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Frontline treatment options in Waldenström Macroglobulinemia

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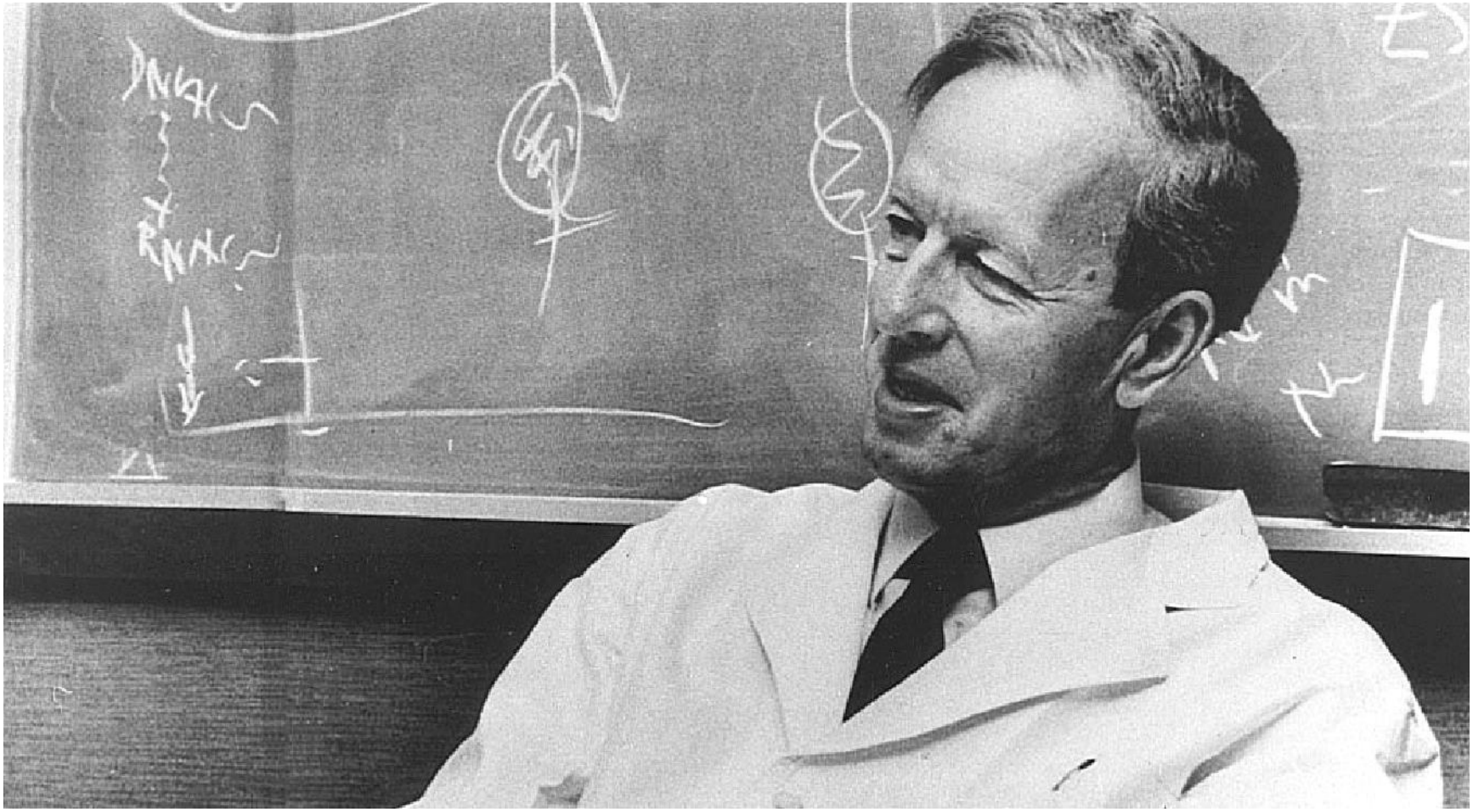
Disclosures

Consulting

- Otsuka Pharmaceuticals
- Biogen IDEC
- Alexion Pharmaceuticals

Research Funding

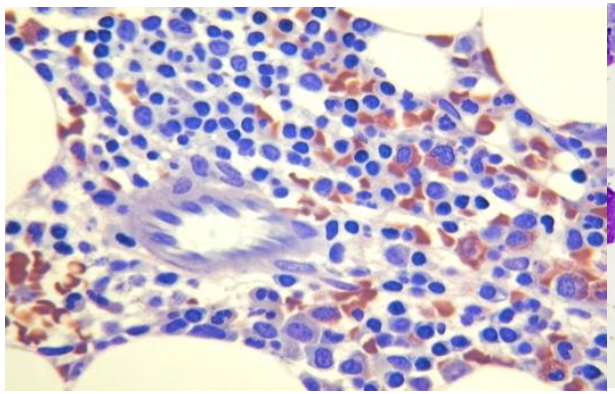
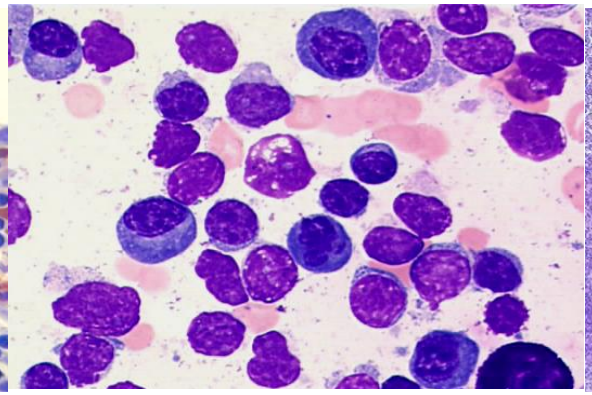
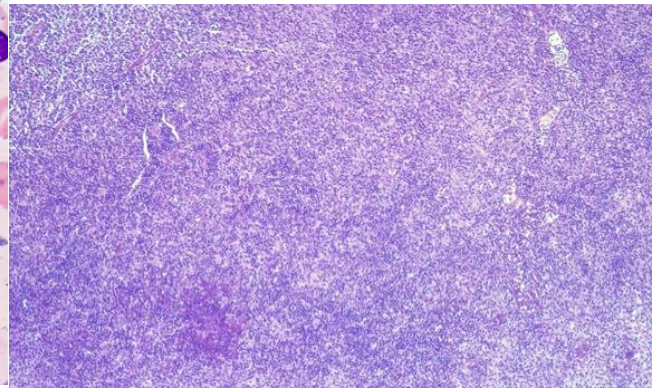
- Millennium Pharmaceuticals
- Gilead Sciences
- Pharmacyclics Inc.
- Abbvie Inc.



Waldenström's Macroglobulinemia – first described by Jan Gosta Waldenström in 1944.

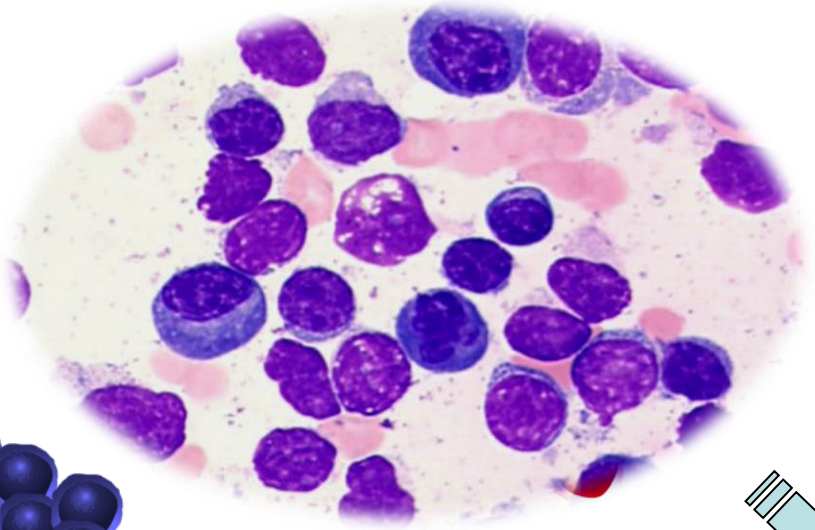
Lymphoplasmacytic Lymphoma

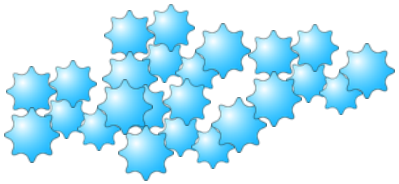
- Cellular Morphology: lymphocytes, lymphoplasmacytic cells, plasma cells
- BM Pattern: interstitial with diffuse or nodular infiltrates with excess mast cells associated with lymphoid aggregates.
- LN/SP: diffuse pattern

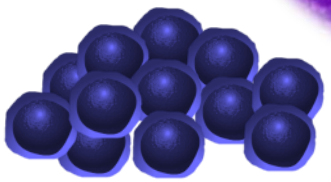
Manifestations of WM Disease

↓HCT, ↓PLT, ↓WBC





Hyperviscosity Syndrome: Nosebleeds, headache, Impaired vision
>4.0 CP



Adenopathy, splenomegaly
≤20% (at Dx)

Hepcidin
↓Fe Anemia

IgM Neuropathy (22%)
Cryoglobulinemia (10%)
Cold Agglutinemia (5%)

Treon, Hematol Oncol 2013

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 lymphadenopathy or hepatosplenomegaly
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloidosis.

Kyle, Semin Oncol 2003
Anderson, JNCCN 2016.

Rituximab

Characteristics

- Anti-CD20 monoclonal antibody
- CD20 is expressed in all B-cells, normal and malignant
- Activates the immune system to kill cancer cells
- Accumulates in the body

Treon et al (2001)

- N=30, retrospective study
- 1-11 infusions; single agent
- IgM went from 2400 to 1500 mg/dl
- Bone marrow involvement went from 60% to 15%
- 60% response rate

Treon J Immunother 2001

Rituximab

Dimopoulos et al (2002)

- N=17; prospective
- 4 weekly doses; repeat at 3 months
- 40% response rate
- Time to response was 3 months
- Time to progression was 16 months

Dimopoulos Clin Lymphoma 2002

Treon et al (2005)

- N=29; prospective
- 4 weekly doses; repeat at 3 months
- 65% response rate
- Time to best response was 17 months

Treon Ann Oncol 2005

Rituximab

Adverse events

- Infusions reactions
- Increased risk of infections
- Low blood counts
- Hepatitis B reactivation

Disadvantages

- Delayed responses
- IgM flare
  - 40% of patients
  - Avoid Rituximab until IgM in "safe range"
- Rituximab Intolerance
  - 7% of patients
  - Consider Ofatumumab

Treon Ann Oncol 2004
Castillo Br J Haematol 2016

Cyclophosphamide-Based Therapy

Greek experience

- N=72; untreated
- Cyclophosphamide/Dexamethasone/Rituximab
- ORR 83%
- CR 7%
- Median PFS 3 years

Dimopoulos J Clin Oncol 2007
Kastritis Blood 2015

A German study

- N=64; untreated
- R-CHOP (n=34) vs. CHOP (n=30)
- Response: R-CHOP 94%; CHOP 67%
- Time to failure: R-CHOP 63 months; CHOP 22 months

Buske Leukemia 2009

Cyclophosphamide-Based Therapy

Disadvantages

- Hair loss
- Low blood counts
- Nausea and vomiting
- Increased risk of infections
- Secondary leukemia ~1%

Proteasome inhibitor-based therapy

Mechanism of action

- Targets the proteasome, among others
- Proteasome is the garbage disposal of the malignant cell
- "Trash" accumulates in the cell and forces it to die

Chen et al (2007)

- N=27
- Bortezomib: IV twice weekly
- ORR: 70%
- CR: 0%
- Nodal response lagging
- Time to response: 2 cycles

Chen J Clin Oncol 2007

Proteasome inhibitor-based therapy

Treon et al (2009)

- BDR; N=25
- Bortezomib: IV twice weekly
- ORR 96%
- CR 12%
- Time to progression: 66 months

Treon, JCO 2009
Treon, ASH 2015

Dimopoulos (2015)

- N=59
- Bortezomib: IV weekly
- First cycle without rituximab
- ORR: 85%
- CR: 3%
- Progression-free survival 42 months

Dimopoulos, Blood 2013

Disadvantages

- Peripheral neuropathy
  - Less when given weekly or SC instead of IV
- Low platelet counts
- Steroids
- Zoster prophylaxis
  - Acyclovir or valacyclovir

Proteasome inhibitor-based therapy

Carfilzomib

- CARD; N=31
- Intravenous twice weekly
- ORR 87%
- CR 3%
- Less neuropathy (<5%)
- Responses less durable in patients with lymphadenopathy

Disadvantages

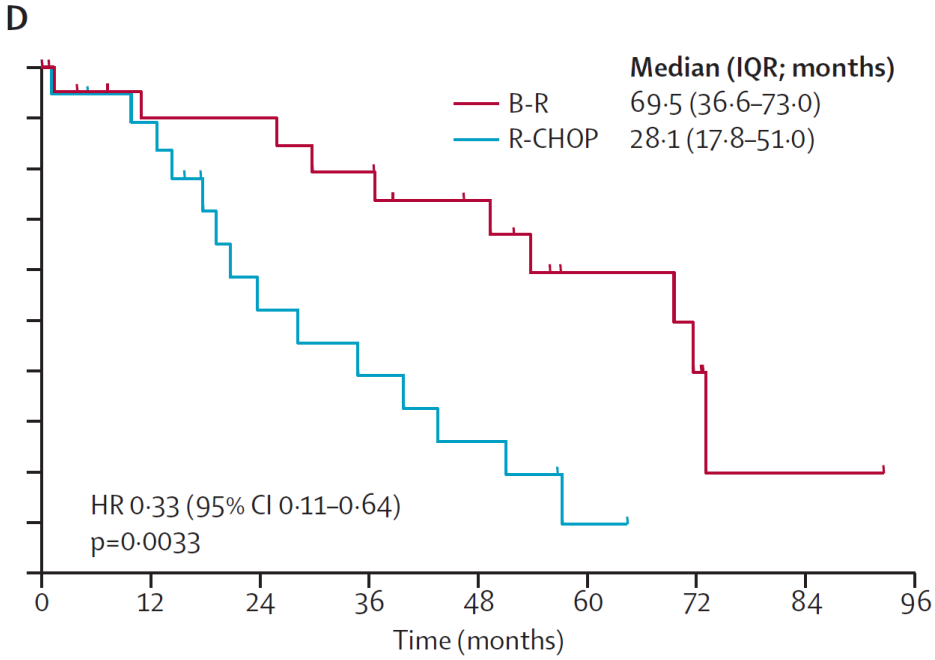
- Increases glucose and cholesterol
- Hypogammaglobulinemia
- Heart problems: HTN, CAD
- Steroids
- Zoster prophylaxis

Treon, Blood 2014

Bendamustine and rituximab

Another German study

- Bendamustine-R (N=22) vs. CHOP-R (N=19)
- Good option for patients with lympadenopathy or enlarged liver/spleen
- ORR 80%
- Progression-free survival 69 months



Rummel, Lancet 2013

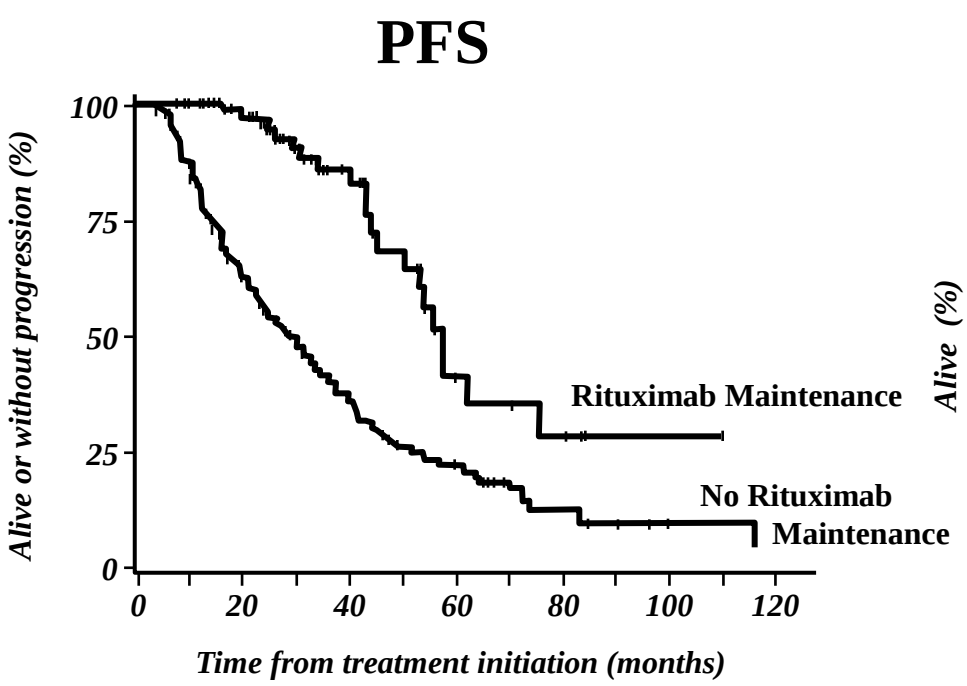
Disadvantages

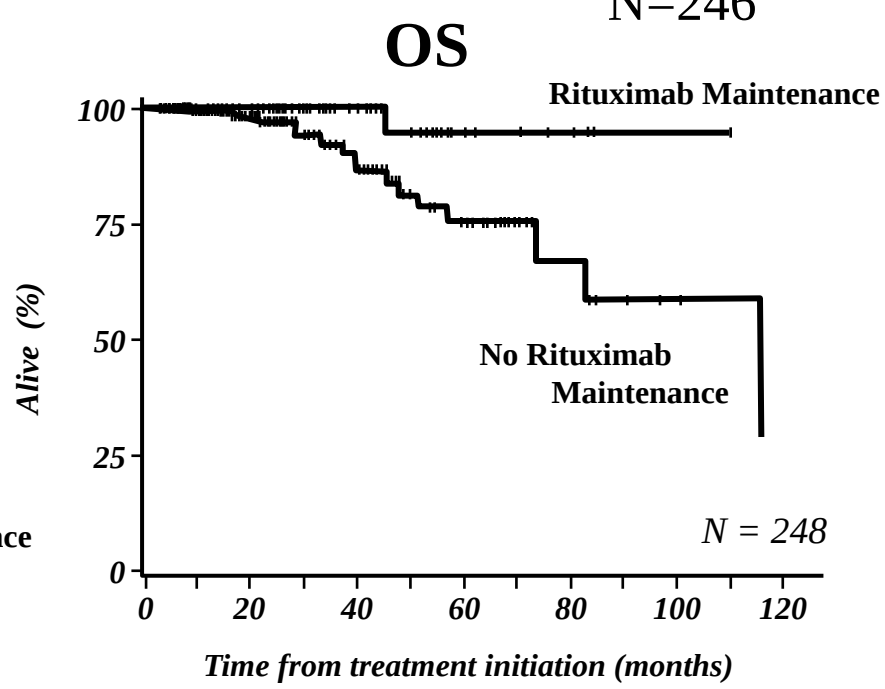
- Potential stem cell toxicity
- Low blood counts
- Infusion reactions
- 1/200 chances of secondary leukemia

To Maintain or Not to Maintain?

Observation vs. maintenance rituximab therapy in rituximab-naïve patients treated with rituximab regimen.

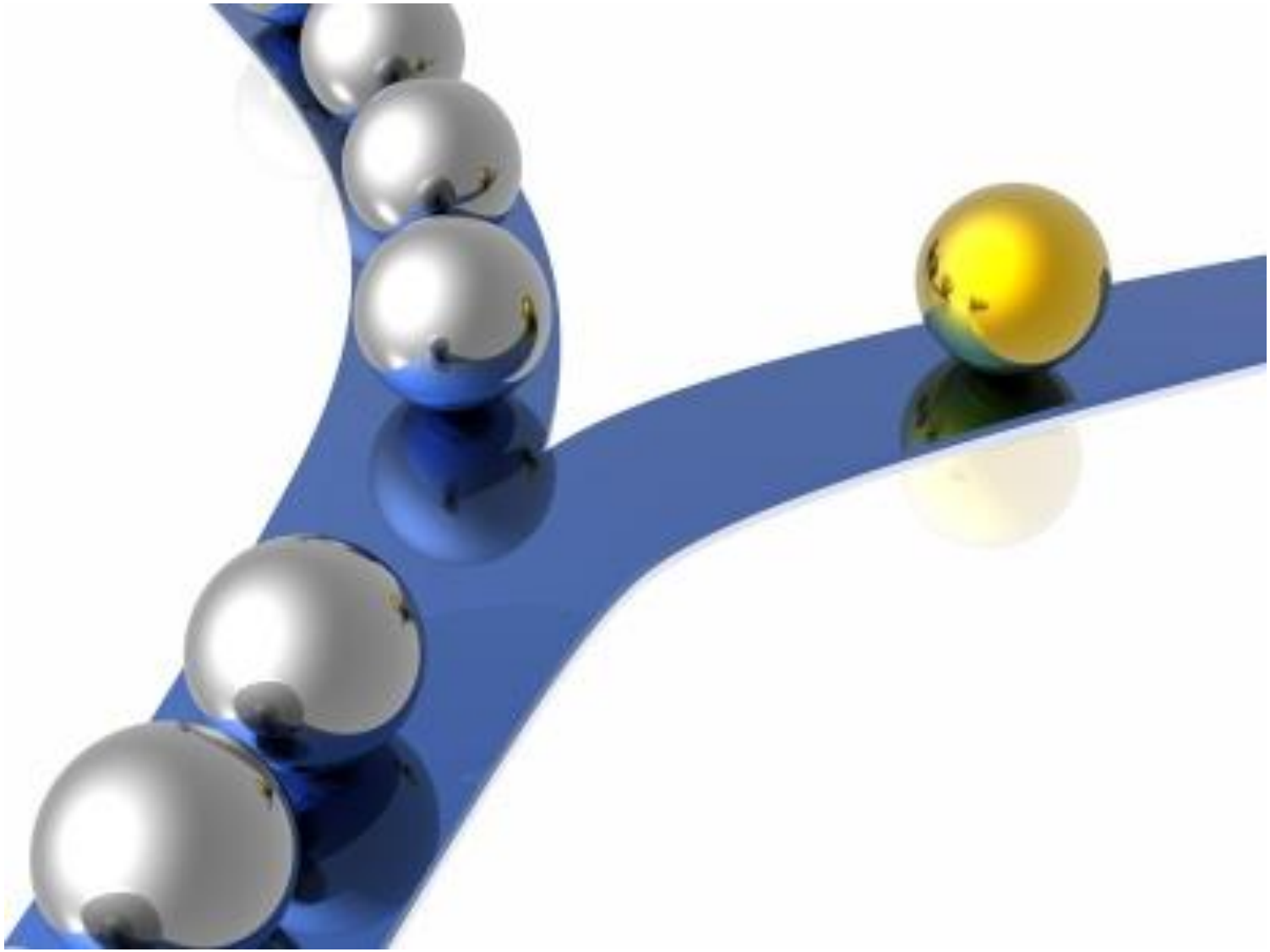
N=246





Problems:
Infusion reactions, increased risk of infections, hypogammaglobulinemia.

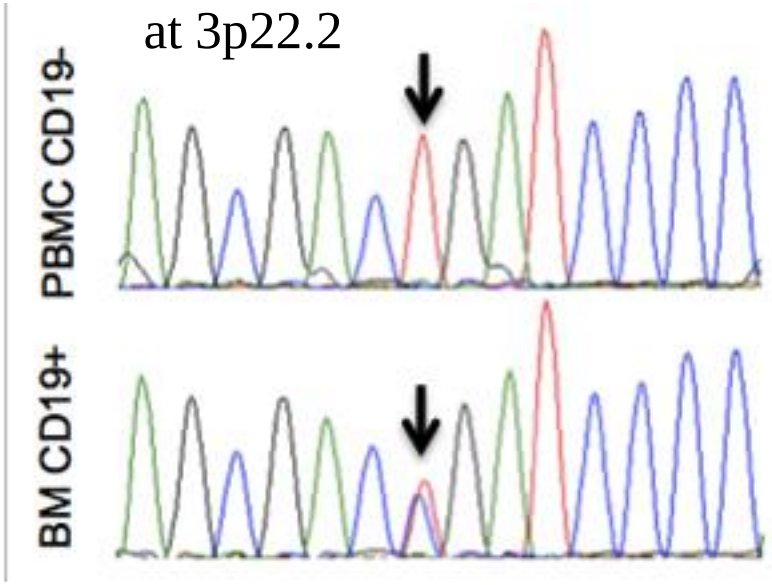
Treon Br J Haematol 2011

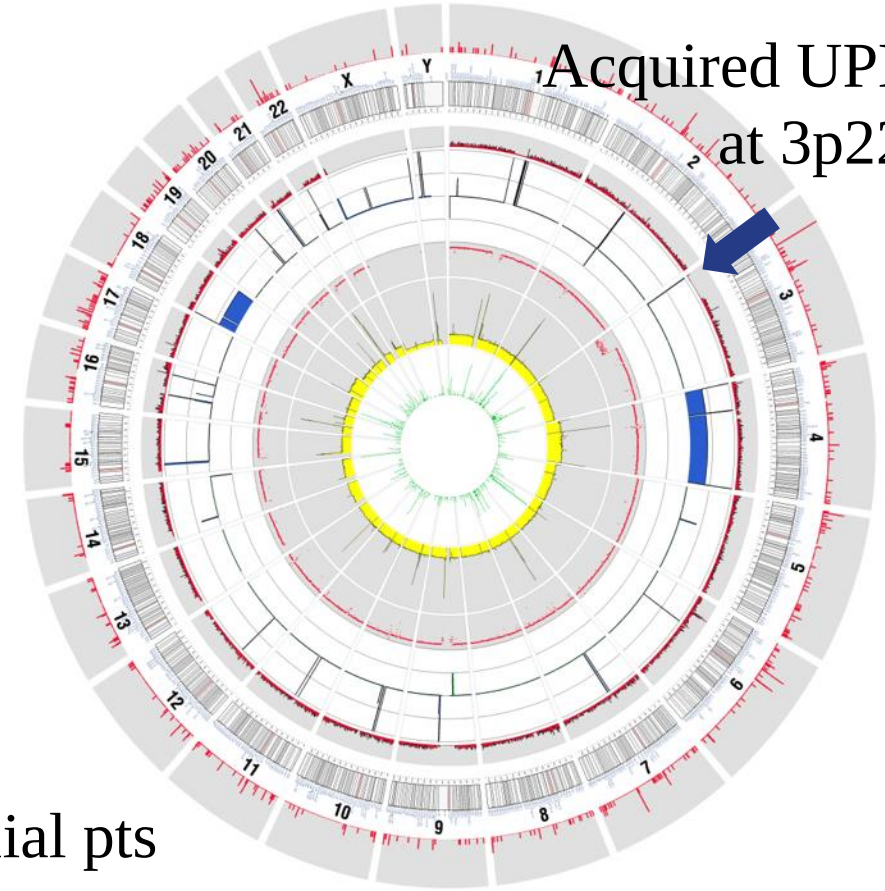


New Directions in WM

MYD88 L265P Somatic Mutation

C to G at position 38186241
at 3p22.2



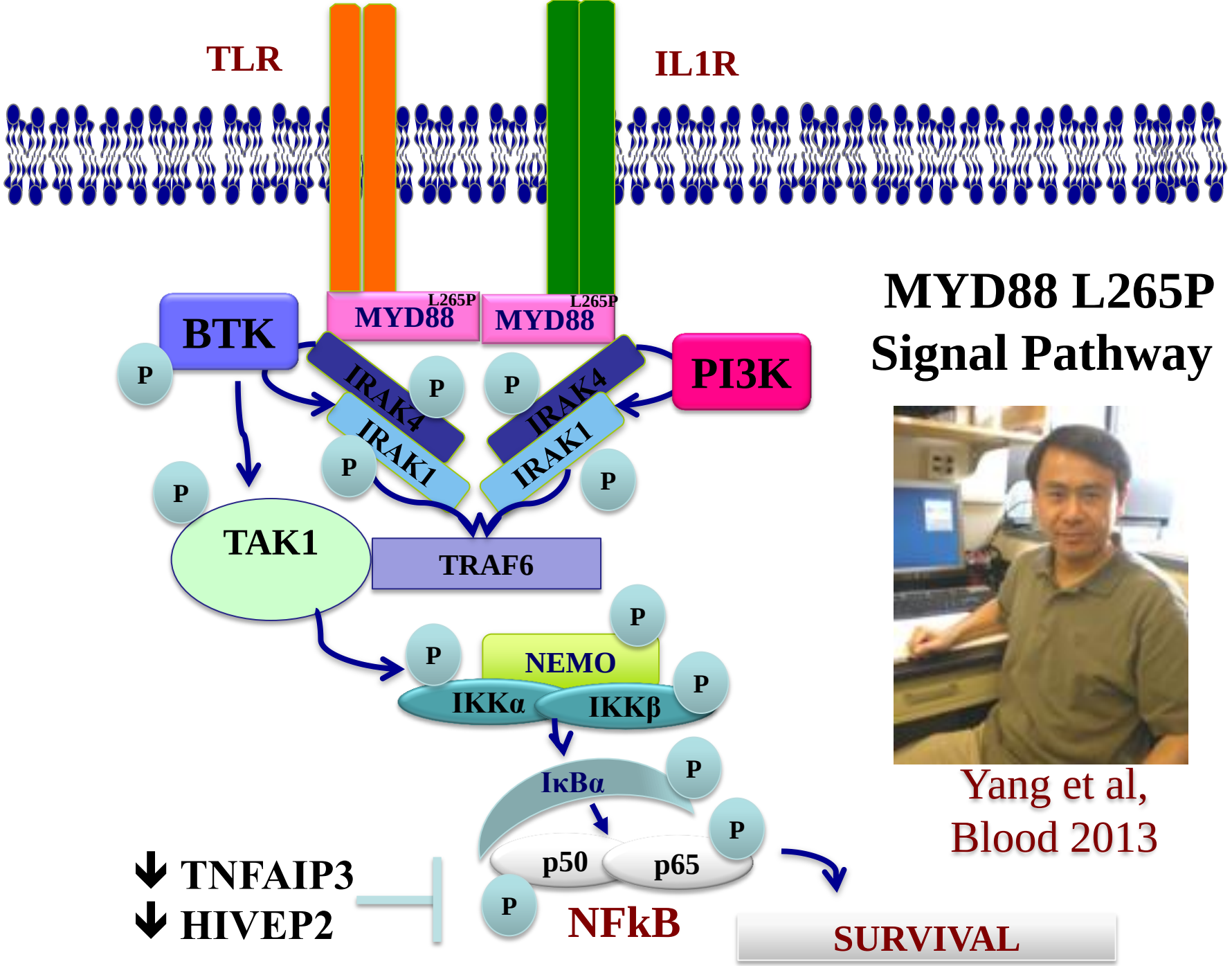


- 91% of WM pts
- 10% IGM MGUS
- No difference sporadic vs. familial pts

Treon, NEJM 2012

MYD88 L265P in WM/IGM MGUS

	METHOD	TISSUE	WM	IGM MGUS
Treon	WGS/Sanger	BM $CD19^+$	91%	10%
Xu	AS-PCR	BM $CD19^+$	93%	54%
Gachard	PCR	BM	70%	
Varettoni	AS-PCR	BM	100%	47%
Landgren	Sanger	BM		54%
Jiminez	AS-PCR	BM	86%	87%
Poulain	PCR	BM $CD19^+$	80%	
Argentou	PCR-RFLP	BM	92%	1/1 MGUS
Willenbacher	Sanger	BM	86%	
Mori	AS-PCR/BSiE1	BM	80%	
Ondrejka	AS-PCR	BM	100%	
Ansell	WES/AS-PCR	BM	97%	
Patkar	AS-PCR	BM	85%	



MYD88 L265P Signal Pathway

Yang et al, Blood 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

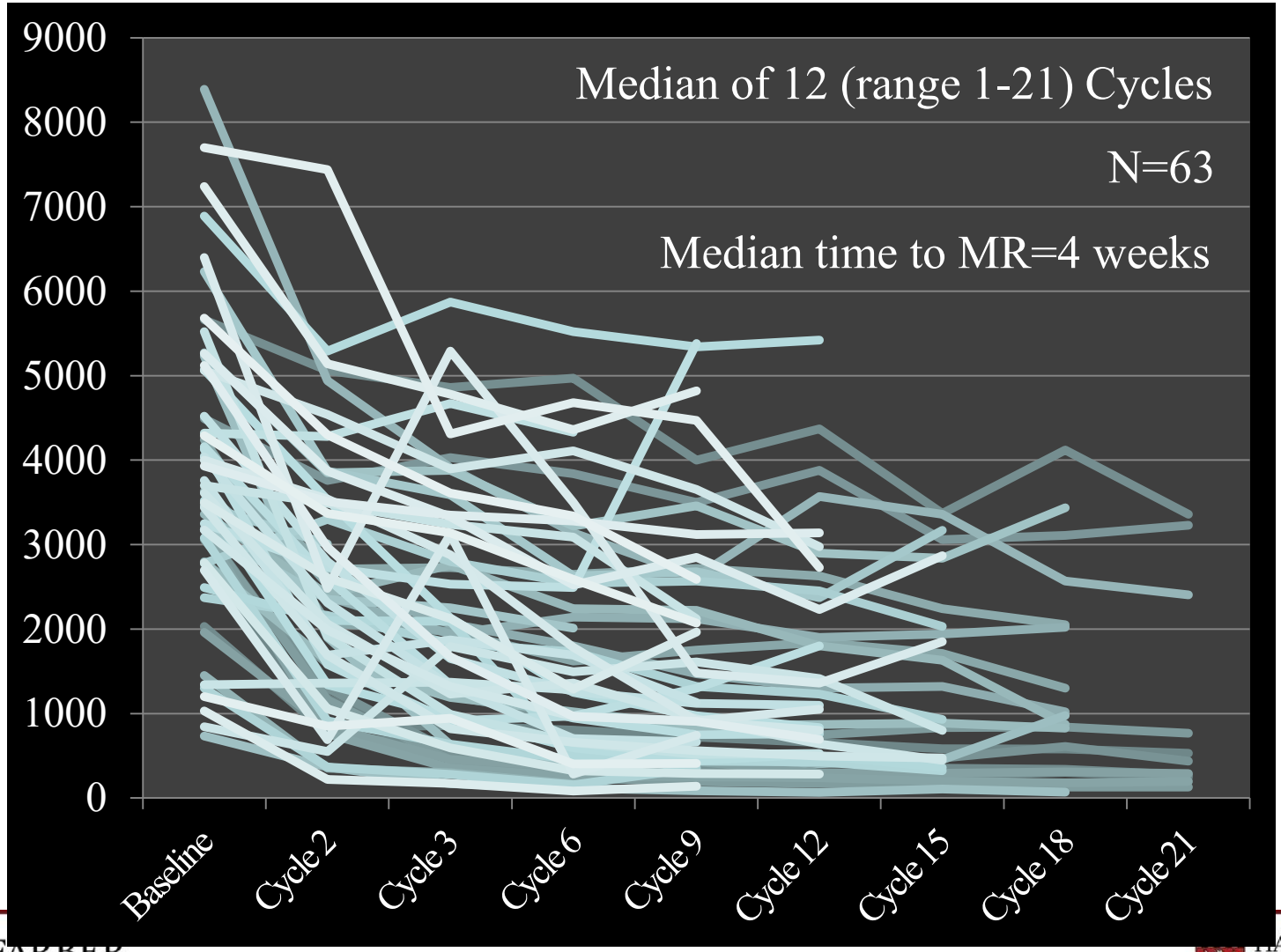
Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D, Christina K. Tripsas, M.A., Kirsten Meid, M.P.H., Diane Warren, B.S., Gaurav Varma, M.S.P.H., Rebecca Green, B.S., Kimon V. Argyropoulos, M.D., Guang Yang, Ph.D., Yang Cao, M.D., Lian Xu, M.S., Christopher J. Patterson, M.S., Scott Rodig, M.D., Ph.D., James L. Zehnder, M.D., Jon C. Aster, M.D., Ph.D., Nancy Lee Harris, M.D., Sandra Kanan, M.S., Irene Ghobrial, M.D., Jorge J. Castillo, M.D., Jacob P. Laubach, M.D., Zachary R. Hunter, Ph.D., Zeena Salman, B.A., Jianling Li, M.S., Mei Cheng, Ph.D., Fong Clow, Sc.D., Thorsten Graef, M.D., M. Lia Palomba, M.D., and Ranjana H. Advani, M.D.

Treon NEJM 2015

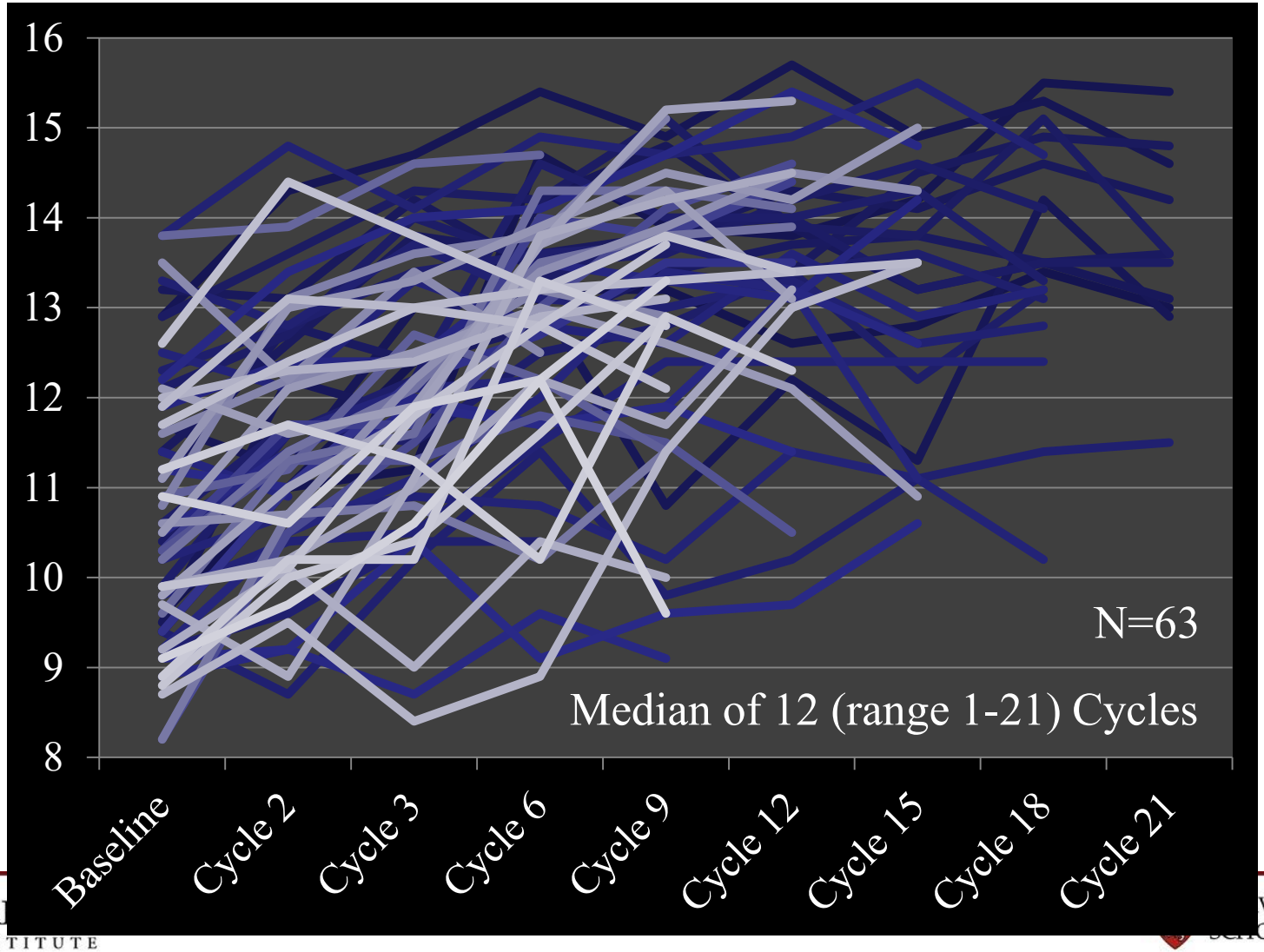
Serial Serum IgM Levels Following Ibrutinib

Best IgM Response: 3,610 to 915 mg/dL; p<0.0001



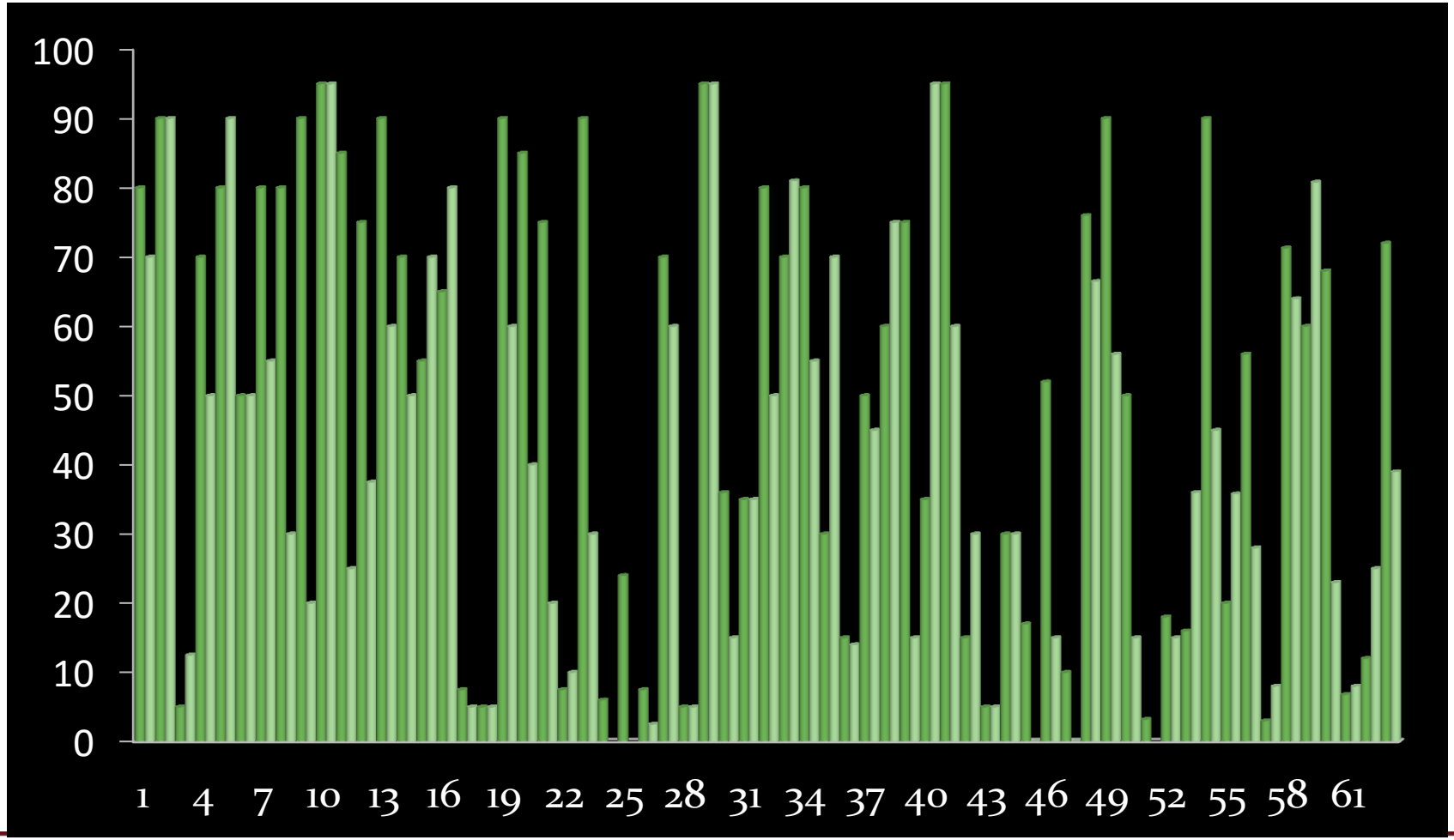
Serial Hemoglobin Levels Following Ibrutinib

Best Hemoglobin Response: 10.5 to 13.5; p<0.0001



Bone Marrow Disease Burden following Ibrutinib

At Best Response 60% to 30%; p< 0.001



Ibrutinib Related Adverse Events

Early

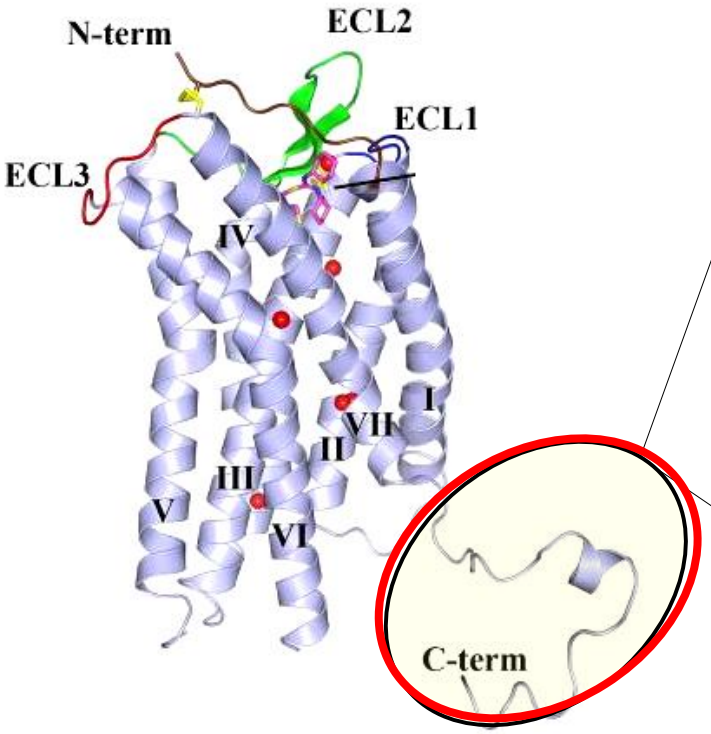
- Anemia
- Neutropenia
- Thrombocytopenia
- Rash
- Nausea
- Diarrhea
- Arthralgias

Delayed

- Increased risk of bleeding
- Atrial fibrillation
- Hypertension

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 Blood 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%	80.9%	57.1%	<0.01
Major RR	88.2%	57.1%	28.6%	<0.01

Treon NEJM 2015

Selected studies in untreated patients with Waldenstrom macroglobulinemia

Agent	N	Overall response rate	Major response rate	Time to response	Progression-free survival
Rituximab	29	66%*	48% (untreated and treated)	3-6 months	14 months
Bortezomib	27	85%*	48% (treated)	1.4 months	8 months
CDR	72	83%	74% (untreated)	4 months	35 months
BDR twice weekly	23	96%	83% (untreated)	1.4 months	66 months
BDR once weekly	38	85%	68% (untreated)	Not reported	42 months
Bendamustine/ rituximab	22	Not reported	Not reported (untreated)	Not reported	69 months
CARD	31	87%	68% (untreated)	2.1 months	Not reached at 36 months

Frontline clinical trials at DFCI

IDR

- Ixazomib, dexamethasone, rituximab
- N=26/26 enrolled
- Minimal toxicity
- Data to be presented at ASH 2016

Ibrutinib

- N=10/30 enrolled
- WGS in all patients on a yearly basis
- MYD88 +/- CXCR4

Novel pathways: novel agents

- Oral proteasome inhibitors – ixazomib, marizomib
- BTK inhibitors – acalabrutinib, BGB-3111
- PI3K-delta – idelalisib, TG-1202
- BCL2 antagonism – venetoclax
- Anti-CD38 therapy - daratumumab
- Anti-CXCR4 therapy – ulocuplomab
- TLR inhibitor – IMO8400
- IRAK1/4 inhibitor
- MYD88 binding inhibitor

Summary

- There are multiple effective options for the frontline treatment of Waldenstrom Macroglobulinemia.
- Rituximab can be used as a single agent.
- Bendamustine, bortezomib, carfilzomib and cyclophosphamide are highly effective when combined with rituximab.
- Exciting clinical trials with oral agents are ongoing.
- Future treatments are likely to be less toxic and more effective.

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