New Insights into the Biology and Therapy of Waldenström's Macroglobulinemia

HARVARD MEDICAL SCHOOL

DANA-FARBER CANCER INSTITUTE

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Disclosures

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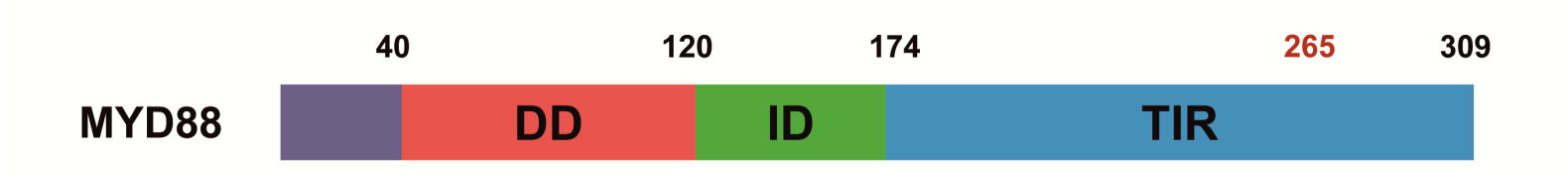
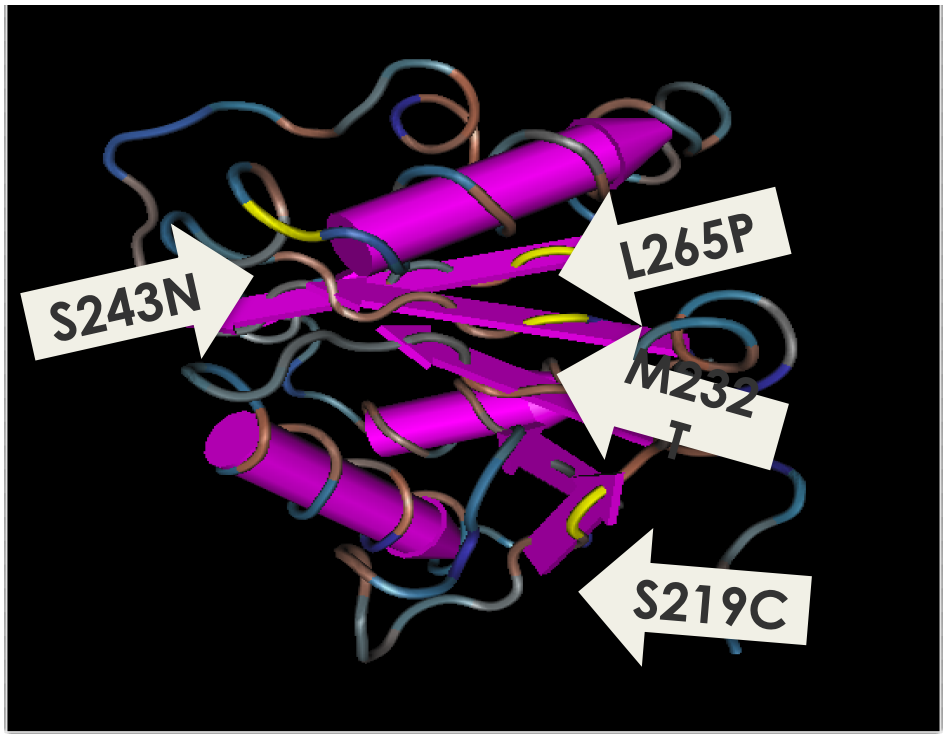
Research Funding

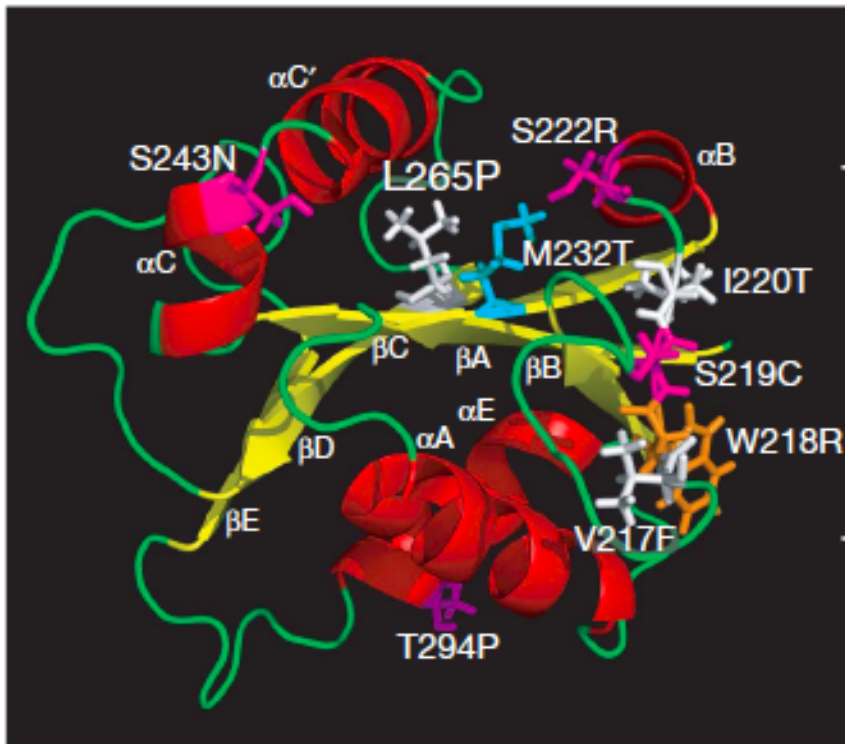
MYD88 Mutations in B-cell LPD



WM



ABC DLBCL

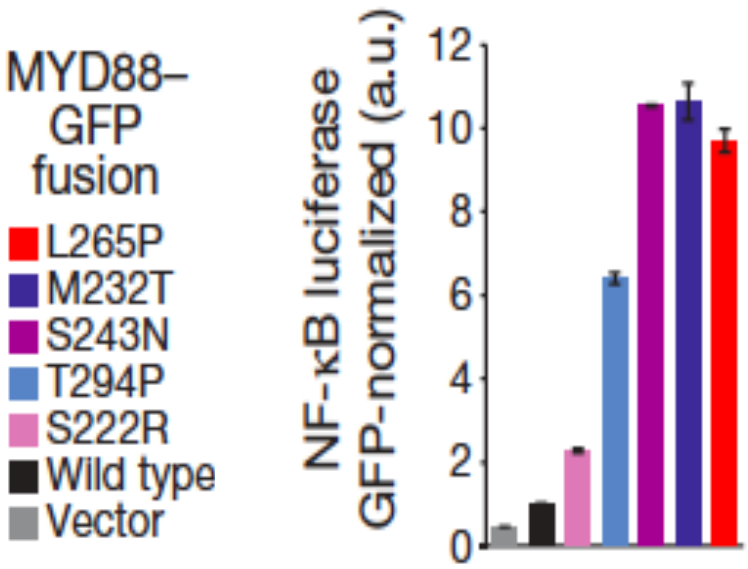


93-95% MYD88 L265P
2% Non-L265P MYD88

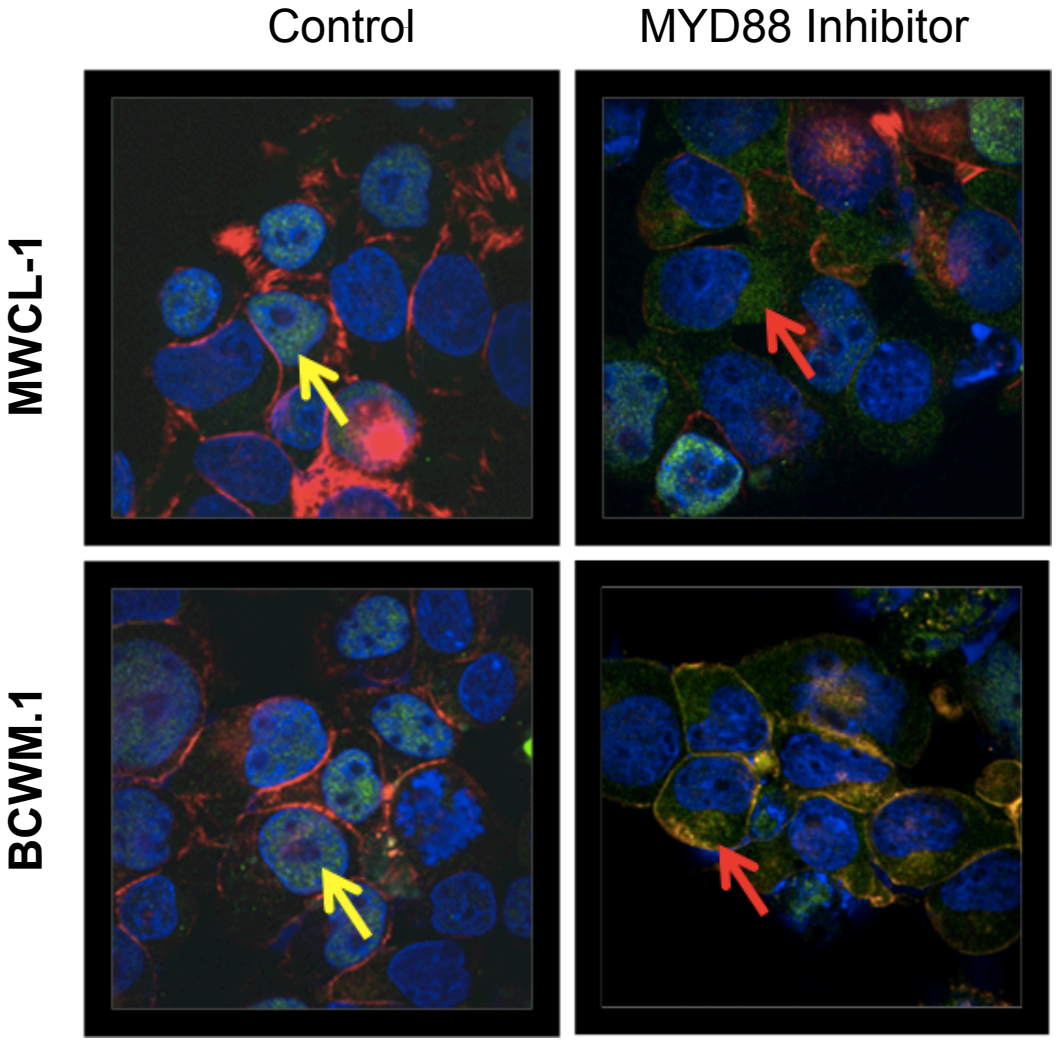
29% MYD88 L265P
10% Non-L265P MYD88

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

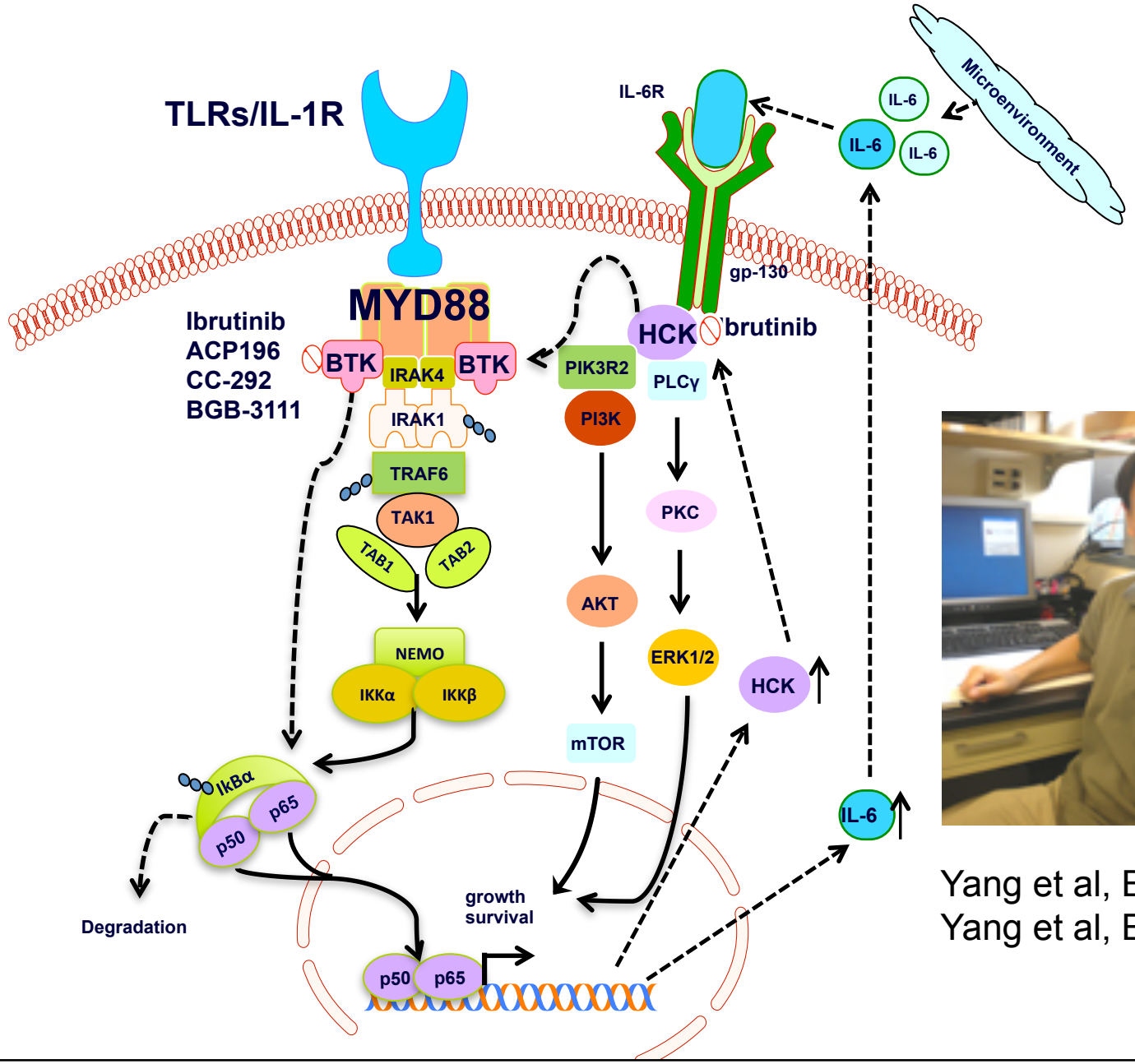


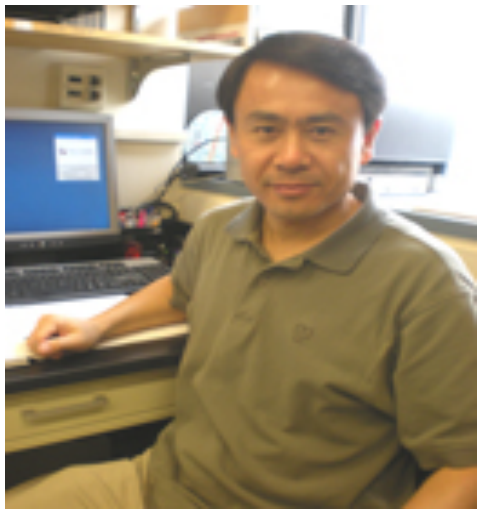
Ngo et al, Nature 2011
Treon et al, NEJM 2012



MYD88 L265P mutated WM cells

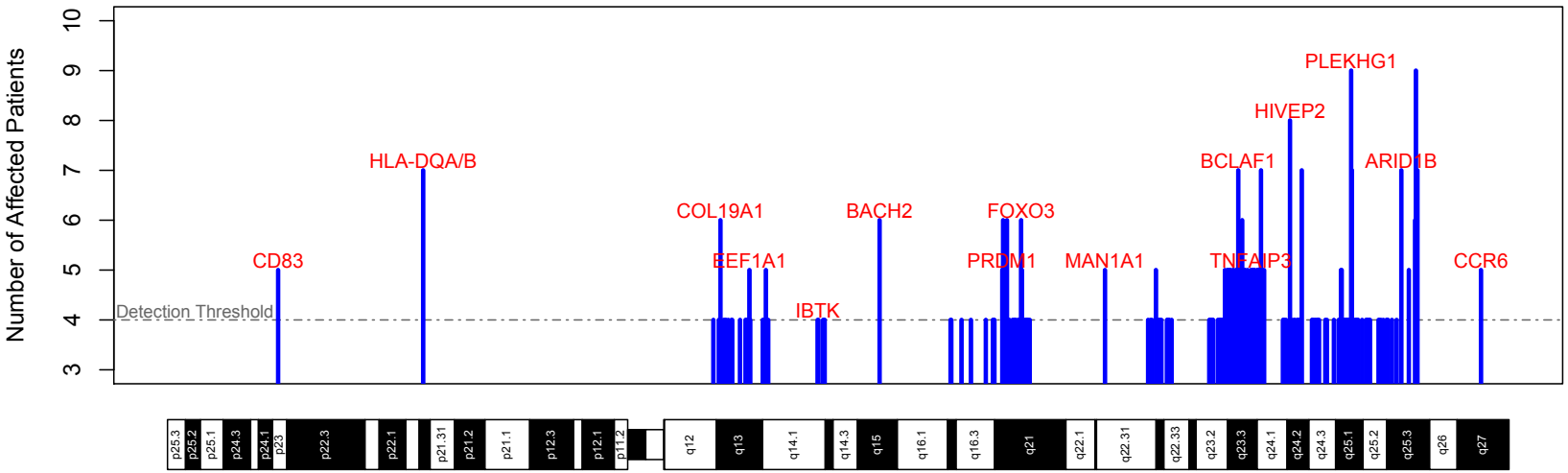
Signaling Pathways Driven by Mutated MYD88 in Waldenström's Macroglobulinemia

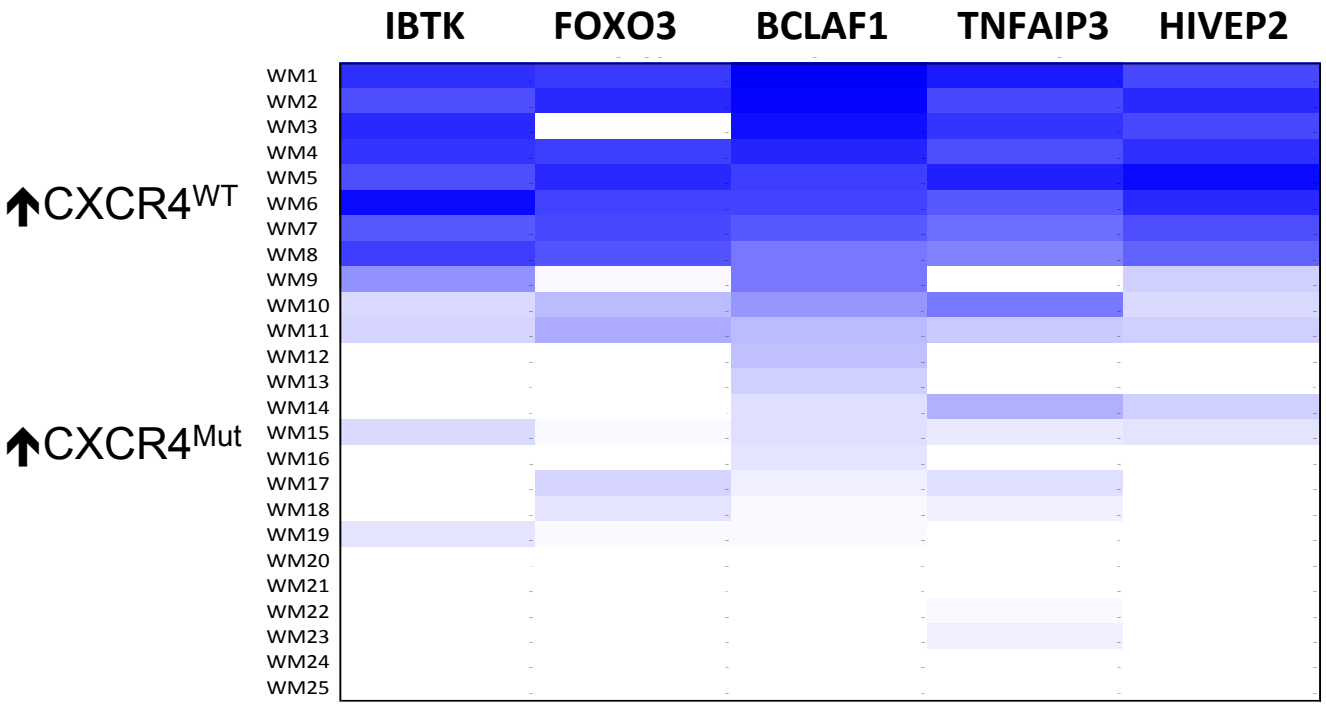


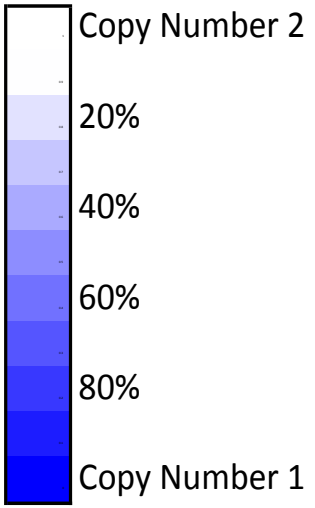


Yang et al, Blood 2013
Yang et al, Blood 2016

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



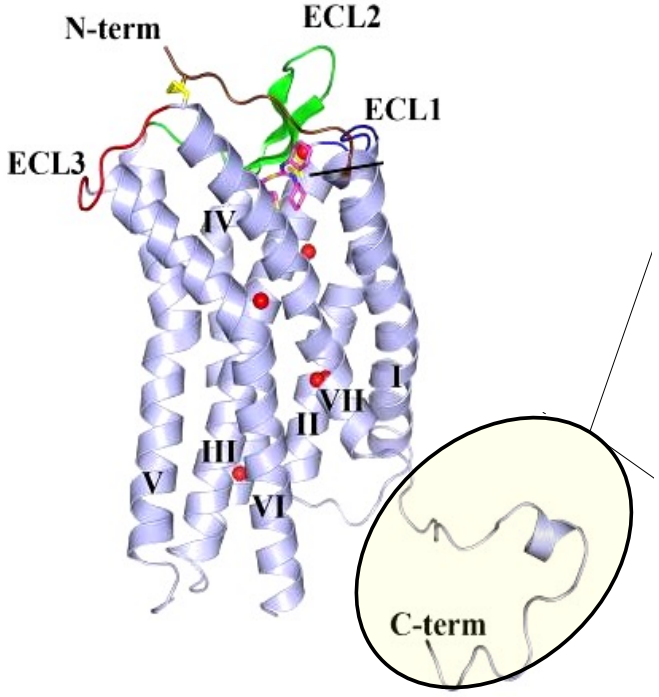




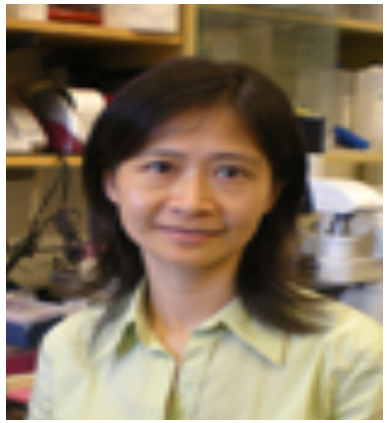
Guerrera et al, IWWM9

CXCR4 C-tail mutations in WM

- 30-40% of WM patients; v. rare in other LPD
- >30 Nonsense, Frameshift Mutations
- Segues with MYD88 mutations
- Transcriptional silencing of MYD88 pathway regulators
- Promote **ibrutinib resistance** through enhanced AKT/ERK signaling.

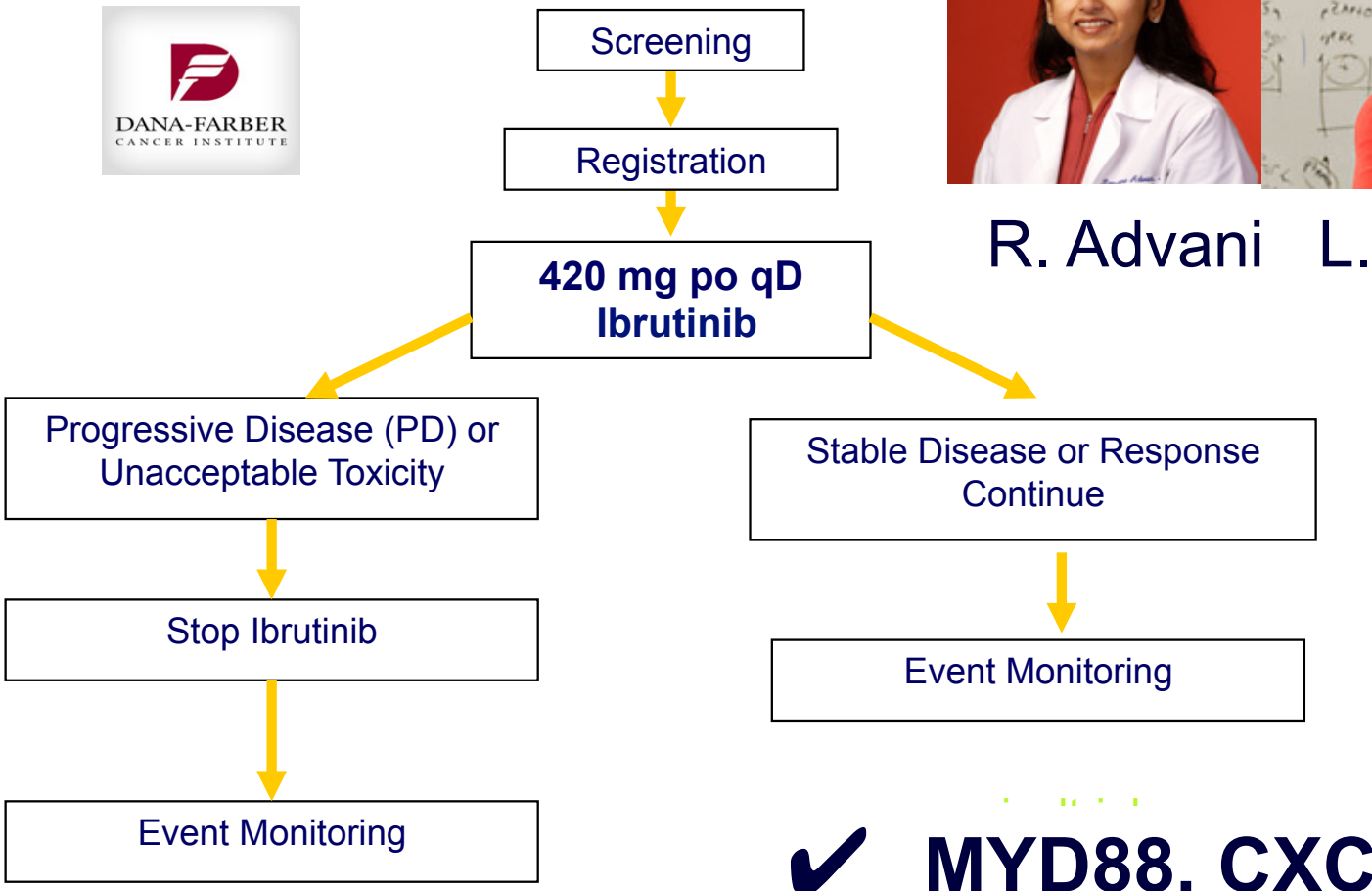


Hunter et al, Blood 2013;
Rocarro et al, Blood 2014:
Poulain et al, Blood 2016;
Cao et al, Leukemia 2014;
Cao et al, BJH 2015



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

R. Advani L. Palomba



✔ **MYD88, CXCR4 Mutation Status**

Best Clinical Responses to Ibrutinib

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

ORR: 91% Major RR (≥ PR): 73%

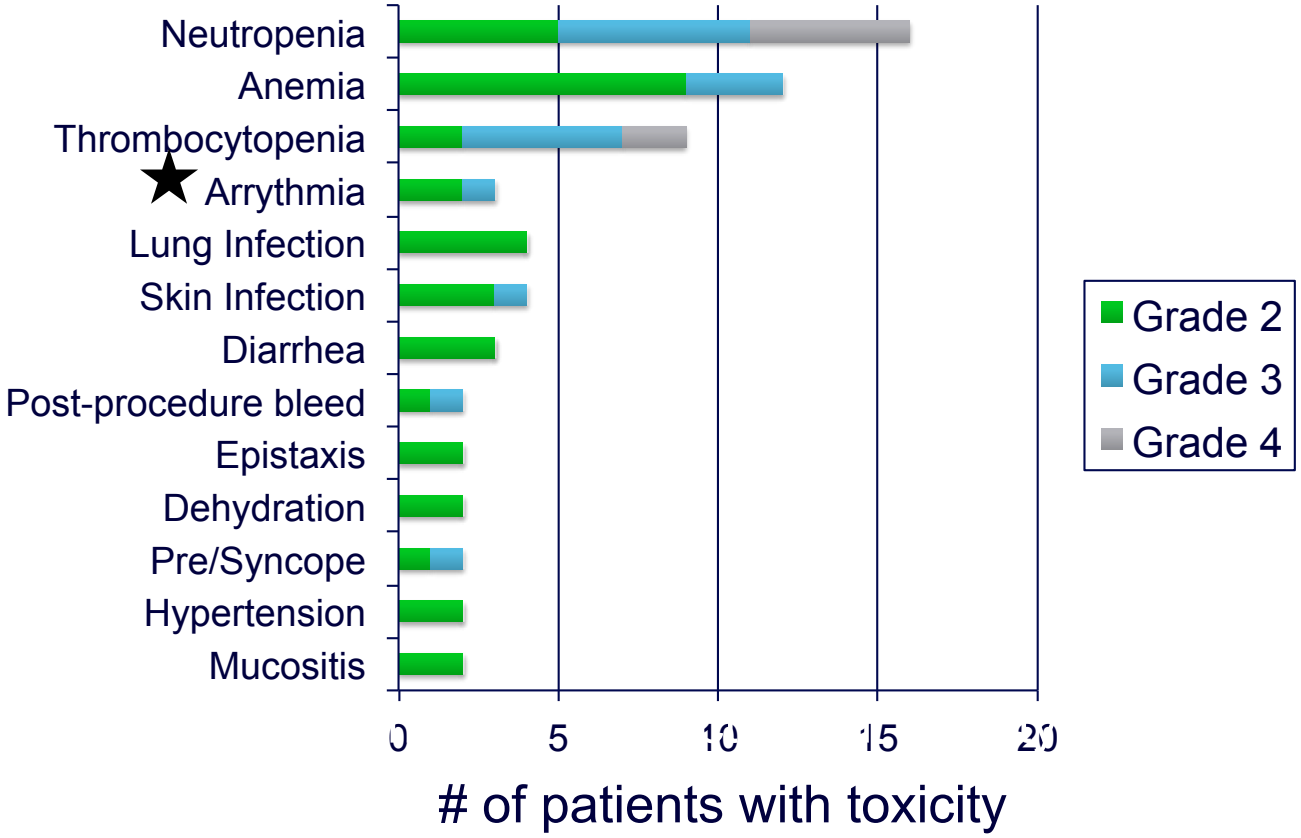
	(N=)	(%)
VGPR	10	16
PR	36	57
MR	11	17

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

Ibrutinib Related Adverse Events in previously treated WM patients

Toxicities >1 patient; N=63

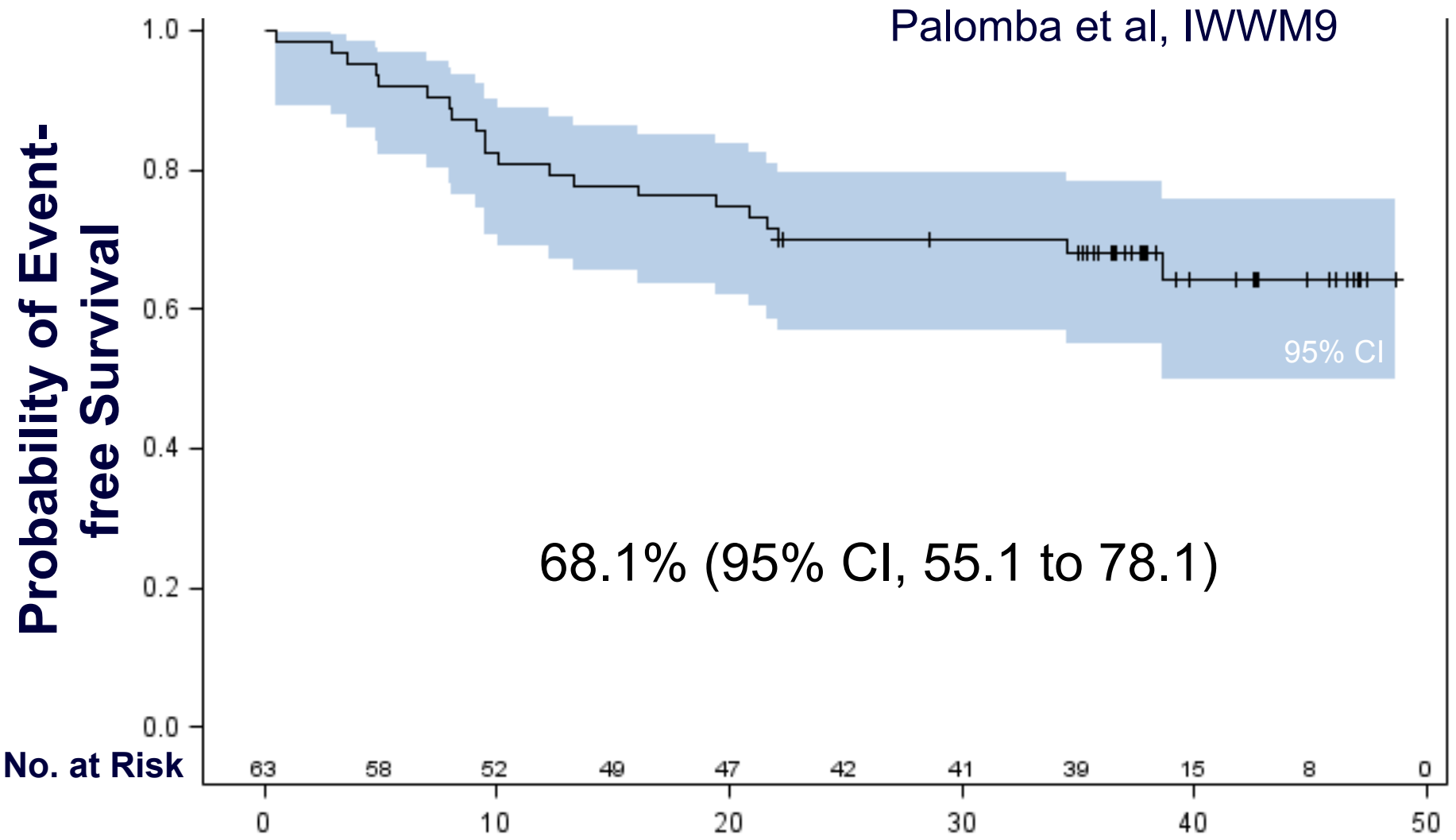


- **No impact on IGA and IGG immunoglobulins**

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

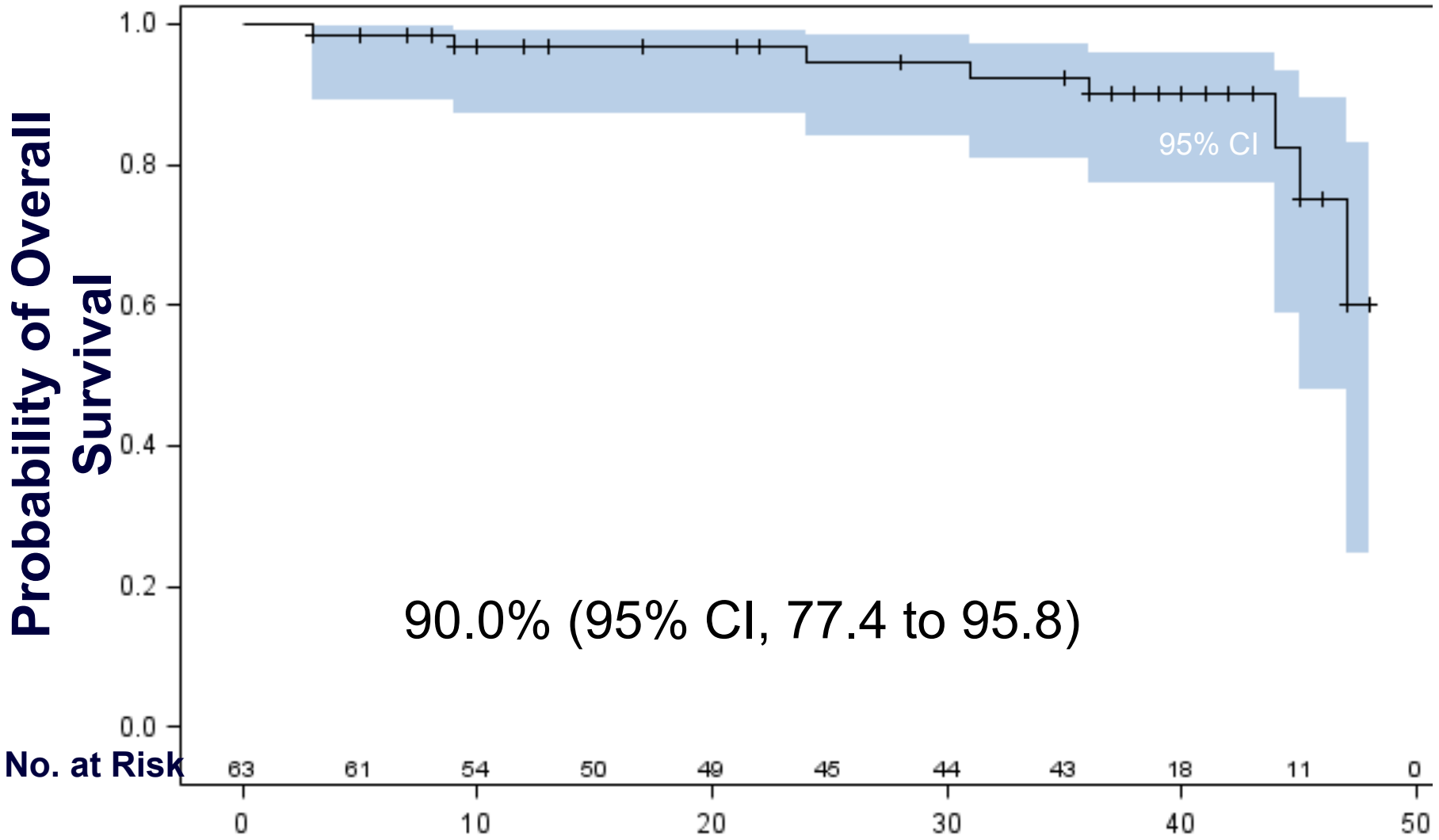
Treon et al, NEJM 2015; Gustine et al, AJH 2016

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

Health Canada Santé Canada

April 5, 2016

September, 2015

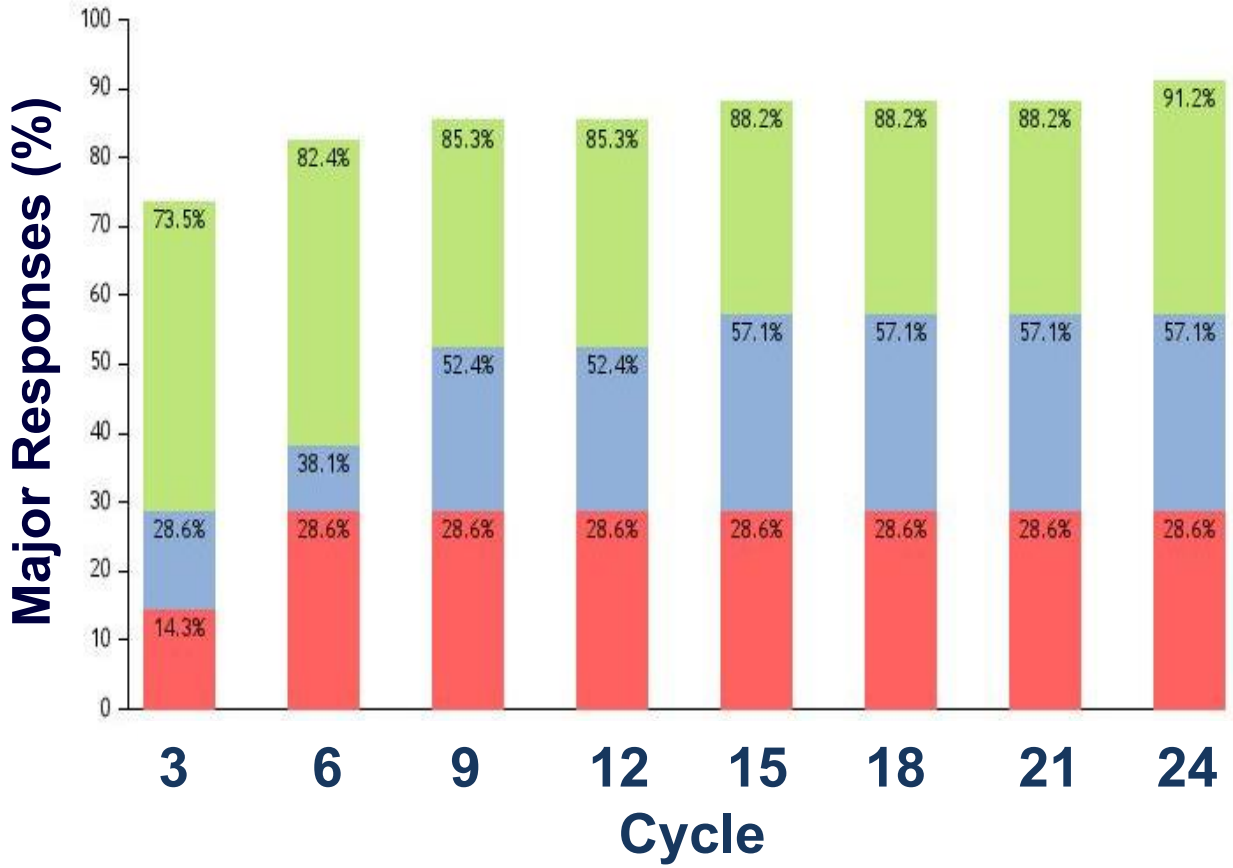
Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations.

	$MYD88^{MUT}$ $CXCR4^{WT}$	$MYD88^{MUT}$ $CXCR4^{WHIM}$	$MYD88^{WT}$ $CXCR4^{WT}$	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

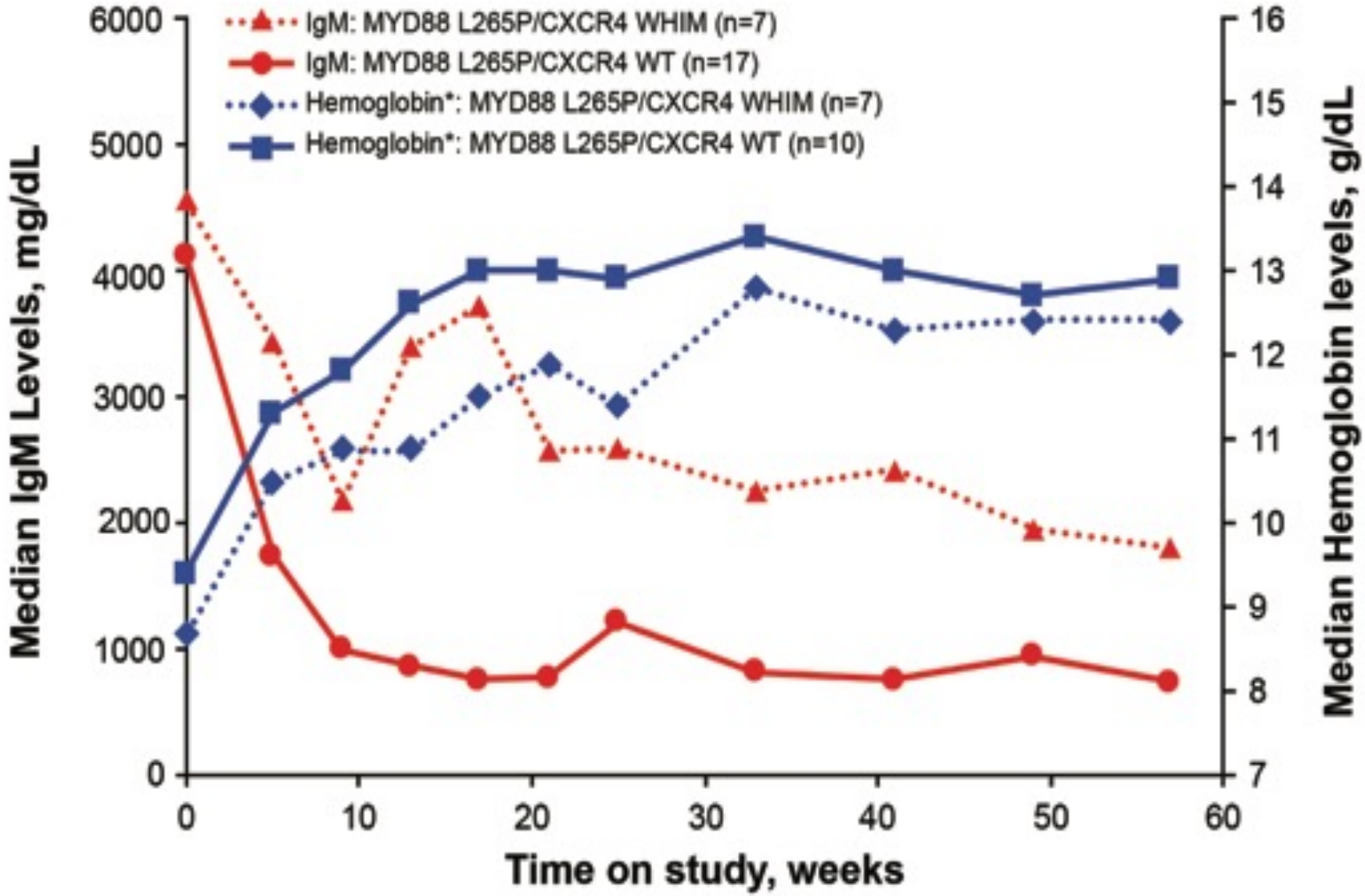
Median time to best response: 8 weeks

18 mo PFS: 86%

18 mo OS: 97%

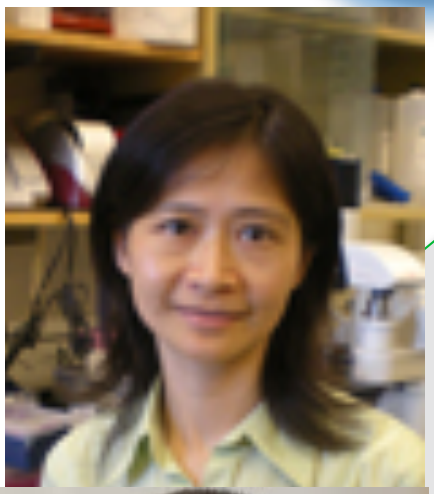
Dimopoulos et al, IWWM9 2016; Lancet Oncol 2017.

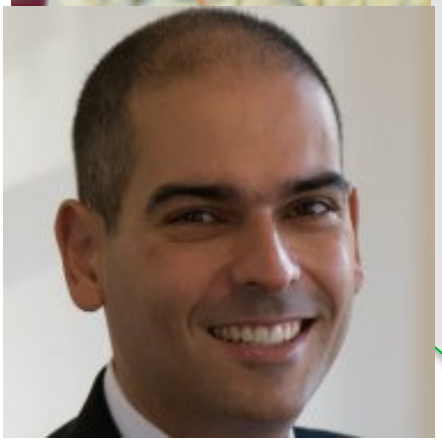
Impact of CXCR4 Mutation Status on IgM and HgB Response

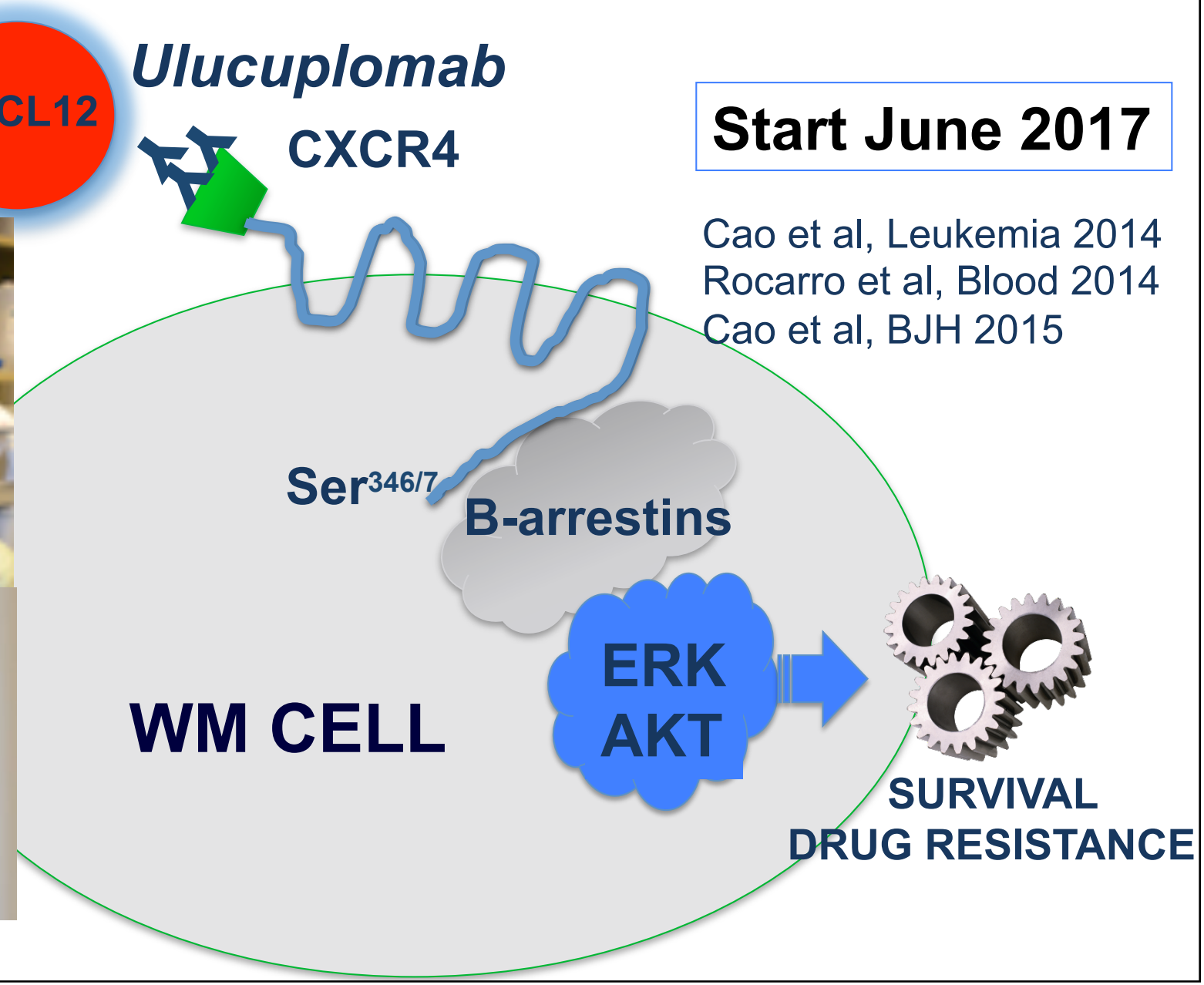


Dimopoulos et al, IWWM9; Lancet Oncology, 2017

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





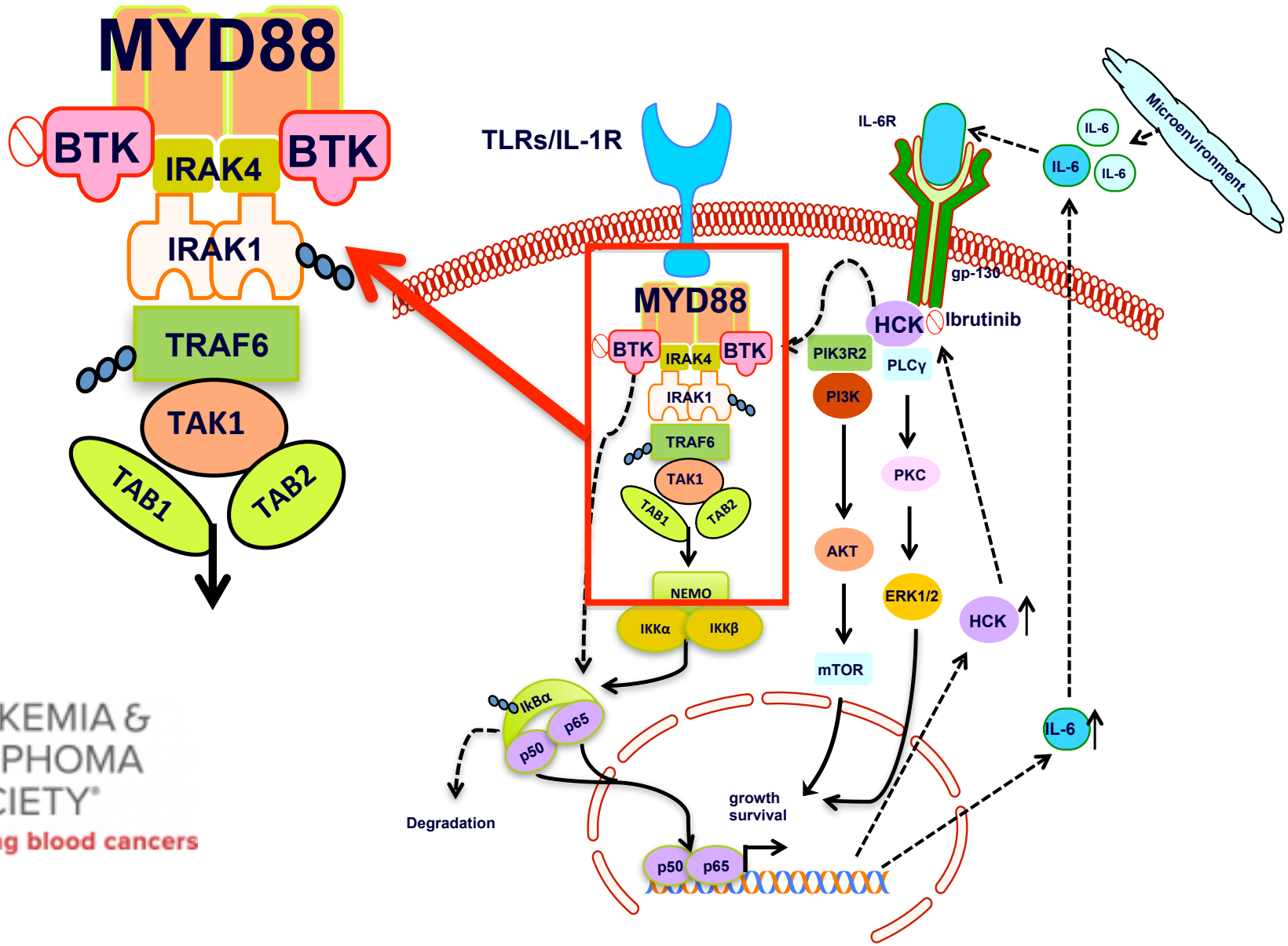


Start June 2017

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

Signaling Pathways Driven by Mutated MYD88 in Waldenström's Macroglobulinemia

Ibrutinib
ACP196
CC-292
BGB-3111



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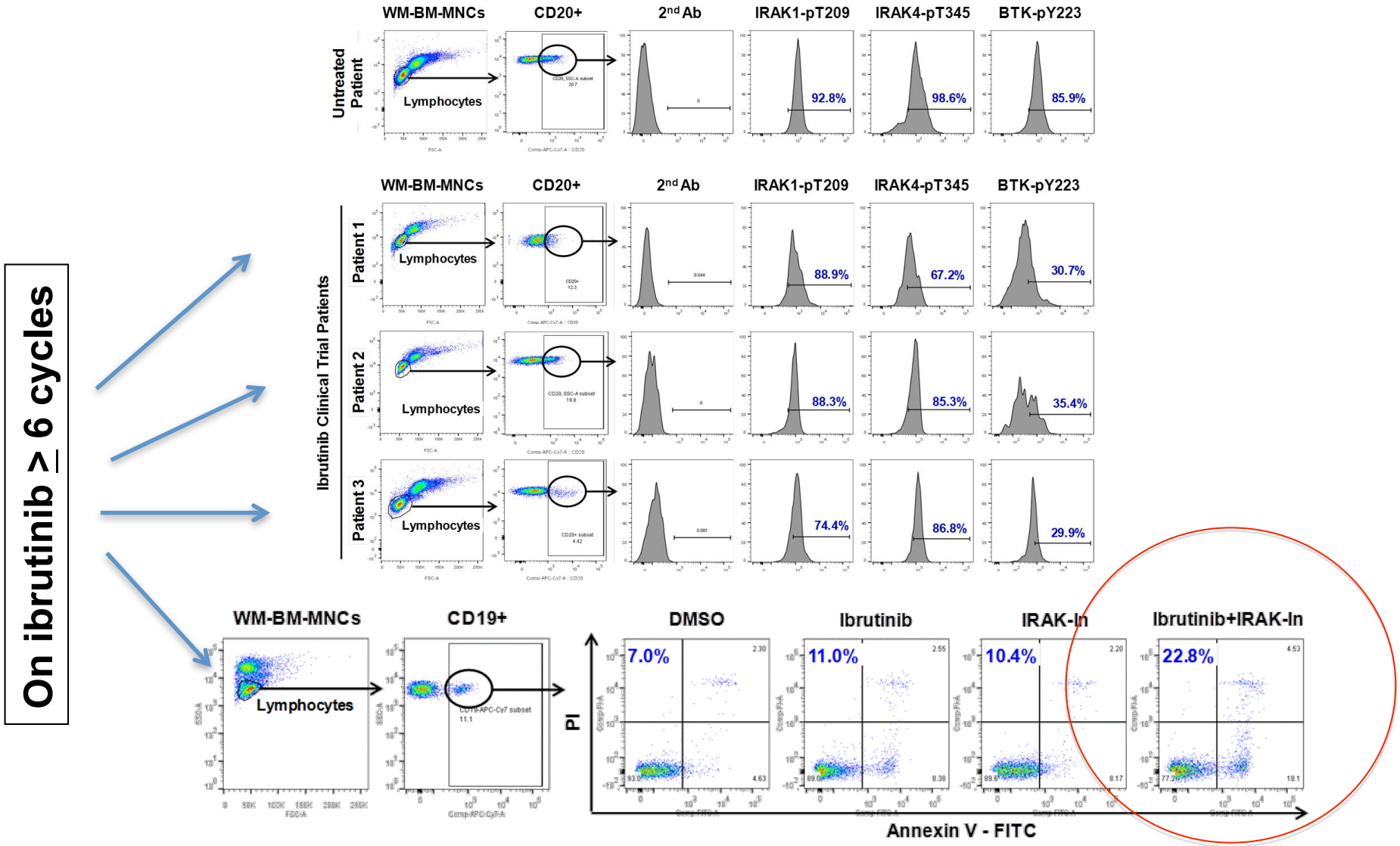
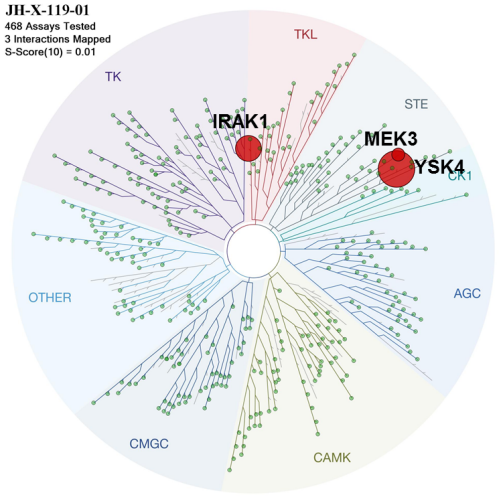
fighting blood cancers

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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fighting blood cancers

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

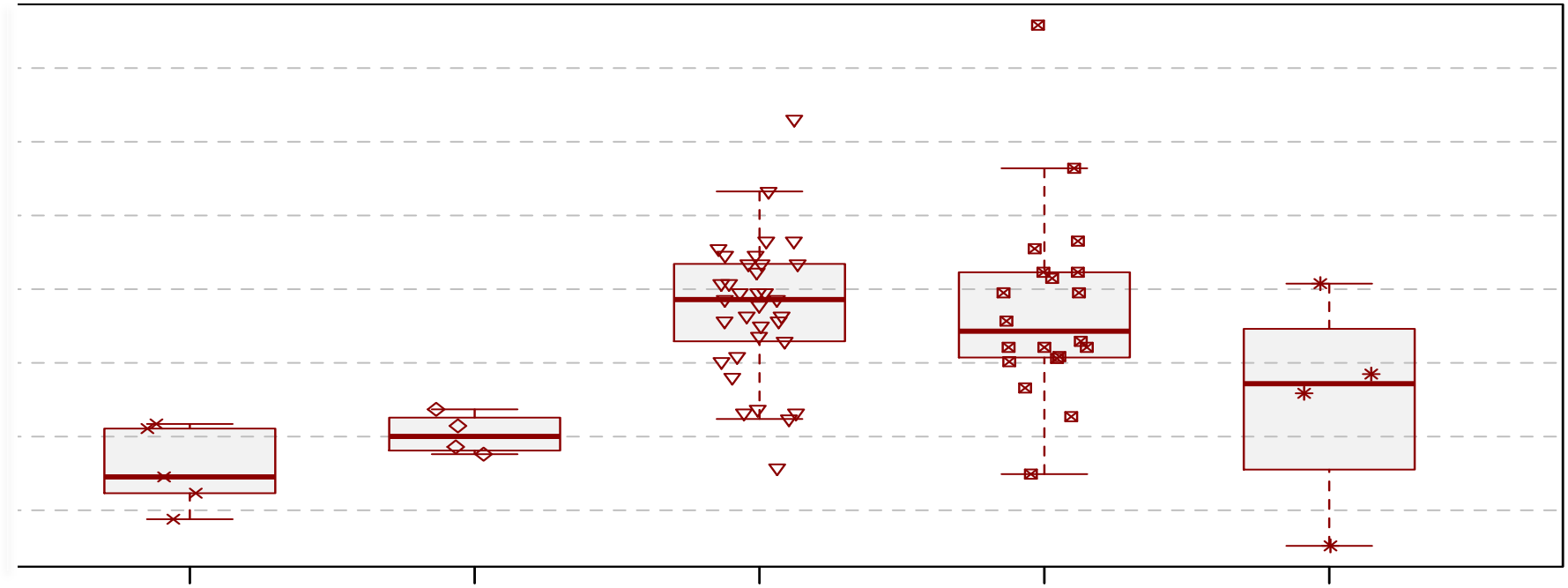
Combination Index

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 $CD19^{+}CD27^{+}$

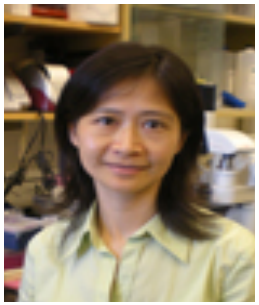
WM $CD19^{+}$ $MYD88^{L265P}$ $CXCR4^{WT}$

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

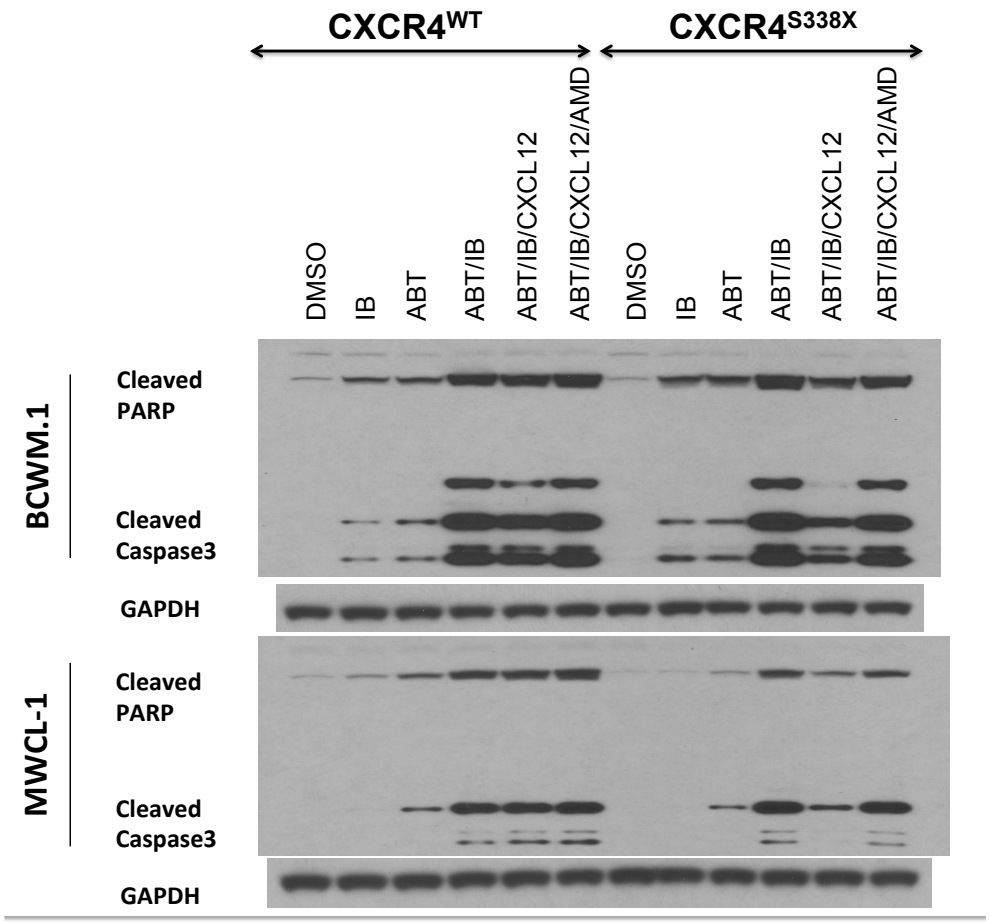
WM $CD19^{+}$ $MYD88^{WT}$ $CXCR4^{WT}$

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

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

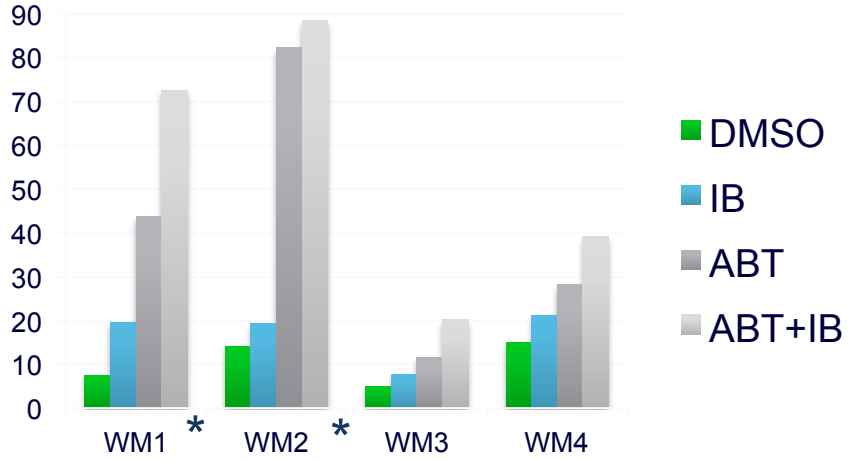


Venetoclax (ABT-199) enhances Ibrutinib killing in MYD88 mutated WM Cells.

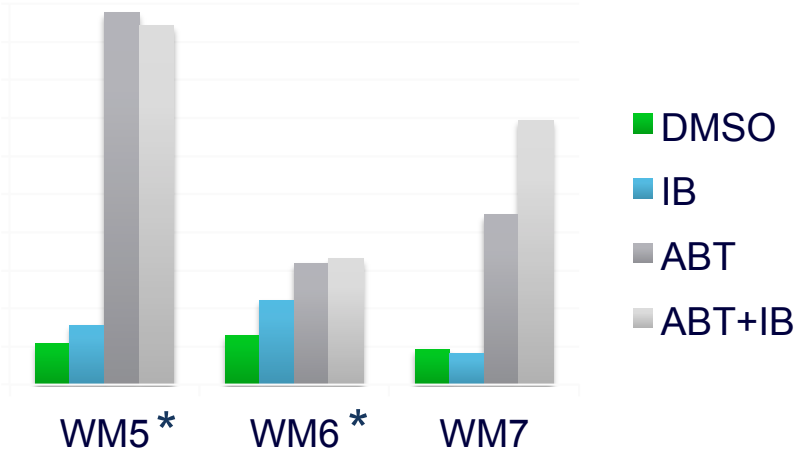


Cao et al, BJH 2015

Untreated

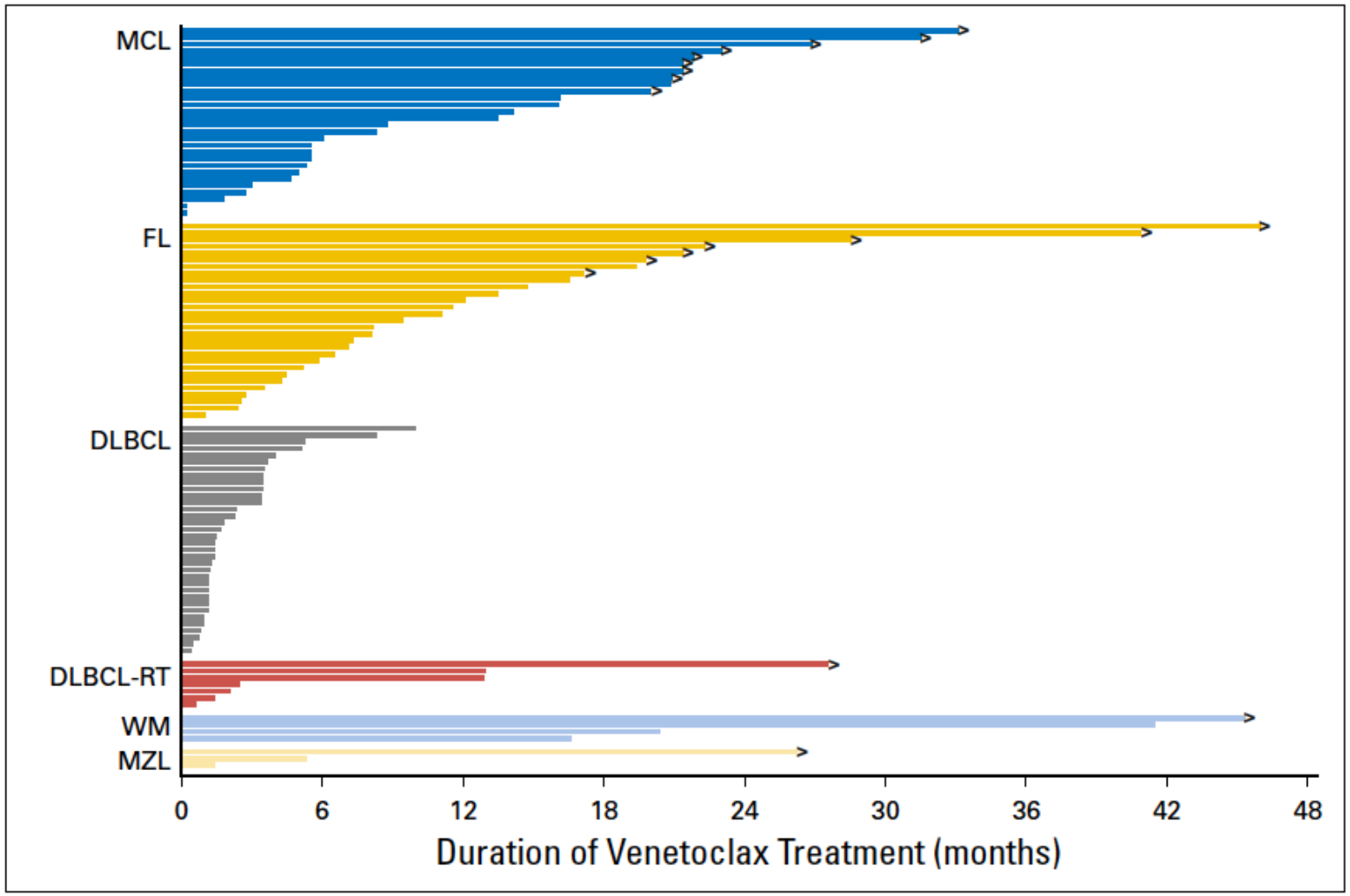


Ibrutinib >6 mo.

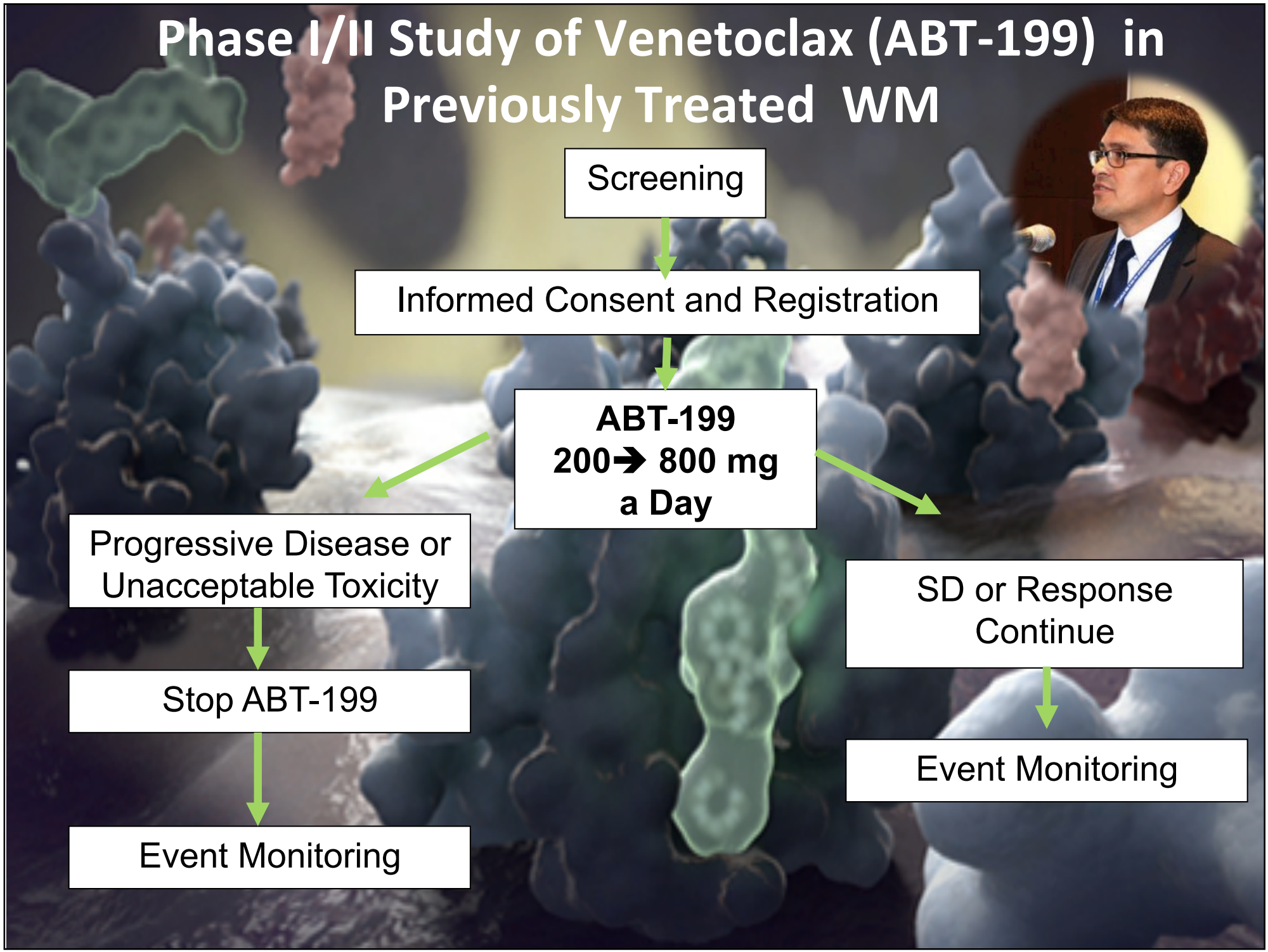


*CXCRWHIM

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.

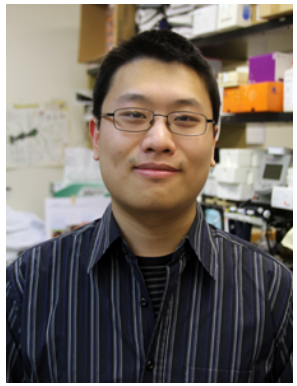
Patient*	L265P positive cells with BTK C481R$^{T>C}$	L265P positive cells with BTK C481S$^{T>A}$	L265P positive cells with BTK C481S$^{G>C}$	L265P positive cells with BTK C481Y$^{G>A}$	L265P positive cells with PLCG2 Y495H$^{T>C}$	L265P positive cells with CARD11 L878F$^{C>T}$
P1	None	None	None	None	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

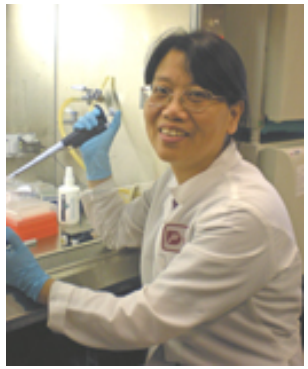
Targeted next-generation sequencing for MYD88, CXCR4, BTK, PLCG2, CARD11, LYN.
All patients are MYD88 Mutated.

P2, P3, P6 are CXCR4 WHIM Mutated.

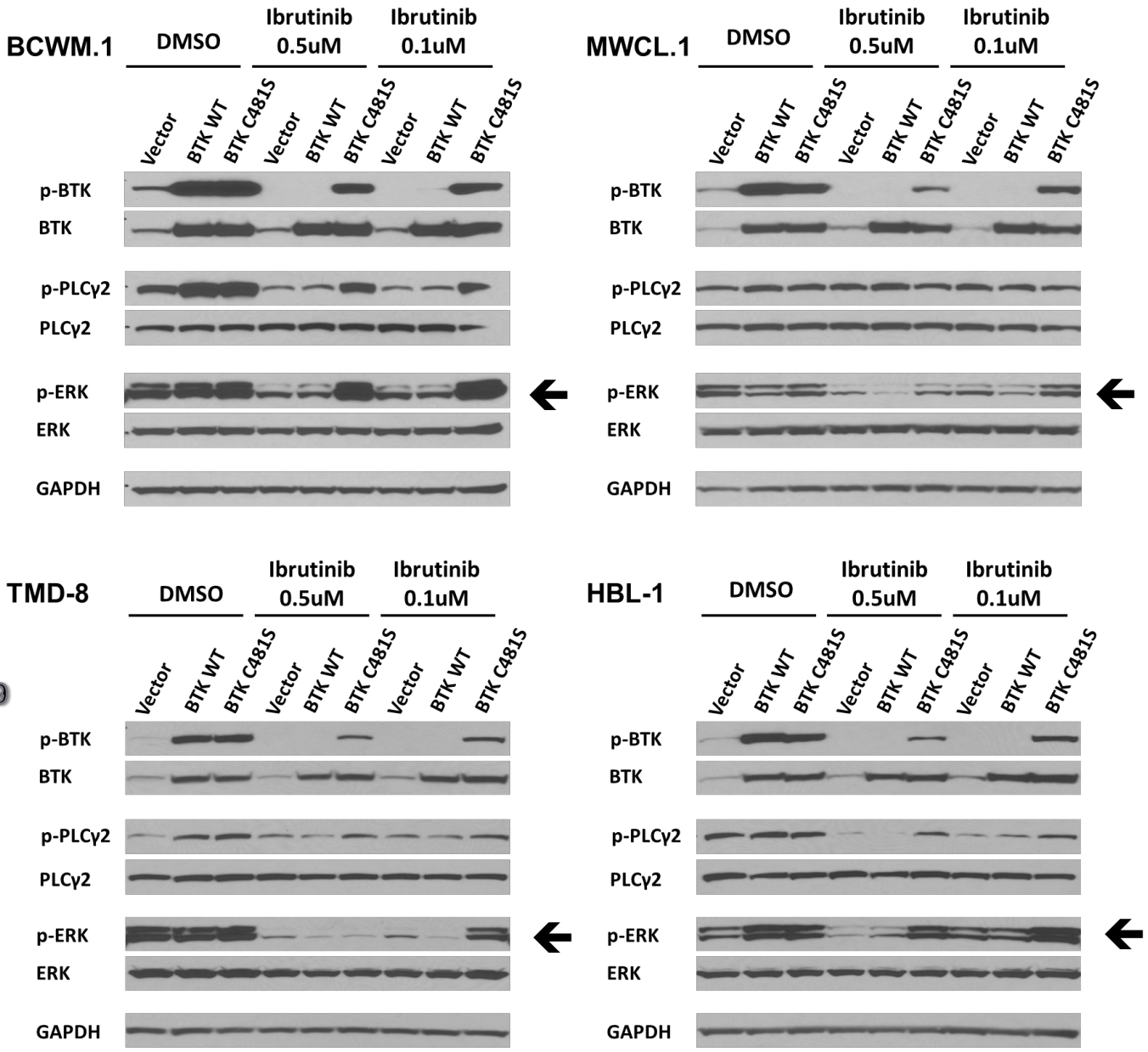
Xu et al, BLOOD 2017

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



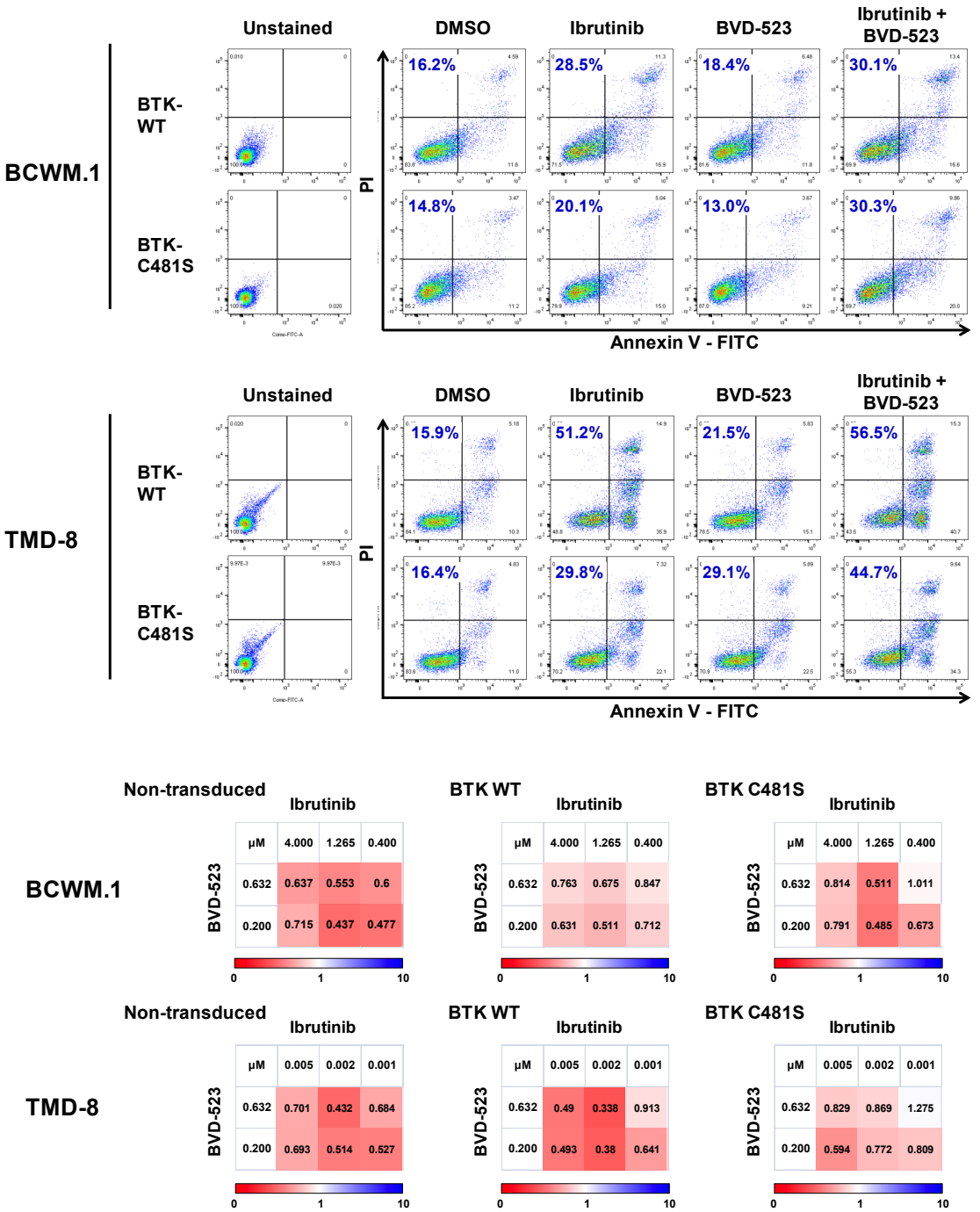


Chen et al, IWWM9



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

Summary

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

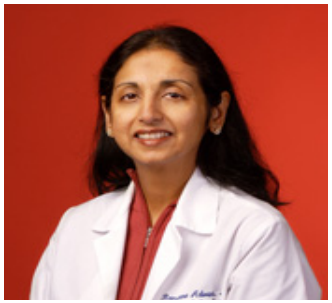
Ibrutinib targets BTK and HCK, and is produces high response rates and durable responses in R/R WM.

CXCR4 mutations are associated with delayed and/or decreased response activity. 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.

Acknowledgements



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