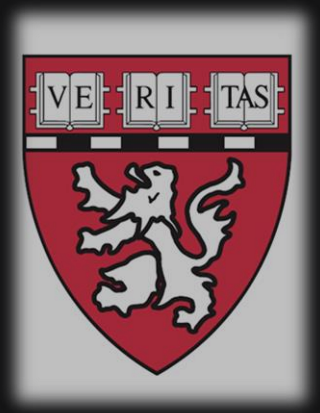
Genomic Based Treatment Advances in Waldenstrom's Macroglobulinemia



Steven P. Treon MD, MA, PhD

Dana-Farber Cancer Institute

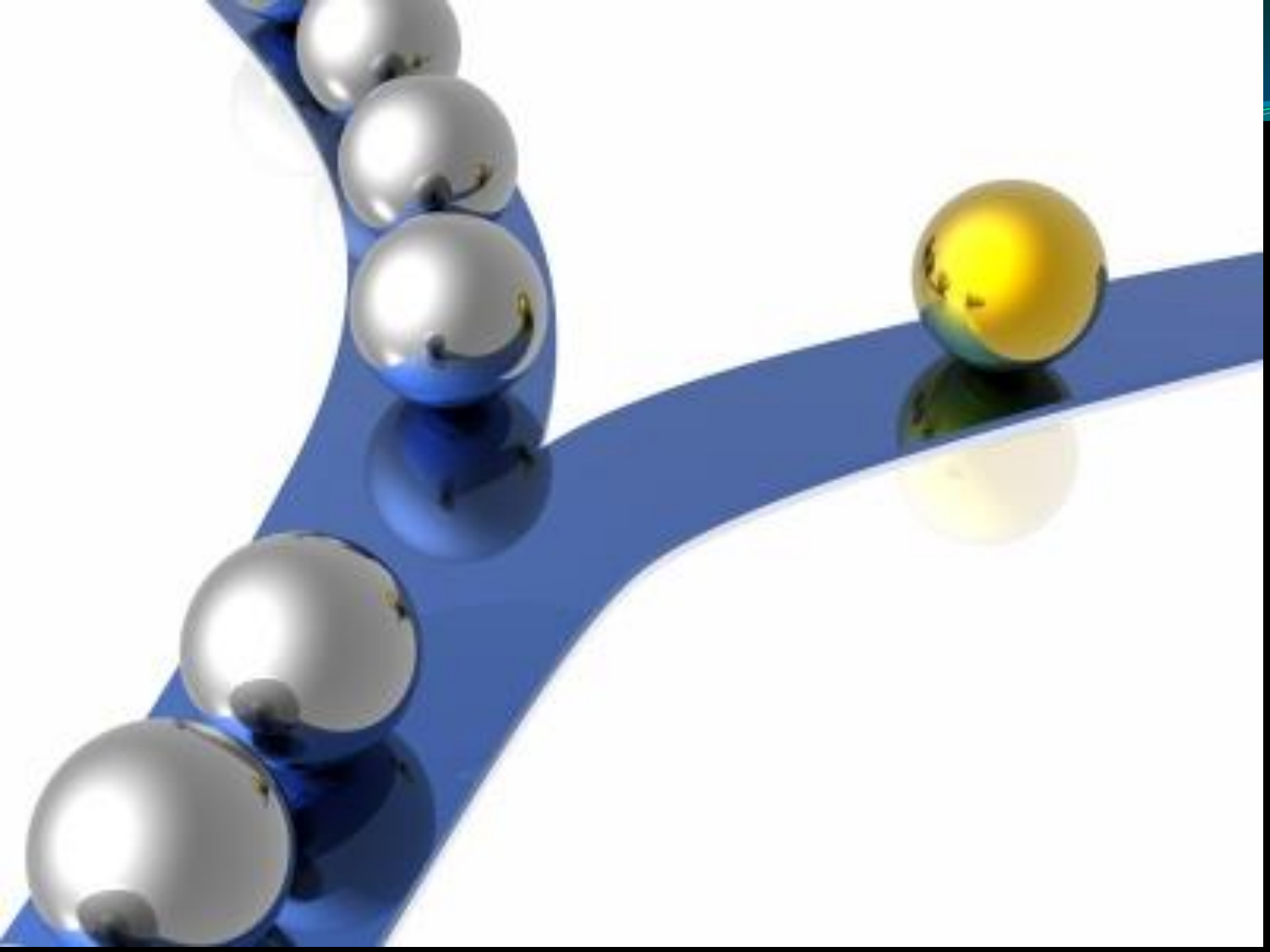
Harvard Medical School


INTERNATIONAL WORKSHOP ON WALDENSTRÖM'S MACROGLOBULINEMIA
IWWM-8
London, UK
2014
8th International Workshop on
Waldenstrom's Macroglobulinemia
and Symposium on Advances in
Multiple Myeloma
IWWM-8 August 16, 2014 Parliament, London, UK

WM Treatment Approach

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%)
Nucleoside Analogues	• Hypogammaglobulinemia-> infections, IVIG • Transformation, AML/MDS (15%)
IMIDS	• Peripheral Neuropathy (60% >grade 2 with Thalidomide) • Aggravated IgM flare (Revlimid and Pomalidomide) • Severe anemia (Revlimid)
Bortezomib	• Grade 2+3 Peripheral neuropathy (60-70%); High discontinuation (20-60%)

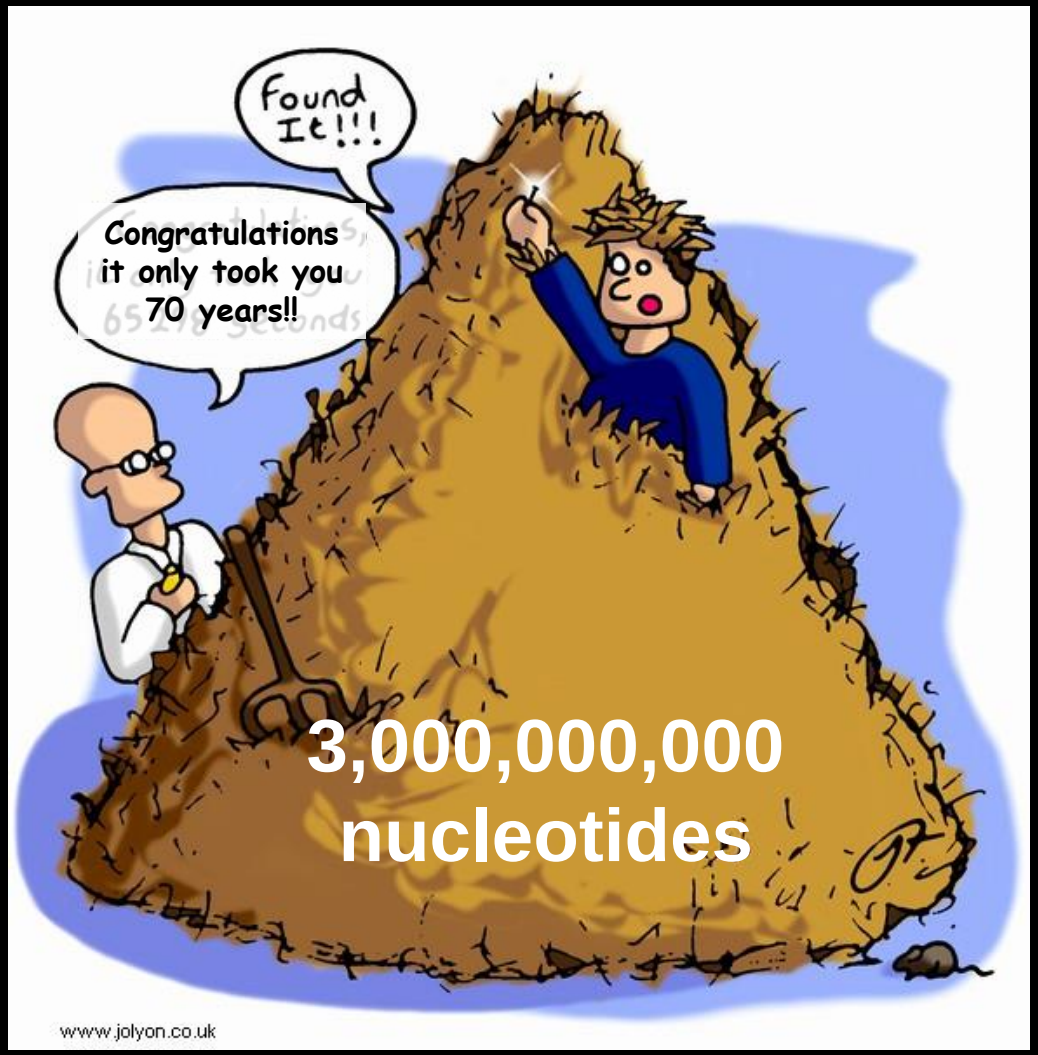


New Directions in WM

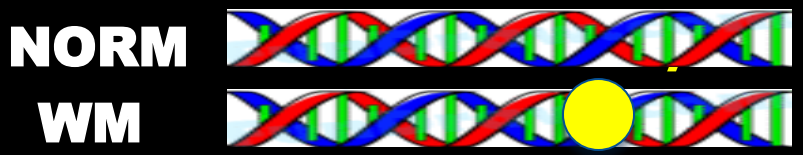
UCLA Summit on WM, Los Angeles 2003

Dedication of Bing Center for WM at DFCI-2005

WHOLE GENOME SEQUENCING IN WM

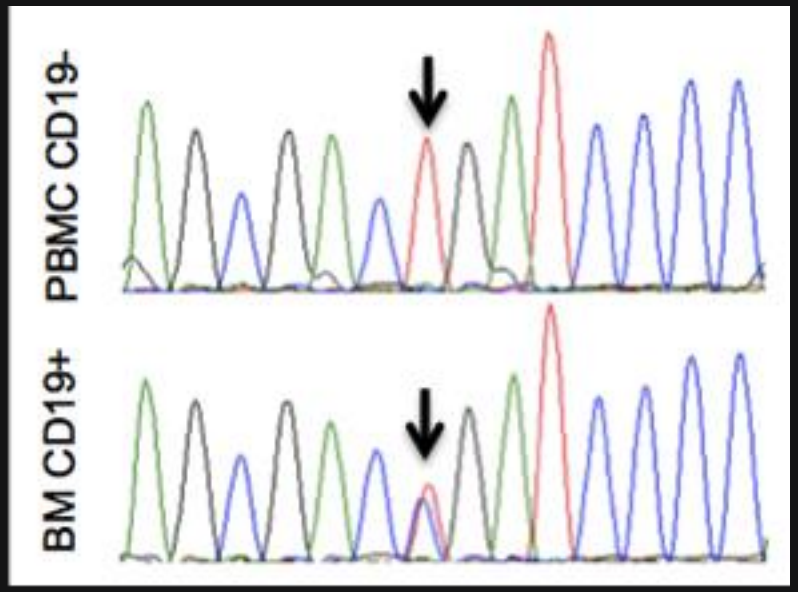


Paired Sequencing from same individuals

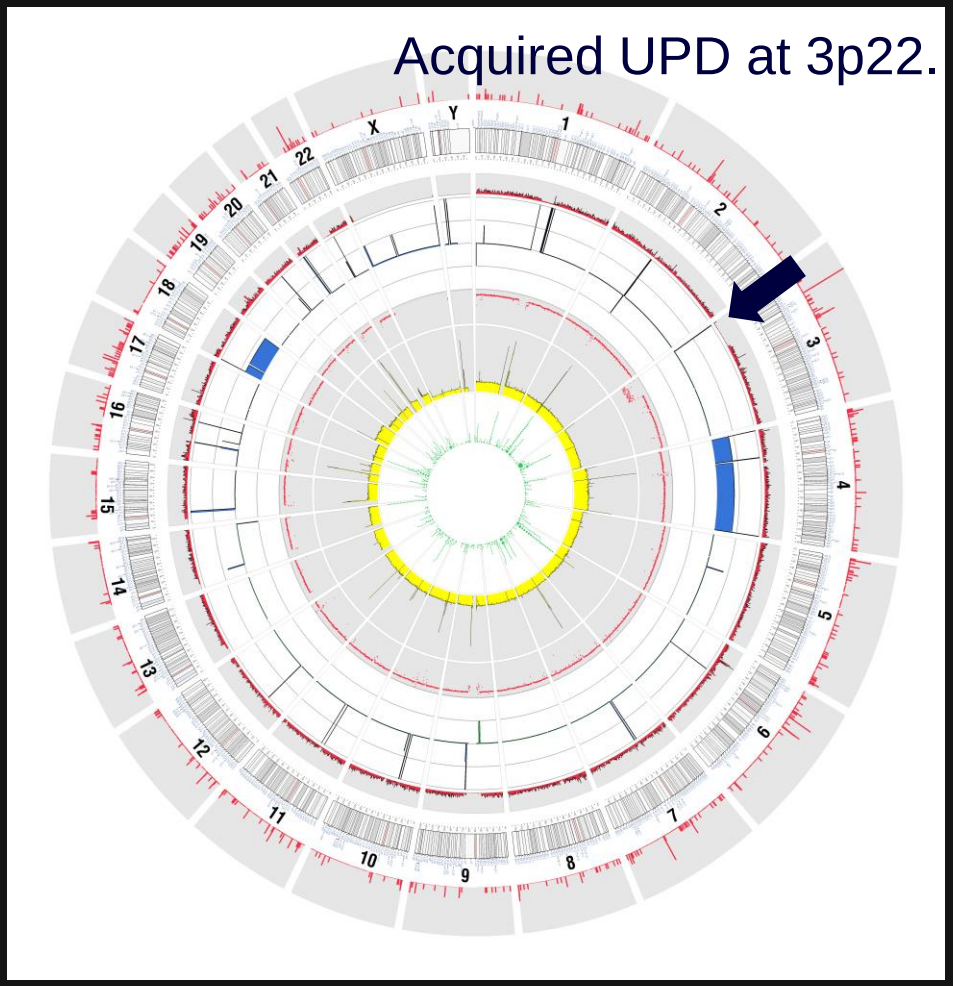


MYD88 L265P Somatic Mutation

C to G at position 38186241
at 3p22.2



MYD88 L265P confirmed by Sanger sequencing in 91% WM pts, 10% IGM MGUS.



Treon et al, ASH 2011; NEJM 2012

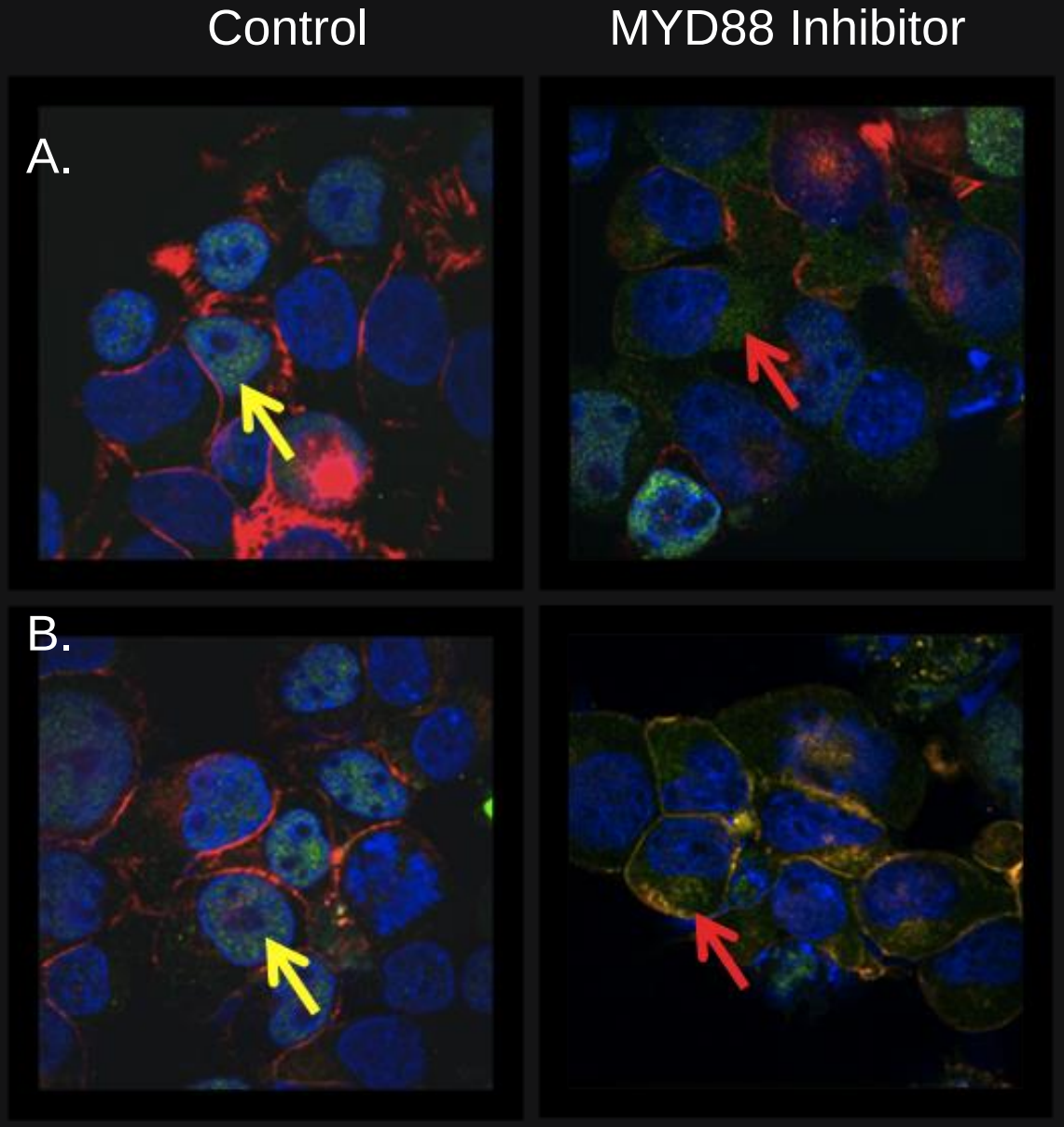
Comment on Poulain et al, page ■■■

A new era for Waldenstrom macroglobulinemia: MYD88 L265P

Steven P. Treon[1] and Zachary R. Hunter[1] [1]BING CENTER FOR WALDENSTROM'S MACROGLOBULINEMIA, DANA FARBER CANCER INSTITUTE AND HARVARD MEDICAL SCHOOL

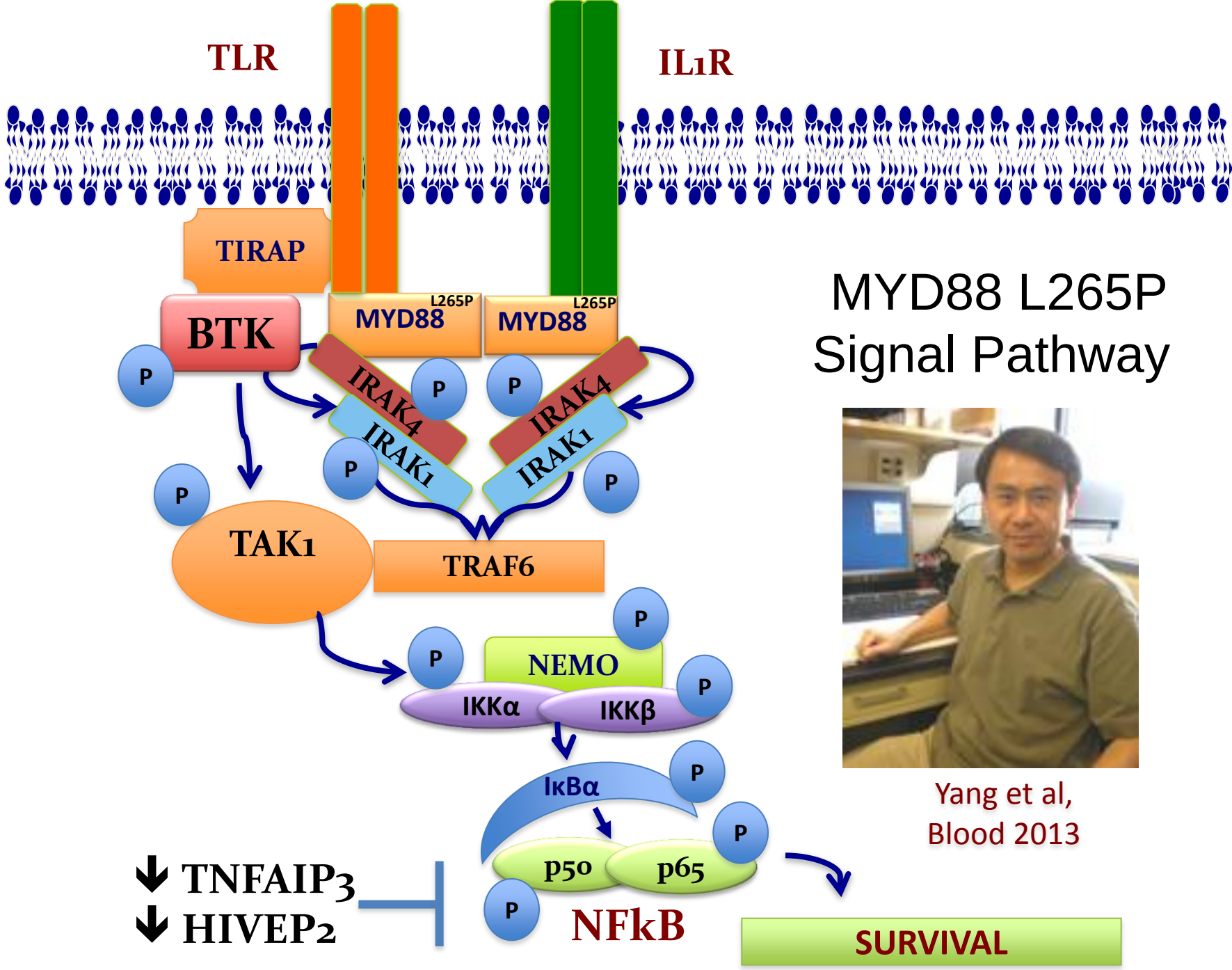
In this edition of *Blood*, Poulain et al demonstrate the high prevalence of the MYD88 L265P somatic mutation in patients with Waldenstrom macroglobulinemia (WM) and provide insight into its biological relevance in the growth and survival of WM.[1]

MYD88 inhibitor blocks p65 NFKB nuclear localization in L265P expressing WM cells.



A. BCWM.1 B. MWCL-1

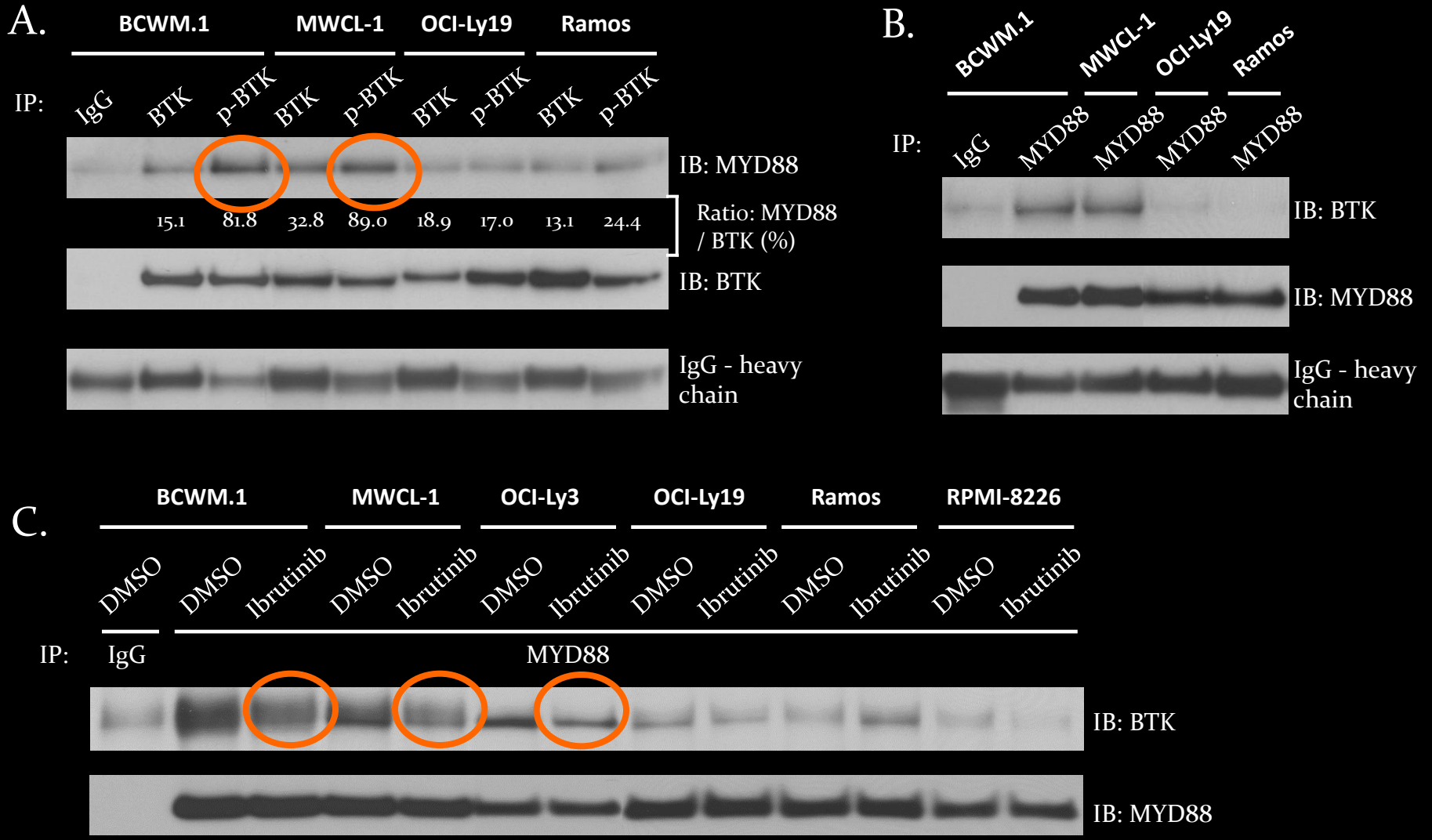
Treon et al, ASH 2011; NEJM 2012



MYD88 L265P Signal Pathway

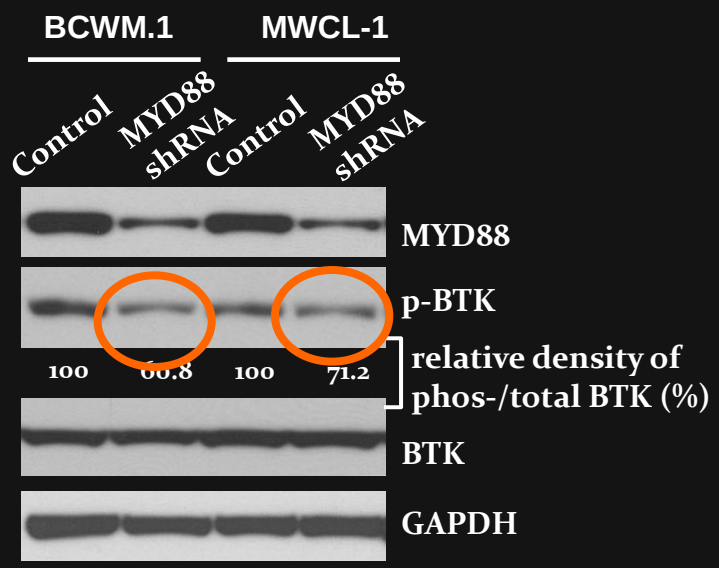
Yang et al, Blood 2013

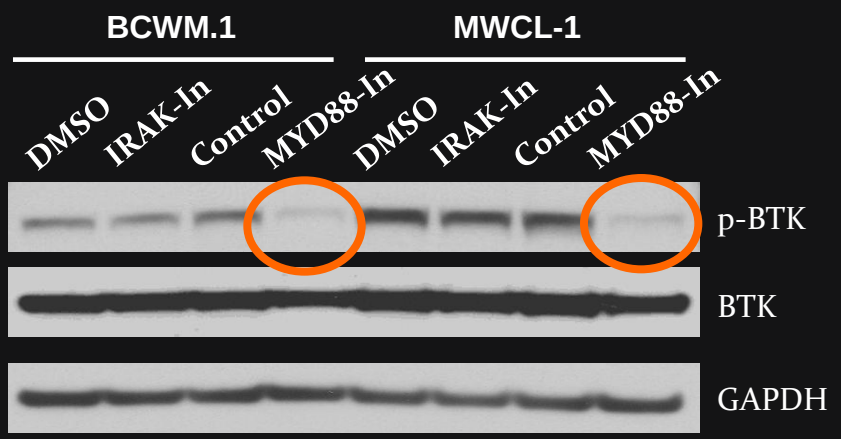
MYD88 binds to Bruton's Tyrosine Kinase (BTK) in L265P expressing WM cells

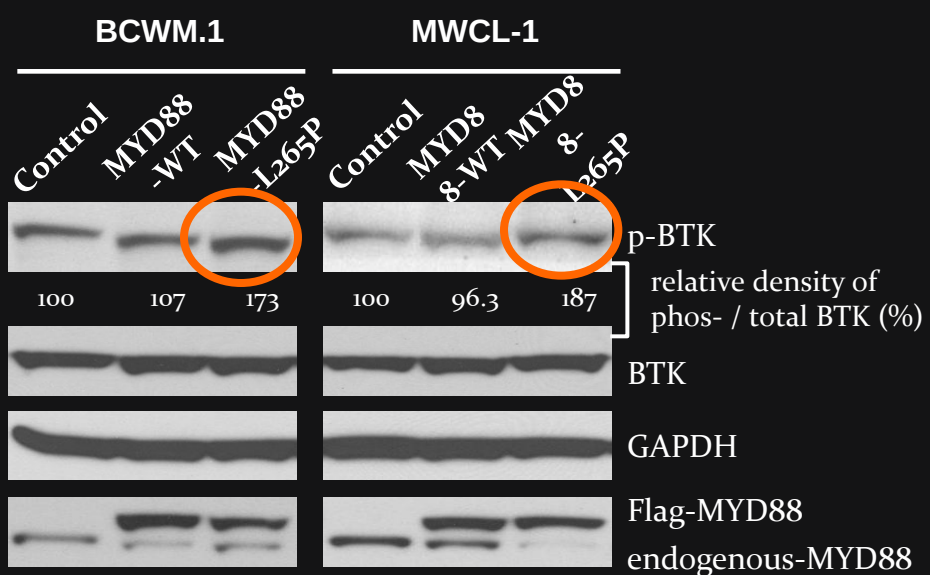


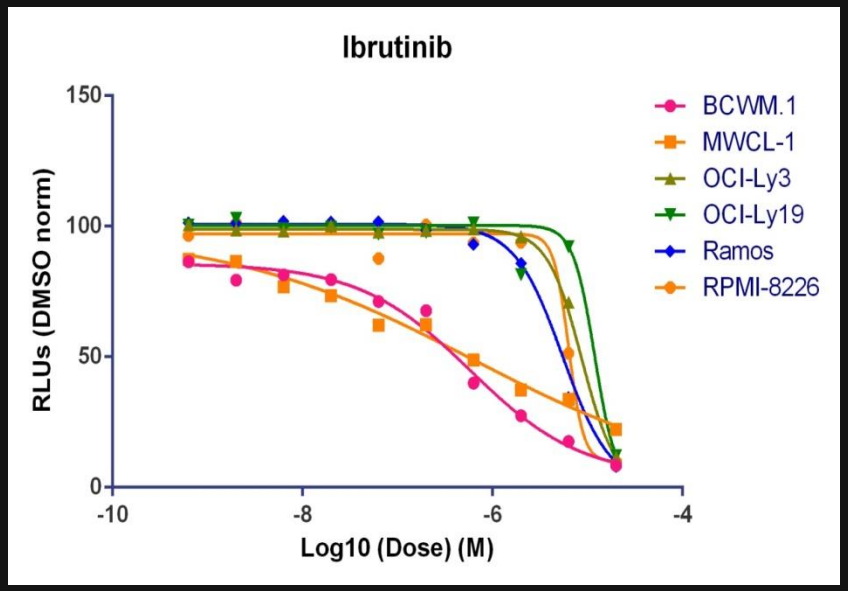
Yang et al, Blood 2013

MYD88 L265P induces BTK in WM cells









Yang et al, Blood 2013

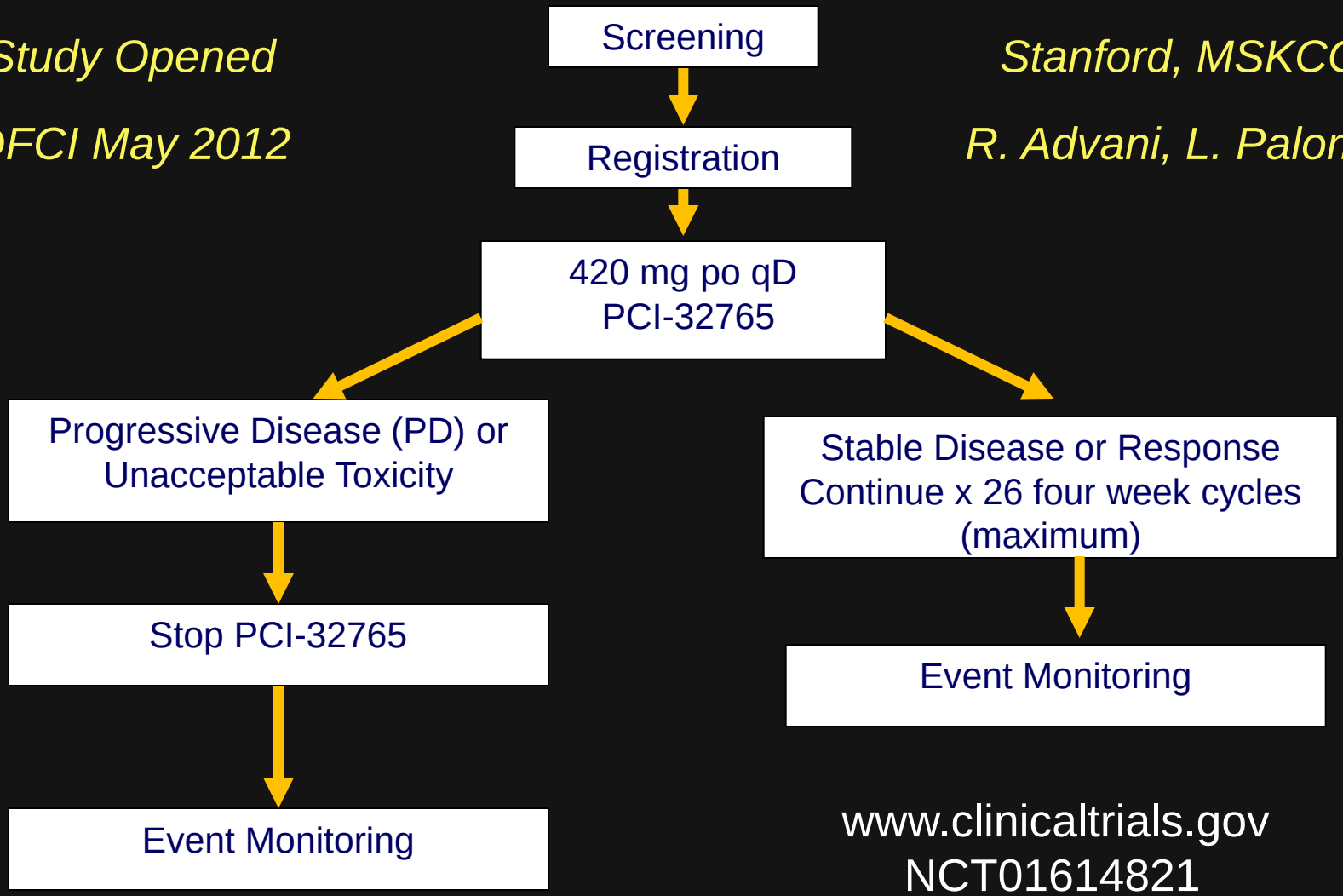
Multicenter study of Ibrutinib in Relapsed/Refractory WM (>1 prior therapy)

Study Opened

DFCI May 2012

Stanford, MSKCC

R. Advani, L. Palomba



www.clinicaltrials.gov
NCT01614821

FDA MEETING NOVEMBER 2012

February 12, 2013 PR Newswire

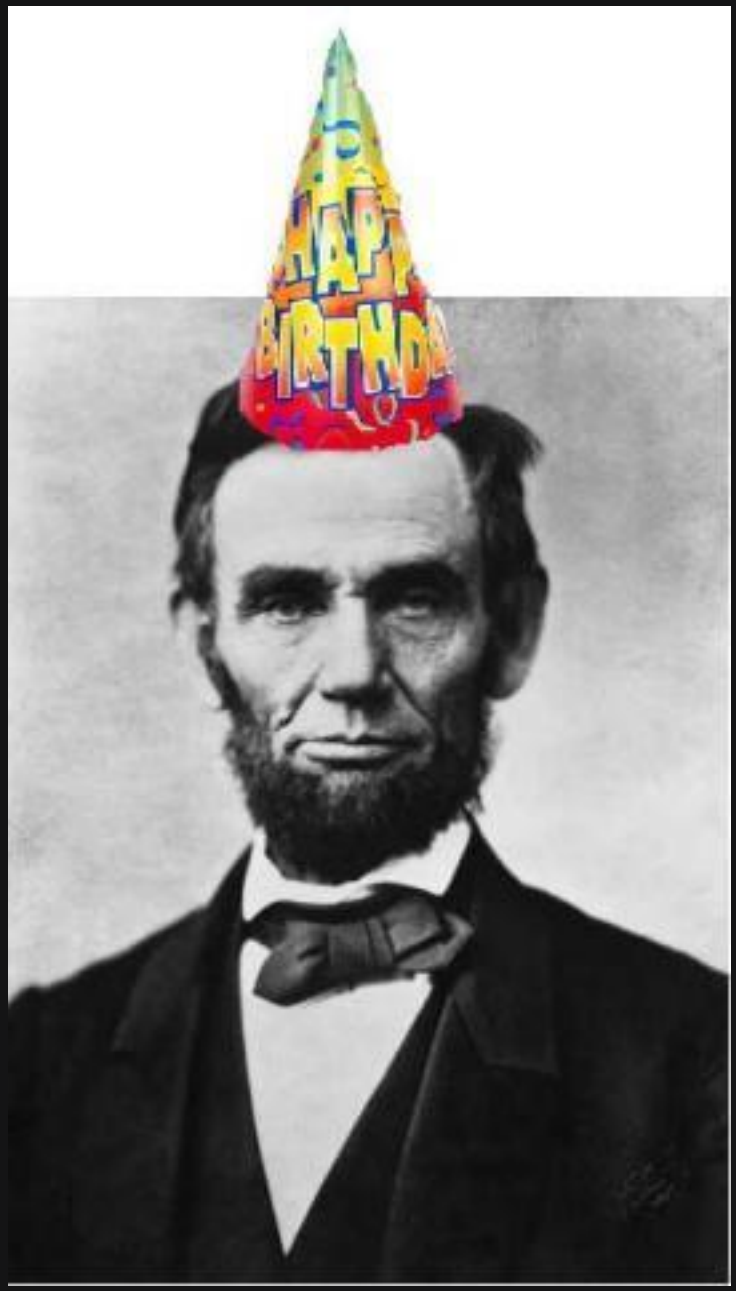
FDA grants ‘breakthrough’ designation for ibrutinib

FDA granted breakthrough therapy designation to ibrutinib for patients with mantle cell lymphoma and Waldenström’s macroglobulinemia.

See Also

The designation, created in 2012, allows for expedited development and review of drugs shown in preclinical studies to offer potentially substantial improvements over existing therapies for patients with serious or life-threatening diseases.

The breakthrough designation could allow the FDA to approve the drug for patients with relapsed or refractory mantle cell lymphoma or Waldenström’s macroglobulinemia after just one expanded early-stage study.



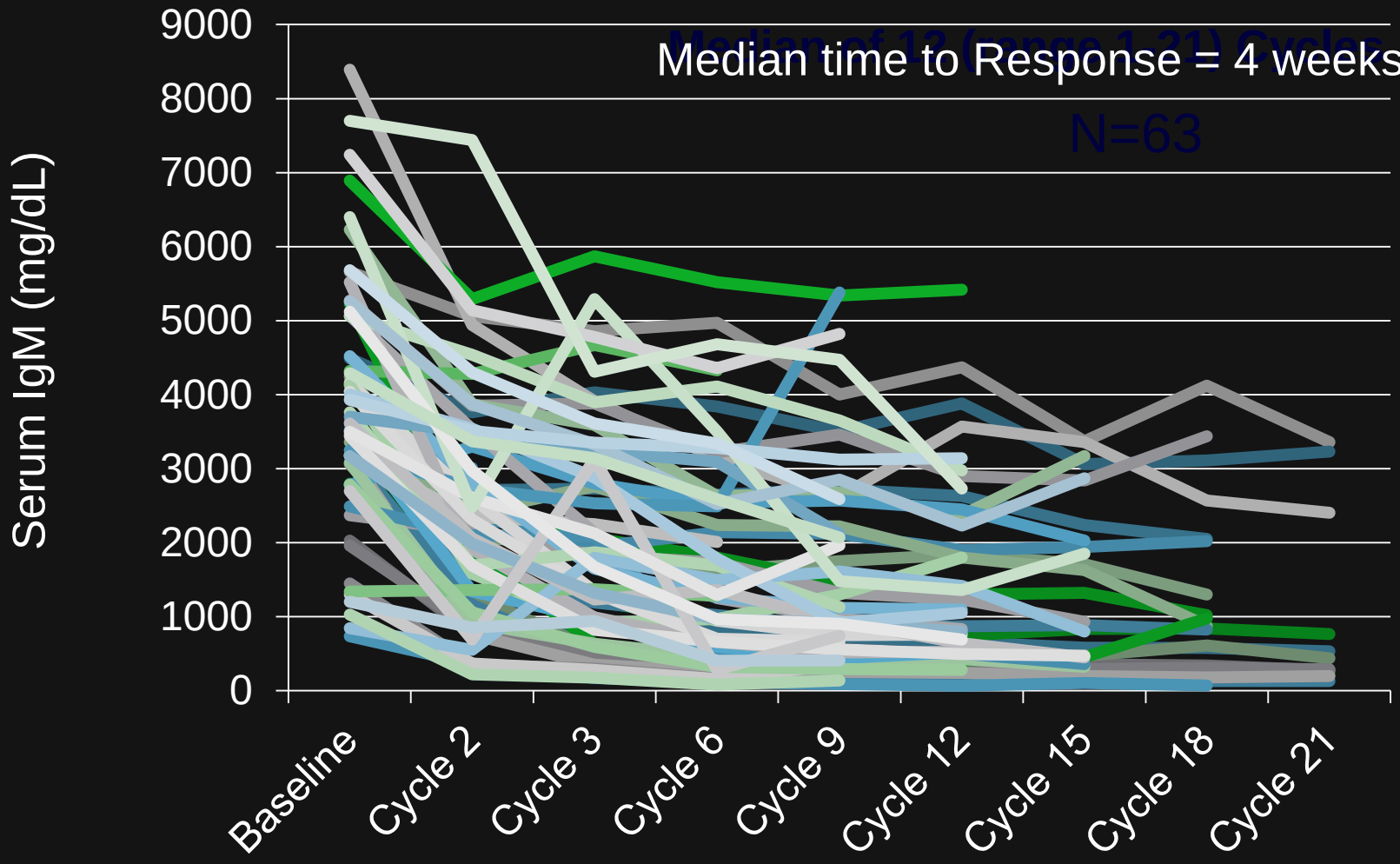
Baseline Characteristics for Study Participants (n=63)

	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 372: 1430, 2015

Serial Serum IgM Levels Following Ibrutinib

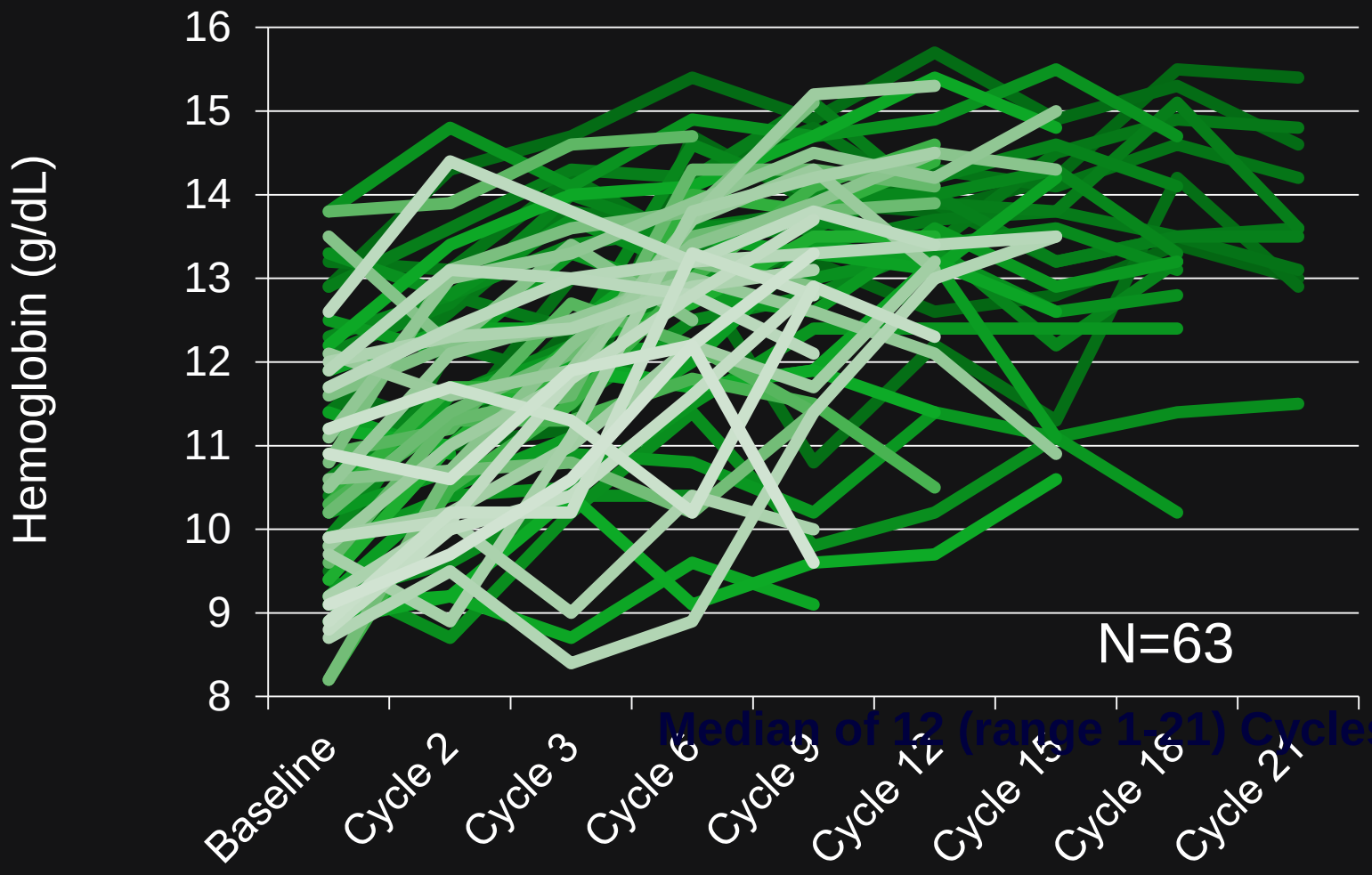
Best IgM Response: 3,520 to 880 mg/dL; p<0.01



Treon et al, NEJM 372: 1430, 2015

Serial Hemoglobin Levels Following Ibrutinib

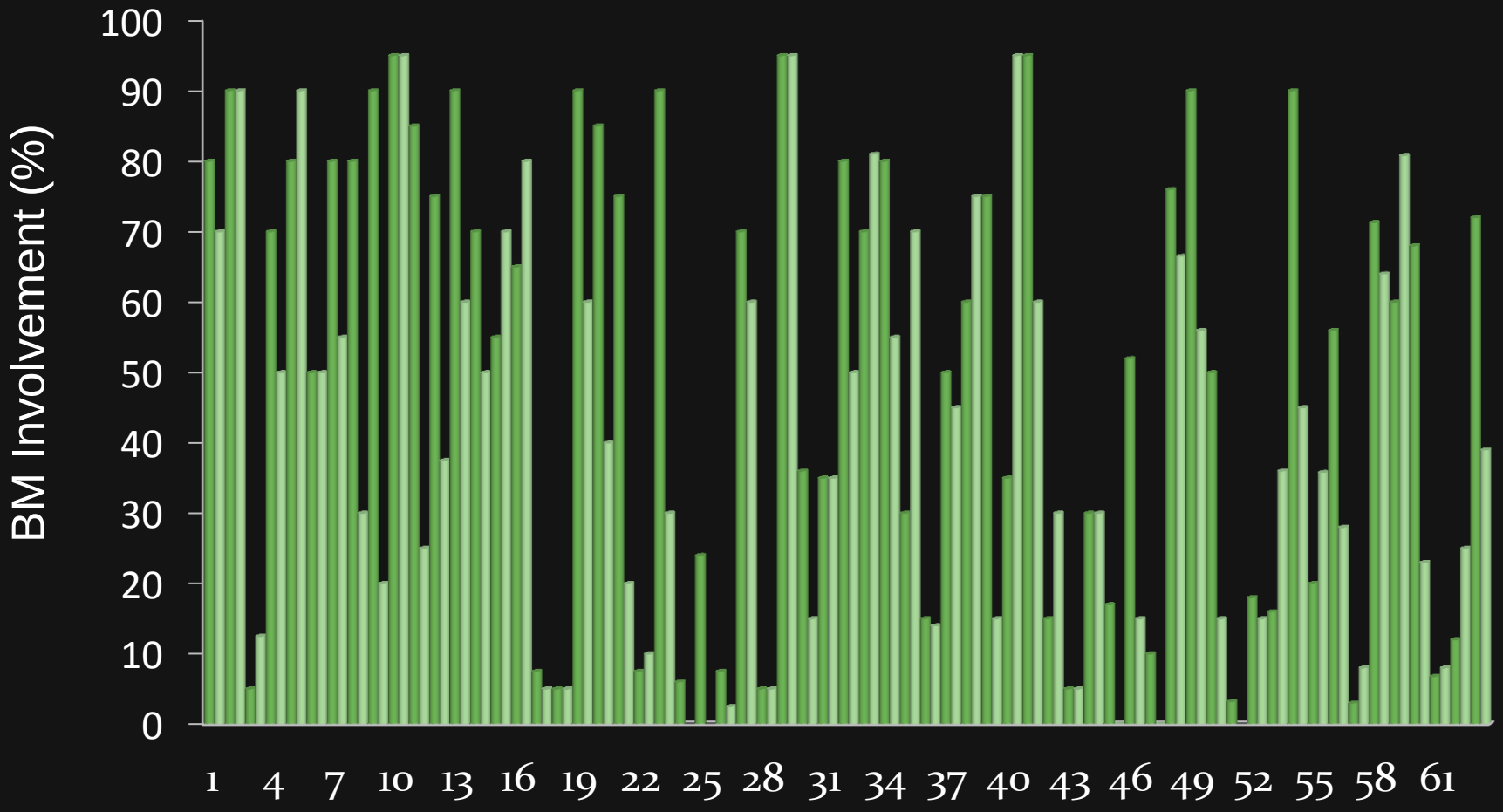
Best Hemoglobin Response: 10.5 to 13.8; p<0.01



Treon et al, NEJM 372: 1430, 2015

Bone Marrow Disease Burden following Ibrutinib

At Best Response 60% to 25%; p< 0.01



N= 61 (with baseline and cycle 6 BM Biopsy)

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, NEJM 372: 1430, 2015

Extramedullary Disease following Ibrutinib

Best response based on serial CT scans

Adenopathy ≥ 1.5 cm

N=	Improved	Stable	Increased	N/A
37	25 (68%)	9 (24%)	1 (3%)	2 (5%)

Splenomegaly ≥ 15 cm

N=	Improved	Stable	Increased	N/A
7	4 (57%)	2 (29%)	0 (0.0%)	1 (14%)

Treon et al, NEJM 372: 1430, 2015 Based on local radiology review

Treatment impact on IgM related peripheral neuropathy

- Peripheral Sensory Neuropathy (n=9)
- Anti-MAG antibody identified in 3 patients
- All had neuropathic progression after rituximab

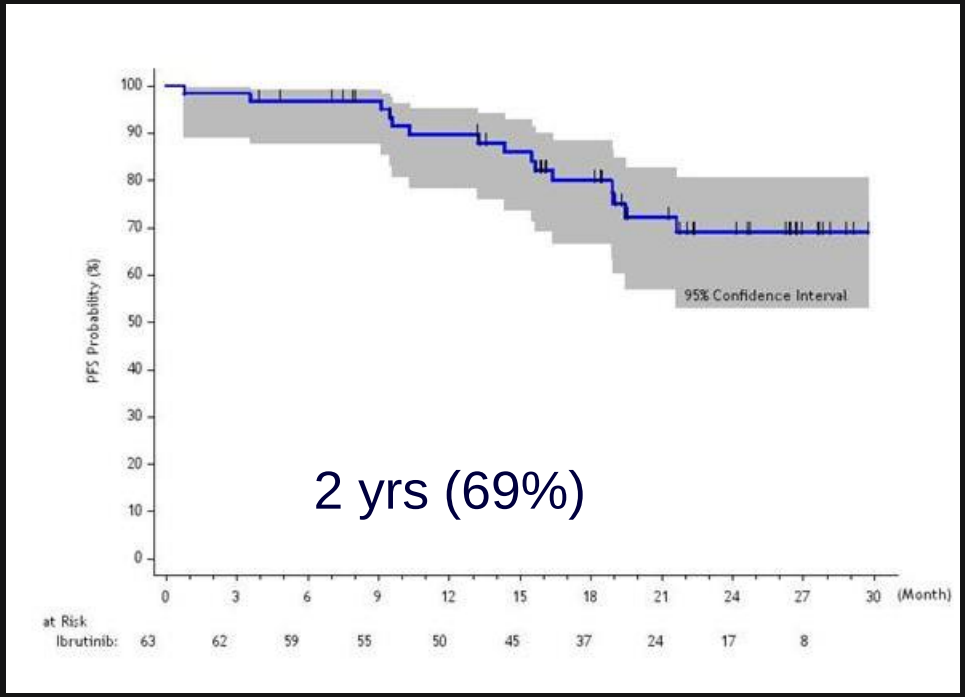
- 8 PR, 1 MR

- 5 improved neuropathy
  4 stable neuropathy

Treon et al, NEJM 372: 1430, 2015

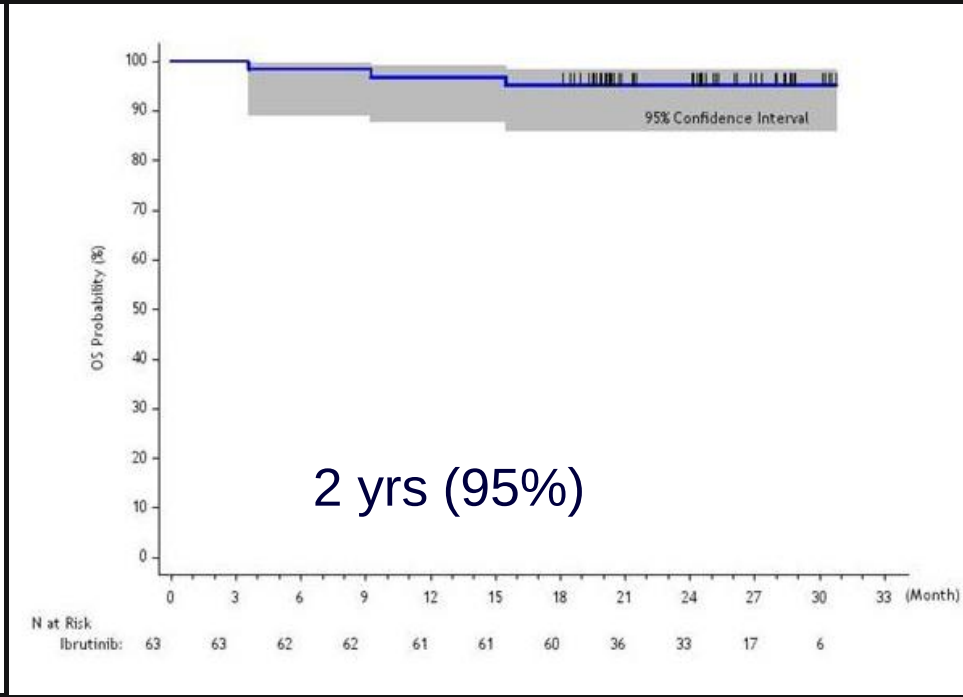
Progression-free and overall survival

PFS



2 yrs (69%)

OS

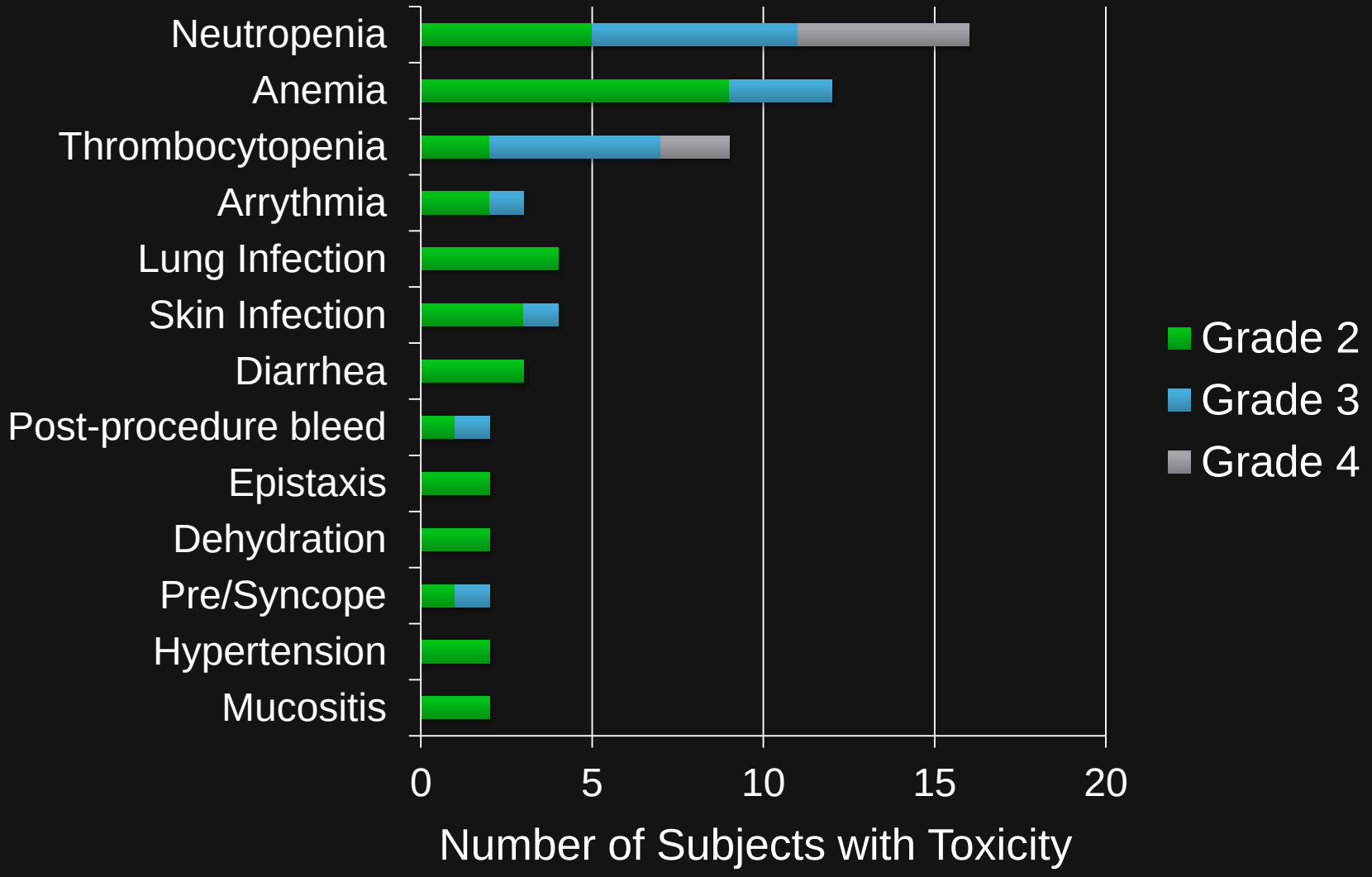


2 yrs (95%)

Treon et al, NEJM 372: 1430, 2015

Ibrutinib Related Adverse Events

Toxicities >1 patient; N=63




FDA MEETING JUNE 2014

FDA News Release

FDA expands approved use of Imbruvica for rare form of non-Hodgkin lymphoma

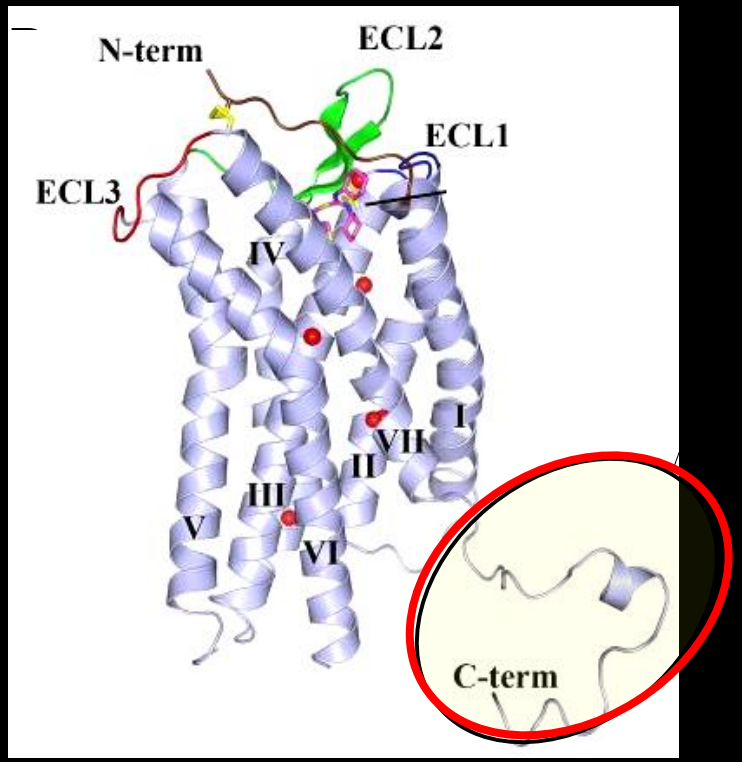
First drug approved to treat Waldenström's macroglobulinemia

For Immediate Release

January 29, 2015

WHIM-like CXCR4 C-tail mutations in WM

Warts, Hypogammaglobulinemia, Infection, and Myelokathexis.



Most common: CXCR4^{C1013G} (S338X)

CXCR4 C-tail mutation in WM

308 320 330 340 350

KFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS

CXCR4 C-tail mutation in WHIM

308 320 330 340 350

KFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS

Somatic WHIM-CXCR4 Mutations were detected in 21/63 patients (34%) on ibrutinib study.

Hunter et al, ASH 2012; ICML 2013; BLOOD 2014

Over 30 types of CXCR4 C-terminal somatic mutations in WM

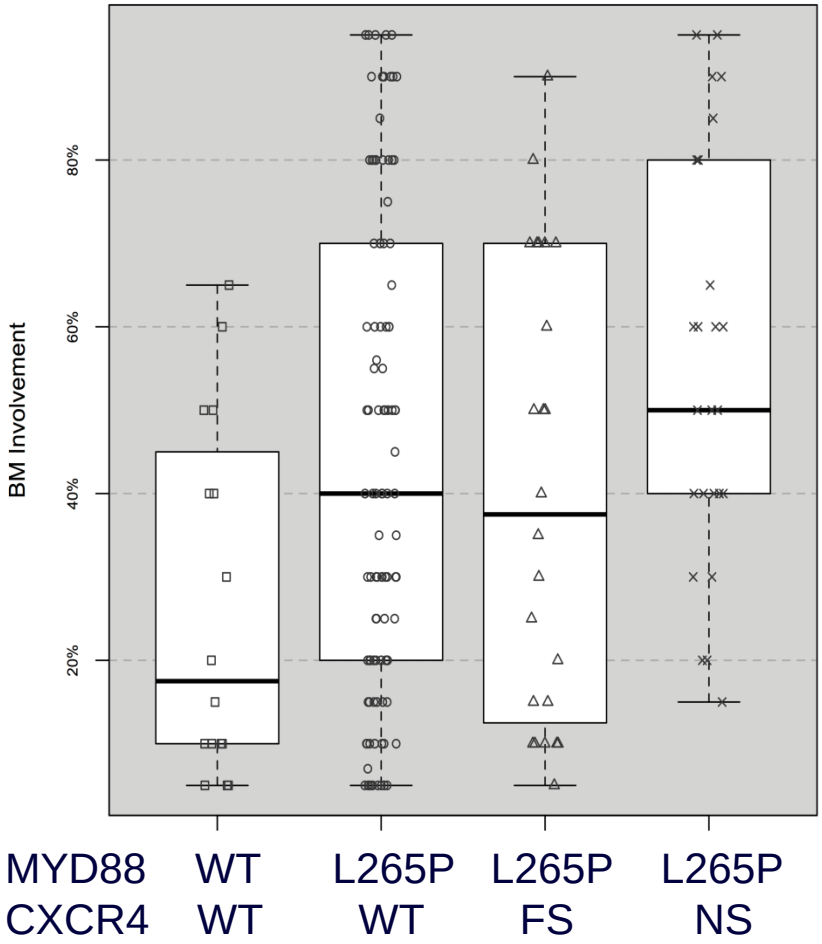
N=	MYD88 Status	CXCR4 Mutation	Nucleotide change	Amino acid change
1	L265P	Nonsense	r.997 A>T[1]	K333X[1]
3	L265P	Nonsense	r.1000C>T	R334X
7	L265P	Nonsense	r.1013C>A	S338X
15	L265P	Nonsense	r.1013C>G[2]	S338X[2]
1	WT	Frameshift	r.931_933insT	T311fs
3	L265P	Frameshift	r.952_954insA	T318fs
2	L265P	Frameshift	r.951_953delACCTC	T318fs
1	L265P	Frameshift	r.954_956insC	S319fs
1	L265P	Frameshift	r.958_960delTG	V320fs
1	L265P	Frameshift	r.963_965insC	R322fs
1	L265P	Frameshift	r.969_971insG	S324fs
1	L265P	Frameshift	r.978_980insT	K327fs
1	L265P	Frameshift	r.984_986insT	L329fs
1	L265P	Frameshift	r.993_995insA	G332fs
1	L265P	Frameshift	r.1005_1007insT	G336fs
2	L265P	Frameshift	r.1013_1015delATCT	S338fs
1	L265P	Frameshift	r.1013_1015delATCTGTTTCCACTGAGT	S338fs
3	L265P	Frameshift	r.1012_1014insT	S338fs
1	L265P	Frameshift	r.1015_1017delCT	S339fs
1	L265P	Frameshift	r.1020_1022delT	S341fs
1	L265P	Frameshift	r.1024_1026delCT	S342fs
1	L265P	Frameshift	r.1030_1041CTGAGTCTTC>GT	S344fs
1	L265P	Frameshift	r.1033_1035delAG	E345fs

Sanger Sequencing

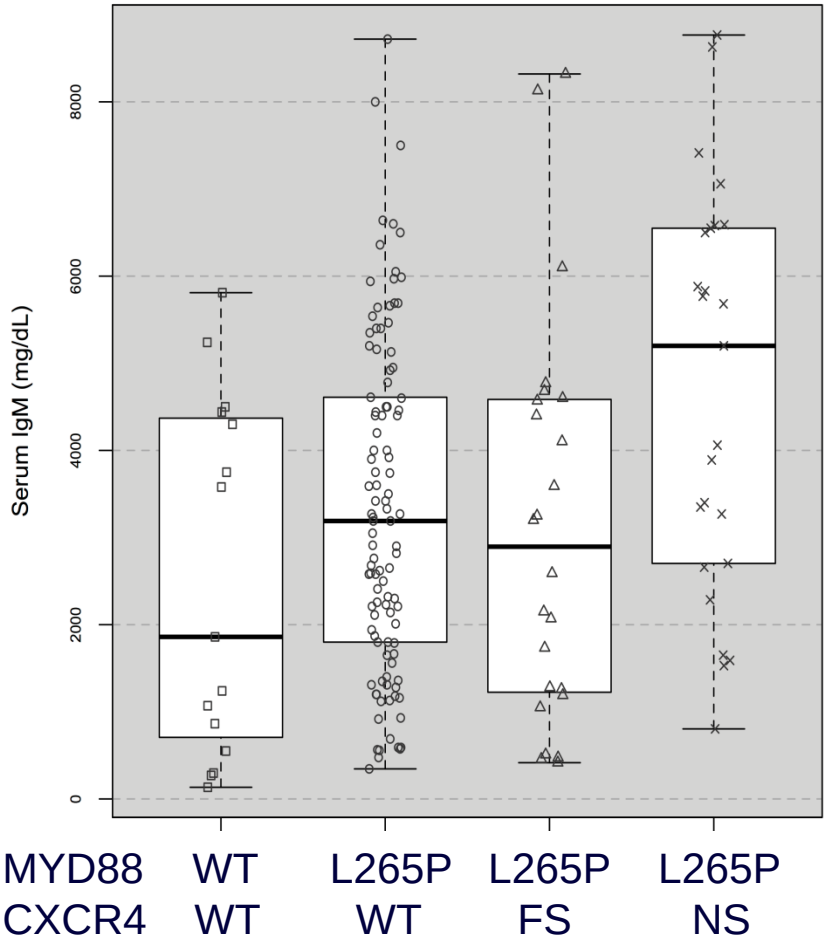
Treon et al, Blood 2014

MYD88 and CXCR4 Mutation Status Impacts Clinical Presentation of WM Patients

BM (%)

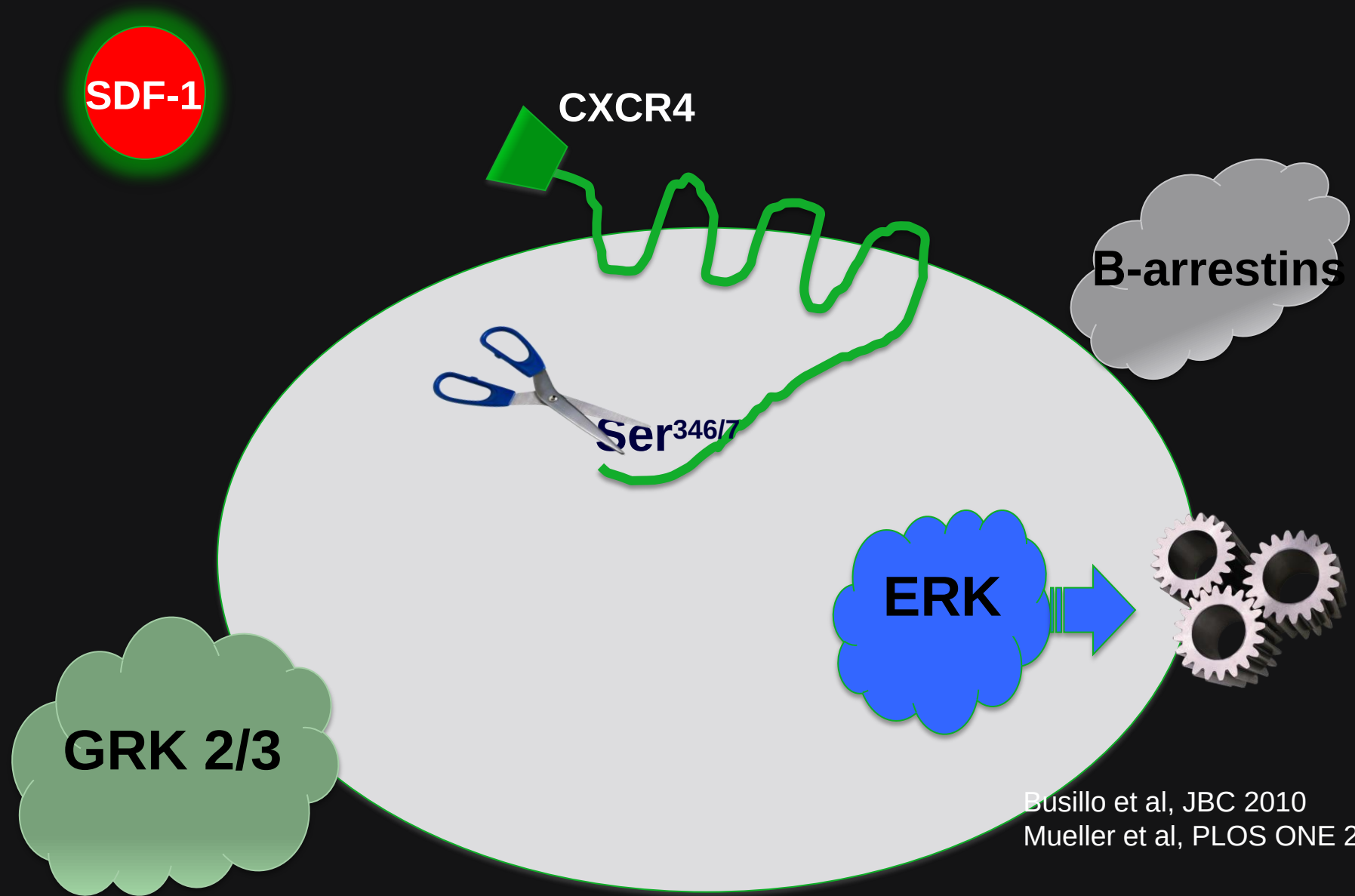


sIGM (mg/dL



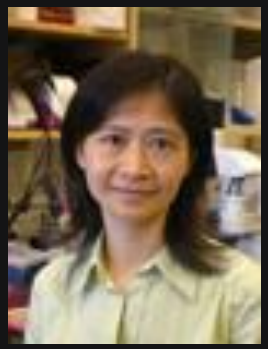
Treon et al, Blood 2014

CXCR4 Signaling in WM Patients with WHIM mutations



Busillo et al, JBC 2010
Mueller et al, PLOS ONE 2013

CXCR4^{WHIM} Mutations and Ibrutinib Killing in WM cells



Cao et al, Leukemia 2014
Cao et al, BJH 2014

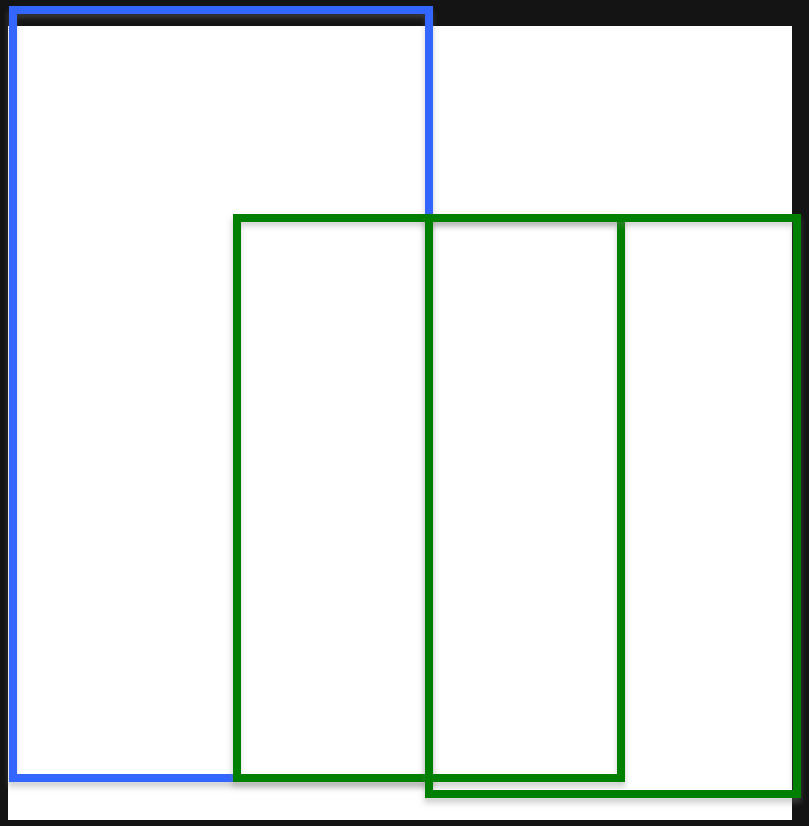
308 320 330 340 350

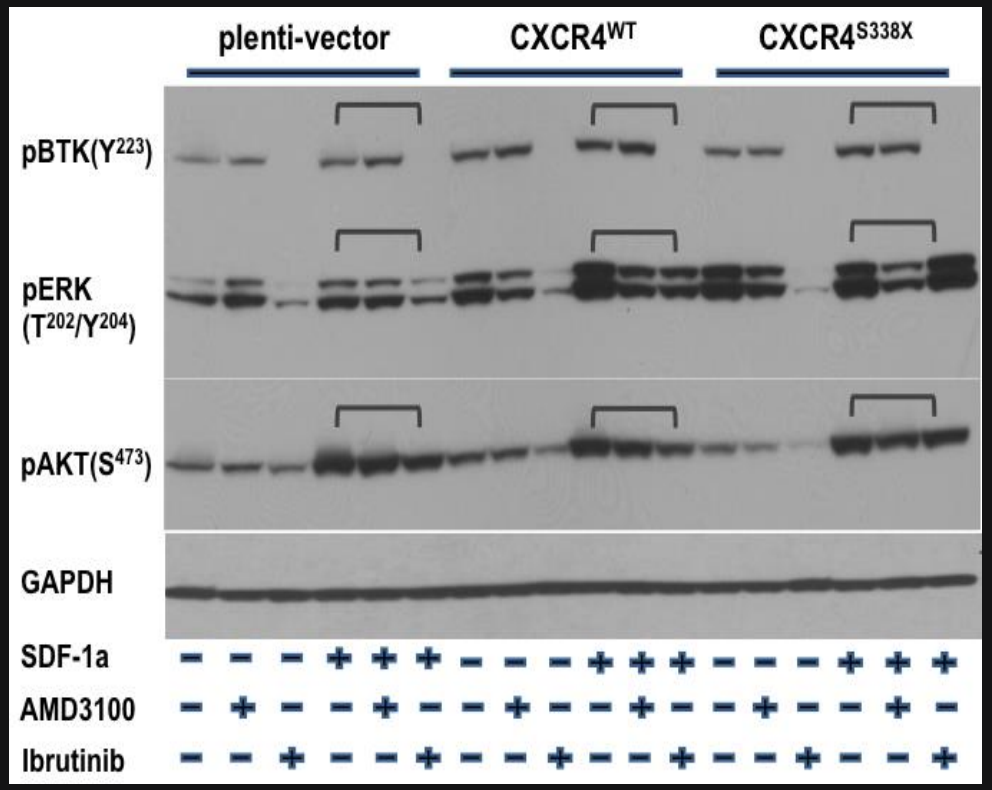
KFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTESESSSFHSS

KFKTSAQHALTSVSRGSSLKILSKGKRGGH

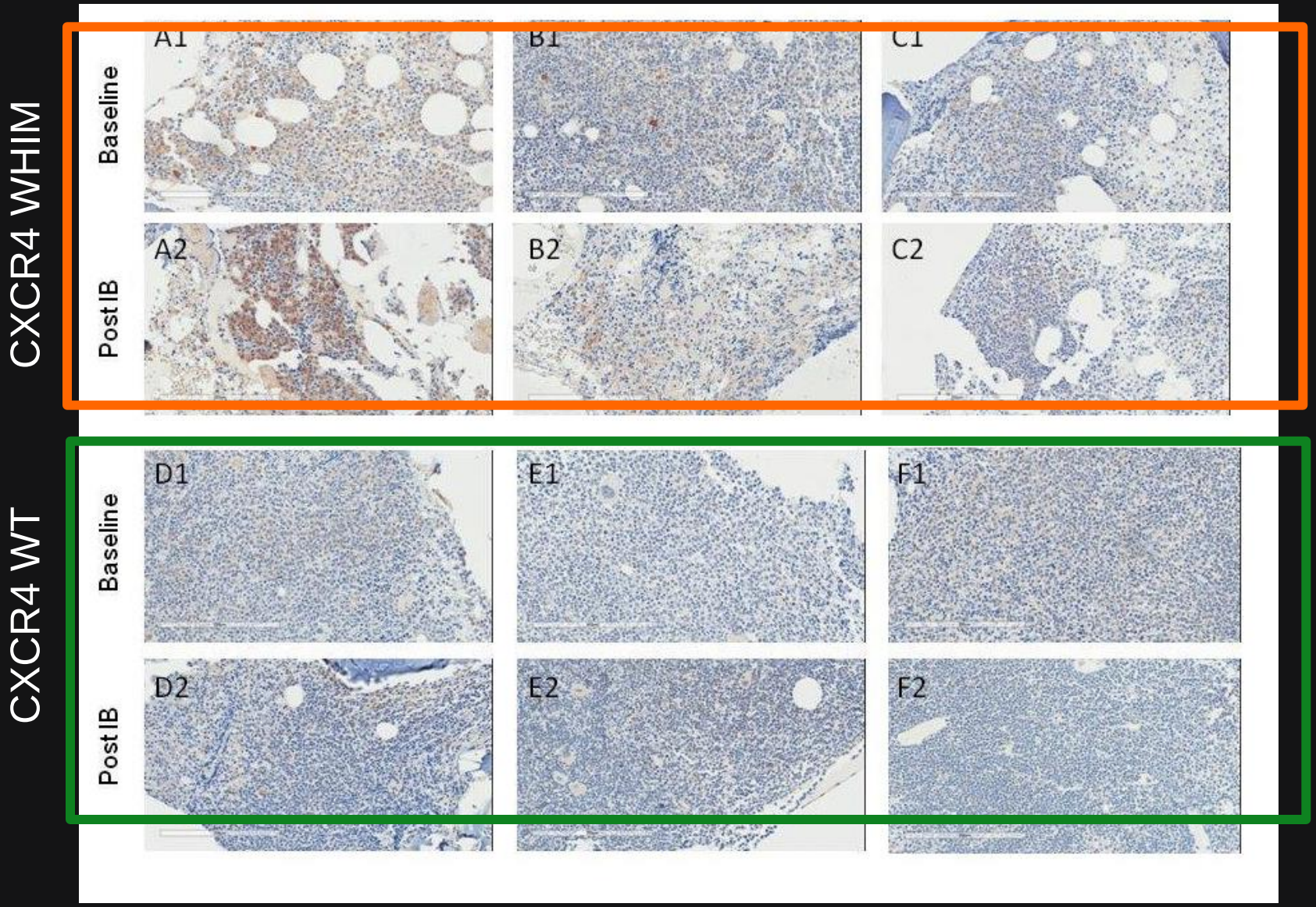
KFKNLCPARTHLCEQRVQPQDPLQRKARVTFICFH

KFKTSAQHALTSVSRGSSLKILSKGKRGGHSSVSTECKFSLQLTQM





Constitutive pAKT expression in CXCR4 WHIM patients on Ibrutinib



Cao et al, Leukemia 2014

MYD88 and CXCR4 mutation status and Responses to Ibrutinib

	$MYD88^{L265P}$ $CXCR4^{WT}$	$MYD88^{L265P}$ $CXCR4^{WHIM}$	$MYD88^{WT}$ $CXCR4^{WT}$	p-value
N=	34	21	7	
Overall RR	100%	85.7%	71.4%**	<0.01
Major RR	91.2%	61.9%	28.6%**	<0.01

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

Treon et al, NEJM 372: 1430, 2015

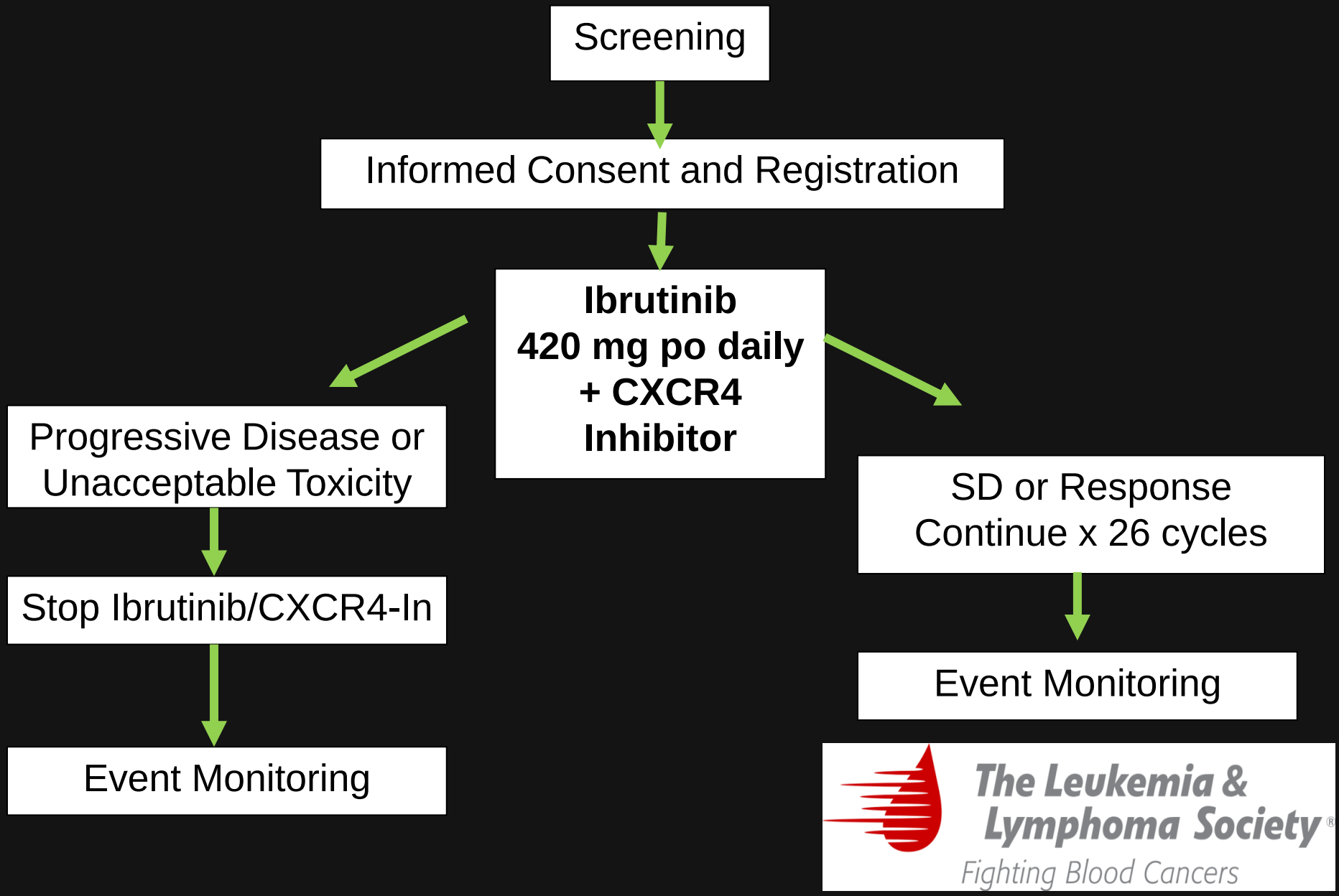
MYD88 and CXCR4 mutation status and Responses to Ibrutinib

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

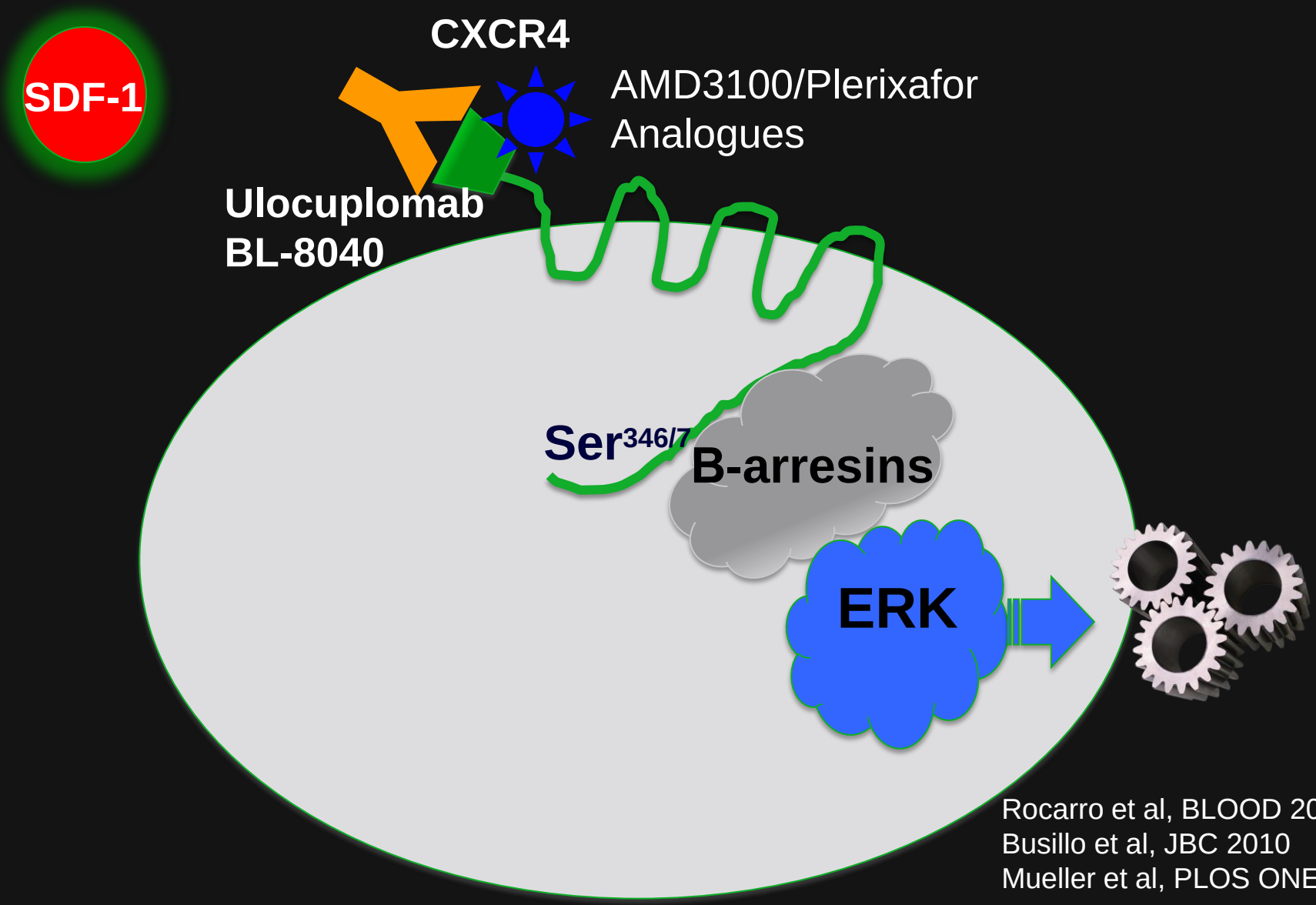
Includes 2 pts subsequently found to have other MYD88 mutations not picked up by AS-PCR

Treon et al, NEJM 372: 1430, 2015
Treon et al, Submitted

Phase II Study of Ibrutinib plus CXCR4-Antagonist in Relapsed/Refractory CXCR4^{WHIM} WM Patients

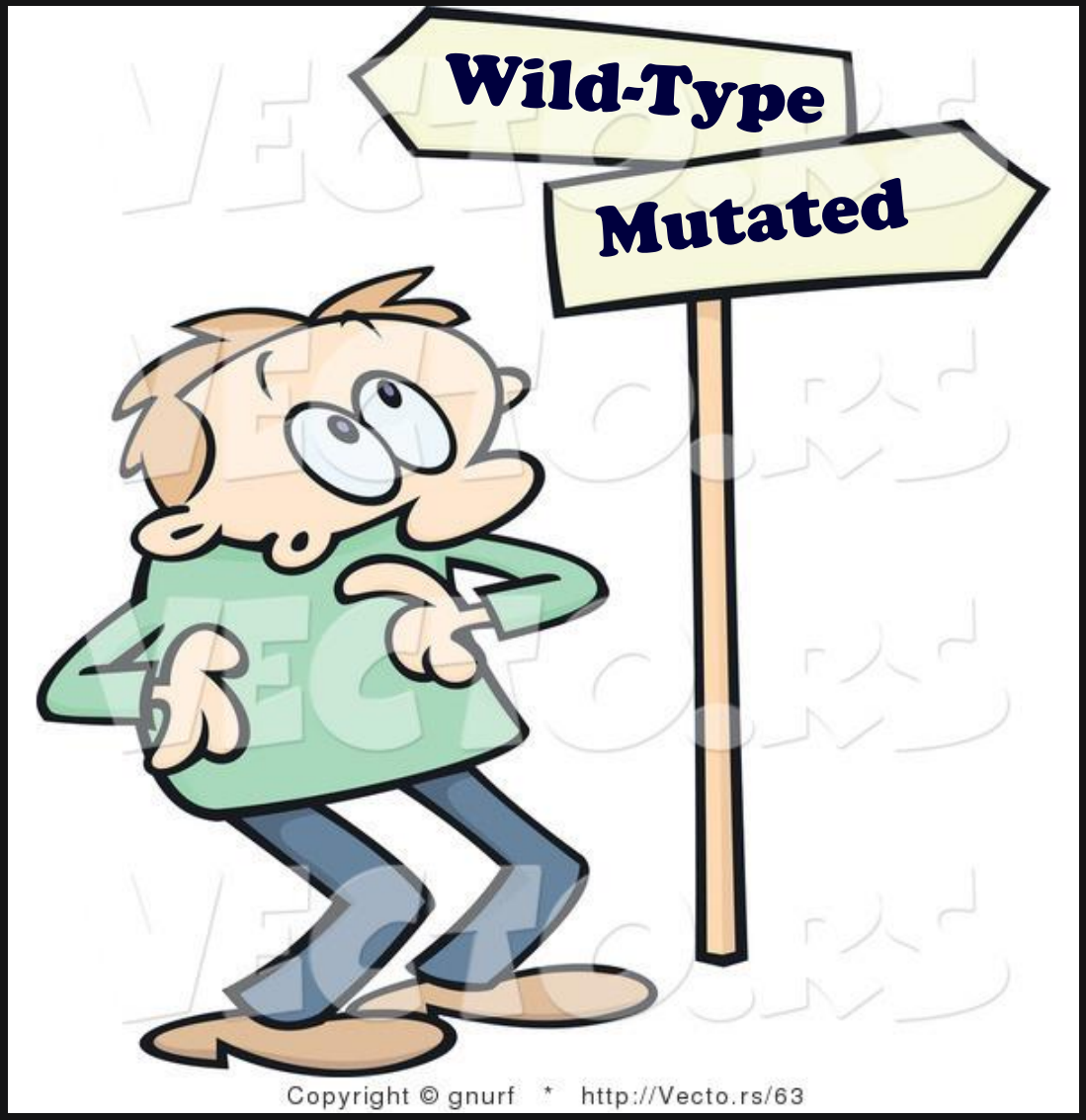


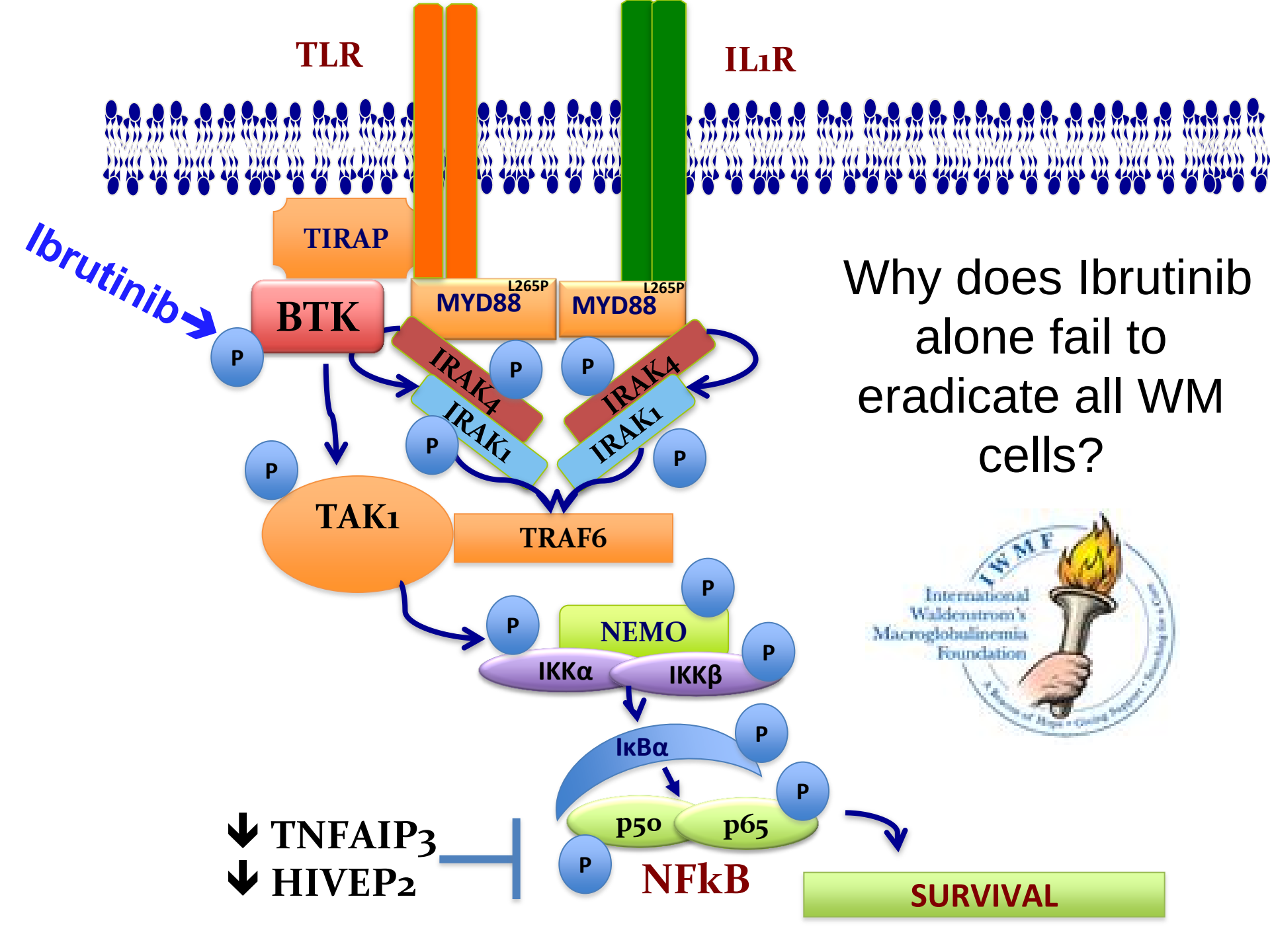
CXCR4 blocking strategies for enhancing Ibrutinib activity in CXCR4^{WHIM} WM Patients



Rocarro et al, BLOOD 2014
Busillo et al, JBC 2010
Mueller et al, PLOS ONE 2013

Unmutated MYD88 Disease in WM

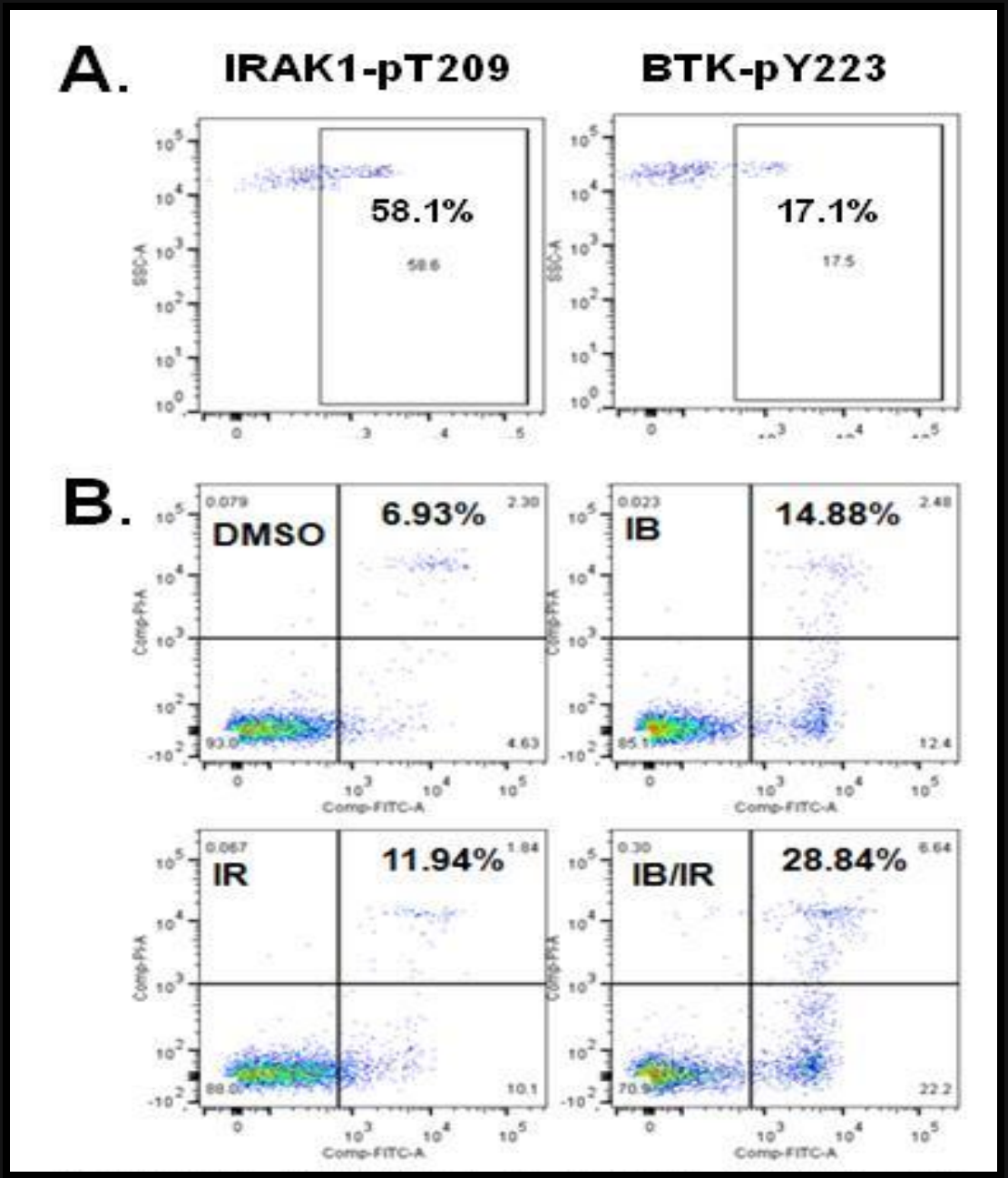




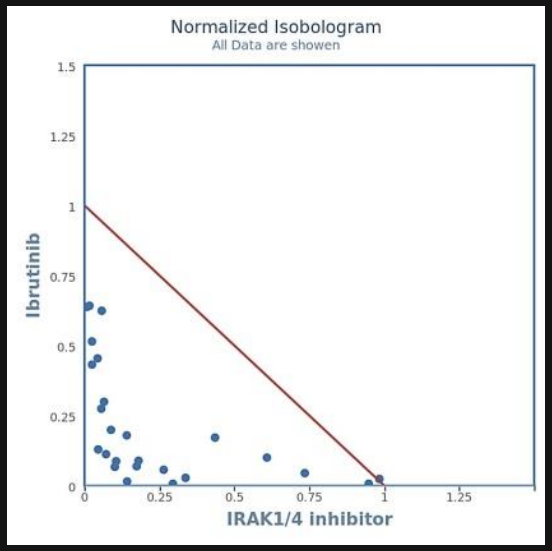
Why does Ibrutinib alone fail to eradicate all WM cells?

International Waldenstrom's Macroglobulinemia Foundation

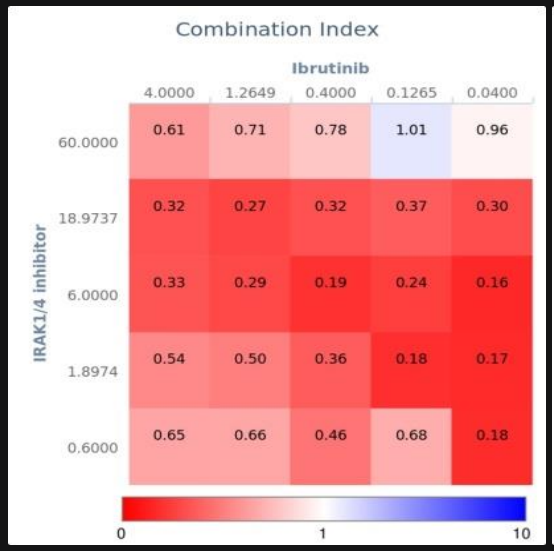
IRAK1 remains active in WM patients on ibrutinib and supports survival of WM cells



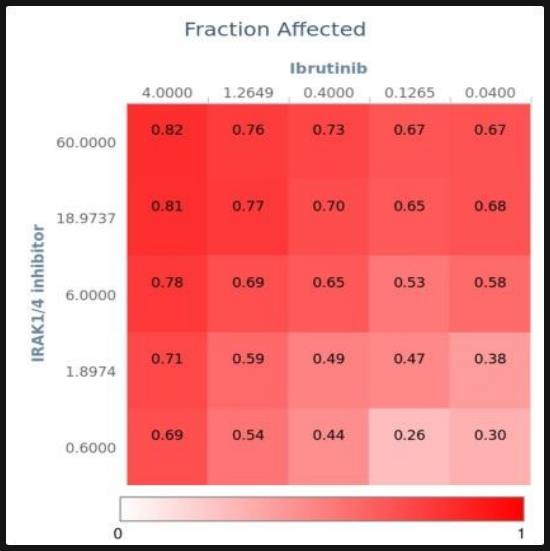
Combination of Ibrutinib and IRAK inhibitors show synergistic NFkB inhibition and WM cell killing (Yang et al, Blood 2013).



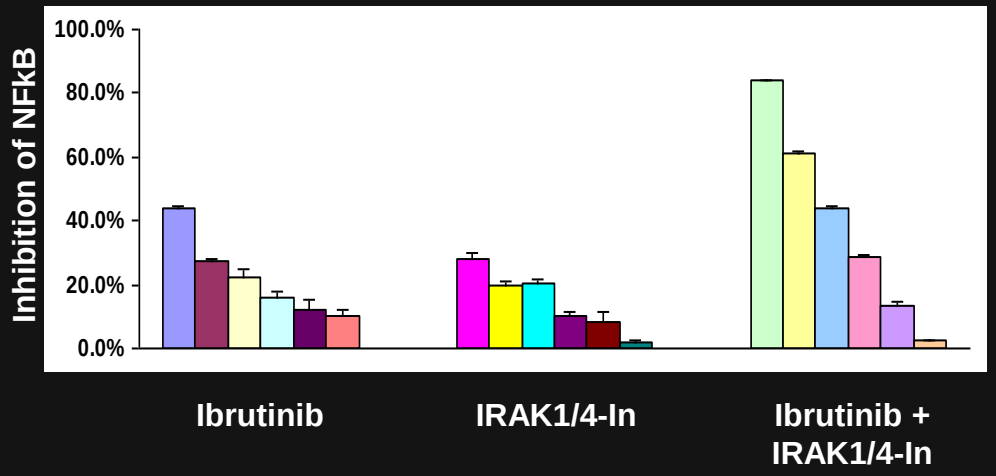
Normalized Isobologram

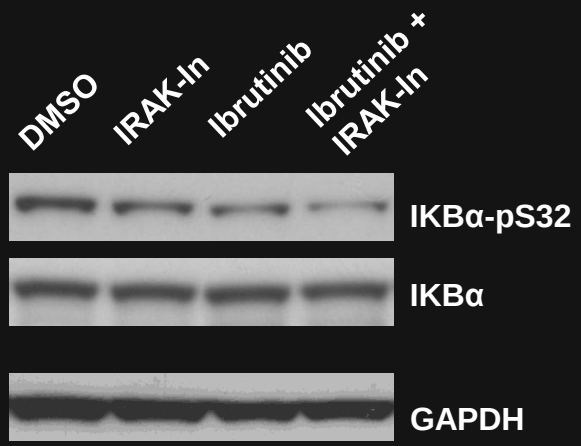


Combination Index

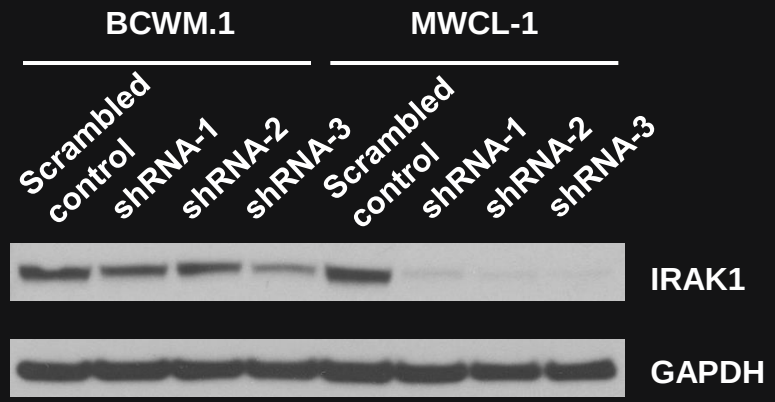


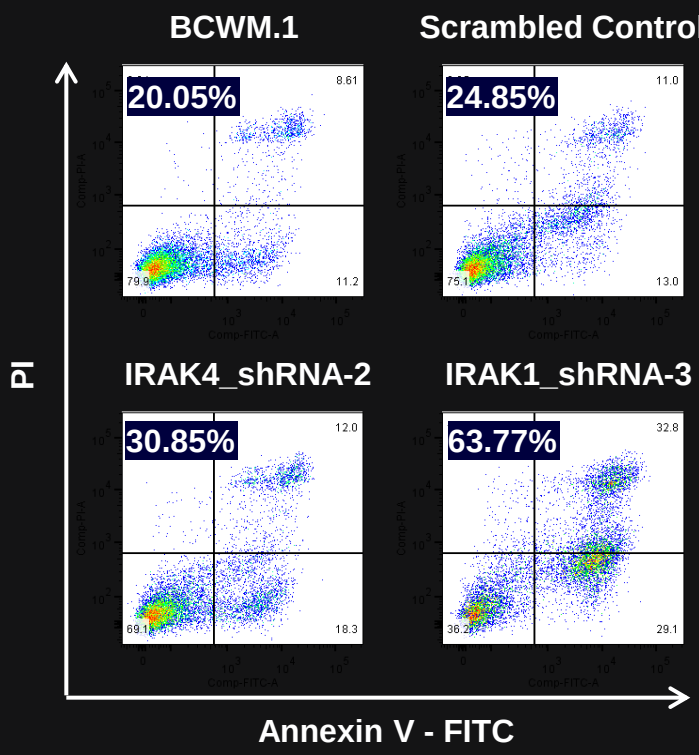
Fraction Affected

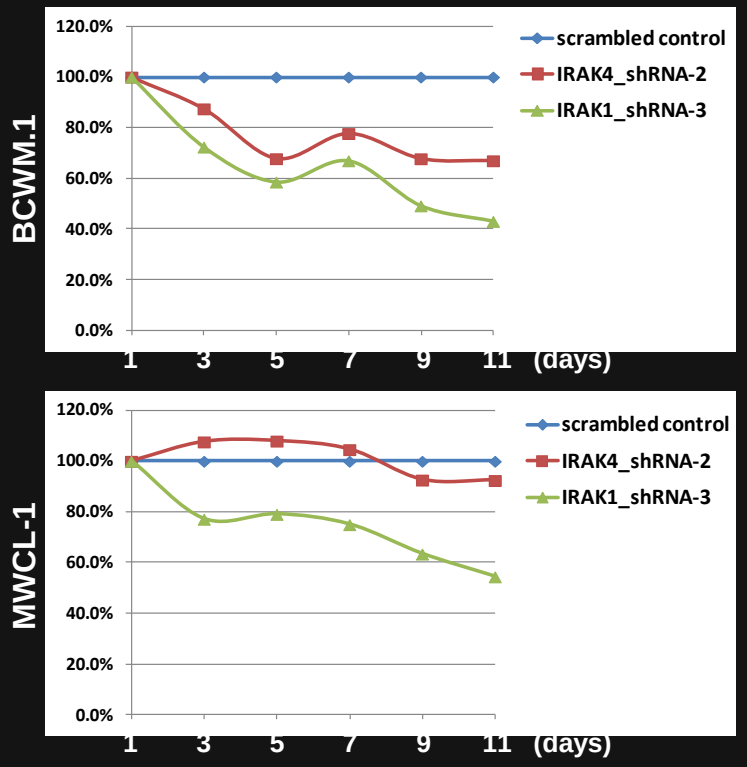




RELATIVE IMPACT OF IRAK1 TO IRAK4 FOR WM SURVIVAL





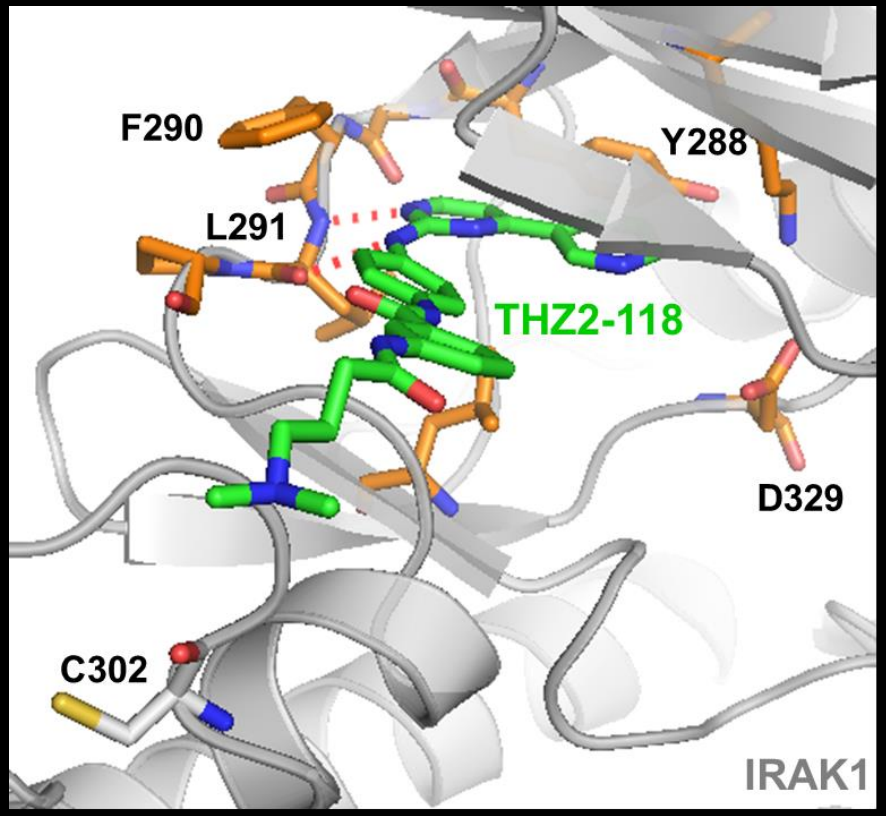


A scaffold selective for IRAK1 over IRAK4

THZ2-118

IRAK1 IC_{50} = 14.2 nM

IRAK4 IC_{50} > 10,000 nM

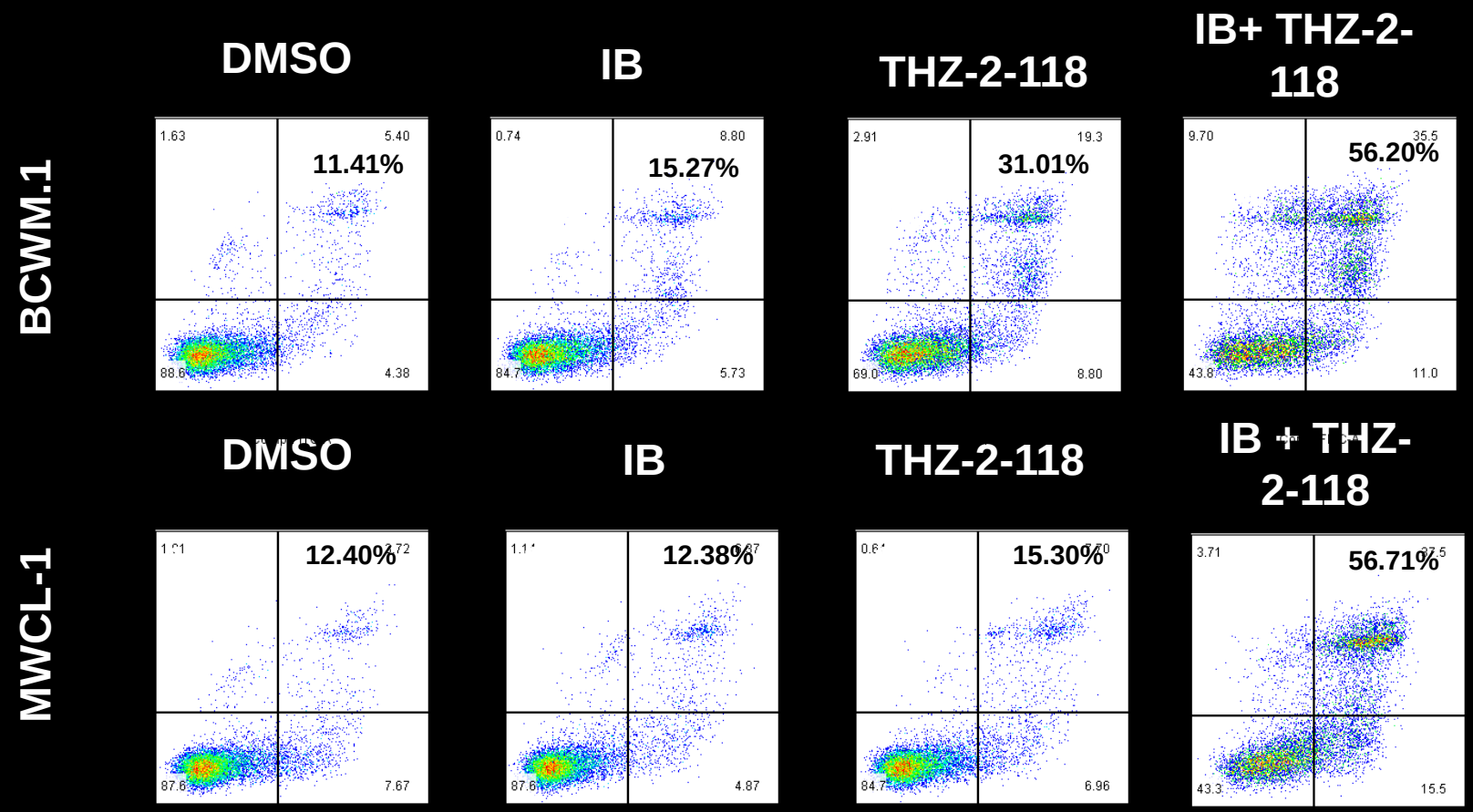


THZ2-118 docked to an IRAK1 homology model

LC-MS/MS analysis confirmed THZ2-118 covalently labels C302 or IRAK1

THZ2-118 does not inhibit signaling of IRAK1C302L

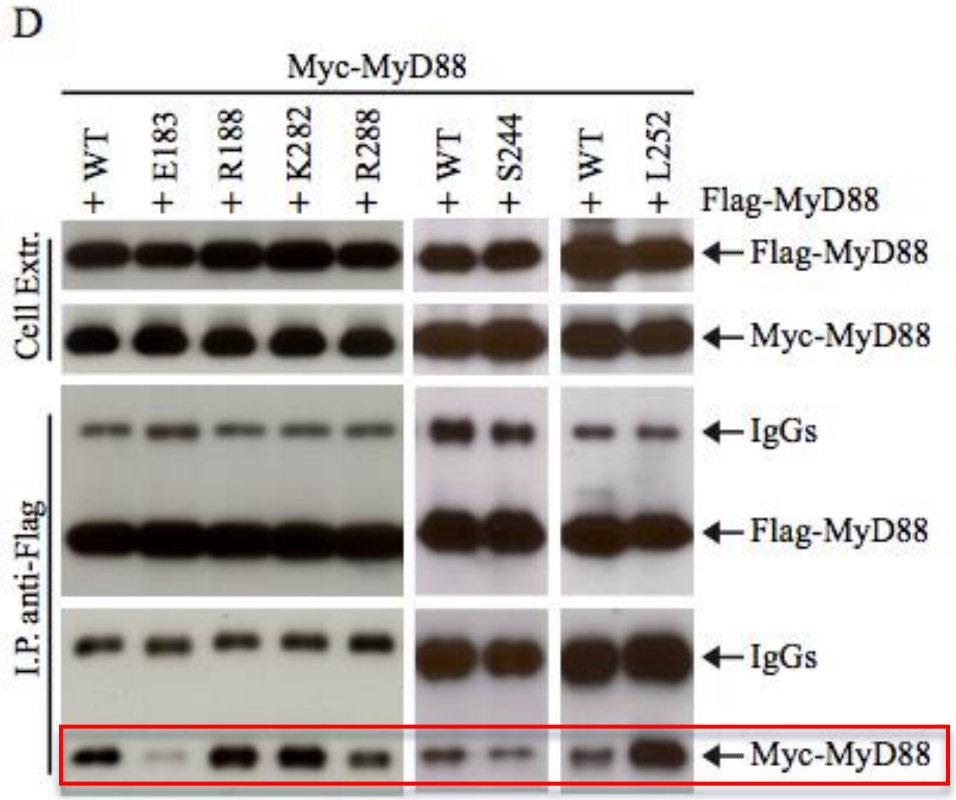
Killing of MYD88 L265P WM cells treated with novel IRAK1 inhibitor in combination with Ibrutinib

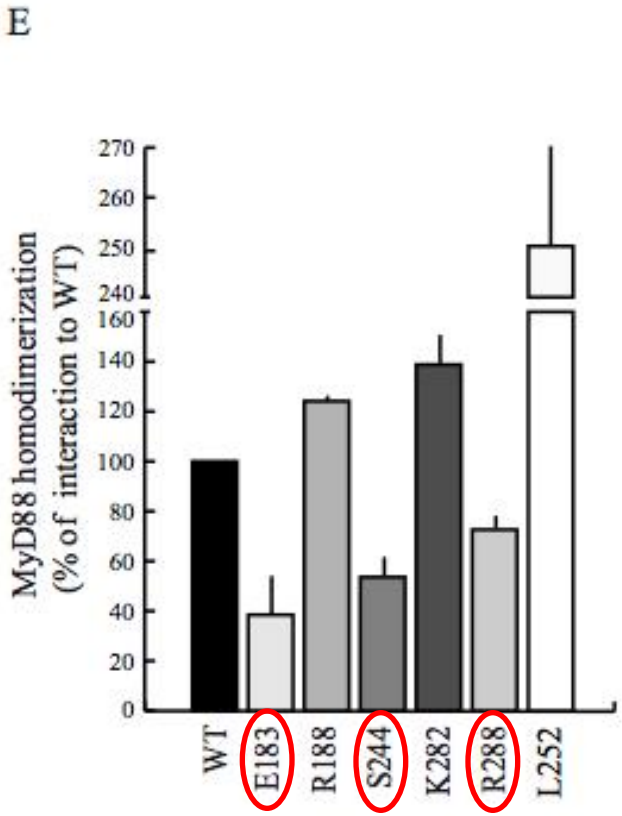


Lead Investigators: Guang Yang, Sara Burhlage

GRAY/TREON LABS

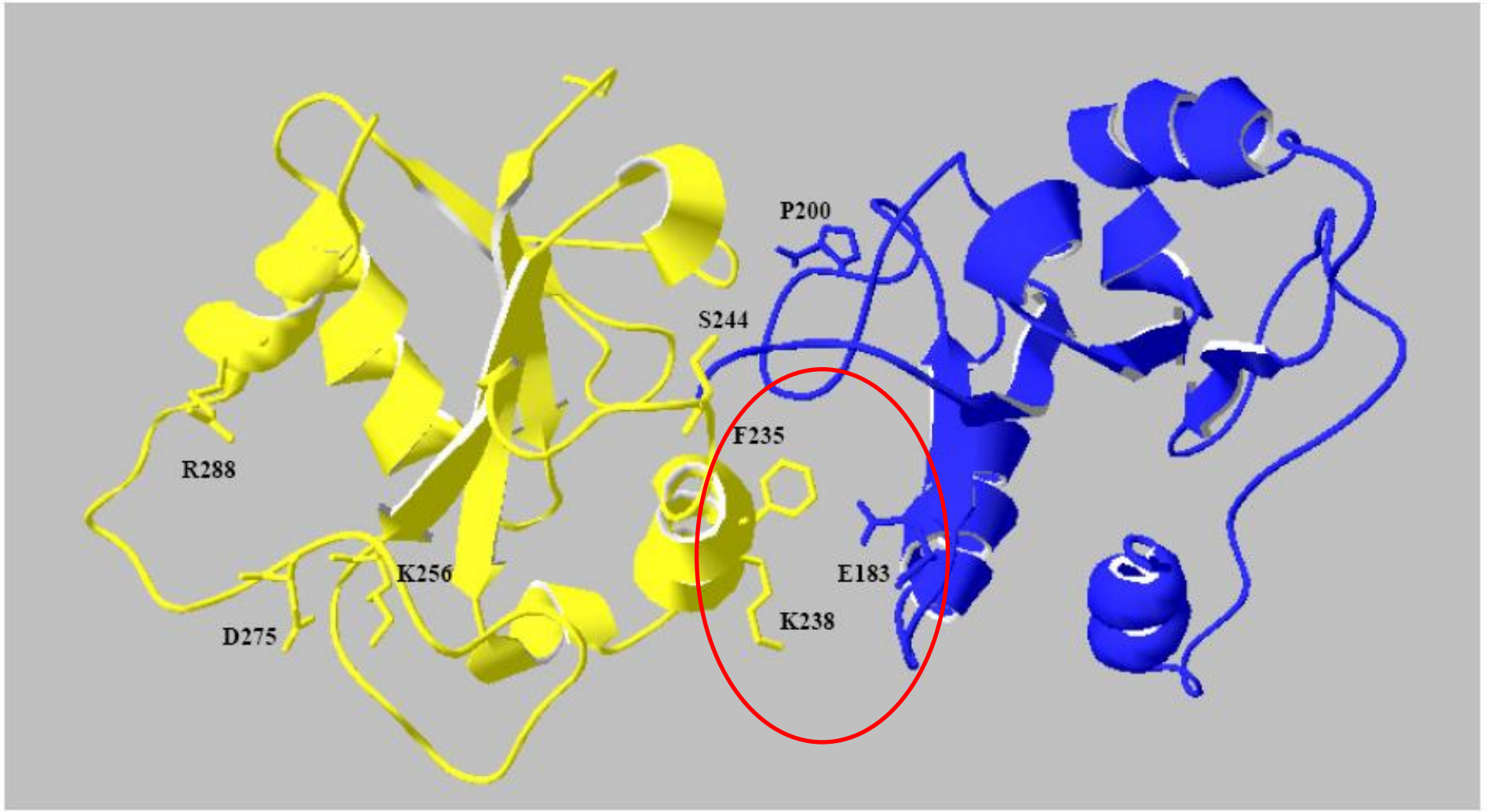
The E183, S244 and R288 residues are required for MyD88 homodimerization





Claudio Sette, JBC 20`14

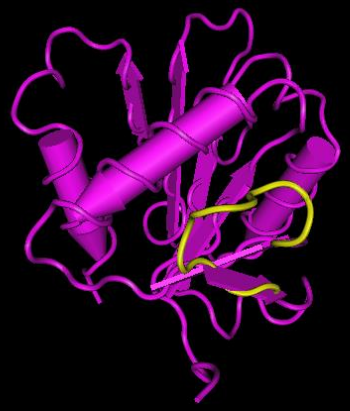
A structural model for MyD88 homodimerization

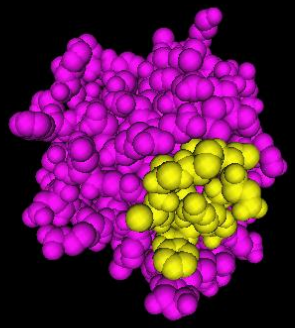


MYD88 Structure and Crucial Peptides in MYD88 TIR Domain for MYD88 Homodimerization

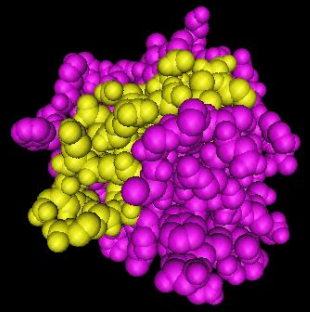
MYD88_TIR domain
L265(P)

MYD88_TIR_BB-loop

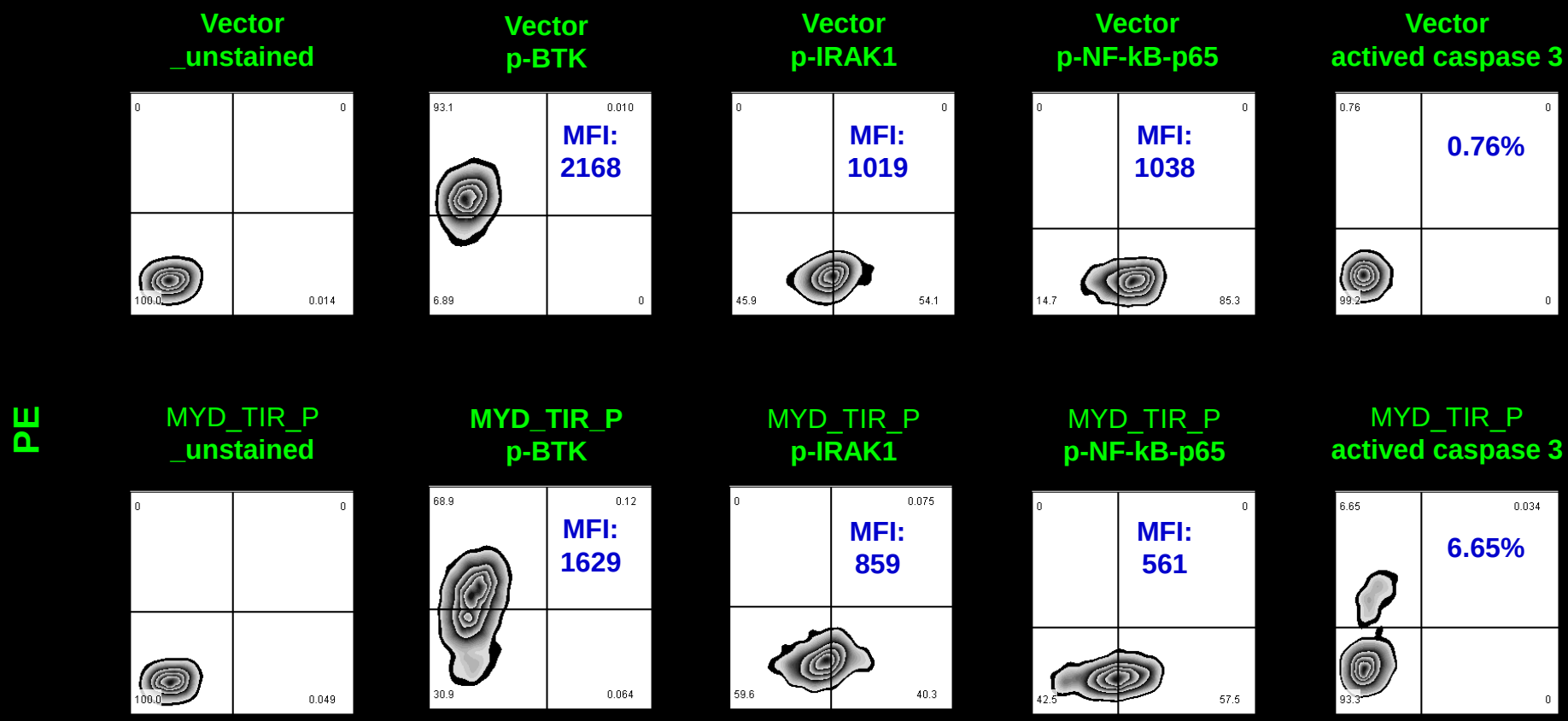




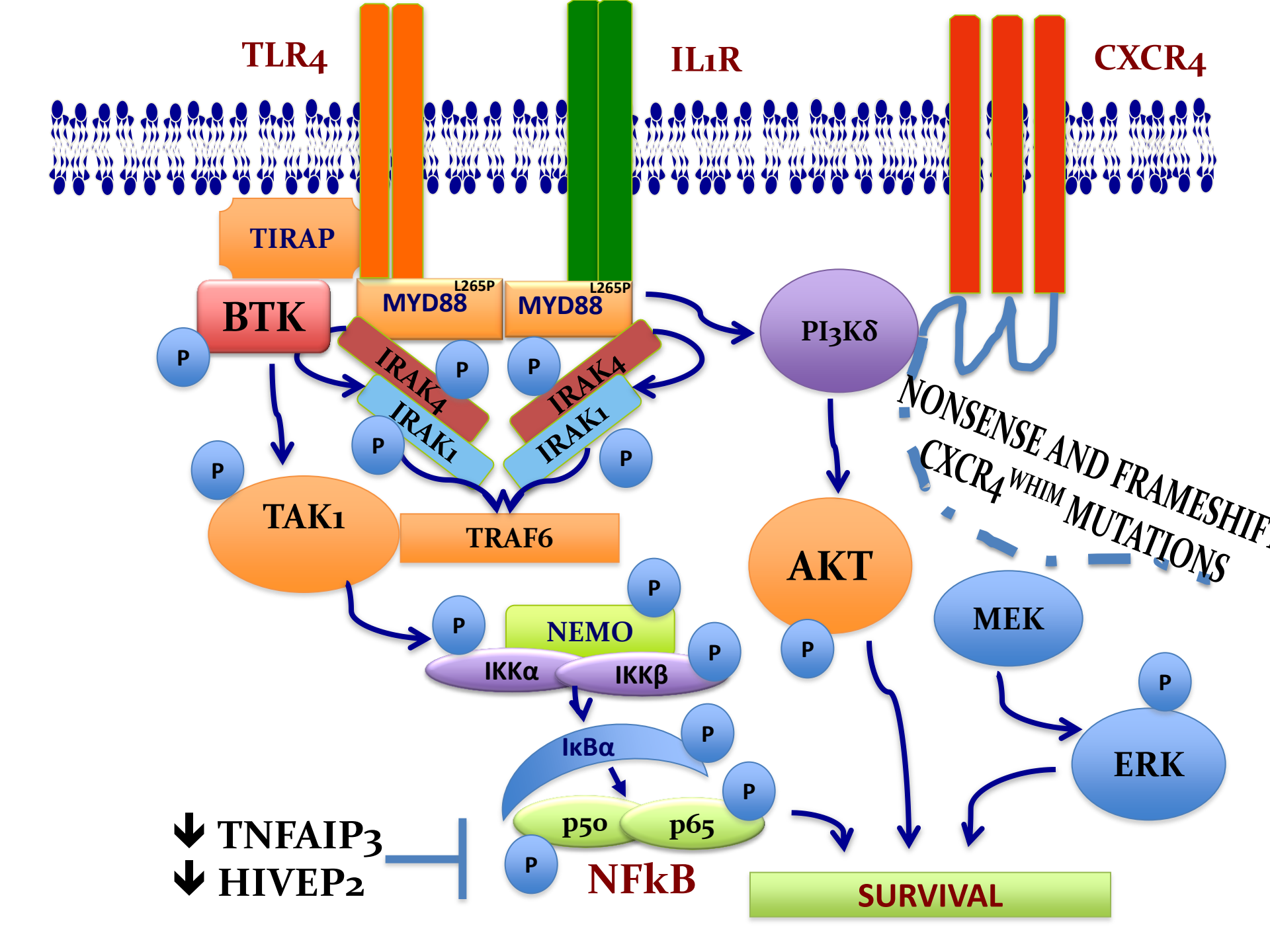
MYD88_TIR_Peptide



MYD88 TIR Domain Blocking Mini-peptides reduces BTK, IRAK1, NF-kB-p65 activation and triggers Caspase-3 in WM Cells



Xia Liu


TLR4
IL1R
CXCR4
TIRAP
BTK
MYD88 L265P
MYD88 L265P
IRAK4
IRAK1
IRAK4
IRAK1
P
TAK1
TRAF6
PI3Kδ
NONSENSE AND FRAMESHIFT
CXCR4 WHIM MUTATIONS
AKT
MEK
ERK
NEMO
IKKα
IKKβ
IκBα
p50
p65
NFkB
↓ TNFAIP3
↓ HIVEP2
SURVIVAL

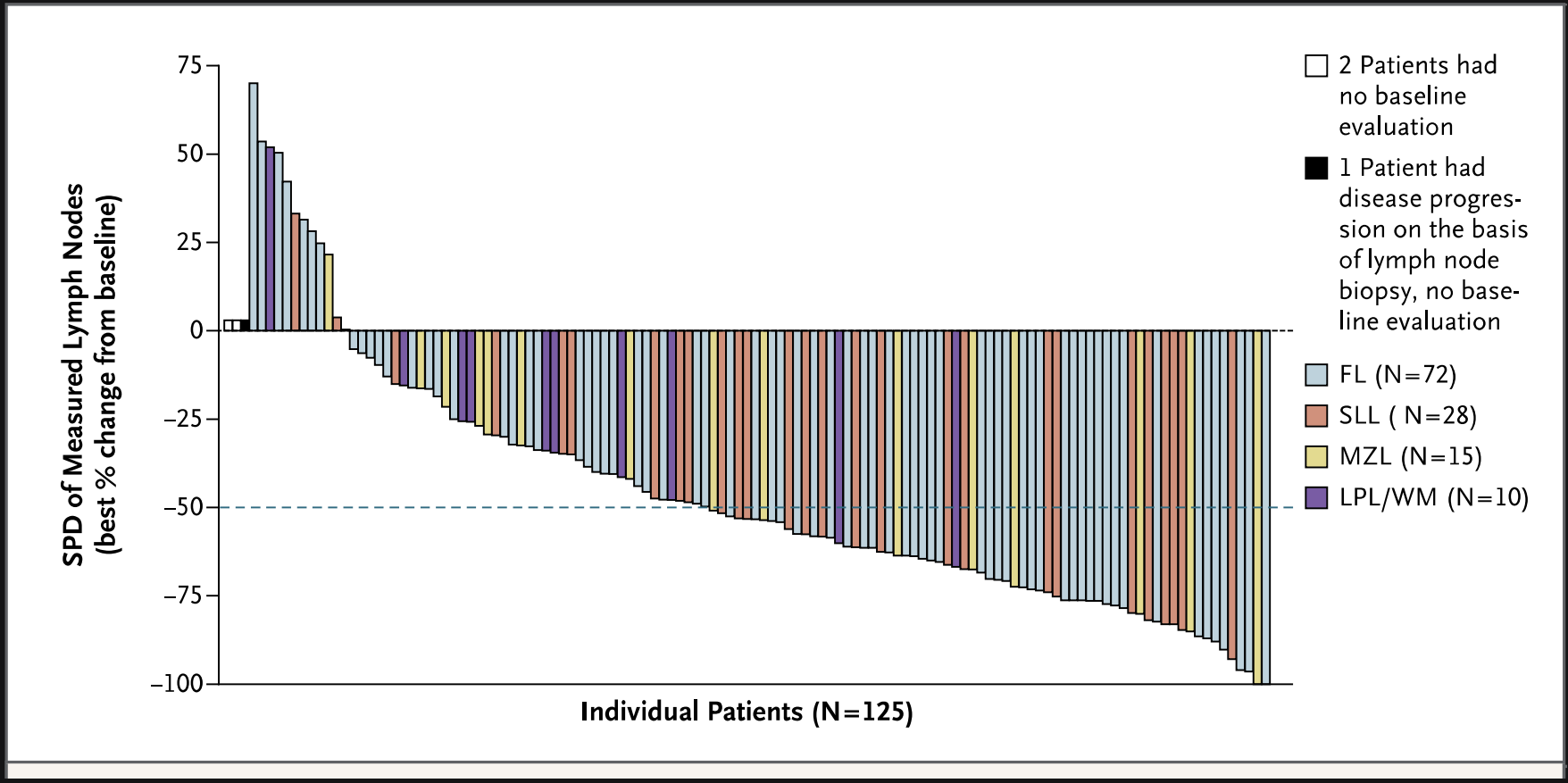
Idelalisib

- Selective, oral inhibitor of PI3K-delta
- Inhibits proliferation and induces apoptosis in many B-cell malignancies
- Inhibits homing and retention of malignant B-cells in lymphoid tissues reducing B-cell survival

Class I PI3K Isoform	α	β	γ	δ
Expression	**Ubiquitous**	**Ubiquitous**	**Leukocytes**	**Leukocytes**
EC_{50} (nM)	**>10,000**	**1419**	**2500**	**9**

*Benson D et al. ASCO 2013, abstr 8526

Responses in relapsed/refractory indolent NHL patients to idelalisib.



Gopal et al, NEJM 2014

Phase II Study of Idelalisib in Relapsed/Refractory WM

Screening

Informed Consent and Registration

Idelalisib 150 mg Twice a Day x 6 months then 150 mg a day

Progressive Disease or Unacceptable Toxicity

Stop Idelalisib

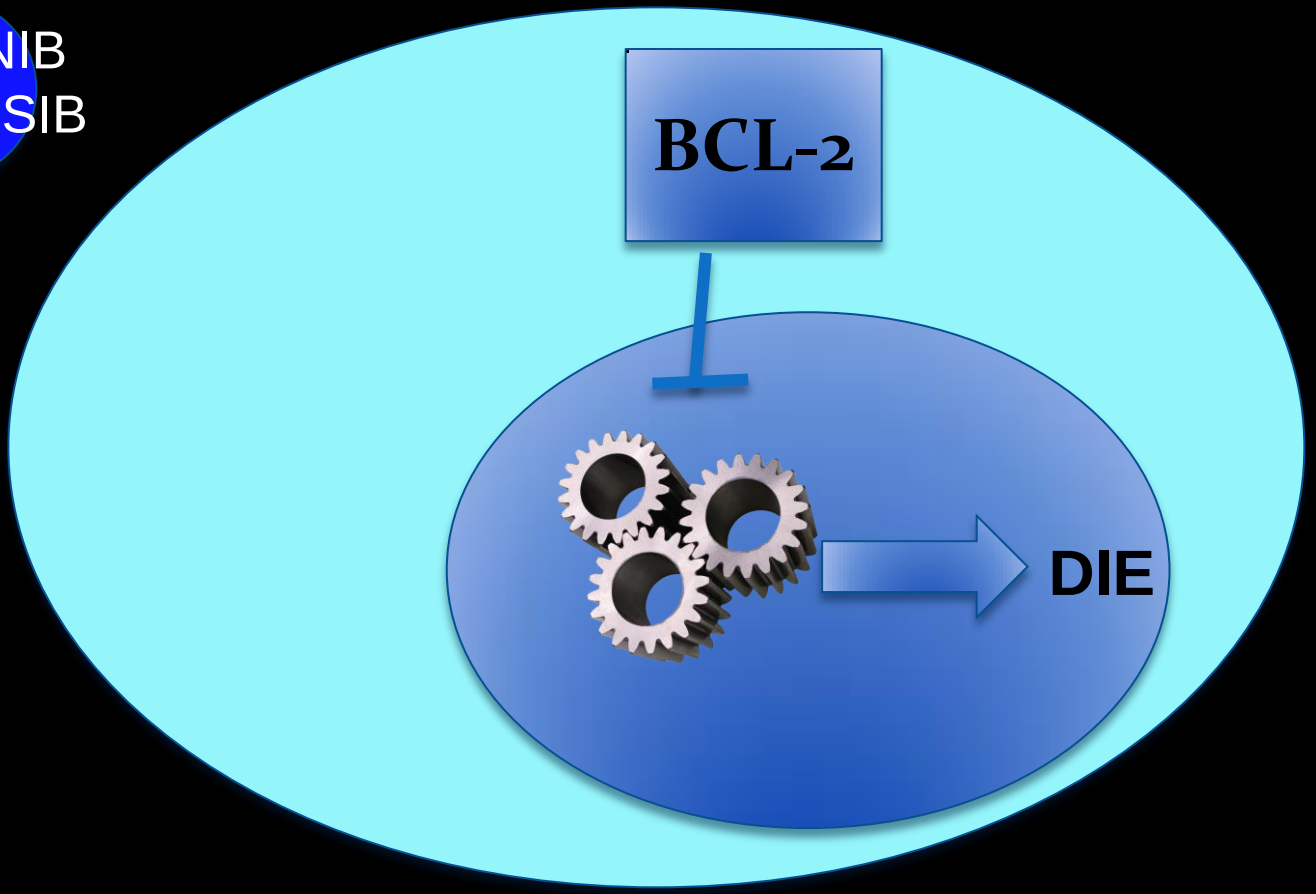
Event Monitoring

SD or Response Continue until PD

Event Monitoring

Targeting BCL-2 in WM

IBRUTINIB
IDELALISIB
ETC.



Chang et al, Leukemia 2006; Cao et al, BJH 2015


36
HAMHUIS
36

Responses to the anti-BCL2 agent ABT-199 in previously treated NHL Patients

Histology	Overall Response (CR + PR)	Complete Response n (%)	Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)
Total (n=33)	53%	3/36 (8)	16/36 (44)	9/36 (25)	7/36 (19)
MCL (n=11)*	82%	1/11 (9)	8/11 (73)	-	1/11 (9)
FL (n=11)	27%	-	3/11 (27)	8/11 (73)	-
DLBCL (n=8)	38%	1/8 (13)	2/8 (25)	1/8 (13)	4/8 (50)
WM (n=3)	100%	1/3 (33)	2/3 (67)	-	-
MZL (n=2)	50%	-	1/2 (50)	-	1/2 (50)
MM (n=1)	-	-	-	-	1/1 (100)

Davids et al, ASH 2013

Phase I/II Study of ABT-199 in Relapsed/Refractory WM

Screening

Informed Consent and Registration

ABT-199 200➔ 1200 mg a Day

Progressive Disease or Unacceptable Toxicity

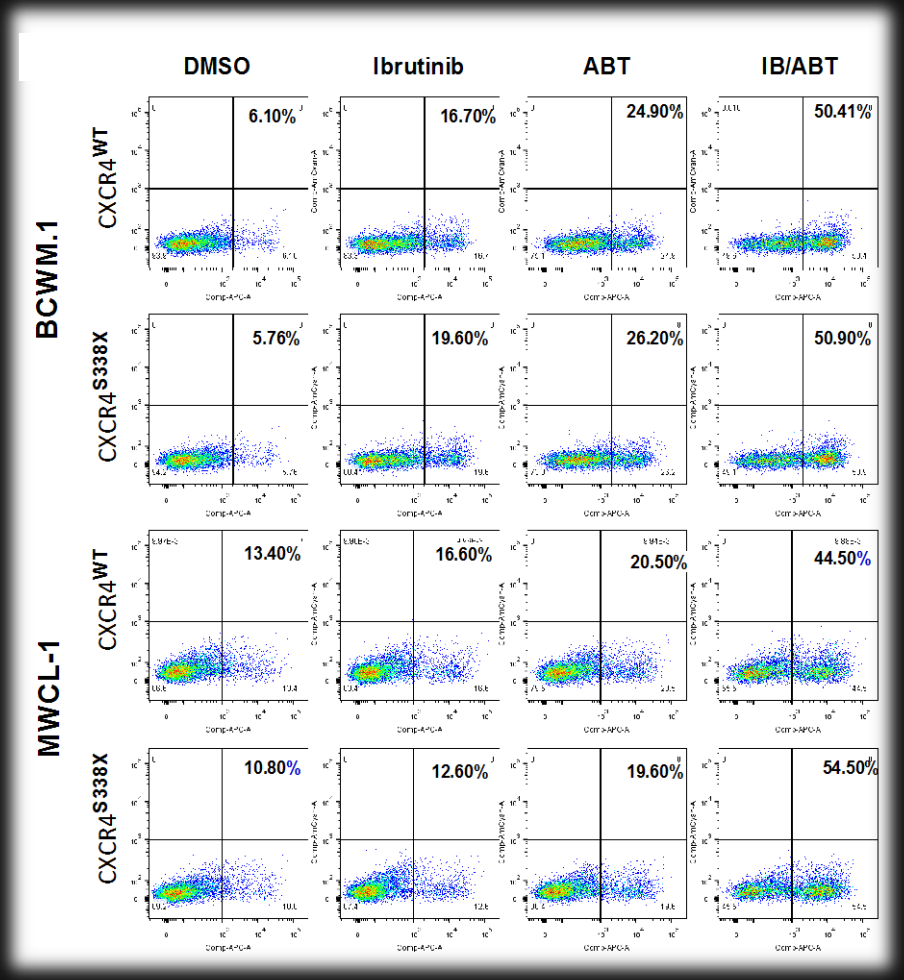
Stop Ibrutinib/Pleixafor

Event Monitoring

SD or Response Continue x 26 cycles

Event Monitoring

ABT-199 enhances Ibrutinib killing in both CXCR4 WT and WHIM WM Cells.



Ibrutinib

GDC-0199	500 nM	158 nM	50 nM	15.8 nM
50 nM	1.53	1.35	1.28	1.20
15.8 nM	1.46	1.10	1.26	1.12
5.0 nM	1.40	1.24	1.26	1.23
1.6 nM	1.26	1.02	1.36	1.23

BCWM.1 CXCR4^{WT}

Ibrutinib

GDC-0199	500 nM	158 nM	50 nM	15.8 nM
50 nM	1.37	1.49	1.24	1.42
15.8 nM	1.32	1.30	1.33	1.17
5.0 nM	1.35	1.50	1.73	1.76
1.6 nM	1.22	1.26	1.03	0.88

BCWM.1 CXCR4^{S338X}

Cao et al, BJH 2015

AbbVie boosts cancer drug pipeline with $21 billion Pharmacyclics deal

BY SUPRIYA KURANE AND **BEN HIRSCHLER**

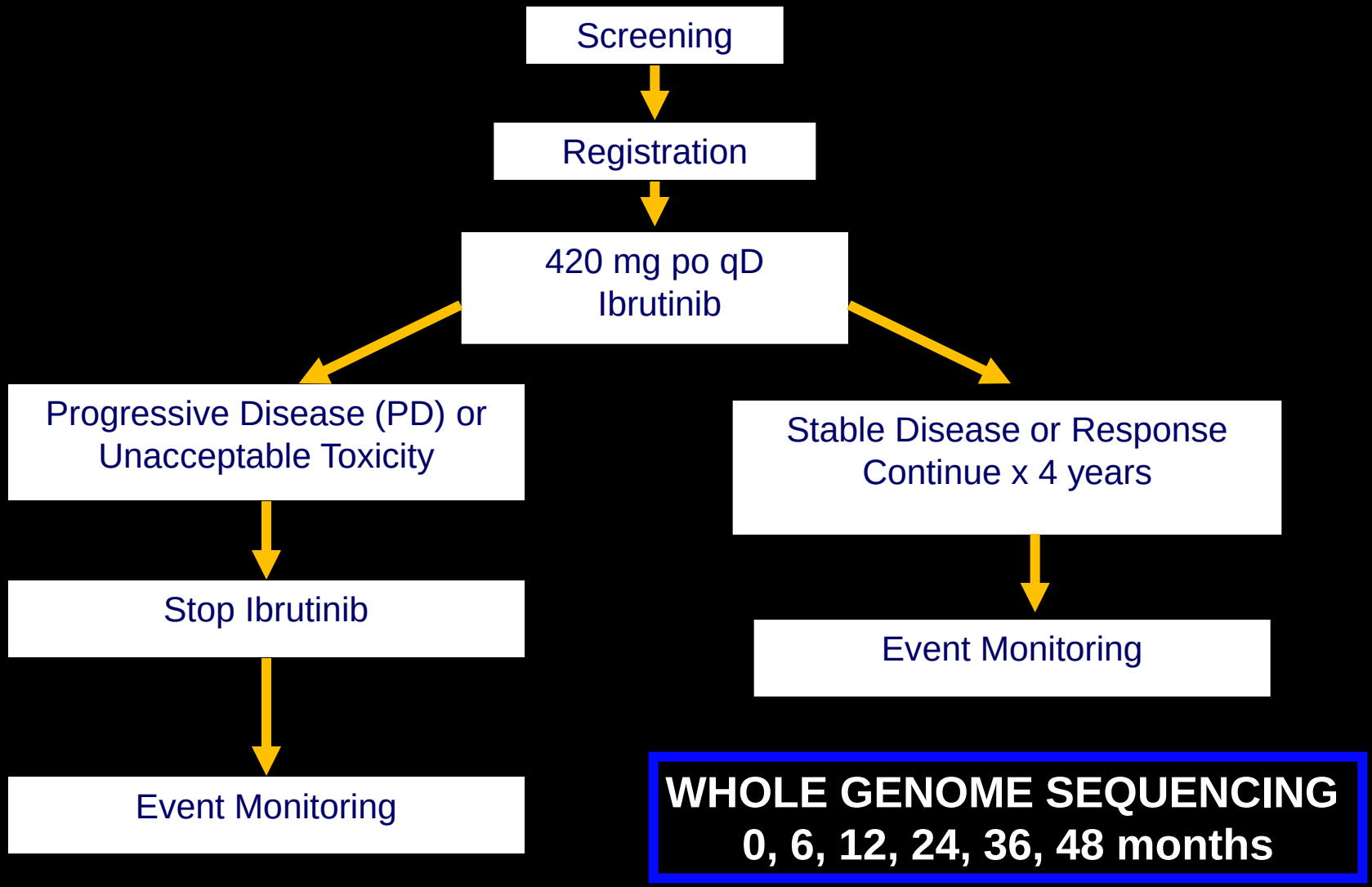
Thu Mar 5, 2015 5:24pm EST

RELATED VIDEO

Can genomic mutations cause resistance to Ibrutinib in WM?

CLL
Cysteine-481
PLCγ2 mutations

Ibrutinib in Untreated Symptomatic WM



Phase II Study of omib/Dexamethasone/Rituximab Untreated WM.

- Ixazomib is an oral proteasome inhibitor
- Active in Multiple Myeloma
- Lower neuropathy potential vs. bortezomib
- Well-tolerated in myeloma patients

- Proteasome Inhibitors may circumvent MYD88 and CXCR4 pathways. (Treon et al, Blood 2014)

www.clinicaltrials.gov

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Summary

- MYD88 L265P is present >90% of WM patients and triggers activation of Bruton's Tyrosine Kinase (BTK) in WM cells.
- The BTK inhibitor ibrutinib is associated with rapid reduction of serum IgM and improved HCT with an ORR of 91%, major RR of 73% in relapsed/refractory patients.
- MYD88 and CXCR4 mutations impact responses to ibrutinib in WM patients.
- Inhibitors to MYD88, CXCR4, BCL2 pathways represent novel approaches to the treatment of WM, alone and in combination.

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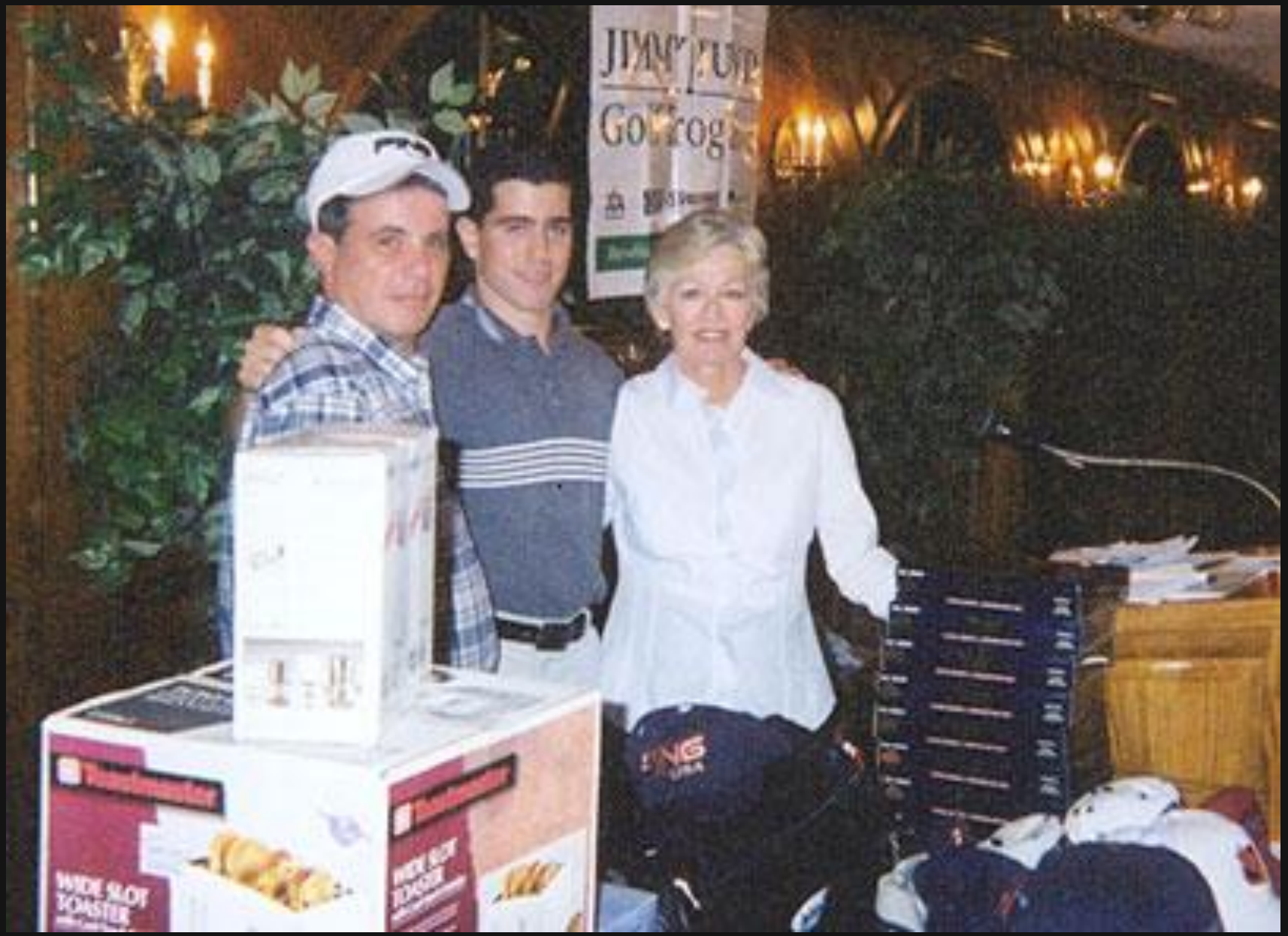
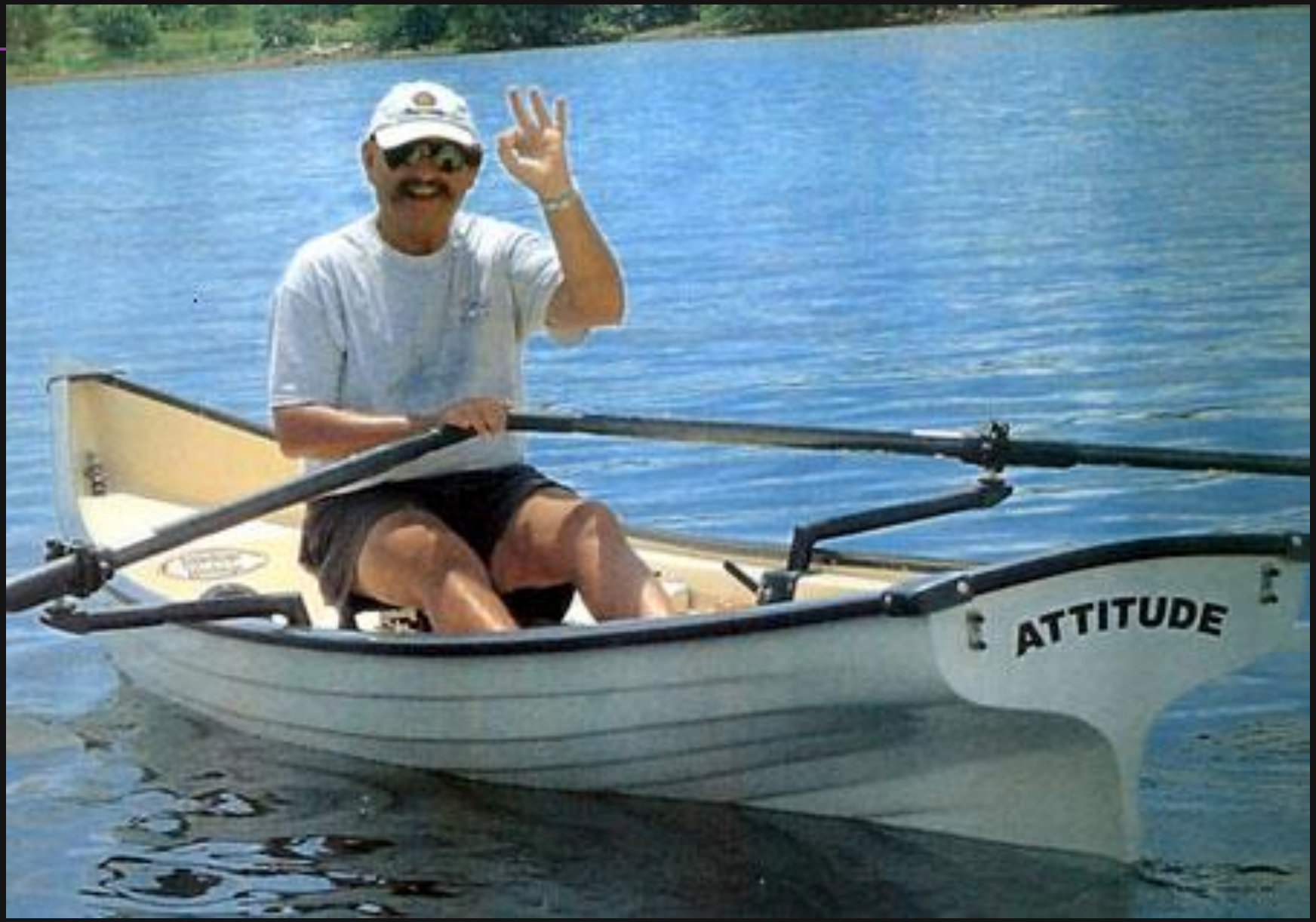
Jimmy Fund Walk-a-thon in Support of WM Research at DFCI



Jimmy Fund Golf Tournament in Support of WM Research at DFCI

Jimmy Fund Golf Tournament in Support of WM Research at DFCI



Row Bob's Row-a-thon in Support of WM Research at DFCI