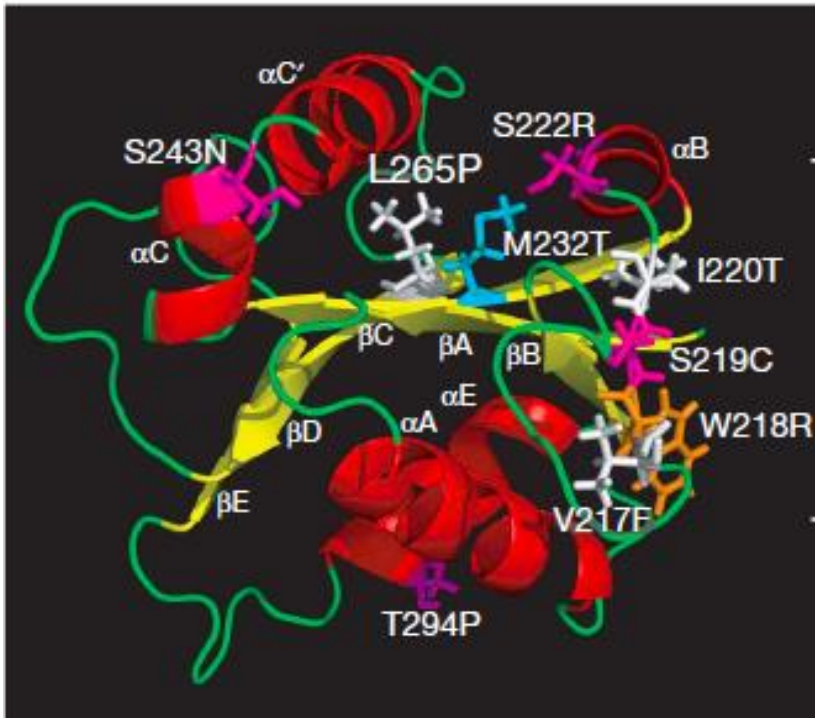
MYD88 Mutations in B-cell LPD

WM



93-95% MYD88 L265P
2% Non-L265P MYD88

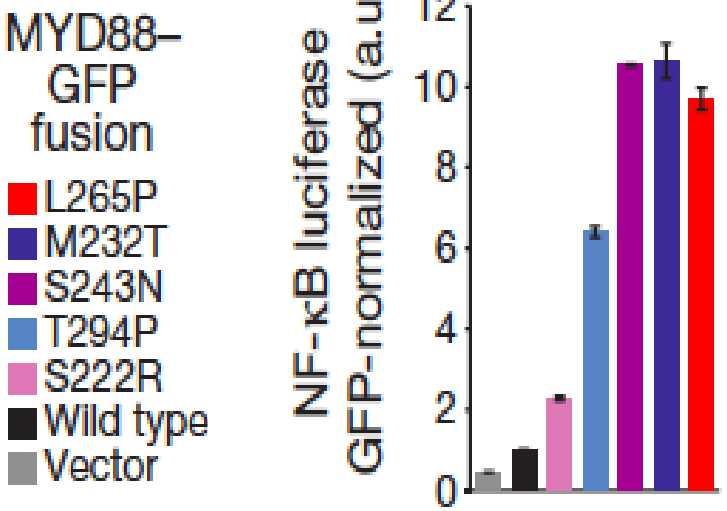
ABC DLBCL



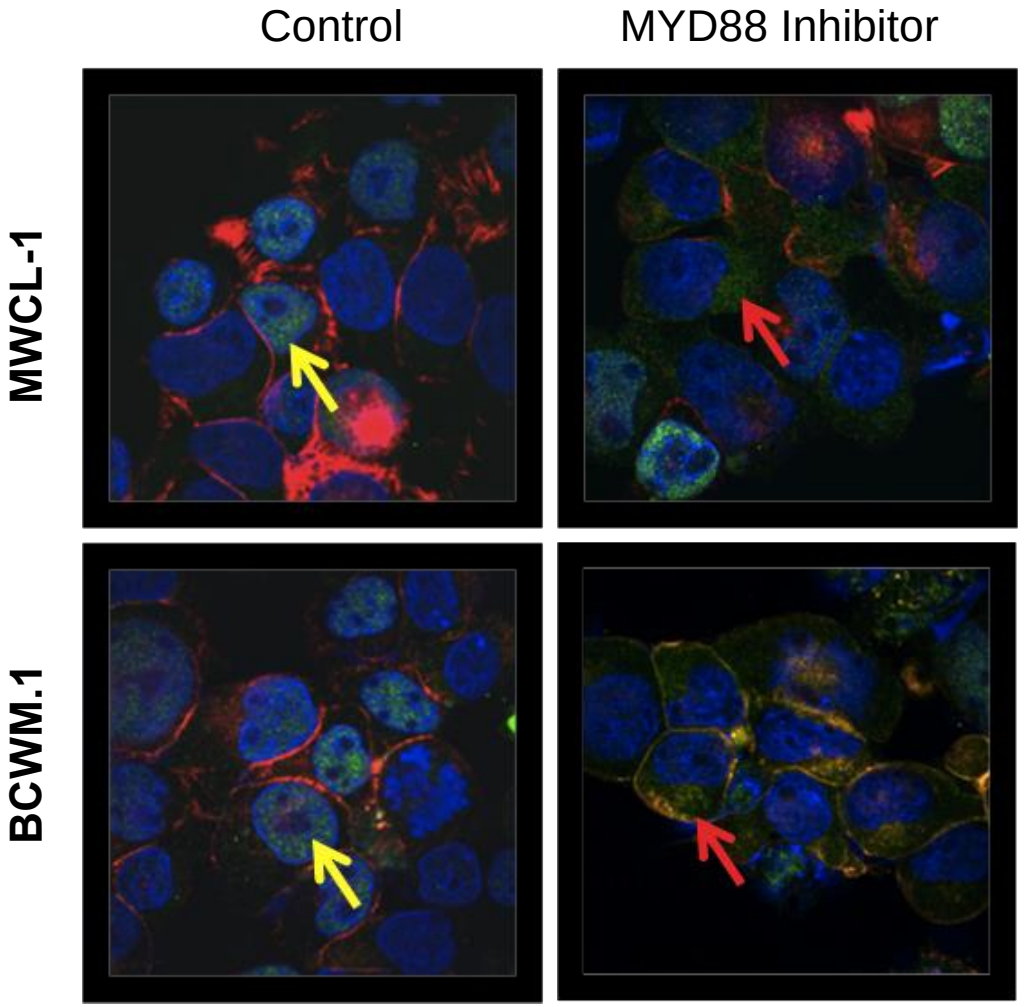
29% MYD88 L265P
10% Non-L265P MYD88

Treon et al, NEJM 2012; Treon et al, NEJM 2015; Jiménez et al, 2013; Varettoni et al 2013; Poulain et al, 2013, Xu et al, 2013.

MYD88 mutations transactivate NFKB

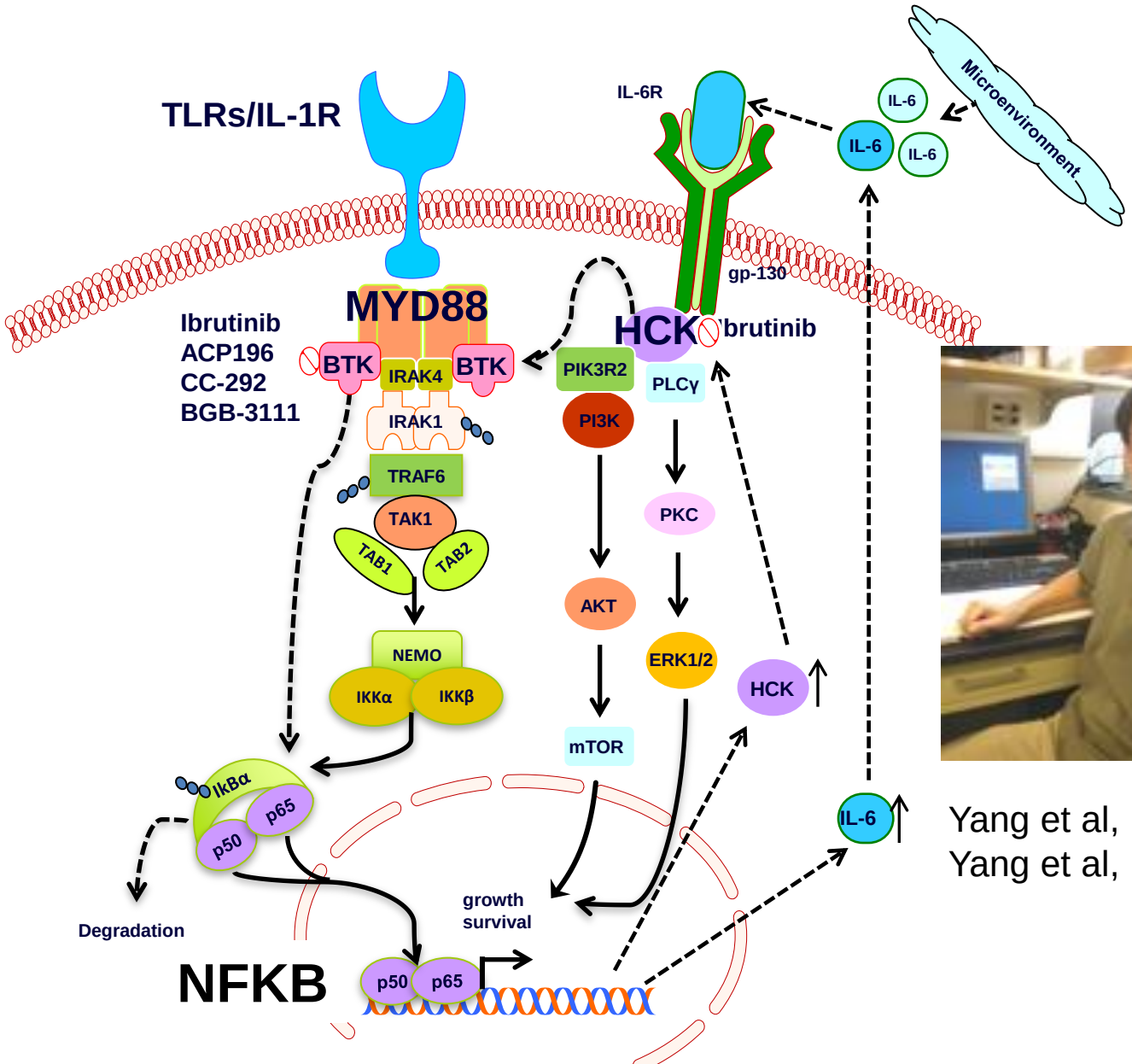


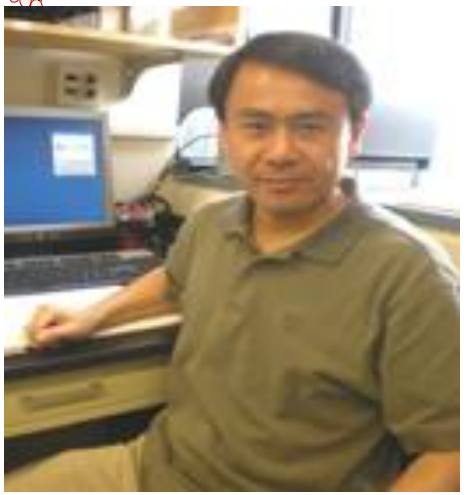
Ngo et al, Nature 2011
Treon et al, NEJM 2012



MYD88 L265P mutated WM cells

Signaling Pathways Driven by Mutated MYD88 in Waldenström's Macroglobulinemia

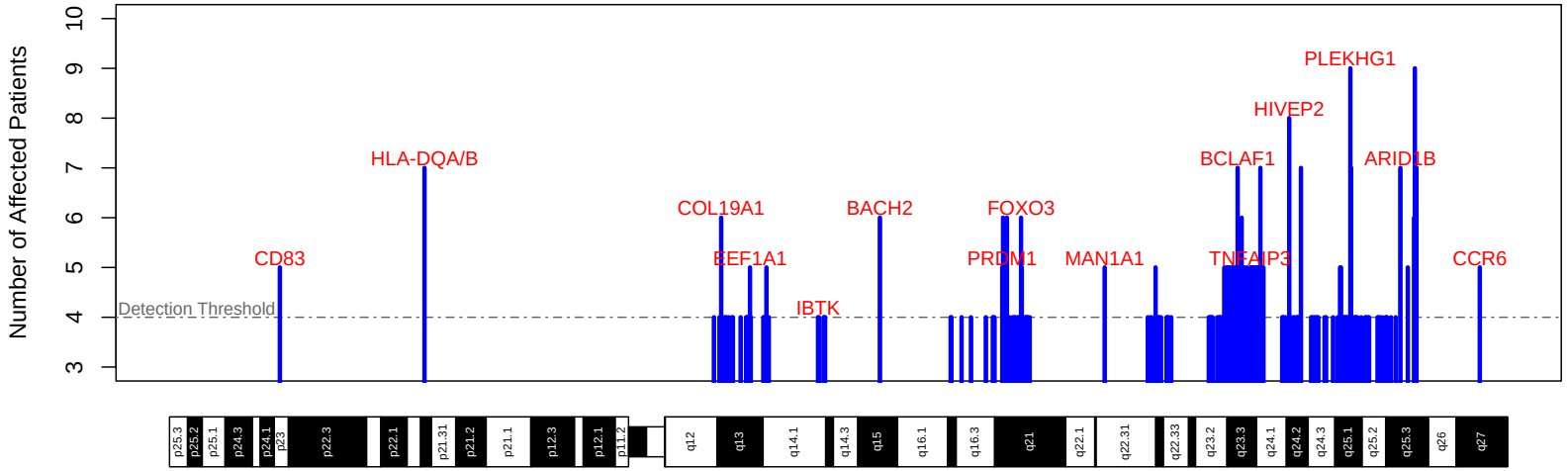




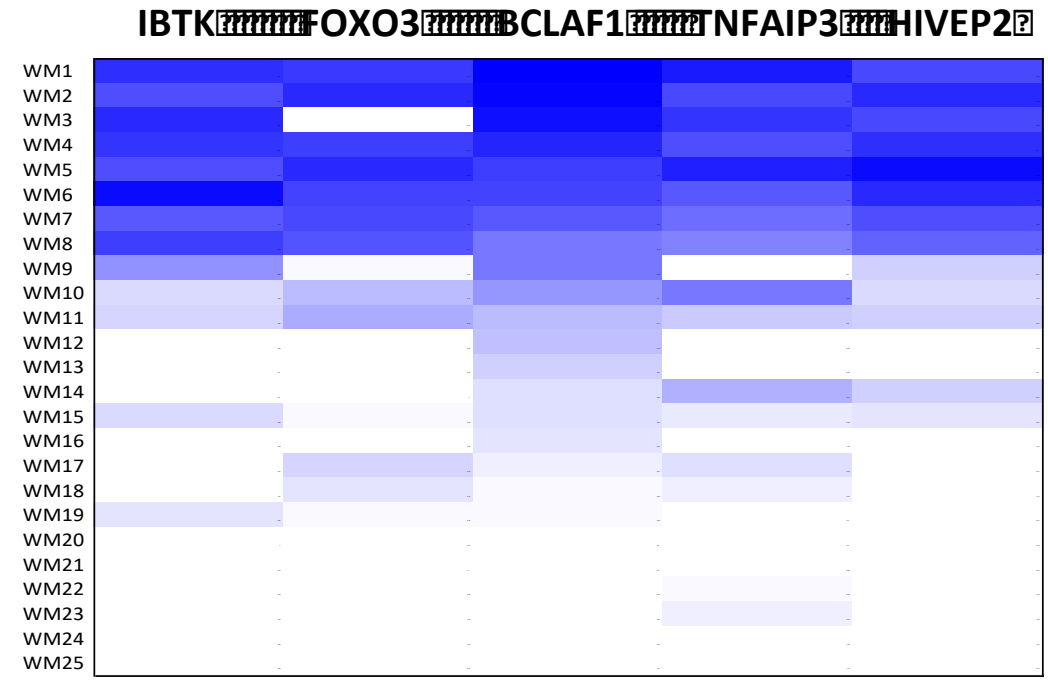
Yang et al, Blood 2013
Yang et al, Blood 2016


YourMech

Chr. 6q clonal loss is common in WM and impacts BTK, BCL2, and NFKB regulatory genes



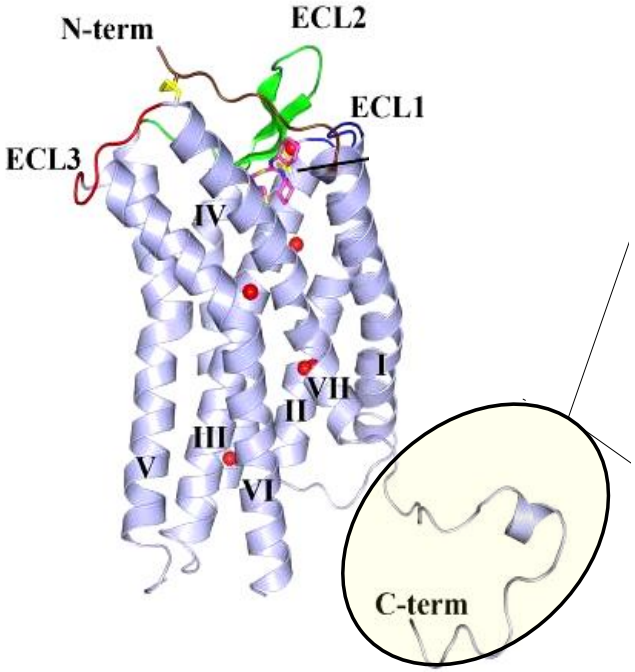
Hunter, et al. 2014



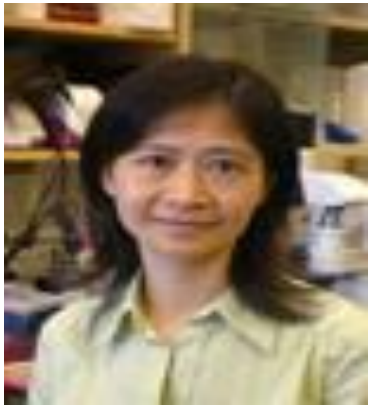
Guerrera et al, IWWM9

CXCR4 C-tail mutations in WM

- 30-40% of WM patients; v. rare in other LPD
- >30 Nonsense, Frameshift Mutations
- Segues with MYD88 mutations
- High serum IgM levels/Hyperviscosity
- Promote **ibrutinib resistance** through enhanced AKT/ERK signaling.



Hunter et al, Blood 2013;
Rocarro et al, Blood 2014:
Poulain et al, Blood 2016;
Cao et al, Leukemia 2014;
Cao et al, BJH 2015



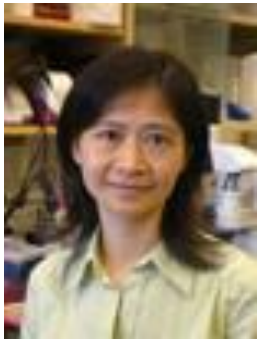
CXCR4 Signaling in WM Patients with WHIM mutations

Plerixafor
Ulucuplomab

Busillo et al, JBC 2010
Mueller et al, PLOS ONE 2013
Cao et al, Leukemia 2014
Rocarro et al, Blood 2014
Cao et al, BJH 2015

SDF-1

CXCR4



B-arrestins

Ser346/7

ERK
AKT

SURVIVAL
DRUG RESISTANCE

GRK 2/3

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

R. Advani L. Palomba

DANA-FARBER CANCER INSTITUTE

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**

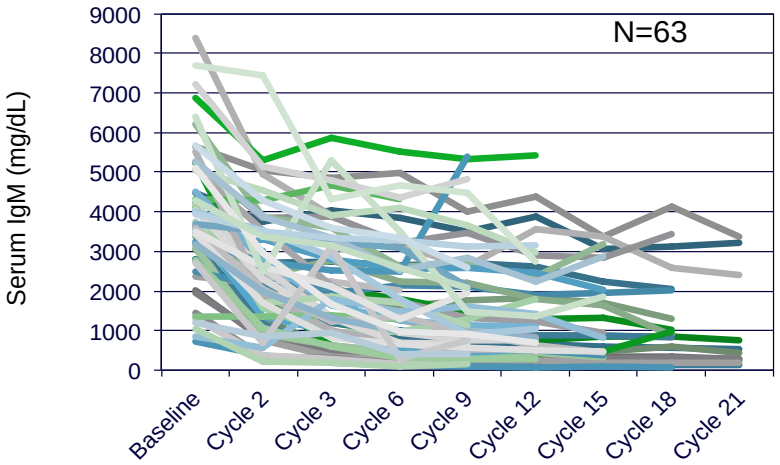
Baseline Characteristics for Study Participants (n=63)

	Median	Range
Age (yrs)	63	44-86
Prior therapies	2	1-9
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; 372:1430

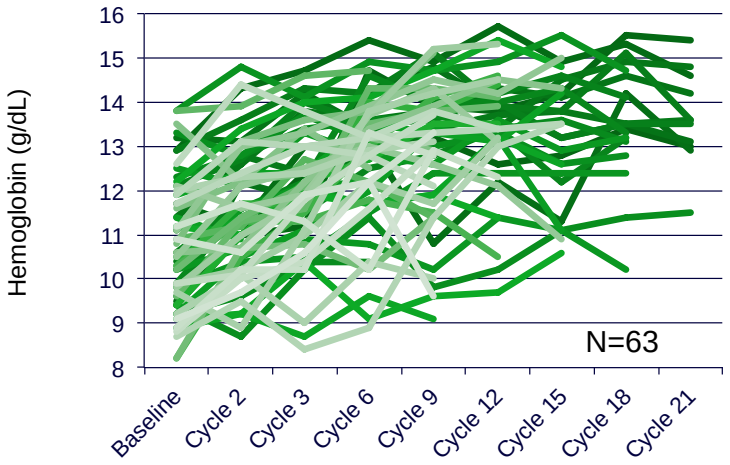
Serum IgM and Hb Levels Following Ibrutinib

Serum IgM



Best IgM Response:
3,520 to 880 mg/dL; p<0.001

Hb



Best Hemoglobin Response:
10.5 to 13.8; p<0.001

Treon et al, N Engl J Med. 2015; 372(15):1430-40.

Best Clinical Responses to Ibrutinib

Median duration of treatment: 19.1 (range 0.5-29.7) months

ORR: 91% Major RR (≥ PR): 73%

	(N=)	(%)
VGPR	10	16
PR	36	57
MR	11	17

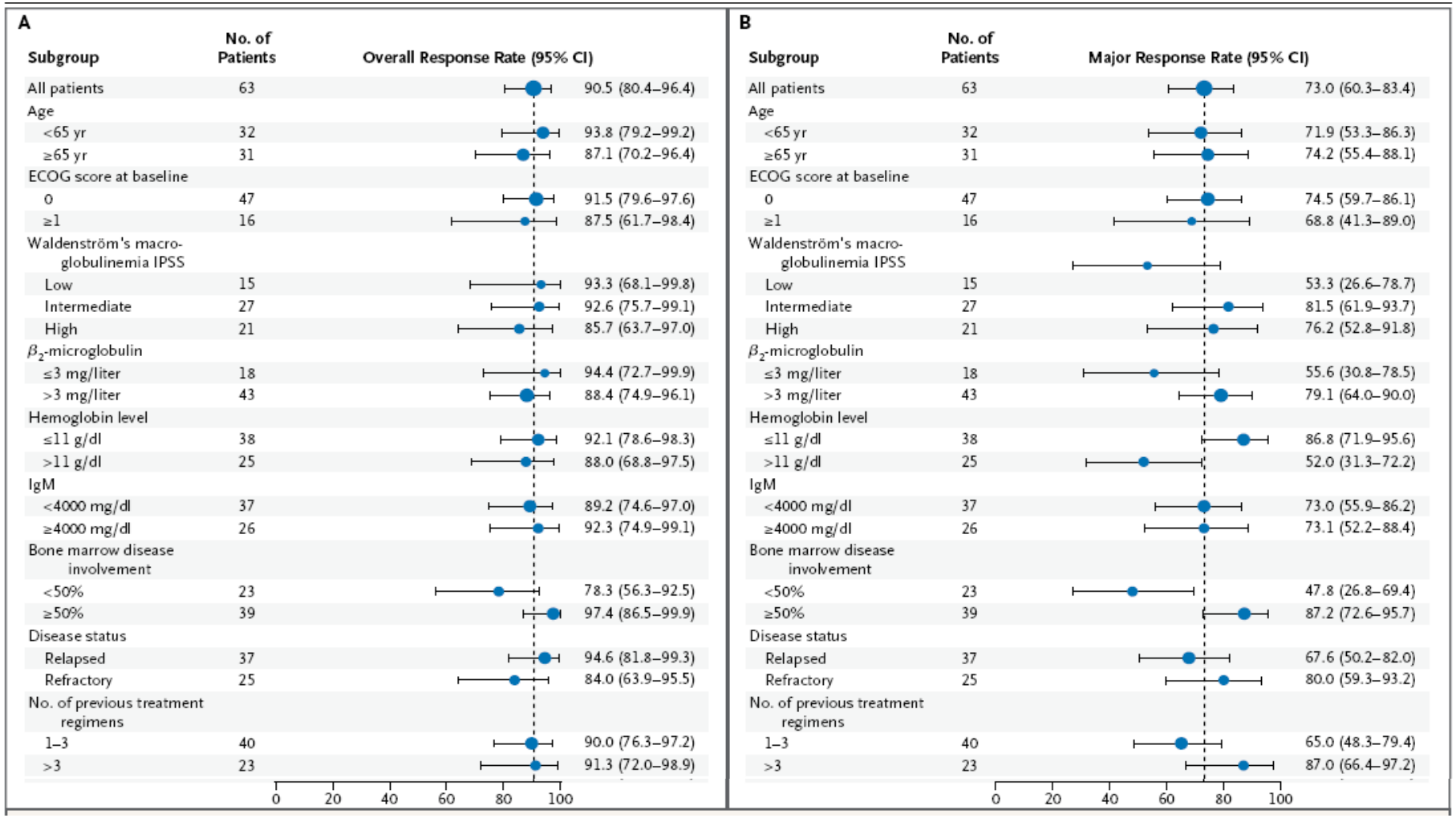
Median time to ≥ MR: 4 weeks
Median time to ≥ PR or better: 8 weeks

Treon et al, N Engl J Med. 2015; 372(15):1430-4

Subgroup Response Analysis

Overall Respose Rate

Major Response Rate



A

Subgroup	No. of Patients	Overall Response Rate (95% CI)
All patients	63	90.5 (80.4–96.4)
Age		
<65 yr	32	93.8 (79.2–99.2)
≥65 yr	31	87.1 (70.2–96.4)
ECOG score at baseline		
0	47	91.5 (79.6–97.6)
≥1	16	87.5 (61.7–98.4)
Waldenström's macroglobulinemia IPSS		
Low	15	93.3 (68.1–99.8)
Intermediate	27	92.6 (75.7–99.1)
High	21	85.7 (63.7–97.0)
β_2-microglobulin		
≤3 mg/liter	18	94.4 (72.7–99.9)
>3 mg/liter	43	88.4 (74.9–96.1)
Hemoglobin level		
≤11 g/dl	38	92.1 (78.6–98.3)
>11 g/dl	25	88.0 (68.8–97.5)
IgM		
<4000 mg/dl	37	89.2 (74.6–97.0)
≥4000 mg/dl	26	92.3 (74.9–99.1)
Bone marrow disease involvement		
<50%	23	78.3 (56.3–92.5)
≥50%	39	97.4 (86.5–99.9)
Disease status		
Relapsed	37	94.6 (81.8–99.3)
Refractory	25	84.0 (63.9–95.5)
No. of previous treatment regimens		
1–3	40	90.0 (76.3–97.2)
>3	23	91.3 (72.0–98.9)

0 20 40 60 80 100

B

Subgroup	No. of Patients	Major Response Rate (95% CI)
All patients	63	73.0 (60.3–83.4)
Age		
<65 yr	32	71.9 (53.3–86.3)
≥65 yr	31	74.2 (55.4–88.1)
ECOG score at baseline		
0	47	74.5 (59.7–86.1)
≥1	16	68.8 (41.3–89.0)
Waldenström's macroglobulinemia IPSS		
Low	15	53.3 (26.6–78.7)
Intermediate	27	81.5 (61.9–93.7)
High	21	76.2 (52.8–91.8)
β_2-microglobulin		
≤3 mg/liter	18	55.6 (30.8–78.5)
>3 mg/liter	43	79.1 (64.0–90.0)
Hemoglobin level		
≤11 g/dl	38	86.8 (71.9–95.6)
>11 g/dl	25	52.0 (31.3–72.2)
IgM		
<4000 mg/dl	37	73.0 (55.9–86.2)
≥4000 mg/dl	26	73.1 (52.2–88.4)
Bone marrow disease involvement		
<50%	23	47.8 (26.8–69.4)
≥50%	39	87.2 (72.6–95.7)
Disease status		
Relapsed	37	67.6 (50.2–82.0)
Refractory	25	80.0 (59.3–93.2)
No. of previous treatment regimens		
1–3	40	65.0 (48.3–79.4)
>3	23	87.0 (66.4–97.2)

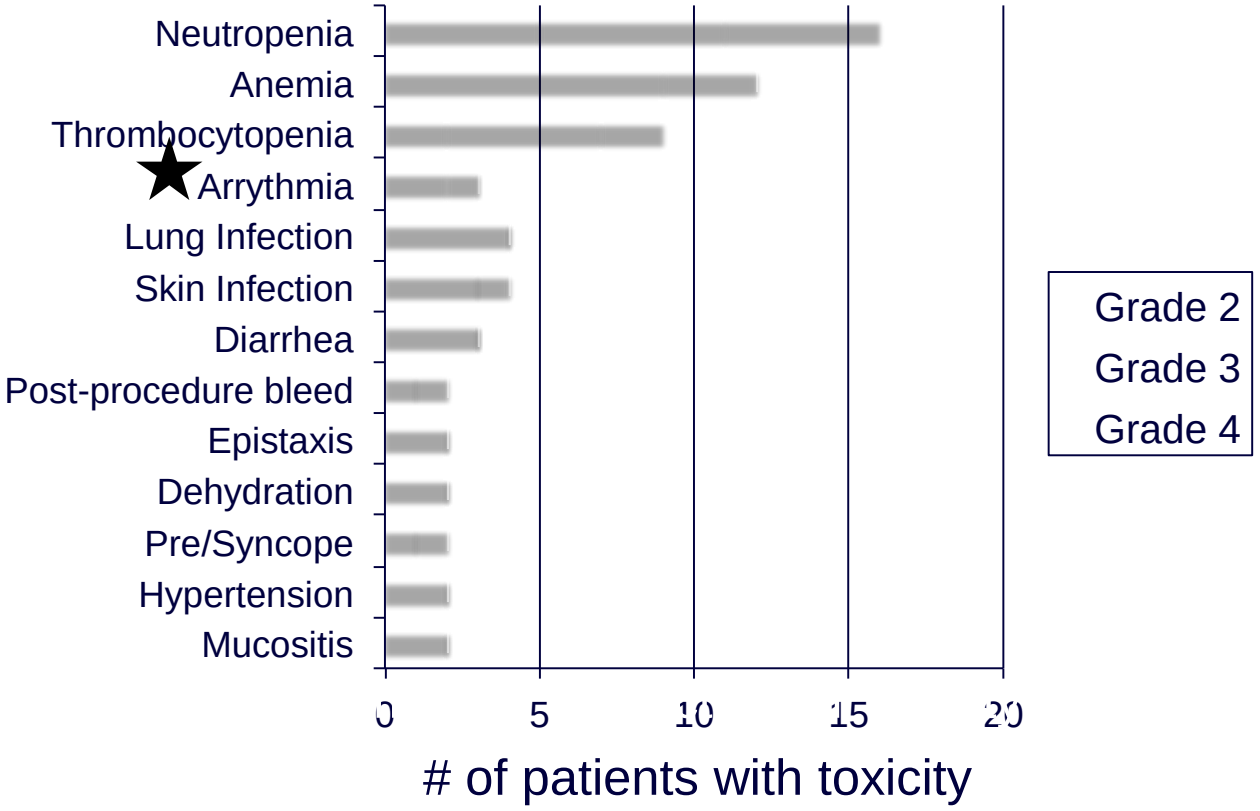
0 20 40 60 80 100

N=63

Treon et al, NEJM 372: 1430, 2015

Ibrutinib Related Adverse Events in previously treated WM patients

Toxicities >1 patient; N=63

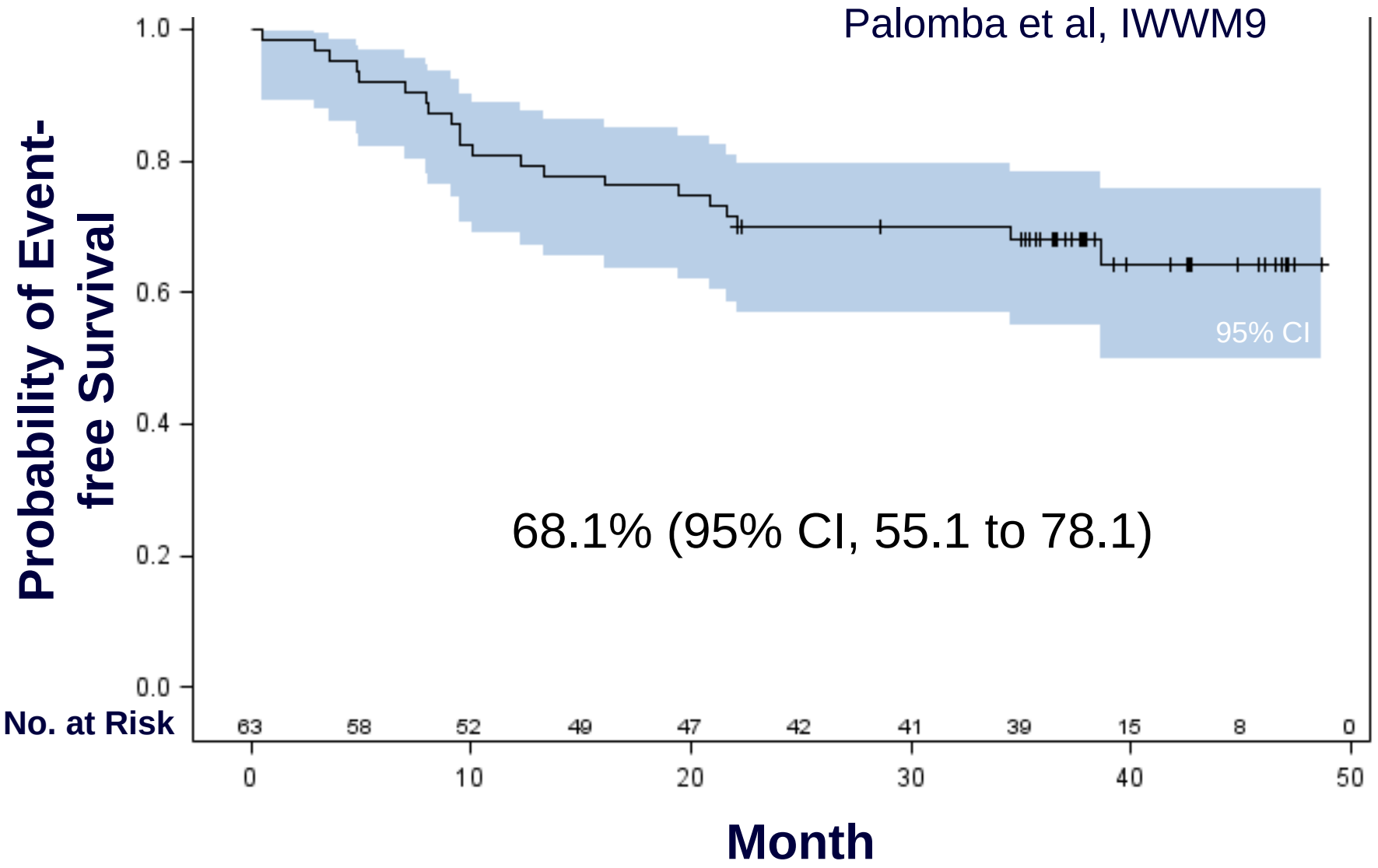


- **No impact on IGA and IGG immunoglobulins**

★10% incidence with larger WM Experience; earlier presentation for those patients with prior Afib history.

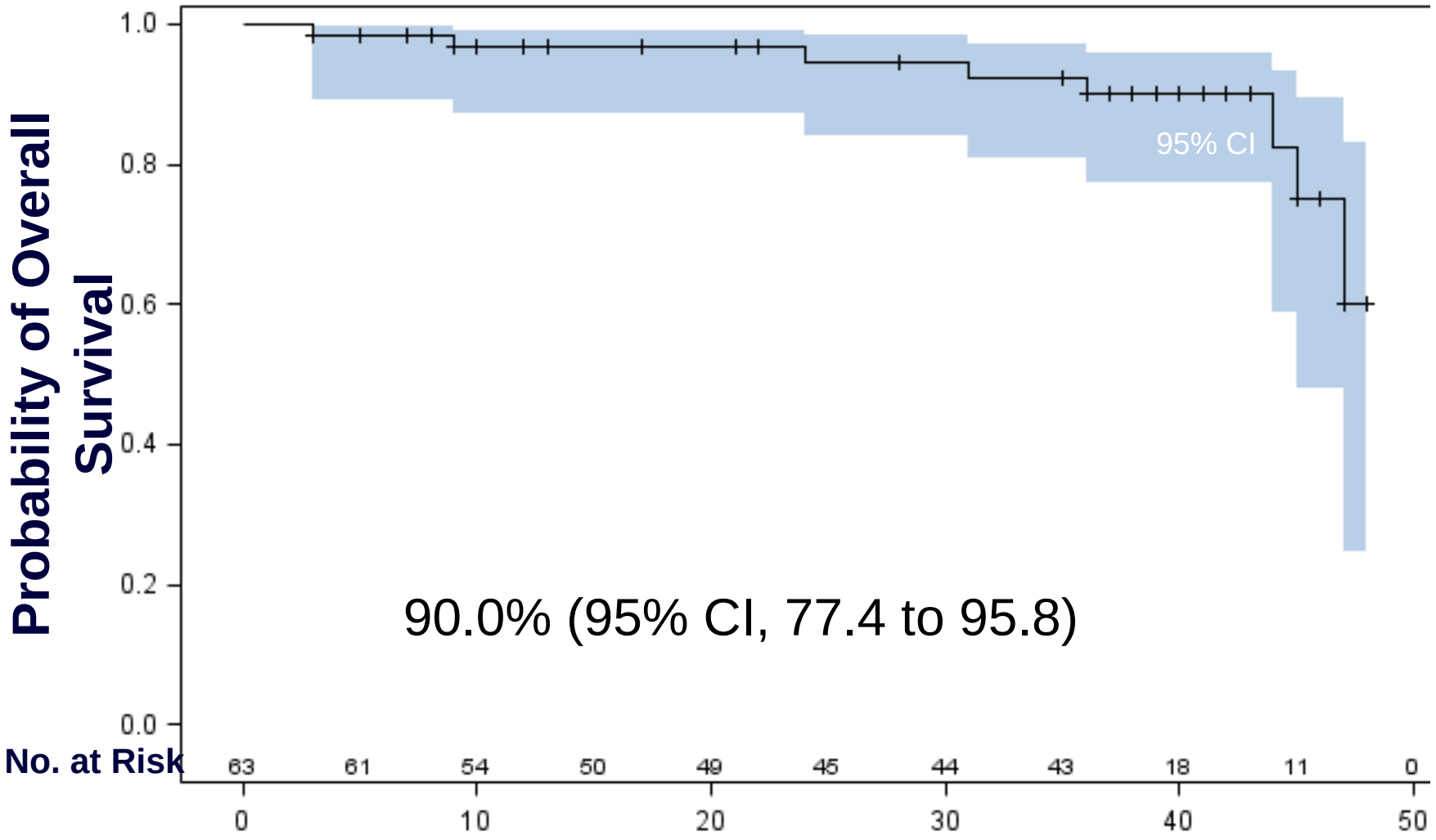
Treon et al, NEJM 2015; Gustine et al, AJH 2016

Ibrutinib in Previously Treated WM: Event-free Survival



Median: 37 mo. follow-up

Ibrutinib in Previously Treated WM: Overall Survival



Median: 37 mo. follow-up

FDA News Release
FDA expands approved use of Imbruvica for rare form of non-Hodgkin lymphoma
First drug approved to treat Waldenstrom's
January 29, 2015

EMA Approval for symptomatic previously treated and chemoimmunotherapy unsuitable frontline WM
First ever for Waldenstrom's
July 8, 2015

EUROPEAN MEDICINES AGENCY
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Health Canada Santé Canada

April 5, 2016

משרד הבריאות
לחיים בריאים יותר

September, 2015

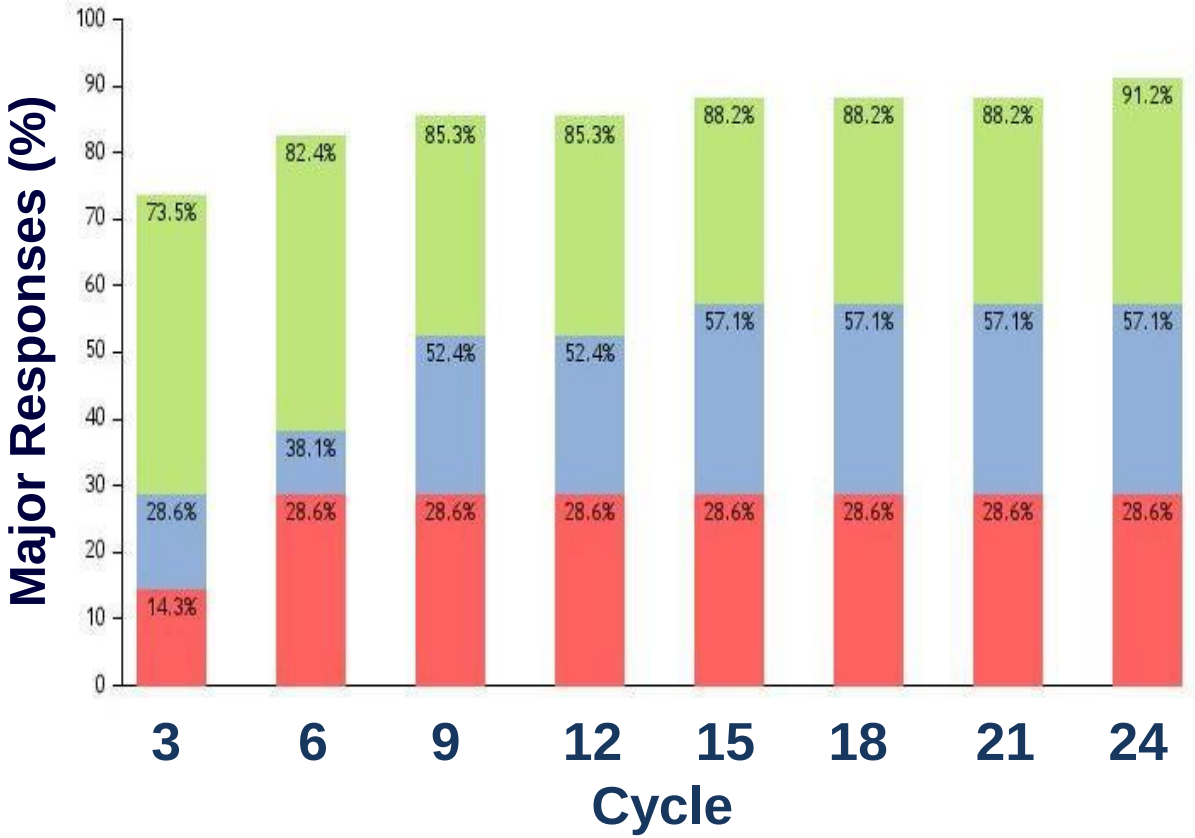
Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations.

	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{WHIM}	MYD88^{WT} CXCR4^{WT}	p-value
N=	36	21	5	
Overall RR	100%	85.7%	60%	<0.01
Major RR	91.7%	61.9%	0%	<0.01

2 patients subsequently found to have other MYD88 mutations not picked up by AS-PCR

Treon et al, N Engl J Med. 2015; 372(15):1430-40; NEJM 2015; Letter, August 6, 2015.

Kinetics of major responses following ibrutinib therapy in genotyped WM patients.



$MYD88^{L265P}$
$CXCR4^{WT}$

$MYD88^{L265P}$
$CXCR4^{WHIM}$

$MYD88^{WT}$
$CXCR4^{WT}$

Treon et al, NEJM 372: 1430, 2015

Ibrutinib in Rituximab-Refractory WM Patients: Multicenter, Open-Label Phase 3 Substudy (iNNOVATE™)

Median Prior Therapies: 4 (range 1-7)
Median follow-up: 18.1 (range 6.3-21.1 months)

ORR: 90% Major RR (≥ PR): 71%

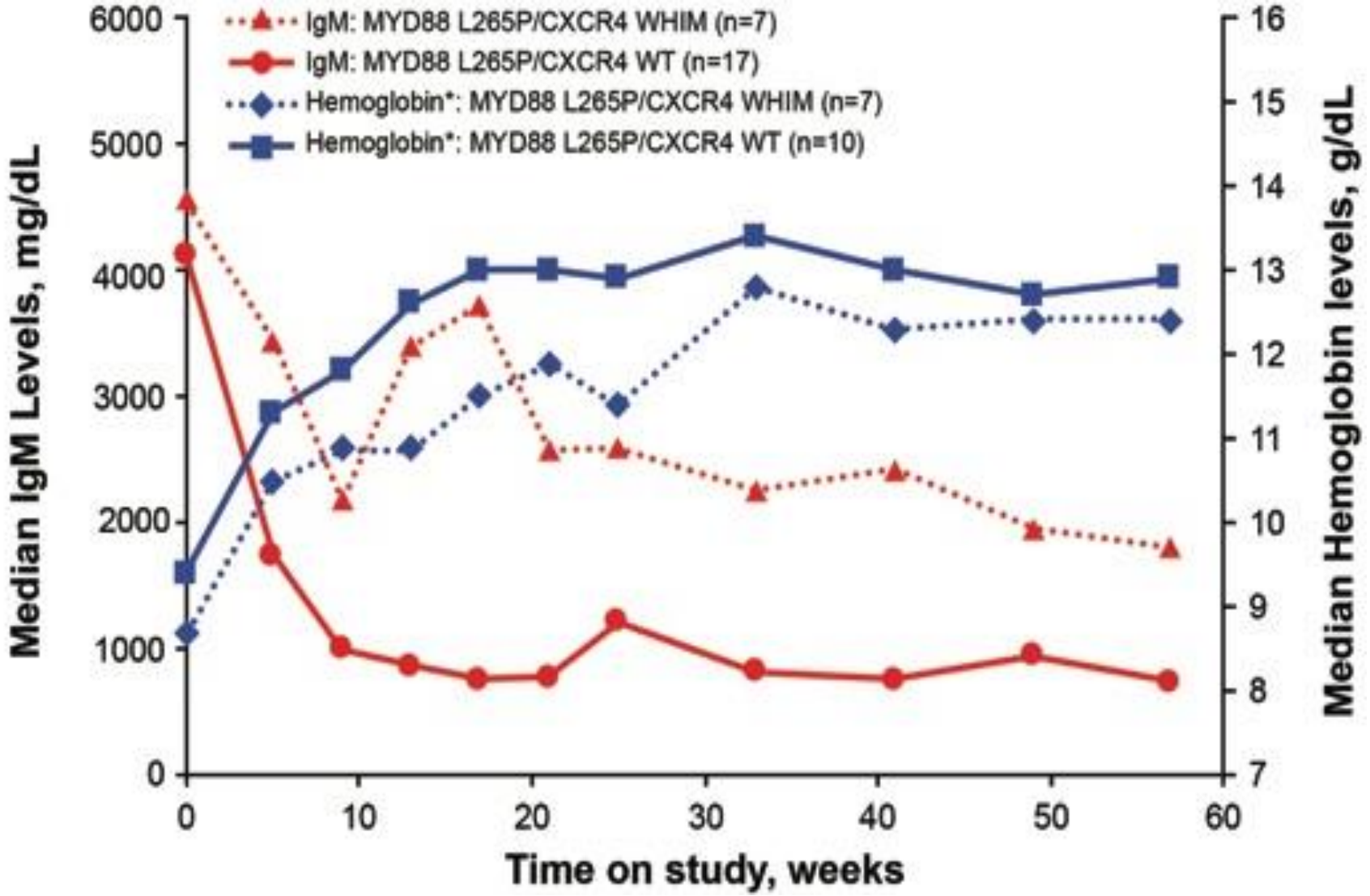
	(N=)	(%)
VGPR	4	13
PR	18	58
MR	6	19

Median time to ≥ MR: 4 weeks
Median time to best response: 8 weeks

18 mo PFS: 86%
18 mo OS: 97%

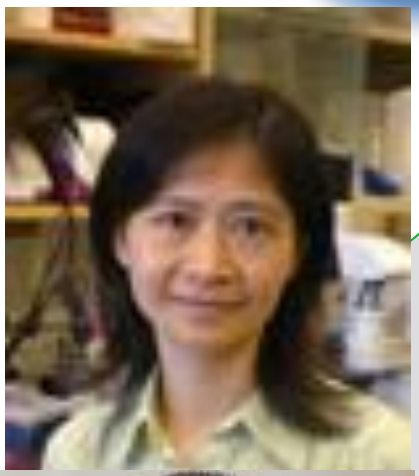
Dimopoulos et al, IWWM9 2016; Lancet Oncol 2017.

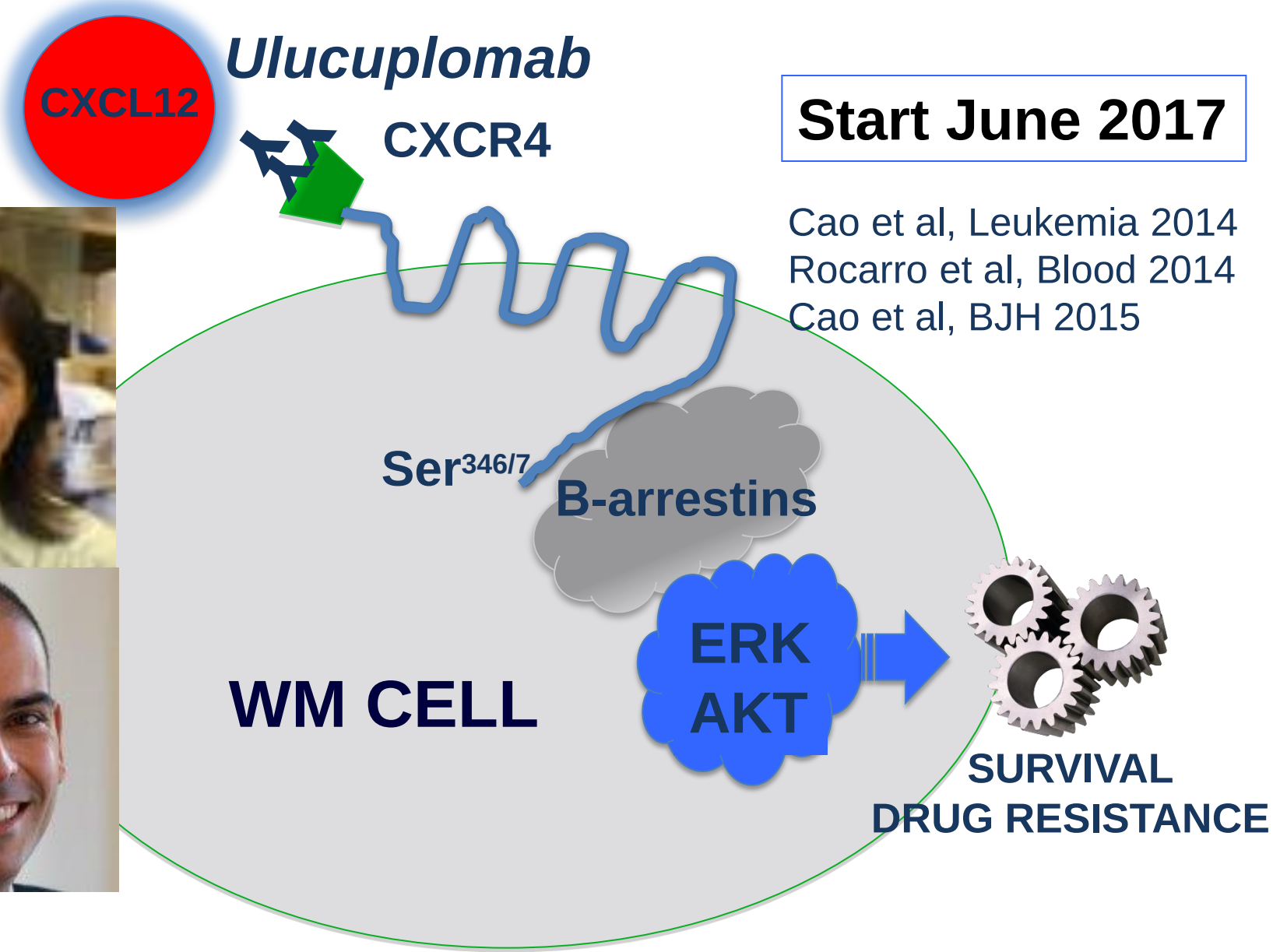
Impact of CXCR4 Mutation Status on IgM and HgB Response



Dimopoulos et al, IWWM9; Lancet Oncology, 2017

Phase I/II Study of Ulucuplomab and Ibrutinib in CXCR4 mutated WM Patients

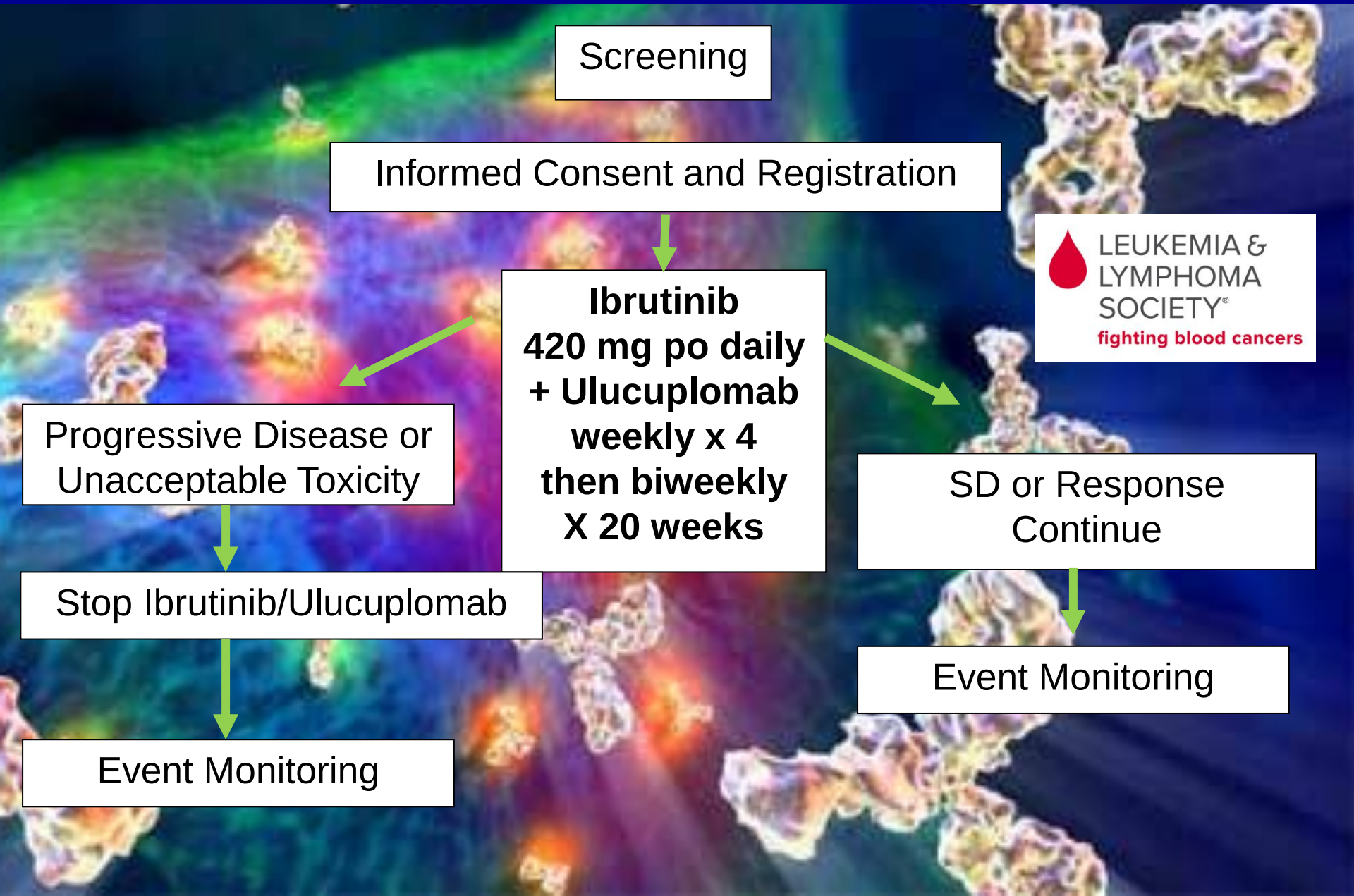




Start June 2017

Cao et al, Leukemia 2014
Rocarro et al, Blood 2014
Cao et al, BJH 2015

Phase II Study of Ibrutinib plus Ulucuplomab in CXCR4^{WHIM} WM Patients



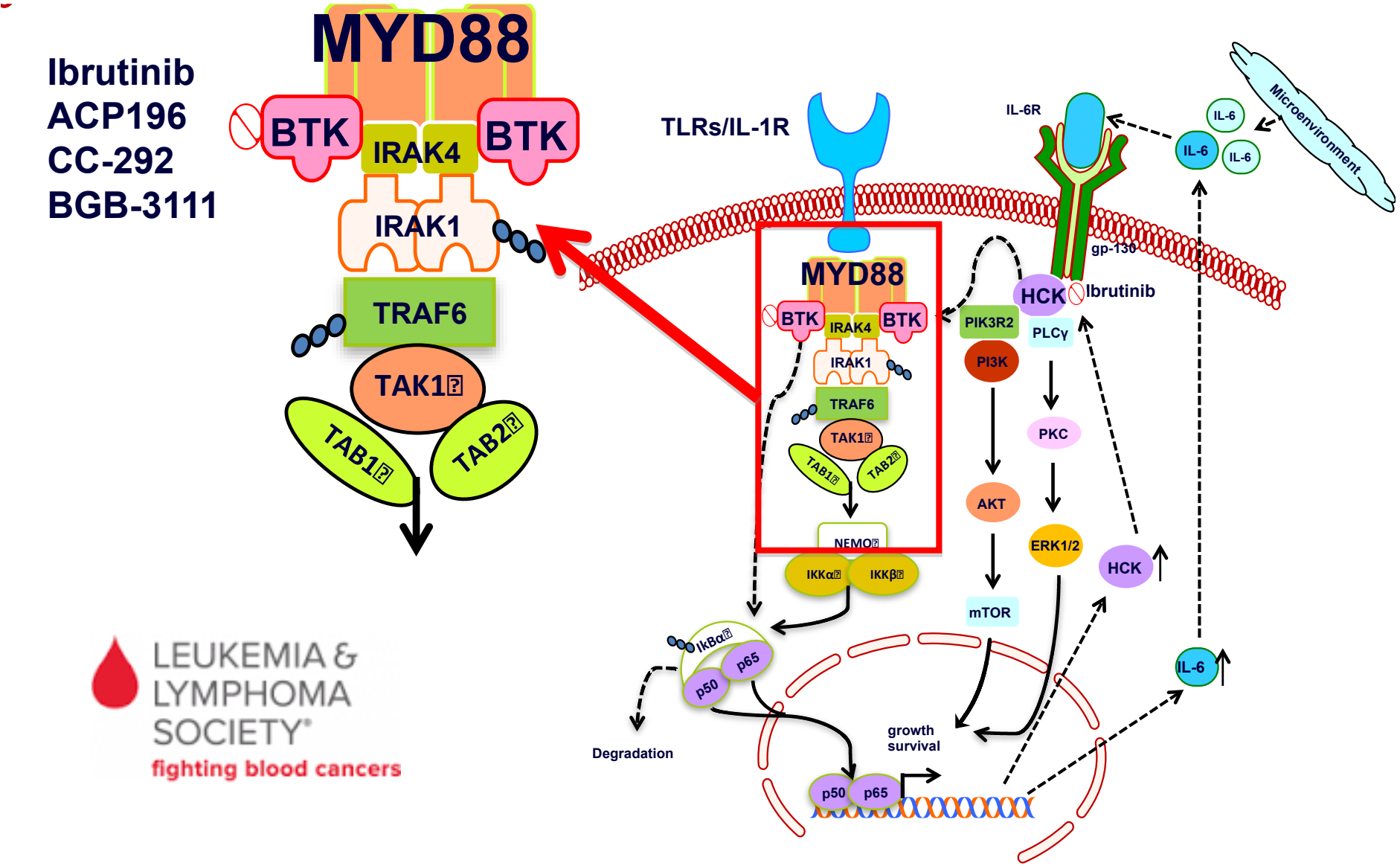
Primary Therapy of WM with Ibrutiinib

N=30
420 mg a day x 4 years
All patients are undergoing whole genome sequencing at 6, 12, 24, 36, 48 months
Clonal sequencing to determne how individual cells respond to ibrutinib.

Study fully enrolled

Strategies to Enhance Ibrutinib Activity in WM

Signaling Pathways Driven by Mutated MYD88 in Waldenström's Macroglobulinemia



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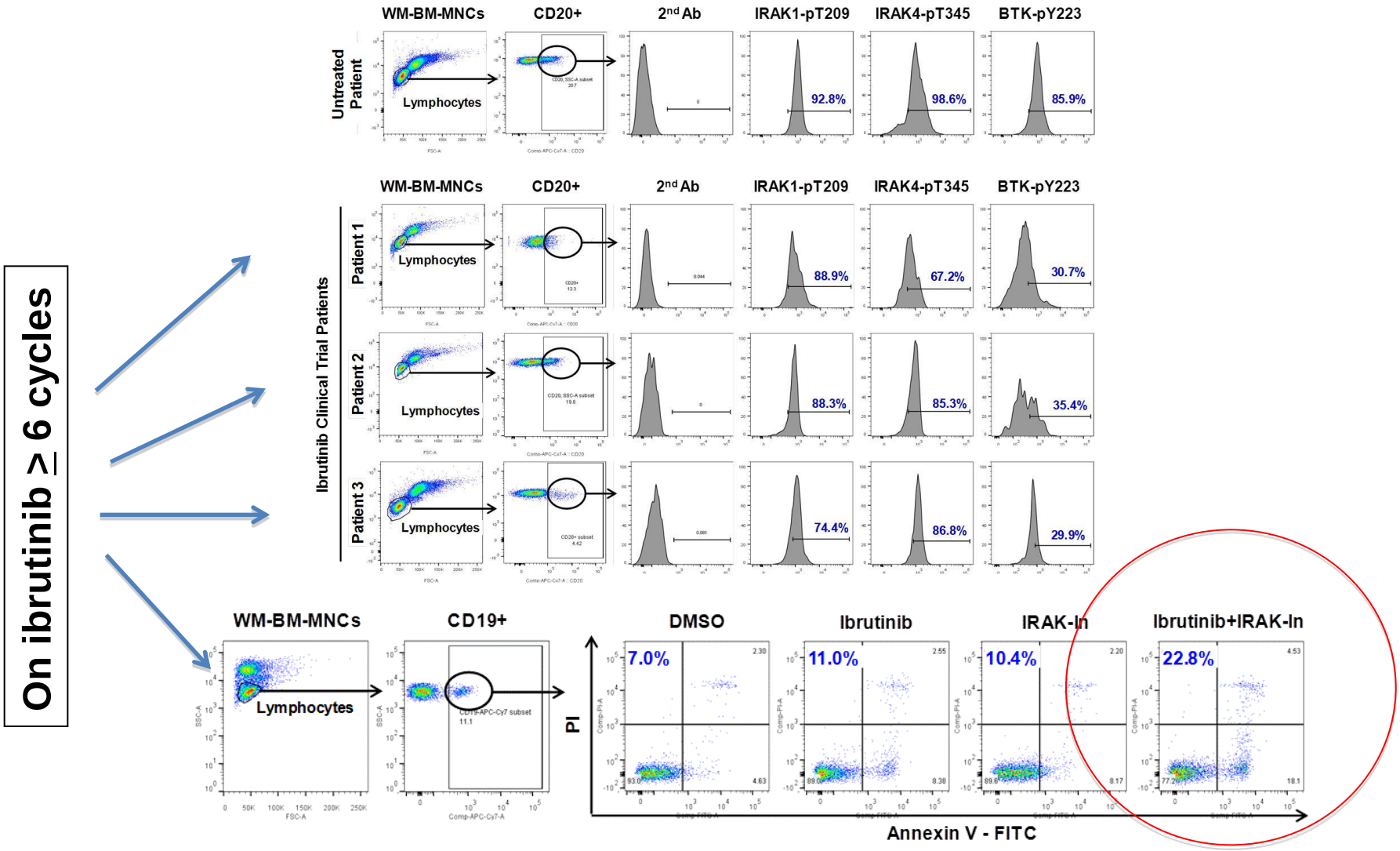
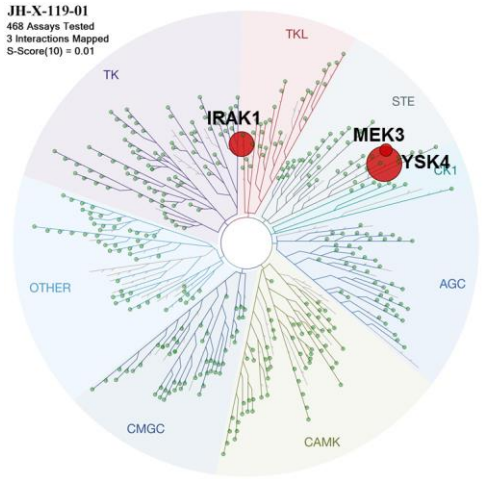
fighting blood cancers

IRAK1/4 kinase survival signaling remains intact in WM cells from ibrutinib treated patients.



Combining of Novel IRAK1 inhibitor JH-X-119 with Ibrutinb Shows Synergism in MYD88 Mutated Cells

Sara Buhrlage Nathanael Gray



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IWMF
International Waldenstrom's Macroglobulinemia Foundation

BCWM.1

Ibrutinib

Combination Index

JH-X-119-01

μM	4.000	1.265	0.400	0.126	0.040
20.000	0.761	0.663	0.752	0.958	1.043
6.325	0.488	0.424	0.454	0.556	0.577
2.000	0.605	0.572	0.734	1.051	1.105
0.632	0.573	0.557	0.622	0.743	0.982
0.200	0.561	0.375	0.397	0.428	0.32

0 1 10

TMD-8

Ibrutinib

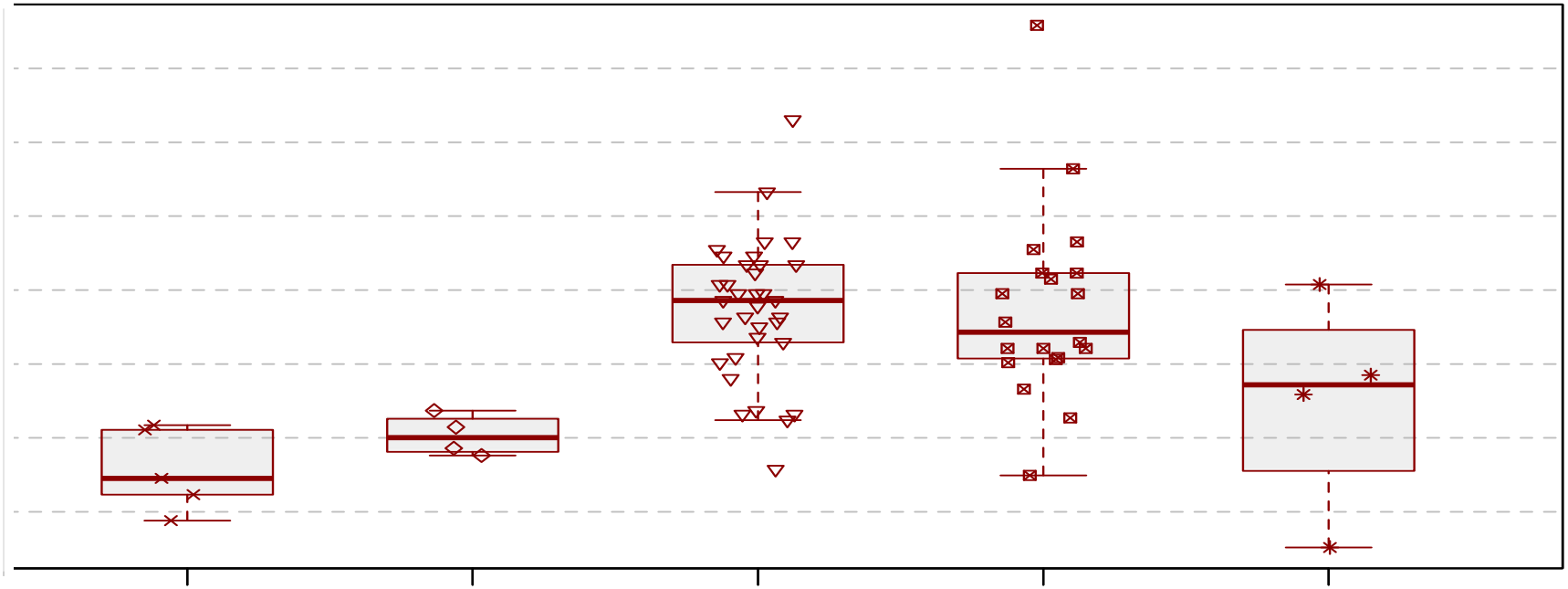
Combination Index

JH-X-119-01

μM	0.040	0.013	0.004	0.001	0.000
20.000	0.193	0.035	0.025	0.066	0.502
6.325	0.126	0.022	0.014	0.08	0.379
2.000	0.375	0.115	0.082	0.343	0.879
0.632	0.914	0.321	0.179	0.485	0.941
0.200	1.112	0.387	0.232	0.649	0.696

0 1 10

BCL-2 is overexpressed in primary WM patient cells by transciptome analysis in MYD88 mutated patients regardless of CXCR4 mutation status.



Healthy Donor $CD19^{+}CD27^{-}$

Healthy Donor $CD19^{+}CD27^{+}$

WM $CD19^{+}$ $MYD88^{L265P}$ $CXCR4^{WT}$

WM $CD19^{+}$ $MYD88^{L265P}$ $CXCR4^{WHIM}$

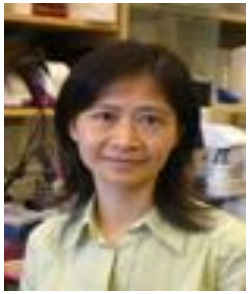
WM $CD19^{+}$ $MYD88^{WT}$ $CXCR4^{WT}$

$p<0.001$ for healthy donor samples versus any $MYD88^{L265P}CXCR4^{WT\ or\ WHIM}$

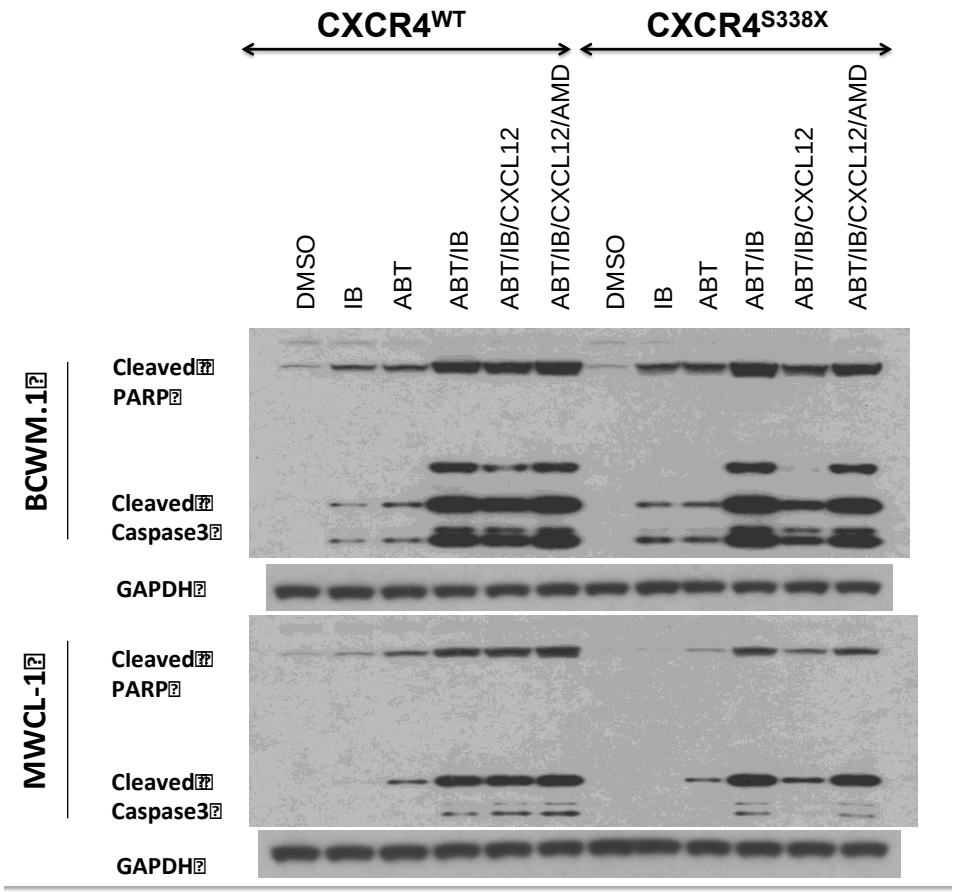
Castillo et al, ICML 2015; Hunter et al, BLOOD 2016


BCL2
giaccherini
13


36
HAMHUIS
36

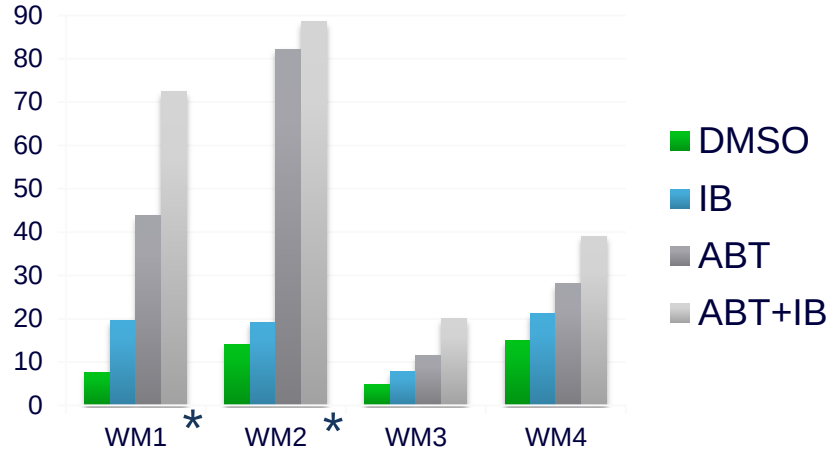


Venetoclax (ABT-199) enhances Ibrutinib killing in MYD88 mutated WM Cells.

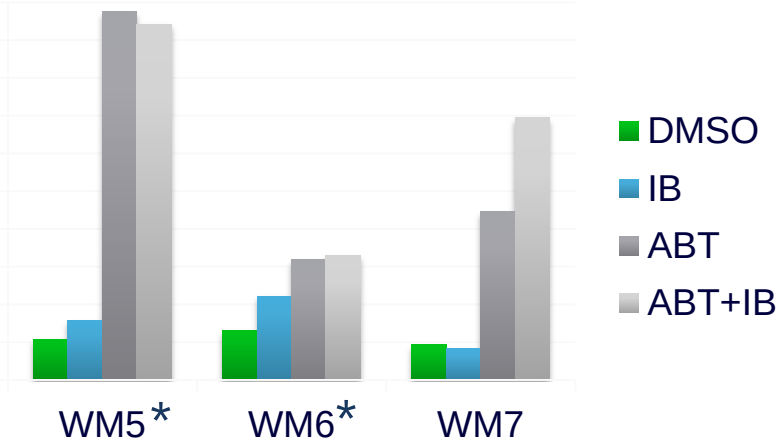


Cao et al, BJH 2015

Untreated

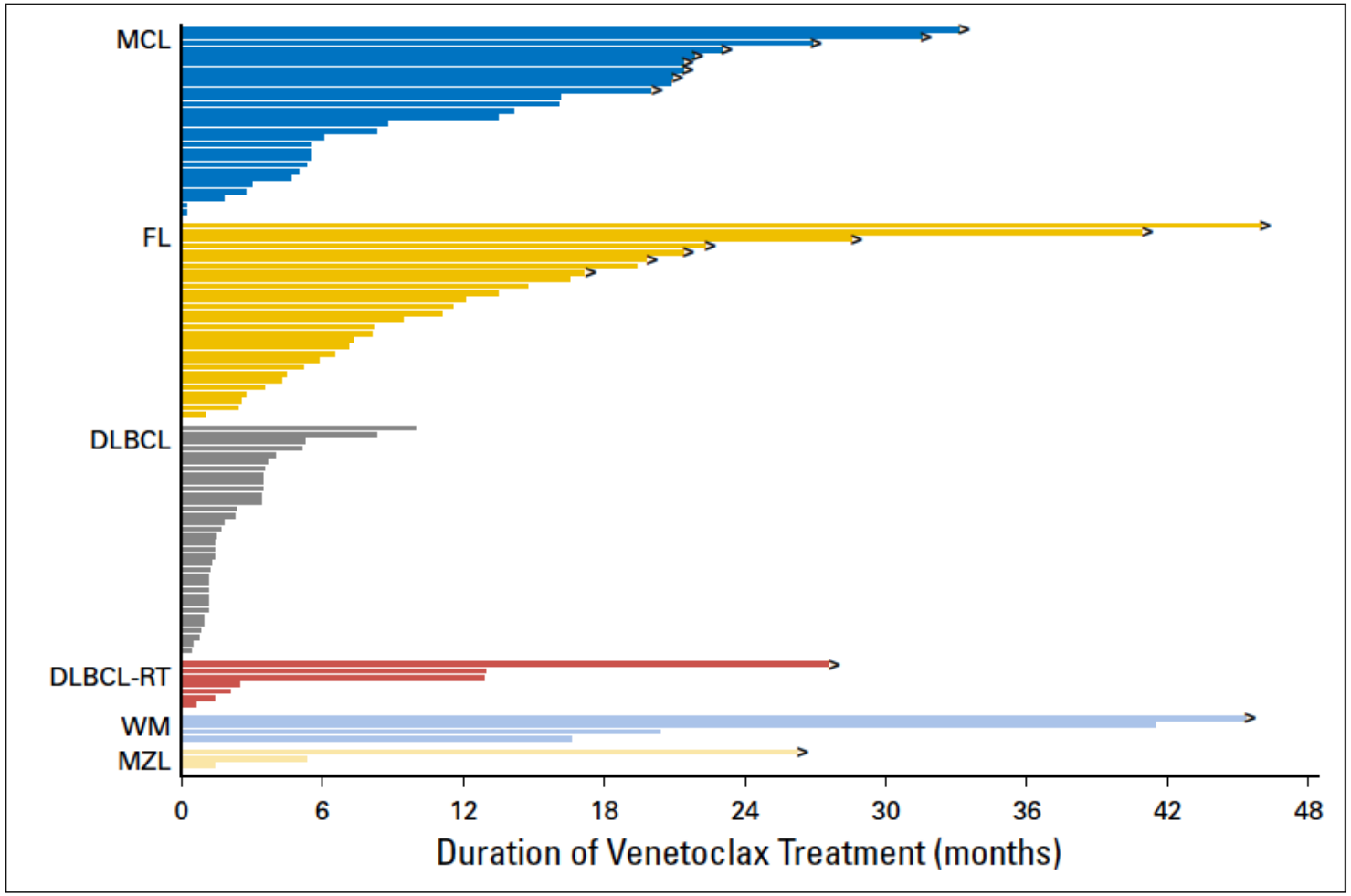


Ibrutinib >6 mo.

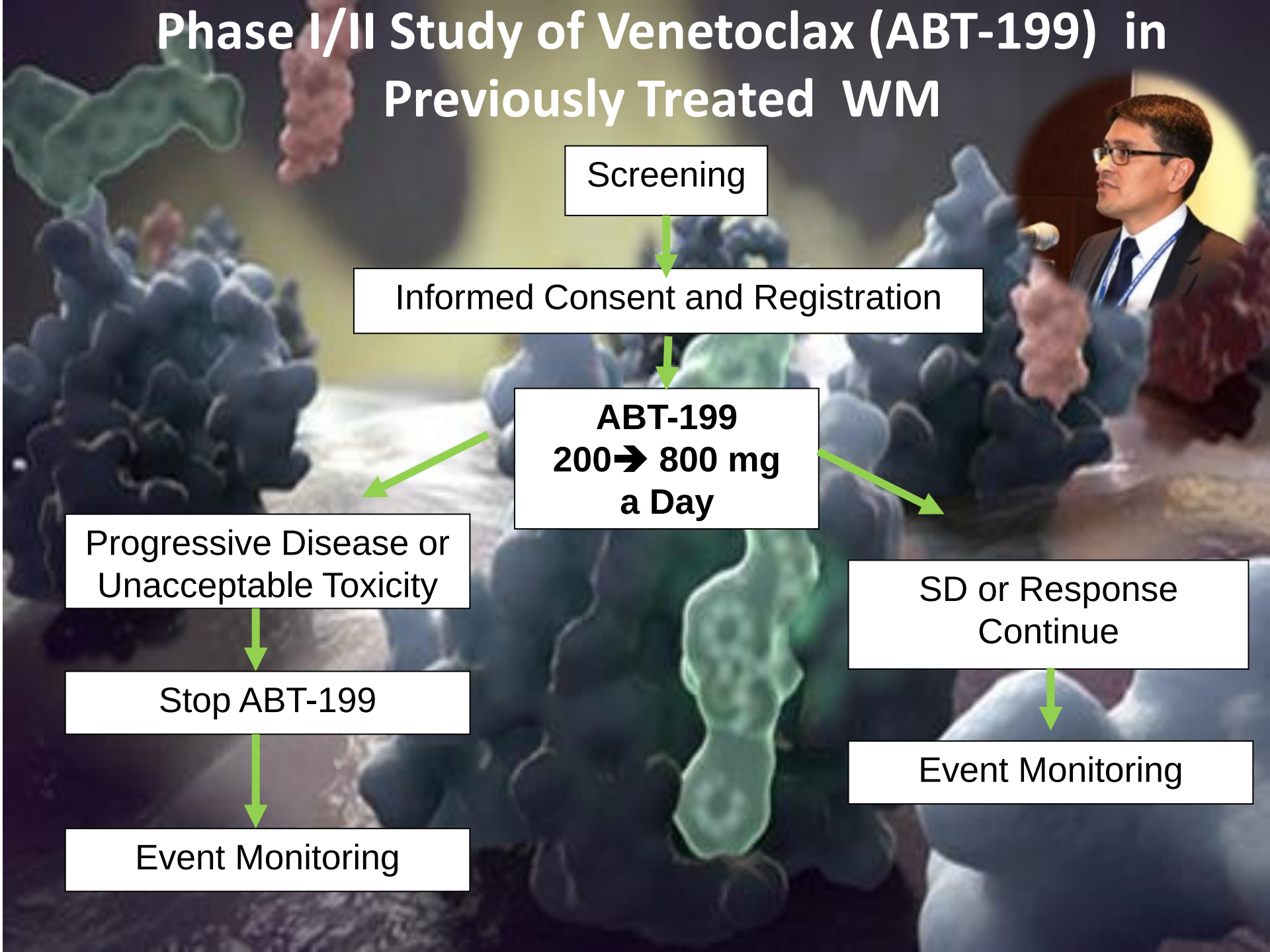


*CXCRWHIM

Activity of the anti-BCL2 agent Venetoclax (ABT-199) in previously treated NHL Patients



Gericitano et al, ASH 2015, Davids et al, JCO 2017


Phase I/II Study of Venetoclax (ABT-199) in Previously Treated WM
Screening
Informed Consent and Registration
ABT-199 200➔ 800 mg a Day
Progressive Disease or Unacceptable Toxicity
Stop ABT-199
Event Monitoring
SD or Response Continue
Event Monitoring

Acquired Resistance in WM Patients on Ibrutinib.

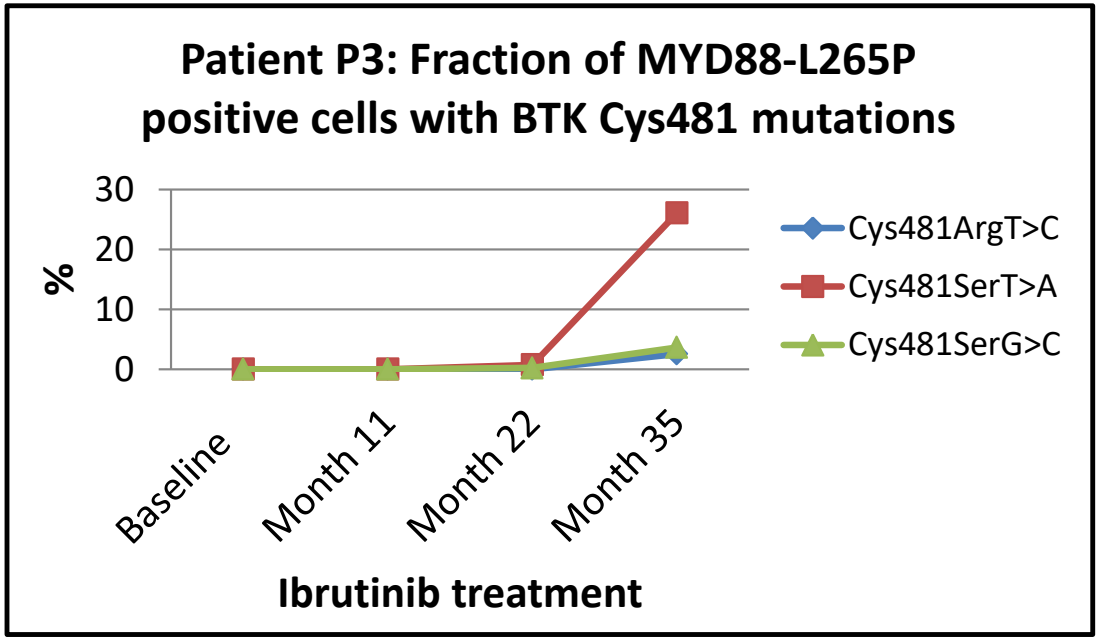
Patient*	L265P positive cells with BTK C481R$^{T>C}$	L265P positive cells with BTK C481S$^{T>A}$	L265P positive cells with BTK C481S$^{G>C}$	L265P positive cells with BTK C481Y$^{G>A}$	L265P positive cells with PLCG2 Y495H$^{T>C}$	L265P positive cells with CARD11 L878F$^{C>T}$
P1	None	None	None	None	None	None
P2	32.4%	6.6%	5.8%	1.0%	None	None
P3	0.3%	34.4%	6.5%	0.3%	None	0.2%
P4	None	None	None	None	None	None
P5	None	None	None	None	None	None
P6	None	None	10.3%	None	11.9%	None

Targeted next-generation sequencing for MYD88, CXCR4, BTK, PLCG2, CARD11, LYN. All patients are MYD88 Mutated.

P2, P3, P6 are CXCR4 WHIM Mutated.

Xu et al, BLOOD 2017

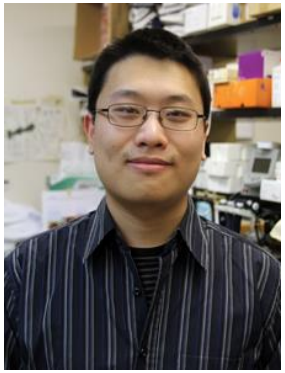
Serial samples from WM Patient P3 with multiple BTK Cys^{481} mutations



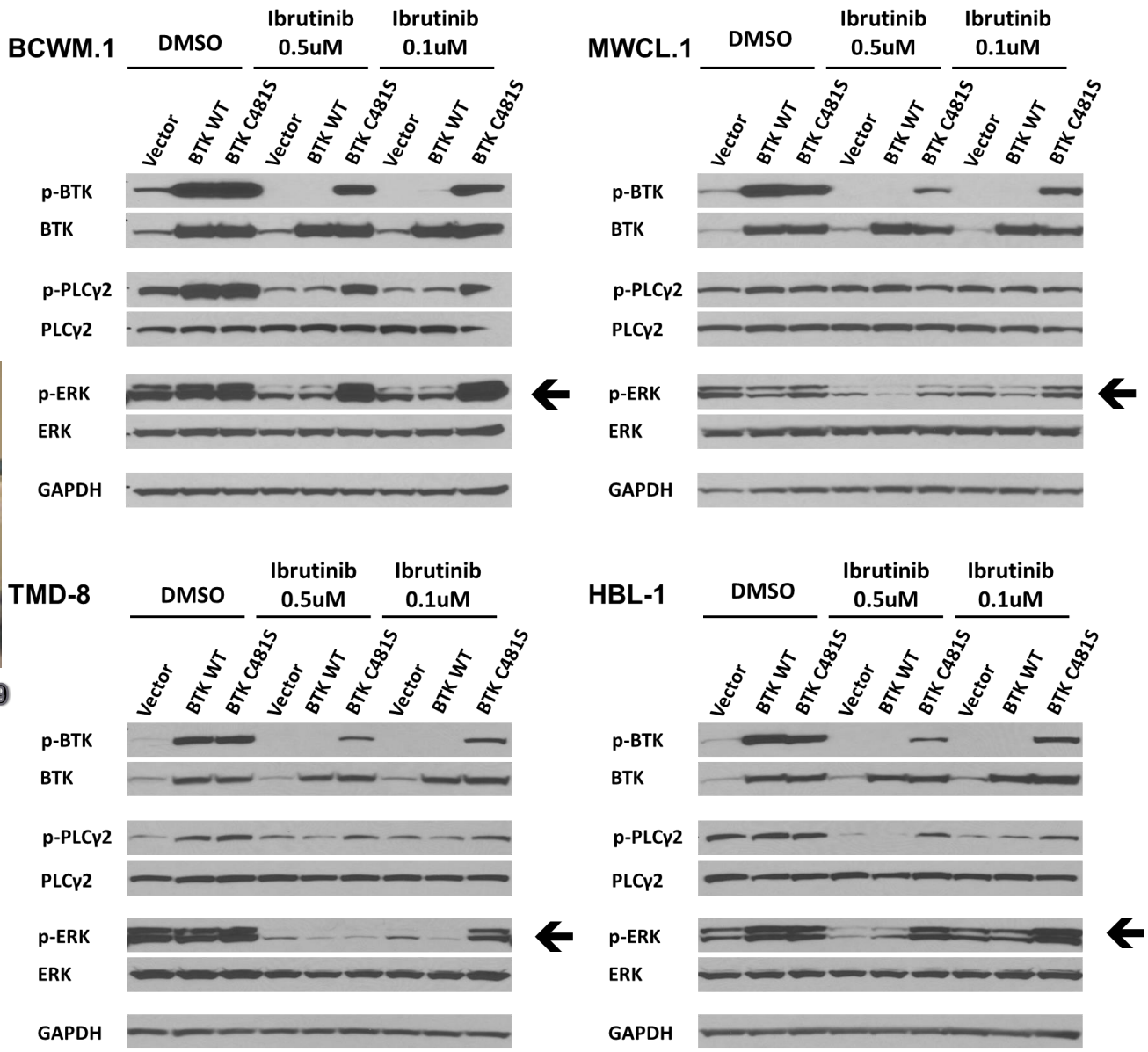
Sampling date	Cys481ArgT>C	Cys481SerT>A	Cys481SerG>C
Baseline	0.00	0.00	0.00
Month 11	0.00	0.00	0.00
Month 22	0.00	0.71%	0.19%
Month 35	2.54%	26.08%	3.62%

Xu et al, BLOOD 2017

BTK C481S expressing cells displayed persistent activation of BTK and ERK1/2 following Ibrutinib treatment.

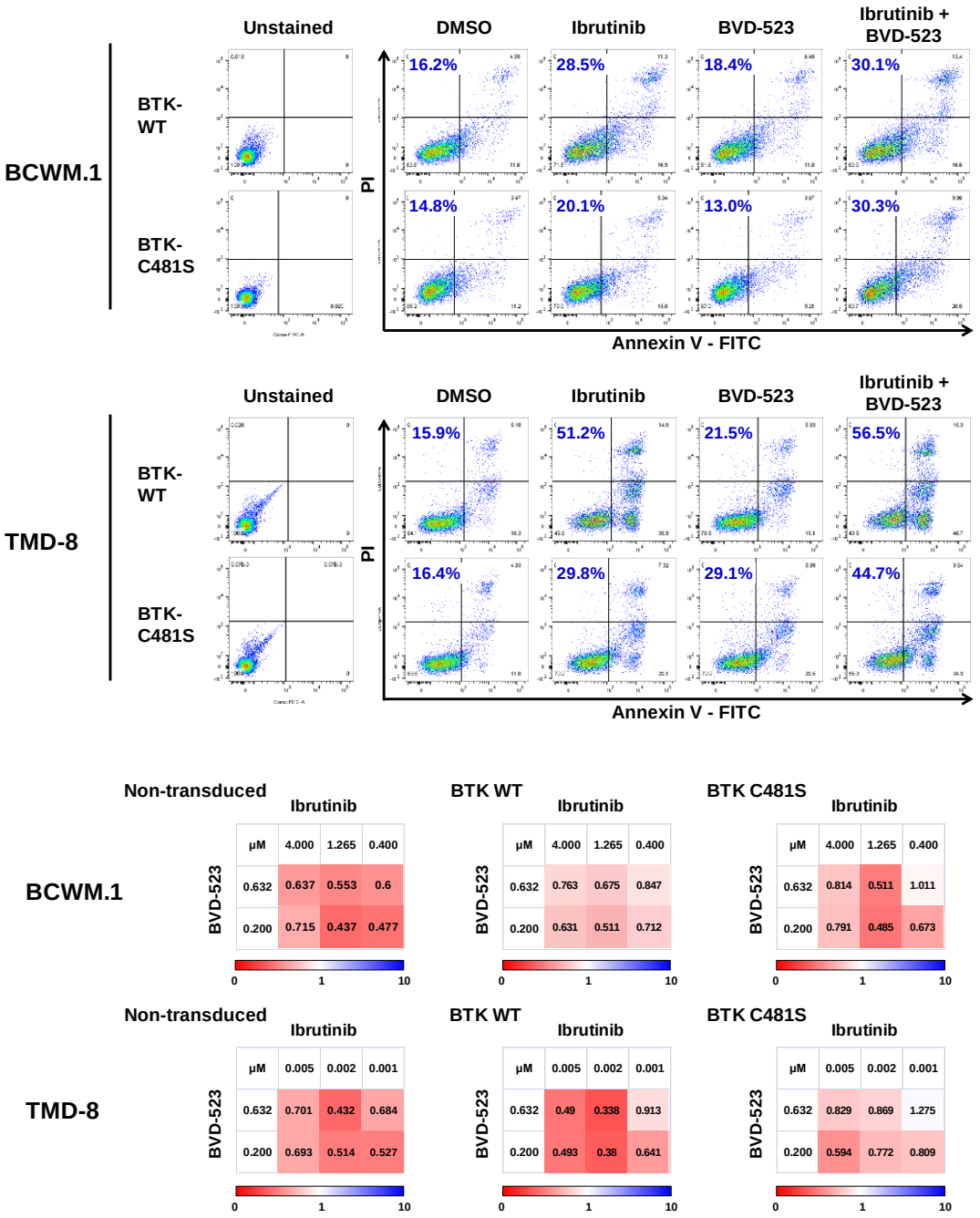


Chen et al, IWWM9



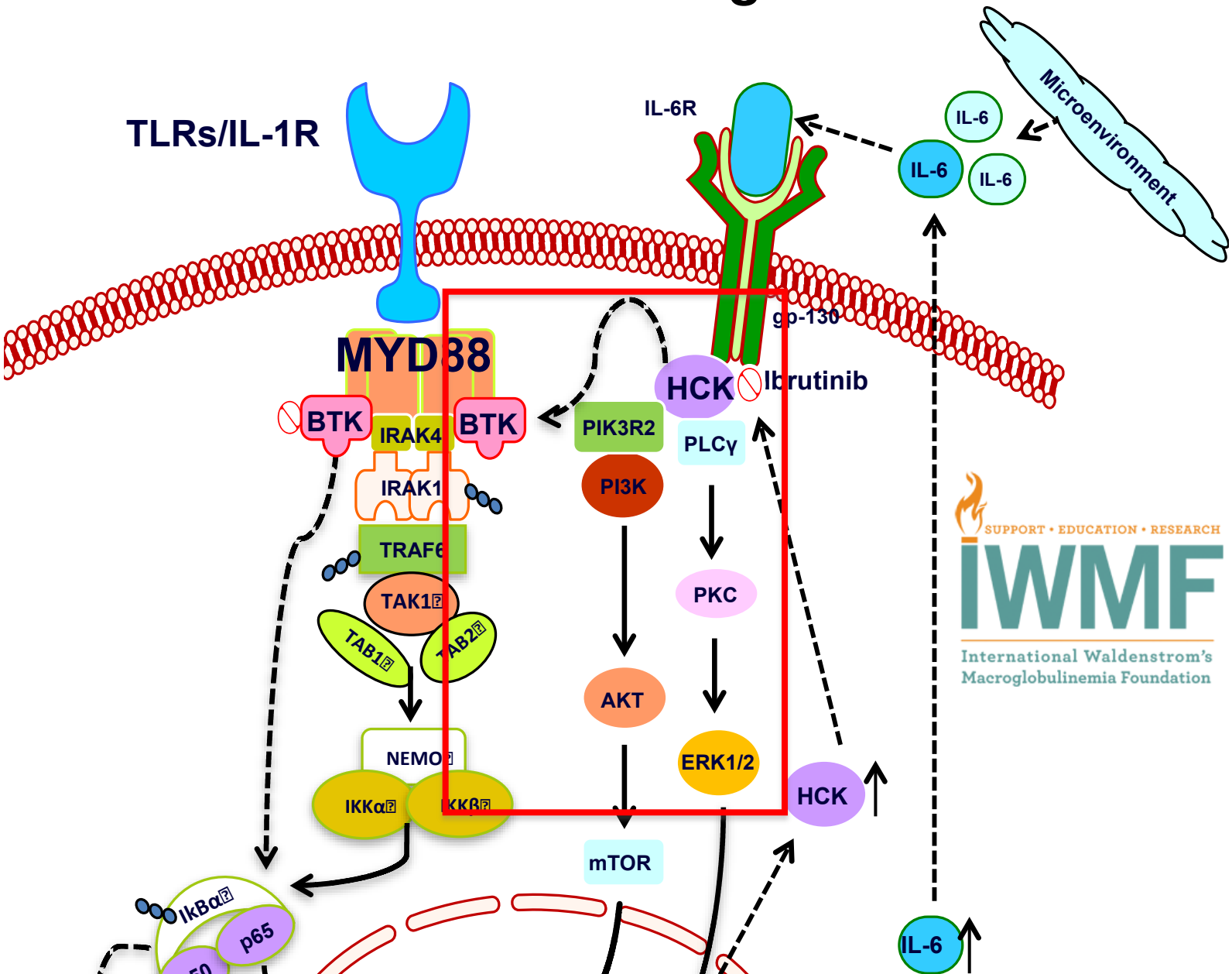
Chen et al, ASH 2016

Enhanced killing in BTK^{Cys481} mutated cells treated with ibrutinib and the ERK inhibitor BVD-523.

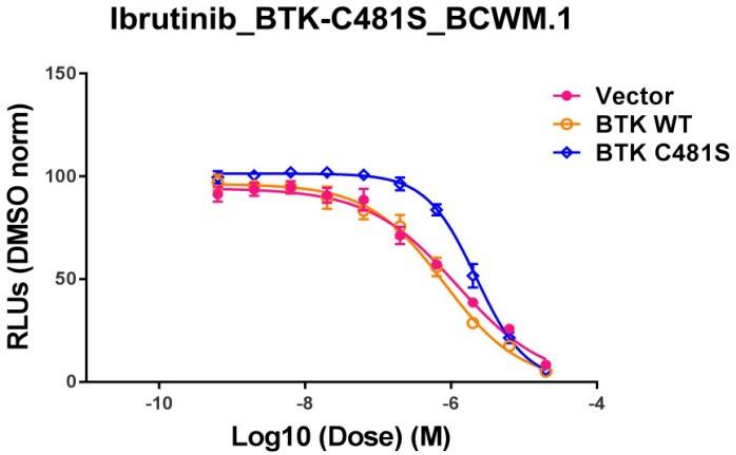


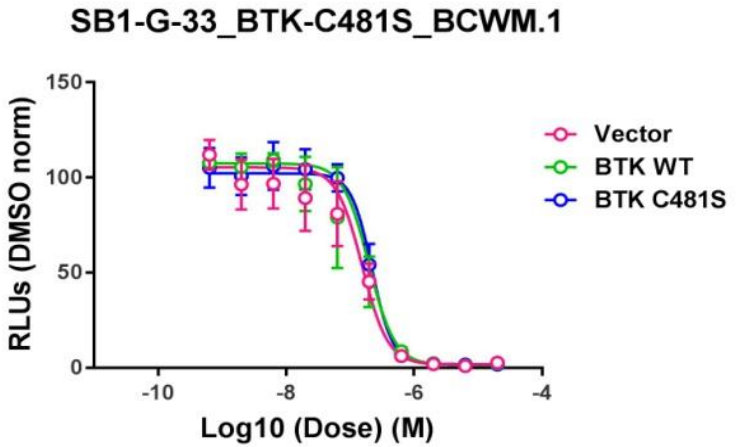
Chen et al, ASH 2016

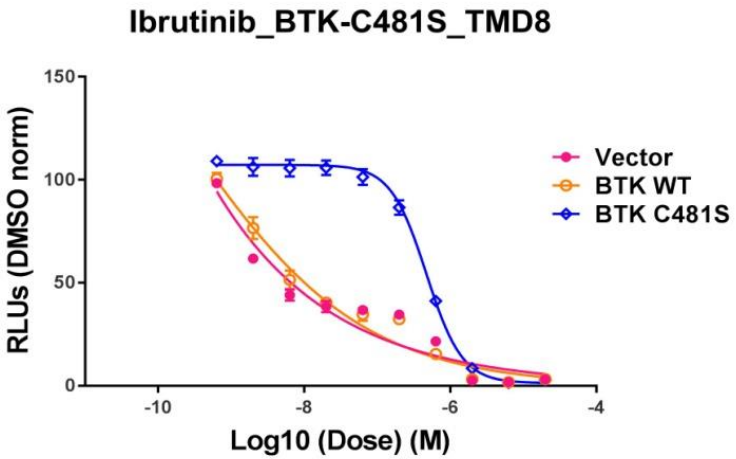
Targeting HCK signaling in MYD88 driven Waldenström's Macroglobulinemia

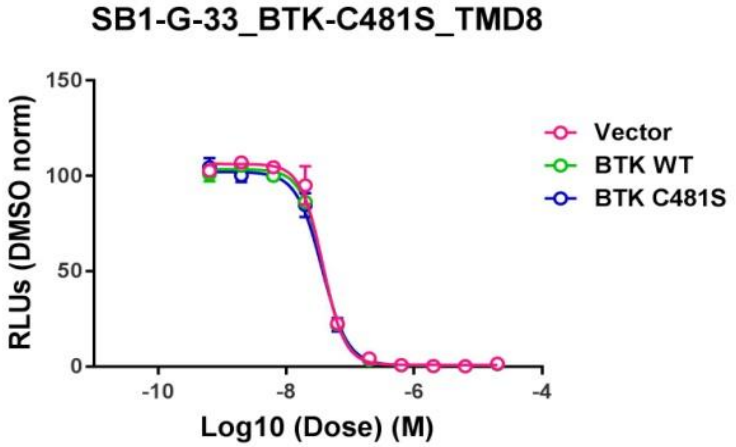


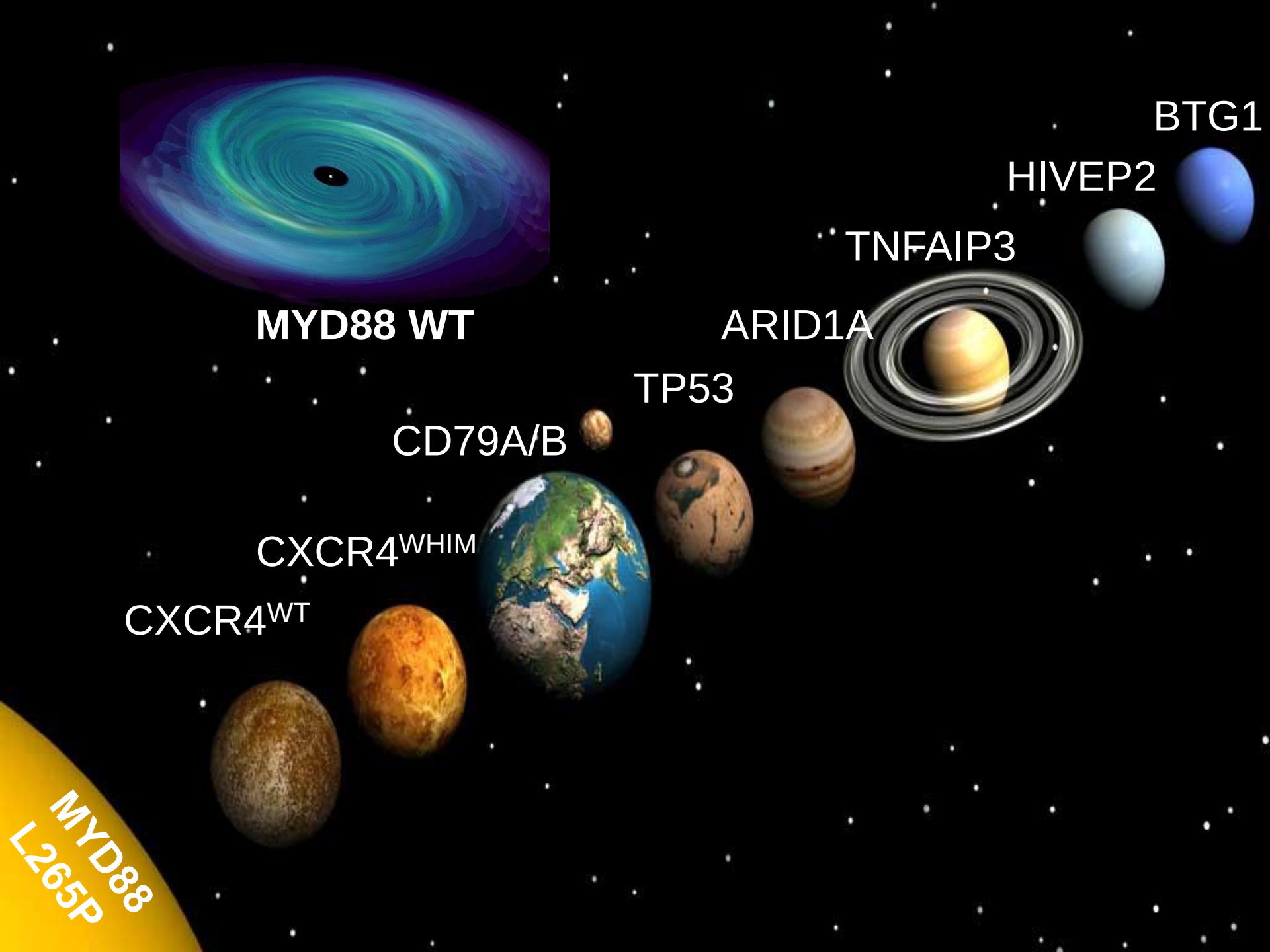
The HCK inhibitor SB1-G-33 overcomes BTK^{C481S} mutated ibrutinib resistant WM and ABC DLBCL cells.









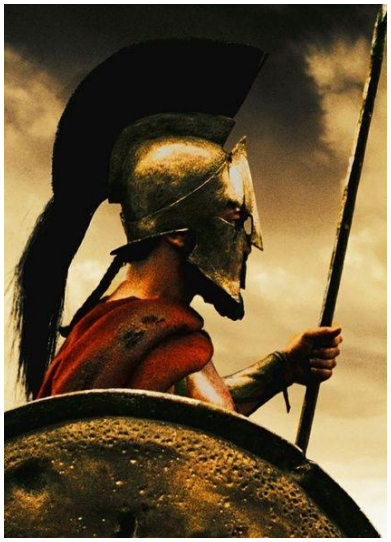

MYD88 WT
BTG1
HIVEP2
TNFAIP3
ARID1A
TP53
CD79A/B
CXCR4WHIM
CXCR4WT
MYD88
L265P

Differential Diagnosis of MYD88 WT WM

N=	Diagnosis	M-protein	sIgM	BM (%)	Flow	IgH
29	Treated WM	IgM	1157	5%	9/27 (+)	3/13 (+)
13	Untreated WM	IgM	1051	20%	12/13 (+)	5/5 (+)
12	IGM MM	IgM	4012	25%	9/10 (+)	7/7 (+)
7	IgM MGUS	IgM	1078	3%	3/7 (+)	2/5 (+)
7	MZL	IgM	403	10%	2/7 (+)	2/4 (+)
5	B CELL LPD	IgM	493	5%	2/4 (+)	2/4 (+)
3	DLBCL	IgM	4130	65%	3/3 (+)	ND
1	CLL	IgM	959	3%	ND	ND

N=77

Unpublished data, DFCI



300 PROJECT

Sequence 300 Symptomatic Untreated WM Patients

-Determine mutations in the DNA by Whole Genome Seq.
-Determine transcriptional (RNA) changes
-Match them to epigenomic changes
-Develop targeted therapies based on mutation profile for individual patients
-Understand impact on disease presentation, course, survival

New Driver Mutations Identified in MYD88 WT WM

Approach to Frontline Therapy of Symptomatic WM

Hyperviscosity, Severe Cryos, CAGG, PN➔ Plasmapheresis

MYD88 Mutated/No CXCR4 mutation

No bulky disease, no contraindications➔ Ibrutinib (if available)
Bulky disease ➔ Benda-R
Amyloidosis ➔ Bortezomib/Dex/Rituximab (BDR)
IgM Peripheral Neuropathy ➔ Rituximab ± Alkylator

MYD88 Mutated/CXCR4 mutation

Same caveats as above
If immediate response needed, either BDR or Benda-R

MYD88 Wild-Type

✓ non-L265P MYD88 mutations
BDR or Benda-R

- **Hold Rituximab until IgM <4000 mg/dL or empiric pheresis is performed.**
- **Consider Maintenance Rituximab**
- **Consider Ofatumumab if R intolerant.**

Salvage Therapy of Symptomatic WM

Consider repeat primary therapy if response >2 years

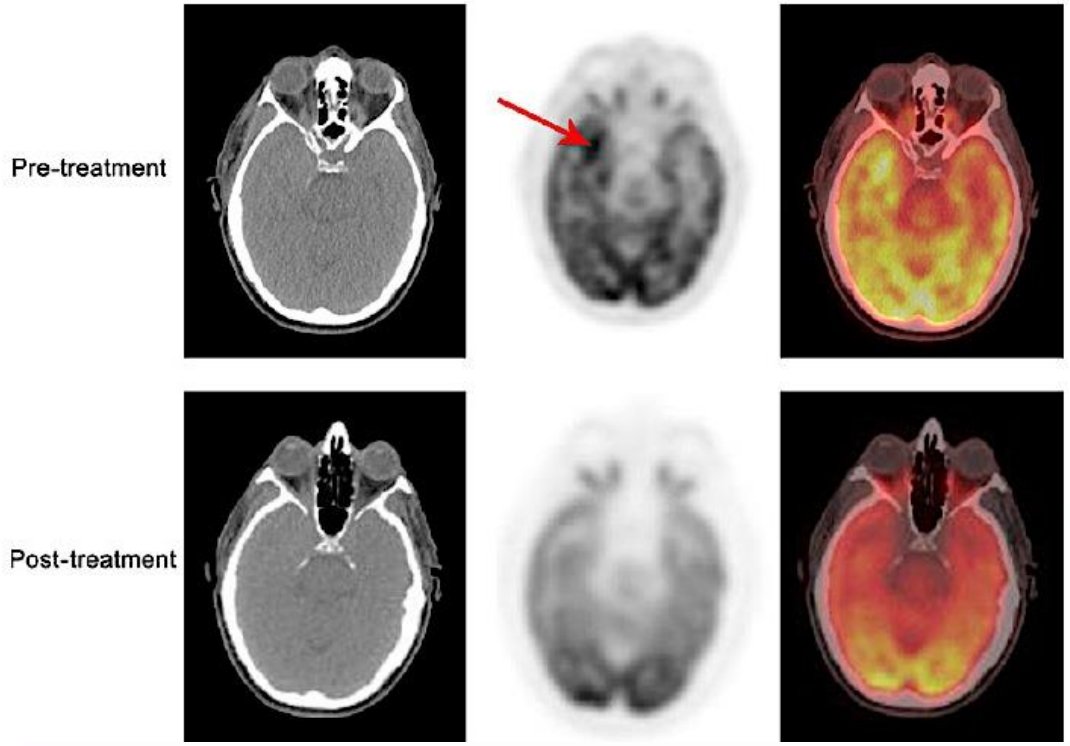
MYD88 Mutated/No CXCR4 mutation
Same caveats as primary therapy

MYD88 Mutated/CXCR4 mutation
Same caveats as primary therapy
If immediate response needed, either BDR or Benda-R

MYD88 Wild-Type
Same caveats as primary therapy
✓ non-L265P MYD88 mutations

- **Everolimus >2 prior therapies**
- **Nucleoside analogues (non-ASCT candidates)**
- **ASCT in multiple relapses, chemosensitive disease**

Ibrutinib (560 mg/day) induced response in a WM patient with Bing Neel Syndrome



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

Summary

MYD88 and CXCR4 mutations are common in WM. MYD88 activates BTK and HCK in WM cells.

Ibrutinib targets BTK and HCK, and is produces high response rates and durable responses in R/R WM.

CXCR4 mutations are associated with delayed and/or decreased ibrutinib response. No major response in MYD88 wild-type patients.

Multiple BTK mutations common with acquired ibrutinib resistance, and associated with mutated CXCR4.

Novel treatment options include agents that target MYD88, CXCR4, and BCL2 signaling.

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International Workshops on Waldenstrom's Macroglobulinemia

Athens 2002

Paris 2004

Kos 2007

Stockholm 2008

Venice 2010

Newport 2012

London 2014

Amsterdam 2016

Young Investigator Award Recipients

IWWM9, Amsterdam 2016

10th International Workshop on Waldenstrom's Macroglobulinemia

New York City, NY
October 10-13, 2018

Patient Symposium
October 14, 2018

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WM Clinic Appointments
Jorge Castillo, MD
Toni Dubeau, NP
Patricia Sheehy, NP

WM Clinical Trials

- **Venetoclax**
- **Ibrutinib/Ulucuplomab**
- **Daratumumab (CD38)**
- **Ibrutinib vs. BGB-3111**

WM Workshop/Patient Symposium