Waldenström's macroglobulinemia: Genetic Basis and Therapy.

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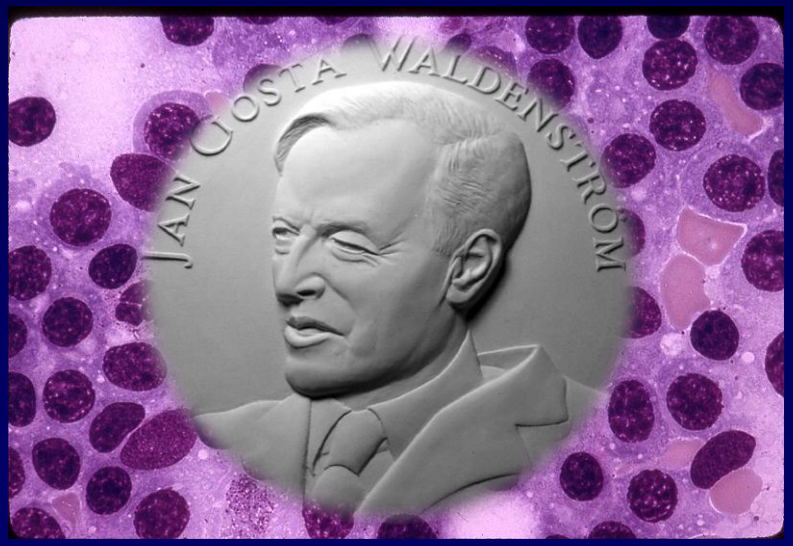
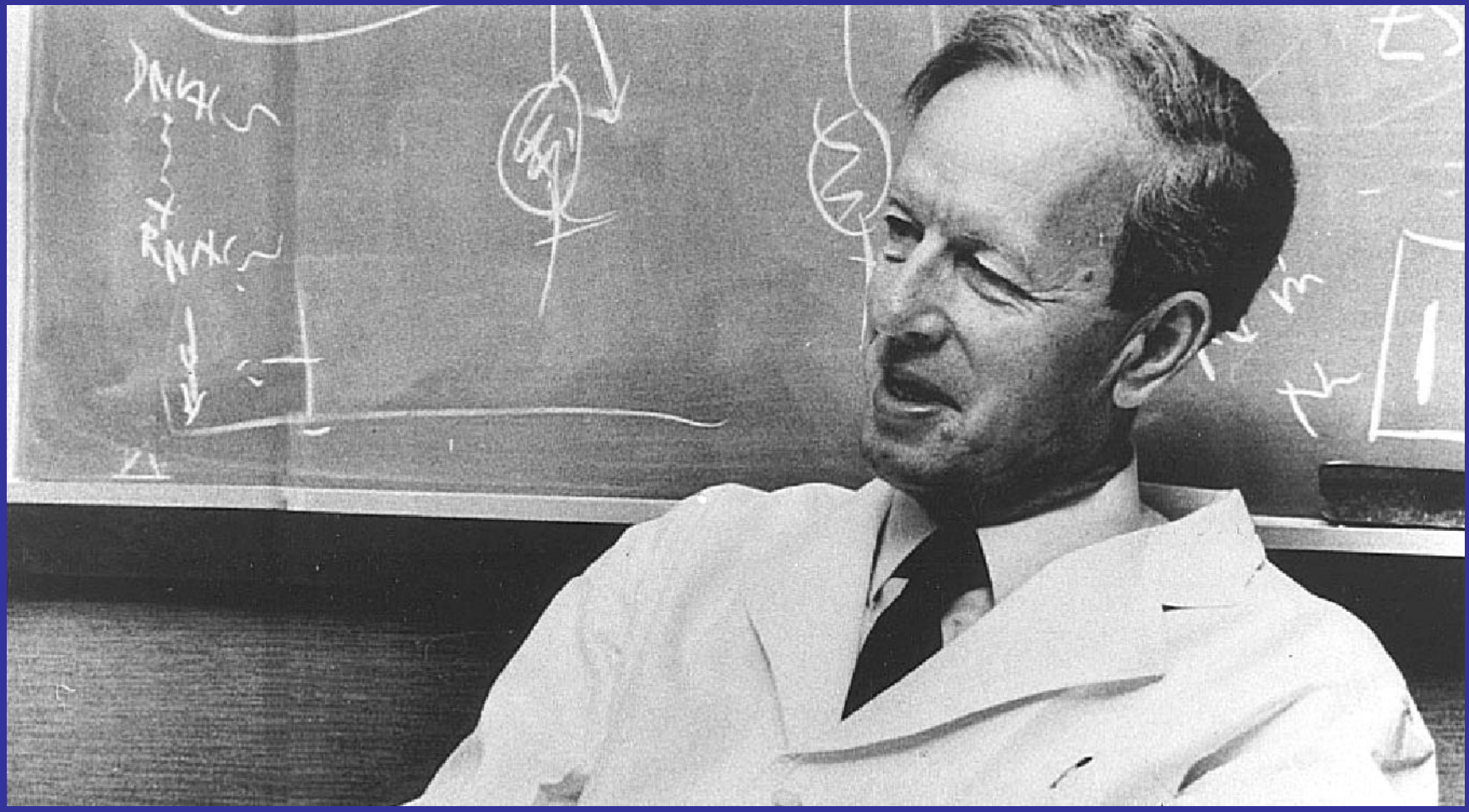
Boston, Massachusetts, United States

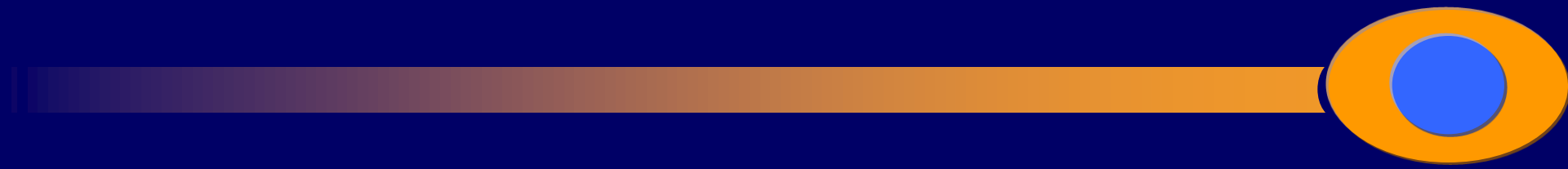




Waldenström's Macroglobulinemia – first described by Jan Gosta Waldenström in 1944.

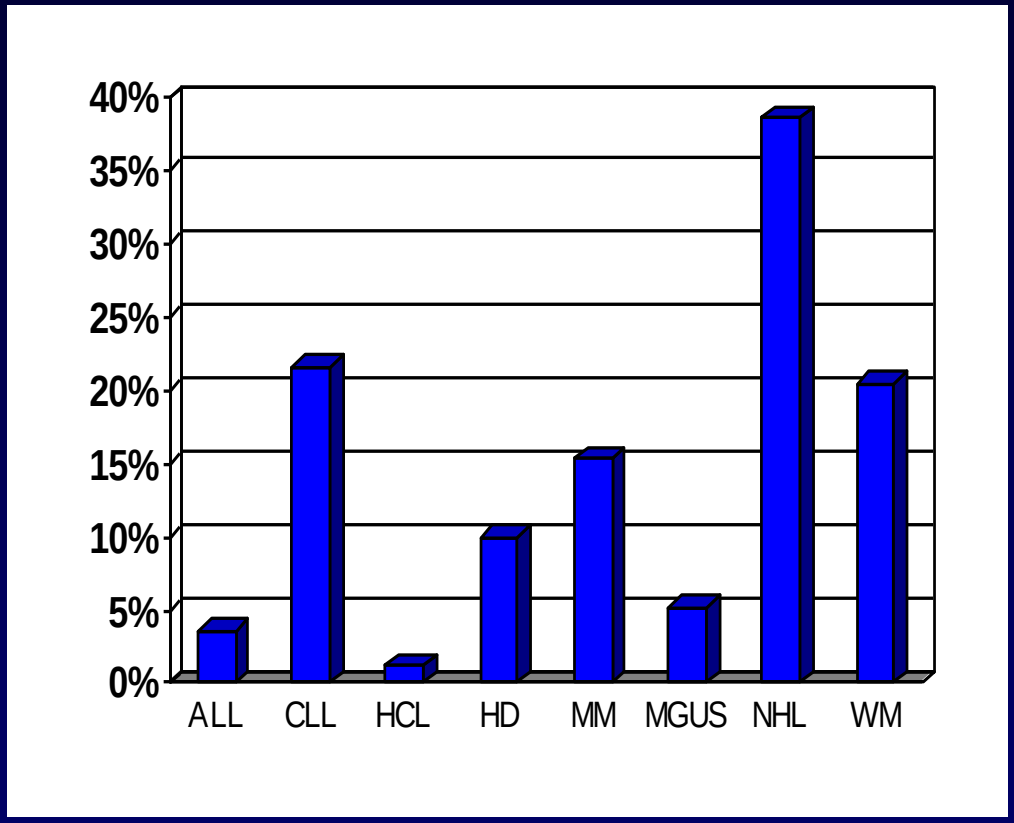
Waldenström's macroglobulinemia: Similar but Different to Myeloma.

Genetic Predisposition



Familial disease predisposition in WM

- N=1076 consecutive patients with clinicopathological diagnosis of WM
- 26.1% of WM patients have a first or second degree relative with a B-cell LPD.



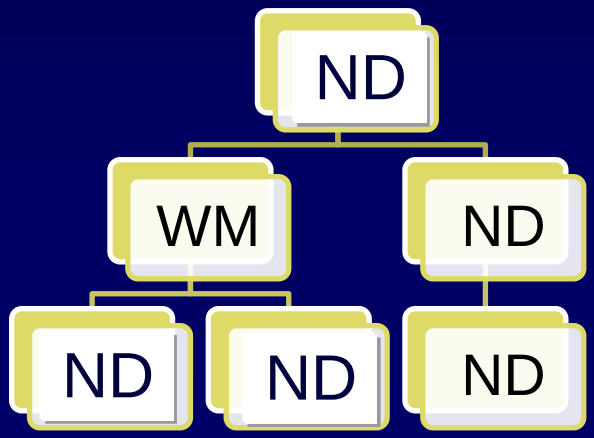
Distribution of B-cell LPD in relatives of 281 Familial WM patients.

Treon et al, ASH 2011.

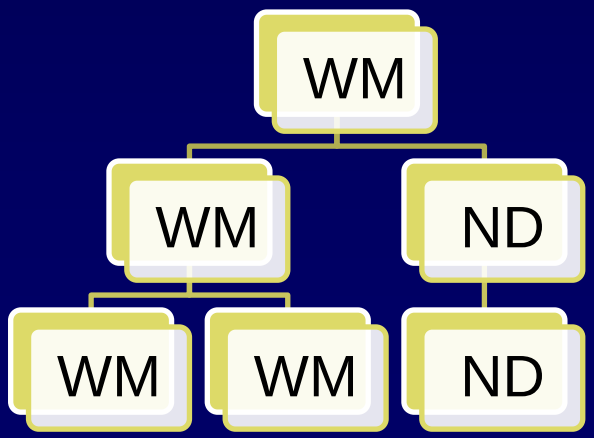
WM Familial Genomics Project

IRB Approved Registry. Over 800 individuals, 187 families enrolled. Detailed familial history for cancer and autoimmune disosders collected, updated biannually. CBCD, quantitative Igs, SPEP, serum, buccal and PB DNA collected on all participants.

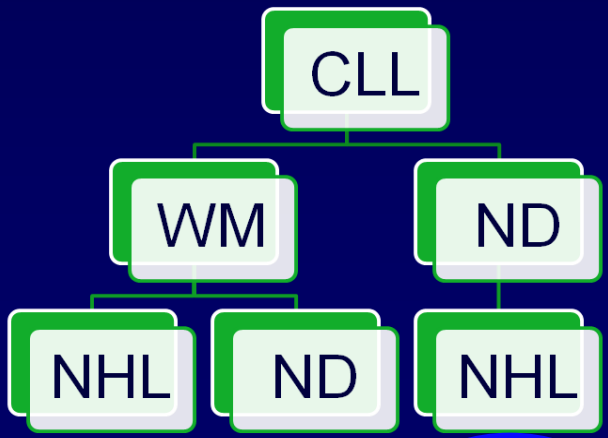
Sporadic



Familial WM Only

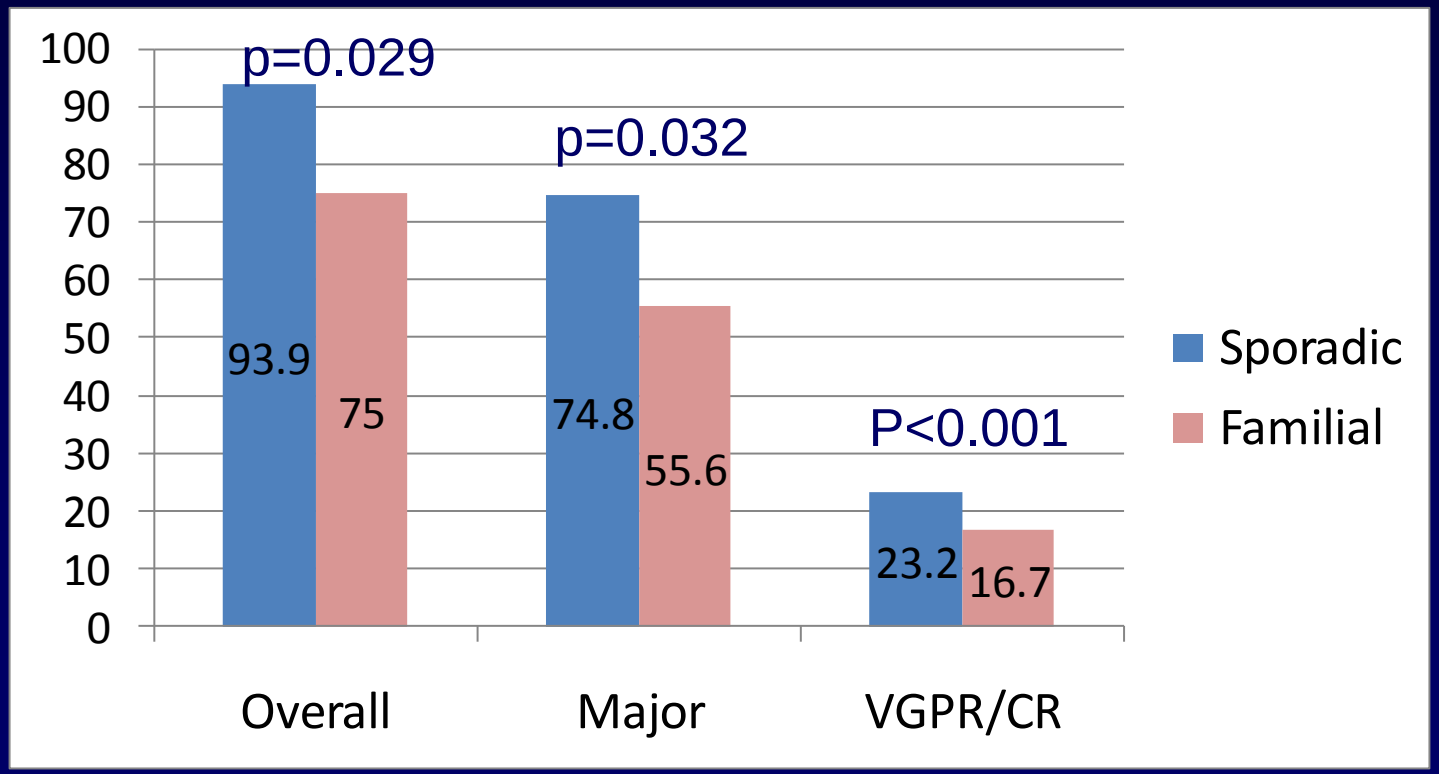


Familial Mixed B-cell



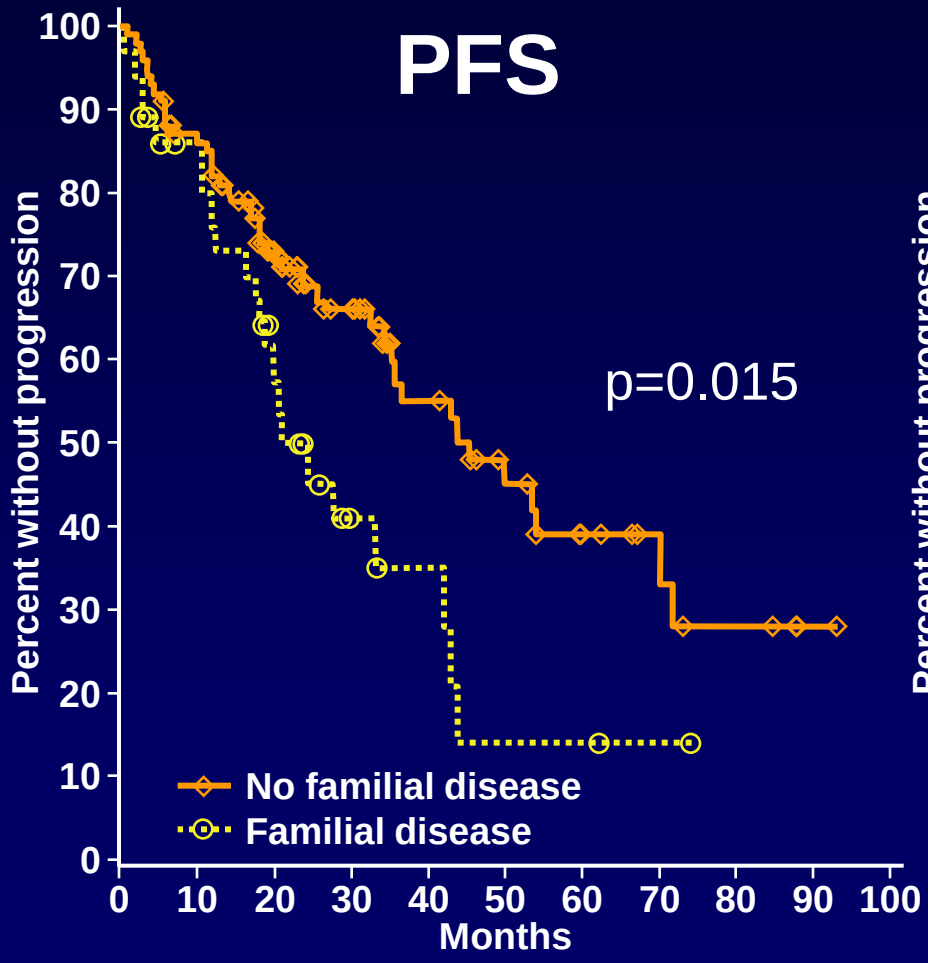
Impact of familial status in rituximab-naïve patients receiving a rituximab containing regimen.

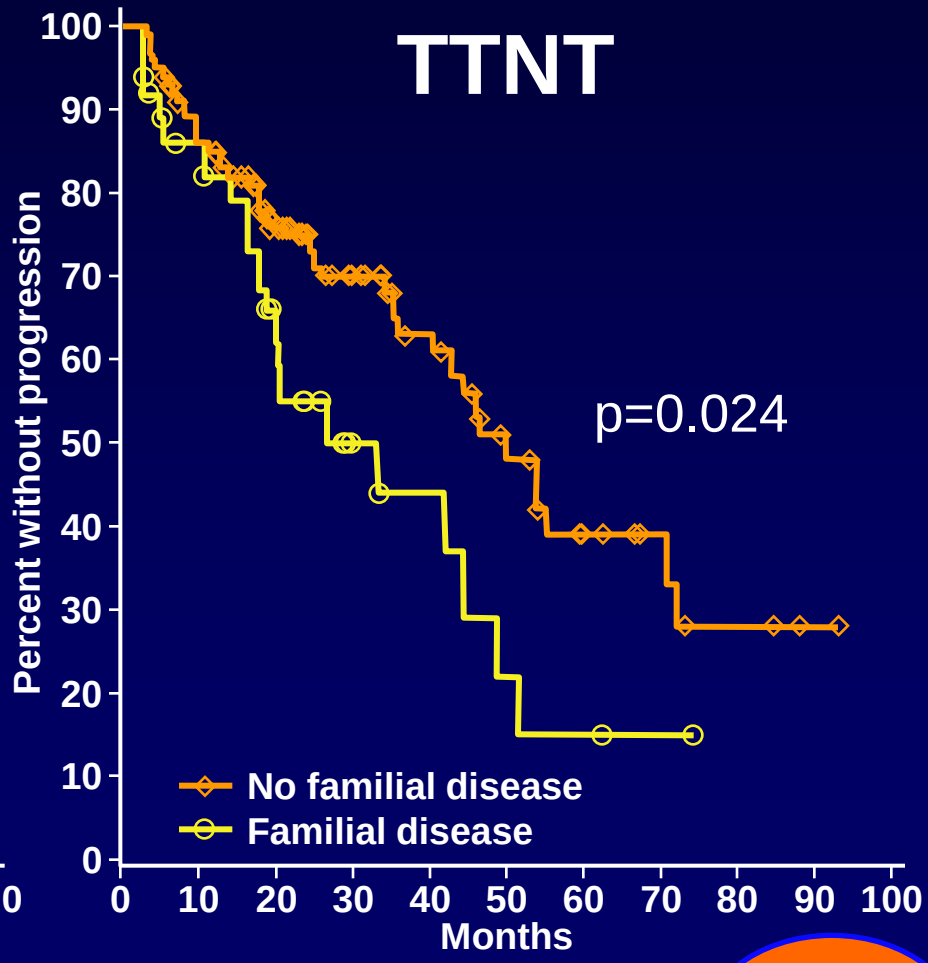
Response to Therapy



Treon et al, ASH 2011

Familial Disease Is Associated with shorter PFS and Time to Next Therapy





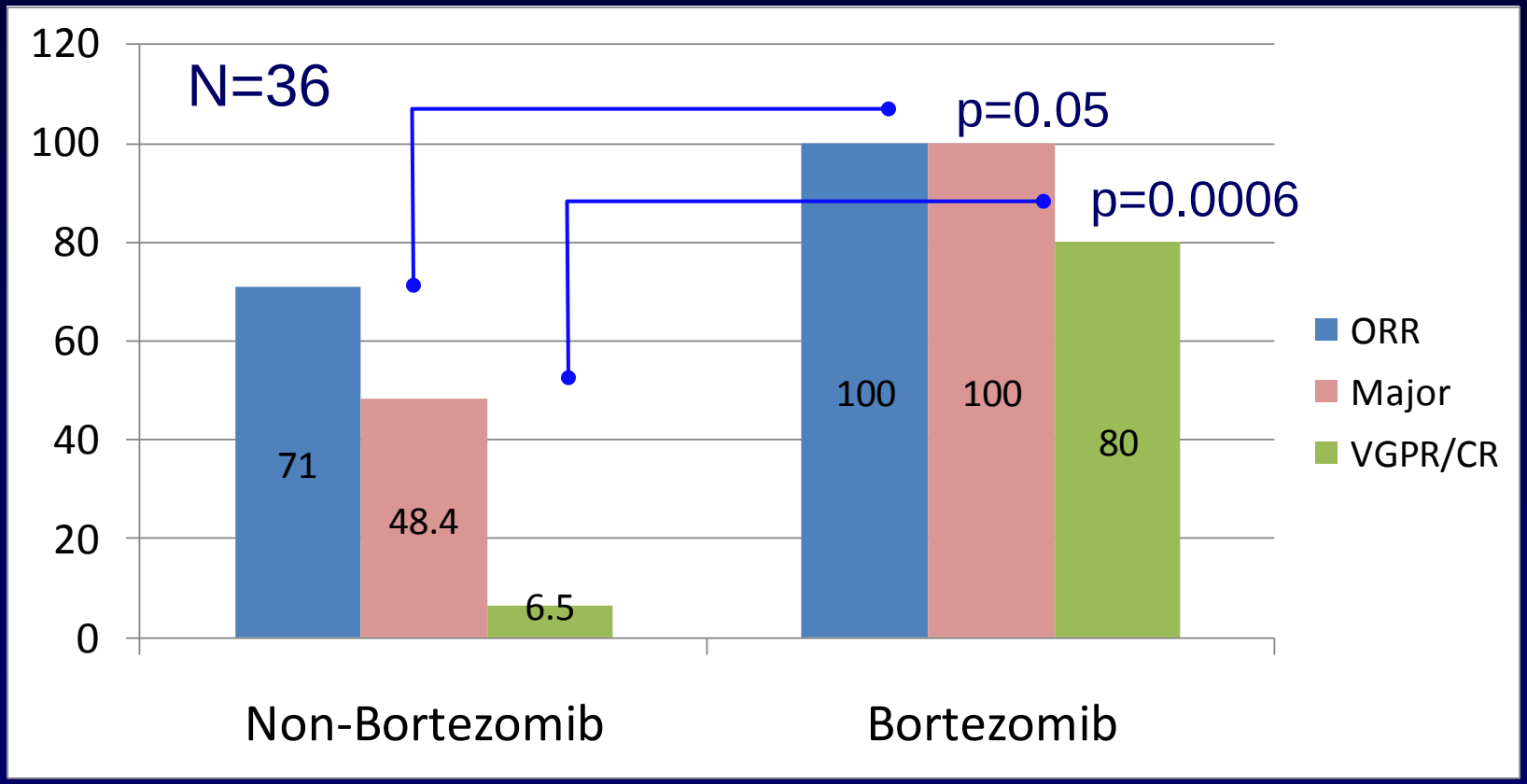
Treon et al, ASH 2011

Familial Disease Status in WM is an Independent Prognostic for PFS

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Fam Disease	1	-0.59016	0.27386	4.6438	0.0312	0.554
Age	1	-0.02276	0.01320	2.9712	0.0848	0.977
sIgM	1	0.0000498	0.0000573	0.7538	0.3853	1.000
sB_2M	1	0.13171	0.05077	6.7293	0.0095	1.141
Hgb	1	0.08309	0.07579	1.2018	0.2730	1.087

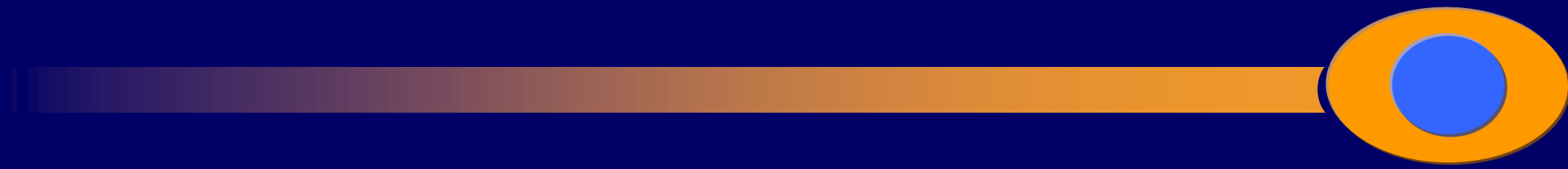
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Fam Disease	1	-0.66490	0.26764	6.1717	0.0130	0.514
IPSS	1	0.20736	0.15232	1.8531	0.1734	1.230

Does the type treatment impact response for familial patients?



Treon et al, ASH 2011

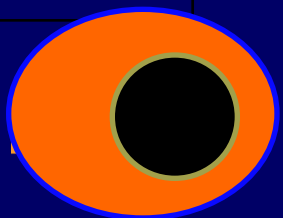
Is there a common genetic predisposition with other cancers in WM patients?



Other Cancers in WM Patients

	Total	Sporadic	Familial, Mixed B-cell	Familial, WM Only
N=	924	685	194	45
Prostate (Males)	54 (9.42%)	**47 (10.7%)**	5 (4.59%)	1 (4.00%)
Breast (Females)	28 (8.00%)	**22 (9.13%)**	6 (6.67%)	0 (0.00%)
Skin (Non-Melanoma)	66 (7.14%)	**56 (8.18%)**	10 (5.15%)	0 (0.00%)
Hematological	26 (2.81%)	16 (2.33%)	8 (4.12%)	2 (4.44%)
Melanoma	20 (2.16%)	15 (2.19%)	4 (2.06%)	1 (2.22%)
Lung	14 (1.40%)	5 (0.73%)	**8 (4.12%)**	1 (2.22%)
Thyroid	10 (1.08%)	10 (1.46%)	0 (0.00%)	0 (0.00%)
GYN	10 (1.08%)	8 (1.16%)	2 (1.03%)	0 (0.00%)
Total	**273 (29.6%)**	**212 (31.4%)**	**53 (25.8%)**	**8 (17.77%)**

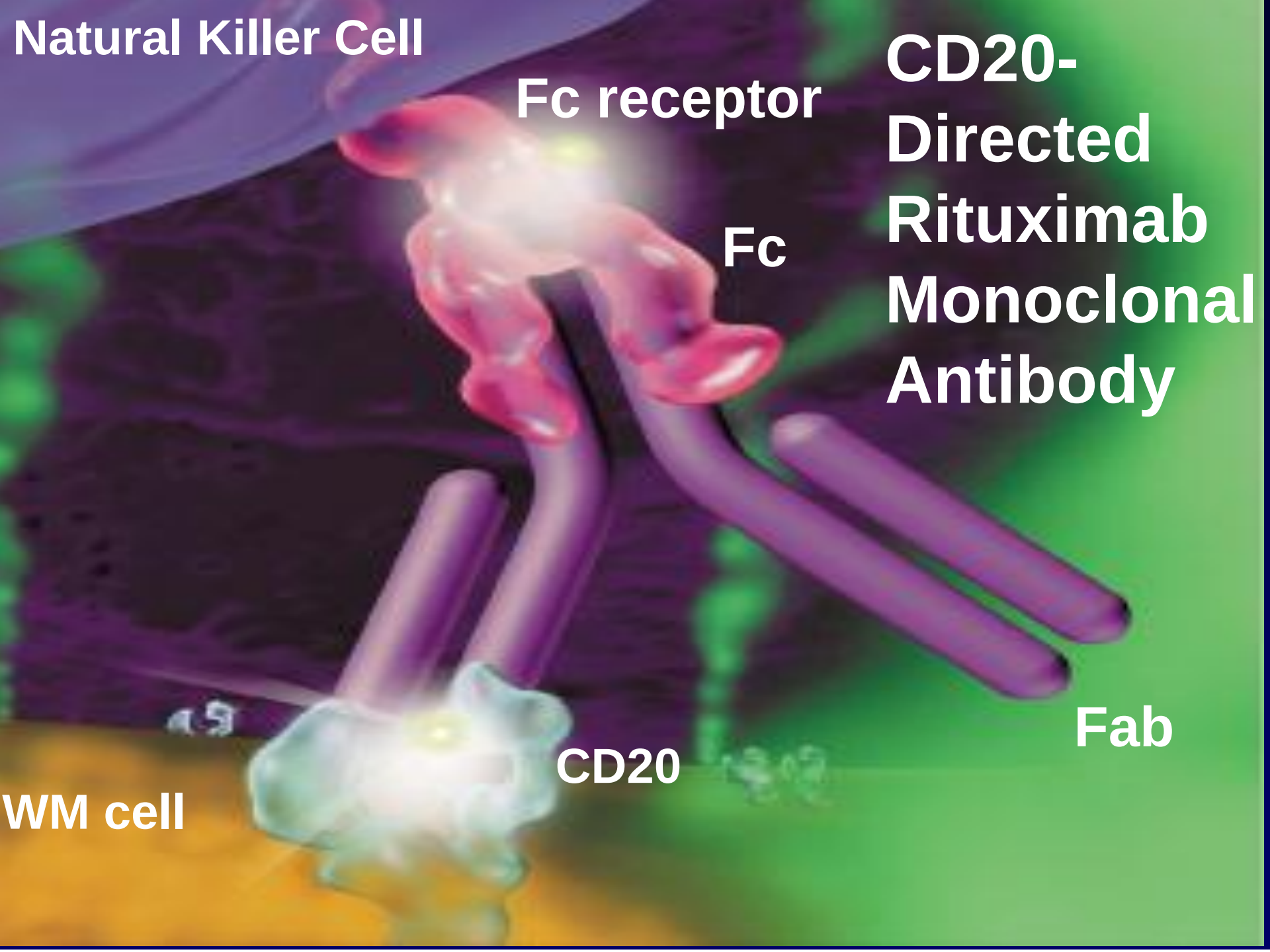
Hanzis et al, CLML 2011



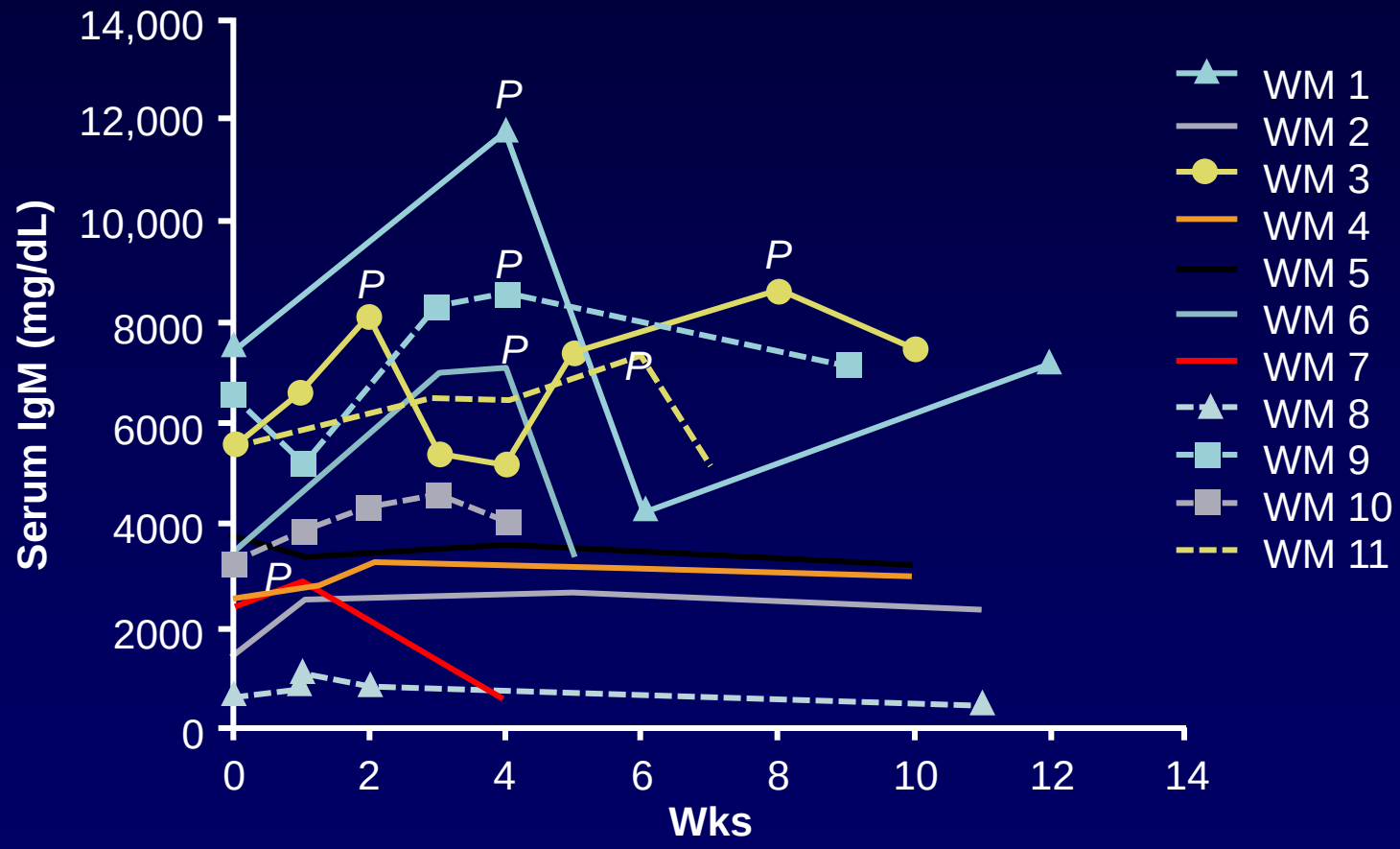
Consensus Panel Recommendations for Initiation of Therapy in WM

- Hb ≤10 g/dL on basis of disease
- PLT <100,000 mm^3 on basis of disease
- Symptomatic hyperviscosity (>4.0 cp)
- Moderate to severe peripheral neuropathy
- Symptomatic cryoglobulinemia, cold agglutinemia, amyloidosis, or symptomatic autoimmune-related events on the basis of disease

Kyle RA, et al. Semin Oncol. 2003;30(2):116-120.


Natural Killer Cell
Fc receptor
Fc
CD20-Directed Rituximab Monoclonal Antibody
Fab
CD20
WM cell

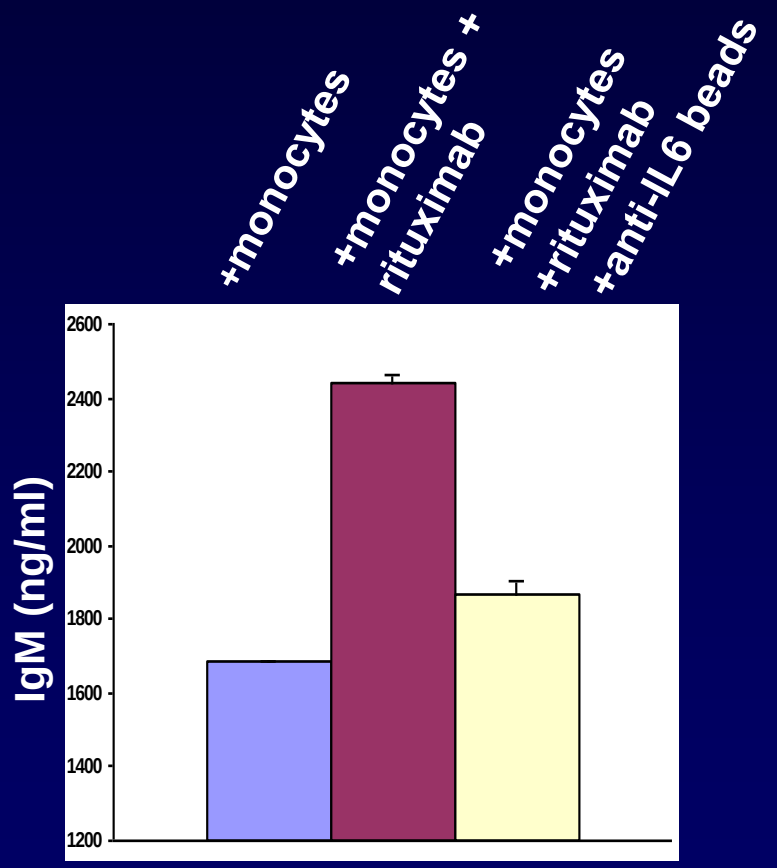
Serum IgM Levels Following Rituximab in Patients With WM

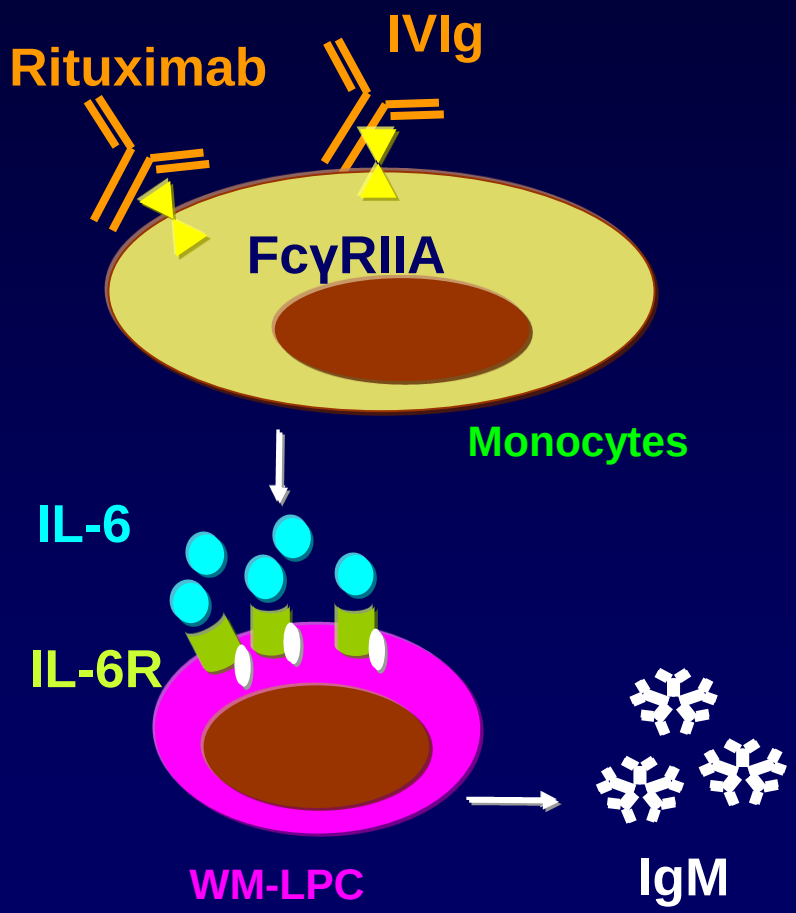


P denotes patient-required plasmapheresis for hyperviscosity.

Treon SP, et al. *Ann Oncol.* 2004;15(10):1481-1483.

Bystander Release of IL-6 by Monocytes May Account for the Rituximab IgM Flare





Primary Therapy of WM with Rituximab-Based Options

Regimen	ORR	CR
Rituximab x 4	25-30%	0%
Rituximab x 8	40-45%	0%
Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, RCD	70-80%	8-10%
Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R	70-90%	5-10%
Rituximab/thalidomide	70%	5%
Rituximab/bortezomib i.e. BDR, VR	70-90%	10-25%
Rituximab/bendamustine	90%	NA

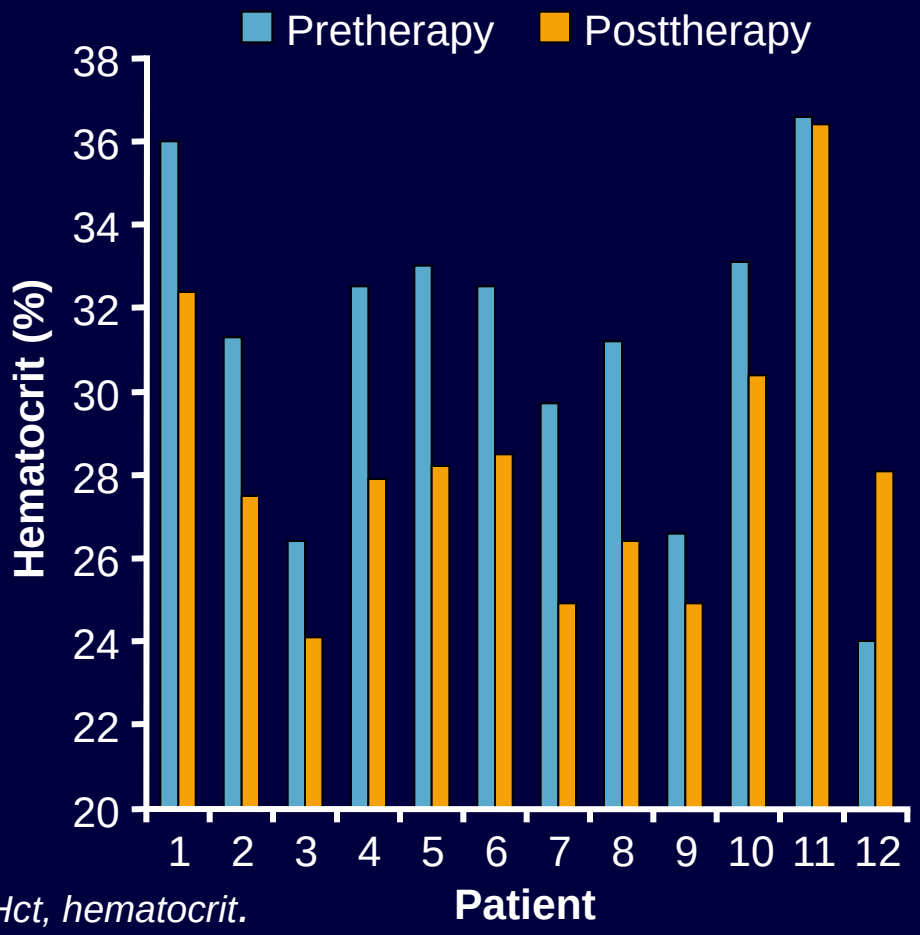
Disease Transformation and MDS/AML Following Nucleoside Analogues in WM

Study	Population	N	Median F/U (mo)	Outcome
Leleu et al, JCO 2009[1]	Prev treated with NA vs. non-NA or untreated	439	60	Histologic Transformation (8%) MDS/AML (5%)
Tamburini et al, Leukemia 2005[2]	Firstline with Fludara/Cyclo	49	41	Histologic Transformation (10%)
Leblond, JCO 1998[3]	Previously treated with Fludara	71	34	Histologic Transformation (10%)
Rakkhit et al, ASH 2008[4]	Untreated; 2CDA based therapy	111	NA	Histologic Transformation (9%)

1. Leleu X, et *al.J Clin Oncol.* 2009;27(2):250-255. 2. Tamburini J, et al. *Leukemia.* 2005;19(10):1831-1834. 3. Leblond V, et al. *J Clin Oncol.* 1998;16:2060-2064. 4. Rakkhit R, et al. *Blood.* 2008;112: Abstract 3065.

Revlimid-Induced Anemia in WM

- Decreased Hct observed in 10/12 pts following first week of lenalidomide monotherapy
- Median Hct decrease: 3.9% (31.9% to 28.0%; *P* = .003)
- No evidence for hemolysis; concurrent thrombocytopenia observed in 1 pt
- 4 patients hospitalized for anemia related complications (Afib, syncope, CHF)



Afib, atrial fibrillation, CHF, congestive heart failure, Hct, hematocrit.

Treon SP, et al. Clin Cancer Res 2008

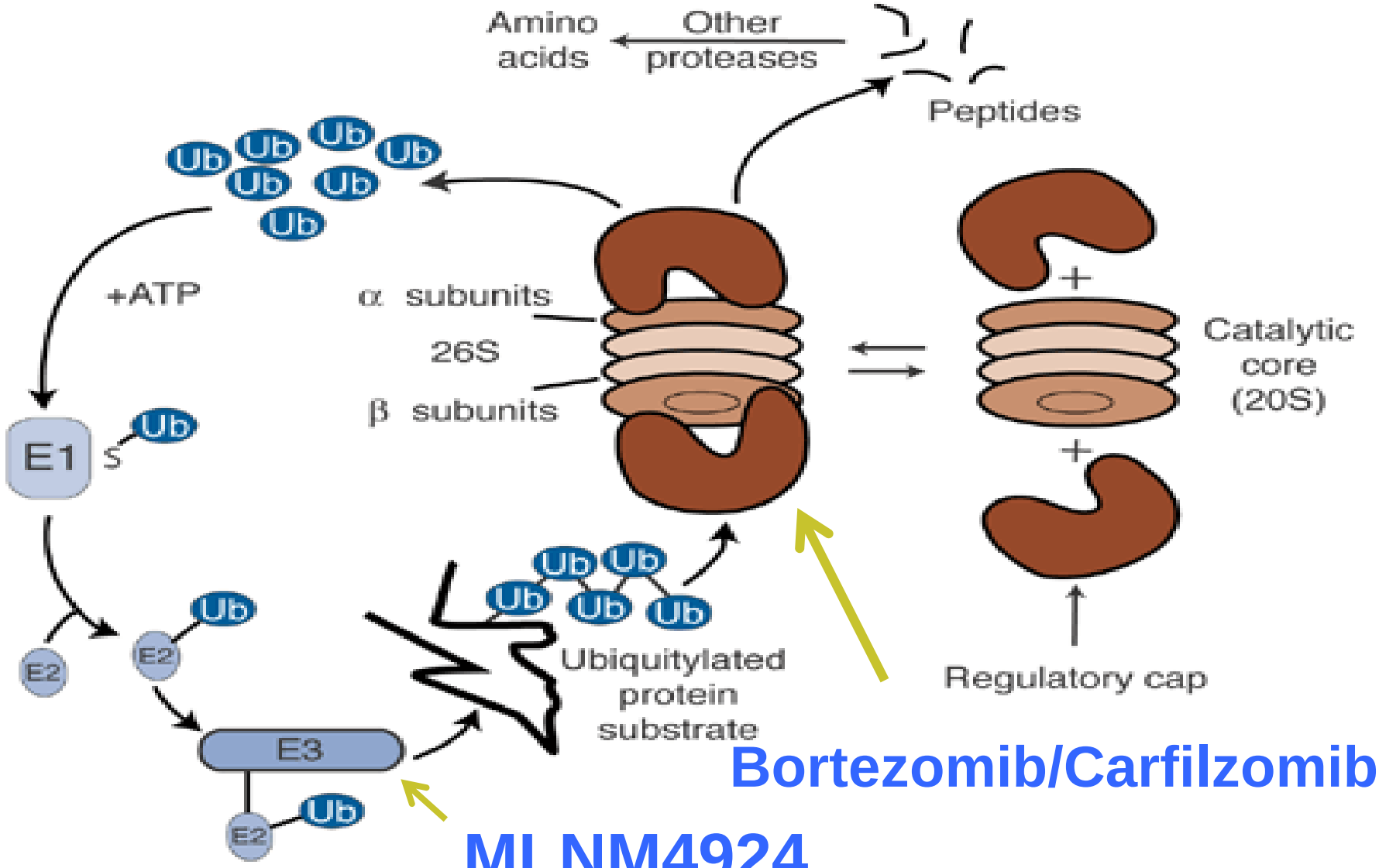
Phase I Study of Pomalidomide, Dexamethasone, and Rituximab (PDR) in WM

Agent	Dose	Schedule
Pomalidomide	0.5, 1, 2 mg QD	52 weeks
Dexamethasone	40 mg wkly IV	Pre-rituximab
Rituximab	375 mg/m^2/wk	W1-4; W12-15

- Aggravated Anemia less pronounced
- Complete remission in first dose cohort
- IgM flare is potentiated

Proteasome Inhibitors

New Proteasome Inhibitors



Bortezomib Combination Therapy in WM

- **Primary**

  Bortezomib (1.3 mg/m^2/biwkly)/Dexamethasone/Rituximab

  ORR 95%; CR 22%; TTP >4 yrs; **30% Grade 3 PN**

  Bortezomib (1.6 mg/m^2/wk)/Rituximab

  ORR 92%; CR 8%; 80% 1 Y PFS; **No Grade 3 PN**

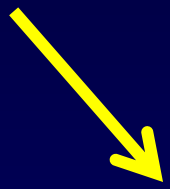
- **Salvage**

  Bortezomib (1.6 mg/m^2/wk)/Rituximab

  ORR 81%; CR 5%; TTP 12 months; 5% Grade 3 PN.

  Bortezomib (randomized wkly vs biwkly)/Rituximab

  ORR 80%; CR 0%; TTP ?; 0% Grade 3 PN.



vs. 10-12% in MM!

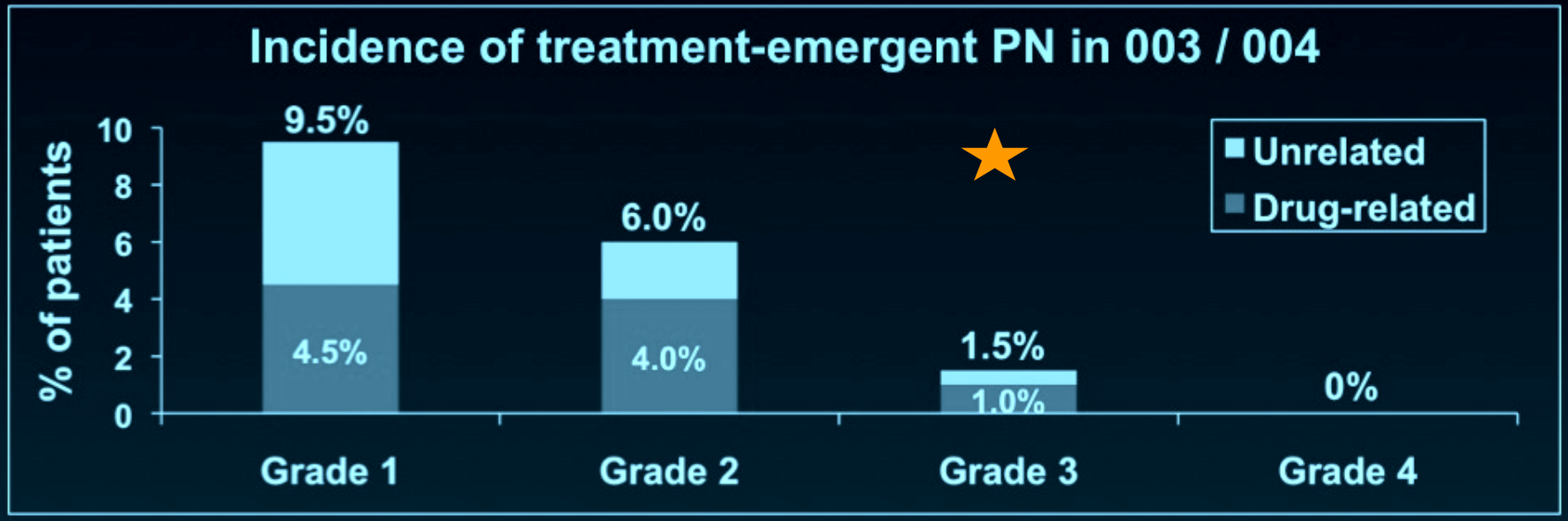
Treon SP, et al. *J Clin Oncol*. 2009;27(23):3830-383. Ghobrial IM, et al. *Blood.* 2010;116: Abstract 832. Ghobrial IM, et al. *J Clin Oncol.* 2010; 28(8):1422-1428. Agathocleous A, et al. *Blood.* 2007;110: Abstract 2559.

Bortezomib-Based Rituximab Therapy

Twice A Week	Once A Week
↑ CR/VGPR	↓ Neuropathy
↑ PFS (?)	
↓ Time to Response	
↓ Rituximab IgM Flare	

Neuropathy Data for Carfilzomib in MM (Pooled Data from 003/004 Studies)

	N=201
Prior history of neuropathy	**155 (78%)**
Related to prior treatment	122 (61%)
Neuropathy symptoms at baseline	**109 (54%)**



Only 1 patient had drug discontinued for PN *(study 004; BTZ-treated arm)*

Wolf JL, et al. ASCO 2010. Abstract 8135 (poster presentation).

Primary Therapy of WM with Carfilzomib, Rituximab, Dex (CARD)

Induction Cycle 1 q21 days

Days 1,2,8,9 Carfilzomib 20 mg/m^2 IV; Dexamethasone 20 mg IV.
Days 2,9 Rituximab 375 mg/m^2

Induction Cycle 2-6 q21 days

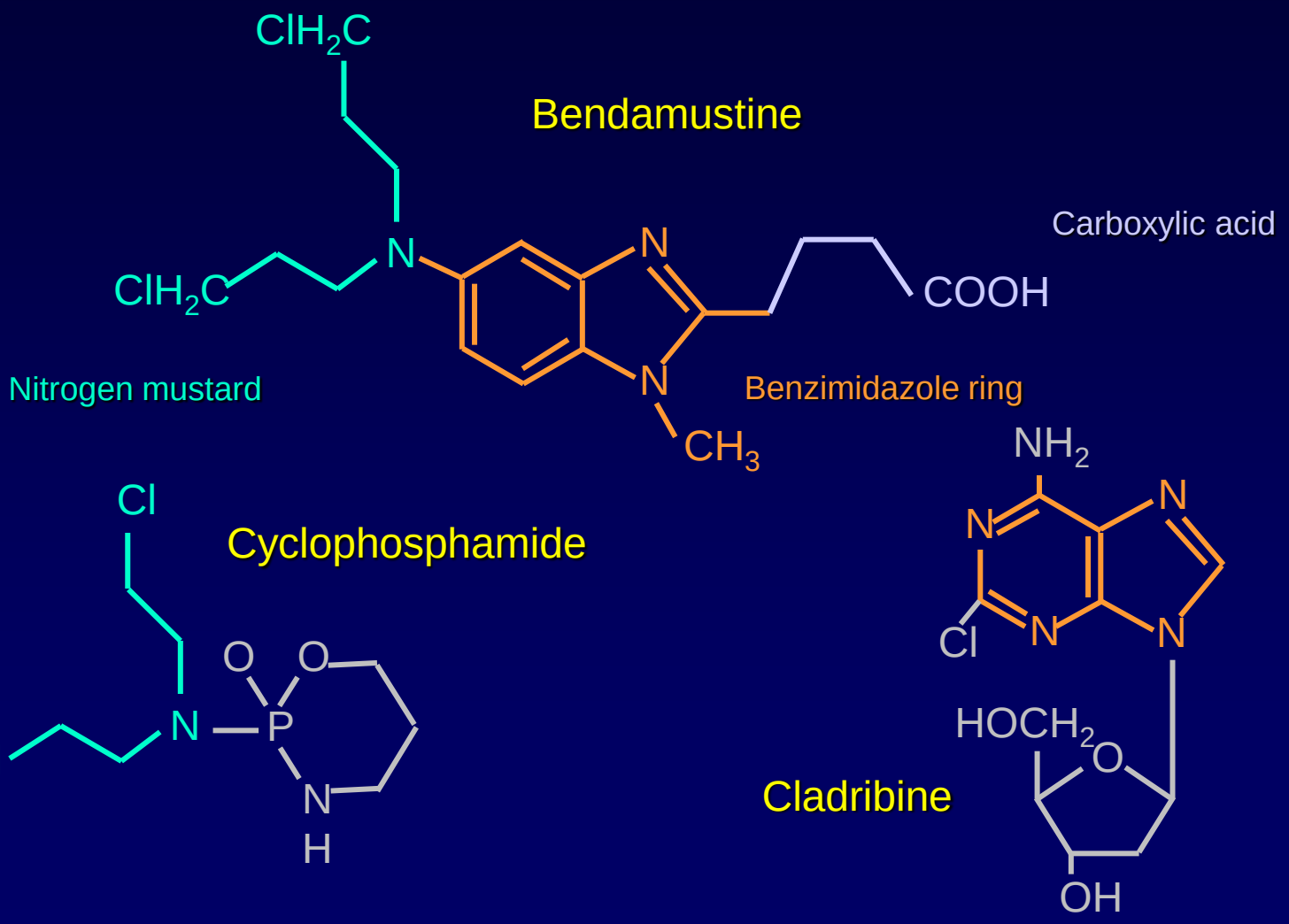
Days 1,2,8,9 Carfilzomib 36 mg/m^2 IV; Dexamethasone 20 mg IV.
Days 2,9 Rituximab 375 mg/m^2

2 months

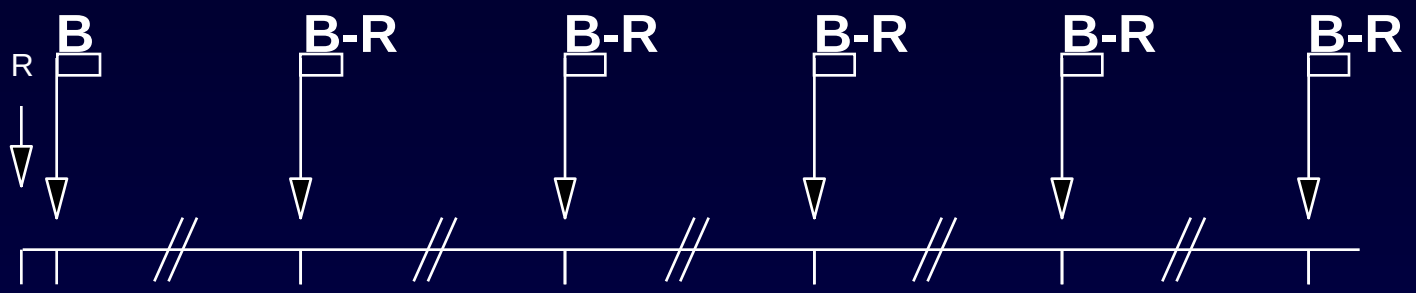
Maintenance Cycles 1-8 q 2 months

Days 1,2 Carfilzomib 36 mg/m^2 IV; Dexamethasone 20 mg IV.
Days 2 Rituximab 375 mg/m^2

Bendamustine in WM



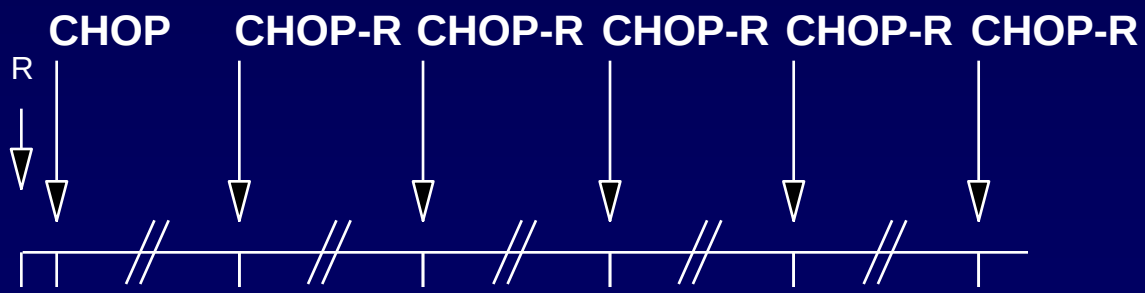
Bendamustine plus Rituximab (B-R)



B = Bendamustine 90 mg/m² — day 1+2, 29+30, 57+58, 85+86, 113+114, 141+142
R = Rituximab 375 mg/m² — day 0, 29, 57, 85, 113, 141

Randomization

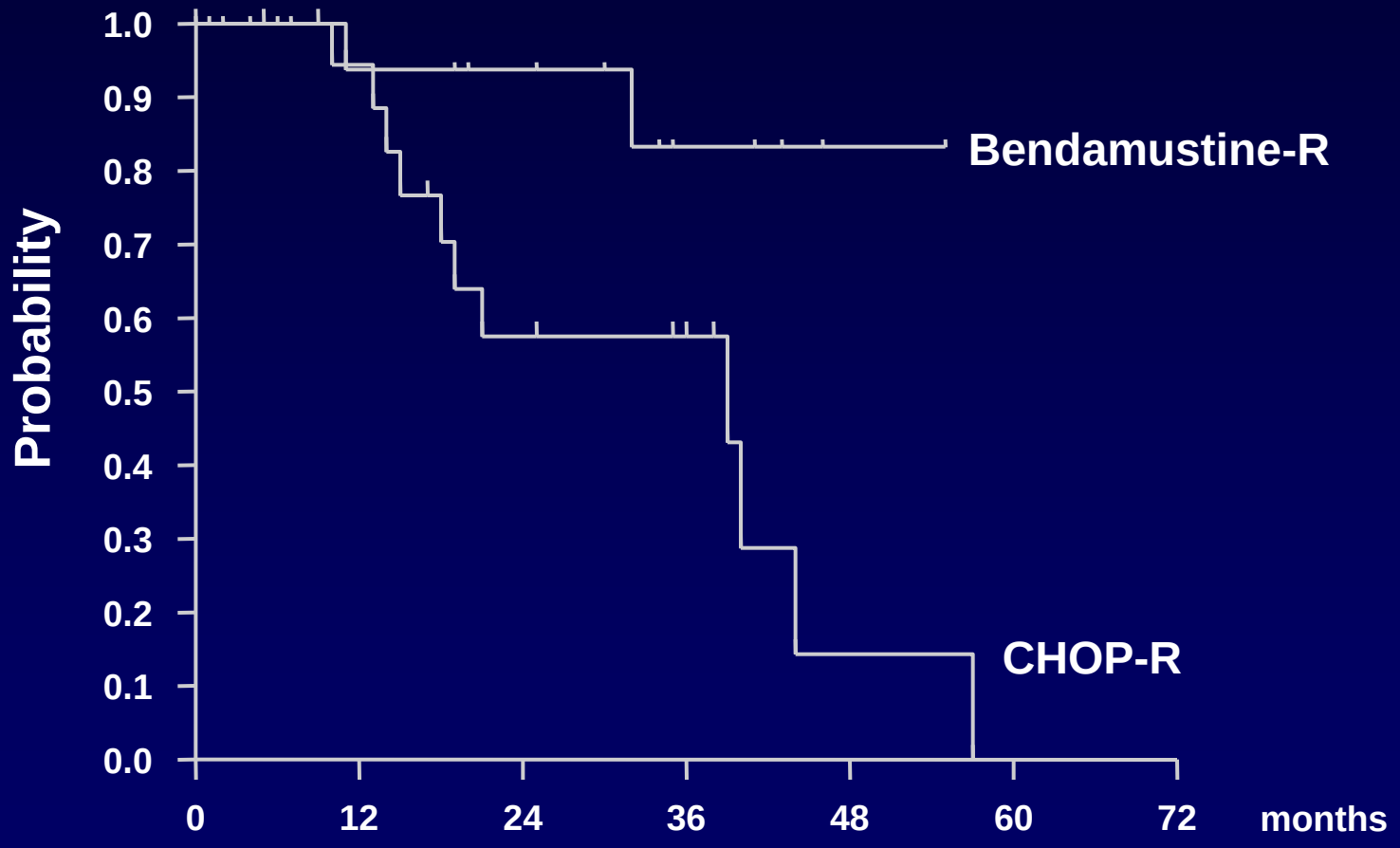
CHOP plus Rituximab (CHOP-R)



CHOP — day 1, 22, 43, 64, 85, 106
Rituximab 375 mg/m² — day 0, 22, 43, 64, 85, 106

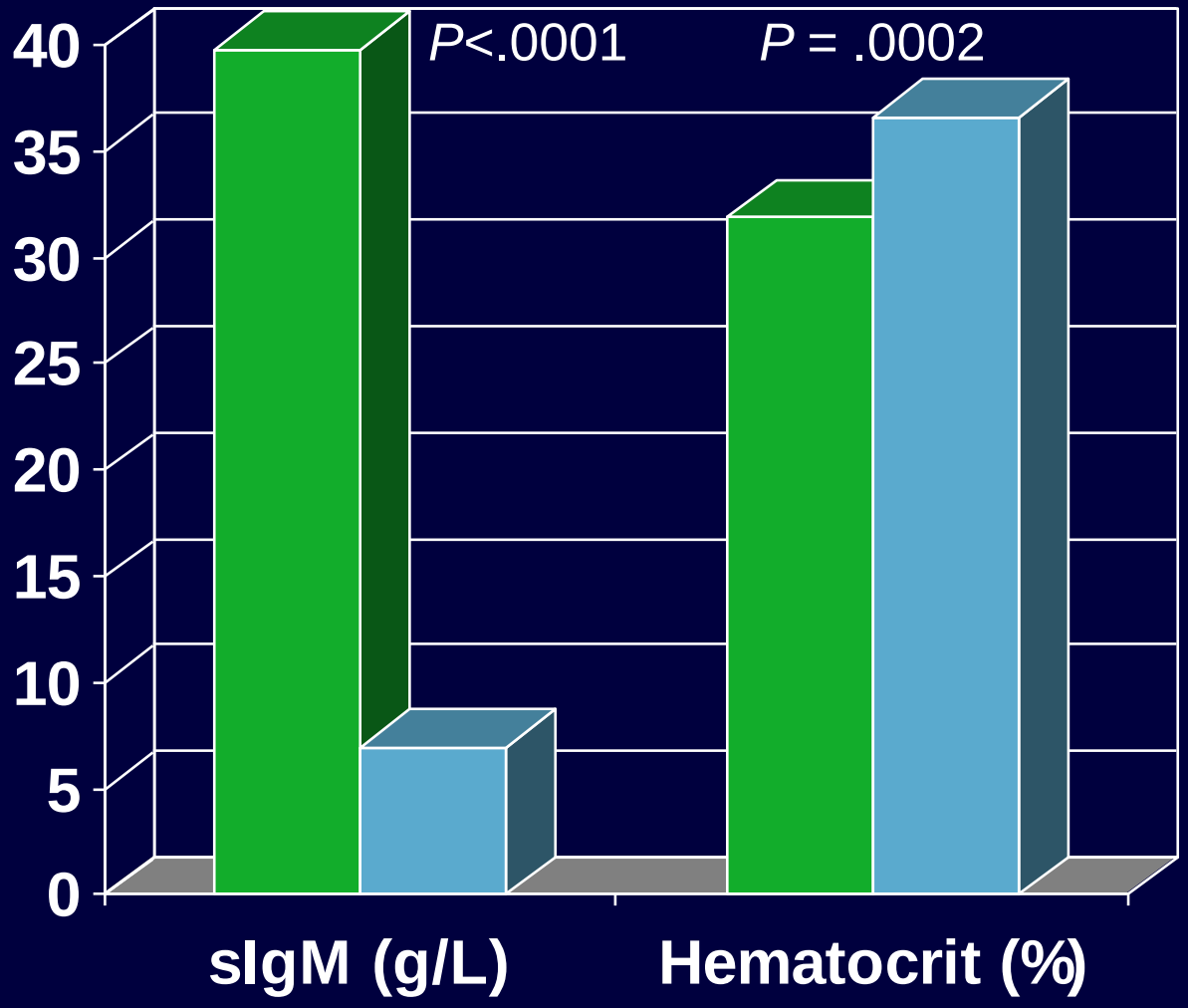
Rummel MJ, et al. *Blood.* 2008;112: Abstract 2596.

PFS: Benda-R vs CHOP-R in Frontline WM



Rummel M, et al. Presented at: Third International Pt Physic Summit on WM; May 1-3, 2009; Boston, Massachusetts, United States.

Bendamustine in Relapsed/Refractory WM

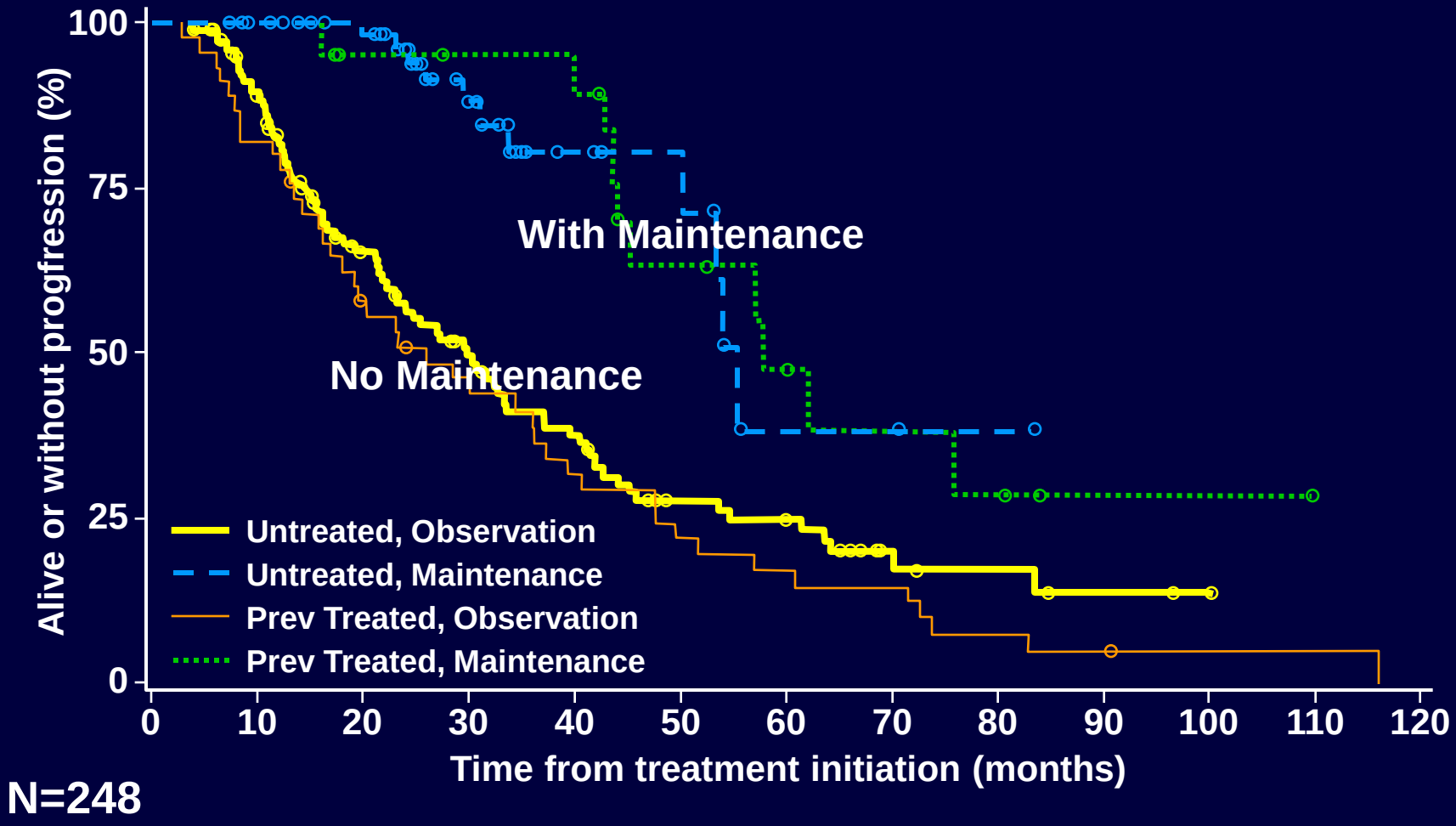


- ORR 83%
- PFS 13.2 mos.

Treon S, et al. *Clin Lymphoma Myeloma Leuk.* 2011;11(1):133-135.

To Maintain or Not to Maintain?

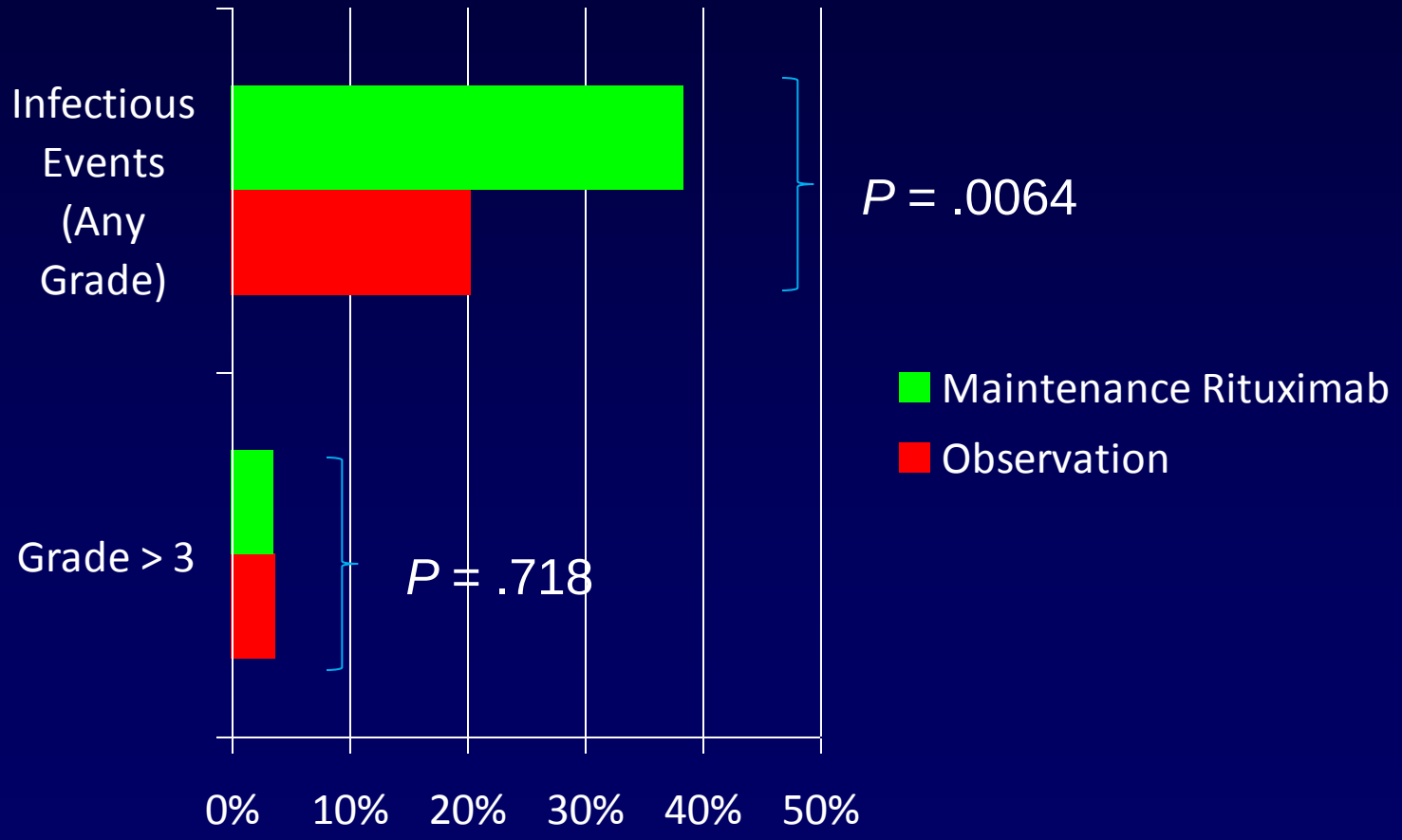
PFS in rituximab naïve WM patients who were observed or given maintenance rituximab therapy.



N=248

Treon S, et al. *Br J Haematol.* 2011 May 25 [Epub ahead of print].

Infectious Events in WM Patients Who Underwent Observation or Maintenance Rituximab Therapy

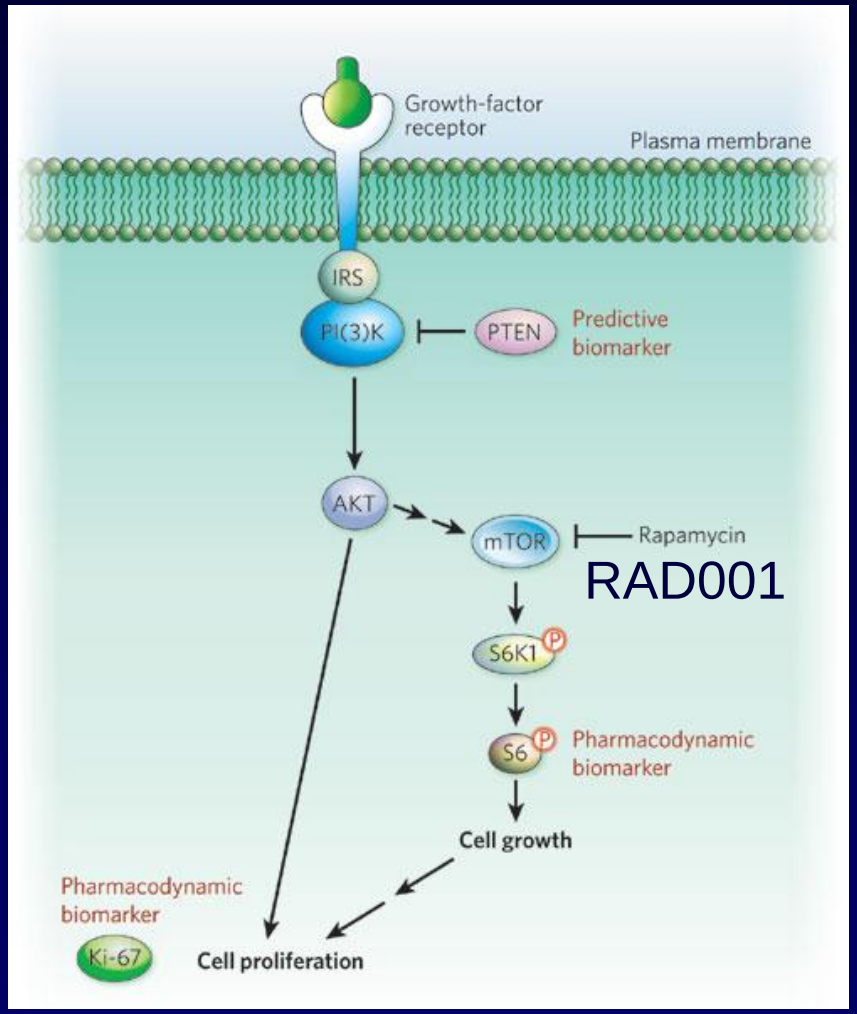


Treon S, et al. *Br J Haematol.* 2011 May 25 [Epub ahead of print].

Other Options for relapsed/refractory patients.

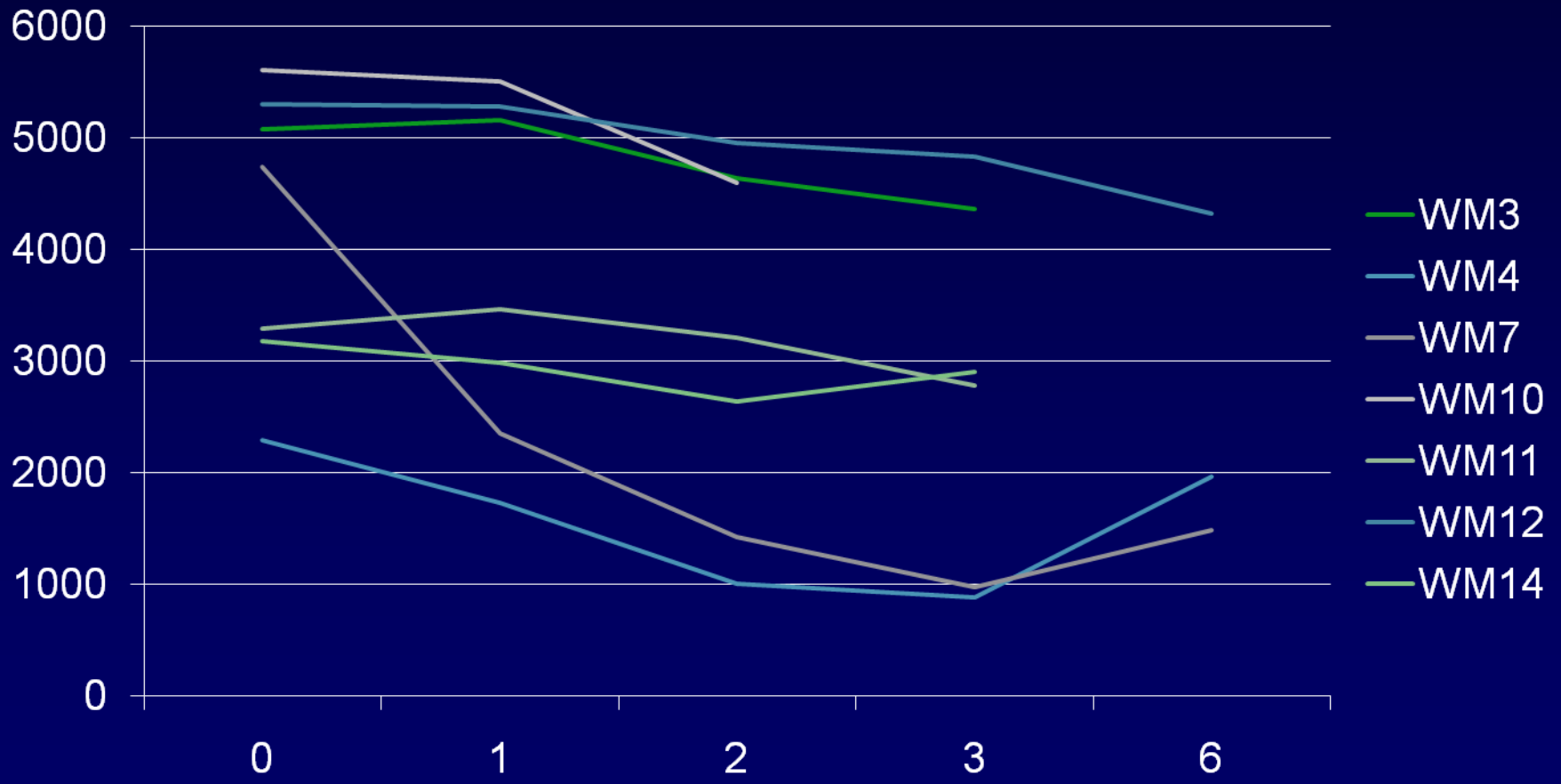
Everolimus in Relapsed/Refractory WM

- N = 50 (DFCI and Mayo)
- 10 mg QD
  - Reduce to 5 mg for AE
- Median prior therapies: 3
- Median IgM: 3330 mg/dL
- ORR: 72%
- Median response:
- NR (3-22+ mos)
- Grade ≥3 thrombocytopenia, pneumonitis, mucositis, and hyperglycemia.



Ghobrial IM, et al. *J Clin Oncol.* 2010;28(8):1408-1414.

IgM Discordance to WM BM Disease Involvement is Common With RAD001



7 non-responders by serial BM biopsies despite reductions in sIgM.

"Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided."

Phillipus Aureolus Paracelsus

Campath in WM

- CD52 widely expressed on WM and BM Mast cells.
- UK Study (n=7):

  -ORR 86%; 1 CR;

  -2 deaths due to Opportunistic Infections.

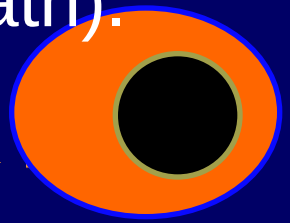
- **Multicenter study by WMCTG (n=28):**

  -ORR 75%; Major RR: 36% (1 CR);

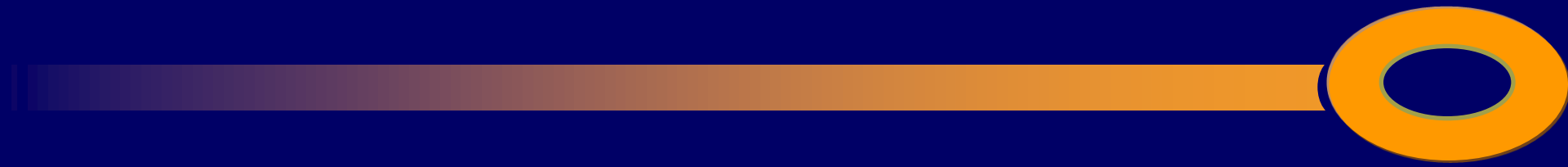
  -TTP 14.5 months ;

  -Cytopenias, CMV (3 deaths); Late ITP (1 death).

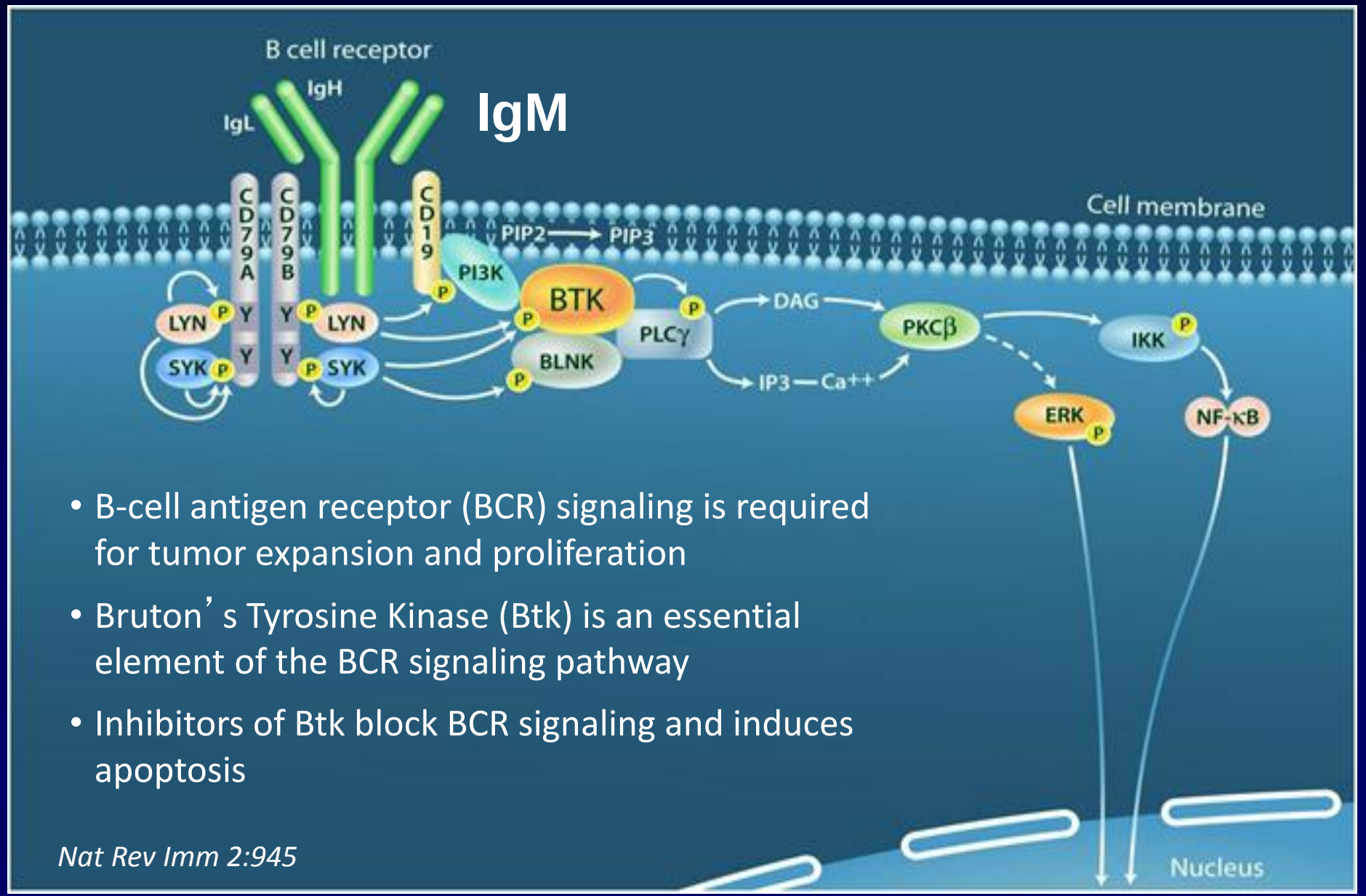
Owen et al, ASH 2003; Treon, Blood 2011.



Novel Directions



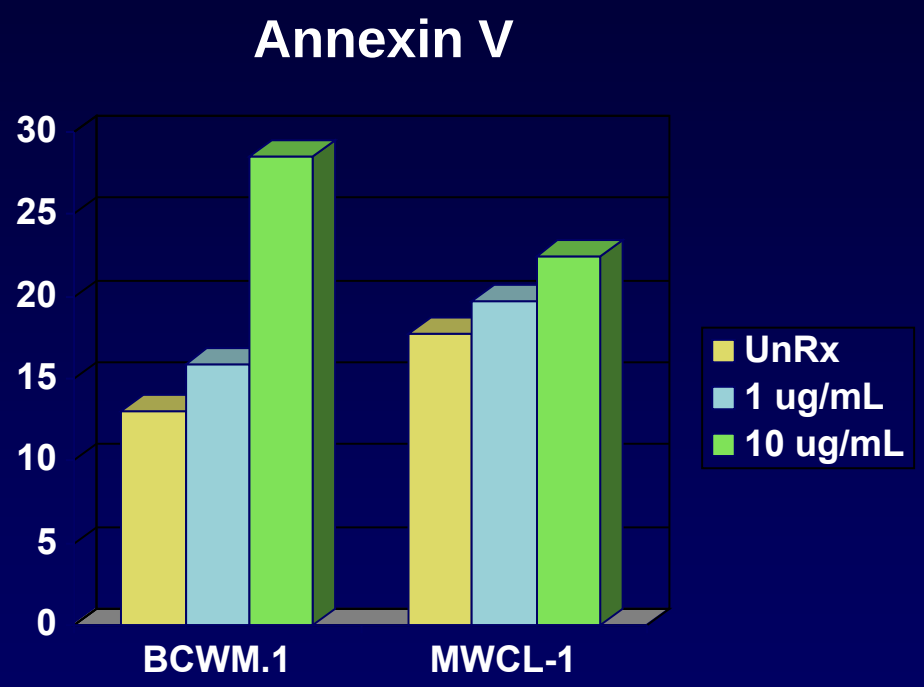
Bruton's Tyrosine Kinase (BTK)



- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- Bruton's Tyrosine Kinase (Btk) is an essential element of the BCR signaling pathway
- Inhibitors of Btk block BCR signaling and induces apoptosis

Nat Rev Imm 2:945

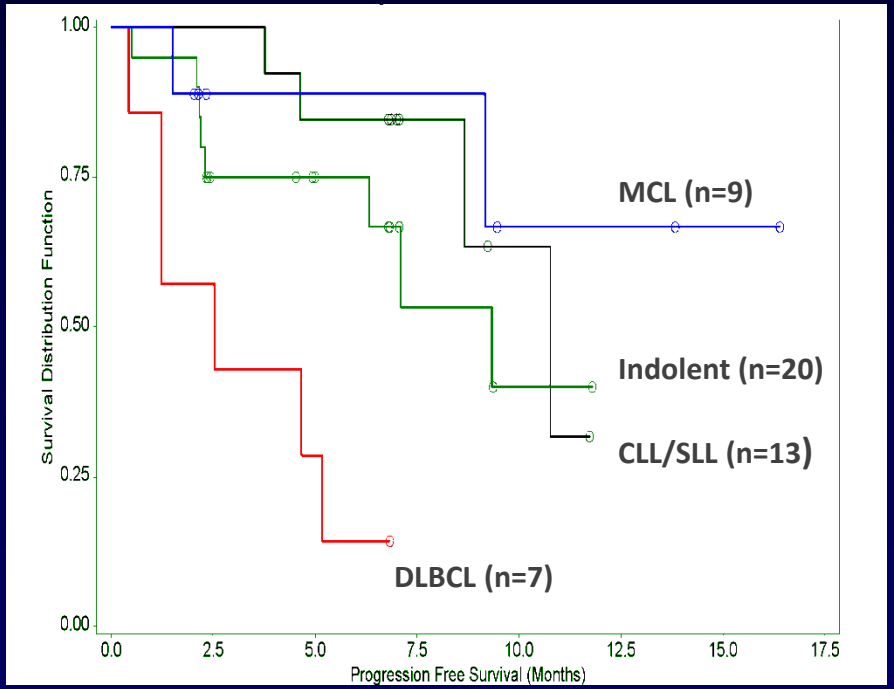
Preclinical Studies of PCI-32765 in WM.



p<0.03 for all comparisons to untreated controls.

PCI-32765 Clinical Experience

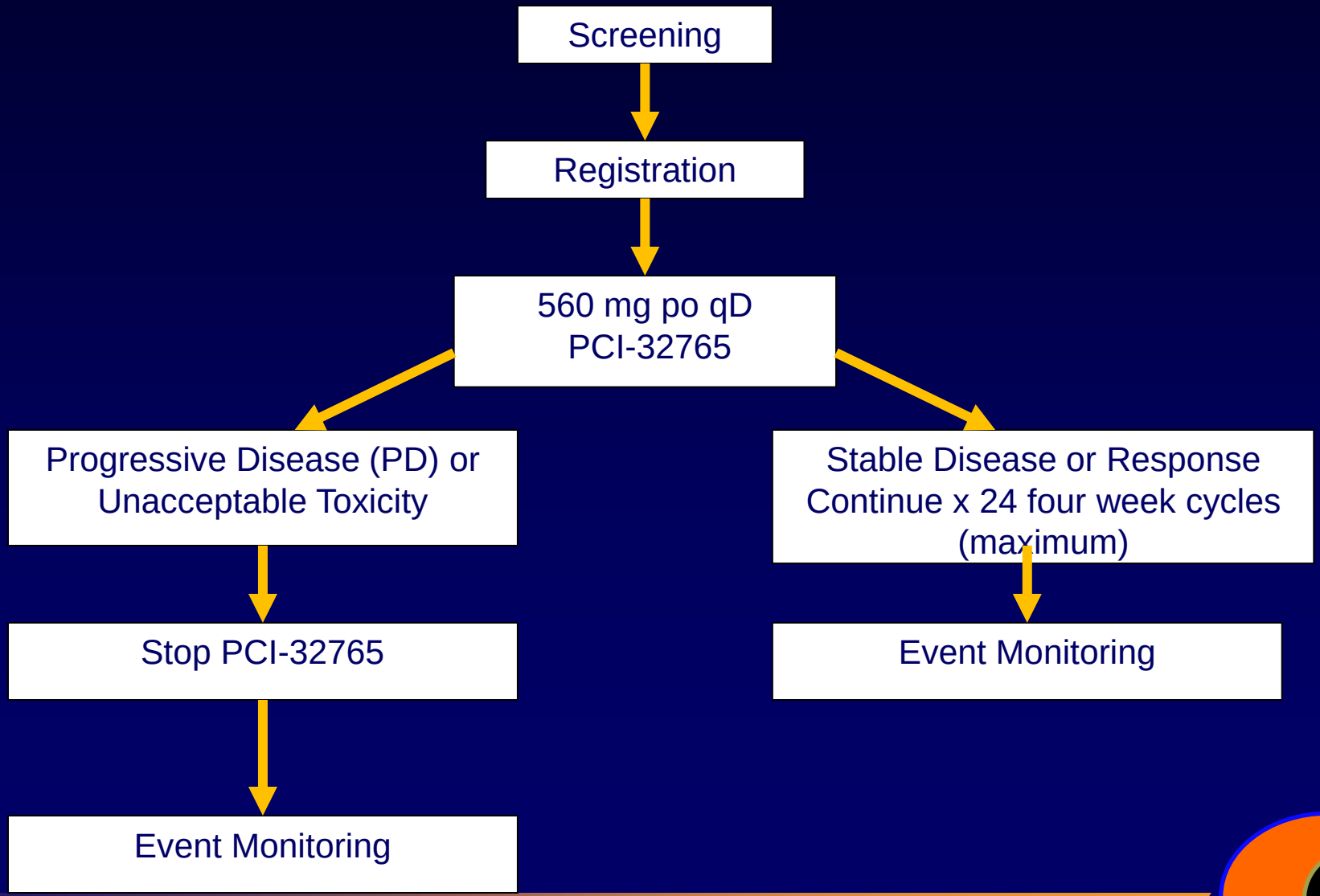
	N	CR	PR	SD	PD	NE	TE TE	ORR % ITT	ORR % Eval
CLL/SLL	16	1	10	2		2	1	69%	85%
FL	16	1	3	5	4	3		25%	31%
MCL	9	3	4	1	1			78%	78%
DLBCL	7		2	1	4			29%	29%
MZL/MLT	4		1	1	1	1		25%	33%
WM	4		2	1			1	50%	67%
TOTAL	56	5	22	11	10	6	2	48%	56%



Most Frequently Observed Toxicities: fatigue, diarrhea, nausea, myalgia, headache, and pneumonia. No apparent hepatic or renal toxicities. No evidence of cumulative hematologic toxicity.

Advani et al. ASCO 2010

PCI 327625 in Relapsed/Refractory WM



WHOLE GENOME SEQUENCING IN WM

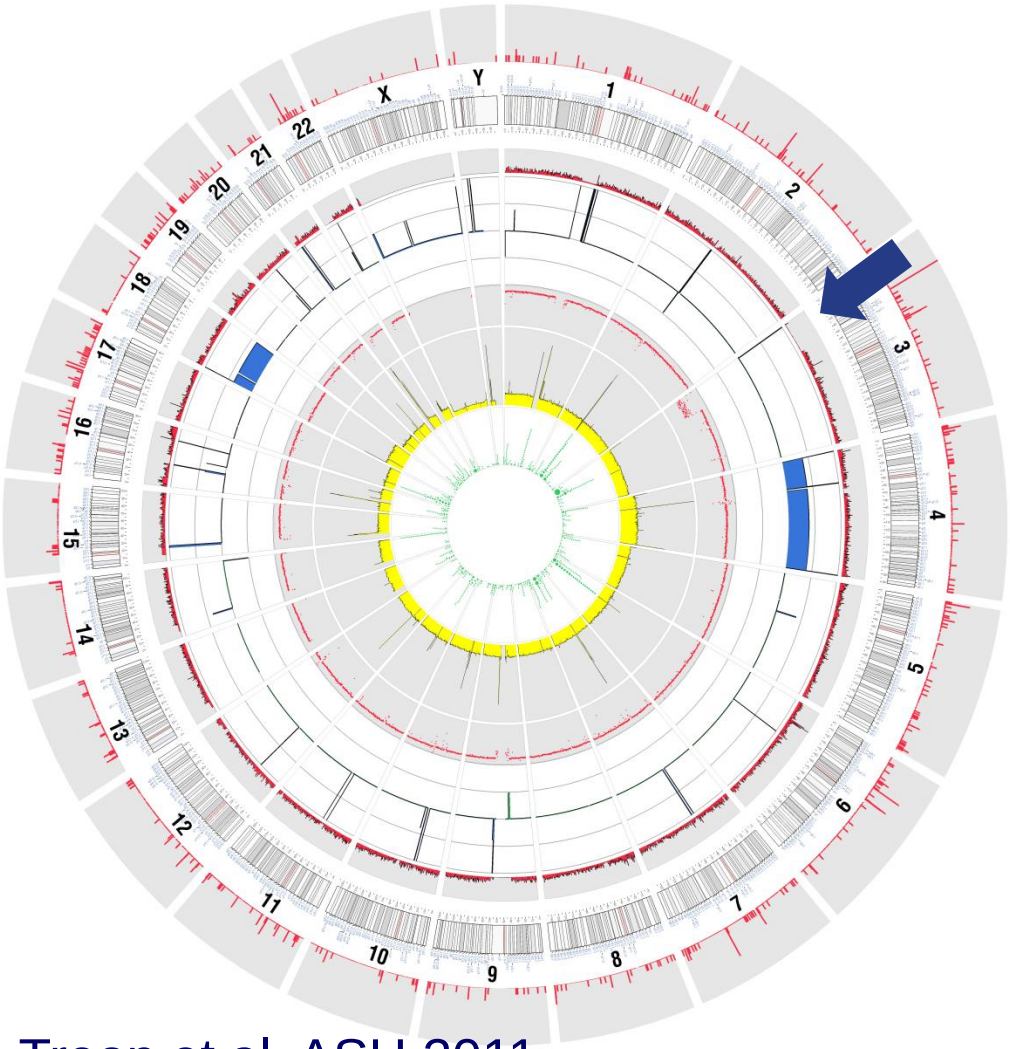
3,000,000,000
DNA molecules

Paired Sequencing
from same individuals

NORMAL ==========

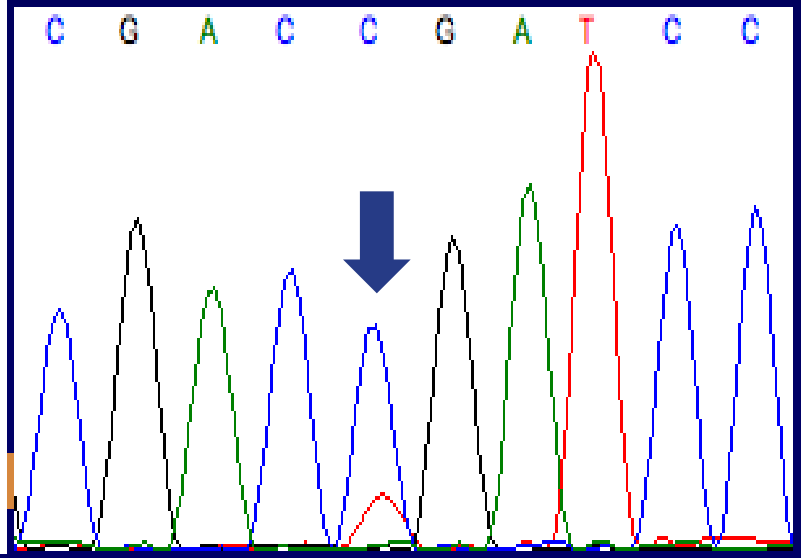
WM ==========*====

Whole Genome Sequencing in 30 patients with WM



Treon et al, ASH 2011.

- *27 of 30 (90%) patients had a somatic mutation in MYD88 (L265P).*
- *Confirmed by Sanger sequencing.*



Sanger sequencing for MYD88 L265P in expanded cohorts of WM, MGUS, MM, and MZL Patients.

	N=	MYD88 L265P	Homozygous (% of L265P pts)
WM	54	49* (90.7%)	5 (10.2%)
IgM MGUS	10	1**(10.0%)[a]	0 (0.0%)
MM	10	0 (0.0%)[b]	0 (0.0%)
MZL	46	3 (6.5%)[c]	0 (0.0%)
Healthy Donors	15	0 (0.0%)[d]	0 (0.0%)

* Identified in both $CD19^+$ and $CD138^+$ selected BM LPC for 14 WM pts.

**Absence confirmed for 7 negative MGUS pts by cloning and sequencing of at least 100 clones. 1 positive patient progressing.

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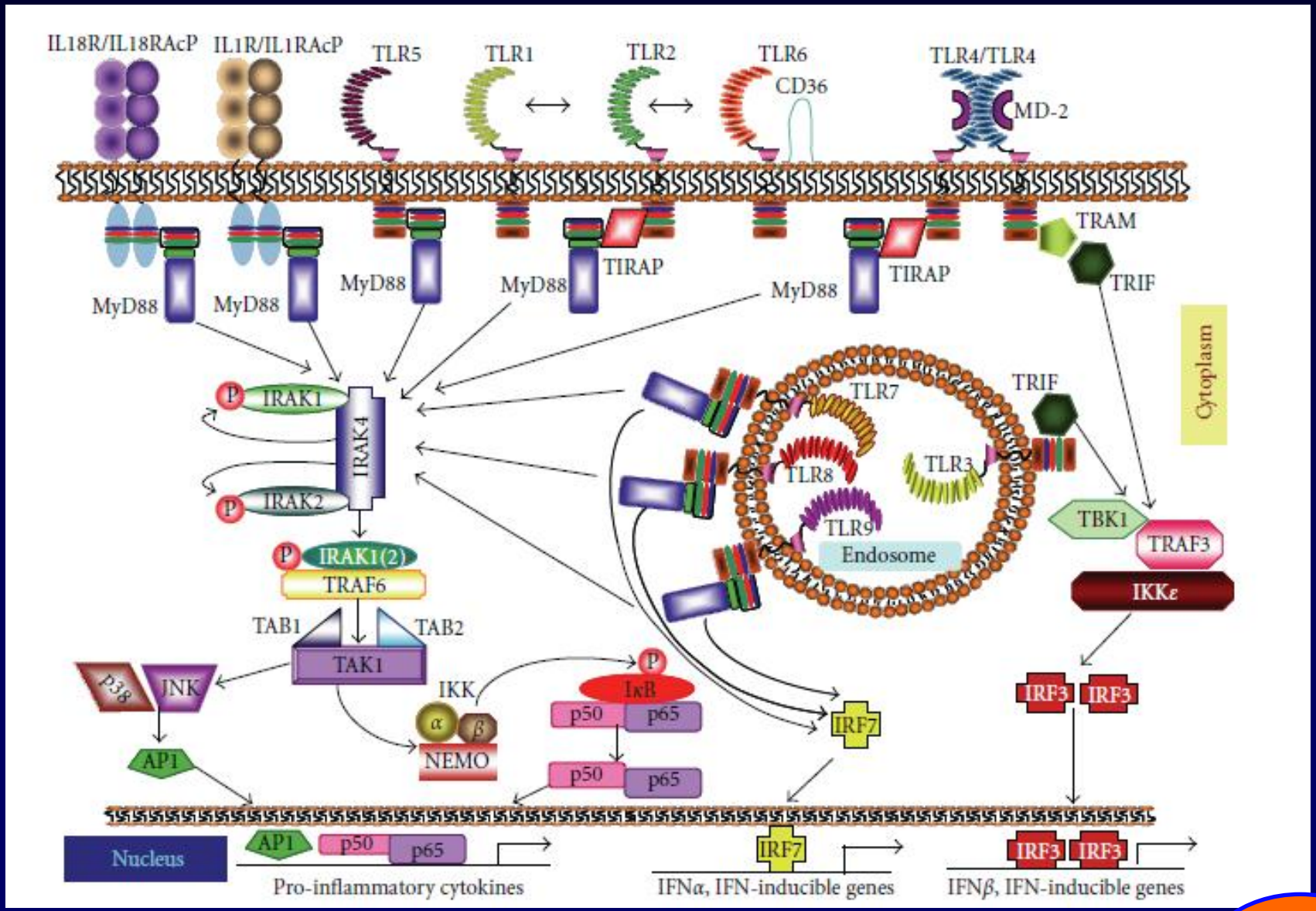
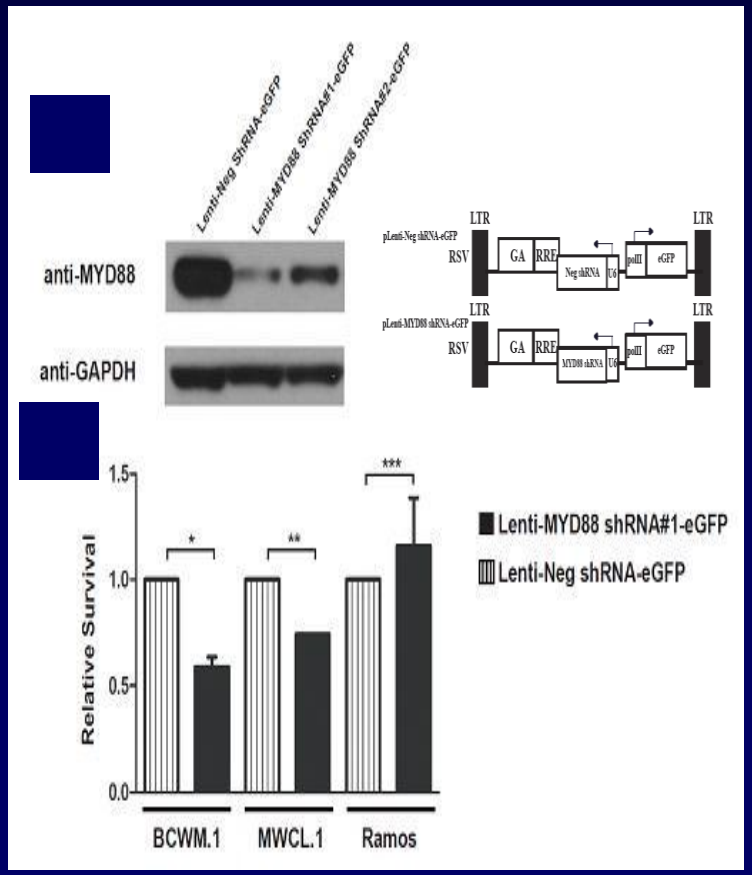
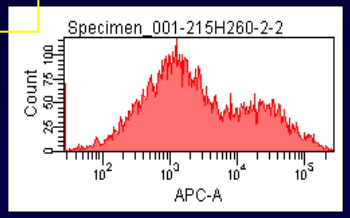
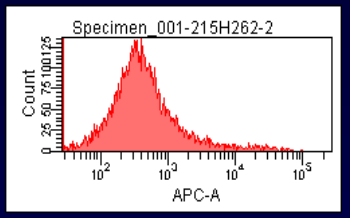
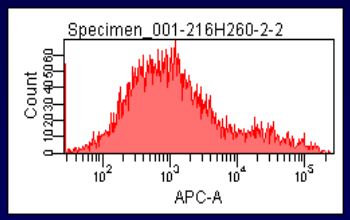
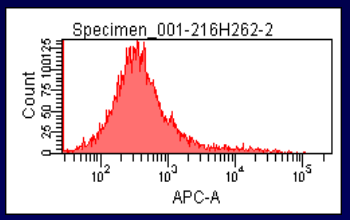
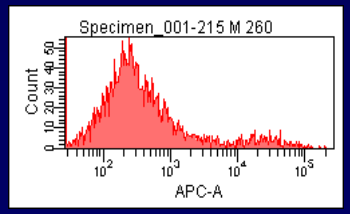
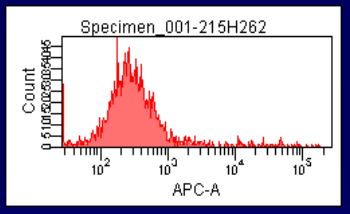
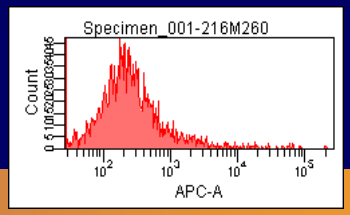
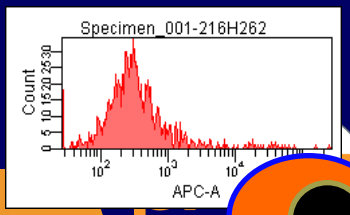

IL18R/IL18RAcP
IL1R/IL1RAcP
TLR5
TLR1
TLR2
TLR6
CD36
TLR4/TLR4
MD-2
TRAM
TRIF
MyD88
MyD88
MyD88
MyD88
MyD88
TIRAP
TIRAP
Cytoplasm
P
IRAK1
IRAK4
P
IRAK2
P
IRAK1(2)
TRAF6
TAB1
TAB2
TAK1
P38
JNK
AP1
IKK
α
β
NEMO
P
IκB
p50
p65
p50
p65
TLR7
TLR8
TLR3
TLR9
Endosome
TRIF
TBK1
TRAF3
IKKε
IRF7
IRF3
IRF3
Nucleus
AP1
p50
p65
Pro-inflammatory cytokines
IRF7
IFNα, IFN-inducible genes
IRF3
IRF3
IFNβ, IFN-inducible genes

Knockdown of MYD88 induces apoptosis in L265P expressing BCWM.1 and MWCL.1 WM cells.

Lentiviral MYD88 Knockdown



Over-expression LentiVector

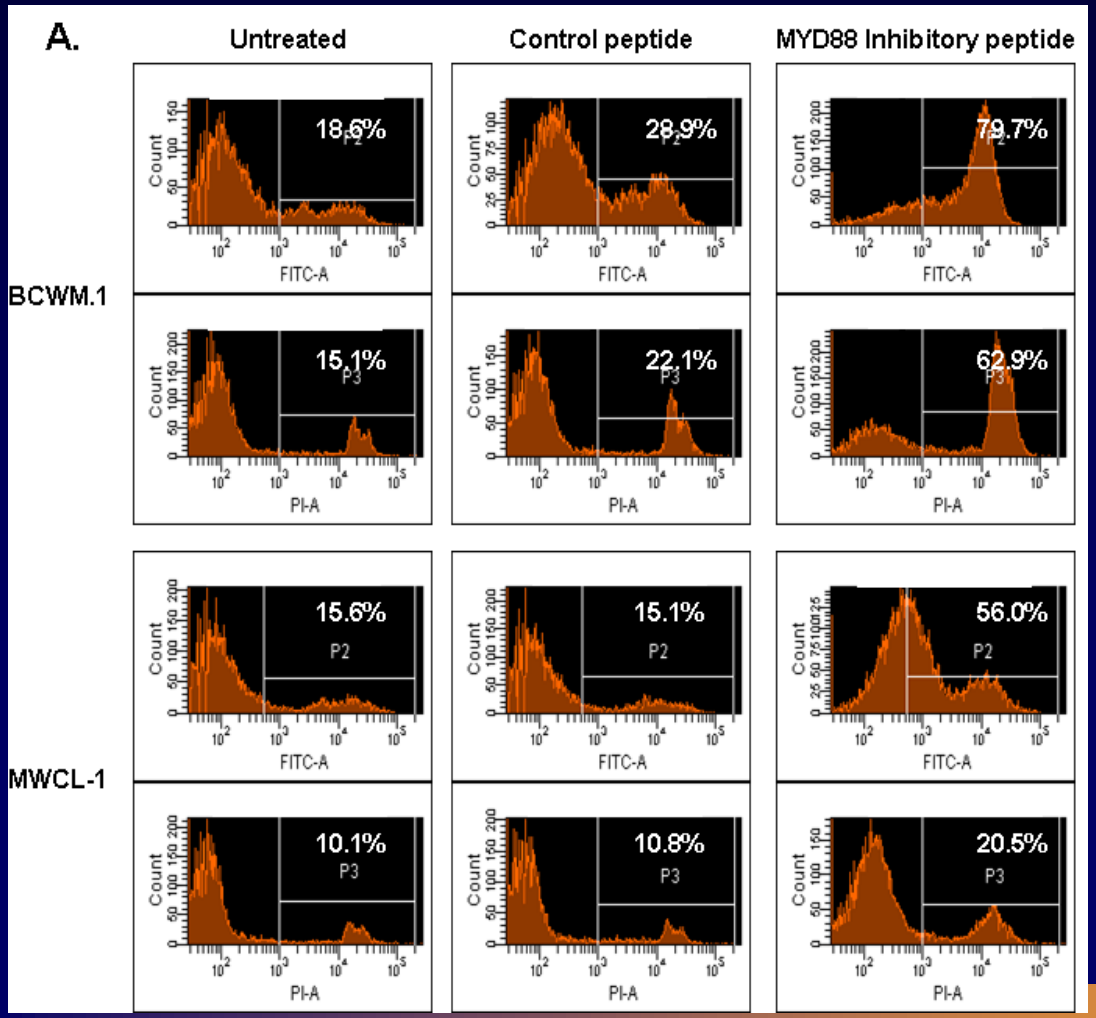
	↓*Myd88*	↓*Scbl Myd88*
	BCWM.1	
MYD88 WT		
MYD88 L265P		
	MWCL.1	
MYD88 WT		
MYD88 L265P		

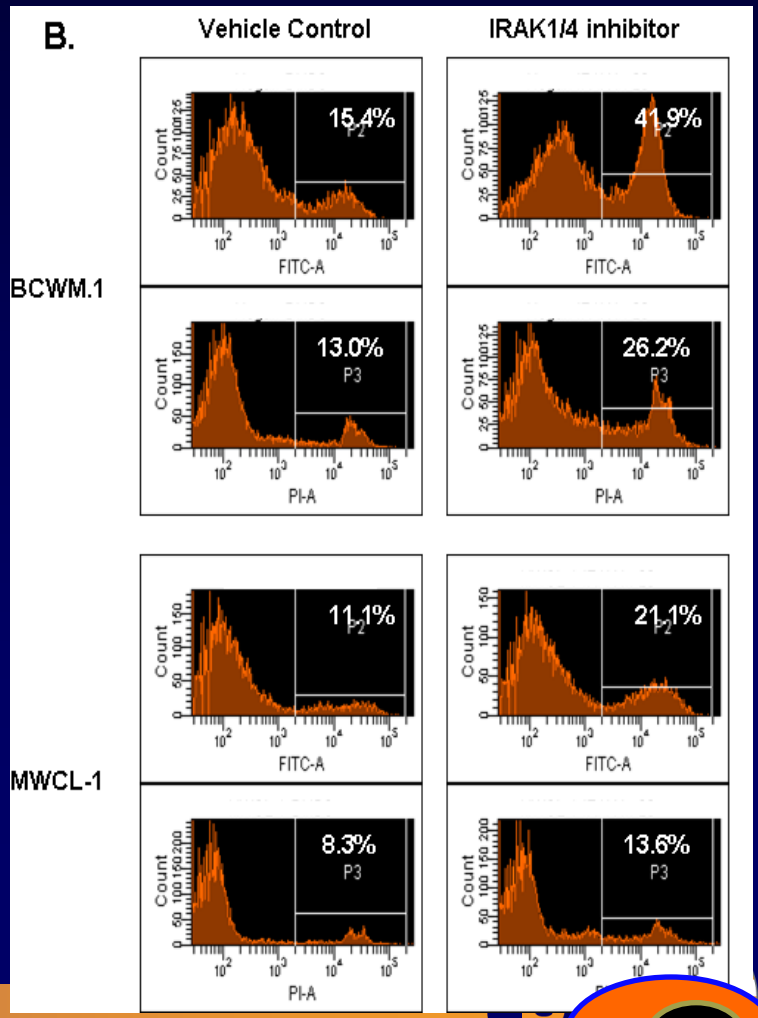
Annexin V Staining

Disruption of MYD88 signaling induces apoptosis of MYD88 L265P expressing WM cells.

MYD88 Homodimer Peptide Inhibitor

IRAK 1/IRAK 4 Kinase Inhibitor





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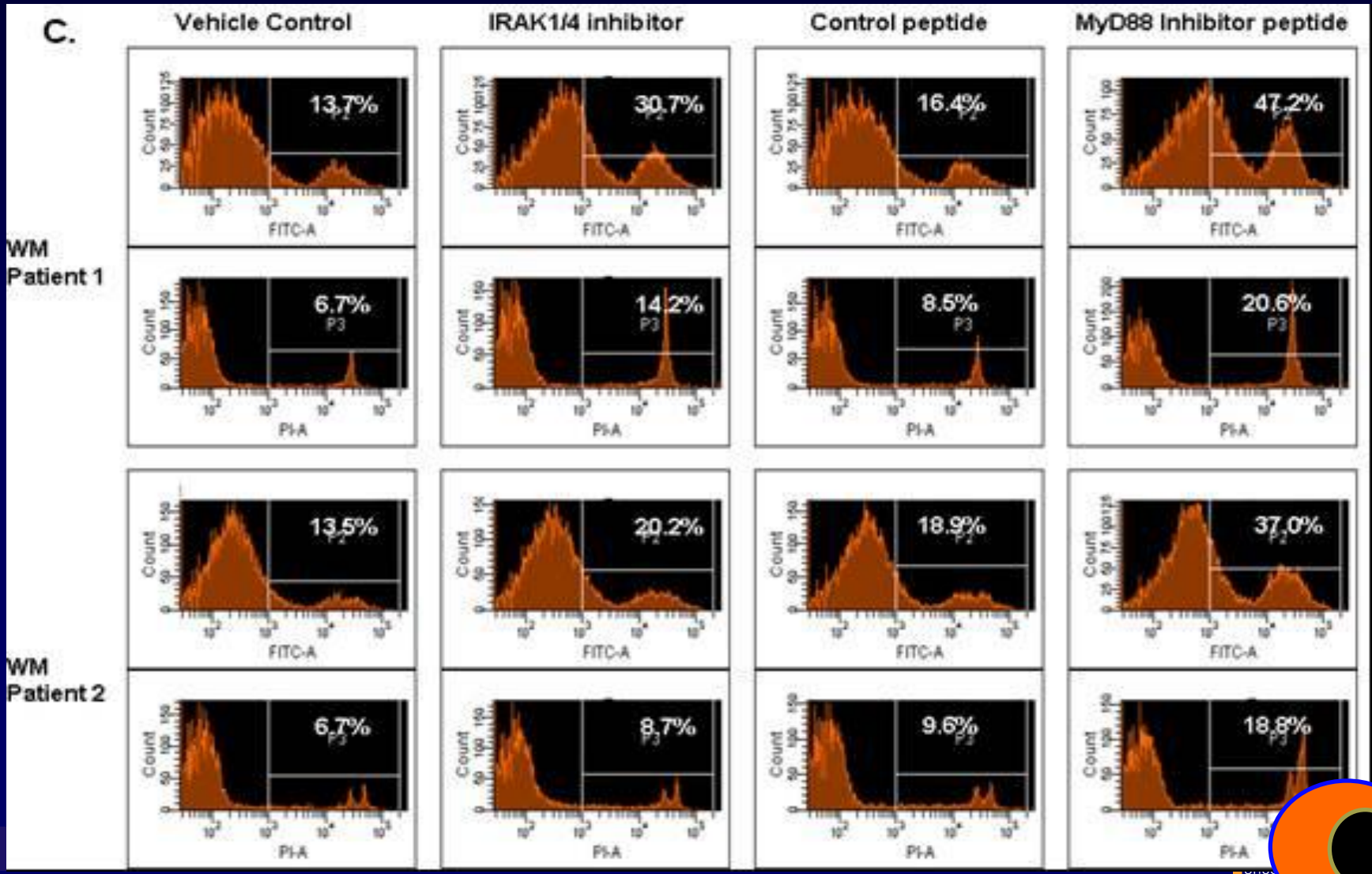
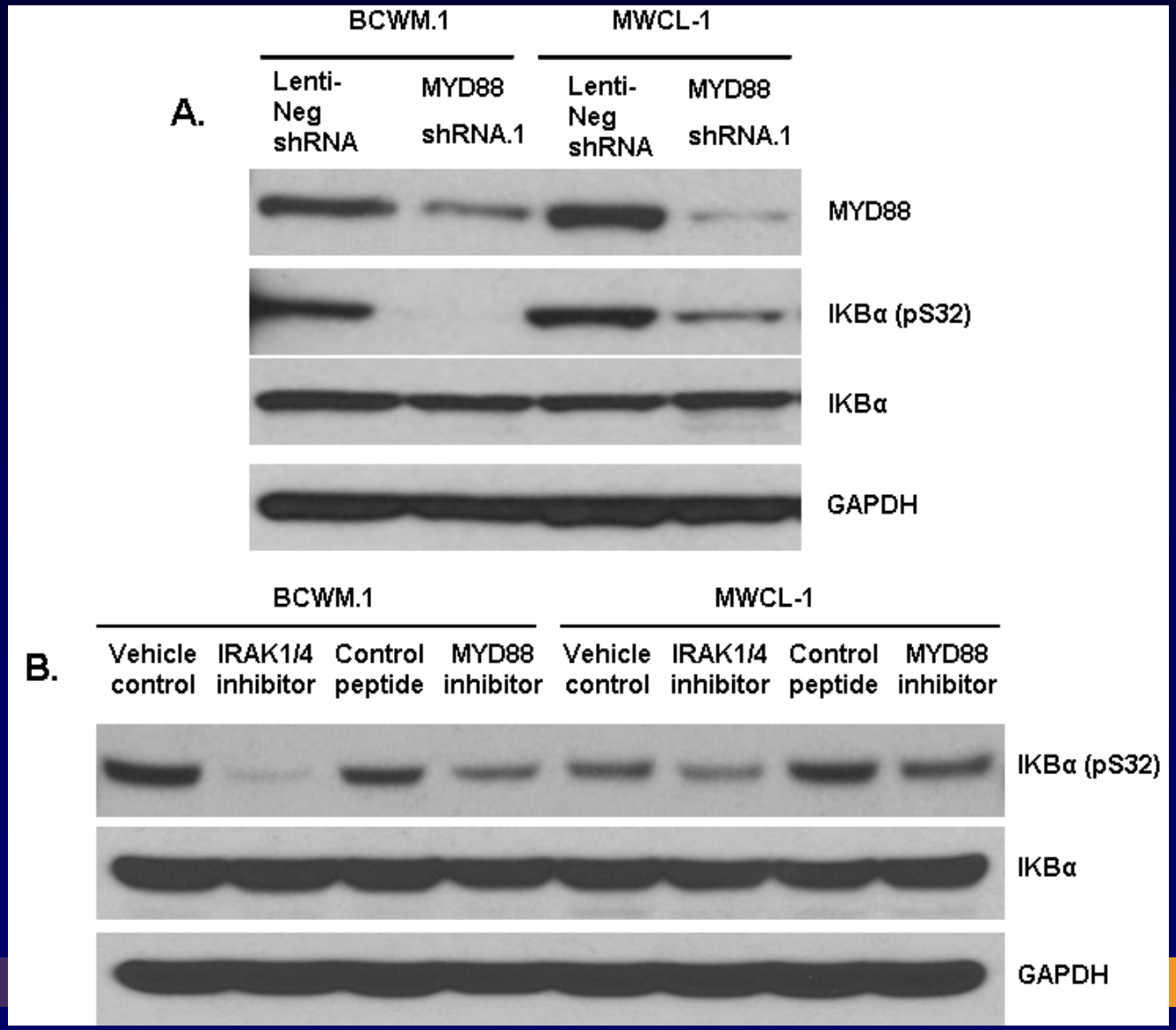
Disruption of MYD88 signaling induces apoptosis of MYD88 L265P expressing patient BM LPC.

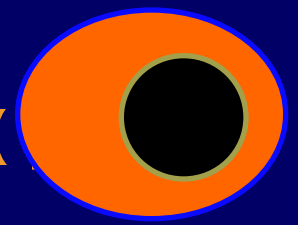


IκBα phosphorylation after knock-down of MYD88 or use of MYD88/IRAK signal inhibitors.



Take Home

- Familial predisposition is common in WM and impacts therapy.
- Bendamustine, bortezomib, cyclophosphamide, and thalidomide–based rituximab therapies are active, and can be used for symptomatic WM.
- Use of nucleoside analogues should be carefully weighed against other options.
- Better categorical responses are associated with improved PFS in rituximab treated patients, and reflect FCGR3A polymorphisms.
- WGS has revealed a somatic mutation in MYD88 in 91% of WM patients and represents a novel target for therapy of WM.



“Do not go where the path may lead, go instead where there is no path and leave a trail”

Ralph Waldo Emerson