NCCN 10th Annual Congress:
Hematologic Malignancies™

Advances in Waldenström's Macroglobulinemia

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Acta Medica Scandinavica. Vol. CXVII, fasc. III—IV, 1944.

Incipient myelomatosis or «essential« hyperglobulinemia with fibrinogenopenia — a new syndrome?

By

JAN WALDENSTRÖM.

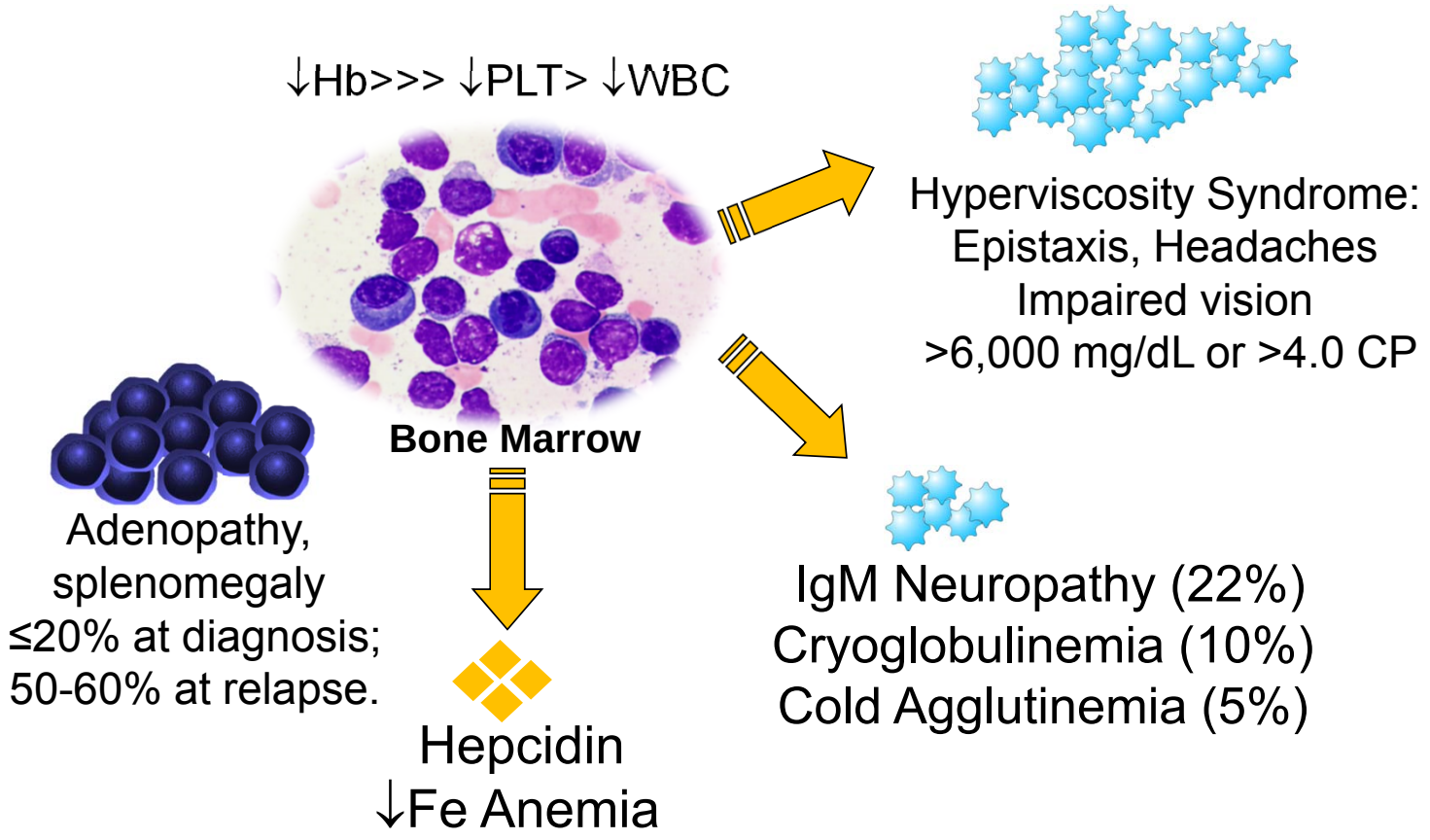
Submitted for publication September 2, 1943.

The real nature of myelomatosis.

The title of this paper may at first seem somewhat surprising. The myeloma has of old had a reputation as a well defined clinical entity. With the aid of the typical changes on the X-ray film and guided by the examination of the cells from a sternal puncture the diagnosis should therefore be easy and there ought not to be found any serious diagnostical troubles. In the following I am going to give a description of two cases, who have several symptoms suggesting myelomatosis but also show decided differences. They are very much alike even as regards details in the chemistry of the blood proteins and it seems probable according to my opinion, that they suffer from the same malady. A third case very much resembles these two patients but also shows other signs, that do not fit in so well with the picture.

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

Clinical Manifestations of WM Disease



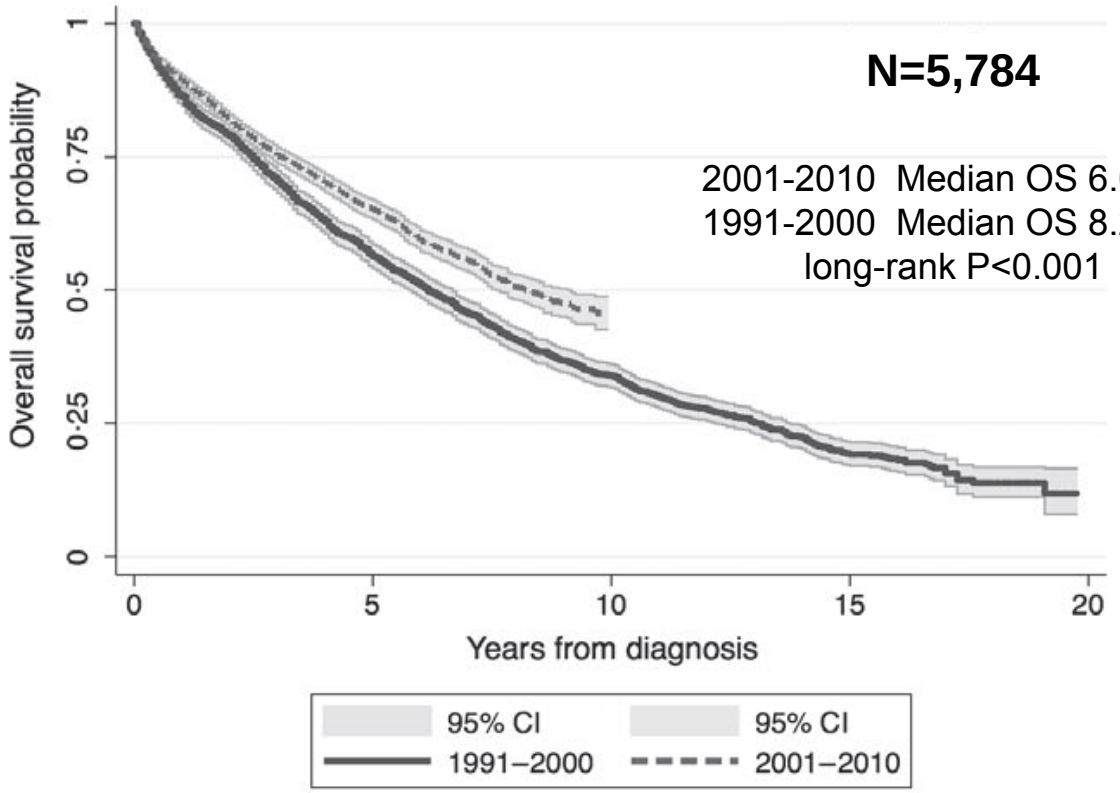
Treon S., Hematol Oncol. 2013; 31:76-80.

Waldenström's Macroglobulinemia: Genetic Predisposition

- Strong familial predisposition (20-25%)
- Ashkenazi Jews (20%)
- Rare in African Americans (<5%)
- IgM MGUS 1.8-2% annual progression rate: 40-90% progress to WM.

Kyle et al, Blood 2003; 102(10): 3759-64; Treon et al, Ann Oncol 2006; 17(3): 488-94; Hanzis et al, Clin Lymph Myeloma 2011; 11(1):88-92.

Overall Survival Trends in WM (SEER)



N=5,784

2001-2010 Median OS 6.0 y
1991-2000 Median OS 8.2 y
long-rank P<0.001

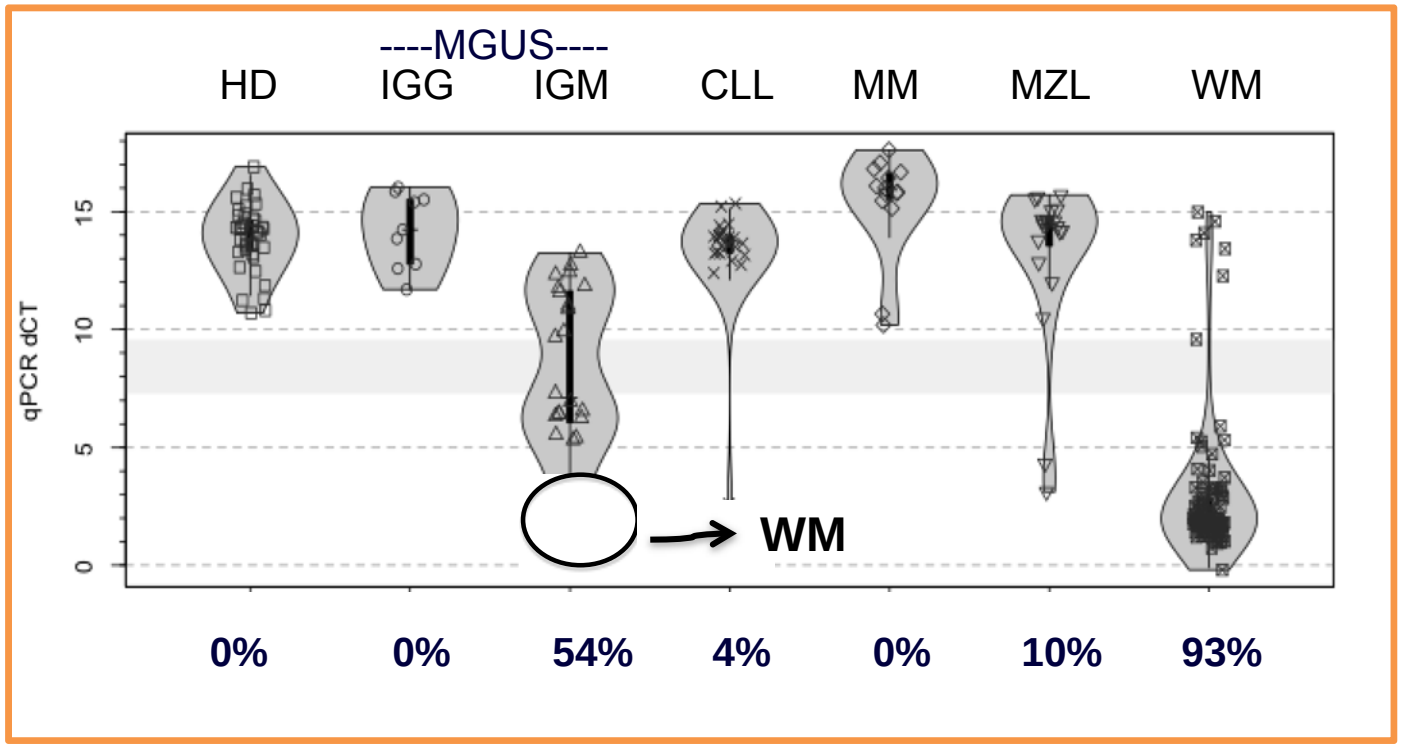
Castillo et al, BJH 2015; 169:81-89.

MYD88 L265P SOMATIC MUTATION IN WM

	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%	

Reviewed in Hematol Oncol Clin North Am. 2014 Oct;28(5):945-70.

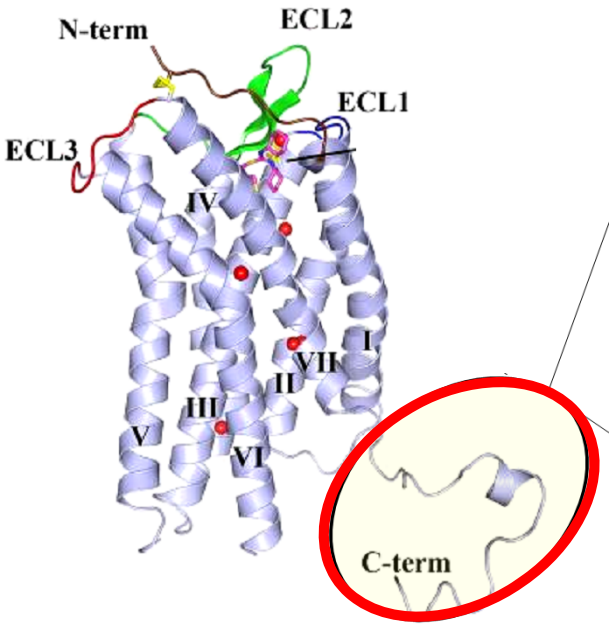
MYD88 L265P by AS-PCR is a useful molecular diagnostic marker for WM.



Xu et al, Blood 2013; 121 (11): 2051-8.

WHIM-like CXCR4 C-tail mutations in WM

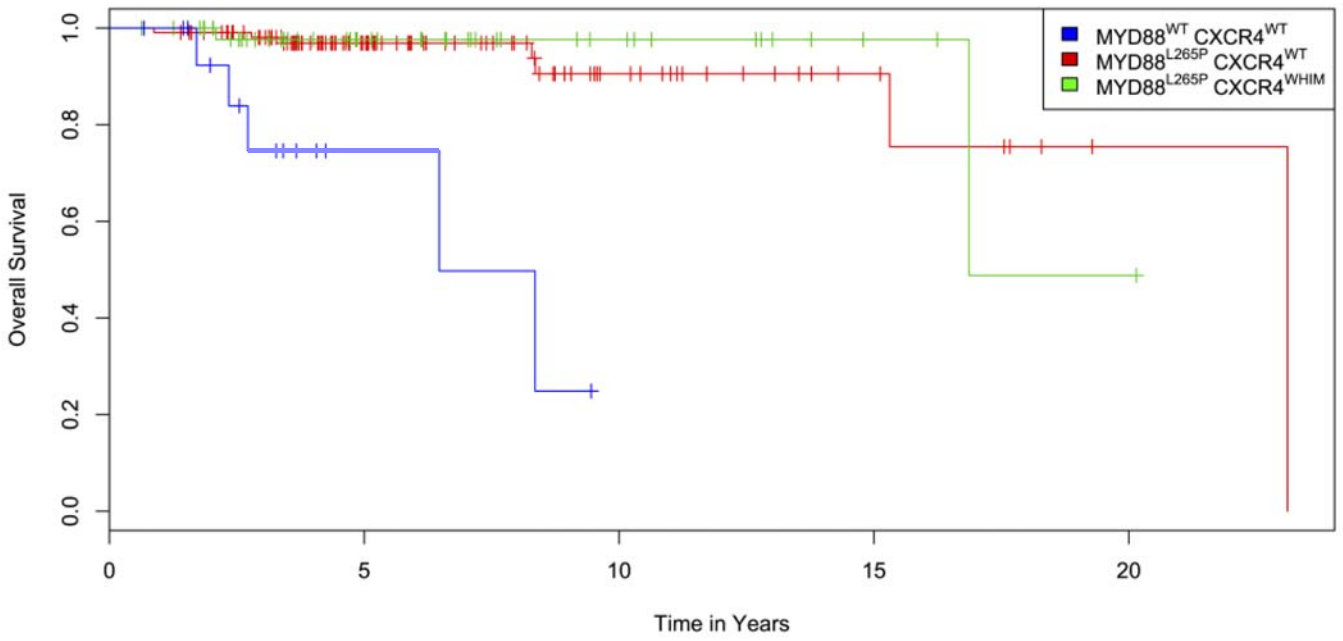
Warts, Hypogammaglobulinemia, Infection, and Myelokathexis.



- CXCR4^{WHIM} Mutations (30-40% of WM patients)
- Almost always associated with MYD88^{L265P}
- > 30 Nonsense and Frameshift Mutations.
- Nonsense mutations associated with higher disease burden, sIGM.

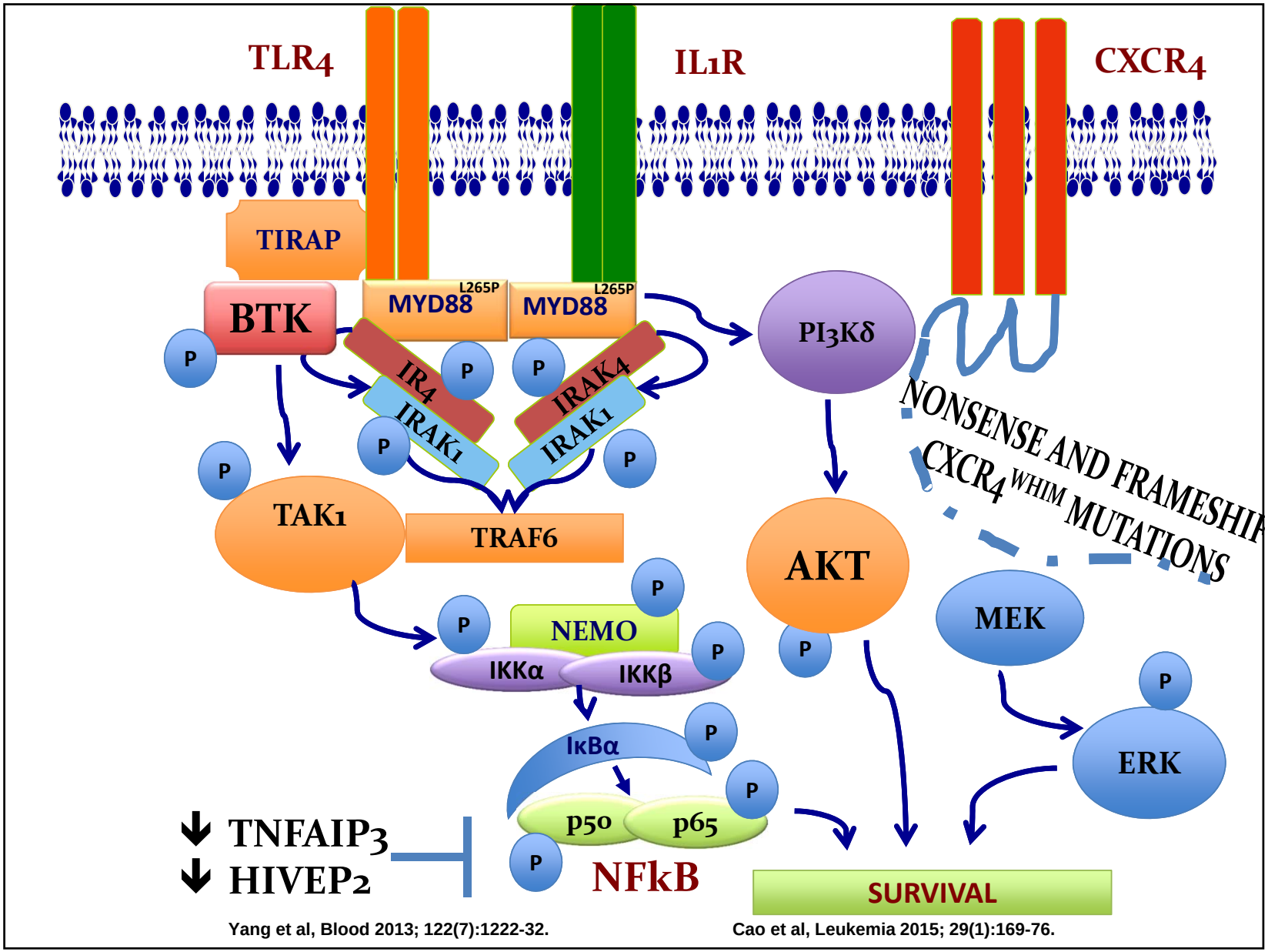
Hunter et al, Blood 2013; Rocarro et al, Blood 2014; Poulain et al, ASH 2014; Schmidt et al, BJH 2014.

Overall Survival is Inferior with MYD88^{WT} Genotype in WM



Adjusted risk of death with MYD88^{WT}
HR 10.54 (95% CI 2.40-46.2; p=0.002).

Treon et al, Blood 2014; 123(18):2791-6.

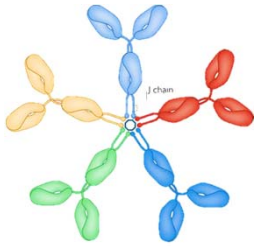


NCCN Guidelines for Initiation of Therapy in WM

- 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

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma (Version 2.2016). © 2015 National Comprehensive Cancer Network, Inc. Available at: NCCN.org.



Plasmapheresis in WM

- Symptomatic hyperviscosity (pre-therapy)
- Severe cryoglobulinemia, cold-agglutinemia (blood warmers)
- Rapidly progressing IgM peripheral neuropathy
- Pre-rituximab in patient with IgM >4,000 mg/dL
- Progressive renal failure due to IgM pathology
- Value unclear in renal failure due to other etiologies

Plasmapheresis should be regarded as a temporary supportive measure, not definitive treatment.

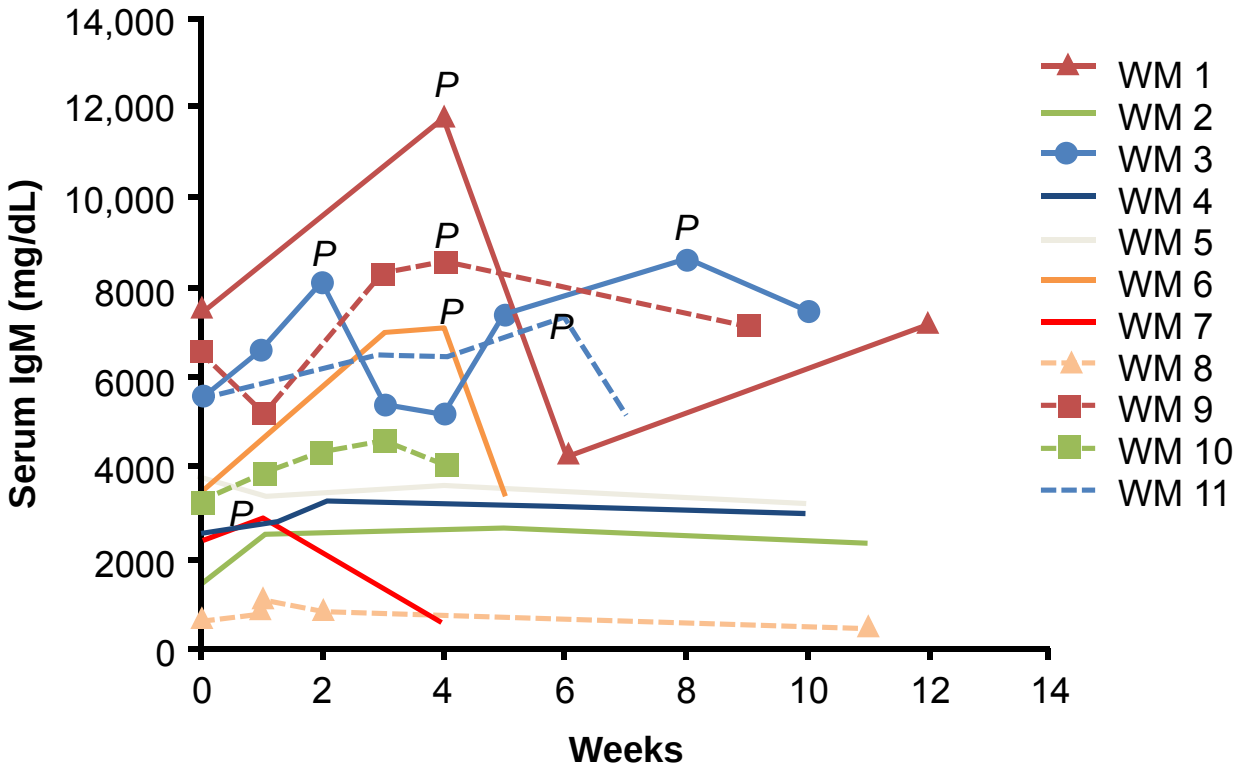
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma (Version 2.2016). © 2015 National Comprehensive Cancer Network, Inc. Available at: NCCN.org.

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%	>42-48
Rituximab/bendamustine	90%	30-40%	69

Reviewed in Dimopoulos et al, Blood 2014; 124(9):1404-11; Treon et al, Blood 2015; 126(6);721-32

Rituximab induced IgM Flare in WM Patients



***P* denotes patient-required plasmapheresis for hyperviscosity.**

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

Post-rituximab IgM flare in WM

	Incidence
Rituximab	40-60%
Rituximab/fludarabine	40%
Rituximab/Cyclophosphamide	30-40%
Rituximab/proteasome inhibitors	10-20%
Rituximab/IMIDS	70-80%

- **IgM flare >25% increase sIGM**

Reviewed in Treon et al, Blood 2015; 126(6);721-32

Clinical Sequelae of Rituximab IgM Flare

- Symptomatic hyperviscosity possible in patients with high serum IgM (>4,000 mg/dL).
- IgM Neuropathy, Cryoglobulins, Cold Agglutinins: Rituximab can potentiate symptoms. Consider PP.
- Patients with IGM> 4,000 mg/dL or Symptomatic HV: Avoid Rituximab until IgM in "safe range" either by plasmapheresis or chemotherapy without rituximab.

Anderson et al, JNCCN 2012; 10(10):1211-9.

Intolerance to Rituximab

- Observed in about 10-15% of WM patients
- Occurs late in induction or during maintenance treatment
- Does not indicate response failure
- Refractory to steroid, H2 blocker pre-therapy
- Hypotension, rigors, flushing, throat closure, urticaria among more common symptoms.
- Switchover to ofatumumab (fully human) is tolerated in 80% of rituximab intolerant patients.
- Test dose (300 mg) of ofatumumab recommended.

Kanan et al, Blood 2014; 124(21): Abstract 2610

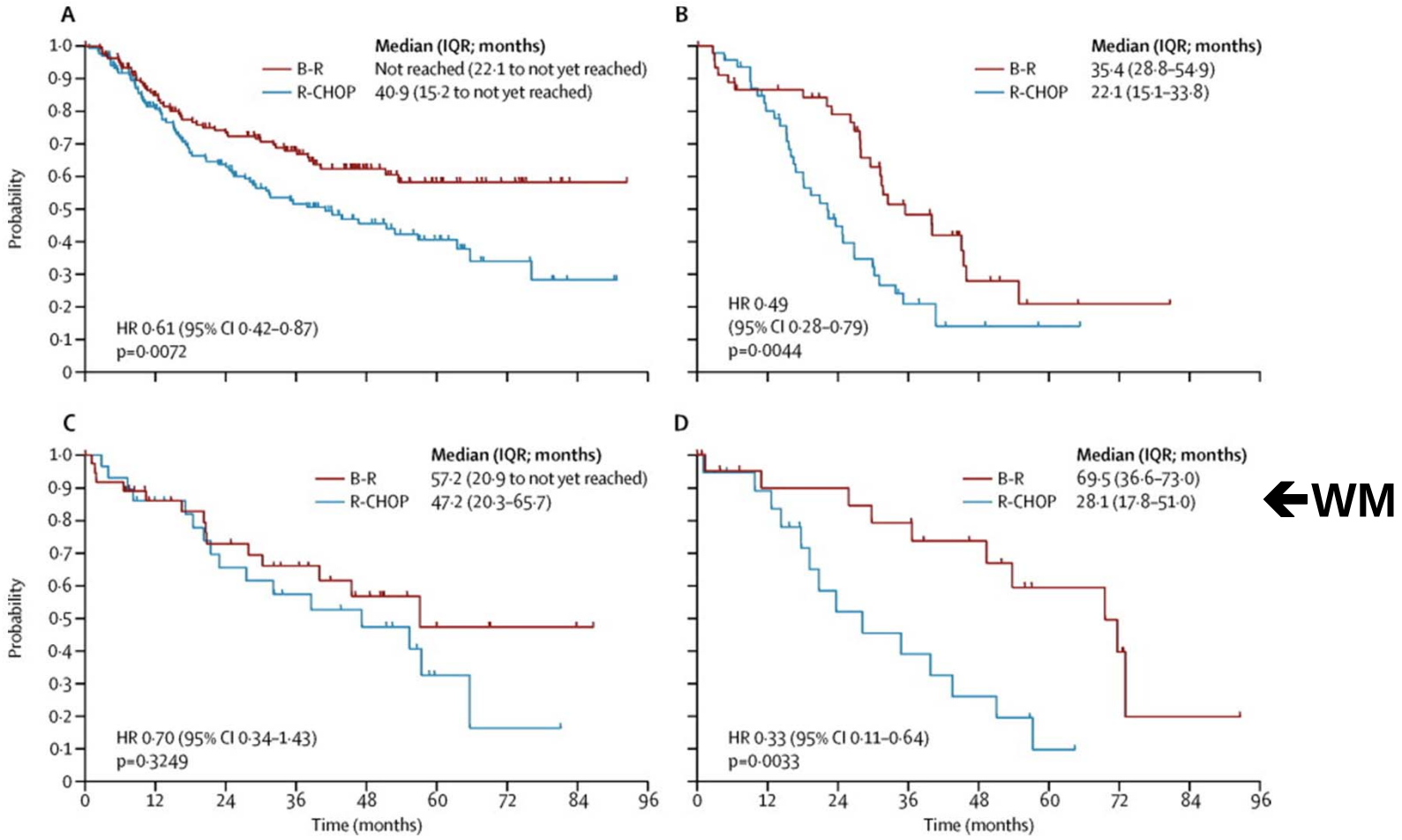
NCCN Guidelines® Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma (Version 2.2016).

Cyclophosphamide-Based Therapy

- Can be given as CHOP-R; CVP-R; CPR; CDR.
- Doxorubicin and vincristine may be dispensed since they do not appear to impact response rates or PFS.
- Lower risk of neutropenia and neuropathy with CDR.
- ORR to CDR is 83%; Major RR 74%.
- Median PFS is 3 years. (Without maintenance)
- SC collection preserved. Long-term toxicity risks modest.

Dimopoulos MA, et al. J Clin Oncol. 2007;25(22):3344-3349. Buske C, et al. Leukemia. 2009;23(1):152-161. Ioakimidis L, et al. Clin Lymphoma Myeloma. 2009;9(1):62-66.

Bendamustine-R vs. CHOP-R: Subset Analysis



←WM

Rummel et al, Lancet. 2013 Apr 6;381(9873):1203-10.

Nucleoside Analogues in WM

- Similar outcomes with fludarabine or cladribine
- Risk of Transformation or MDS/AML is 10-15%
- Stem cell collection impacted by nucleoside analogues; avoid in ASCT candidates
- Consider Impact on future therapy (Bendamustine)
- Fewer courses/reduced dose frequency in elderly

Treon et al, Blood 2008; 113(16):3673-8; Leleu et al, JCO 2009; 27(2): 250-5; Thomas et al, Proc. 5th International Workshop on WM 2008; Treon et al, Clin Lymphoma 2011; 11(1):133-5.

Proteasome Inhibitors in Frontline WM

	REGIMEN	ORR	Major RR	PFS
CHEN ET AL	BORT	78%	44%	16 MOS
GHOBRIAL ET AL	VR	88%	66%	75% PFS AT 1 YR
TREON ET AL	BDR	96%	83%	>48 MOS
DIMOPOULOS ET AL	BORT→BDR	85%	68%	42 MOS
TREON ET AL	CaRD	87%	68%	>16 MOS

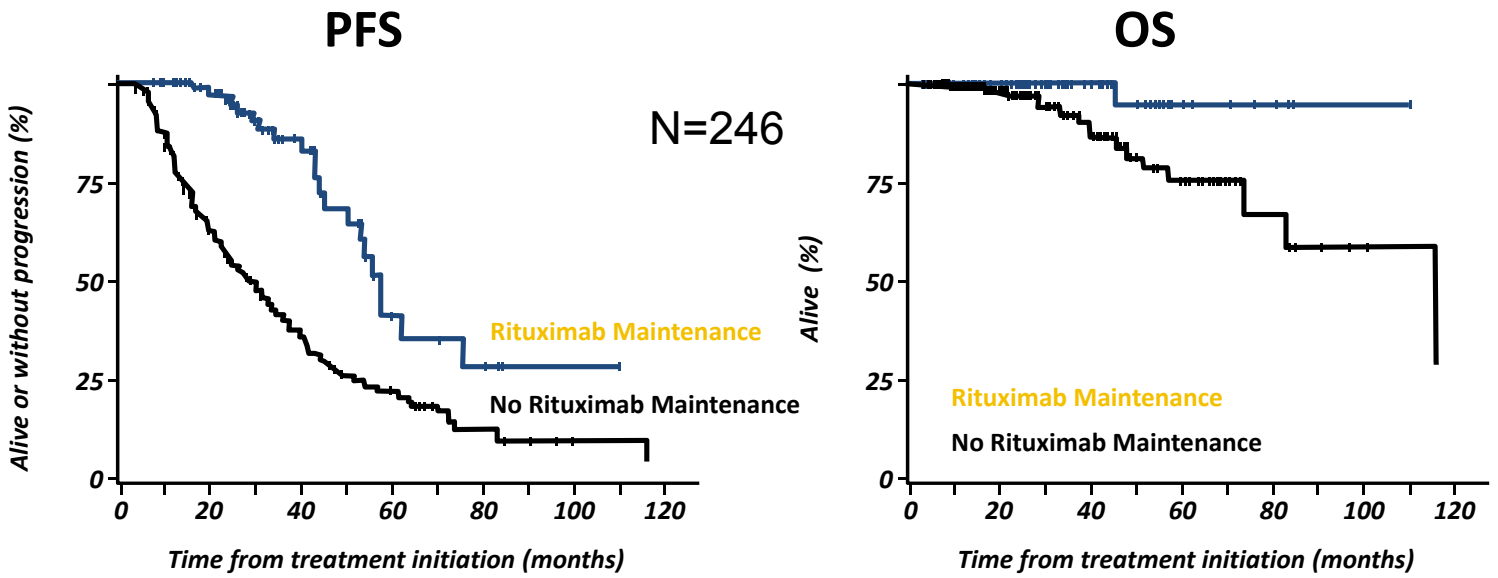
Chen et al, JCO 2007; 25(12): 1570-5; Ghobrial et al, AJH 2010; 85(9): 670-4; Treon et al, JCO 2009; 27(23):3830-5 Dimopoulos et al, Blood 2013; 122(19):3276-82; Treon et al, Blood 2014; 124(4):503-10.

PI-Related Peripheral Neuropathy

	GRADE 1,2	GRADE ≥3	PI-DISCONTINUED
2X WEEK BORT	40-70%	20-30%*	20-30%
1X WEEK BORT	20-40%	5-20%	10-20%
CaRD	20%	0%	0%

Chen et al, JCO 2007; 25(12): 1570-5; Treon et al, CCR 2007; 13(11): 3320-5; JCO 2009; 27(23): 3830-5; Ghobrial, JCO 2010; 28(8):1422-8; AJH 2010; 85(9): 670-4; Agathocleous et al, BJH 2010; 151(4): 346-53; Dimopoulos et al, Blood 2013. 122(19):3276-82.

Observation vs. maintenance rituximab therapy in WM patients.



	Observation	Maintenance	p=
Median PFS	28.6 months	56.3 months	0.0001

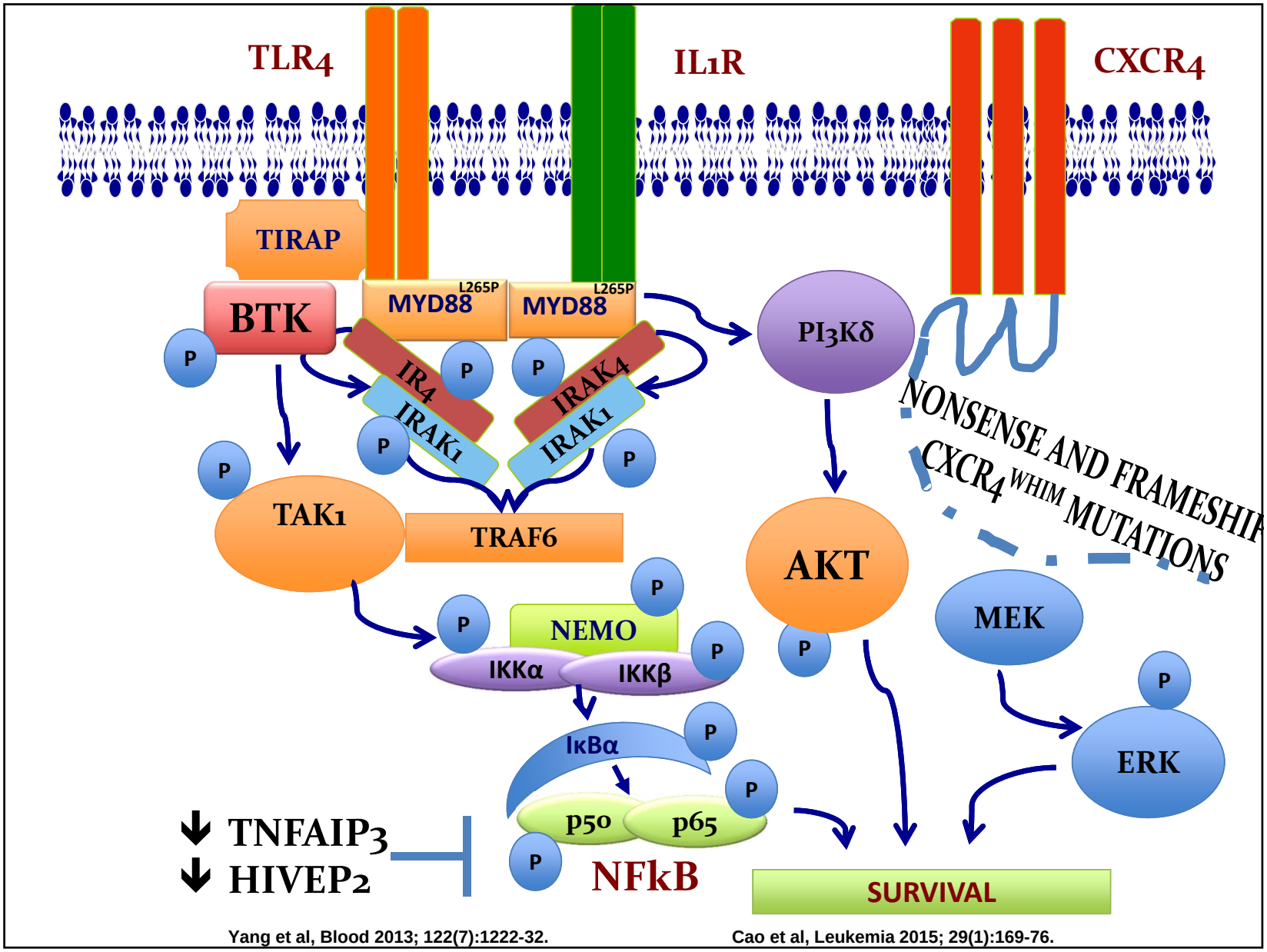
	Observation	Maintenance	p=
Median OS	116 months	>120 months	0.0095

Treon et al, BJH 2011;154(3):357-362.

Hypogammaglobulinemia in WM

- Most WM patients have IgA and IgG hypogammaglobulinemia at baseline
- IgA and IgG decline with B-cell depleting therapies including rituximab
- Recurring sinobronchial infections can result when sIgG <300 mg/dL
- Rituximab maintenance should be stopped
- IVIG should be considered in patients with recurring infections.

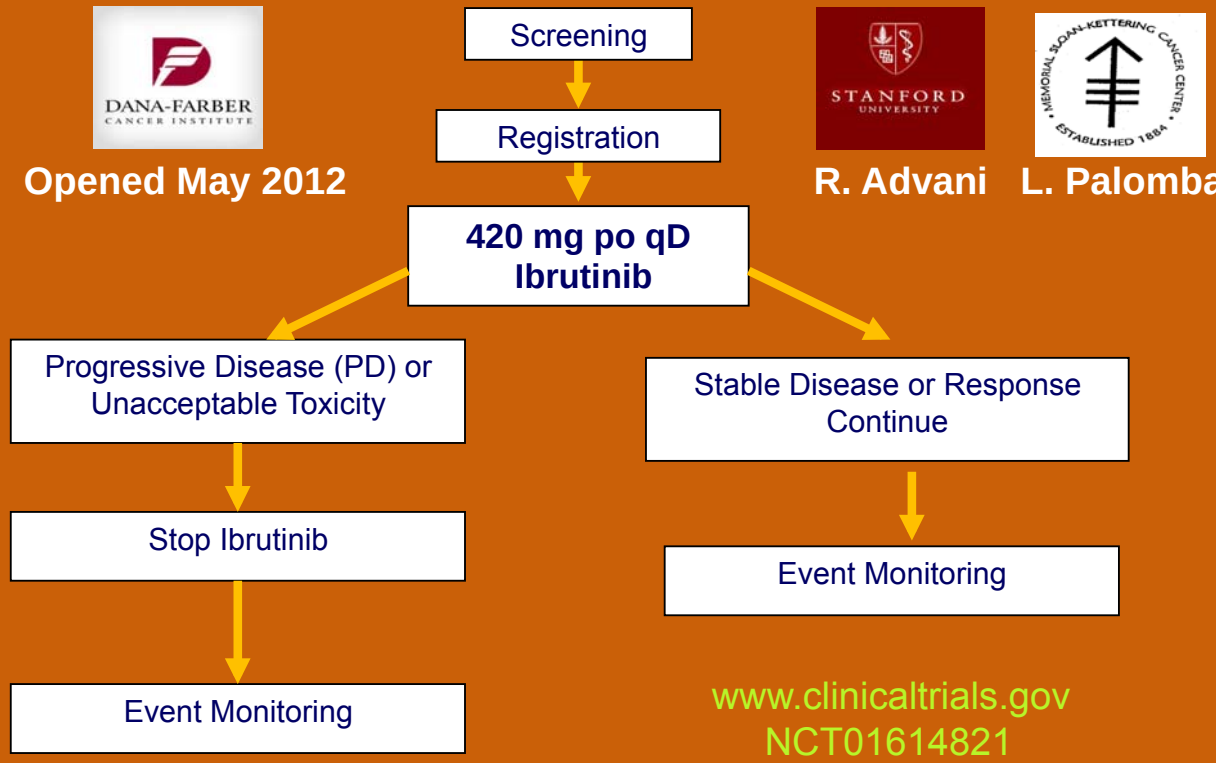
Hunter et al, Haematologica 2010; 95(3):470-5; Treon et al, Blood 2015 (Epub Online).



Yang et al, Blood 2013; 122(7):1222-32.

Cao et al, Leukemia 2015; 29(1):169-76.

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



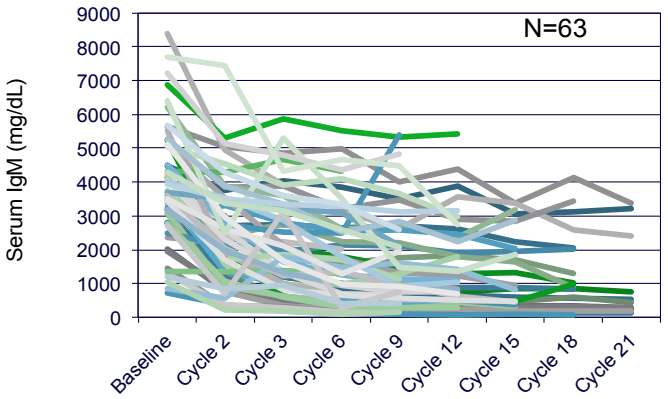
Opened May 2012

R. Advani **L. Palomba**

www.clinicaltrials.gov
NCT01614821

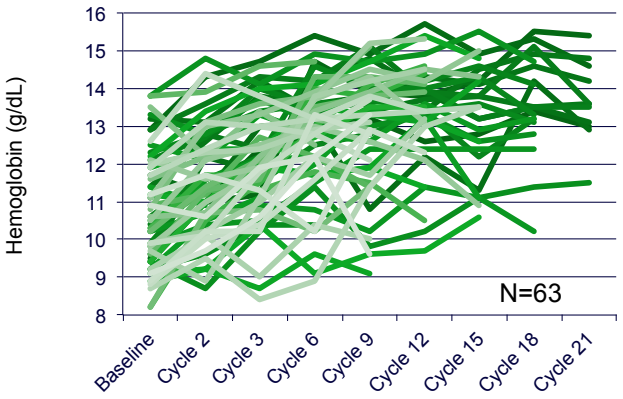
Serum IgM and Hb Levels Following Ibrutinib

Serum IgM



Best IgM Response:
3,520 to 880 mg/dL; p<0.001

Hb



Best Hemoglobin Response:
10.5 to 13.8; p<0.001

Treon et al, N Engl J Med. 2015; 372(15):1430-40.

Best Clinical Responses to Ibrutinib

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

ORR: 91% Major RR (≥ PR): 73%

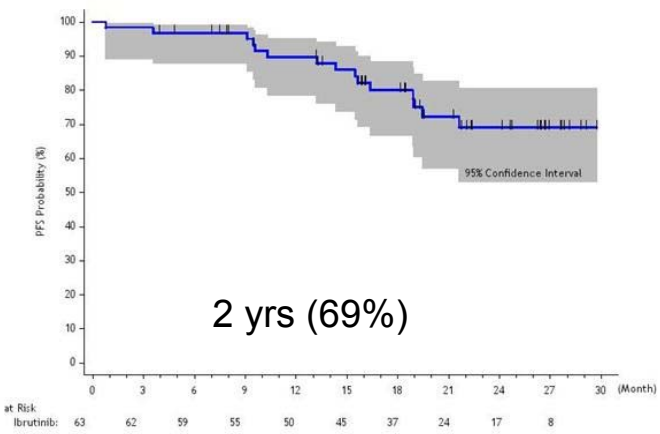
	(N=)	(%)
VGPR	10	16
PR	36	57
MR	11	17

Median time to ≥ MR: 4 weeks
Median time to ≥ PR or better: 8 weeks

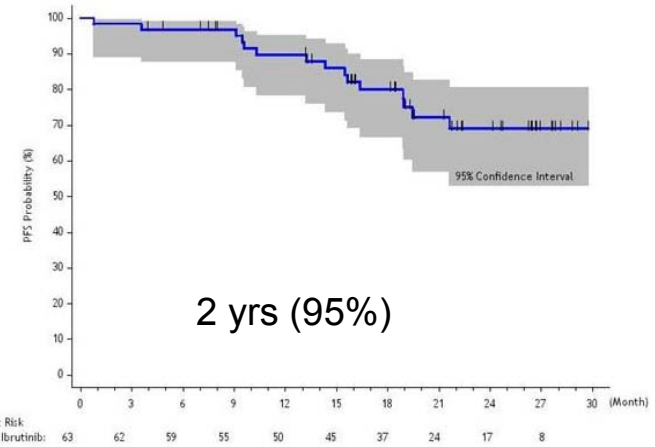
Treon et al, N Engl J Med. 2015; 372(15):1430-40.

Progression-free and overall survival for 63 previously WM patients treated with ibrutinib.

PFS



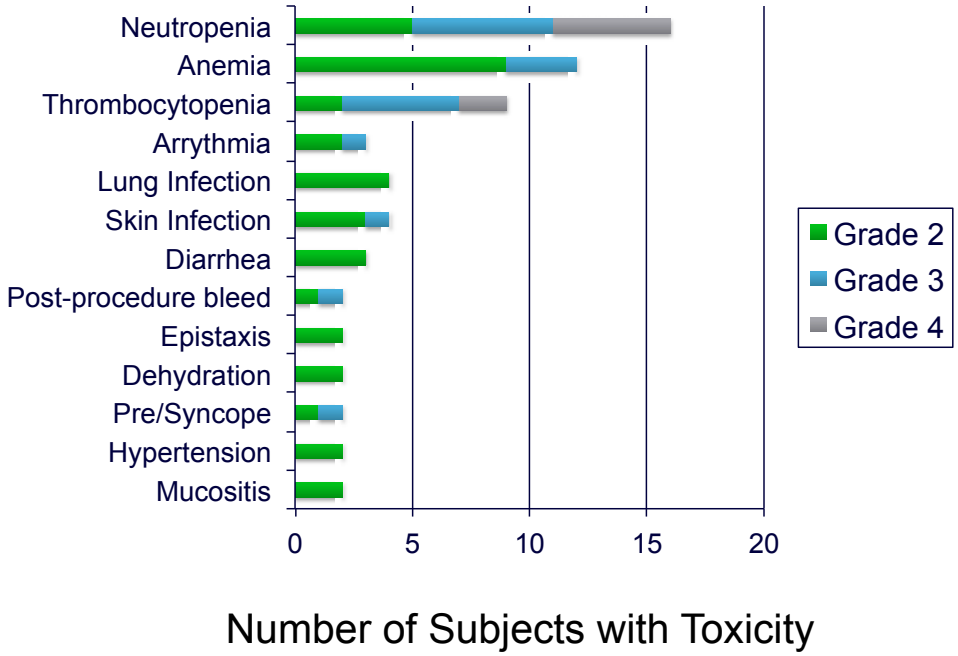
OS



Treon et al, N Engl J Med. 2015; 372(15):1430-40.

Ibrutinib Related Adverse Events in previously treated WM patients

Toxicities >1 patient; N=63



Treon et al, N Engl J Med. 2015; 372(15):1430-40.

FDA News Release
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
July 8, 2015

Responses to ibrutinib are impacted by MYD88 and CXCR4 mutation status.

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

Summary

- MYD88 and CXCR4 mutations are highly prevalent in WM
- Asymptomatic patients, not meeting consensus criteria for treatment, should be observed closely
- Treatment options for symptomatic patients include rituximab alone, or in combination with alkylators, nucleoside analogues, proteasome inhibitors, and ibrutinib.
- Rituximab induced IgM flares are common, and can promote hyperviscosity crisis or potentiate IgM related morbidity in WM.
- Ibrutinib responses are impacted by MYD88 and CXCR4 mutation status.

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