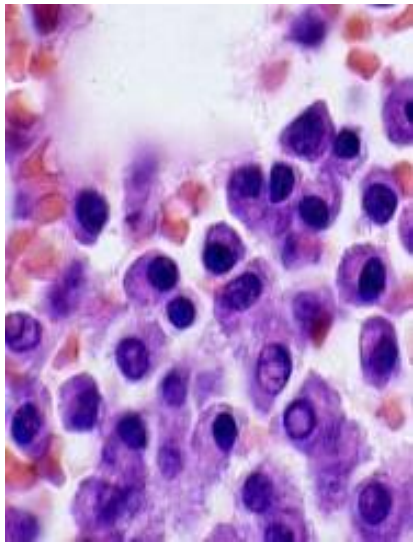
I Need Treatment – First-Line WM Treatments & Side Effects

IWMF Educational Forum
Grapevine, TX
5/1/2015



Larry Anderson, MD, PhD

Plasma Cell Disorder and

Stem Cell Transplant Specialist

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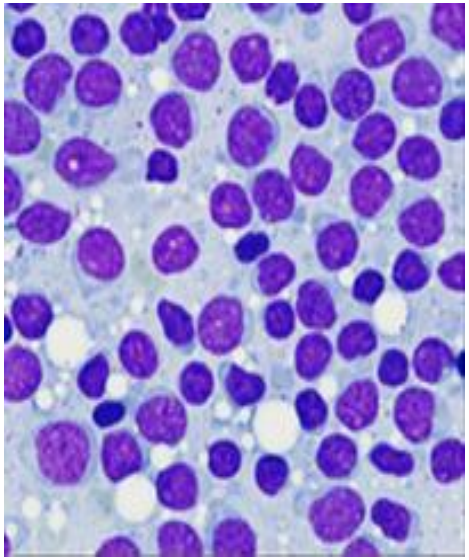

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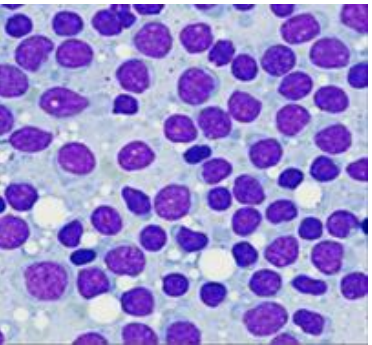
Diagnosis of Waldenström's Macroglobulinemia (WM) aka Lymphoplasmacytic Lymphoma (LPL):

Characteristic combination of :

1. **Monoclonal IgM protein (Immunoglobulin) secretion (although <5% LPL can be Non-IgM but not called WM)**

2. **Infiltration of the bone marrow with a clone of lympho-plasmacytic cells (>10%)**

   - **B lymphocytes partially differentiated into PCs, growth is out of control unless "Smoldering"**



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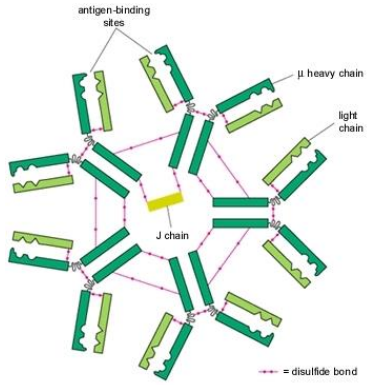
Signs/Symptoms of WM/LPL (Who needs Treatment?)

- **<u>No lytic bone lesions</u> or else it is IgM Myeloma**
- **Low blood counts**
  - **Anemia (Hgb <10) or Low platelets (Plt <100)**
- **Hyperviscosity (Sludging due to very high IgM)**
  - **Dizziness, blurry vision, nose bleeds**
- **Enlargement of spleen, liver or bulky lymph nodes (>5cm)**
- **Neuropathy (anti-MAG, Sulfatide, GM1, etc)**
- **Cold Agglutinins or Cryoglobulins (monoclonal)**
- **Fevers/Night Sweats/Weight Loss**
- **Systemic Amyloidosis**



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Management of Asympotomatic (Smoldering) Waldenstrom's

- **If Asymptomatic but BMBx shows >10% LPL OR M-spike ≥ 3 g/dL IgM then Smoldering WM, if both levels lower then IgM MGUS**
- **Only treat patients if they have symptoms:**
  - **Splenomegaly, bulky adenopathy, low blood counts (Hgb <10, Plt <100), fevers/seats/weight loss, hyperviscosity, Neuropathy, Amyloidosis, etc**
- **No improvement of survival proven if treat patients before symptoms!**
- **Watch and Wait: Recheck labs (CBC, IgM, SPEP) and symptoms every 3 months for the 1st year, then every 4-6 months if stable**
- **Only 2-12%/year will progress and ~25% will NEVER need treatment after >20 yrs!! (Kyle et al, Blood 2012)**
- **10 Year Survival for SWM is 75%**

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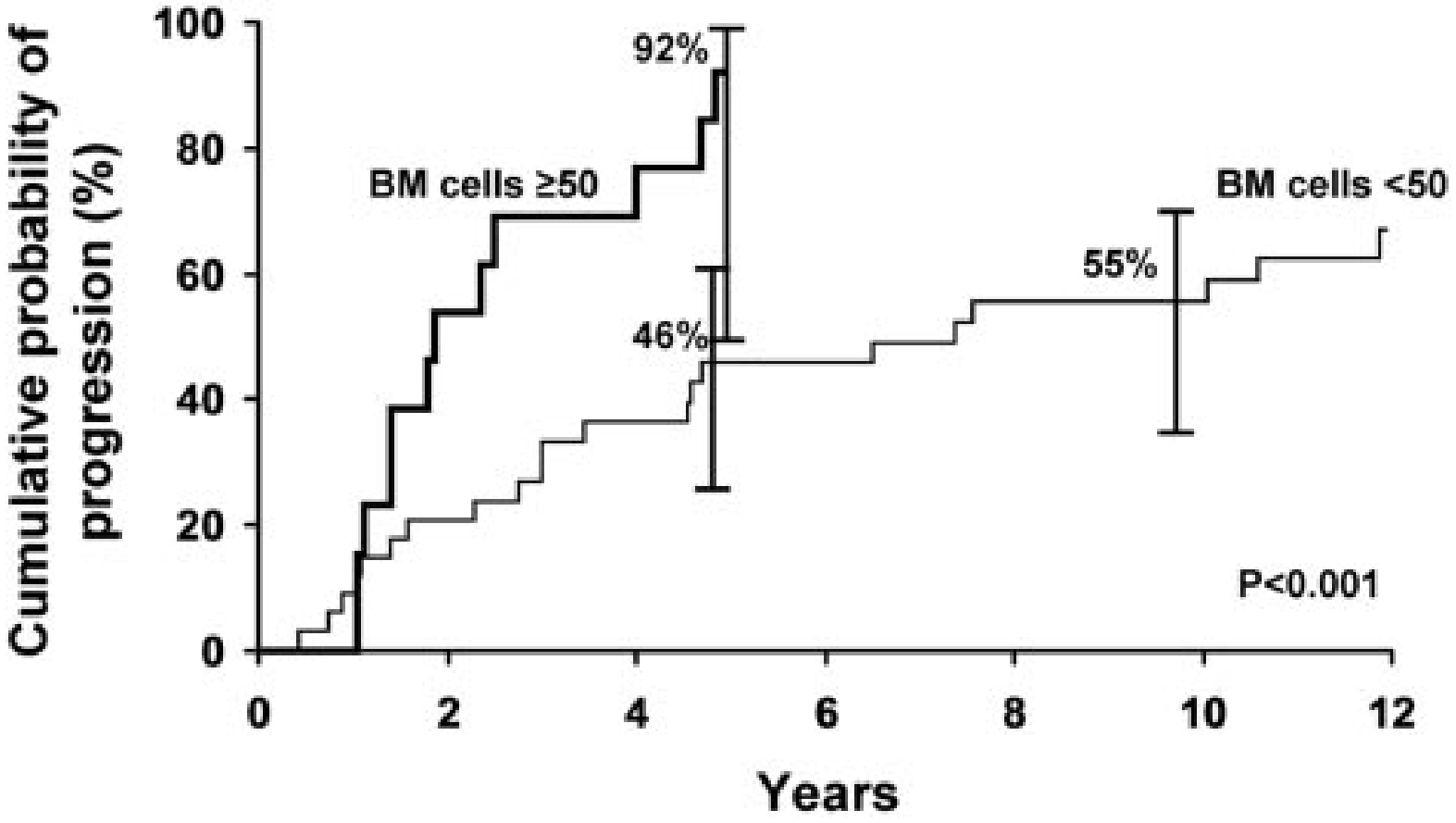
Natural History of Smoldering WM



Kyle et al, Blood 2012

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Management of Active/Symptomatic WM

- **Many choices of therapies including (Not curative but effective):**
  - **Rituximab anti-CD20 antibody (Can cause IgM flare and Hyperviscosity if IgM >5000 at baseline)**
  - **Bendamustine (better than cytoxan in STiL study)**
  - **Cytoxan or Chlorambucil (Alkylator Chemotherapy)**
  - **Velcade (Bortezomib) (proteosome inhibitors)**
  - **Fludarabine/2CDA (Purine analogs)(stem cell tox)***
  - **Thalidomide (NOT Revlimid due to risk of anemia)**
  - **Combinations of the above (Now BRD, VRD, CPR, and RCD shown to be highly effective)**
  - **Stem Cell Transplant in some cases**

How do we decide how aggressive to be?

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International prognostic scoring system for Waldenström macroglobulinemia

Pierre Morel,[1,2] Alain Duhamel,[3] Paolo Gobbi,[4] Meletios A. Dimopoulos,[5] Madhav V. Dhodapkar,[6] Jason McCoy,[7] John Crowley,[7] Enrique M. Ocio,[8] Ramon Garcia-Sanz,[8] Steven P. Treon,[9] Veronique Leblond,[2,10] Robert A. Kyle,[11] Bart Barlogie,[12] and Giampaolo Merlini[4]

BLOOD, 30 APRIL 2009 • VOLUME 113,

587 patients with clearly defined criteria for diagnosis and treatment.
Five adverse factors (<u>At Diagnosis</u>) were identified:

Age >65
Hemoglobin < 11.5 g/dL
platelets < 100
Beta 2- microglobulin > 3 mg/L
Serum IgM monoclonal protein (M-spike) > 7.0 g/dL.

<u>Low-risk</u>: (27%) with 0 or 1 of the adverse characteristics
<u>Intermediate-risk</u>: (38%) with 2 adverse factors or only advanced age
<u>High-risk</u>: (35%) with > 2 adverse characteristics.

Five-year survival rates were 87%, 68%, and 36%, respectively (*P* < .001).

LDH also divided high risk patients into 2 subgroups with different Overall Survival = 94 vs 35 mo and other studies also show free light chains as an adverse factor

Consider more aggressive therapy for higher Risk WM

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WM Response Criteria

- **CR (Complete Response)**
  - **Normal IgM, Negative SPEP (No M-spike) AND Negative Immunofixation (serum and urine),**
- **nCR (Near CR)**
  - **Negative SPEP/UPEP but POSITIVE Immunofixation**
- **VGPR (Very Good Partial Response)**
  - **> 90% reduction in IgM OR M-spike**
- **PR (Partial Response)**
  - **≥ 50% reduction in IgM OR serum M-spike**
- **MR (Minor Response)**
  - **≥ 25% reduction but <50% reduction**

Owen et al, Br J Haematol. 2013

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Patient #1

- 55 y/o WF with h/o early Breast Cancer 2001 (lumpectomy/radiation, aromatase), early Uterine Cancer 1999 (TAH/BSO), hypothyroid, on routine f/u late 2008 noted to have elevated total protein 8.9, globulin 4.9
- Workup showed M-spike 2.4 IgM Kappa, Total IgM 3630, Free Kappa 93.1mg/L, K/L 50.9, Viscosity 1.9, Beta 2 Micro 2.6, Hgb 12.4, Plt 339, no lytic lesions or adenopathy
- Bone Marrow Bx done 1/2/09: LPL involving 40% of cellularity, aspirate diff shows 31% Lymphs + 8% PCs, Flow shows clonal Kappa Restricted LPL/WM
- Should we start treatment now??

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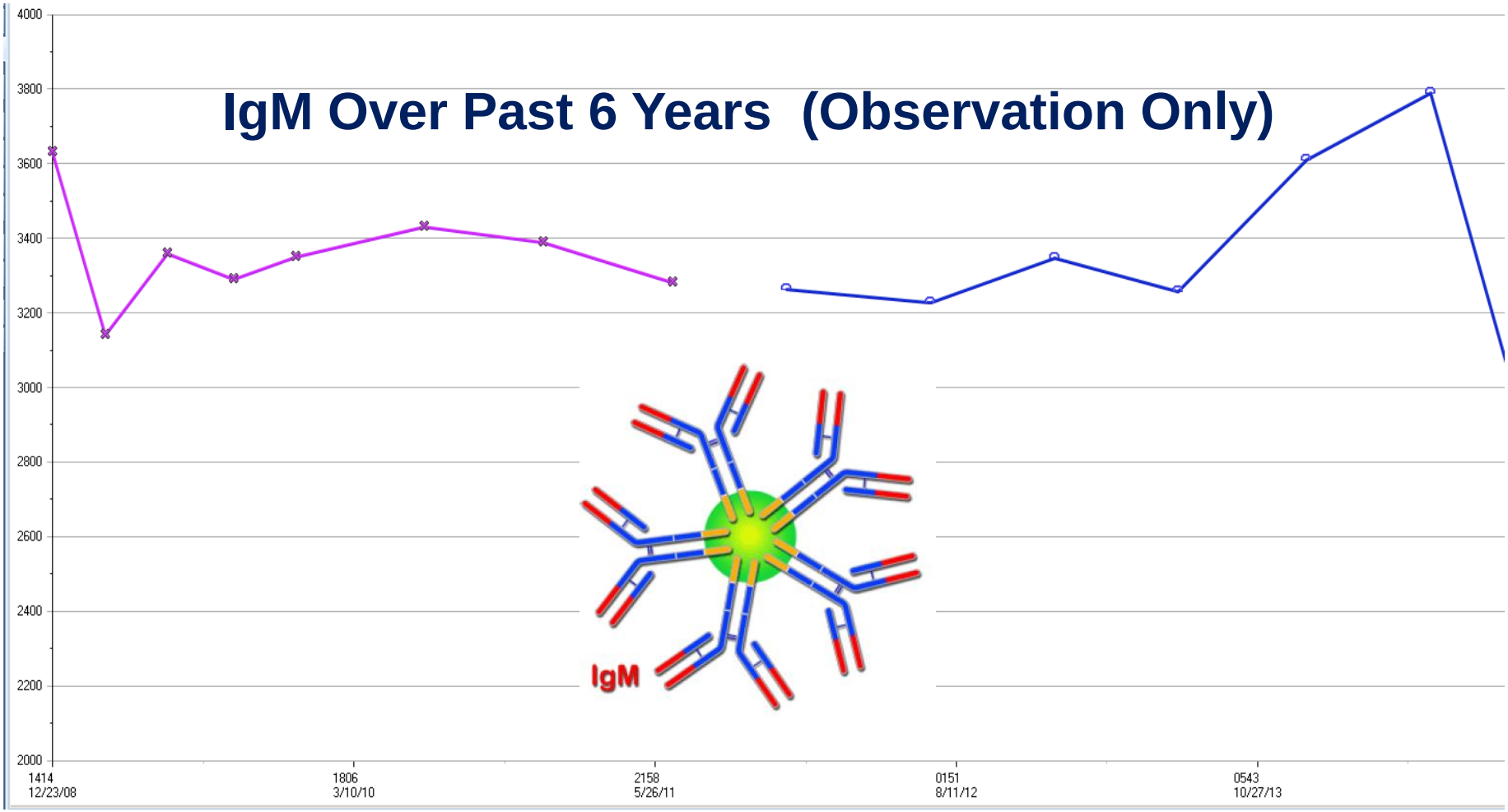
Patient #1, cont'd

- **No Splenomegaly, bulky adenopathy, Cytopenias, B-Symptoms, hyperviscosity, Neuropathy, skeletal survey neg, CT scans neg**
- **Therefore "Smoldering WM" and NO need for treatment**
- **Watch and wait with repeat labs and checkup every 3 months the 1st year, 4 months the 2nd year, then at least every 6 months if stable with no progression**
- **Graph of IgM …….**

Patient #1, cont'd



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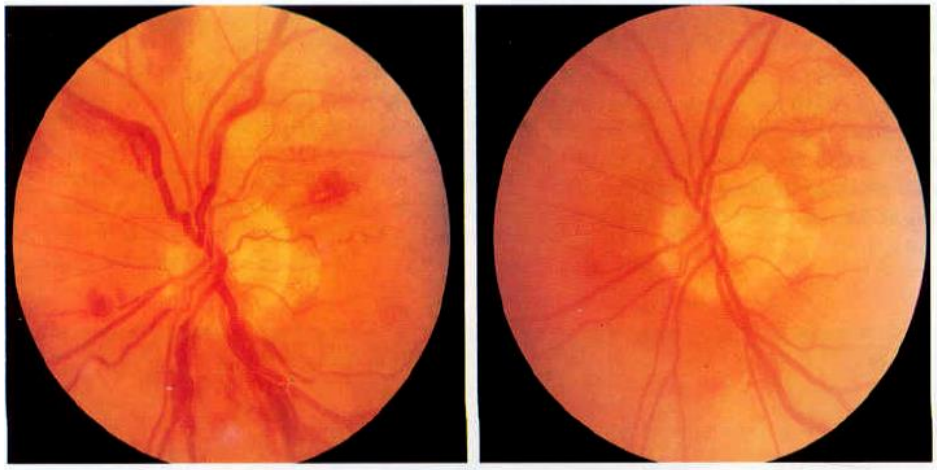
1st Question for Treatment:

- **Does the patient have Hyperviscosity?**
  - **Blurry vision, bleeding, dizziness**
- **If so then Plasmapheresis (to filter out IgM) is needed BEFORE other therapy**
- **Rarely seen with IgM <4000**



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Choice of Therapy in WM

- **Historically treated much like other Lymphomas with Cytoxan based therapy:**
  - **Current Options for Cytoxan regimens:**
    - **R-CHOP, R-CVP, CP-R, DRC**
  - **DRC and CPR are now preferred**
  - Clin Lymphoma Myeloma. 2009 Mar;9(1):62-6.
    CHOP-R (ORR, 96%; CR, 17%);
    CVP-R (ORR 88%; CR 12%);
    CP-R (ORR, 95%; CR 0%); (1000 mg/m2 cytoxan q 21d)
    Higher incidence for neutropenic fever and neuropathy for CHOP-R and CVP-R versus CPR ($P < .03$).
  - **Do NOT use vincristine or Adriamycin in WM since NO added benefit and only add risk of toxicity (Unless transformed to Large Cell Lymphoma)**

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Rituximab alone for Waldenström's Macroglobulinemia

69 symptomatic WM patients – rituximab x 4 doses
ORR 52% - 27% PR, 25% MR
Infusion reactions common, improve after 1st dose
Median duration of response – 27 months
Gertz et al, Leuk Lymphoma. 2004 Oct;45(10):2047-55.

Same study – evaluated IgM levels for "flare"
54% had an increase in IgM
27% still elevated at 4 months
No factors predicting an increase in IgM levels could be identified.
Ghobrial et al. Cancer. 2004 Dec 1;101(11):2593-8.

Primary Treatment of Waldenstrom's Macroglobulinemia with Dexamethasone, Rituximab and Cyclophosphamide (DRC): Long Term Follow-up Analysis of a Phase II Study.

Meletios A. Dimopoulos, et al , Abstract 2887, ASH 2011

- 72 patients enrolled. Update of Results from J Clin Oncol 2007
- Dexamethasone 20 mg IV followed by rituximab on day 1 and oral cyclophosphamide 100 mg/m2 bid on days 1 to 5 (total dose 1000 mg/m2). every 21 days for 6 courses (Like R-CHOP but withOUT vincristine and Adria)
- 83% Overall Responses, 7% complete, 67% partial and 9% minor responses.
- As of 6/09, 42 pts had progression but 14 patients have not yet required 2nd line treatment. Median TTP 35 months and time to next treatment 51 months.
- The probability for 5-year PFS and OS is 59% and 74%, respectively.
- Most respond again to rituximab-based regimens at relapse.

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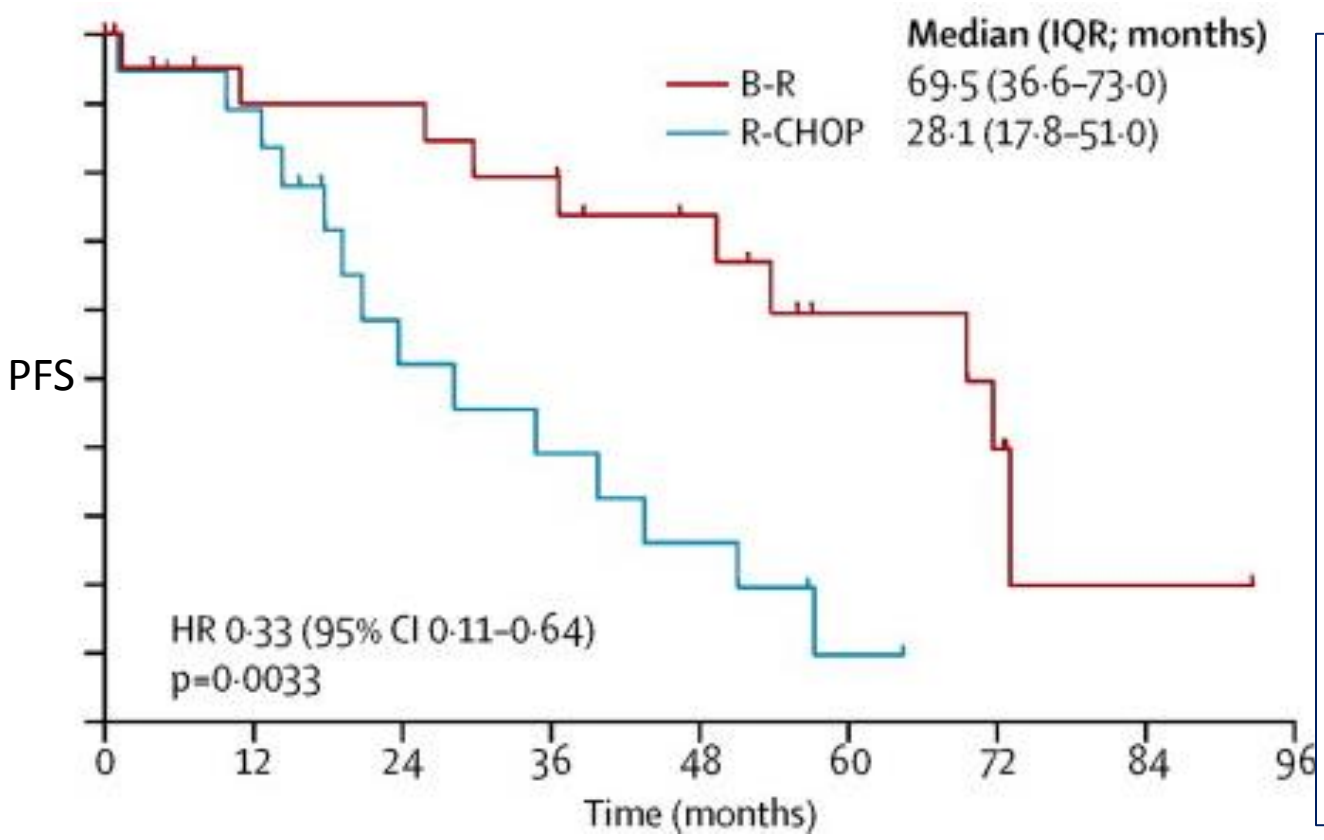
Bendamustine plus Rituximab (BR) compared with R-CHOP in WM patients : A subset analysis in the prospective randomized STIL trial



Rummel et al, Lancet 2013

In WM Subset:

BR better than R-CHOP for CR (39.6% vs 30.0%, *P* = 0.26) and time to next treatment (not reached vs 37.5 mos, *P* = .001)

Less infections, alopecia, stomatitis, neutropenia, and neuropathy

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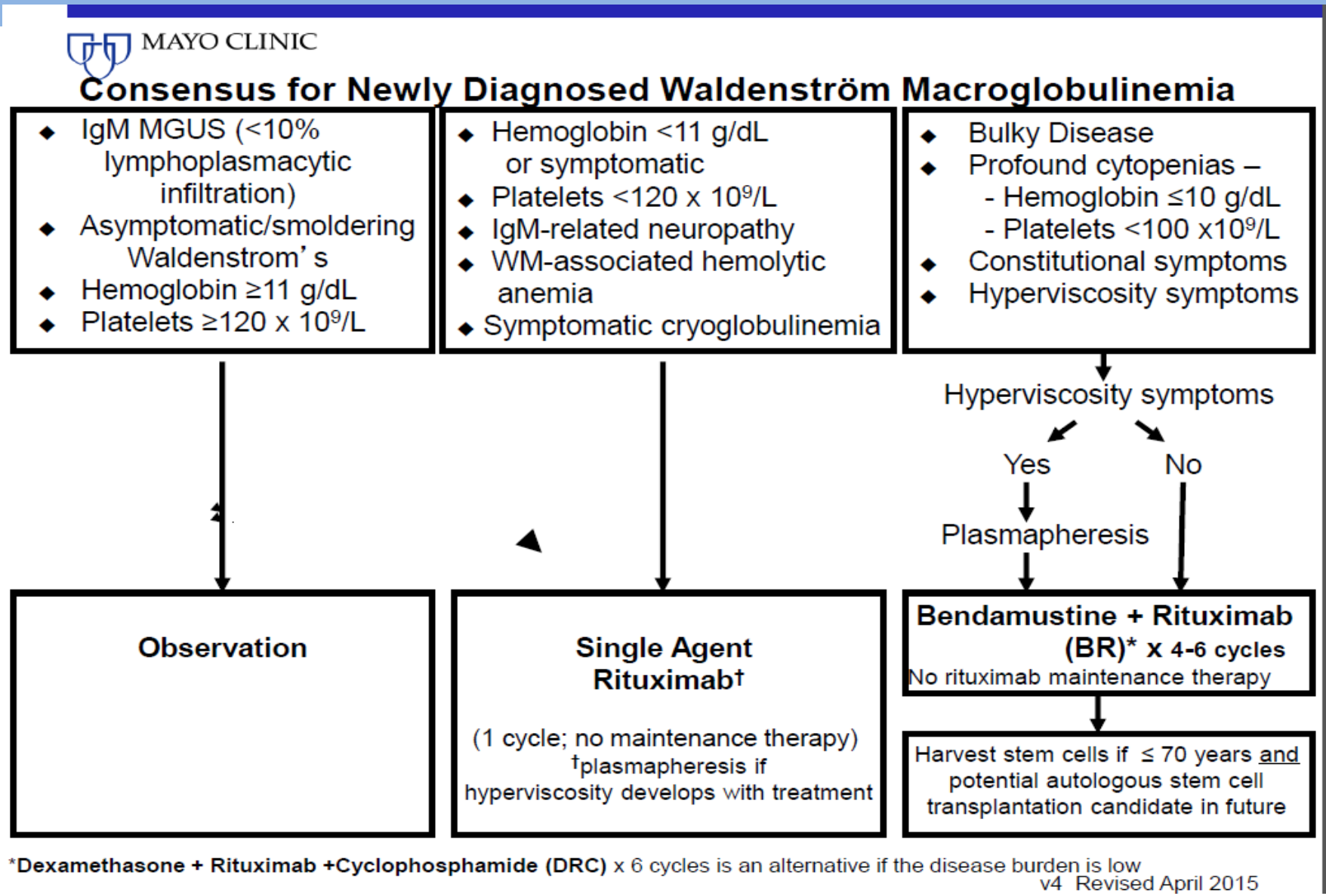
Mayo Clinic mSmart Guidlines

mSmart.org April 2015 Update



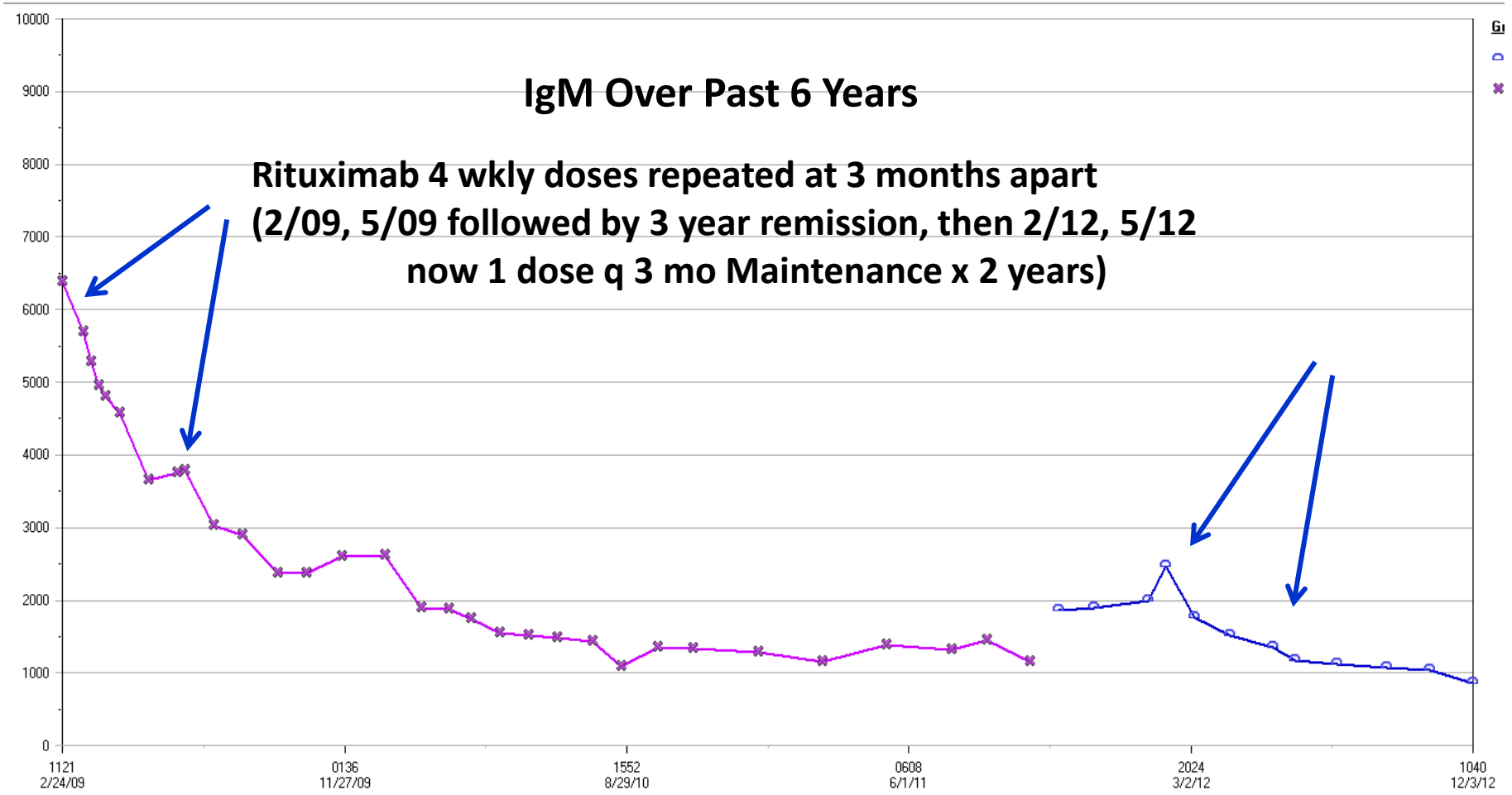
Patient #2

- 80 y/o WF with increasing back pain, osteoporosis, compression fractures. Workup showed anemia w/ Hgb 9.5, elevated total protein, M-spike > 3 g/dL
- Referred for Treatment of “Multiple Myeloma”
- IgM 6380, M-spike 3.6 g/dL IgM Lambda, Hgb 9.1, viscosity 2.3, Beta 2 Micro 4.74, Lambda 60
- BMBx showed similar findings to the previous case with 54% Lymphoplasmacytic Infiltrate.
- Imaging confirmed several compression fractures and osteoporosis but <u>NO lytic lesions</u>

Pt #2, cont'd

- **IgM >5000 but elderly, no hyperviscosity, tried DRC with oral cytoxan in combination with Rituxan but had terrible nausea with one dose of oral cytoxan so changed to single agent Rituxan and did well without IgM flare**
- **4 weekly doses followed by another 4 weekly doses 3 months later (weeks 12-15)**
- **Graph of IgM …….**

Patient #2, cont'd



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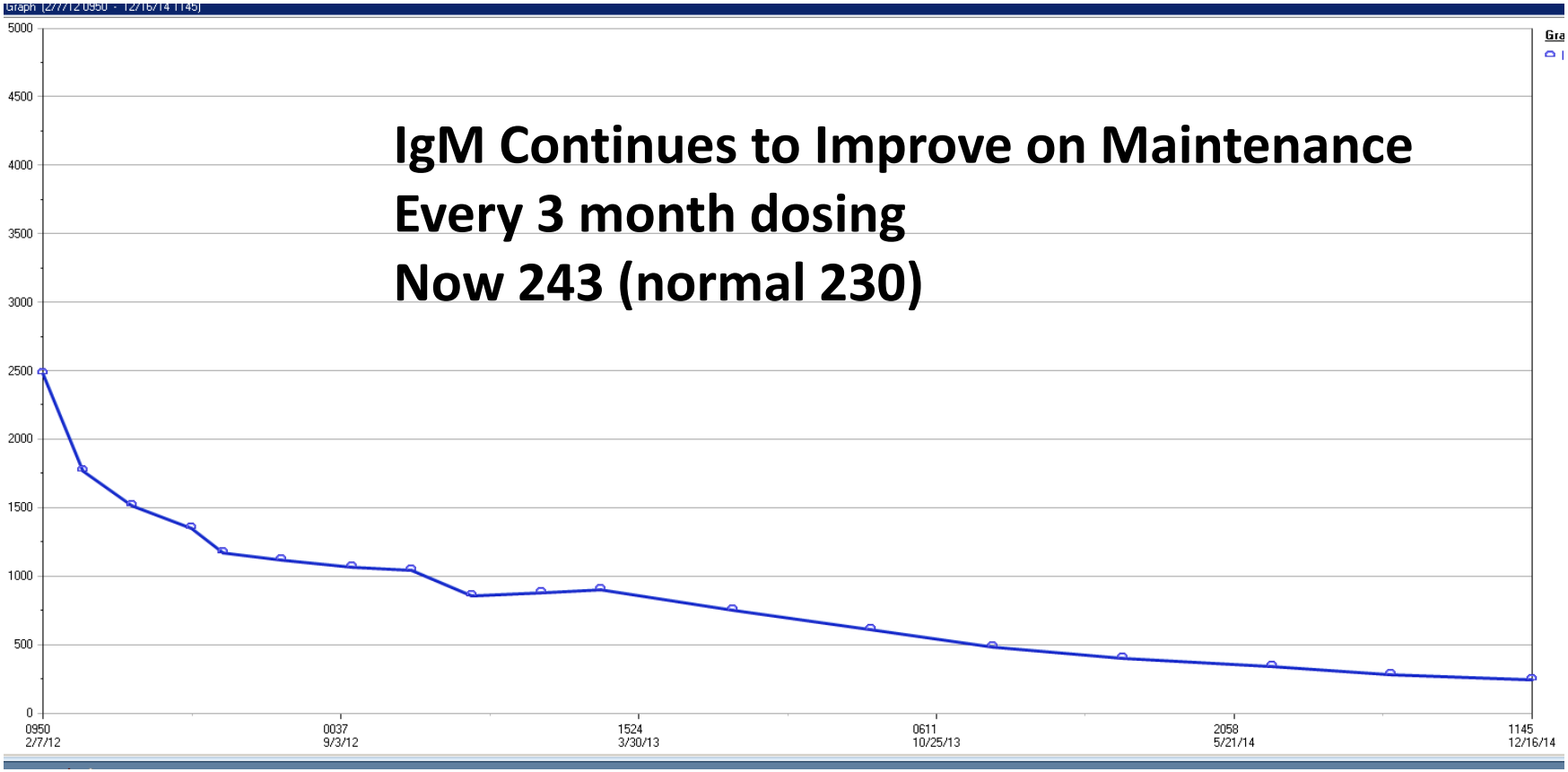
Pt #2, cont'd



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Maintenance Rituximab is associated with improved clinical outcome in Rituximab naive patients with WM who respond to a Rituximab-containing Regimen

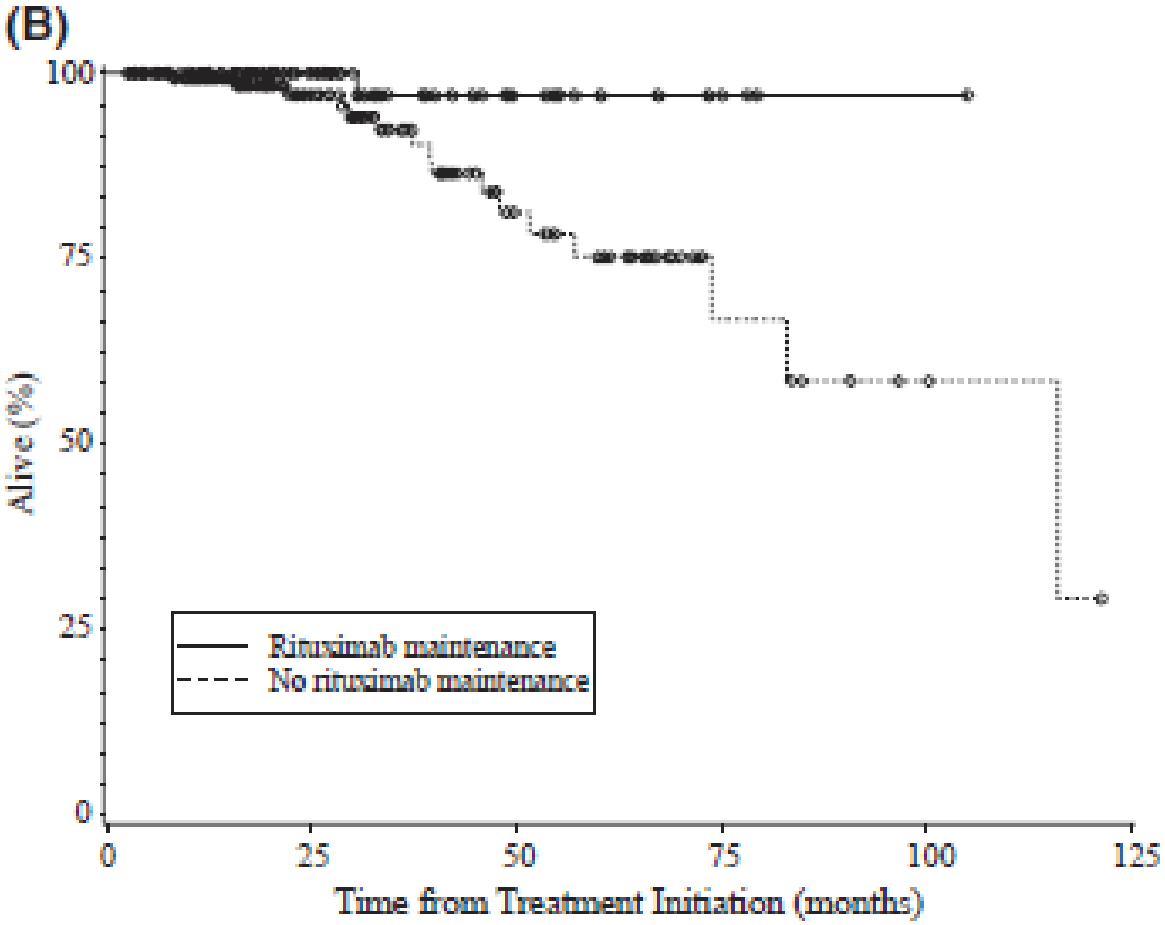
Treon et al, Br J Haematol. August 2011

- Not just longer to relapse but also lived longer!!

- Randomized trial needed to confirm

- Responses improved in (10%) of "Observed" and (41%) of Maintenance Rituximab patients

- Main risk: Infections such as Sinusitis and Bronchitis



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Primary Therapy of Waldenström Macroglobulinemia With Bortezomib, Dexamethasone, and Rituximab: WMCTG Clinical Trial 05-180

Journal of Clinical Oncology, AUGUST, 2009

Steven P. Treon, Leukothea Ioakimidis, Jacob D. Soumerai, Christopher J. Patterson, Patricia Sheehy, Marybeth Nelson, Michael Willen, Jeffrey Matous, John Mattern II, Jakow G. Diener, George P. Keogh, Thomas J. Myers, Andy Boral, Ann Birner, Dixie L. Esseltine, and Irene M. Ghobrial

For patients requiring immediate disease control, Bortezomib (Velcade) Dexamethasone, and Rituximab (BDR or VRD) achieves rapid dz control.

Time to response in WM patients treated with BDR was 1.1 months

Overall response rate was 96% with 35% at least VGPR and 22% of patients achieving a Complete or Near Complete Response (compared to <10% with other combinations tested).

With a median follow-up of 2 years, 80% of patients remained free of disease progression, including all patients achieving a VGPR or better in this study.

Peripheral Neuropathy was the most common toxicity leading to discontinuation of bortezomib in 61% of patients. (usually resolved but Need to explore weekly dosing)

Prophylaxis for shingles with acyclovir or valtrex is needed!!

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Phase II Trial of Weekly Bortezomib in Combination with Rituximab in Untreated Patients with Waldenstrom's Macroglobulinemia.

Irene M. Ghobrial, et al, Abstract 3752 (ASH 2009)

Bortezomib IV weekly at 1.6 mg/m2 on days 1, 8, 15, q 28 days x 6 cycles
Rituximab weekly on cycles 1 and 4. Dexamethasone not added.
N=26

At least MR in (24/26) 92%
2 (8%) in complete remission (CR) or near CR
15 (54%) in partial response (PR)
7 (27%) in minimal response (MR)
2 (8%) had stable disease.
By using IgM all 26 patients (100%) had at least a minor response

Median progression-free survival and overall survival have not been reached.
To date, six (23%) patients have developed progressive disease

Only Five patients developed grade 2 peripheral neuropathy including 4 who did not have neuropathy at baseline.

The combination of weekly bortezomib and rituximab showed significant activity and minimal neurological toxicity in patients with untreated WM.

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Summary of Changes in the latest IWWM compared to the previous 4th IWWM (2014 vs 2009)

Dimopoulos et al, Blood 2014

Clinical condition	New recommendation (2014)	Old recommendation (2009)
Cytopenias	DRC, bendamustine-rutuximab, bortezomib-rituximab	DRC, thalidomide + rituximab
High M-protein, transplant candidate	Bendamustine-rutuximab, bortezomib-rituximab	R-CHOP, DRC
High M-protein, non-transplant candidate	Bendamustine-rutuximab, bortezomib-rituximab	Nucleoside analogs + rituximab; nucleoside analogs + rituxi
Comorbidities and cytopenias	Rituximab	Rituximab

IWWM Guidelines from 2014

Dimopoulos et al, Blood 2014

Clinical situation/individual patient characteristics	Primary choice(s)	Alternative (s)
Patients with WM-related cytopenias or organomegaly	Rituximab-based combination	Bortezomib/rituximab
	DRC	
	Bendamustine/R	
Patients with symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia	Bortezomib followed by bortezomib/rituximab	Fludarabine/rituximab ± cyclophos
	Bendamustine/rituximab	
Patients with paraprotein related neuropathy	Rituximab alone	Fludarabine/R
	DRC	Bendamustine/rituximab
Elderly patients with poor PS	DRC	Rituximab monotherapy
	Oral fludarabine	Chlorambucil
Elderly patients not eligible for systemic intravenous therapy	Oral fludarabine	Chlorambucil
Young patients eligible for ASCT	DRC	Bendamustine/rituximab
	Bortezomib/rituximab	R-CHOP

Patient #3

- 62 y/o WF (Daughter of Patient #2)
- Was seeing PCP at UTSW for back pain and URI, found to have elevated total protein.
- 1/6/14: Returned to PCP for results of SPEP: M-spike 2.27 g/dL. She called me and I saw her for new pt consult same day expecting to see WM!
- Kappa FLC 174, IgM 5686, BMBx showed 30-40% PCs, Kappa restricted, IgM+, Cyclin D1+, FISH showed t(11;14)
- Xrays: subcortical lytic lesion of the left hip greater trochanter, 1.5cm lytic lesion of L1 on PET/CT
- Stage IIA IgM Myeloma, NOT WM, treated with Velcade/Revlimid/Dex and Auto SCT, in VGPR on maintenance Revlimid
- 20% of WM patients have FHx of BCM

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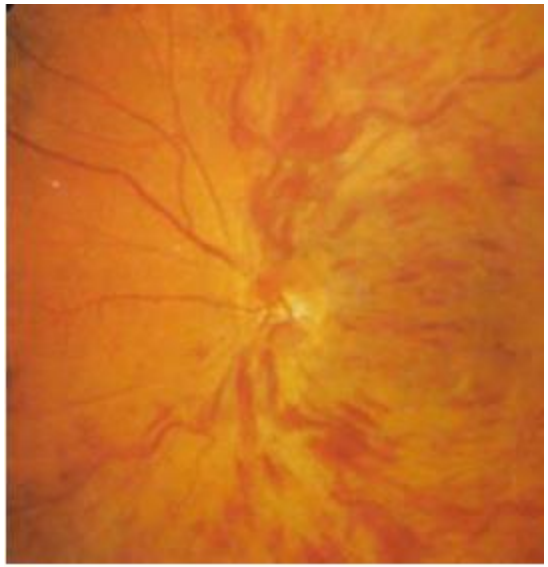
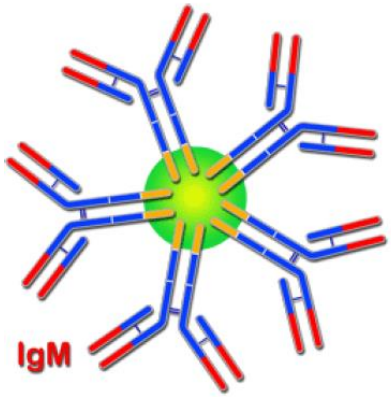
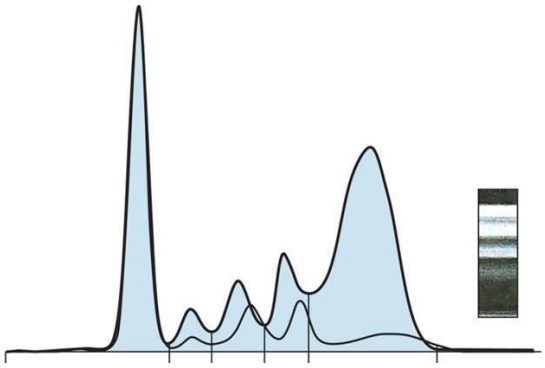
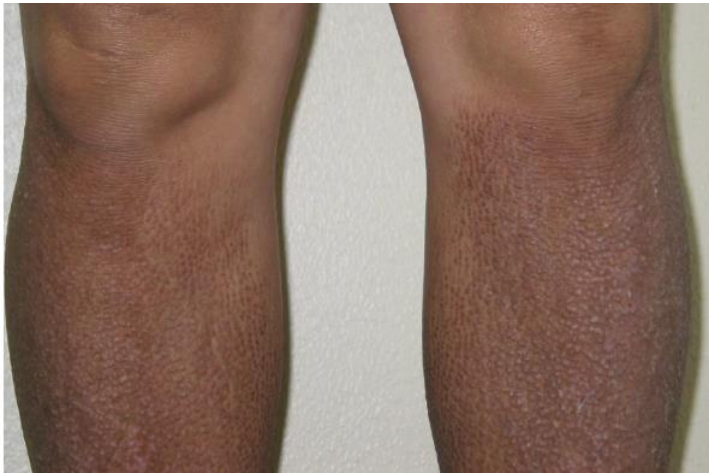
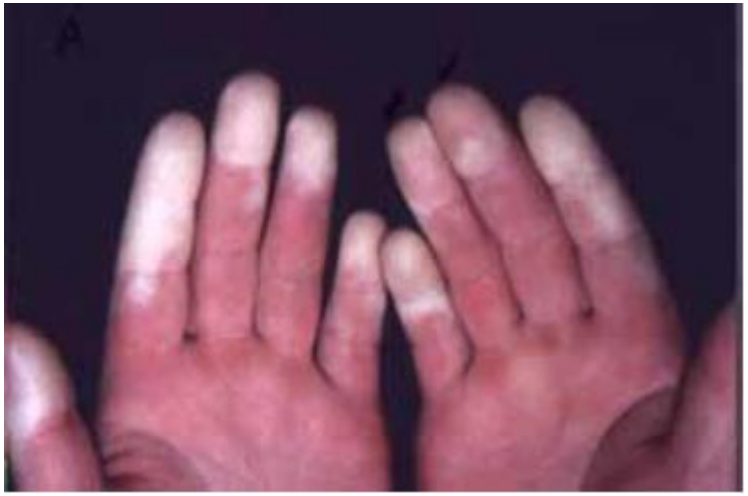
Questions ?











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