Waldenström's Macroglobulinemia: Management

VE RI TAS

HARVARD
MEDICAL SCHOOL

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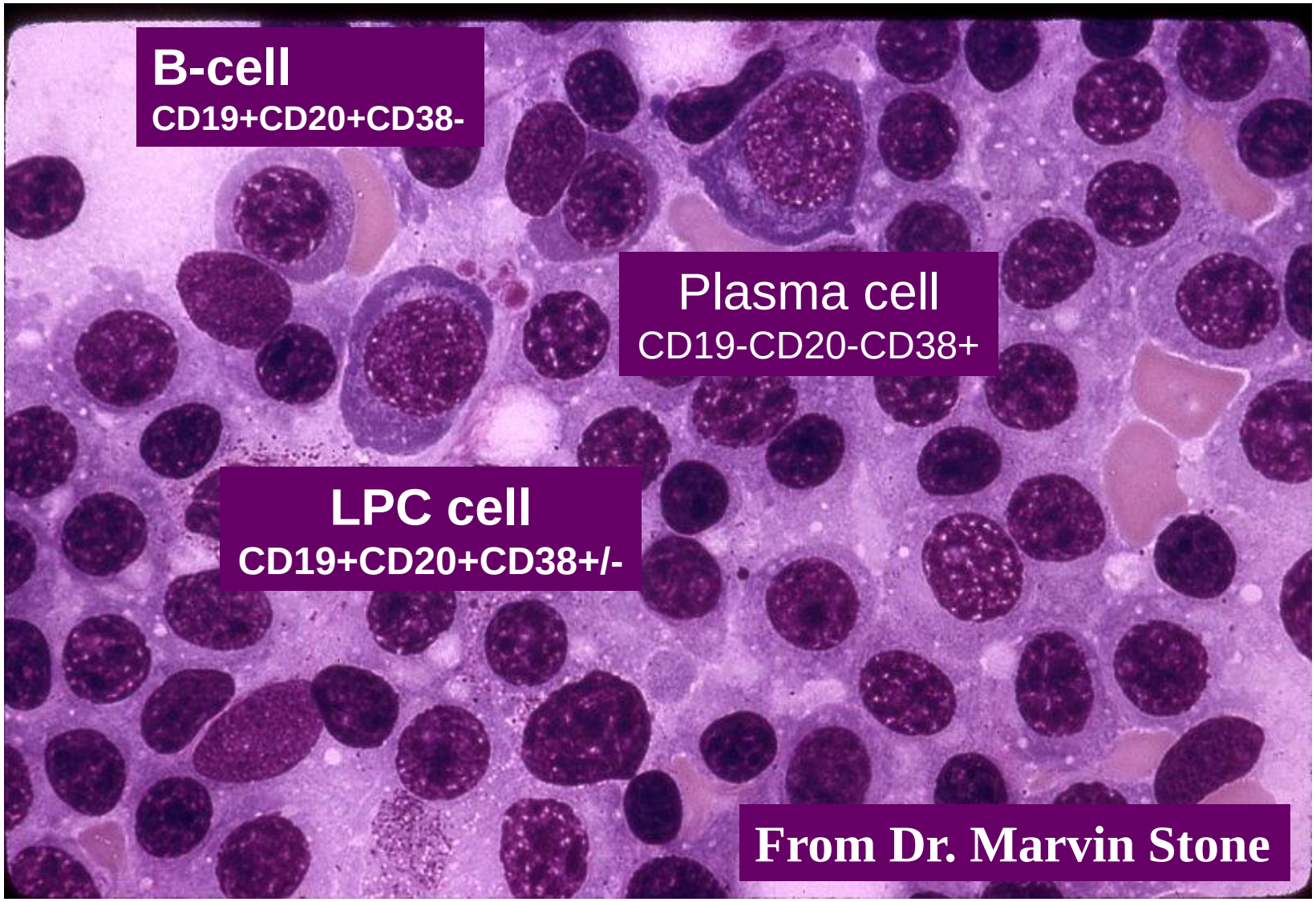
Chair, WM Clinical Trials Group

Disclosures

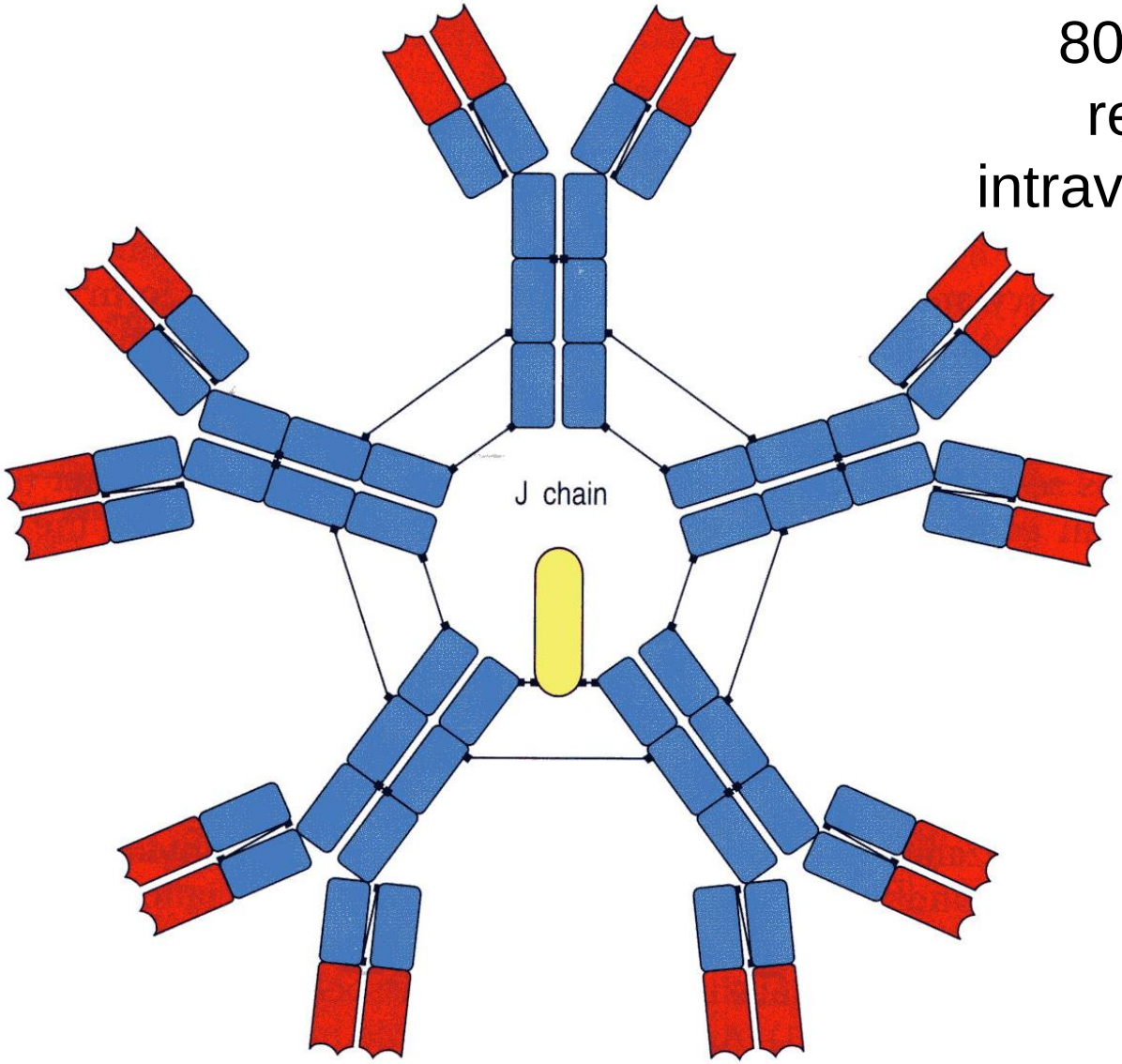
Principal Investigator Role		Pharmacyclics, Inc., Bristol Myers Squibb
Employee		NONE
Consultant		Janssen Pharmaceuticals, Inc., Pharmacyclics, Inc.
Major Stockholder		NONE
Speaker's Bureau		NONE
Scientific Advisory Board		NONE

Presentation includes discussion of the following off-label use of a drug or medical device:	
venetoclax, ulocuplomab, daratumumab, rituximab, bendamustine, SNS-062, dexamethasone,thalidomide,fludarabine,acalabrutinib,Ulucuplomab,everolimus ,cyclophosphamide, bortezomib,BGB-311, venetoclax	



WHO Classification: IgM secreting lymphoplasmacytic lymphoma

Pentameric IgM



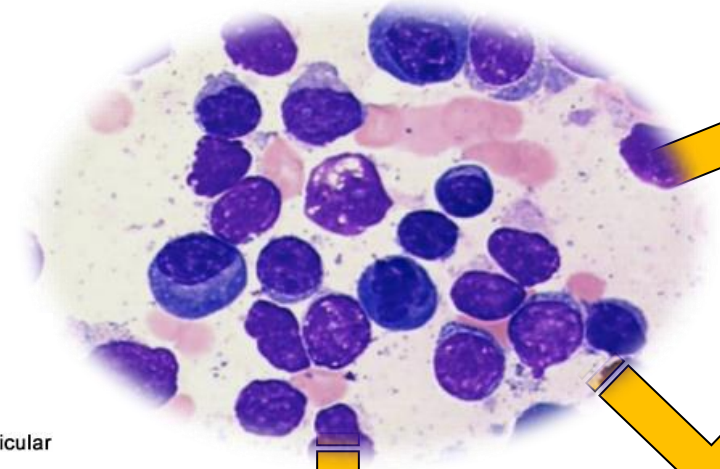
80-90% sIgM retained in intravascular space

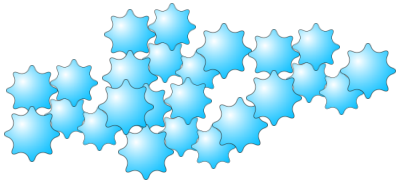
Manifestations of WM Disease

Bing Neel Syndrome

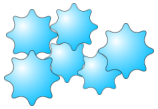
Bone Marrow

↓Hb>>> ↓PLT> ↓WBC

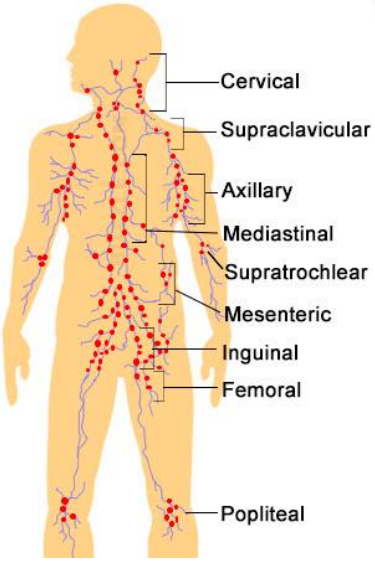




Hyperviscosity Syndrome:
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP



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



≤20% at diagnosis;
50-60% at relapse.

Hepcidin
↓Fe Anemia

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

NCCN Guidelines for Initiation of Therapy in WM

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

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

Primary Therapy of WM with Rituximab

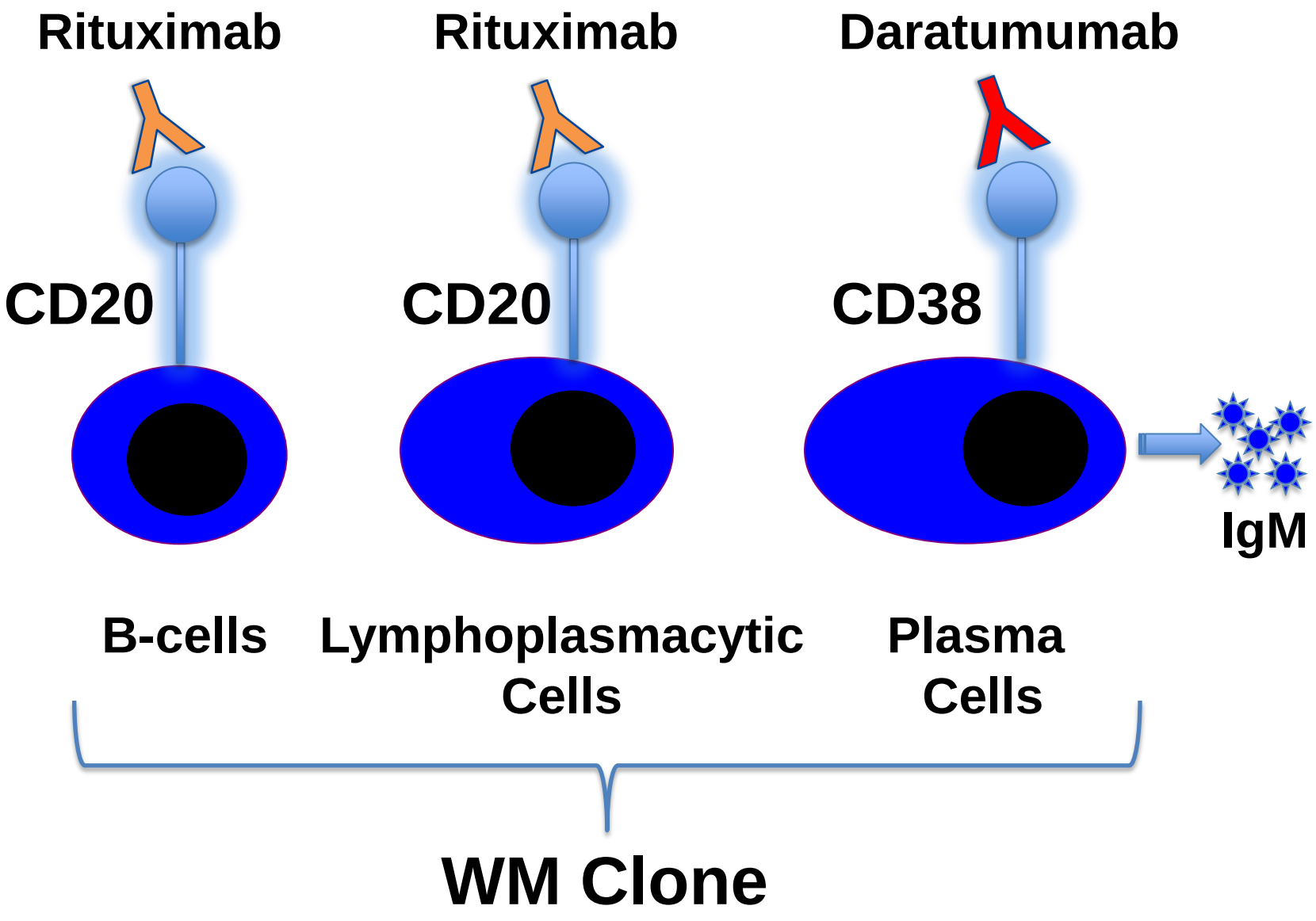
Regimen	ORR	VGPR/CR	TTP (mo)
Rituximab x 4	25-30%	0-5%	13
Rituximab x 8	40-45%	5-10%	16-22
Rituximab/thalidomide	70%	10%	30
Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, CDR	70-80%	20-25%	30-36
Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R	70-90%	20-30%	36-62
Rituximab/Proteasome Inhibitor 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 (10-15%)
Fludarabine	• Hypogammaglobulinemia-> infections, IVIG • Transformation, AML/MDS (15%)
Bendamustine	• Prolonged neutropenia, thrombocytopenia (especially after fludarabine) • AML/MDS (5-8%)
Bortezomib	• Grade 2+3 Peripheral neuropathy (60-70%); High discontinuation (20-60%)

Targeting the Entire WM Clone with Monoclonal Antibodies



Phase II Study of Daratumumab in Relapsed/Refractory WM Patients

Screening

Informed Consent and Registration

Daratumumab
Weekly X 4
Biweekly X 4
Monthly X 12

Progressive Disease or Unacceptable Toxicity

Stop Daratumumab

Event Monitoring

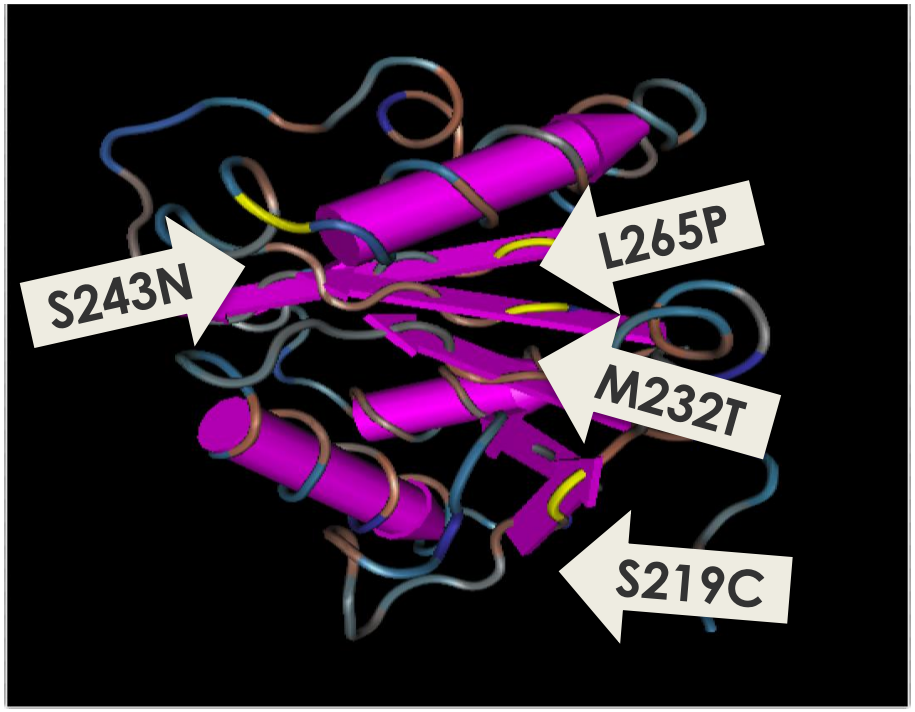
SD or Response Continue

Event Monitoring

DFCI, MSKCC, Stanford

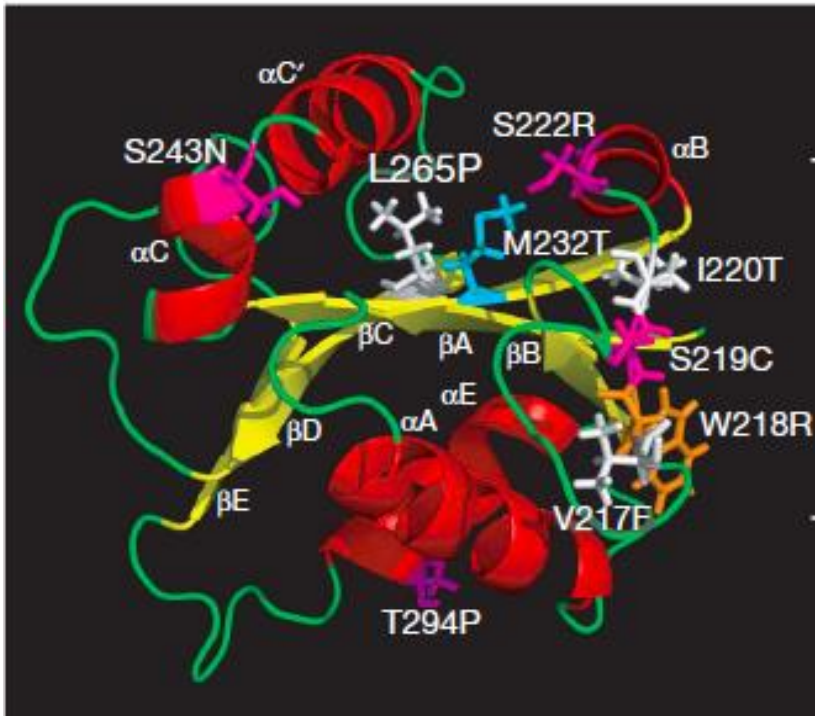
MYD88 Mutations in B-cell LPD

WM



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

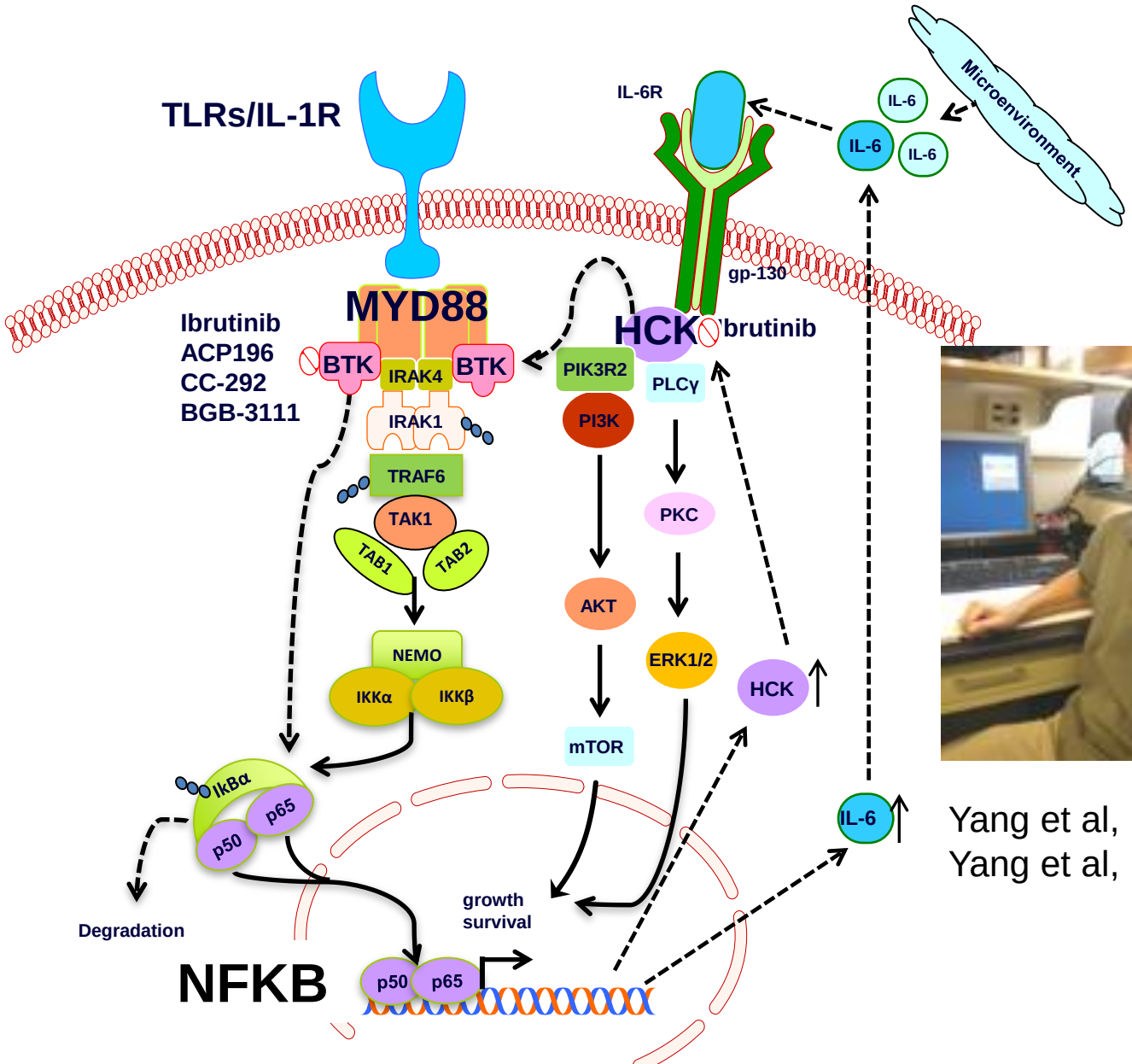
ABC DLBCL

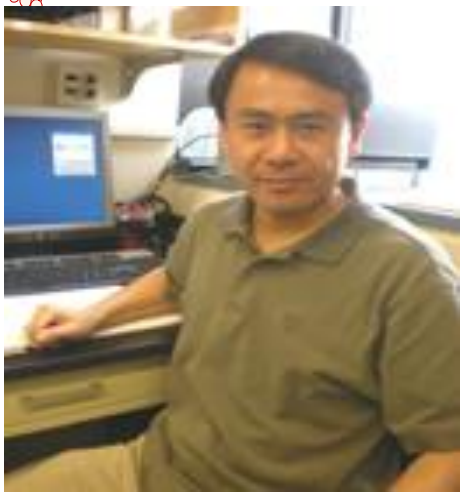


29% MYD88 L265P
10% Non-L265P MYD88

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.

Signaling Pathways Driven by Mutated MYD88 in Waldenström's Macroglobulinemia

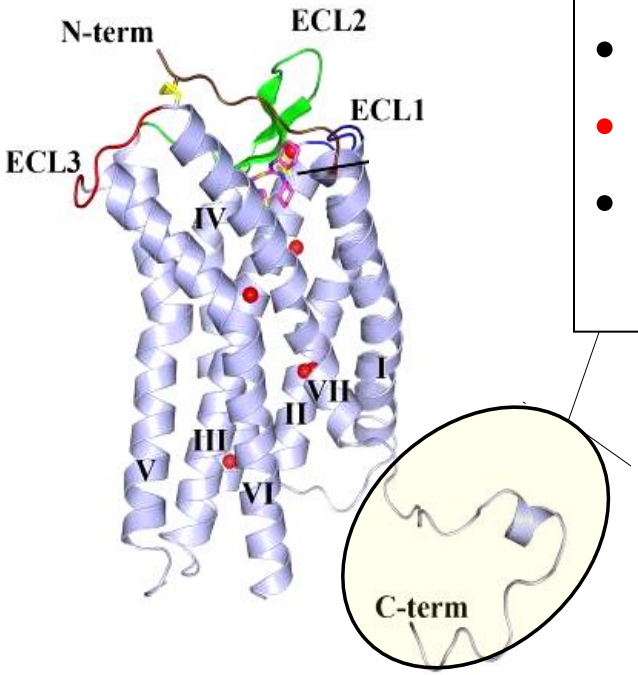




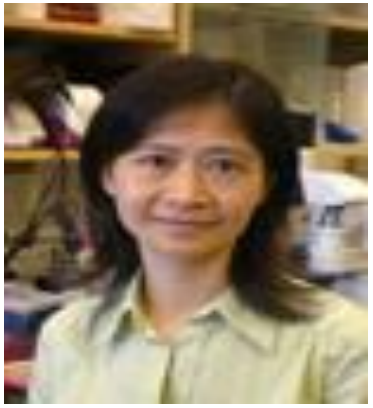
Yang et al, Blood 2013
Yang et al, Blood 2016

CXCR4 C-tail mutations in WM

- 30-40% of WM patients; v. rare in other LPD
- >30 Nonsense, Frameshift Mutations
- Accompany 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



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

www.clinicaltrials.gov
NCT01614821

Median Prior Therapies: 2 (1-9)

✔ **MYD88, CXCR4 Mutation Status**

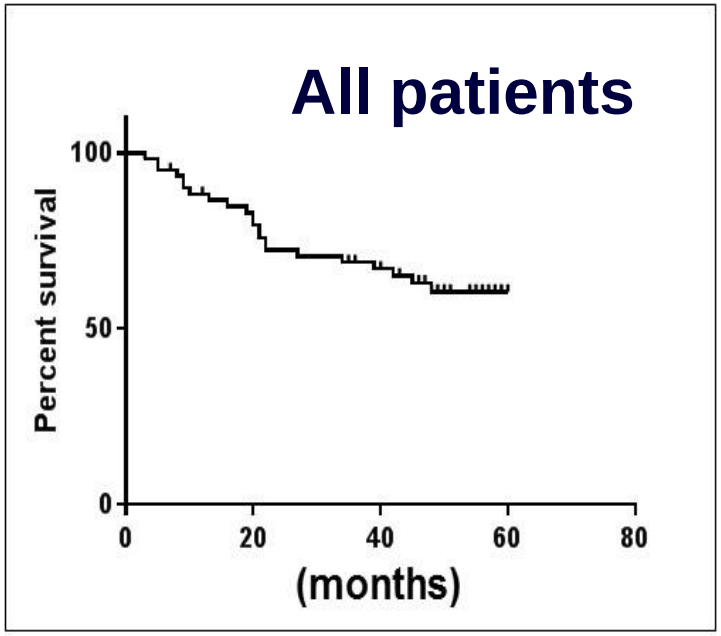
Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations.

	ALL	$MYD88^{Mut}$ $CXCR4^{WT}$	$MYD88^{Mut}$ $CXCR4^{Mut}$	$MYD88^{WT}$ $CXCR4^{WT}$	P-value
N=	**63**	36	21	5	
ORR	**90.4%**	100%	85.7%	60%	0.005
Major (>PR)	**77.7%**	97.2%	66.6%	0%	<0.001
VGPR	**27.0%**	44.4%	9.5%	0%	0.007
Time to Minor Response (mos.)	**1.0**	1.0	1.0	1.0	0.10
Time to Major response (mos.)	**2.0**	2.0	6.0	N/A	0.05

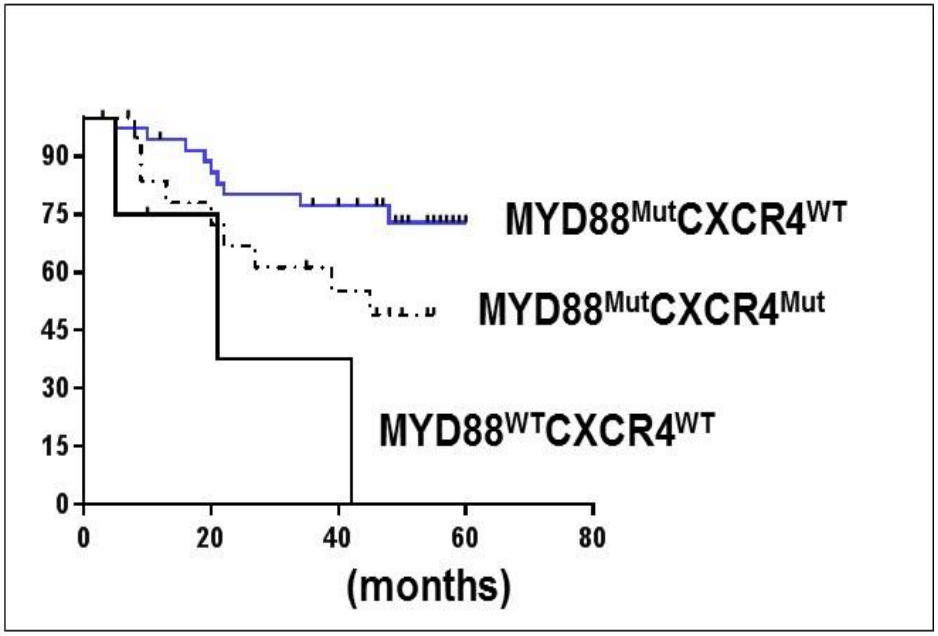
Treon et al, ASH 2017

Ibrutinib in Previously Treated WM: PFS

A.



B.

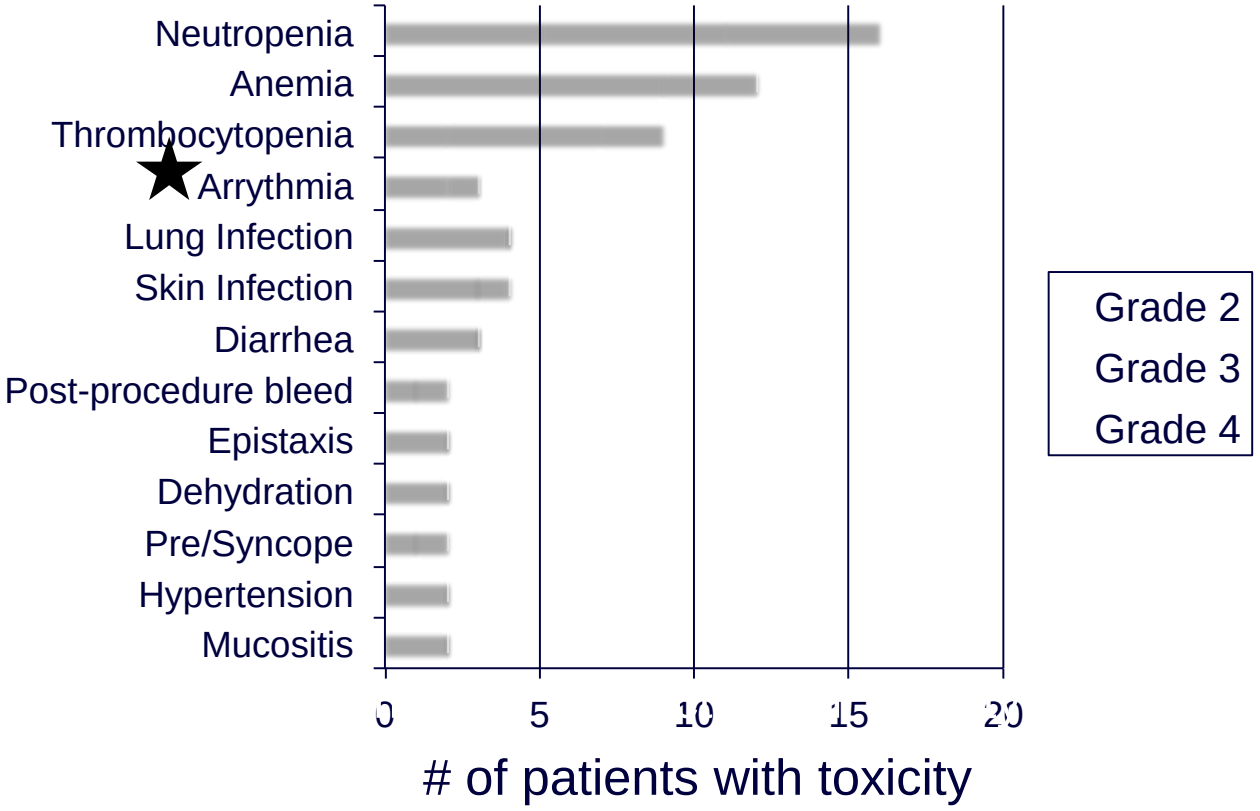


Median PFS > 5 years

Treon et al, ASH 2017

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

FDA expands approved use of Ibrutinib 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

May 22, 2015

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

July 8, 2015

משרד הבריאות
לחיים בריאים יותר

September, 2015

Health Canada Santé Canada

April 5, 2016

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%

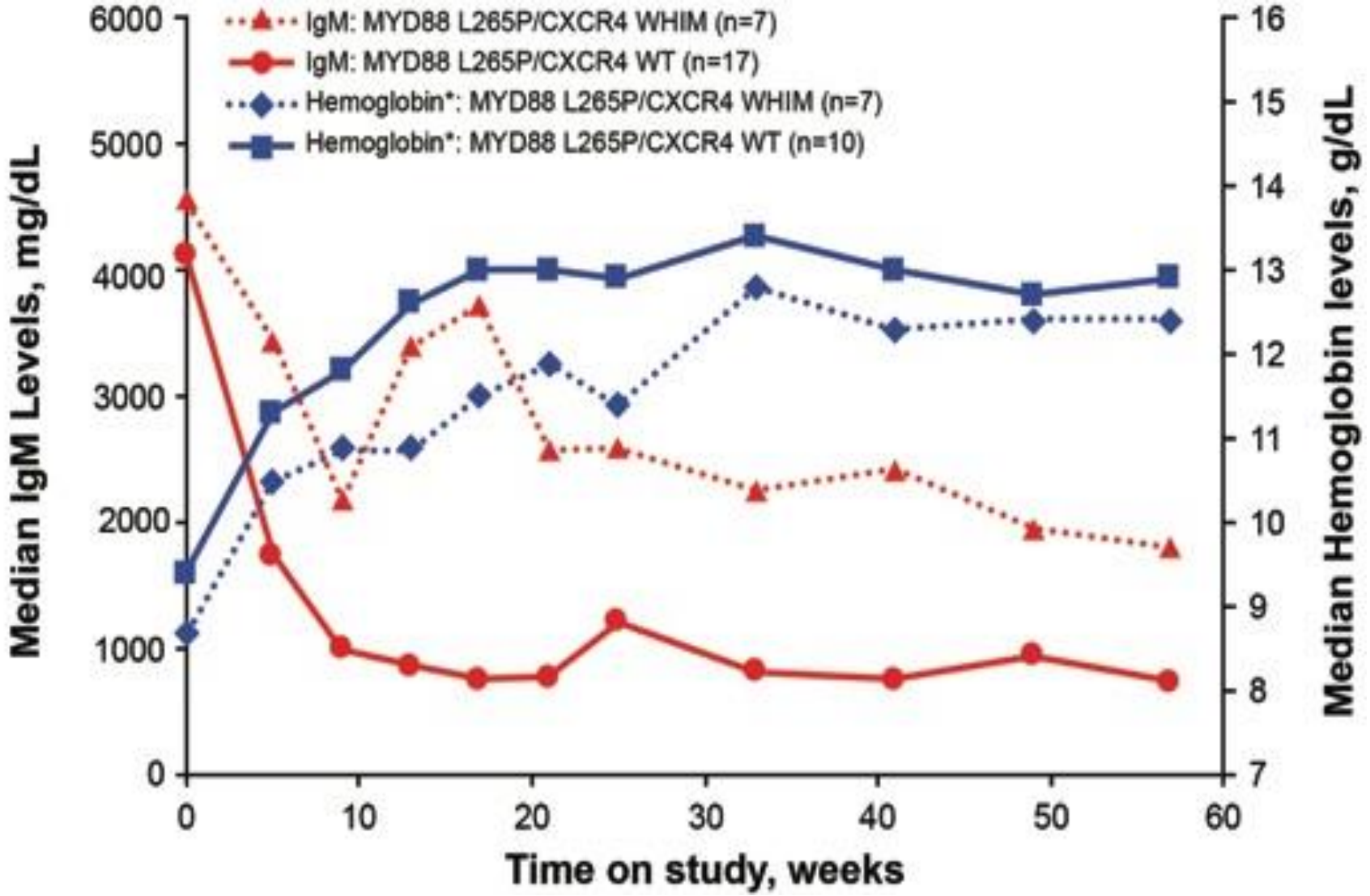
	(N=)	(%)
VGPR	4	13
PR	18	58
MR	6	19

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

Primary Therapy of WM with Ibrutinib Monotherapy Patient Characteristics

Characteristic	Patients (N=30)
Age, years	67 (43-83)
Male sex	23 (77%)
IPSSWM score	
Low	5 (17%)
Intermediate	11 (37%)
High	14 (47%)
Serum IgM level, mg/dl	4369 (844-10,321)
Hemoglobin level, g/dl	10.3 (7.5-14.5)
Serum β2-microglobulin, mg/l	3.8 (2.0-7.6)
Adenopathy ≥1.5 cm	10 (30%)
Splenomegaly ≥15 cm	5 (17%)
Bone marrow involvement, %	65 (5-95)
MYD88 mutation	30 (100%)
CXCR4 mutation	14 (47%)

Primary Therapy of WM with Ibrutinib Monotherapy Responses

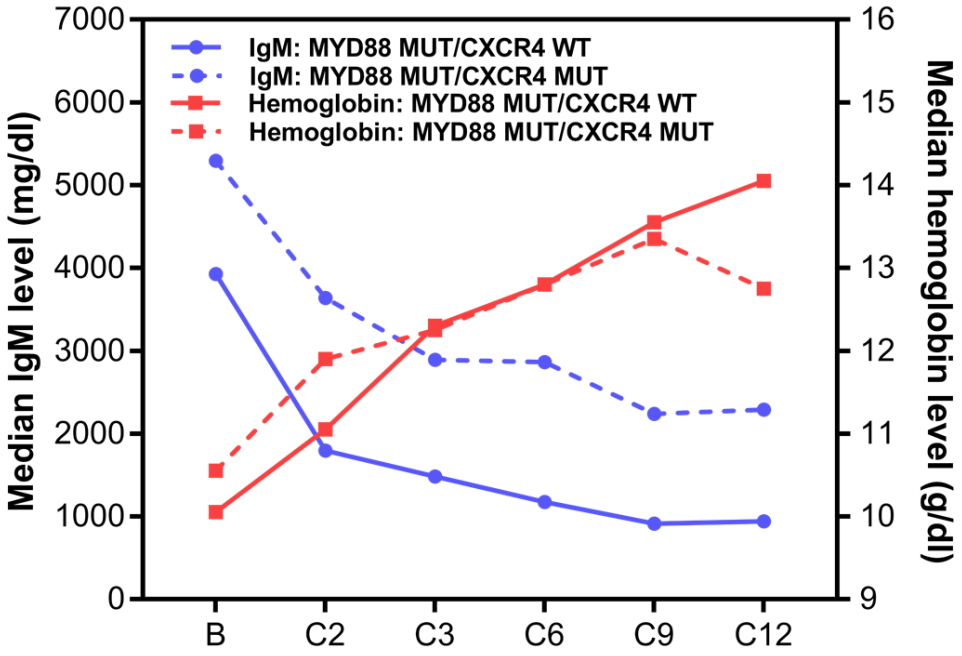
	All Patients (n=30)	*MYD88*^{MUT} *CXCR4*^{WT} (n=16)	*MYD88*^{MUT} *CXCR4*^{MUT} (n=14)	P-value
Overall responses (%)	97	100	93	0.47
Major responses (%)	80	88	71	0.38
Very good partial responses (%)	17	25	7	0.34
Median time to response (months)				
Minor response (≥MR)	1.0	1.0	2.0	0.10
Major response (≥PR)	2.0	2.0	8.0	0.05

Median time on ibrutinib: 8.1 (range 2.0-16.4 months)
Data cutoff: July 15, 2017

Treon et al, ASH 2017

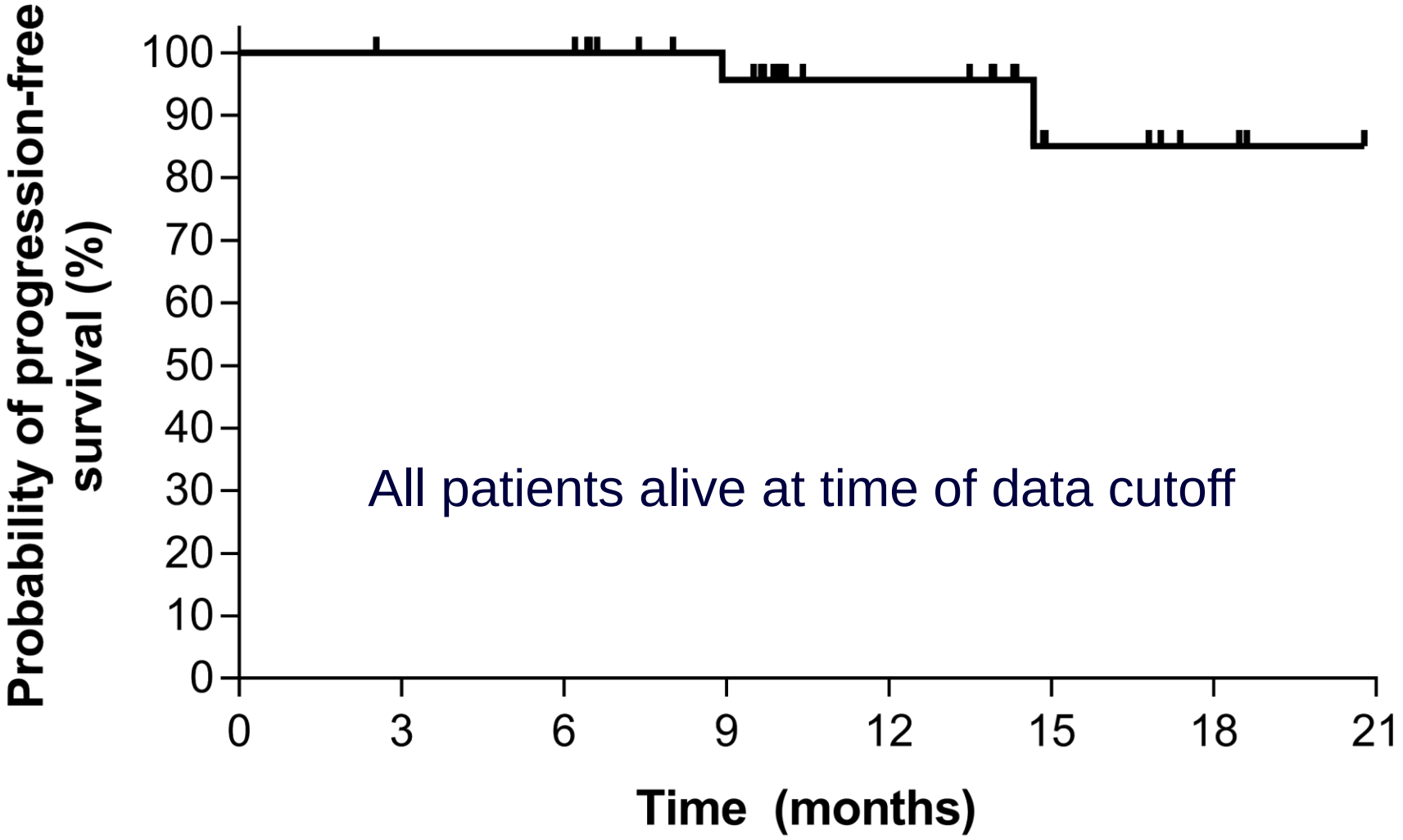
Primary Therapy of WM with Ibrutinib Monotherapy Responses

Best Overall Responses (All patients)
sIGM: 4,369 → 1,780 mg/dL
Hb: 10.3 → 13.6 g/dL
BM: 65% → 20%



Treon et al, ASH 2017

Primary Therapy of WM with Ibrutinib Monotherapy Responses



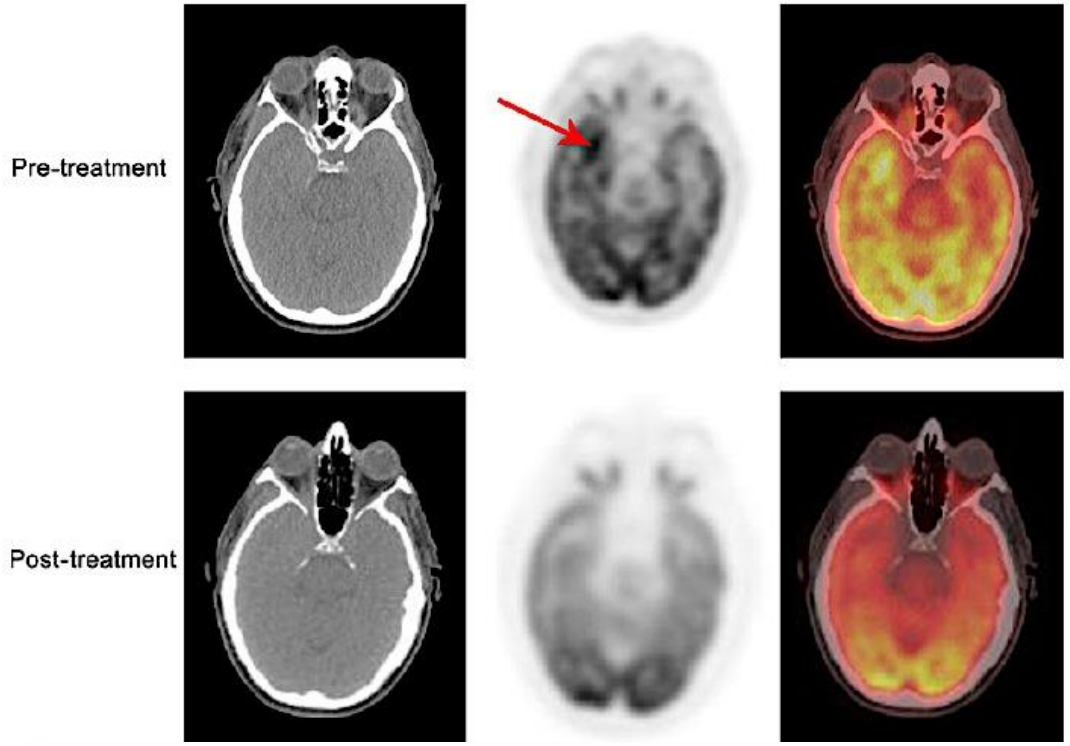
Treon et al, ASH 2017

Primary Therapy of WM with Ibrutinib Monotherapy Adverse Events

Event or Abnormality, N (%)	Grade 2	Grade 3	Total Grades 2-4
Alanine transaminase elevation	0	1 (3)	1 (3)
Arthralgias	1 (3)	0	1 (3)
Asparate transaminase elevation	0	1 (3)	1 (3)
Atrial fibrillation	2 (6)	0	2 (6)
Bruising	1 (3)	0	1 (3)
Drug-induced hepatitis	0	1 (3)	1 (3)
Foot pain	0	1 (3)	1 (3)
Hypertension	2 (6)	1 (3)	3 (10)
Muscle cramps	1 (3)	0	1 (3)
Neutropenia	3 (10)	0	3 (10)
Procedural hemorrhage	1 (3)	0	1 (3)
Thrombocytopenia	0	1 (3)	1 (3)
Upper respiratory infection	1 (3)	0	1 (3)
Urinary tract infection	2 (6)	0	2 (6)
Vasculitic rash	1 (3)	0	1 (3)

*Listed are adverse events that were deemed by the investigators to be possibly, probably, or definitely associated with the study drug; no related grade 4 toxicities were observed.

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

Other BTK Inhibitors

- **Acalabrutinib** (Phase II Study Completed, Awaiting Results)
- **BGB-3111** (Phase II Study Completed, Phase III randomized study for newly diagnosed and previously treated patients is ongoing)
- **SNS-062** (Non-covalent inhibitor that binds to a different site from other BTK inhibitors; use in resistant disease due to BTK mutations)

Strategies to Enhance BTK Inhibitors in WM

iNNOVATE Study in WM

Treatment Naïve + Previously Treated

45 centers in 9 countries

1:1 Randomization N = 150

ARM A: ibrutinib 420mg
+ Rituximab 375mg/m² x 8 infusions
(weeks 1,2,3,4,17,18,19, and 20)

ARM B: Placebo
+ Rituximab 375mg/m² x 8 infusions
(weeks 1,2,3,4,17,18,19, and 20)

N=31

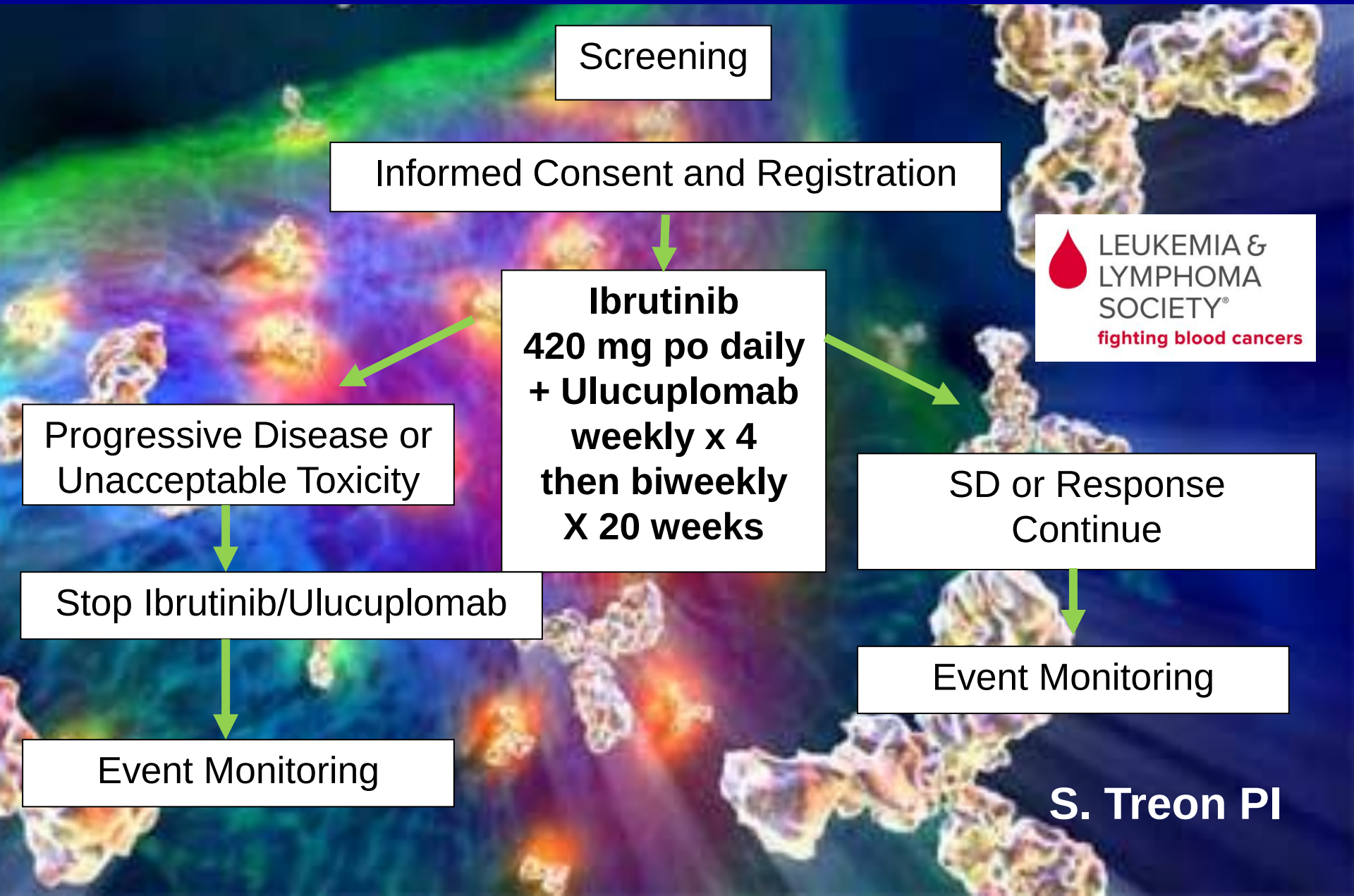
ARM C: ibrutinib 420mg
Subjects considered
refractory to prior rituximab

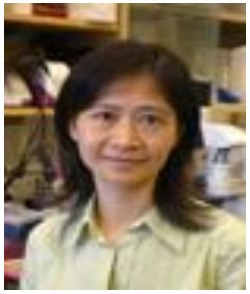
ABC patients genotyped for MYD88 and CXCR4

What is still unknown after iNNOVATE?

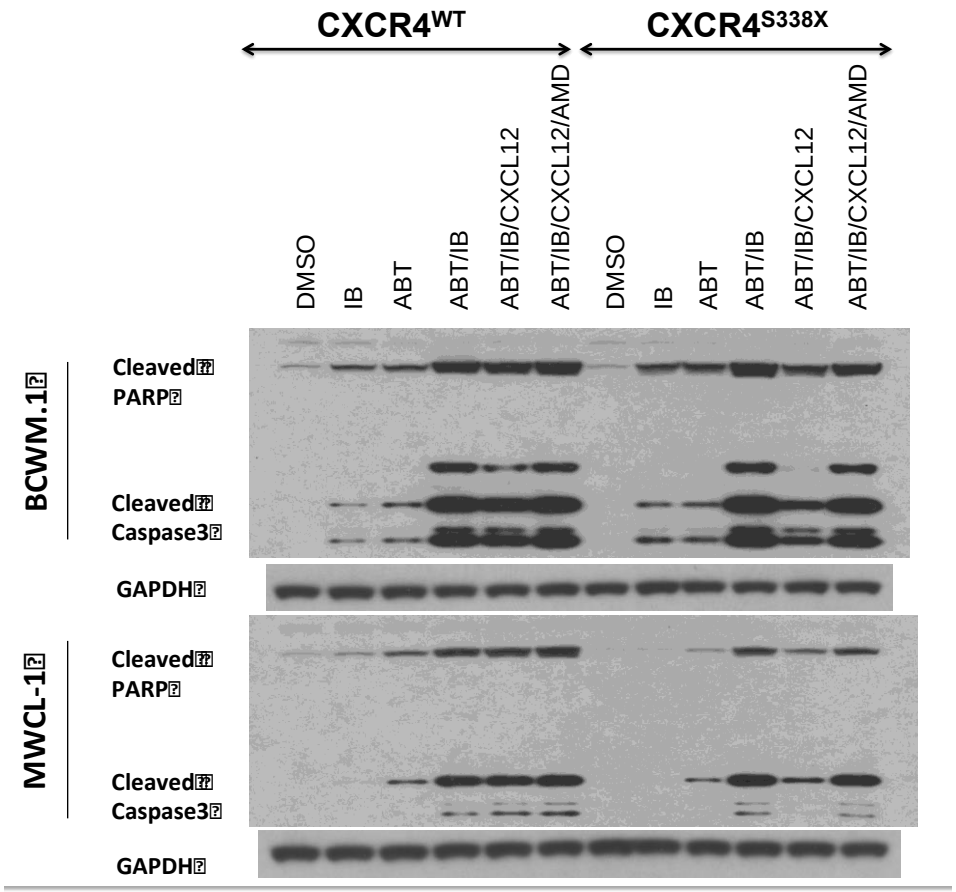
I think we all agree…we need another study

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



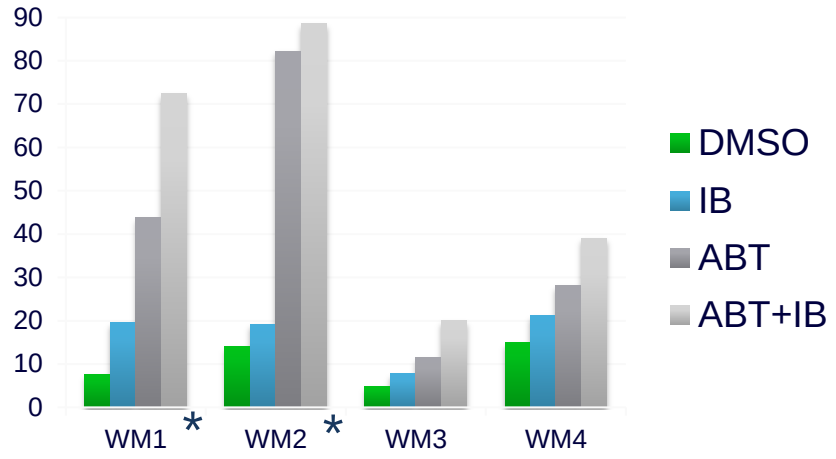


Venetoclax (ABT-199) enhances Ibrutinib killing in MYD88 mutated WM Cells.

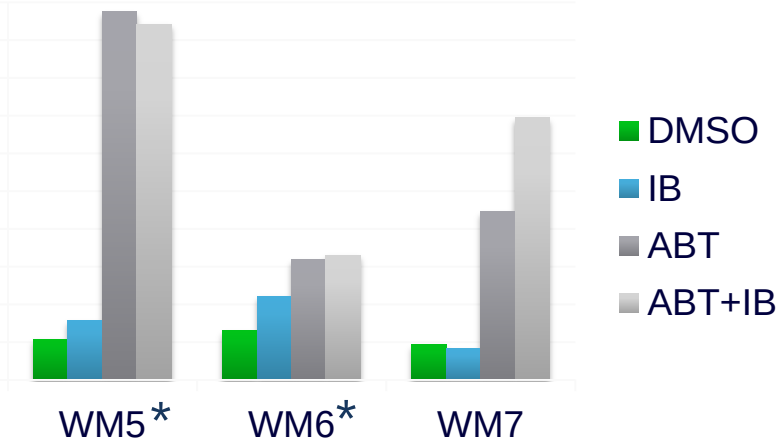


Cao et al, BJH 2015

Untreated

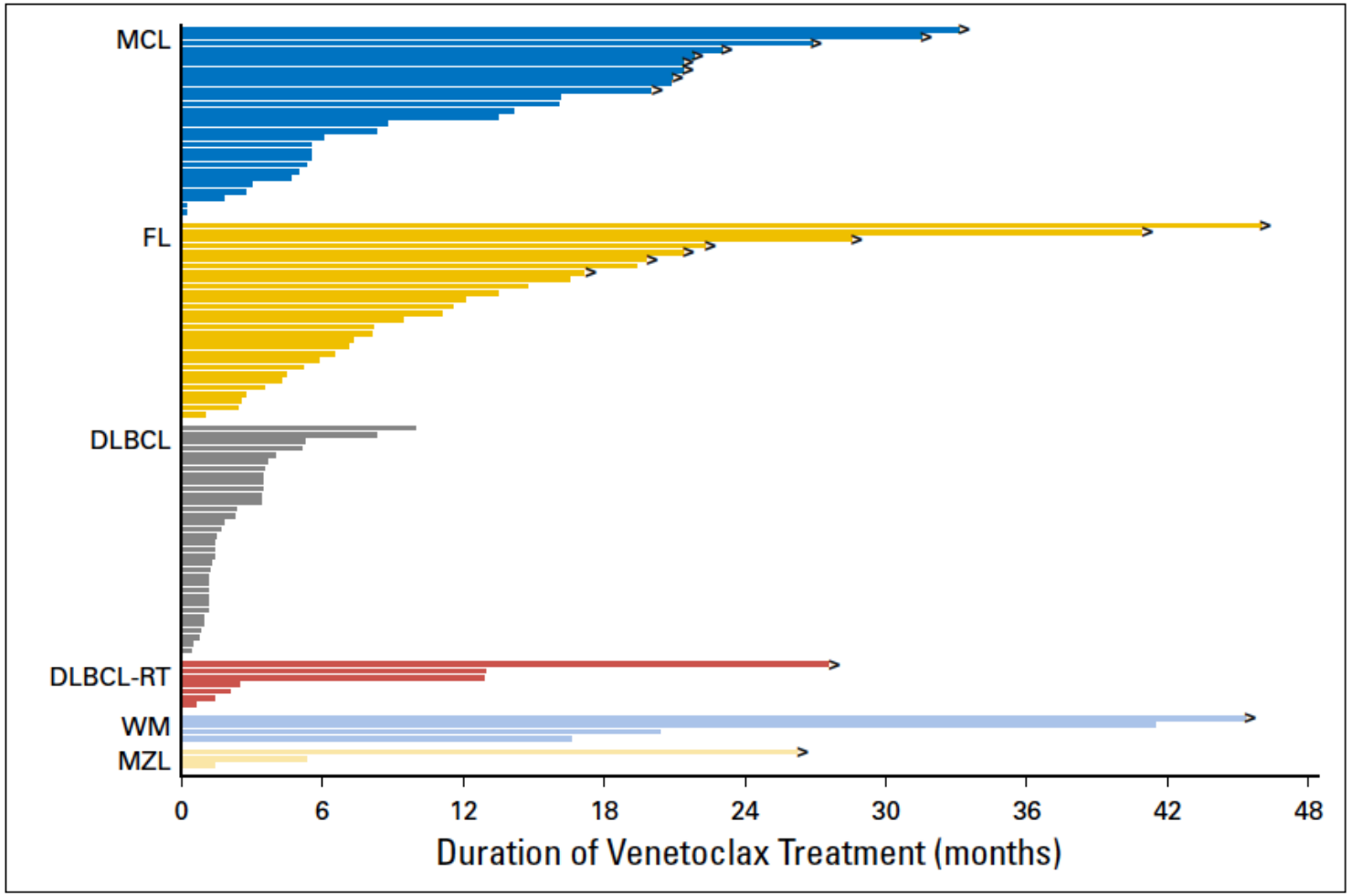


Ibrutinib >6 mo.



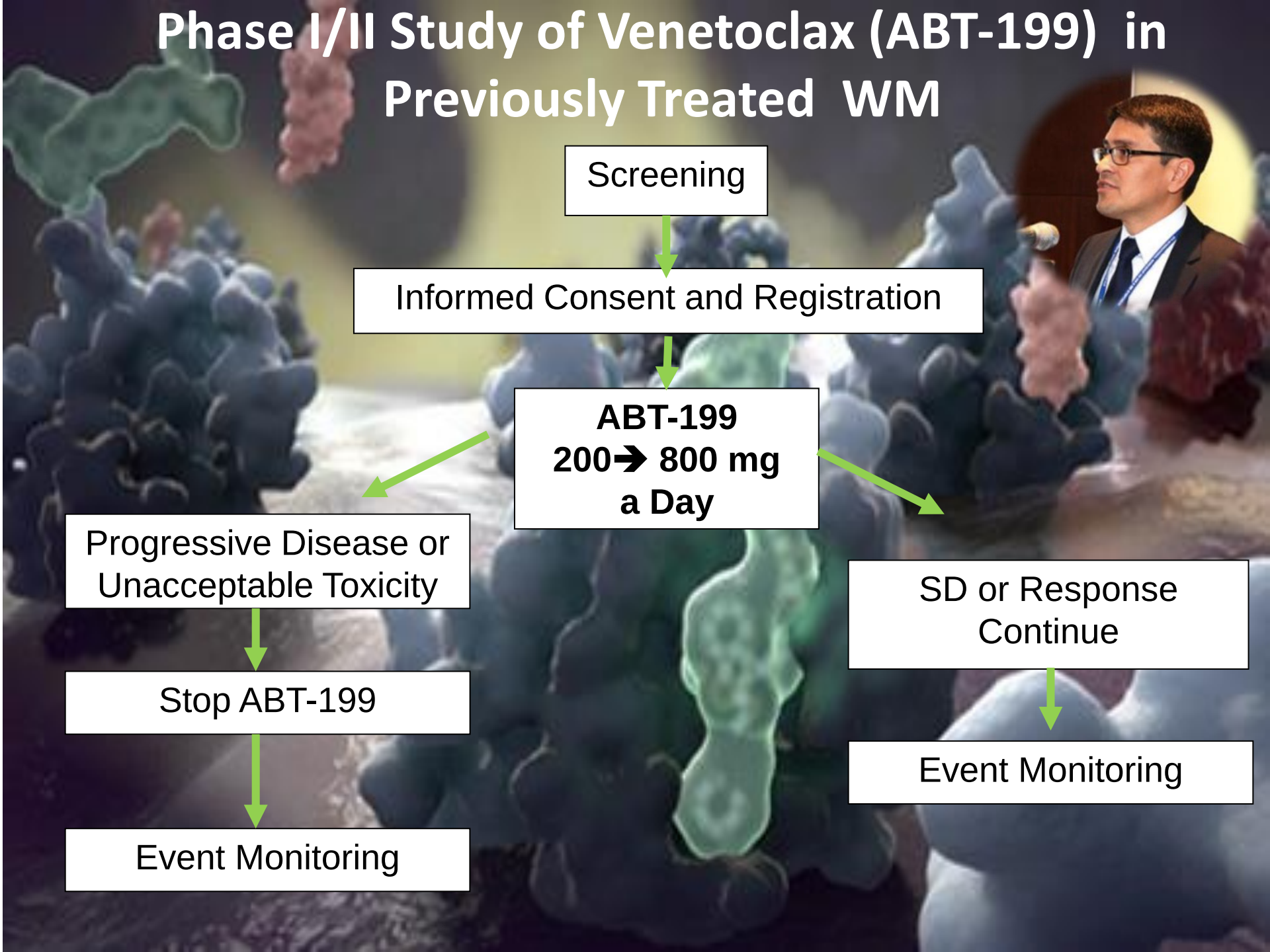
*CXCRWHIM

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



Davids et al, JCO 2017

Phase I/II Study of Venetoclax (ABT-199) in Previously Treated 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

Hunter et al, JCO 2017

- **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**

Hunter et al, JCO 2017

Bing Center for WM

Acknowledgements

Peter S. Bing M.D.
Edward and Linda Nelson
Bailey Family
Tannenhauser Family
Kerry Robertson Family
Aburdene Family
Coyote Fund
Orzag Family
Bliss Family
Bauman Family
Bonnie Andersen
D'Amato Family
Cole Family