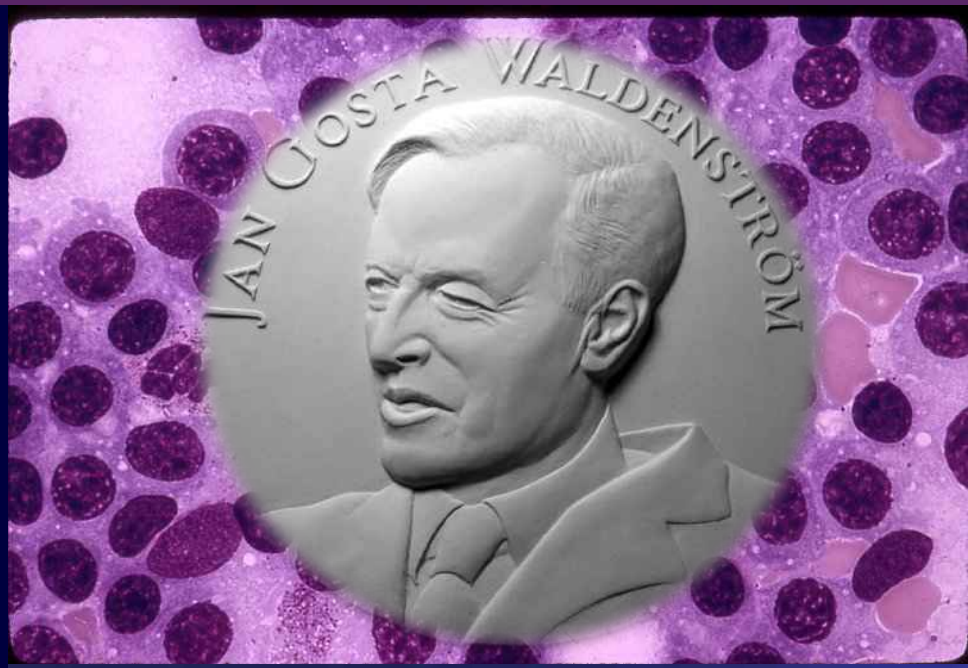
Waldenstrom's Macroglobulinemia: Advances in the Biology and Therapy.

Steven P. Treon, MD, MA, PhD

Director, Bing Center for Waldenstrom's Macroglobulinemia
Dana Farber Cancer Institute
Harvard Medical School



Closing Ceremonies, 2nd International Workshop on WM-Athens, 2002.


THE SECOND INTERNATIONAL
WORKSHOP ON
WALDENSTRÖM'S MACROGLOBULINEM
ENS 2002

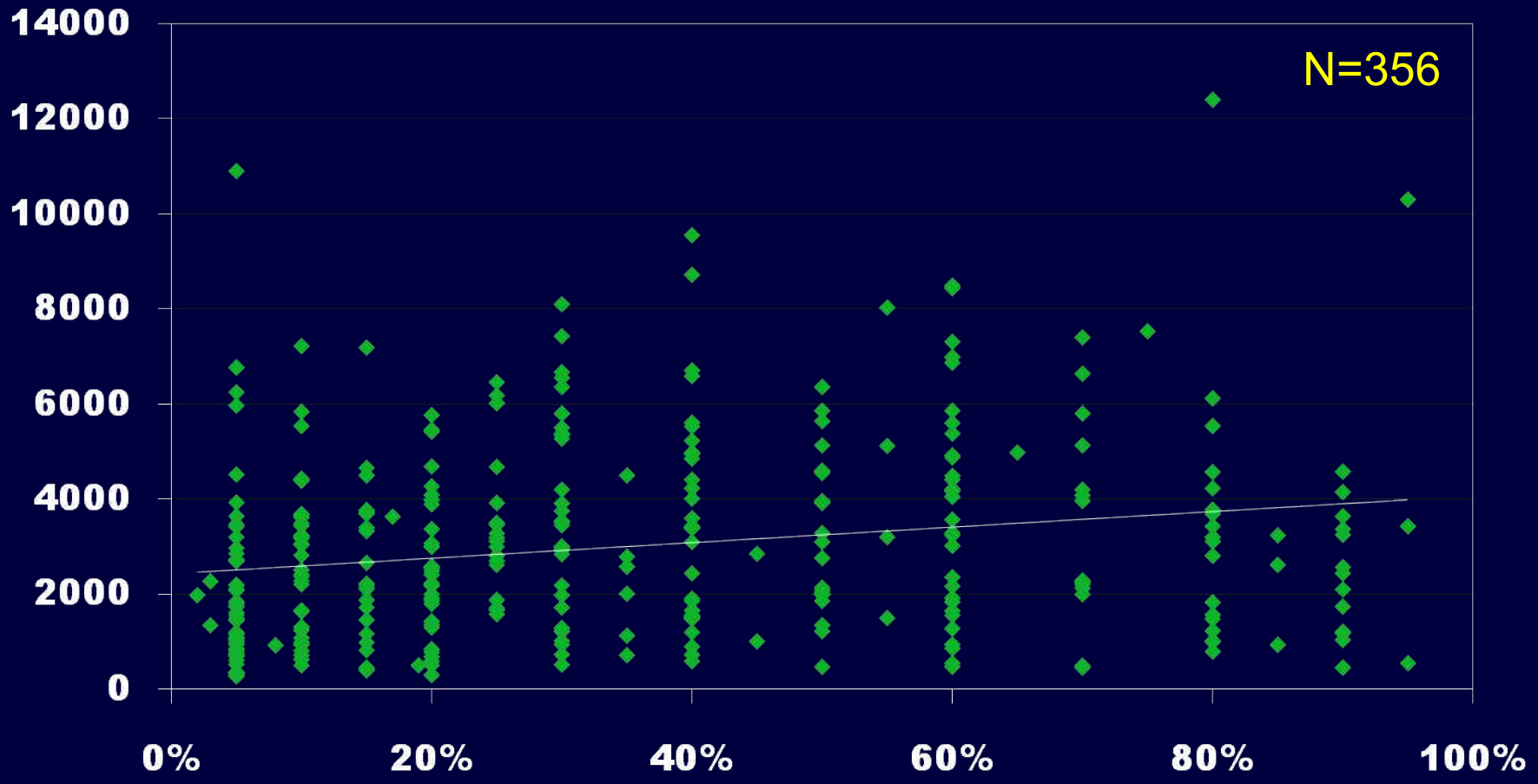
Clinicopathological definition of WM

- Pathological diagnosis of lymphoplasmacytic lymphoma using REAL/WHO criteria.
- Presence of a monoclonal IgM protein, irrespective of serum level;

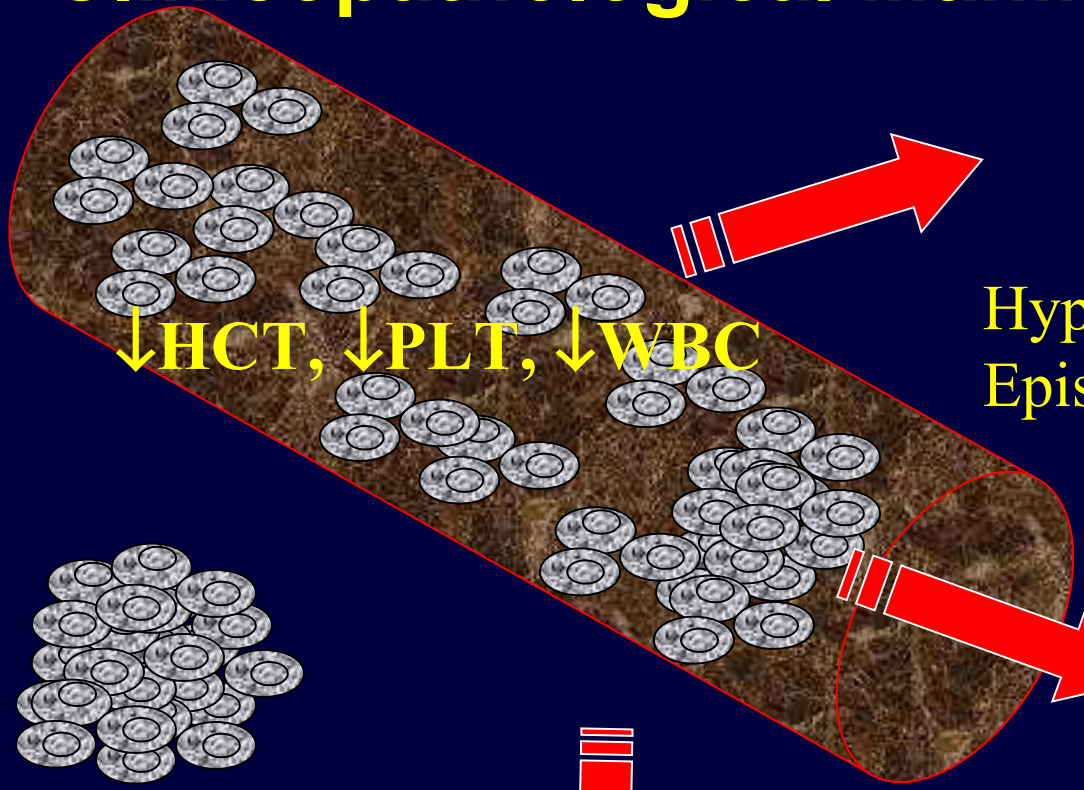
Owen et al, Semin Oncol 2003

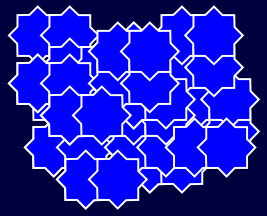
IWWM2, ATHENS 2002

Comparison of Serum IgM and Bone Marrow Involvement in WM



Clinicopathological Manifestations of WM

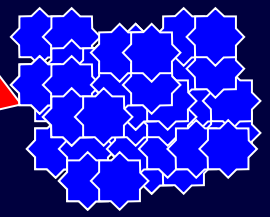




Hyperviscosity Syndrome:
Epistaxis, HA, Impaired vision
>3.5 to 4.0 CP

Adenopathy, SM
<18%

Fatigue, Constitutional Sxs

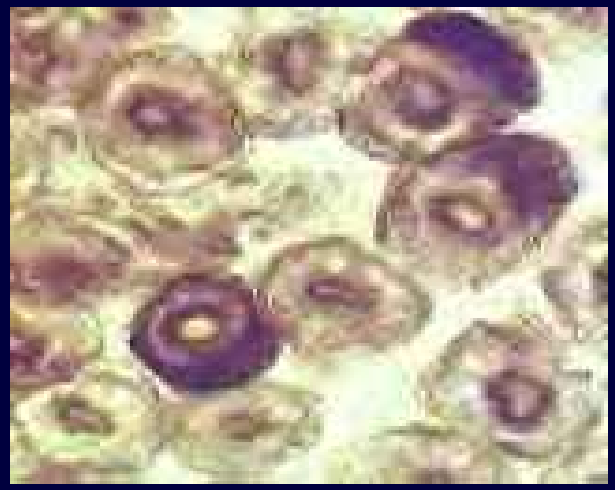


IgM Neuropathy (20%)
Autoimmune D/O (15%)
Cryoglobulinemia (5-20%)
Cold Agglutinemia (5-10%)
Amyloidosis (5-15%)

Courtesy of Marvin J. Stone M.D.

IgM Related Neuropathies in WM

- Observed in about 20% of WM patients
- IgM can often be found to react with specific neural antigens; these autoantibodies define very specific clinical syndromes.
  - Myelin Associated Glycoprotein (MAG)
  - Ganglioside M1 (GM1)
  - Sulfatide



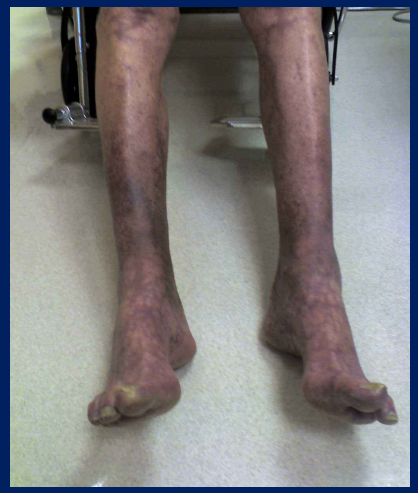
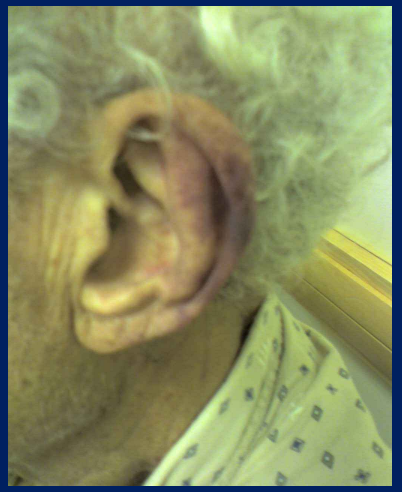
MAG antibody staining

Courtesy Todd Levine, MD

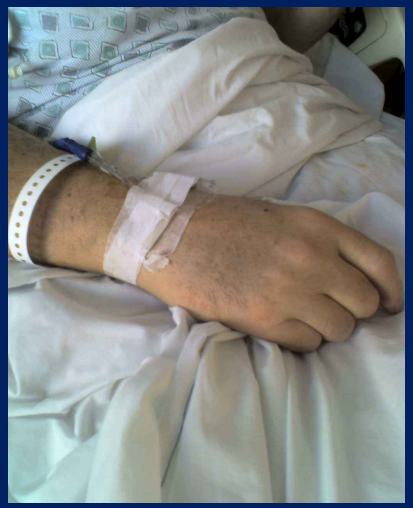
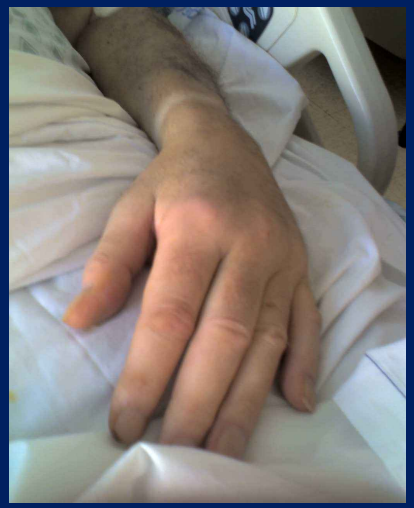
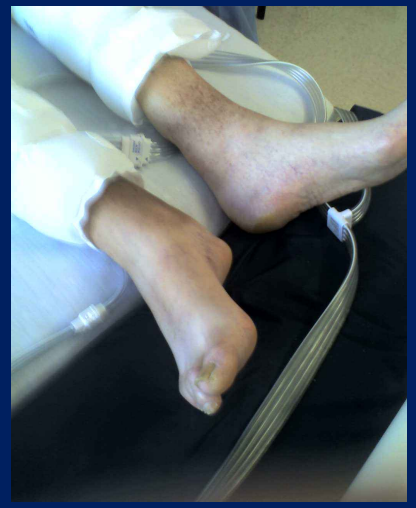
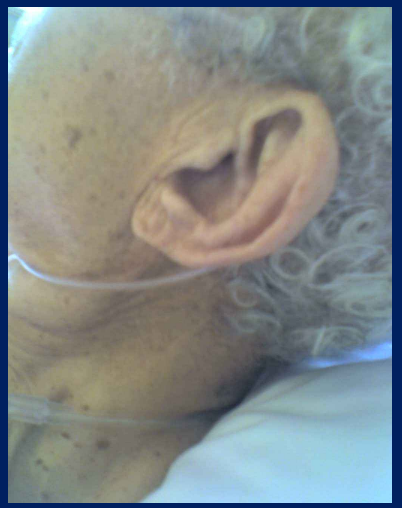
Cryoglobulinemia in a patient with Waldenstrom's macroglobulinemia

Pre-Pheresis



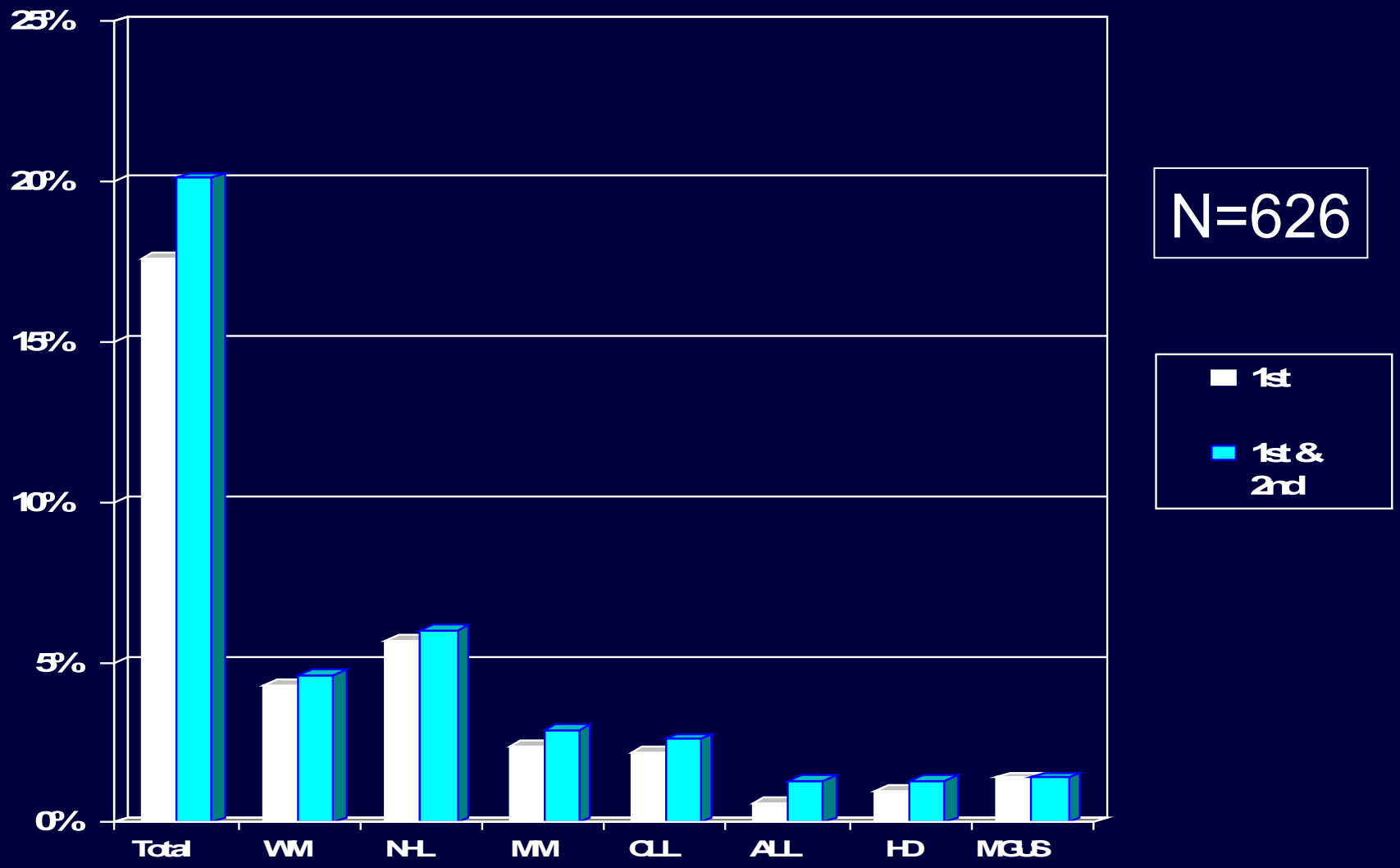



Post-Pheresis

Genetic Basis of Waldenstrom`s Macroglobulinemia

Familial B-cell Disorders among First and Second Degree Relatives of Patients with WM.

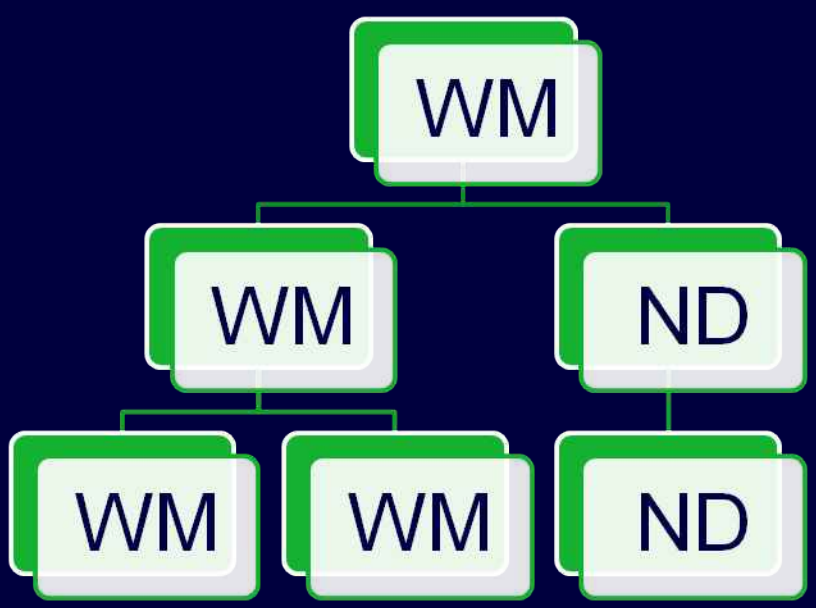


Presentation for Familial WM Patients

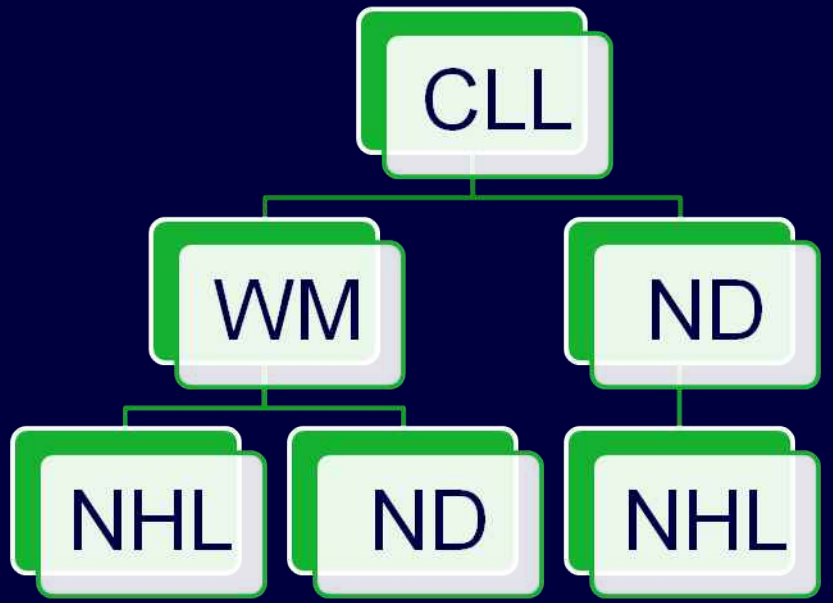
- Younger age
- Greater bone marrow involvement
- Higher serum IgM levels
- Absence of Peripheral Neuropathy

Treon et al, Ann. Oncol 2005

Familial Disease Patterns in WM



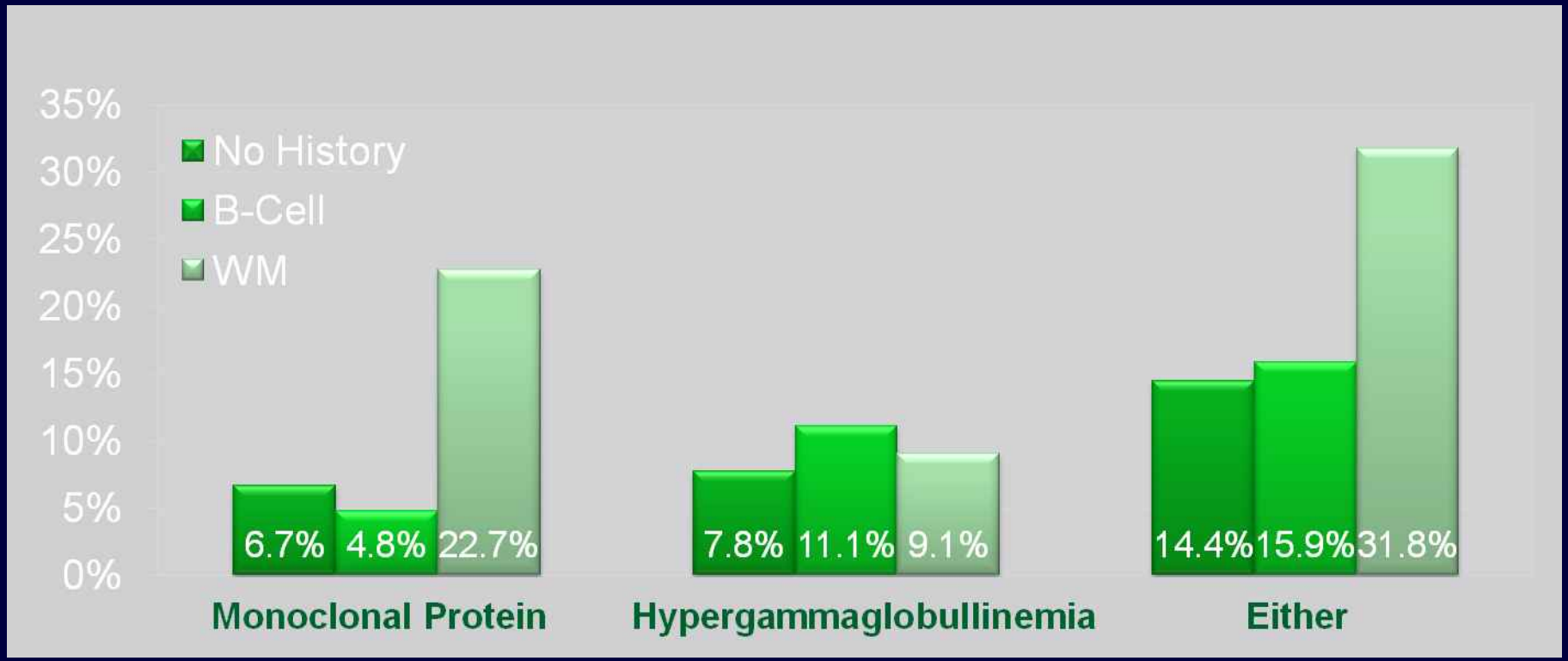
WM Alone



B-cell Disorders

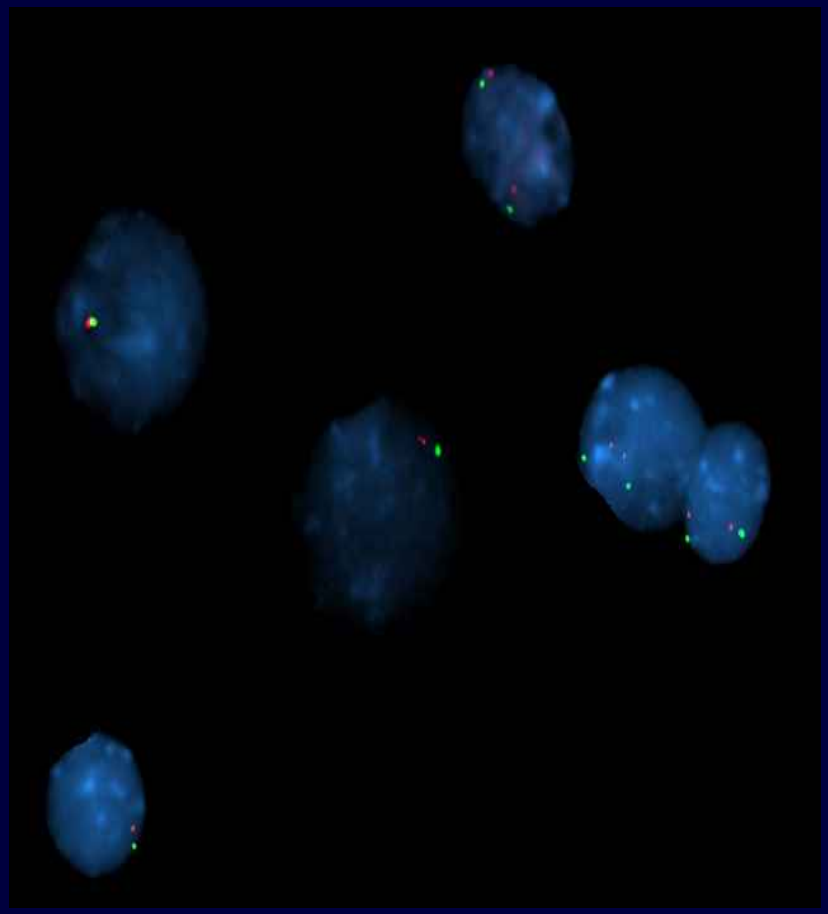
Hunter et al, IWWM5 2008

WM Familial Predisposition Study at DFCI



Hunter et al, 5th IWWM 2008

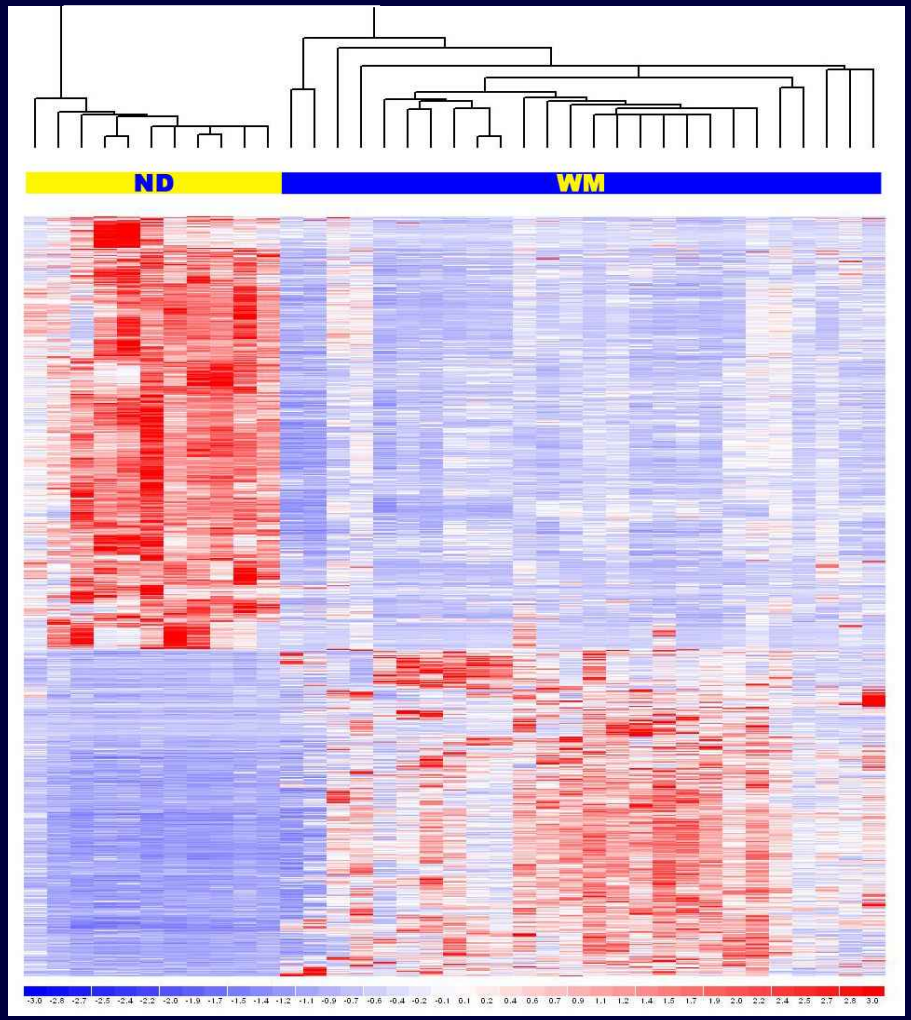
Deletions of chromosome 6q21-25 are common in patients with WM



- Present 30-50% of WM pts;
- Present in Familial and Non-Familial Cases;
- May distinguish IgM MGUS from WM;
- Prognostic significance controversial;.

Schop et al, Blood 2002; Treon et al, Ann Oncol 2006; Ocio et al, BJH 2007; Chang et al, IWWM5 2008.

Gene expression profiling in WM

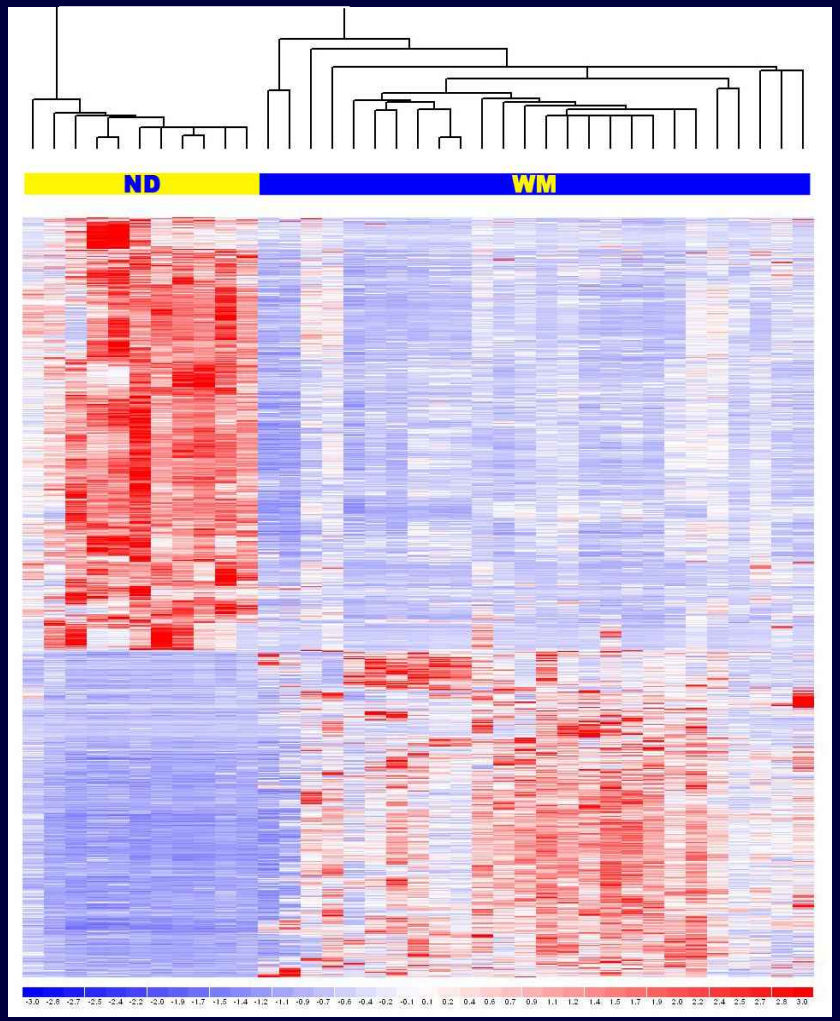


- Identification of genes which distinguish WM patients with:
  - -Familial WM
  - -High ISS (≥3) Score
  - -Previous single agent rituximab therapy

Hatjiharissi et al, IWWM5 2008

Hunter et al, ASH 2009 (Submitted)

Micro RNA profiling in WM



- Identification of MicroRNAs associated with:
  - -Serum IgM levels
  - -BM Disease Burden
  - -Extramedullary Disease
  - -Identification of impaired senescence gene

Hunter et al, ASH 2009 (Submitted)

Familial WM Study

- 482 individuals including WM probands;
- 148 families: 89 (60.1%): Sporadic,

  17 (11.5%): WM Only

  42 (28.4%) : Mixed B-cell
- SNP 6.0 analysis of genomic DNA
- Homozygous loss identified in SNP for

  88.9% of WM pts from Mixed B-cell Cohorts.

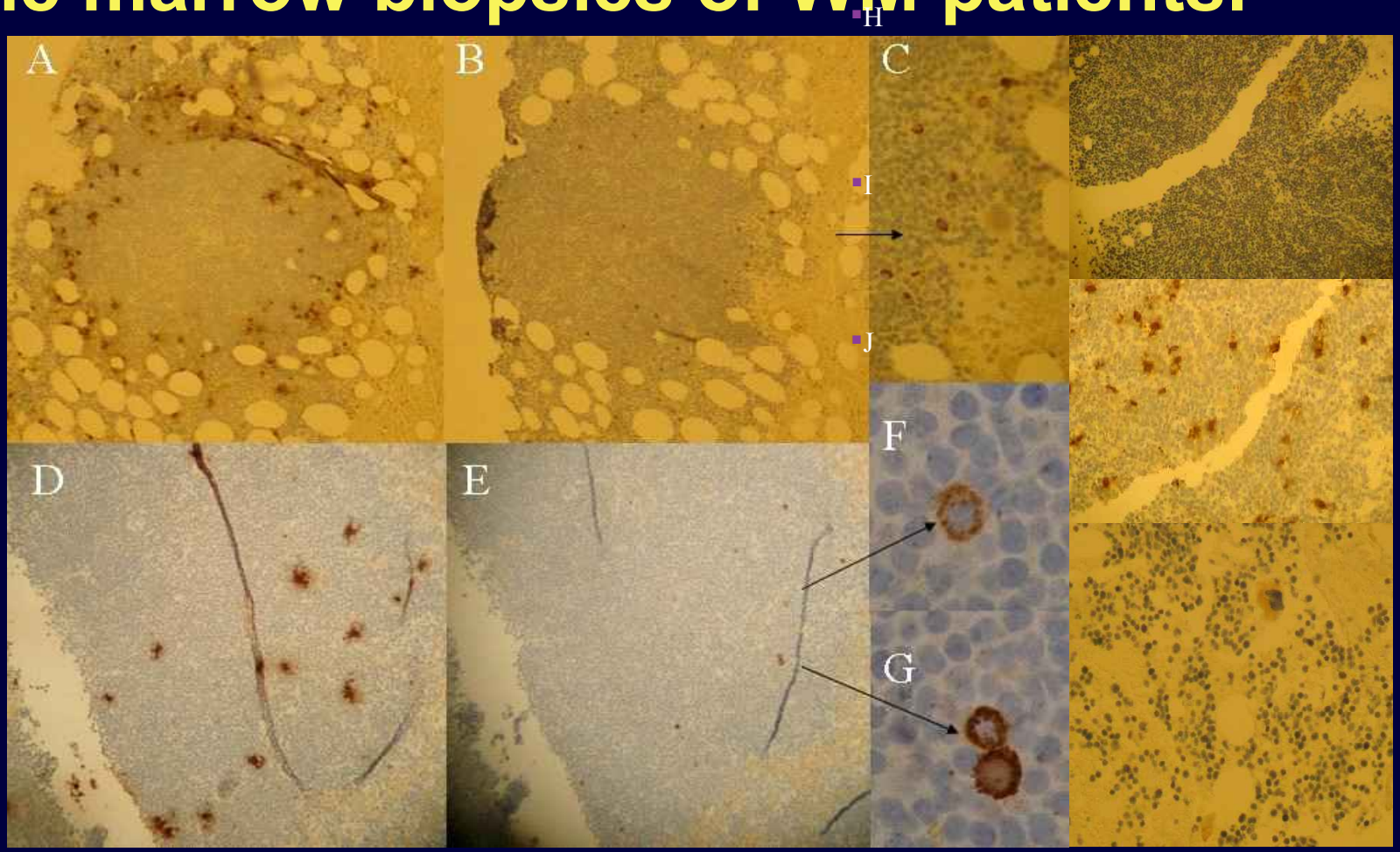
Hunter et al, ASH 2009 (submitted)

Bone Marrow microenvironment in Waldenstrom`s Macroglobulinemia

Increased CD40L expressing mast cells in bone marrow biopsies of WM patients.

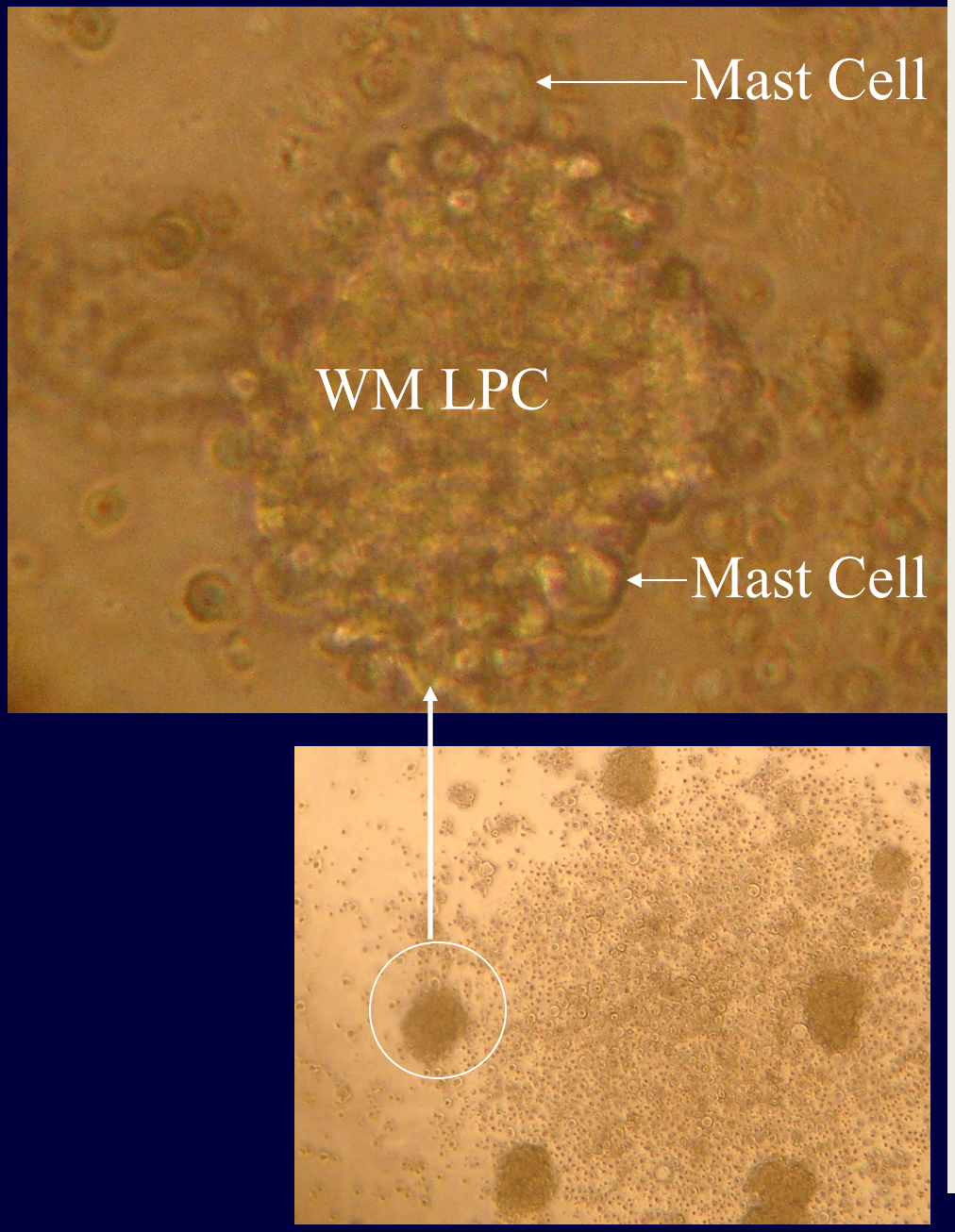
WM-1

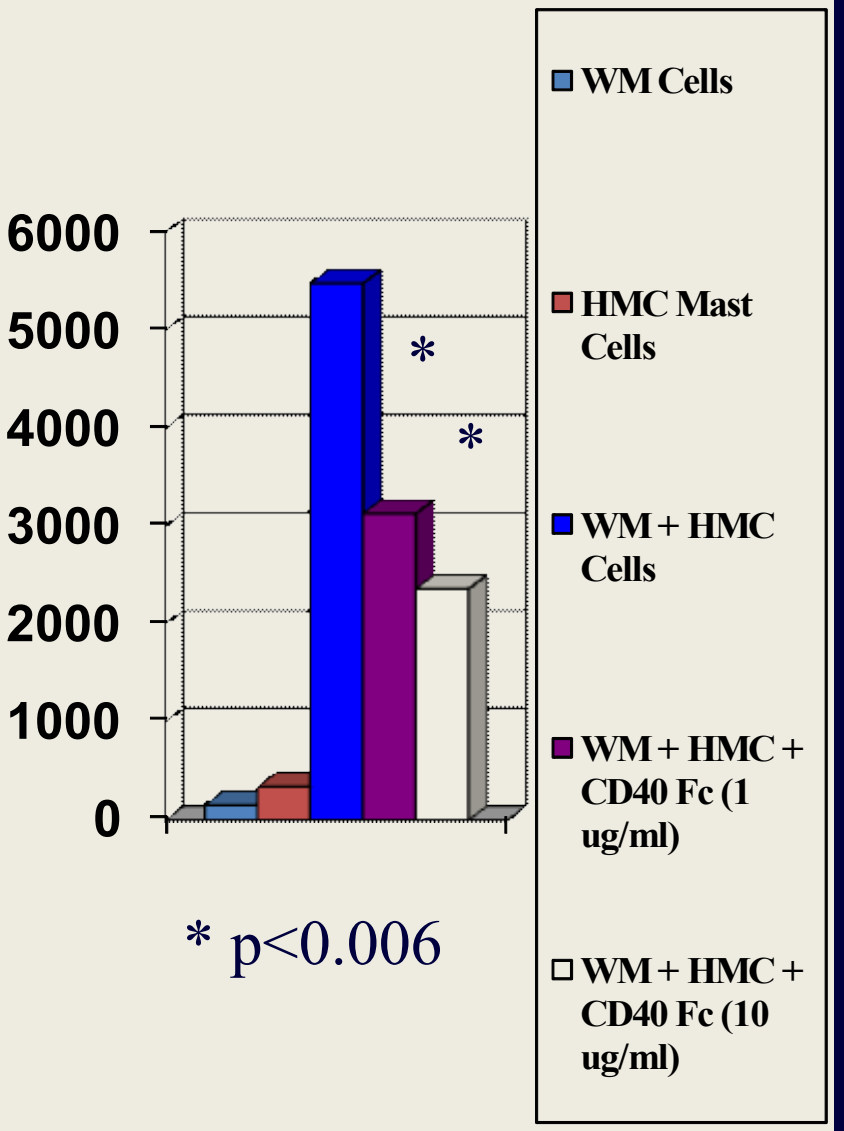
WM-2



- Tryptase CD40 Ligand

Tournilhac et al, Ann Oncol 2006

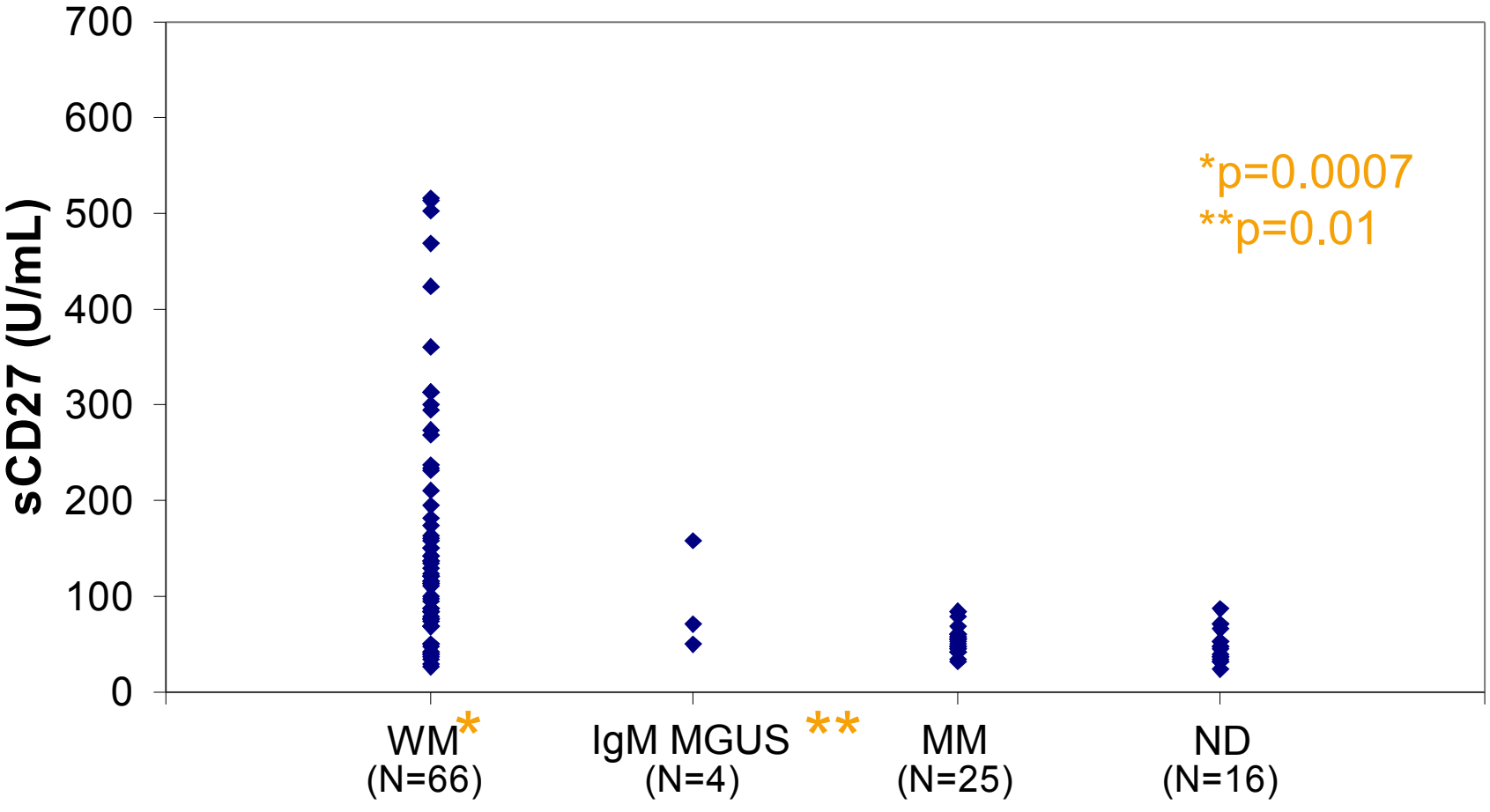




* p<0.006

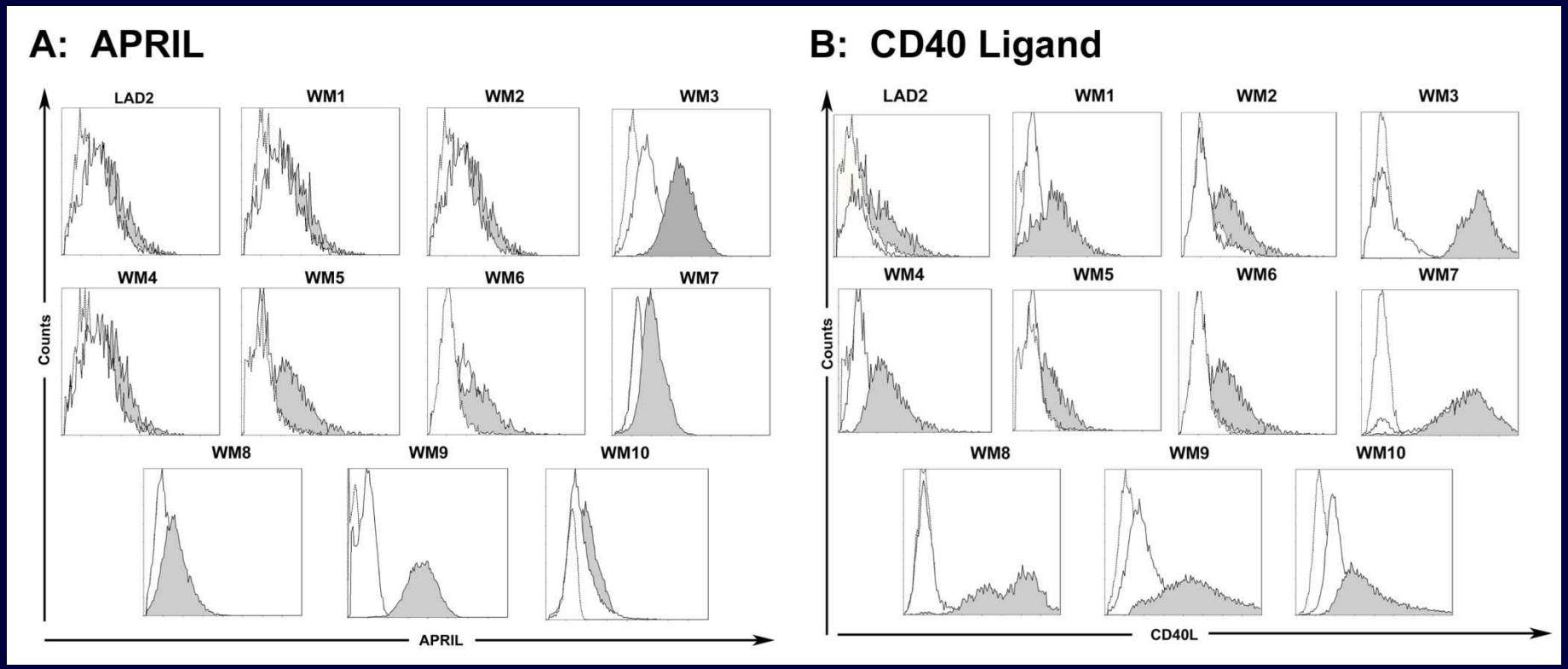
Tournilhac et al, Ann Oncol 2006

Soluble CD27 levels are elevated in WM



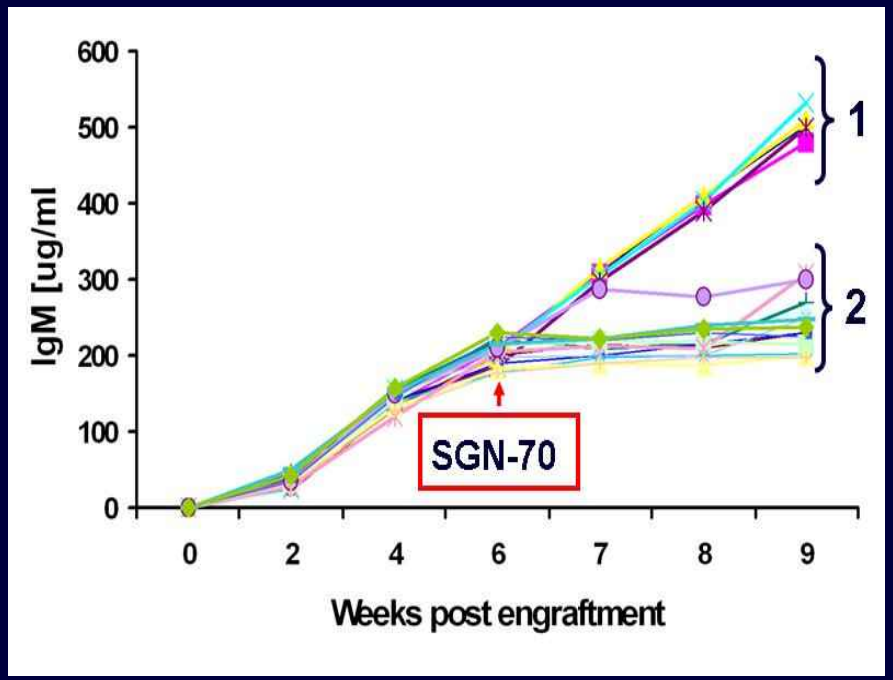
Ho et al, Blood 2008; Ciccarelli et al, IWMW 2008

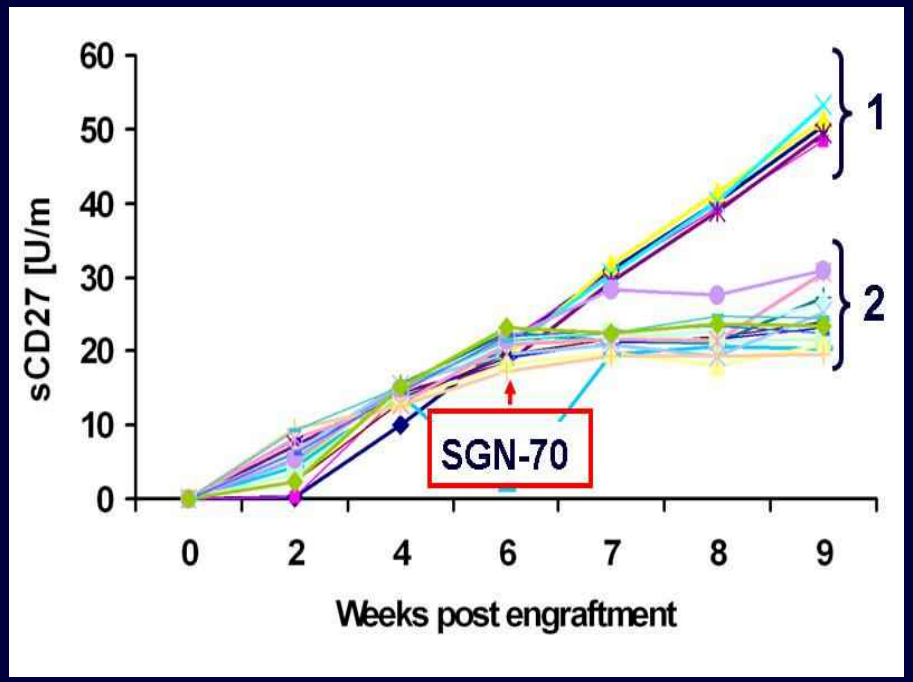
Soluble CD27 induces APRIL and CD40L on WM patient mast cells through CD70 which is blocked by the SGN-70 antibody.



Ho et al, Blood 2008

Human sIgM and sCD27 after engraftment and treatment of BCWM.1 bearing SCID-hu mice with SGN-70.

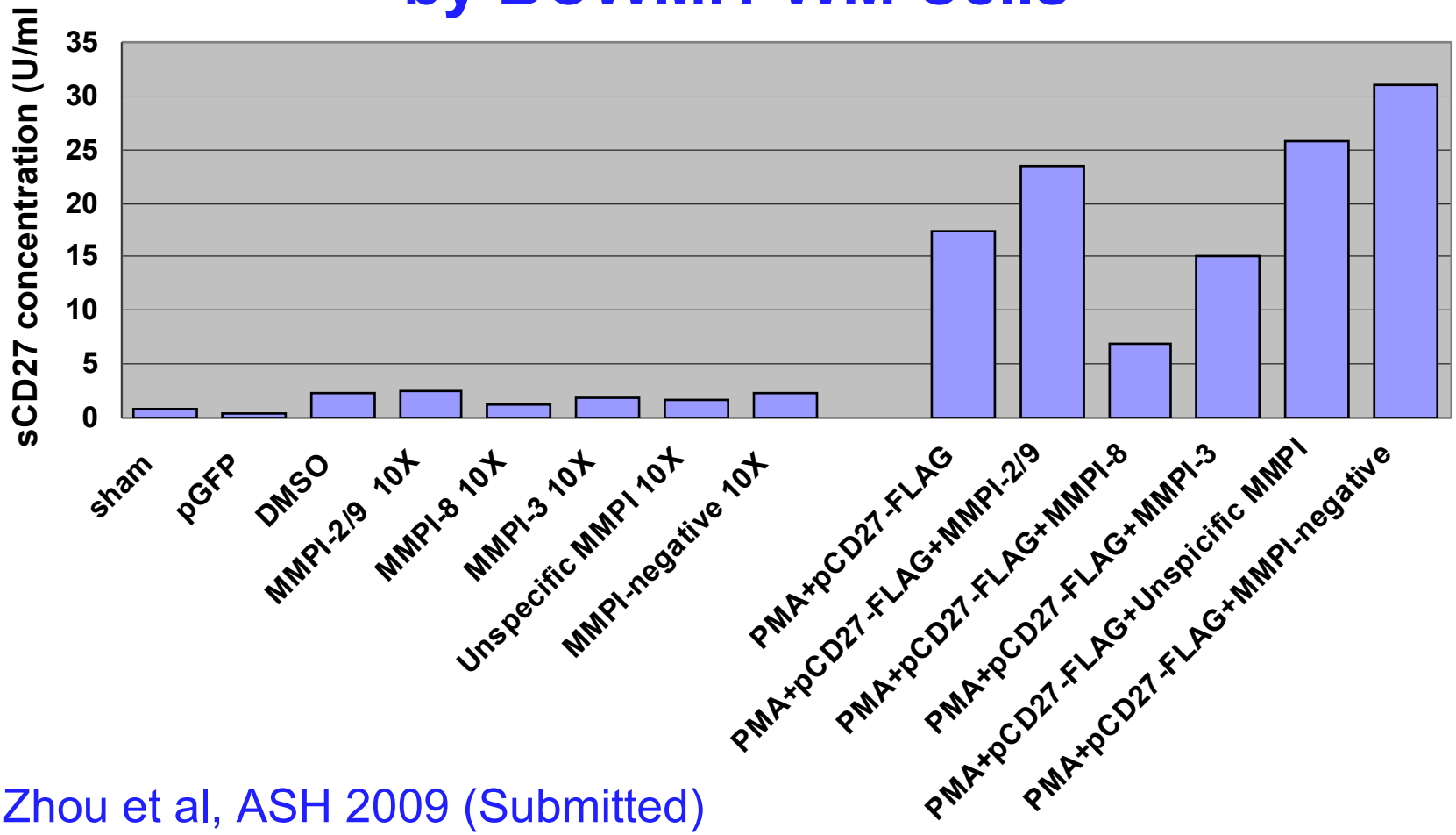




SCID, severe combined immunodeficiency

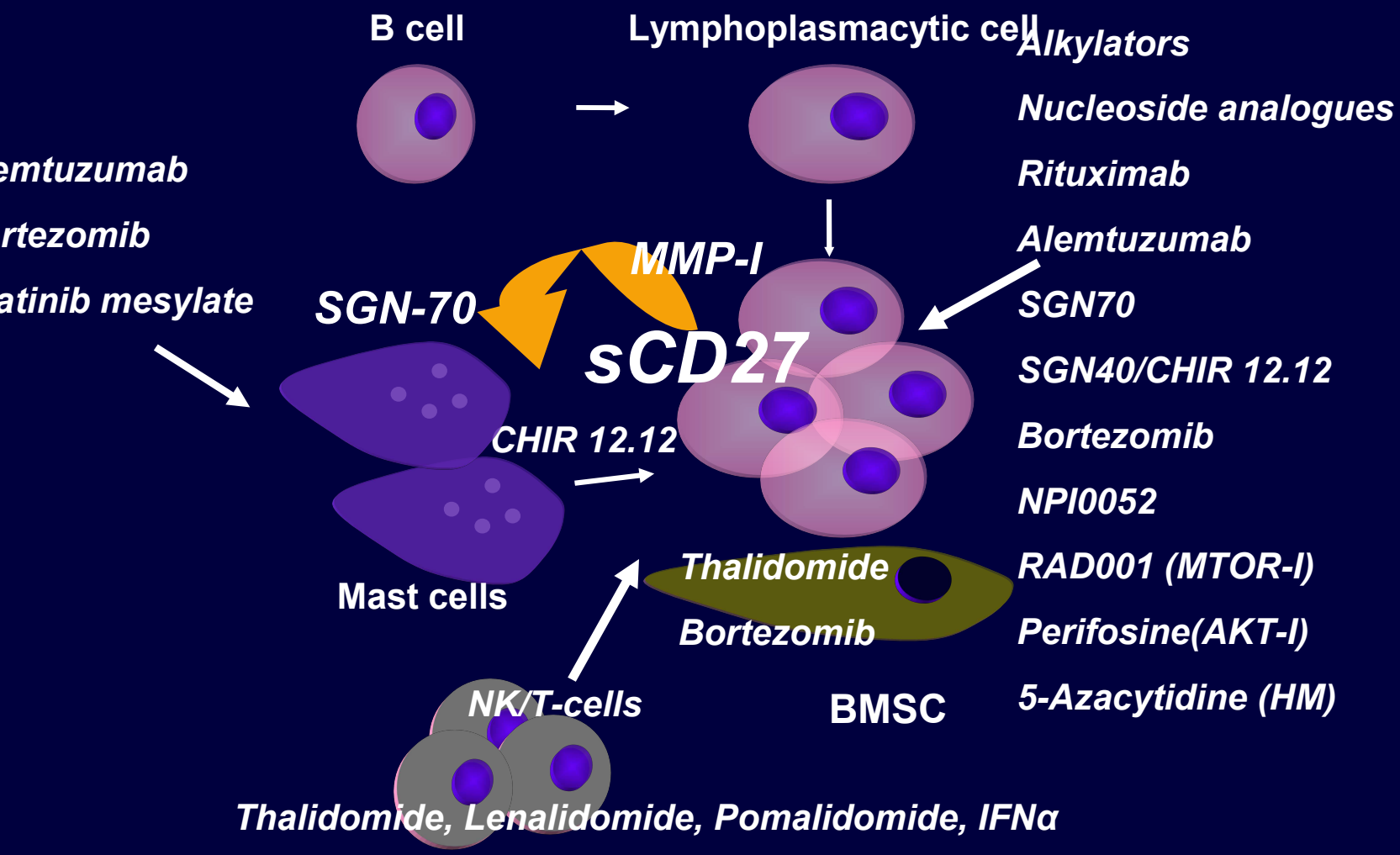
Ho AW, Blood 2008.

MMP 3 and 8 mediate soluble CD27 release by BCWM.1 WM Cells



Zhou et al, ASH 2009 (Submitted)

Therapeutic Targets in Waldenstrom's Macroglobulinemia



Management of Waldenstrom`s Macroglobulinemia

Consensus panel recommendations for initiation of therapy in WM

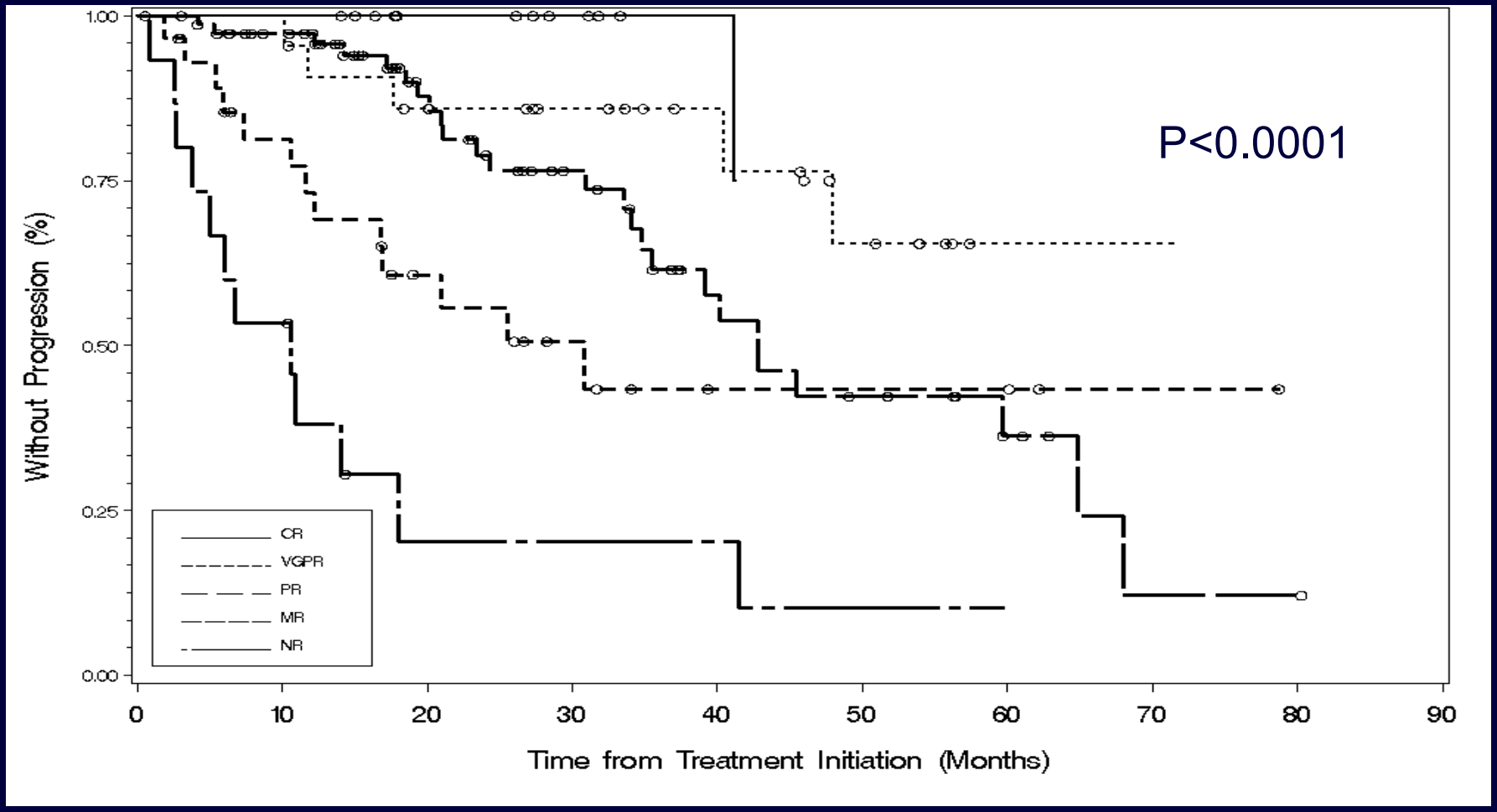
- Hb <10 g/dL on basis of disease
- PLT <100,000 mm3 on basis of disease
- Symptomatic Hyperviscosity (>4.0 cp)
- Moderate to severe peripheral neuropathy
- Symptomatic cryoglobulinemia, cold agglutinemia, amyloidosis, or symptomatic autoimmune related events on the basis of disease.

Kyle et al, Semin Oncol 2003

Overall and CR Rates to therapy in WM

	ORR	CR
alkylator therapy (chlorambucil)	30-50%	0-5%
nucleoside analogues	30-70%	0-10%
monoclonal antibodies	40-50%	0-5%
bortezomib	40-60%	0-5%
combination therapies		
nucleoside analogues/rituximab	70-90%	5-10%
cytoxan based therapy/rituximab	70-90%	5-15%
thalidomide/rituximab	78%	5%
bortezomib/dex/rituximab	90%	20%

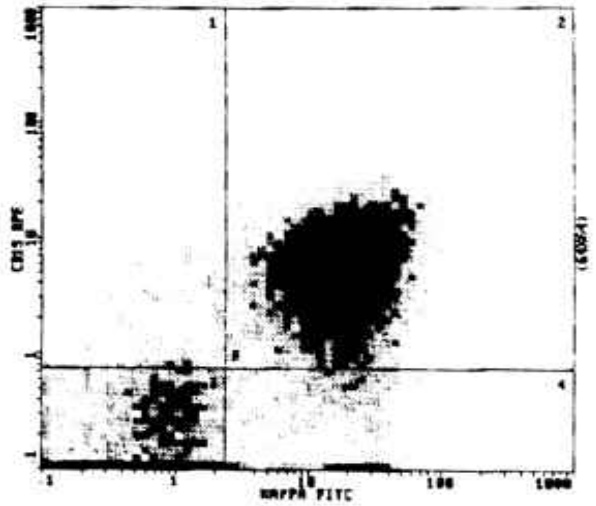
Progression free survival is predicated on categorical response in WM



Treon et al, 3rd Intl Summit on WM 2009

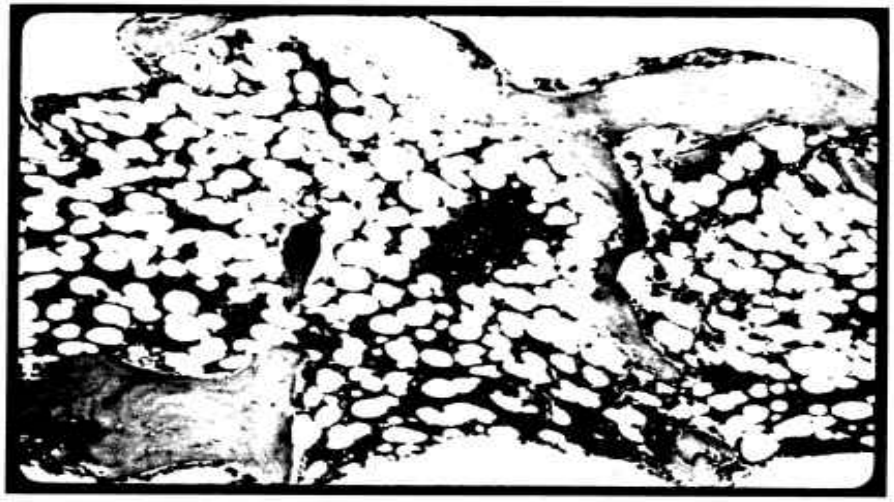
Pre-rituximab therapy

CD19

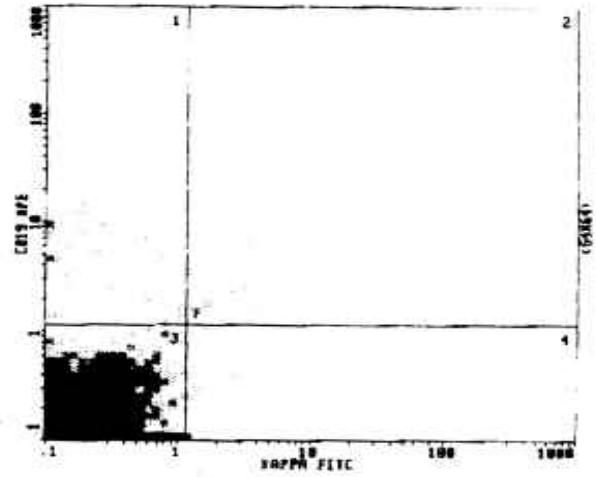


kappa

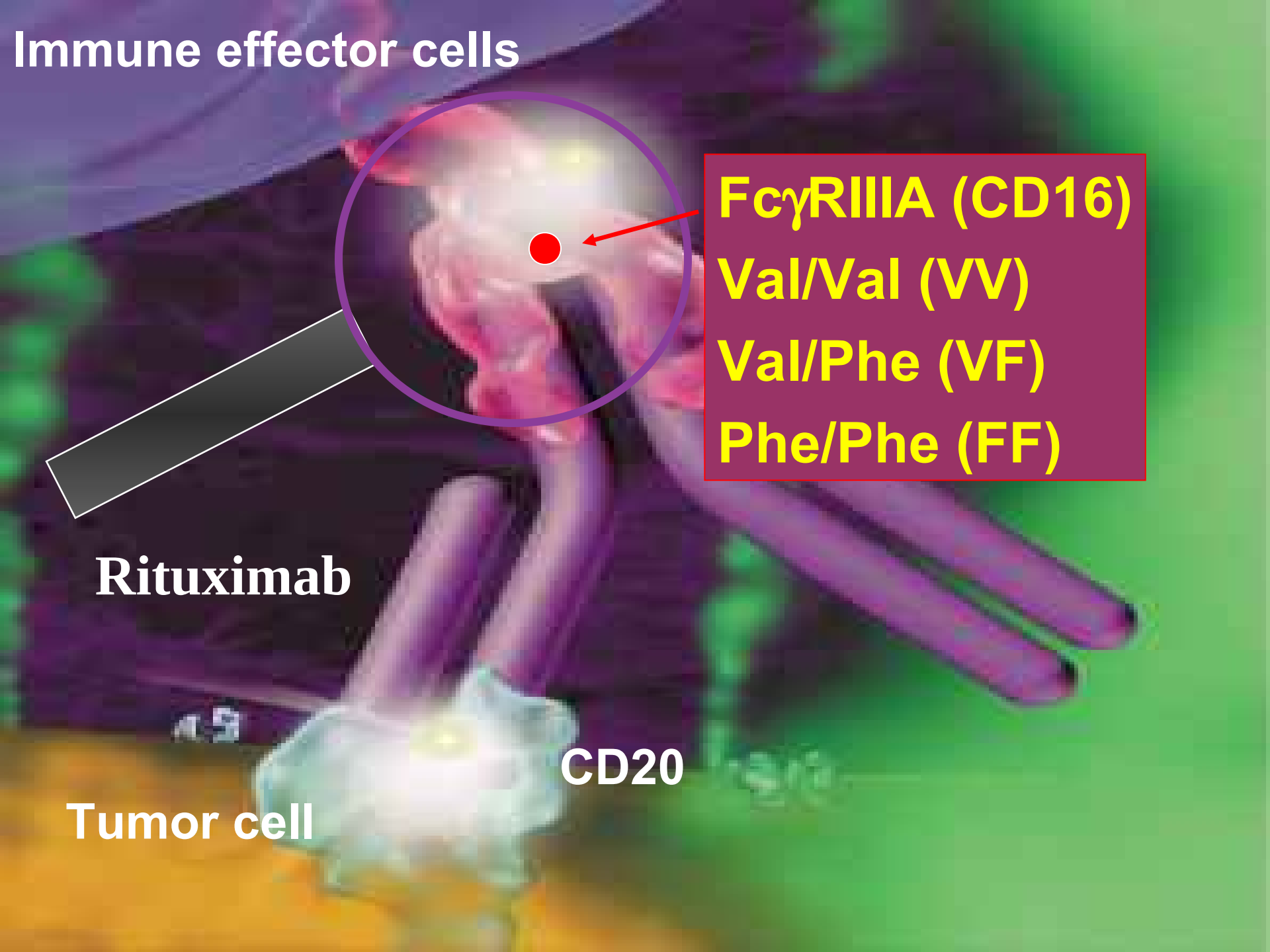
Post-rituximab therapy



CD19

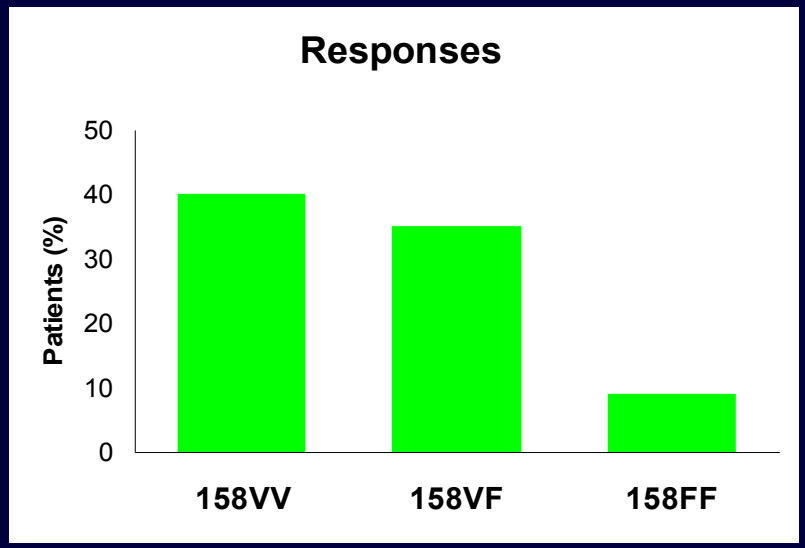


kappa


Immune effector cells
FcγRIIIA (CD16)
Val/Val (VV)
Val/Phe (VF)
Phe/Phe (FF)
Rituximab
CD20
Tumor cell

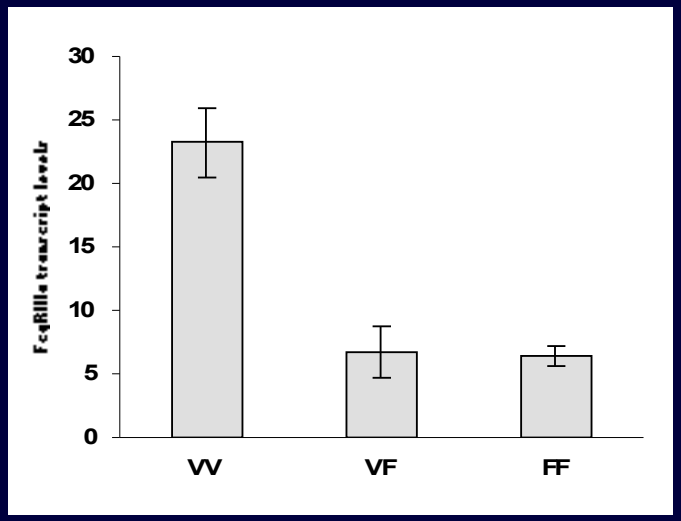
FcγRIIIa-158 Polymorphisms and Response to Rituximab in WM

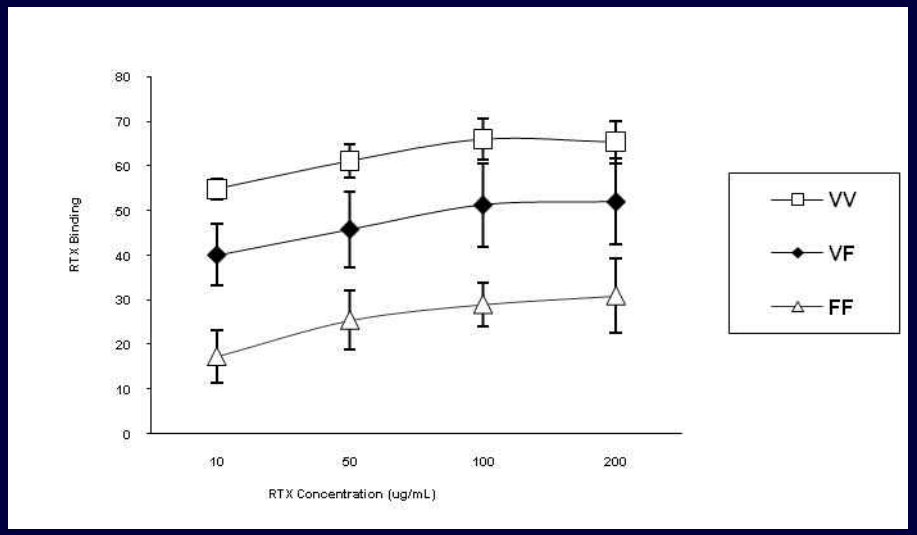
WM patients carrying at least one valine amino acid at position 158 (V/V or V/F), achieved a four-fold higher best overall response rate, *p=0.03*) versus patients who were homozygous for phenylalanine (F/F).

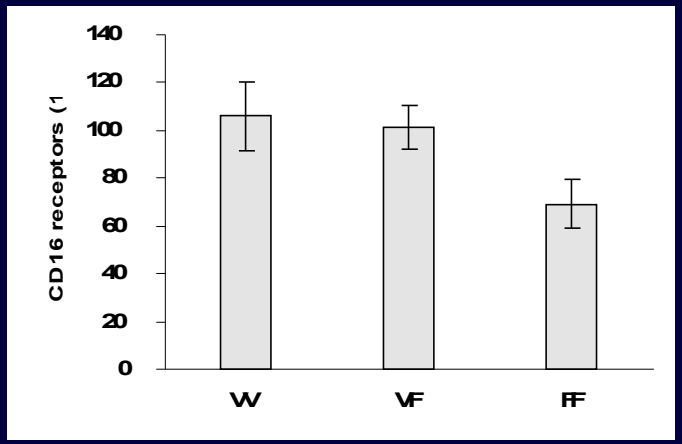


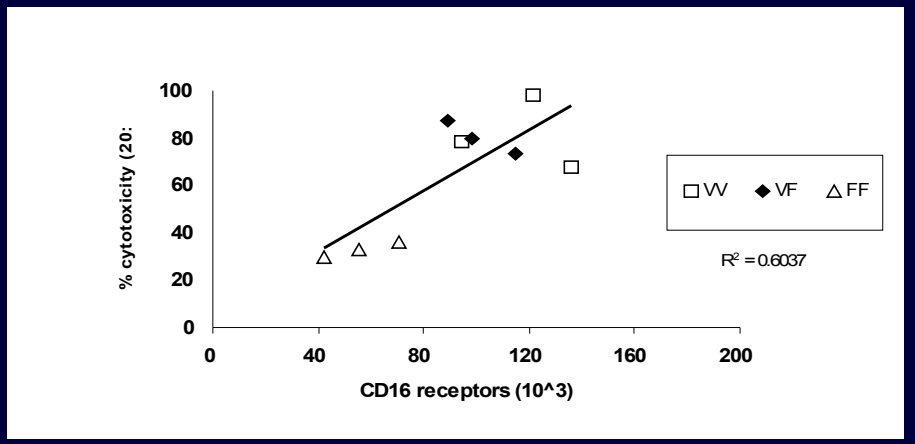
Treon et al, JCO 2005

FcγRIIIa-158 V/- is associated with higher CD16 expression, rituximab binding and ADCC activity.









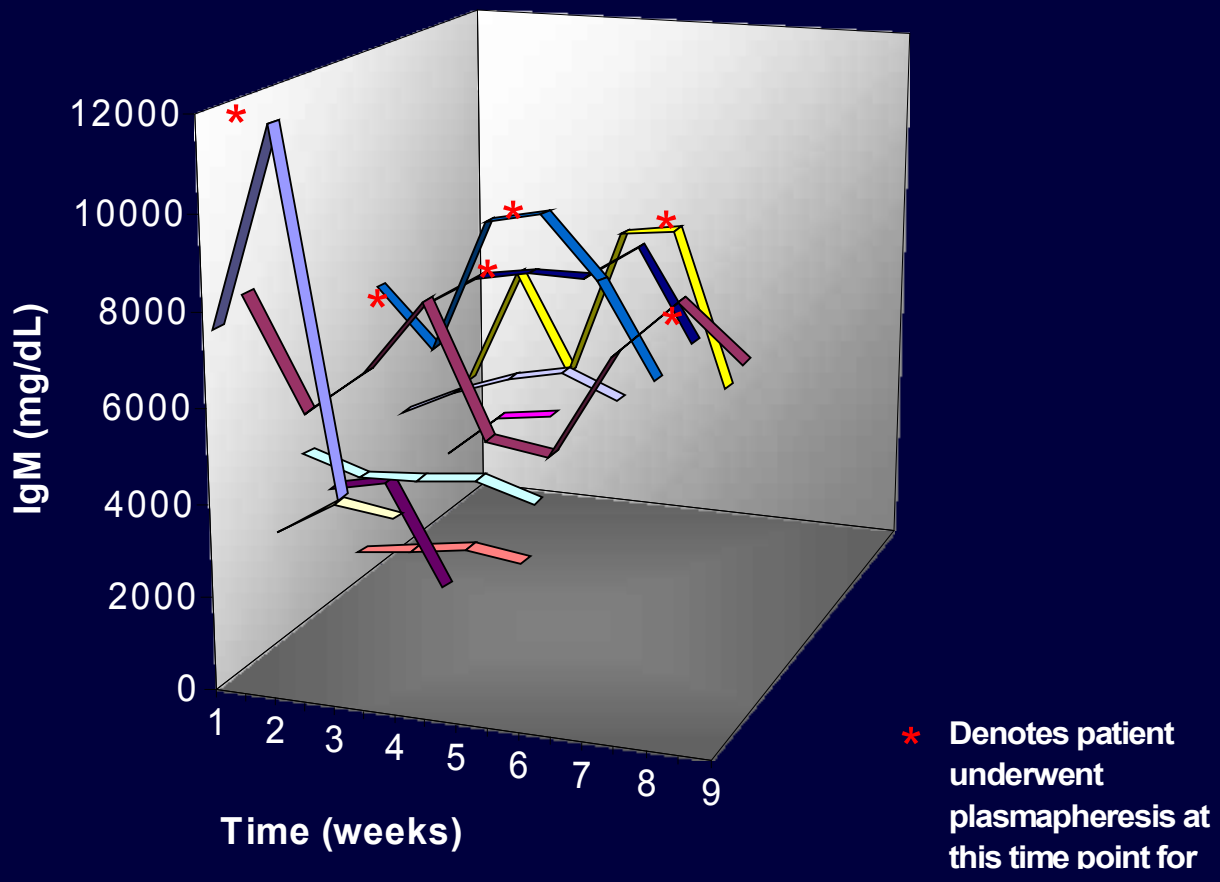
Hatjiharrisi et al, Blood 2007

Polymorphisms of FcγRIIIA Predict Categorical Response to Rituximab Combination Therapy in WM.

- 64 WM patients treated with rituximab in combination with cyclophosphamide (n=43), thalidomide (n=14), or lenalidomide (n=7) on a study.
- Expression of FcγRIIIA-158 (V/-) observed in 3/9 (33.3%) WM patients who were non-responders; 20/38 (52.62%) patients attaining a major (≥ PR) response, and 5/7 (71.42%) patients who attained a CR/VGPR.

Yang et al, ASH 2009 (submitted)

IgM Flare following Rituximab in WM



Donnelly et al, ASH 2001; Dimopoulos et al, JCO 2002;
Treon et al, Ann Oncol 2004; Ghobrial et al, Leuk Lymphoma 2004.

Rituximab induced IgM flare occurs in patients receiving combination therapy.

- Monotherapy (60%)
- Fludarabine/Rituximab (40%)
- Cyclophosphamide/Prednisone/Rituximab (20-30%)
- Thalidomide/Rituximab (50%)
- Lenalidomide/Rituximab (75%)
- Bortezomib/Dexamethasone/Rituximab (9%)

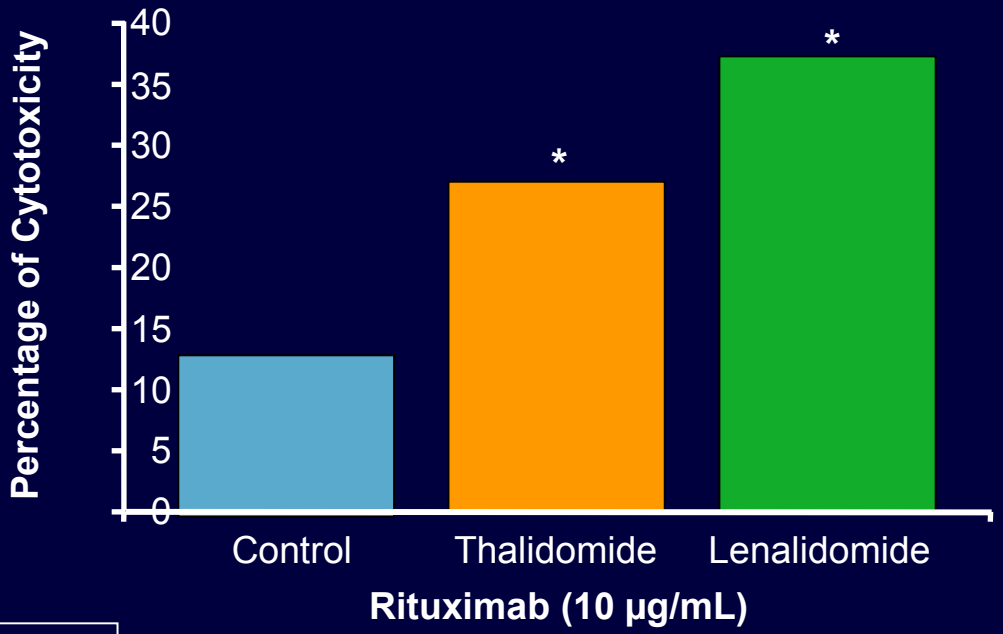
Treon et al, Ann Oncol 2004; Nichols et al, ASH 2004; Treon et al, Blood (accepted); Treon et al, Clin Cancer Res (accepted);

Secondary Malignancies WM Patients Treated With Nucleoside Analogues (NA)

- *N = 463 patients with WM*
- *Long term outcome of NA treated patients compared to patients treated without a nucleoside analogue or who remained on watch and wait*
- *Incidence of transformation to aggressive lymphoma increased by 7-fold and MDS/AML by 3-fold in NA treated patients.*
- *Overall survival for transformed patients was not different vs. non-transformed patients and may reflect effective salvage with CHOP-R.*

Leleu, et al. JCO 2009

Augmented Rituximab-Induced ADCC by thalidomide and lenalidomide treated NK cells

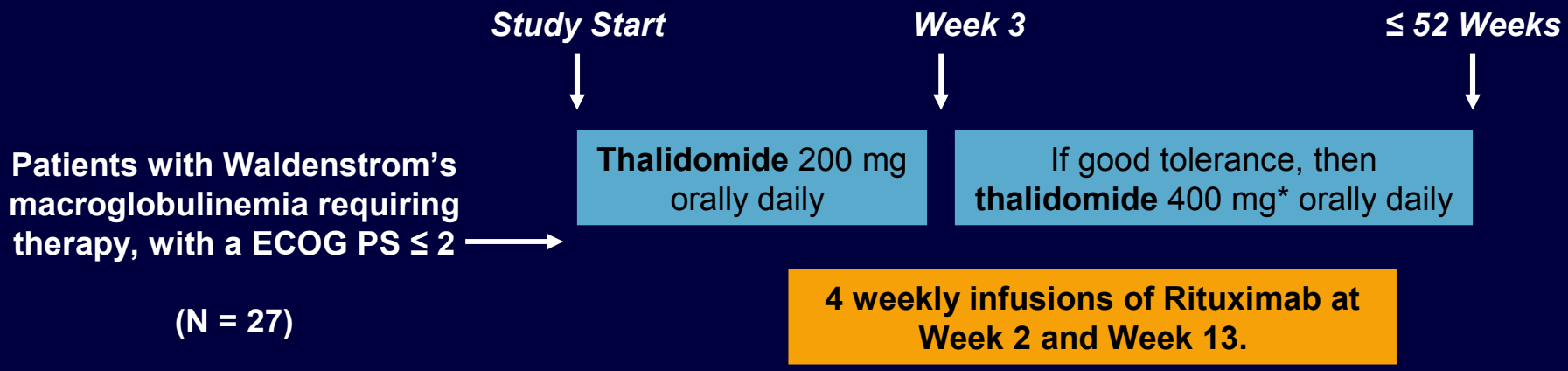


*$P < 0.02$
ARH-77 CD20+ LPC

ADCC, antibody-dependent cell-mediated cytotoxicity.

Hayashi et al; Br J Haematol 2005; 128:192-203.

Phase II Study: Treatment of WM With Thalidomide and Rituximab



*Dose reduction to 50 mg once daily allowed due to adverse events.

ECOG PS, Eastern Cooperative Oncology Group performance status.

ClinicalTrials.gov. Available at: http://clinicaltrials.gov/show/NCT00142116. Accessed June 5, 2007.

Thalidomide and Rituximab in WM: Responses

- N = 25 patients; 23/25 received intended therapy
- Of evaluable patients
  - CR = 1 (4%)
  - PR = 15 (65%)
  - MR = 2 (8%)
  - SD = 1 (4%)

70% (CR + PR)

78% (CR + PR + MR)

- Median follow-up of 42 months, median TTP was 35 months for all pts, and 38+ months for responders

CR, complete response, MR, minimal response, PR, partial response, TTP, time to progression, SD, stable disease.

Treon et al, Blood 2008

Thalidomide and Rituximab in WM: Adverse Events

- Grade ≥ 2 toxicities
  - **Neuroparasthesias (44%)**
  - **Somnolence (12%)**
  - **Confusion (12%)**
  - **Rash (8%)**
  - **Tremors (8%)**
  - **Bradycardia (8%)**
- Among patients experiencing neuroparasthesias, 10 demonstrated resolution to grade 1 (n = 3) or complete resolution (n = 7) at a median of 6.7 months (range: 0.4-22.5)

Treon et al, Blood 2008

Phase II Study: Treatment of WM With Lenalidomide and Rituximab

Patients with Waldenstrom's macroglobulinemia, CD20+, ECOG PS ≤ 2, no cancer treatment in previous month

(N = 25)

→

Lenalidomide 25 mg once daily, Days 1-21 of 28, repeated up to 48 weeks or until not tolerated or disease progression

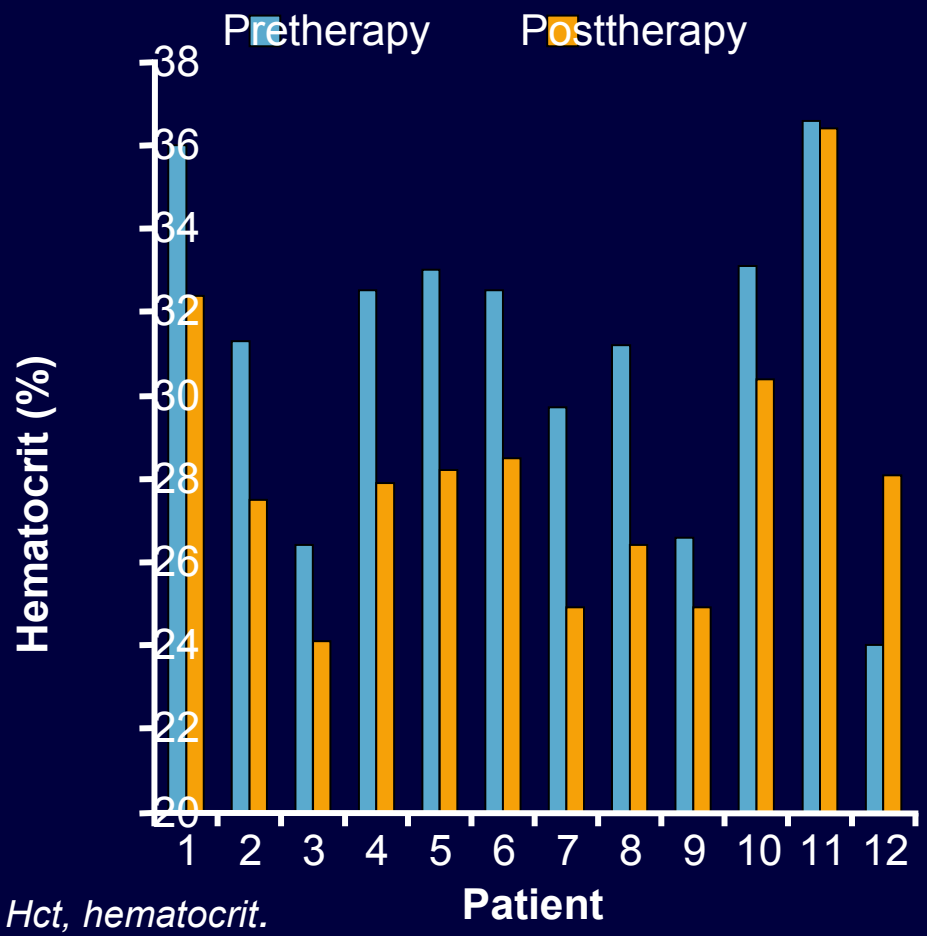
Rituximab IV weekly, Weeks 2-5 then Weeks 13-16 if disease has improved

*Dose reduction to 10 mg once daily allowed due to adverse events.

ECOG PS, Eastern Cooperative Oncology Group Performance Status.
Clinical Trials.gov. Available at: http://clinicaltrials.gov/show/NCT00142168. Accessed June 5, 2007.

Lenalidomide-Induced Anemia in WM

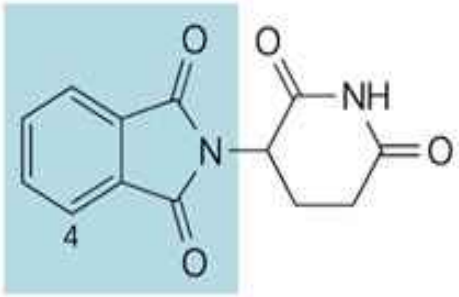
- Decreased Hct observed in 10/12 pts following first week of lenalidomide monotherapy
- Median Hct decrease: 3.9% (31.9% to 28.0%; *P* = .003)
- No evidence for hemolysis; concurrent thrombocytopenia observed in 1 pt
- 4 patients hospitalized for anemia related complications (Afib, syncope, CHF)



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

Treon SP, et al. Clin Cancer Res 2008

Thalidomide

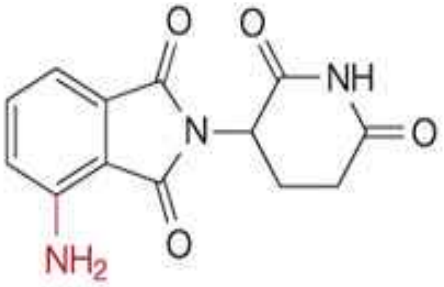


Pthaloyl ring

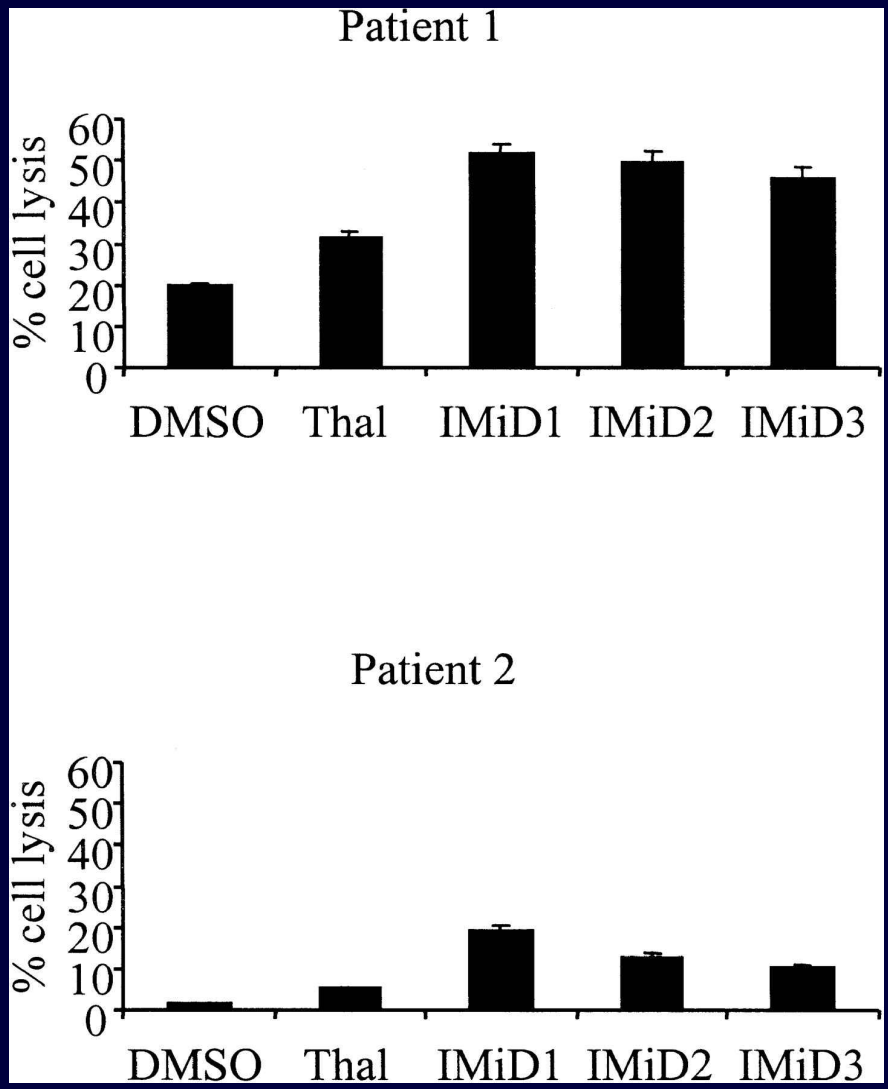
Lenalidomide

(IMiD3)

Pomalidomide



(IMiD1)



Davies et al, Blood 2001

Phase I/II Study of Pomalidomide, Dexamethasone, Rituximab (PDR) in Waldenstrom's Macroglobulinemia.

Pomalidomide	1,2,3,4 mg po QD	4 years
Rituximab	375 mg/m2/week	W1-4; W12-15; then q3 months x 8.
Dexamethasone	40 mg weekly IV	pre-Rituximab

Bortezomib Monotherapy in relapsed/refractory WM

Study	N	# Cycles*	ORR	PR
Dimopoulos	10	6	60%	60%
Treon et al	27	6	85%	44%
Chen et al	27	6	78%	41%

*Median number of cycles given.

- Grade ≥ 3 sensory neuropathy in 20% to 30% of patients, reversible in most patients

ORR, overall response rate; PR, partial response, WMCTG, Waldenstrom's Macroglobulinemia Clinical Trials Group.

Dimopoulos et al, Haematologica 2006; Treon SP, et al. Clin Cancer Res 2007 13;3105-3106. Chen et al. Hematologica 2005;90 (S1):155;

Bortezomib, Dexamethasone, and Rituximab as Primary Therapy for WM

- Cycles 1-4 (each cycle every 21 days)
  - Days 1, 4, 8: bortezomib, dexamethasone
  - Day 11: bortezomib, dexamethasone, rituximab
- Maintenance cycles 5-8 (each cycle separated by 3 months)
  - Day 1, 4, 8: bortezomib, dexamethasone
  - Day 11: bortezomib, dexamethasone, rituximab
- Dosages
  - Bortezomib: 1.3 mg/m^2
  - Dexamethasone: 40 mg
  - Rituximab: 375 mg/m^2

The Waldenström's Macroglobulinemia Clinical Trials Group ®

BDR Response Assessment

- Median cycles: 7 (range 3-8)
- Overall Responses
  - CR/nCR: 5 (22%)
  - PR: 14 (61%)
  - MR: 3 (13%)
  - SD: 2 (9%)

83%

95.6%

- Median time to response 1.1 months
- With a median follow-up of 22.8+ months, 18/23 patients remain progression free.

CR, complete response; MR, minor response; PR, partial response; SD, stable disease.

Treon SP, et al. JCO 2009.

BDR in WM: Adverse Events

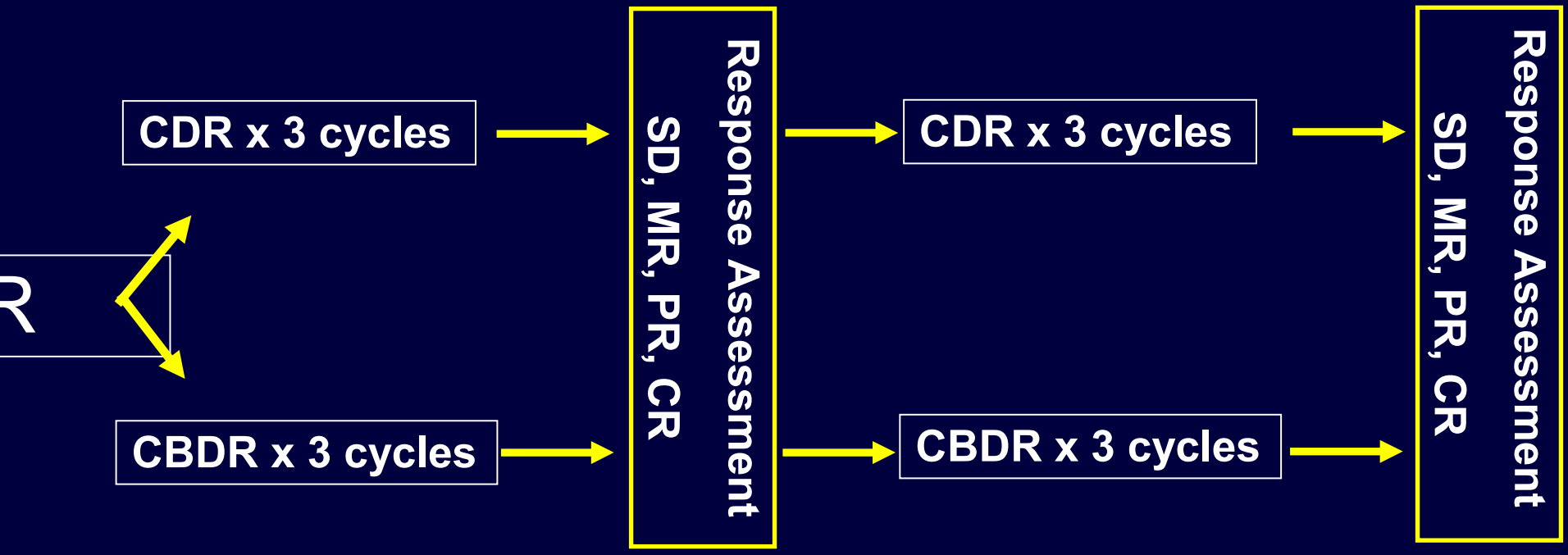
- Grade ≥ 2 toxicities
  - Neuroparasthesias (69%); grade 3 (30%)
  - Neutropenia (30%)
  - Thrombocytopenia (9%)

13/16 (81%) resolved to ≤ grade 1 at a median of 6.0 months.

- Among first 7 patients on study, 4 developed herpes zoster outbreak prompting initiation of valtrex at 1 gm po qD. Only one subsequent herpes zoster outbreak occurred in a patient who did not fill her script for valtrex.

Treon et al, JCO 2009.

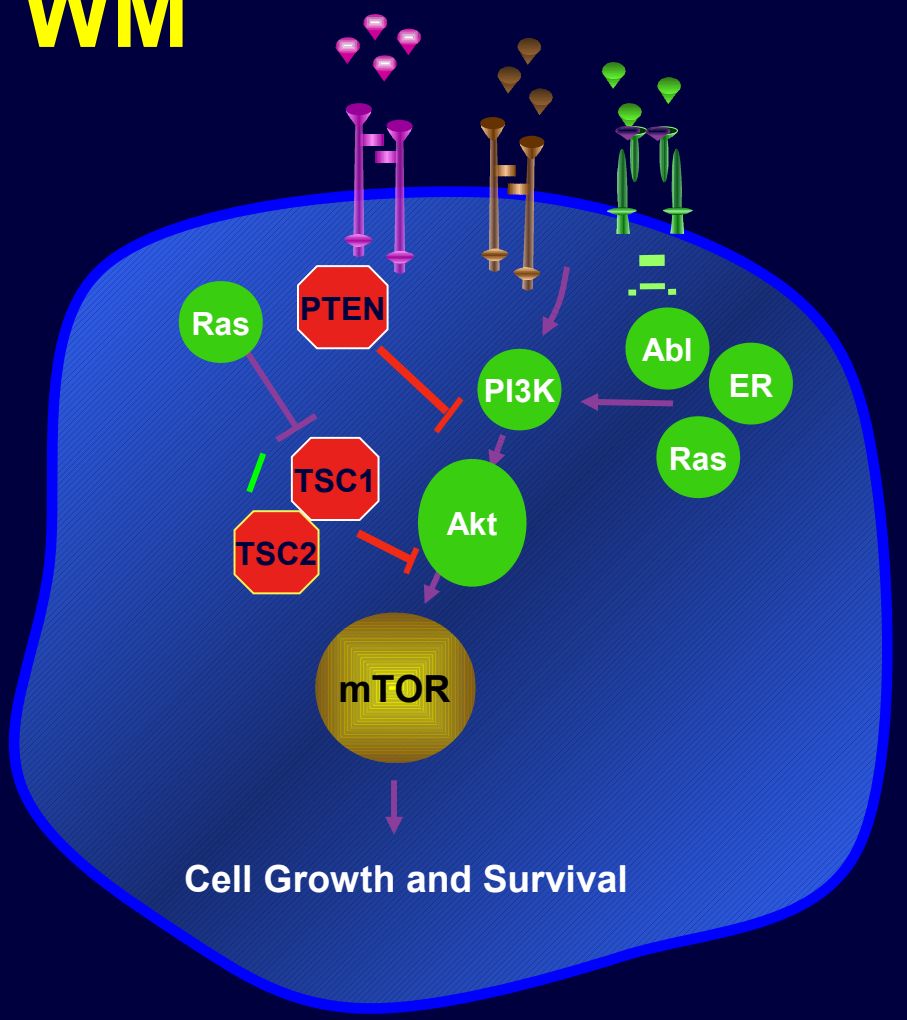
Randomized study of CDR vs. CBDR in newly diagnosed WM.



Cyclophosphamide (C) =1000 mg/m2 on day 1
Bortezomib (B) =1.6 mg/m2 weekly on days 1,8,15
Prednisone (P)= 100 mg qD days 1-5
Rituximab (R)= 375 mg/m2 on day 1

Phase II Study of RAD001 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 duration of response: NR (3-22+ months)
- AE: >grade 3 included thrombocytopenia; PNA; mucositis; hyperglycemia.



Ghobrial et al, ASH 2008; Submitted.

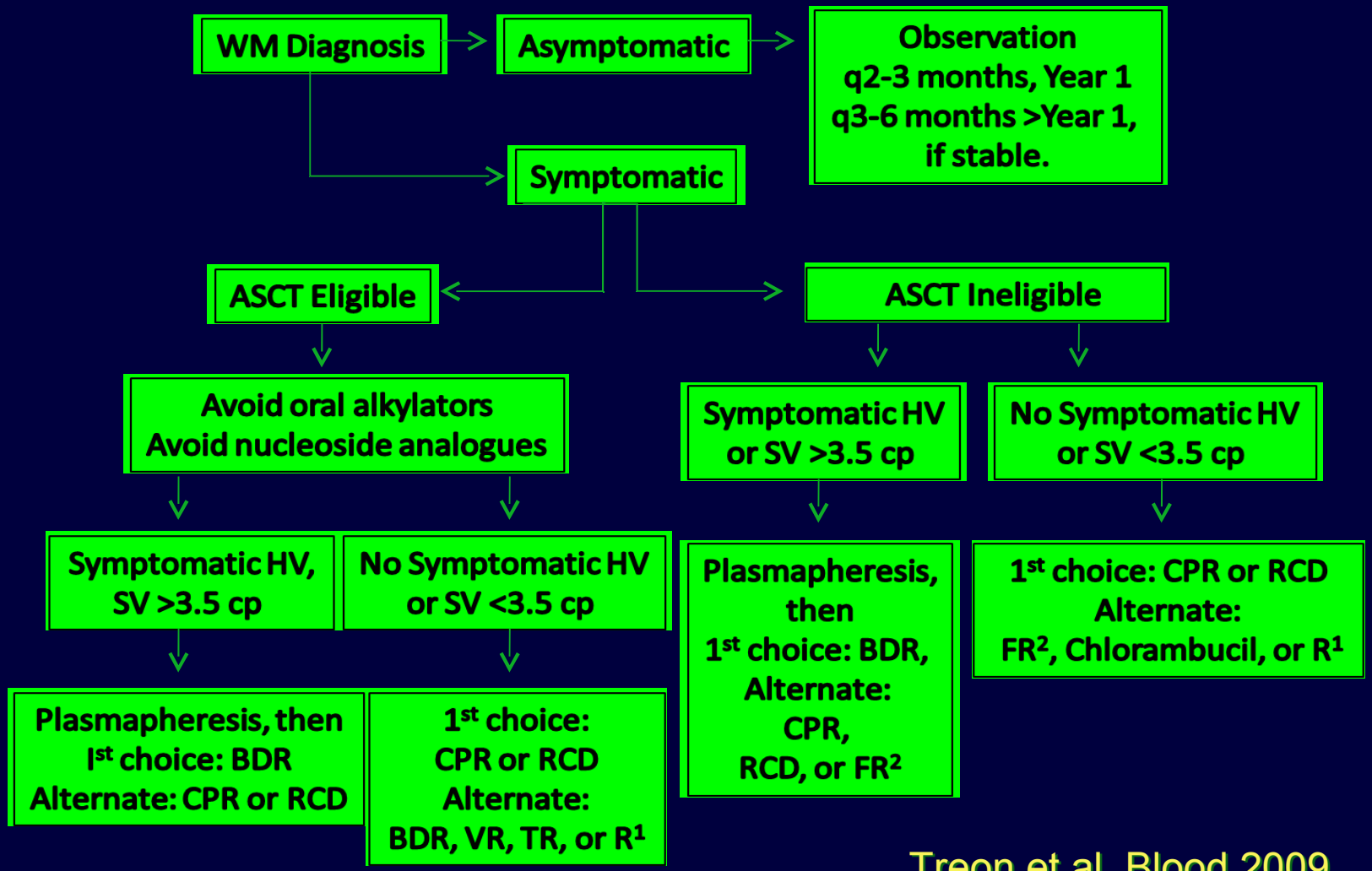
Phase II Study of RAD001 for Primary Therapy of WM.

N=60
Eligibility: Symptomatic, Untreated WM.
Dose: 10 mg qD, reduction to 7.5, 5.0 mg for AE.
Duration: 4 yr or progression.
Primary Endpoints:
Safety, ORR, 2 and 4 yr PFS.

Summary

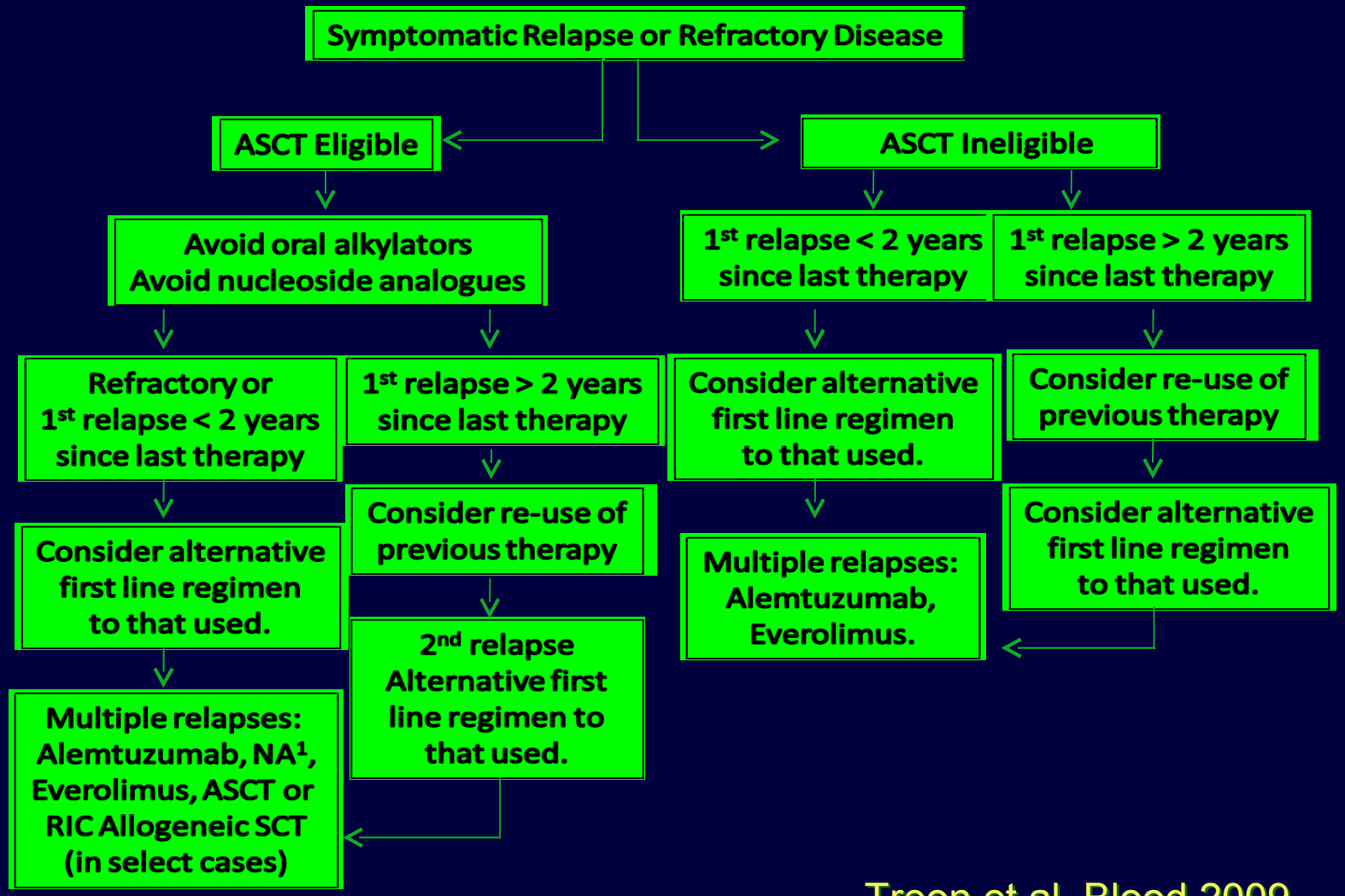
- Watch and wait is appropriate unless patients are symptomatic;
- Use of alkylators and nucleoside analogues should be carefully considered due to potential long-term consequences;
- In patients with high IgM levels, plasmapheresis should be considered before rituximab therapy due to the IgM flare;
- Bortezomib and thalidomide based therapies are active and can be considered in the upfront treatment of WM. Lenalidomide should be avoided to aggravated anemia.

Upfront Therapy for WM



Treon et al, Blood 2009

Salvage Therapy for WM



Treon et al, Blood 2009

Waldenstrom Award

Nobel Hall

Stockholm, Sweden 2008