MAYO CLINIC

Waldenström's Macroglobulinemia

Morie Gertz
Mayo Clinic

Scottsdale, Arizona

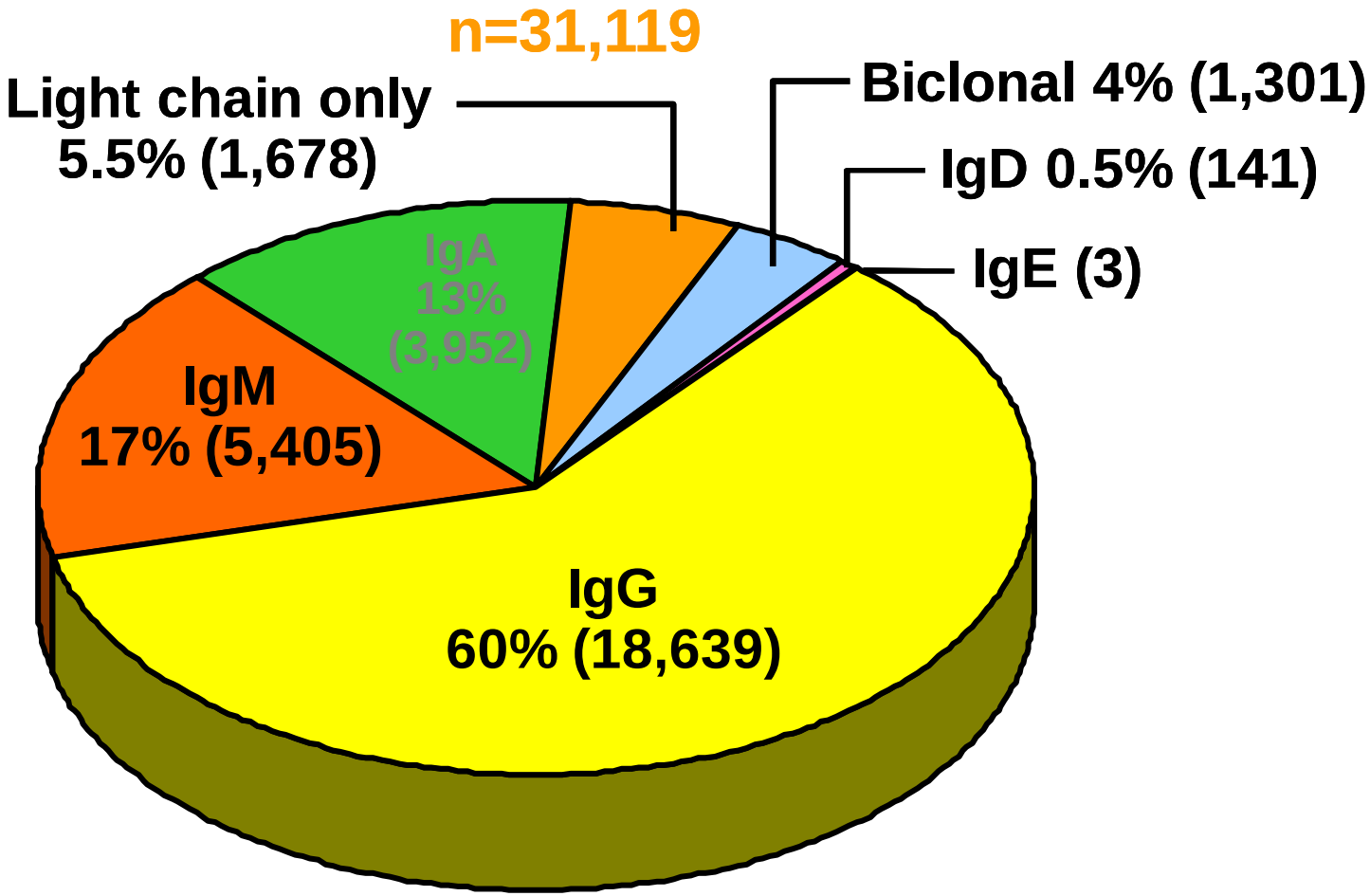
Rochester, Minnesota

Jacksonville, Florida

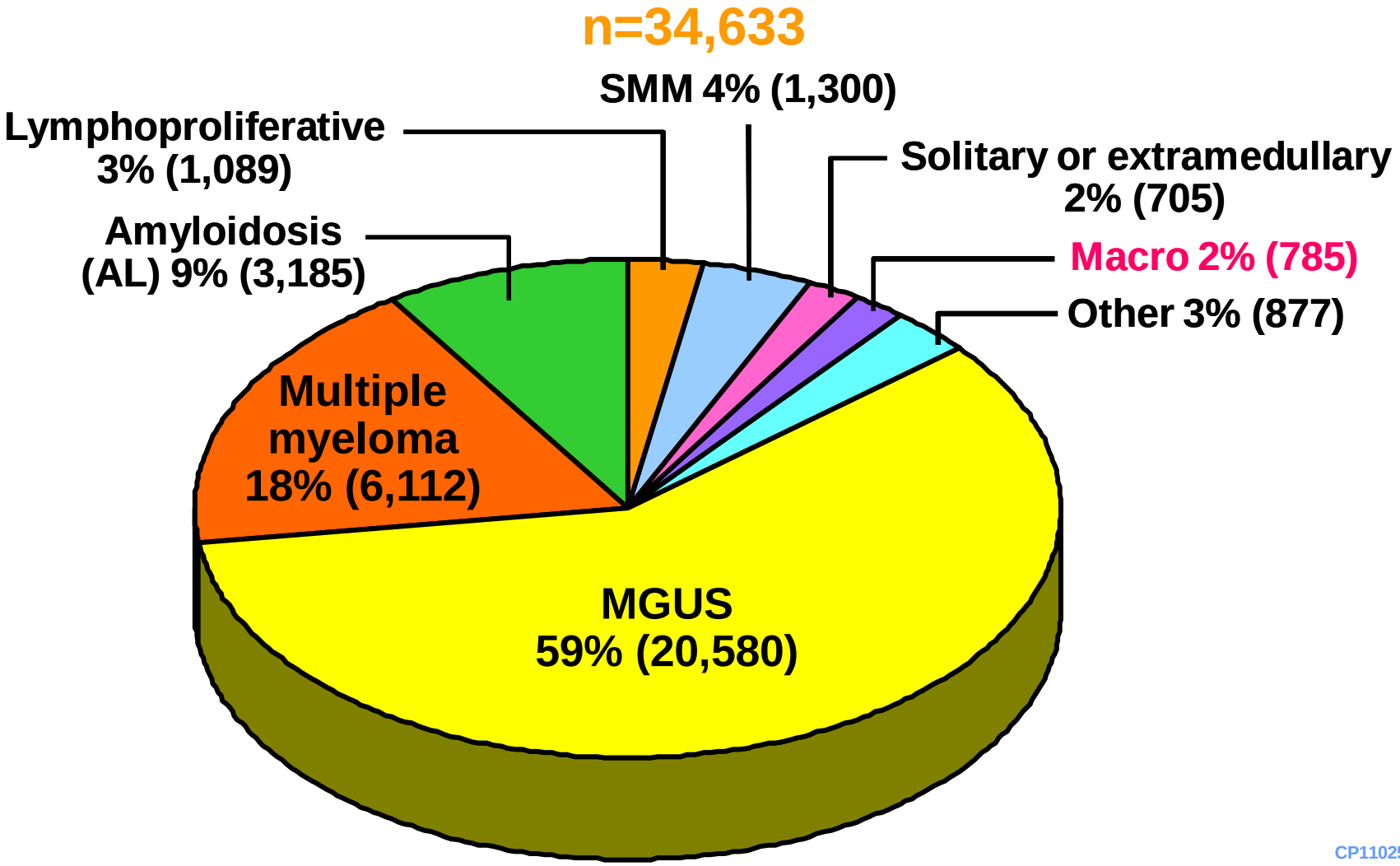
Disclosures

- Honoraria & Advisory Board: Millenium
- Honoraria: Celgene
- No drugs are FDA approved for Waldenström's so rituximab, CHOP, thalidomide, lenalidomide, fludarabine melphalan, etc. are all off label uses.
- No influence on this presentation

Monoclonal Serum Proteins
Mayo Clinic

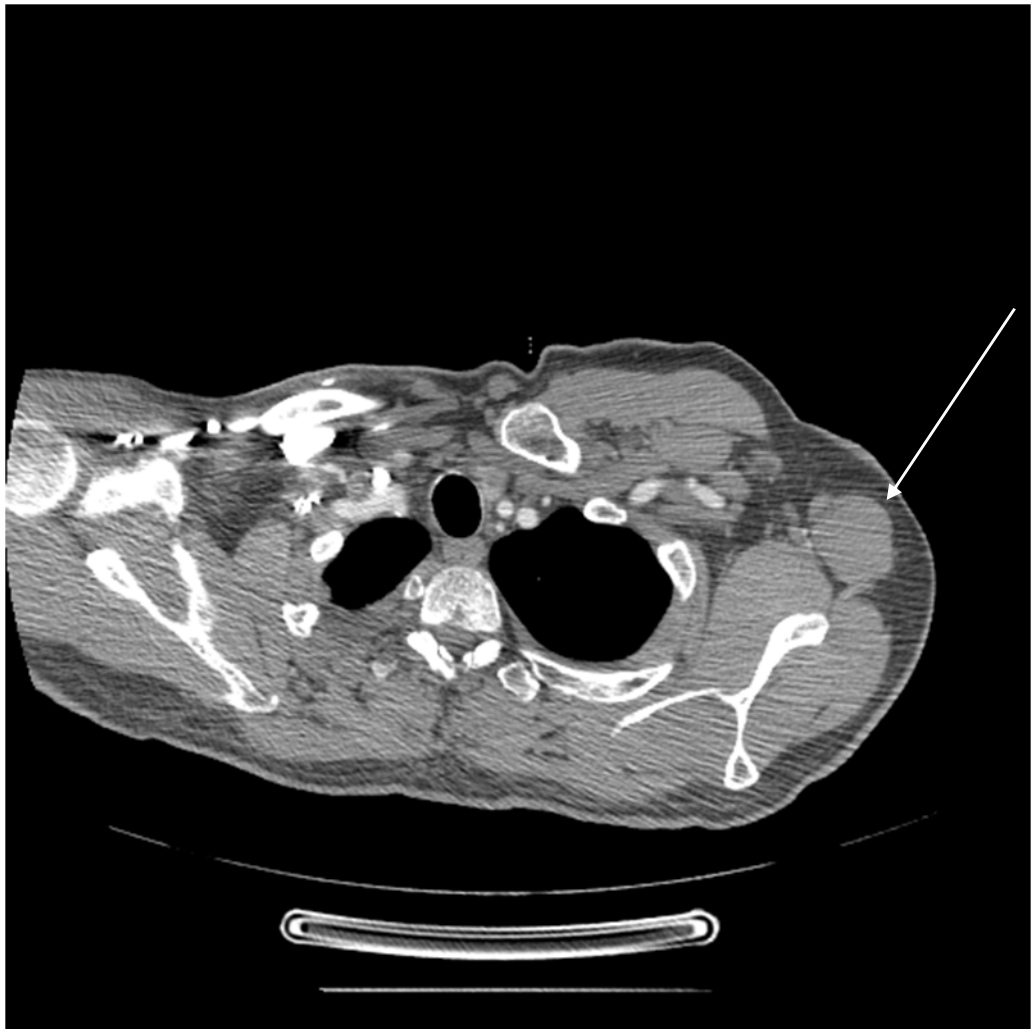


Monoclonal Gammopathies
Mayo Clinic



CP1102576-1

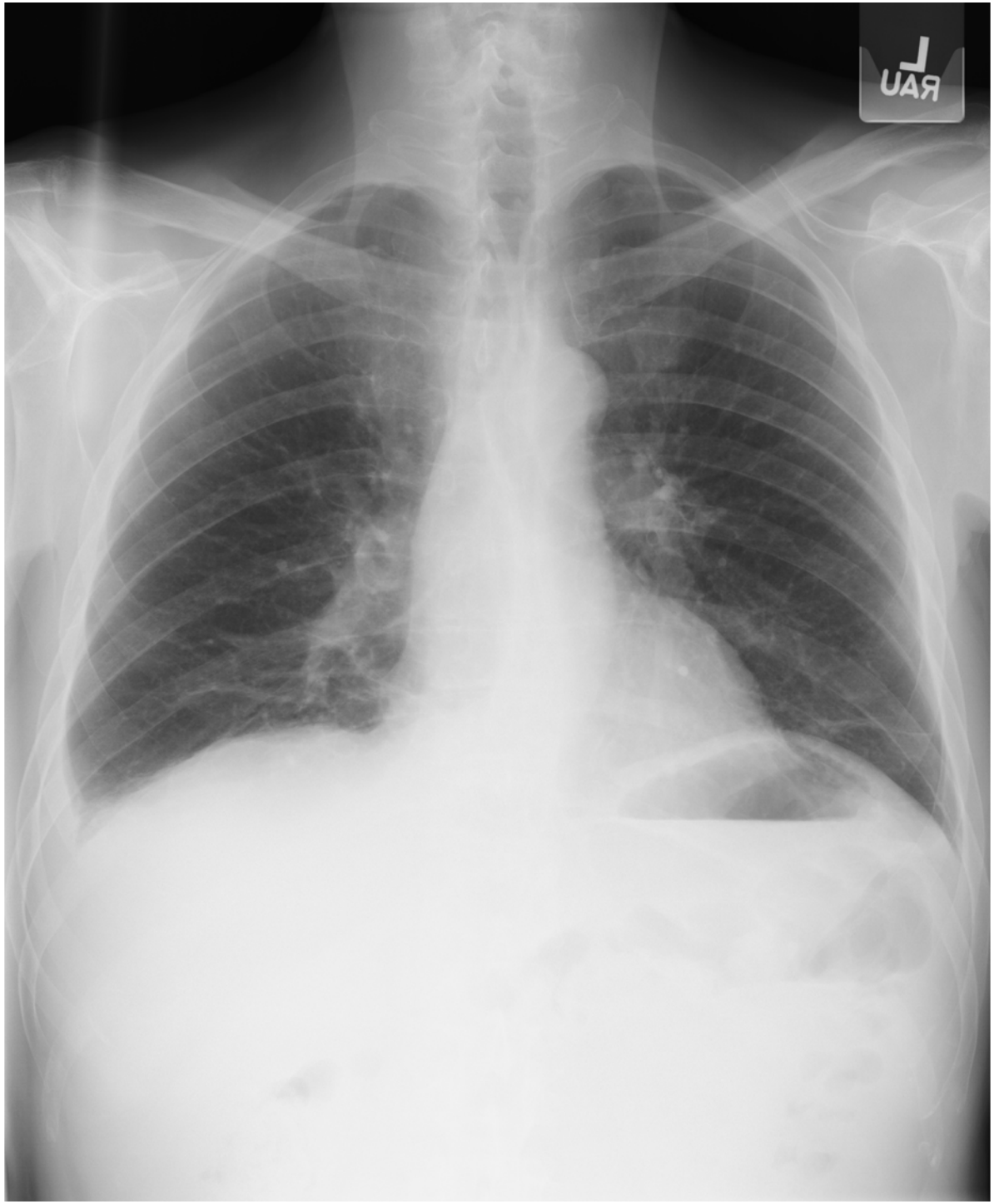
- 68 yo M cough, weight loss, adenopathy
- Fatigue 90 kg to 75 kg, Dyspnea on Exertion
- CT scan adenopathy

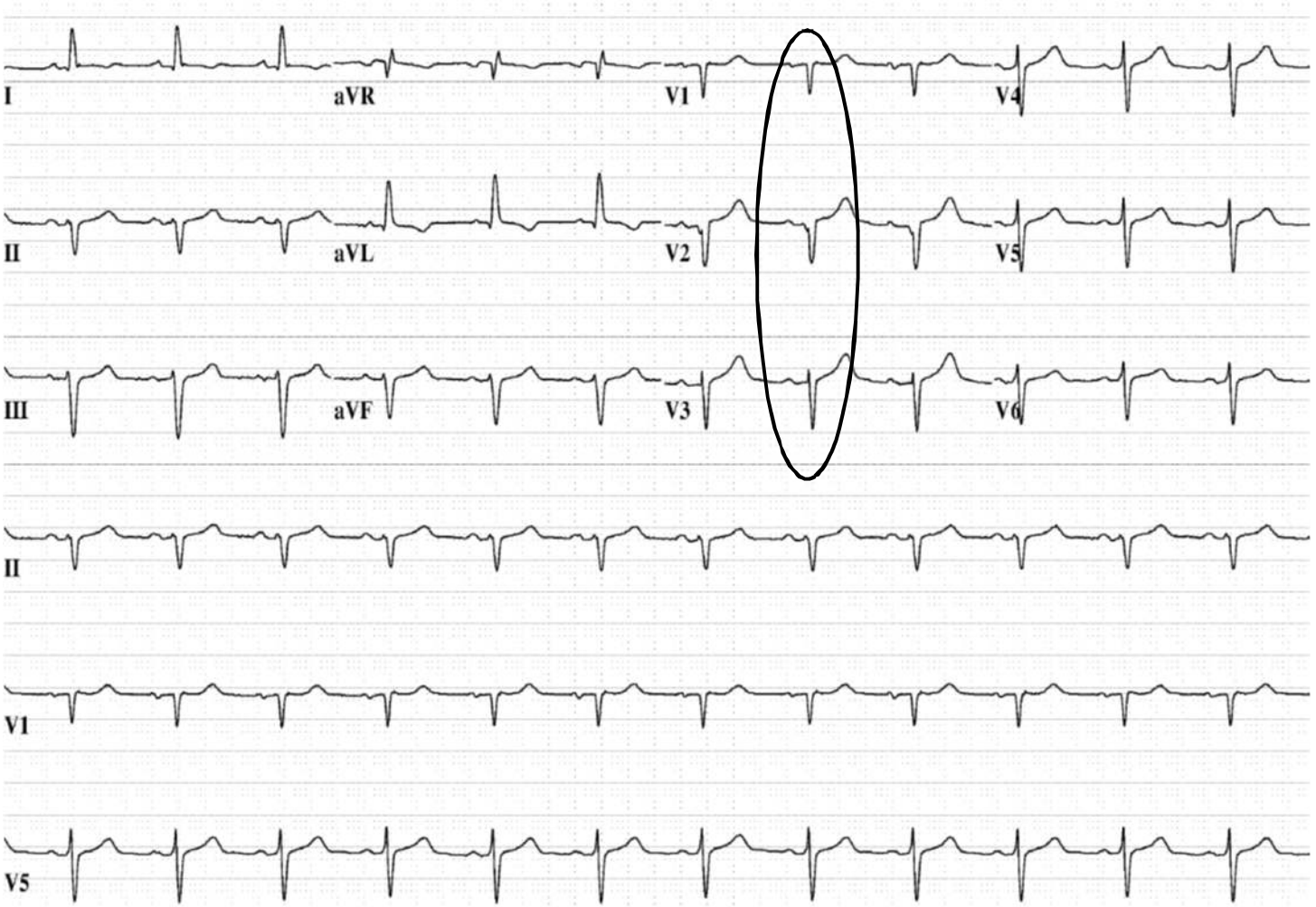


- Lymphoplasmacytic Lymphoma CD19+, CD20+
- IgMκ 0.6 g/dL. 785 mg/dL Hb 13.8
- Urine 258 mg/24 hours M spike 20% κ +Mκ

- Rituximab x 4 Weight loss continues increasing fatigue
- R-CVP x 2 cycles & constitutional fatigue increases
- During 1 Rituximab infusion bradycardia
- Echo & Treadmill done & negative
- Marrow: Normocellular with no morphologic or immunophenotypic features of involvement by lymphoma

bilateral pleural effusions, right greater than left




I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
V1
V5

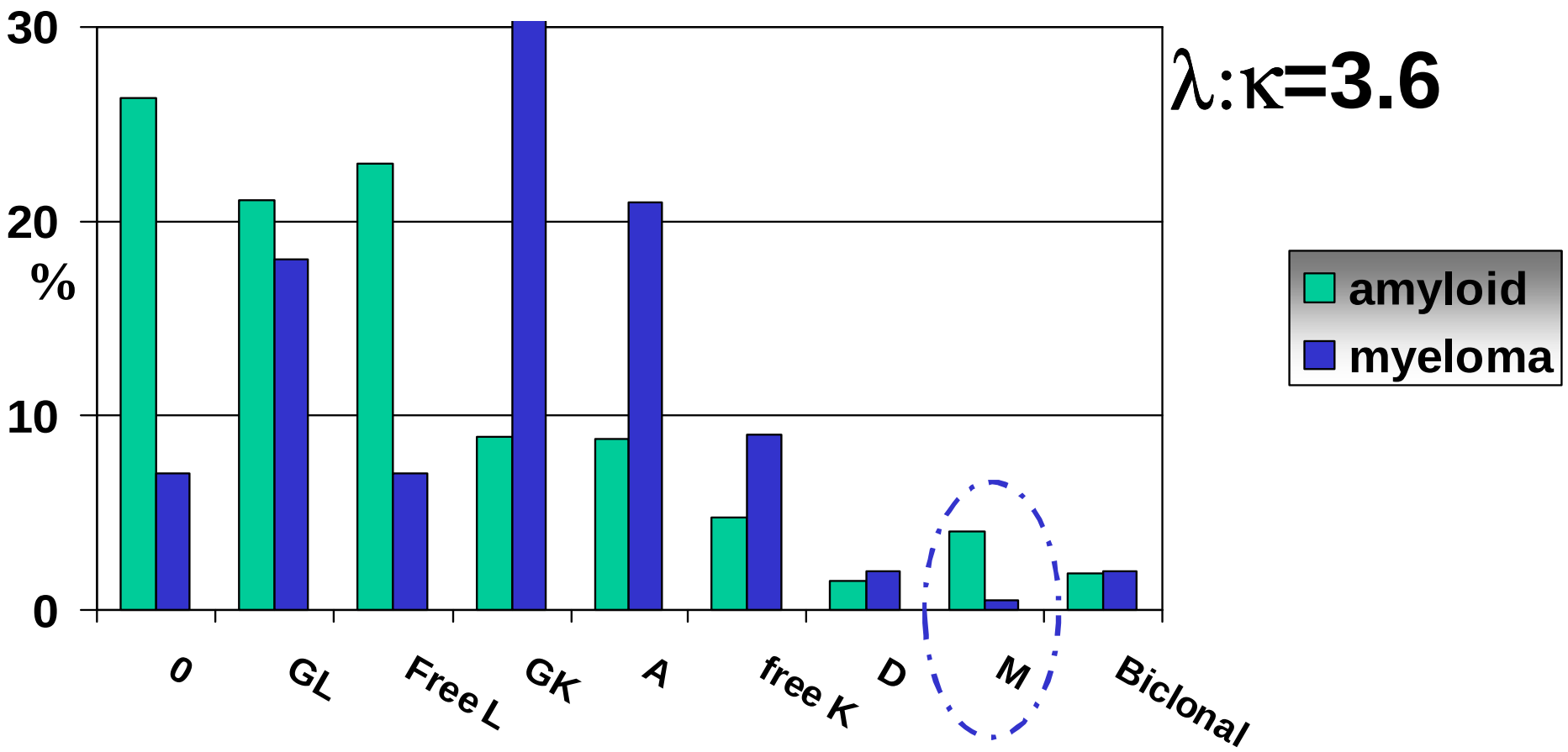
- BNP 816 (N<64)
- Troponin 0.03
- Echo Septal thickness 16 mm consistent with amyloidosis EF 60%
- Review of axillary node biopsy 5 months after reveals extensive amyloid deposition
- Alternate therapy begun

57 M

- persistent epistaxis
- small retinal hemorrhages
- Hb 6.1 IgM κ 3.4 g/dL 4890 mg/dL
- Outside path 60% replacement
- Rituximab dexamethasone still bleeding still transfusion dependent
- Refer 2nd opinion

- 60% monoclonal kappa plasma cells.
- There is no expression of CD20
- 100% of 100 plasma cells had fusion of CCND1 and IGH and
- 100% were monosomy 13.
- numerous poorly defined lytic lesions
- Alive at 75 mos with refractory disease receiving transfusions & TPE

Serum M Proteins in AL & Myeloma (IgM can be MM)



Message 1

- Get the diagnosis right
- Just because there is an IgM doesn’t make it macroglobulinemia
- Pt had IgM amyloidosis & although fulfilled criteria for WM had nothing to do with his sx, Patient with viscosity hd PCM
- Without amyloidosis no clear reason to treat
- Rituximab not active in IgM myeloma

Patient Referred for Therapy WM

- 67M Mκ Aug 1986; 376 mg/dL over 17 years rising to 1330. Fall in his Hb 9.6
- M-spike β region
- Dx WM Cladribine recommended
- No adenopathy
- Marrow: 15-20% LP lymphoma nodular & interstitial
- Seeks second opinion small IgM, marrow <40%

Laboratory Evaluation of Man Referred with WM

- Hb 10.2, reticulocytes 3%, M-spike 1.0; Haptoglobin <14 (n>30), LDH WNL
- T/D Bilirubin 1.6/0.3
- DAT 2+, Anti-Complement 2+
- Cold Agglutinin titer 1:131,072 (2^{17})
- Observation 6 months stable Hb

COLD AGGLUTININ PATIENT

- After 22 months of additional observation: Acute Bronchitis on a Cruise ship
- Hb 6.5, Retic Count 6%, LDH 339, Bili 2.5
- Dexamethasone ⇒ glucose 610
- Rituximab x 4 weeks
- 2 months later Hb 12.2, Haptoglobin <14, Plasma Hb 75.8 (nl<15)
- 4.5 years later followed grade 3 renal cell Hb 10.9

COLD AGGLUTININ PATIENT

- Titer of Cold Agglutinin 1:65536 (2^{16})
- Coombs 2+
- No M spike on SPEP, Mκ by IF only
- IgM 379 (from 1450 14 months earlier)

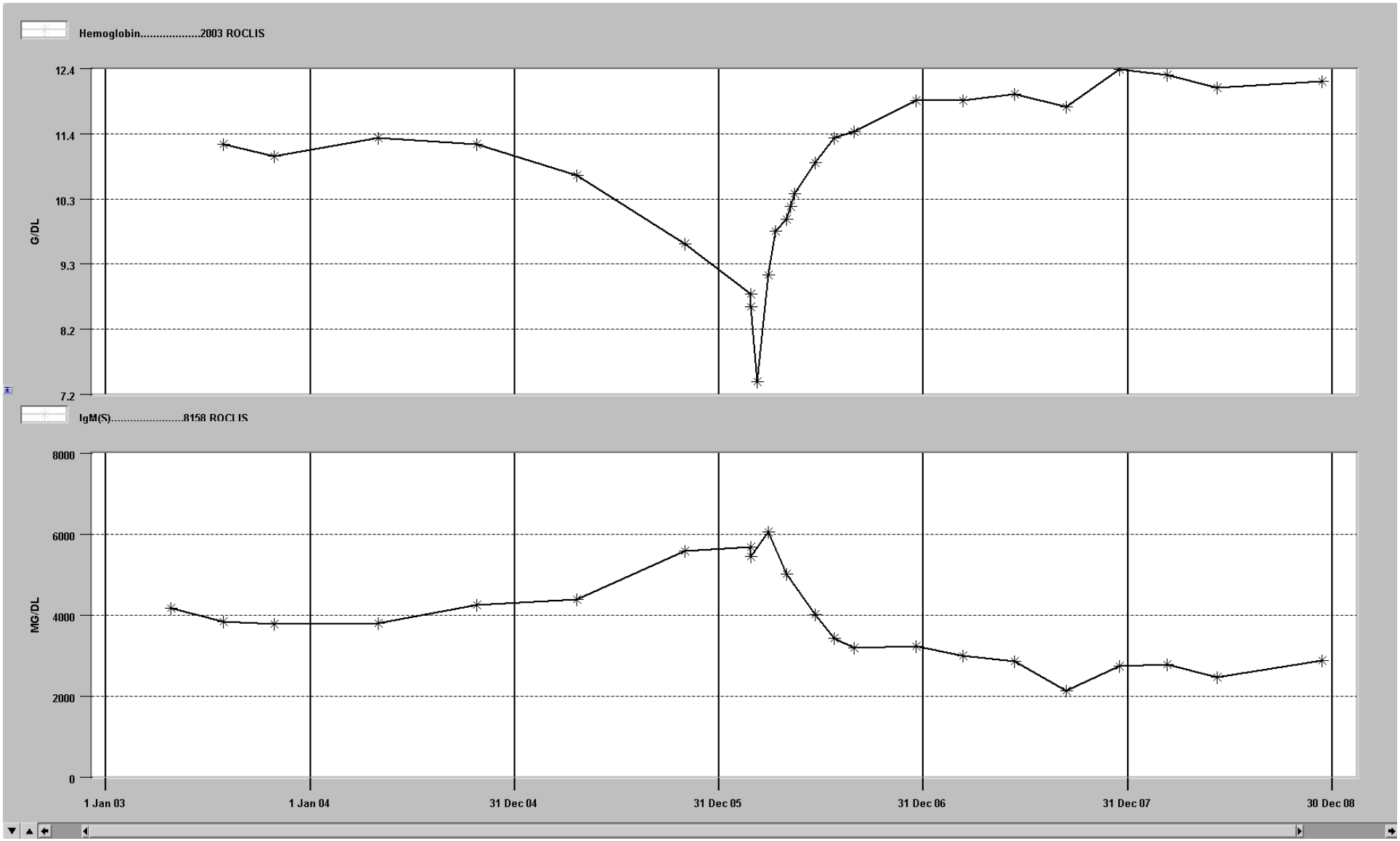
Message 2

- IgM proteins do funny immunologic things that have nothing to do with the “tumor mass”

56 yo F Increasing Fatigue Audience Response Question

- Hb 11.2; ESR 114; γ-spike 3.0; IgM 4170; β-2M 2.34; viscosity 2.5; Urine .246 89% κ Ct abd mild adenopathy Marrow 30 % replacement

- 1.Rituximab alone 2. R+combos 3. PNA 4. alkylator based 5. Steroids 6. other

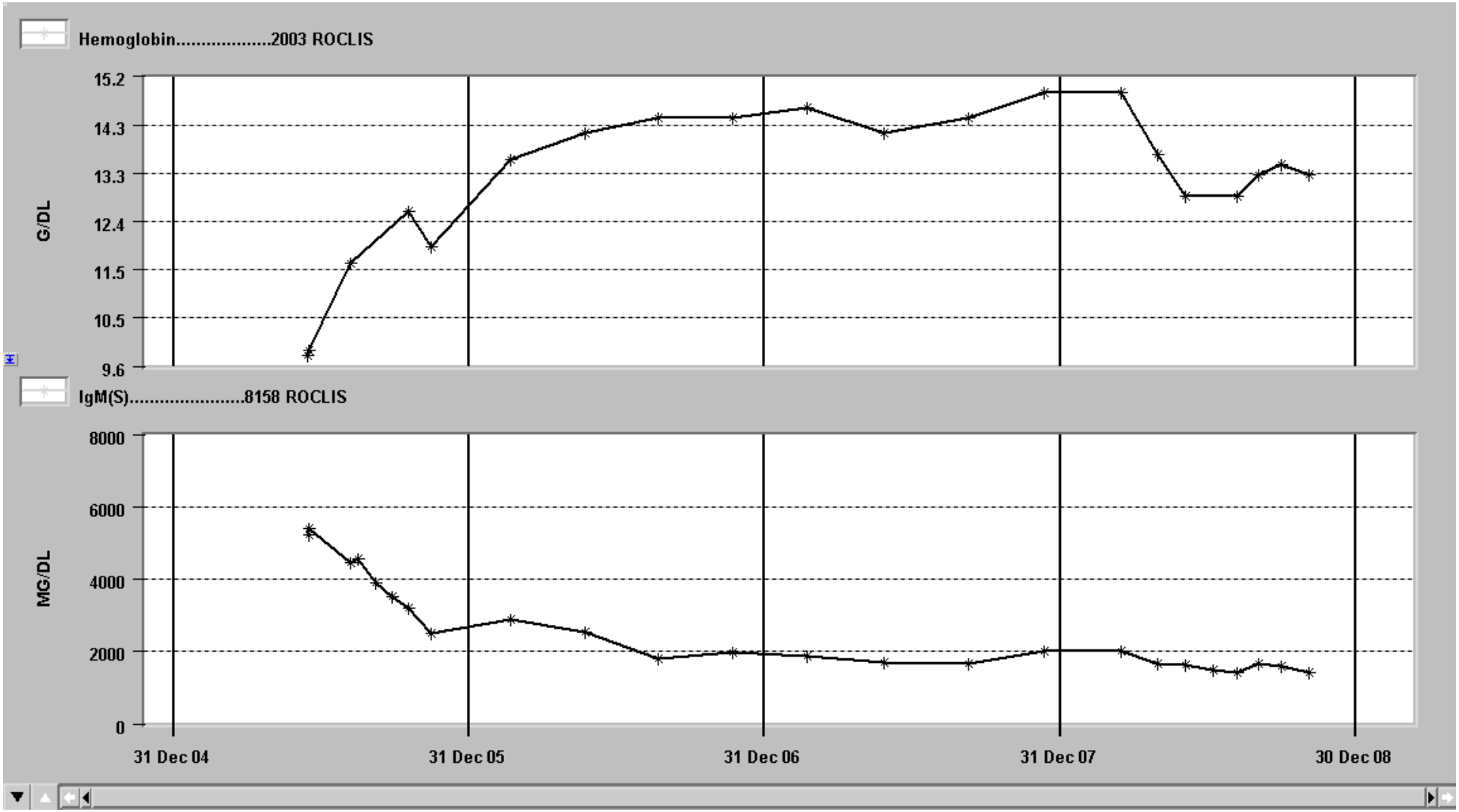

Hemoglobin.....2003 ROCLIS
12.4
11.4
10.3
9.3
8.2
7.2
G/DL
IgM(S).....8158 ROCLIS
8000
6000
4000
2000
0
MG/DL
1 Jan 03
1 Jan 04
31 Dec 04
31 Dec 05
31 Dec 06
31 Dec 07
30 Dec 08

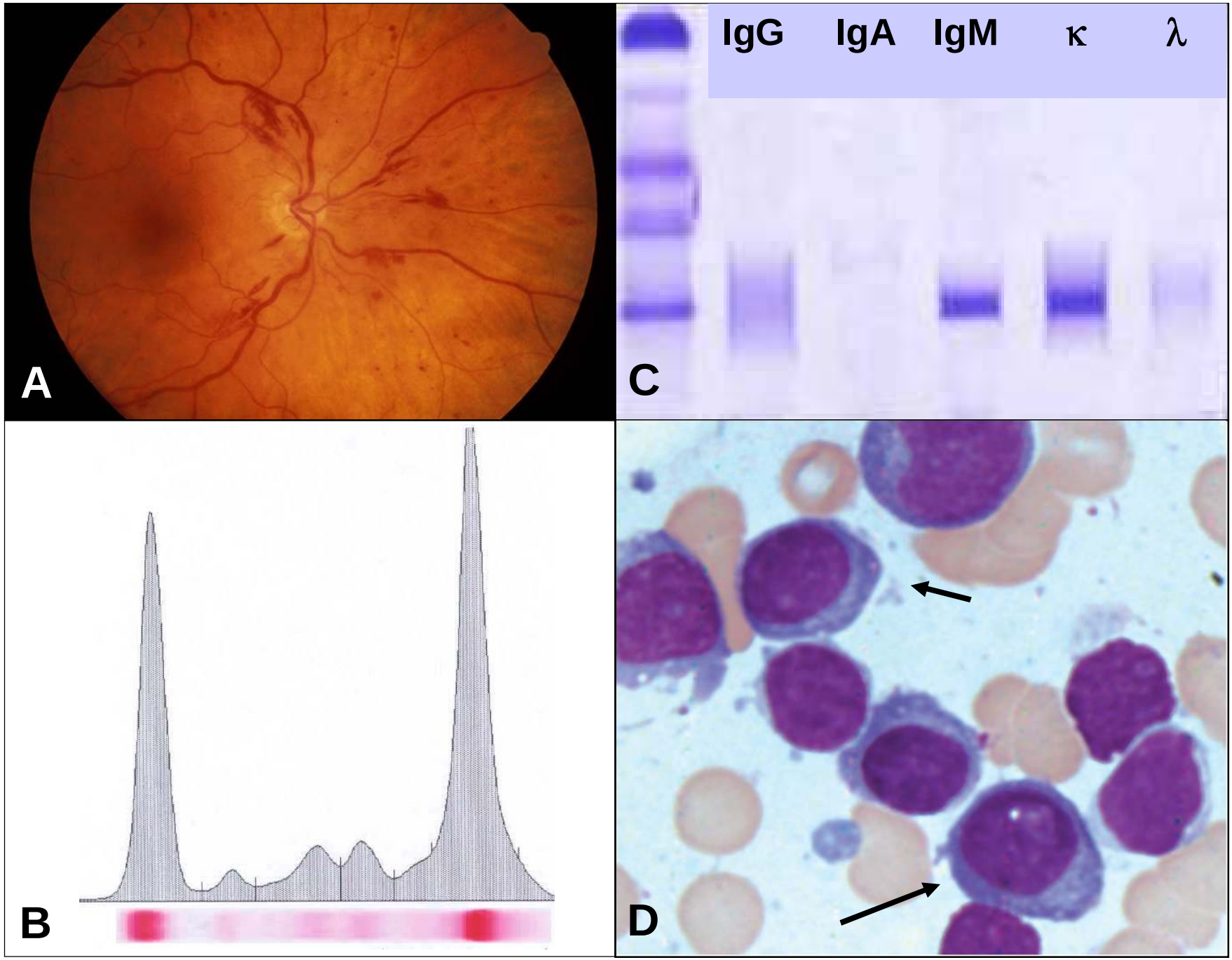
Message 3

- Even when it is Waldenström's that does not always require therapy

45 YO runner
Audience Response Question

- From marathons to 4 mi run walks
- Hb 9.8 γ spike 3.9 IgM 5390 viscosity 2.0 β-2M 2.32 Ct abd visible not enlarged nodes Marrow 50% involvement
- 1.Rituximab alone 2. R+combos 3. PNA 4. alkylator based 5. Steroids 6. other


Hemoglobin.....2003 ROCLIS
15.2
14.3
13.3
12.4
11.5
10.5
9.6
G/DL
IgM(S).....8158 ROCLIS
8000
6000
4000
2000
0
MG/DL
31 Dec 04
31 Dec 05
31 Dec 06
31 Dec 07
30 Dec 08


A
IgG
IgA
IgM
κ
λ
C
B
D

Incidence of WM

- 95,797 NHL diagnosed 1988 - 2007, 1835 (1.9%) were WM.
- Median age at diagnosis of WM 73
- The overall annual age-adjusted incidence was 3.8 per 1,000,000 persons ranging from 0.3 in patients aged <50 years to 28.5 in patients aged ≥80 years.

Cancer. 2011 Dec 2. doi: 10.1002/cncr.26627.

Incidence of WM

- Incidence of WM was higher in men (5.4) than in women (2.7;) and was higher in whites (4.1) than in Blacks (1.8)
- The annual percentage change for the whole population was 1.01%
- . Significant annual percentage change increases were seen in the group aged 70 to 79 years (1.24%)

Cancer. 2011 Dec 2. doi: 10.1002/cncr.26627.

Waldenstrom's Characteristics

Macroglobulinemia is not:

- **Lymphoplasmacytic lymphoma t(9;14) not seen, IgH translocations not seen**
- **Marginal zone lymphoma (MALT) t(11;18) not seen, t(11;14) absent MZL**
- **Myeloma/CLL deletion 13q14 not seen**
- **CLL -17p not seen, nor +12**
- **Follicular lymphoma t(14;18) not seen**
- **6q- 40-50 %; MYD88 60-90%**

Definitions of IgM-Related Phenomenon in Macroglobulinemia

	IgM Monoclonal Component	Symptoms of Tumor Mass/Infiltration (Adenopathy Anemia)	Marrow Infiltration >10%	IgM-Mediated Symptoms
MGUS	+	−	−	−
Smoldering macroglobulinemia	+	−	+	−
IgM-related disorder (eg, cold agglutinin hemolytic anemia, type II cryoglobulin, neuropathy, amyloidosis)	+	−	±	+
Macroglobulinemia	+	+	+	±

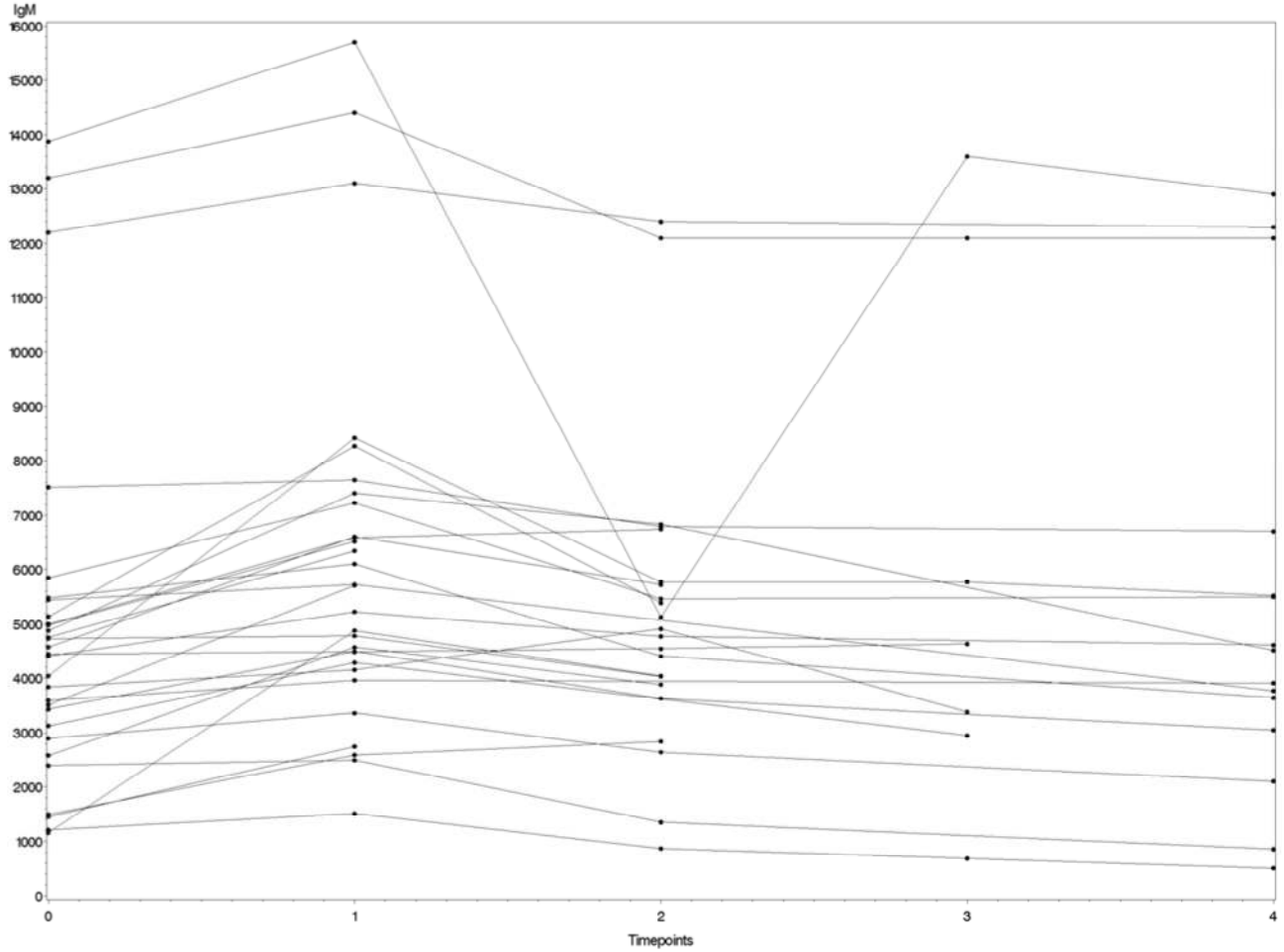
MACROGLOBULINEMIA Classification

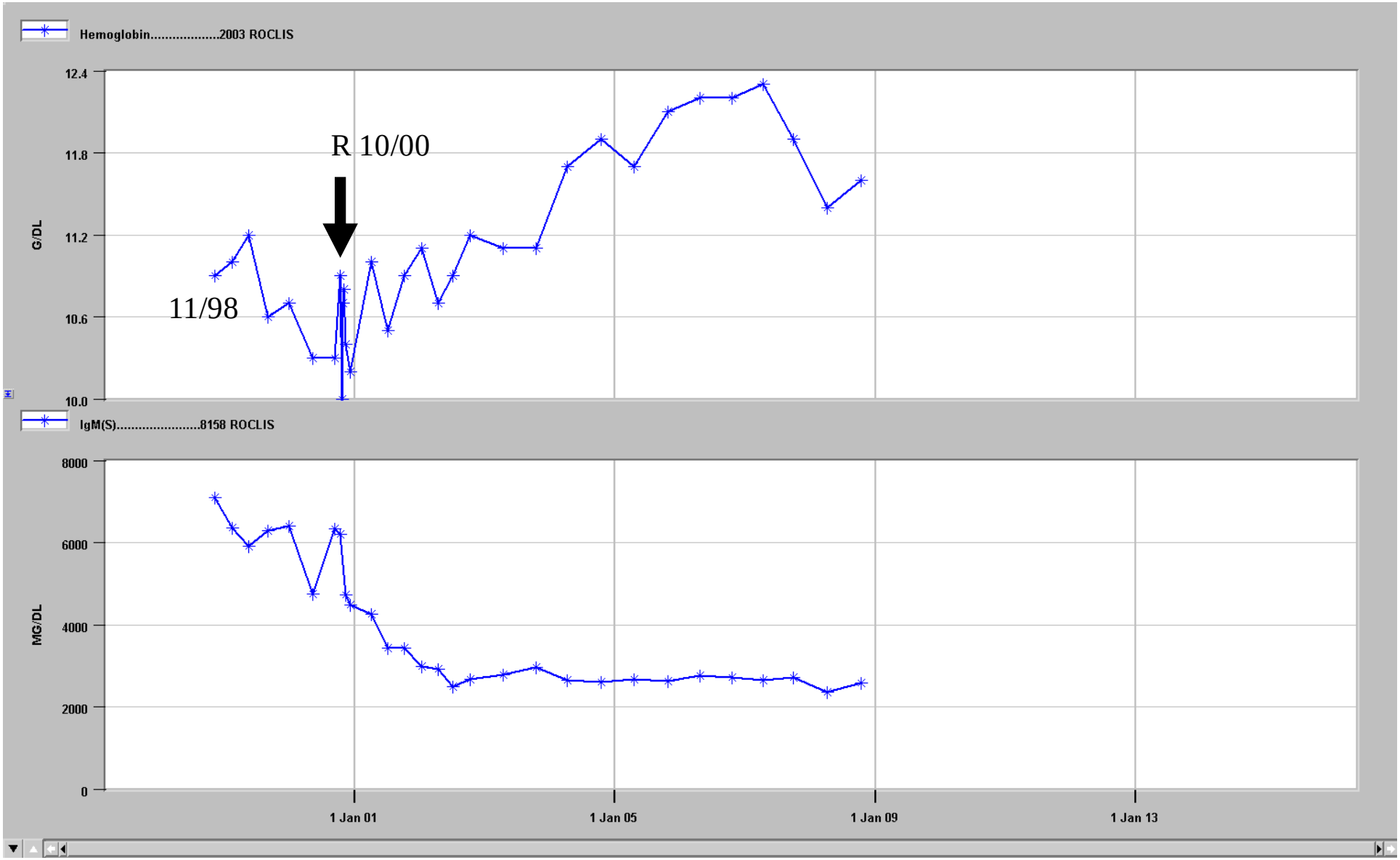
- MGUS
- IgM Related Disorders
  - Cryoglobulinemia
  - Cold agglutinin hemolysis
  - Amyloidosis, IgM assoc. Peripheral Neuropathy
- Macroglobulinemia
  - Asymptomatic (Smoldering)
  - Symptomatic

MACROGLOBULINEMIA Evaluating Therapy

- Overall Mortality & Disease Specific Mortality: Competing Hazards
- Delayed Responses often result in underestimates of response in multicenter trials with fixed response dates per protocol (17% of responses not achieved until 6 months in SWOG Fludarabine study)
- Minor responders 25-50% may do just as well as 50-99% responders, & may not be reported

Rituximab Flare





No other therapy for 8 years no maintenance
Time to max response 4 years

Audience Response

The most common genetic abnormality seen in Waldenström macroglobulinemia is?

– 13 or -13q

t(11;14)

-17p

6q-

t(4;14)

ISSWM

- Age >65
- Hb≤11.5
- platelets ≤100
- β-2microglobulin>3mg/L
- IgM>7000
- Low risk (0 or 1 excluding age) 5 Yr 87%
- High risk(3,4,5) 5 yr 36%
- Intermediate (2 or age>65) 5 yr 68%

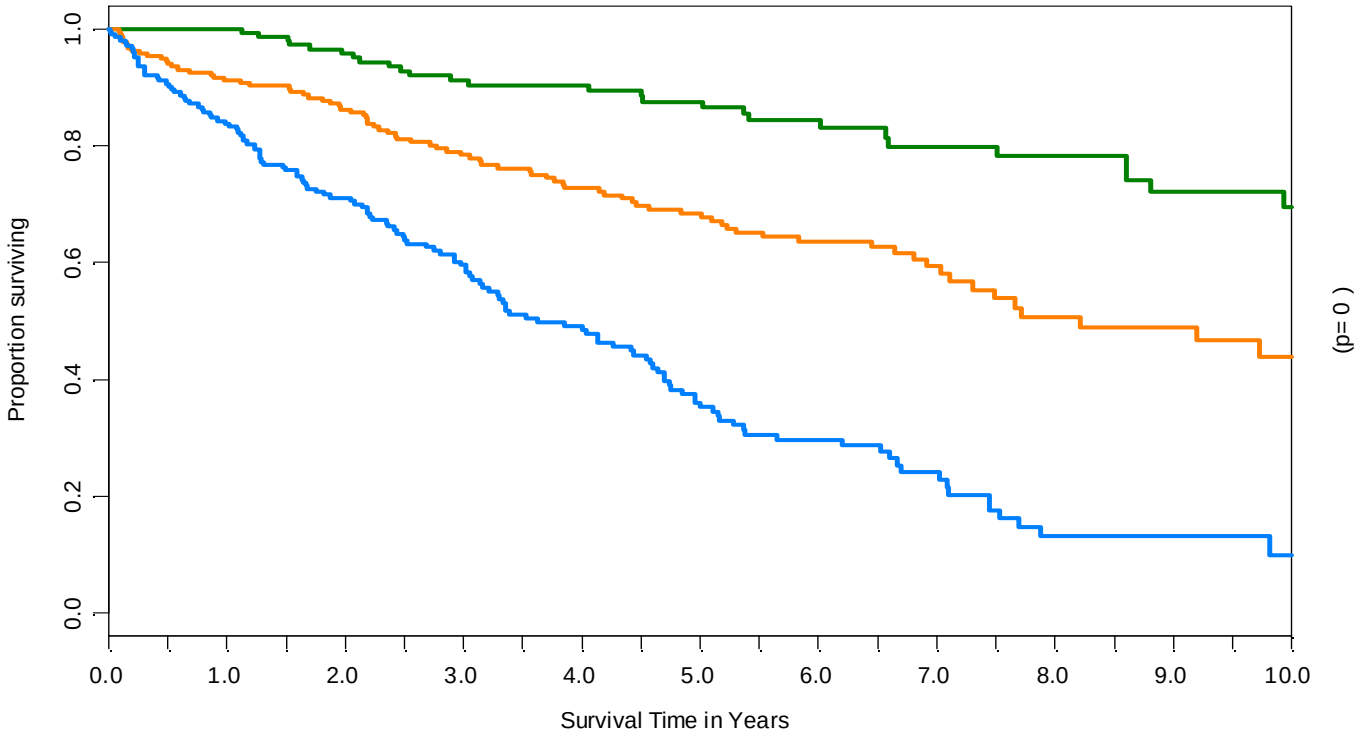
ISSWM: International Staging System for WM

Factors Associated with Prognosis in the IWMSS

- Age >65
- Hemoglobin <11.5 gr/dL
- Platelet count <100k/ml
- B2-microglobulin >3 mg/dL
- Monoclonal IgM concentration >7 gr/dL

Risk Category	Factors	Median survival (months)
Low	0 or 1 (except age)	142.5
Intermediate	Age>65 or 2	98.6
High	>2	43.5

IWMSS: International WM Staging System



Number of patients at risk:

Low	155	152	133	110	96	87	64	51	43	33	25
Inte	216	194	174	143	126	106	79	50	32	23	14
High	203	170	136	95	73	48	31	20	9	6	3

Audience Response

Which of the following is not associated with adverse prognosis in Waldenström macroglobulinemia?

LDH

Age

Hemoglobin

Platelet Count

Beta2 Microglobulin

Serum Monoclonal Protein

What should be the goal of therapy

- CR No M protein by IF
- VGPR 90% reduction of *IgM*
- PR >50% reduction
- MR 25-50% reduction
- Stab <25% reduction
- When does one abandon a regimen & cross over for an inadequate response
- What are the endpoints to follow?-Why did you start therapy to begin with

Macroglobulinemia Treatment – Chlorambucil

- **46 patients randomized to pulse vs daily**
- **Dose adjusted to induce leukopenia**
- **Median: M prot 4.2 g/dL, Hb 9.9 g/dL**
- **Median age 63, viscosity >4 (39%)**
- **Response rate pulse therapy – 88%**
- **Response rate continuous – 68% (P=NS)**
- **Survival 65 months – 4 Rx MDS**

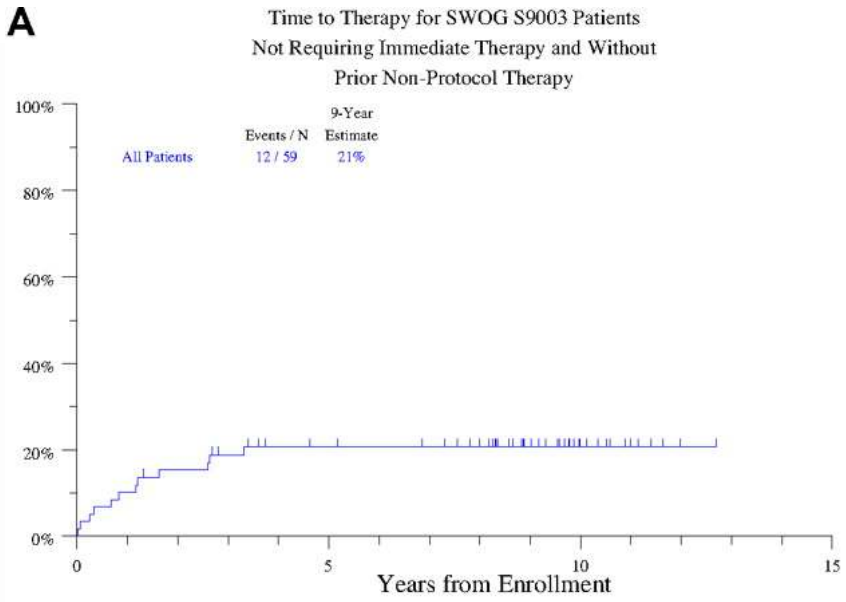
Macroglobulinemia
Response

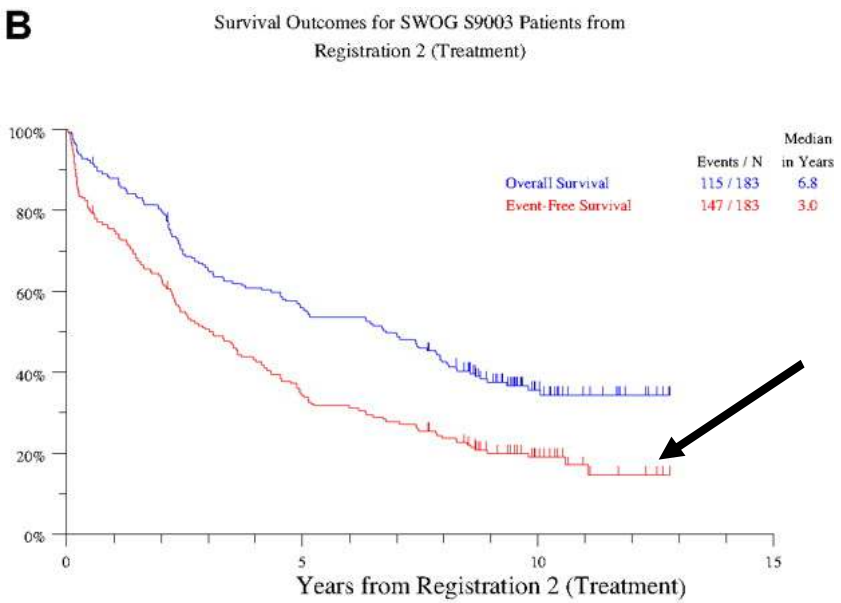
M-spike ↓50% (%)	**70**
Time to maximal response (mo)	**19**
Response duration (mo)	**30**
Hemoglobin ↑ ≥2 g/dL (%)	**61**
Time to 50% response (mo)	**6.8**
Response duration (mo)	**15**
Overall response (%)	**74**

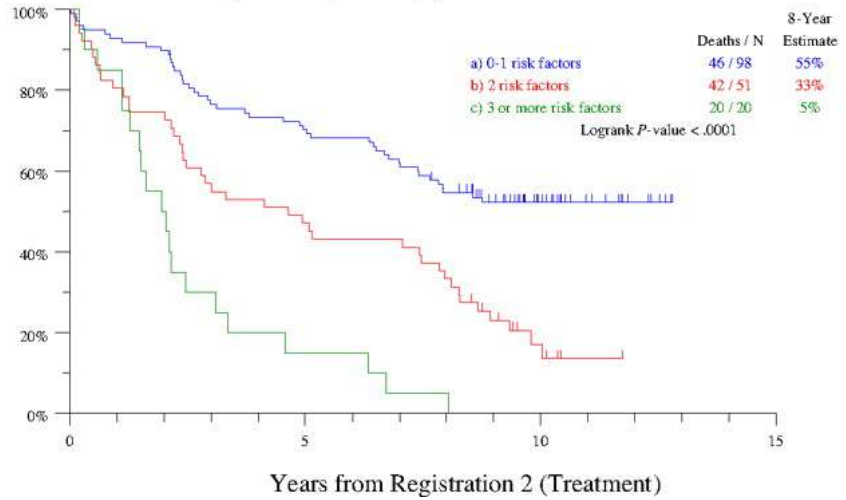
MACROGLOBULINEMIA CHLORAMBUCIL

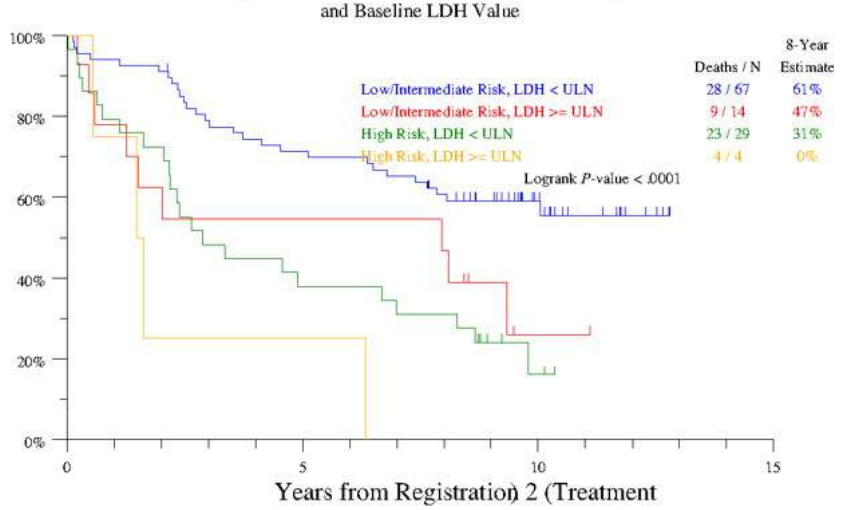
Study	N	Setting	Regimen	Major RR%	Median Response Duration
Facon	11	Untx Rx	Chl (continuous)	31%	NA
Kyle	24	Untx Rx	Chl (continuous)	75%	26 months
	22	Untx Rx	Chl (intermittent)	64%	46 months
Dimopoulos	77	Untx Rx	Chl, P	72%	NA
Petrucci	31	Untx Rx	M,C,P ->CP (continuous)	74%	66 months
Case	33	Untx Rx and 3 Rx	M-2 (BCNU,V,M,P)	82%	43 months (CR), 39 months (PR)

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY









S9003 Fludarabine Dhodapkar, M. V. et al. Blood 2009;113:793-796

Rituximab CTX Dex WM

- 34 newly diagnosed median age 75
- Hb<10 59%, IgM >4 g/dl 37%
- Ritux d1 375/M^2, CTX 100mg/M^2 po bid d1-5, dex 20 iv d1, repeat q21 x 6
- CR+PR 74%, 1 year PFS 85%, 5 deaths 3 disease specific
- Prog: Fludar + Mitox, 2/2 mobilized

DRC Regimen

- Dexamethasone 20 mg IV day 1
- Rituximab 375 mg/m^2 IV day 1
- Cyclophosphamide 100 mg/m^2 PO BID days 1−5 (total dose 1000 mg/m^2)

DRC courses are repeated every 21 days for 6 courses

- N=72
- CR = 7%
- PR = 67%
- MR = 9%
- SD = 8%
- PD = 8%

ORR = 83%

Median time to 50% IgM reduction was 4.1 months (range, 0.7−14)

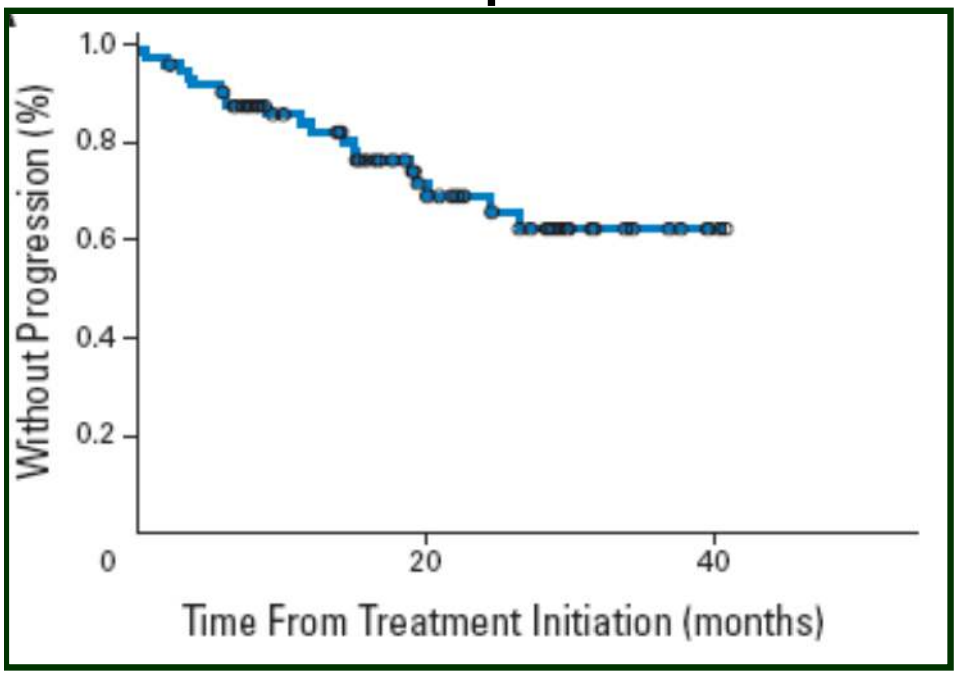
IgM flare in 32%, ≥25% IgM increase in 11%

Dimopoulos MA et al. J Clin Oncol. 2007;25(22):3344-3349

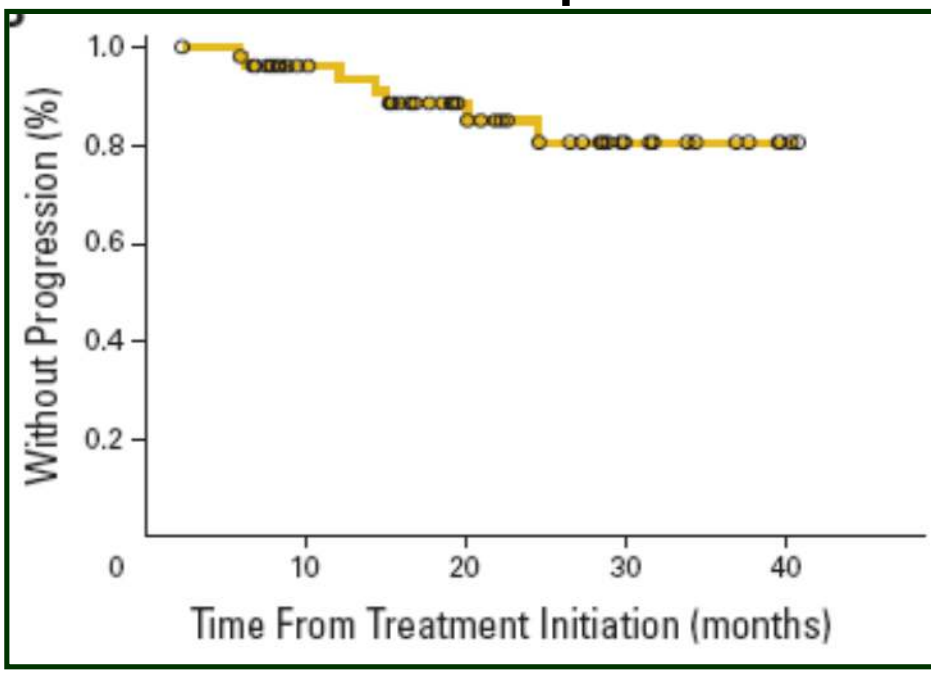
DRC Regimen

2-year PFS rate for all patients was 67% and 80% for responders

TTP for all patients



TTP for responders



Lymphadenopathy was associated with shorter TTP (*P*=.02).

2-year survival without additional treatment was 78%.

2-year overall survival rate was 81%.

Dimopoulos MA et al. J Clin Oncol. 2007;25(22):3344-3349

Rituximab Fludarabine WM

- Rituximab 375mg/m^2 once weekly weeks 1-4, 17,18,30,31
- Fludarabine 25 mg/M^2 x 5 days weeks 5,9,13,19,23,27
- 42 patients median age 61
- CR 3, PR 32, MR 4 overall 90%
- Median time to best response 11.5 mos TRM 5%, 36/39 FFP med 17 mo

Rituximab and Subcutaneous 2-Chloro-2'-Deoxyadenosine Combination Treatment for Patients With Waldenström Macroglobulinemia

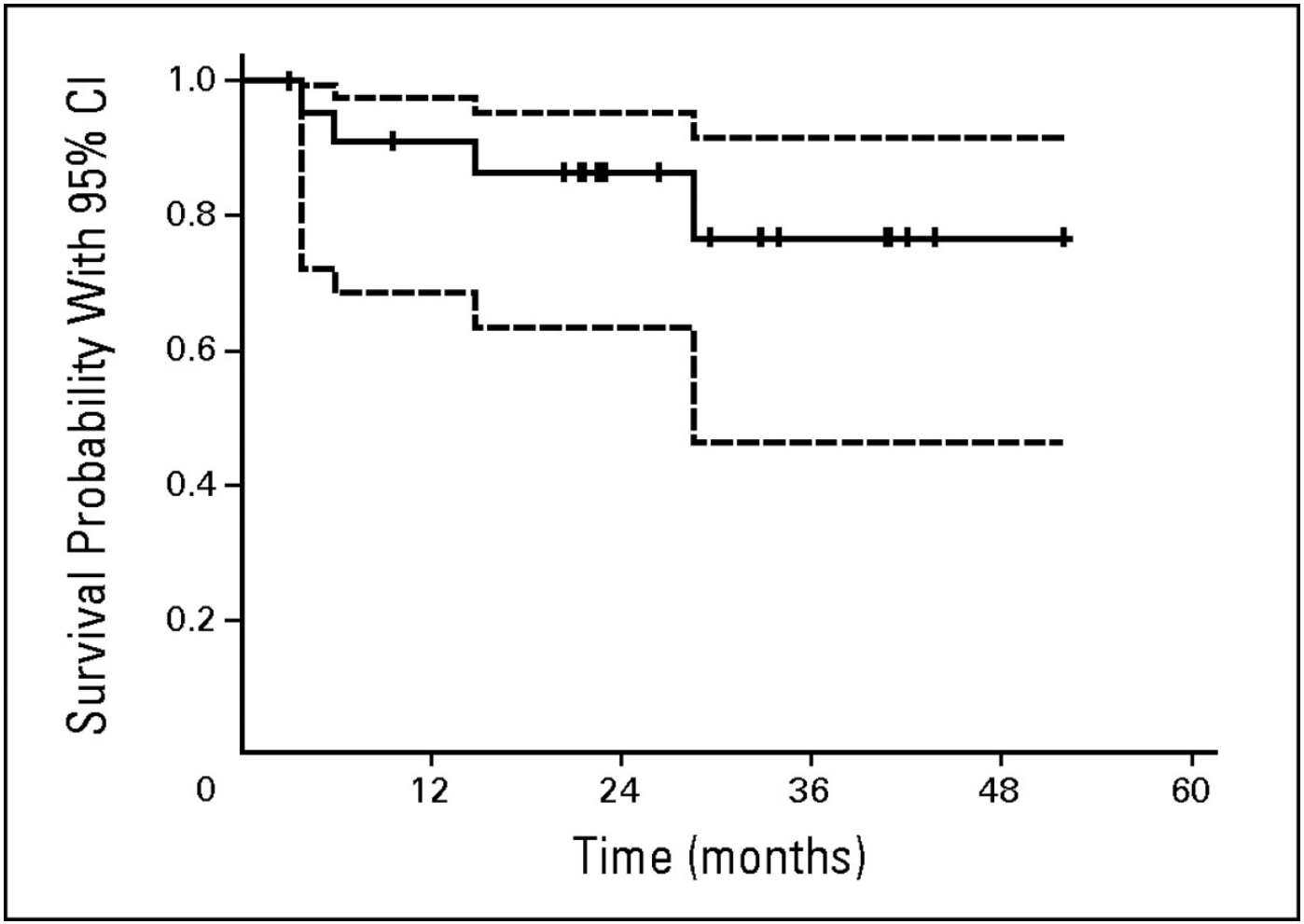
Table 2. Frequency Distribution of Clinical Response by IPSS Risk

Clinical Response	Risk						Total	
	Low		Intermediate		High			
	No.	%	No.	%	No.	%	No.	%
CR	3	12.0	3	12.0	1	4.0	7	28.0
MR	0	0	1	4.0	2	8.0	3	12.0
PR	3	12.0	1	4.0	8	32.0	12	48.0
SD	1	4.0	1	4.0	0	0	2	8.0
PD	0	0	0	0	1	4.0	1	4.0
Total	7	28.0	6	24.0	12	48.0	25	

NOTE. Fisher's exact test $P = .138$.

Laszlo, D. et al. J Clin Oncol; 28:2233-2238 2010

Time to treatment failure



Laszlo, D. et al. J Clin Oncol; 28:2233-2238 2010

FCR n=43

Table 2. Response Rates After Combined Fludarabine, Cyclophosphamide, and Rituximab in 43 Patients With Waldenstrom Macroglobulinemia Enrolled in the Current Study

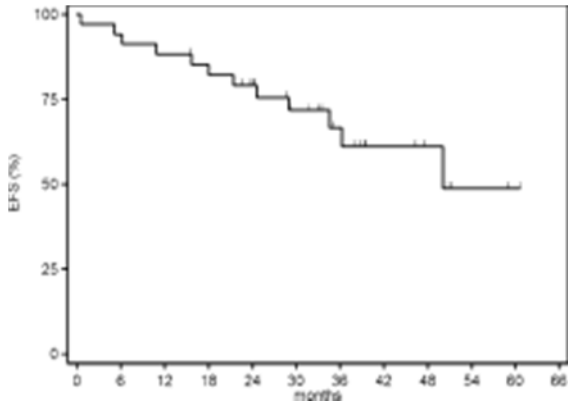
	No. of Patients (%)	
Response	**End of Treatment**	**Best Response During Follow-Up**
Overall response rate	34 (79)	34 (79)
Major response	32 (74.4)	33 (76.7)
Complete remission	5 (11.6)	8 (18.6)
Very good partial remission	9 (20.9)	6 (13.9)
Partial remission	18 (41.8)	19 (44.1)
Minor response	2 (4.6)	1 (2.3)
Stable disease	4 (9.3)	4 (9.3)
Progressive disease/failure	1/4 (11.6)	1/4 (11.6)

In 5 patients, an improved response was achieved during follow-up after a median of 6 months (range, 3-12 months). In 1 patient, a minor response converted to a PR, and 3 patients who were categorized with VGPRs achieved CR. Considering the best response, we observed a 76.7% major response rate (33 patients), including 18.6% CRs (8 patients), 13.9% VGPRs (6 patients), and 44.1% PRs. No statistical difference in terms of response was observed between pretreated and untreated patients, although, in naive patients, a trend was detected toward achieving a better quality of response (43% vs 14%; *P* = .086) (Table 3) 4.

Cancer

Volume 118, Issue 2, pages 434–443, 15 January 2012

EFS responders 48 mos.



IMID's IN WM

	Thal + R	Lenalid + R
# Patients	25	16
Age	62 (42-86)	65 (49-85)
IgM	3670(924-8610)	4000(1180-7130)
Ht	34.1(23.6-42.6)	32.1(24-36.6)
β2-M	2.6(1.4-9.3)	3.3(1.8-6.0)
CR+PR	16/23= 0.7	4/12=0.33
TTP	35 mo	15.6
Rx	R 8 dose T 200 Neuropathy 50%	R 8 dose Len 25 mg 21/28

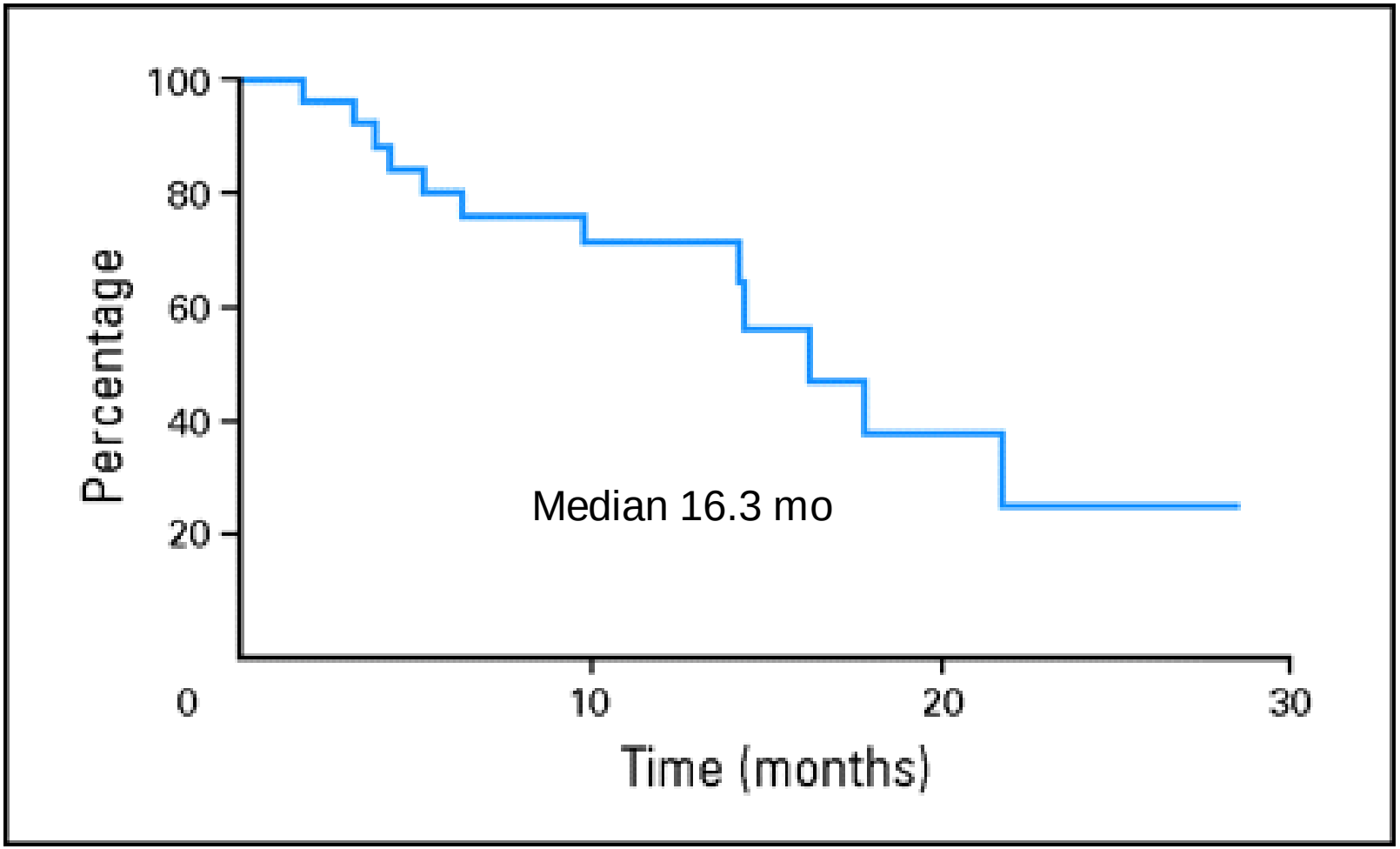
Soumerai et al Kos June 07

Bortezomib
NCIC

- B 1.3 mg/ M2 1,4,8,11 plateau + 2 cycles
- 27 previously treated
- 44% PR 34% MR; Median TTP 16.3 mo.
- Time to response median 2 months
- Hb rose over 10 in 66%
- Neuropathy 74% Gr 3 in 5 leading to cessation of Rx in 12

Chen et al ASCO 2006; 7543; JCO 2007

Bortezomib for Relapsed WM



ECOG Registration Trial

- R vs RBort
- 4 months of therapy 4 doses vs 4 & 1,4,8,11

BortDR Response Assessment

N = 23

Overall Responses

- CR: 3 (13%)
- nCR 2 (9%)
- VGPR: 3 (10%)
- PR: 11 (48%)
- MR: 3 (13%)

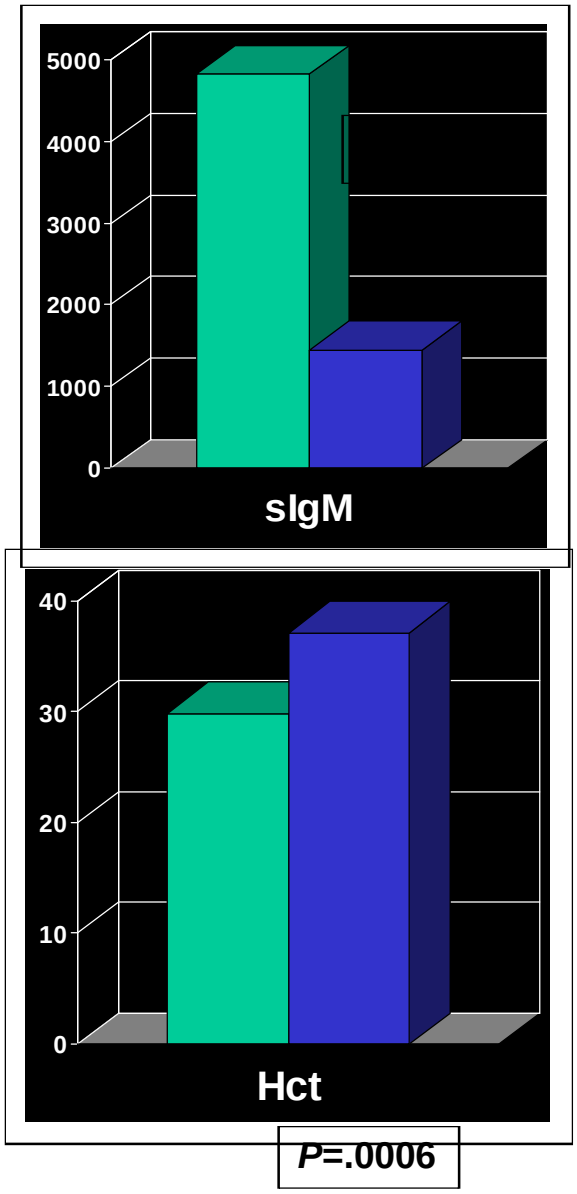
83% (CR + nCR + VGPR + PR)

91% (CR + nCR + VGPR + PR + MR)

Median time to response 1.4 months

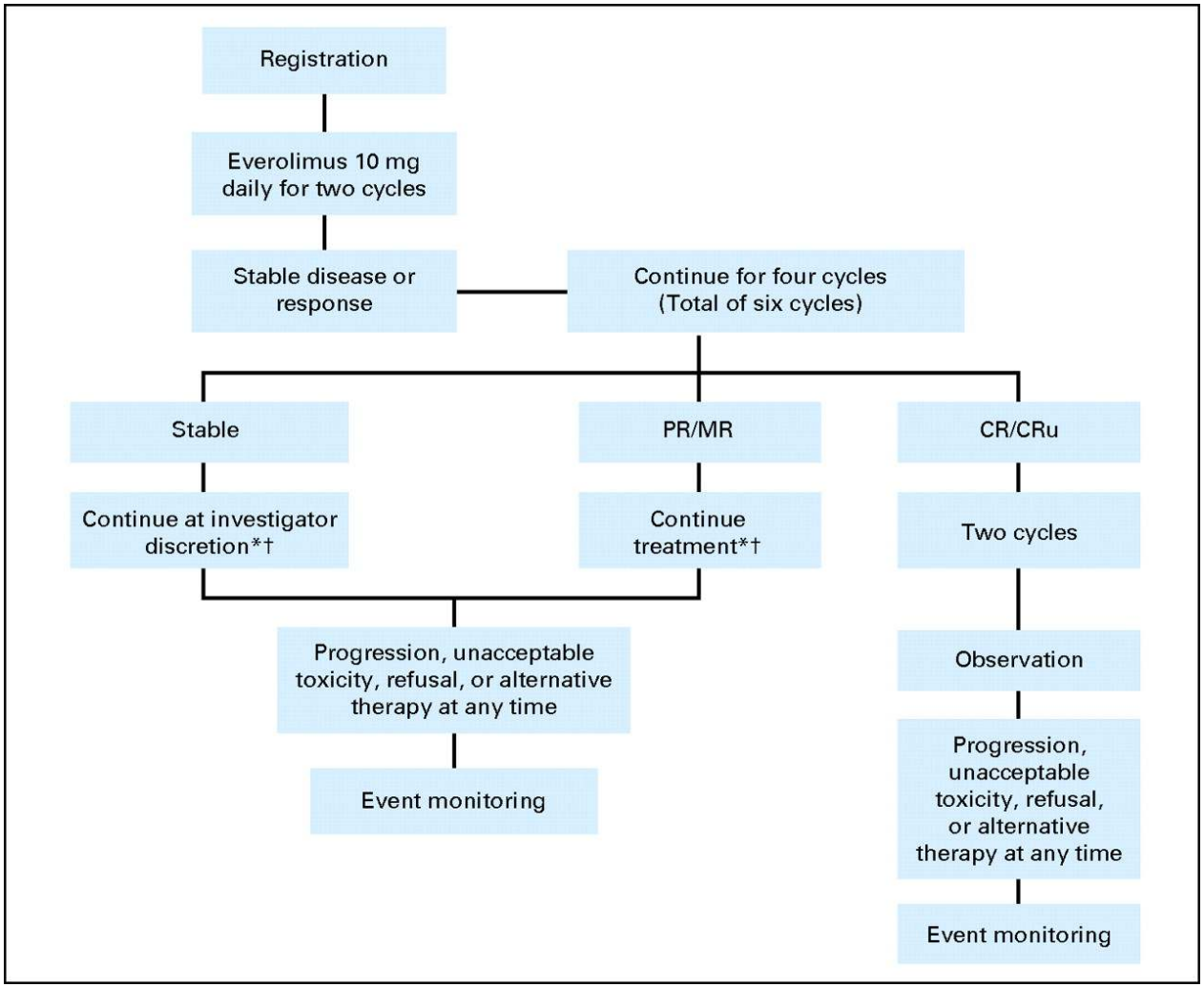
With a median follow-up of 22.8 months (range, 3.3 to 33.2 months), all patients are alive

18/23 patients remain free of disease progression



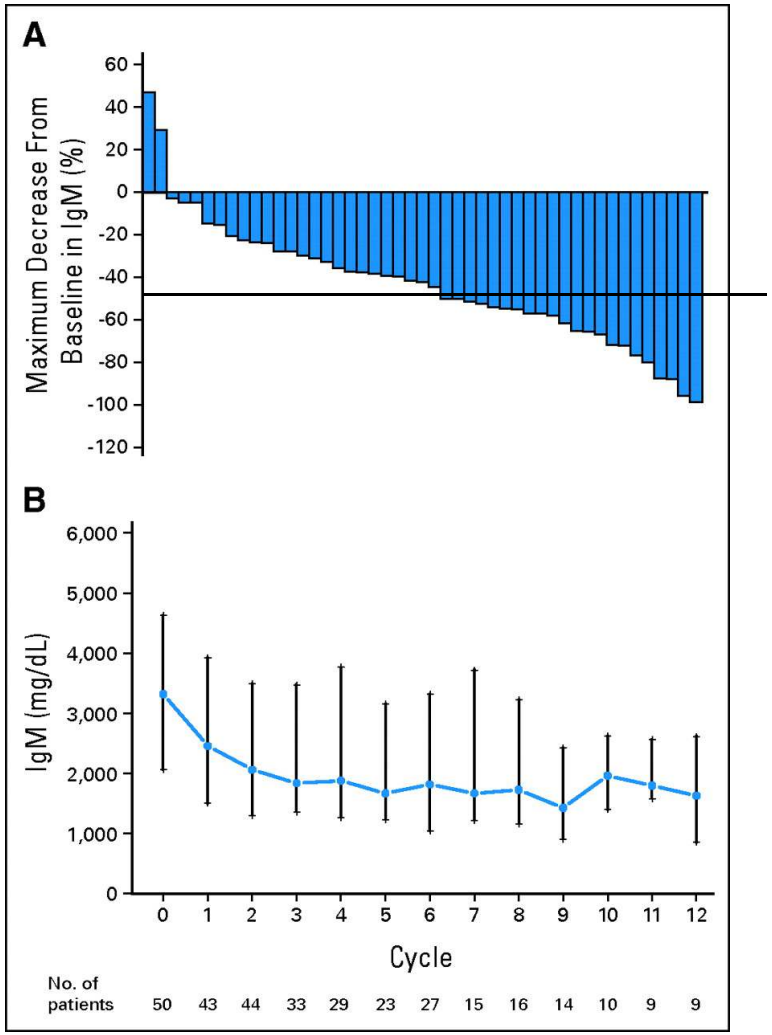
Treon SP et al. J Clin Oncol. 2009; 27(1):120-126

CONSORT diagram.



Ghobrial I M et al. JCO 2010;28:1408-1414

(A) Maximum percent decrease from baseline in immunoglobulin M (IgM) over all cycles in response to everolimus per patient.



Ghobrial I M et al. JCO 2010;28:1408-1414

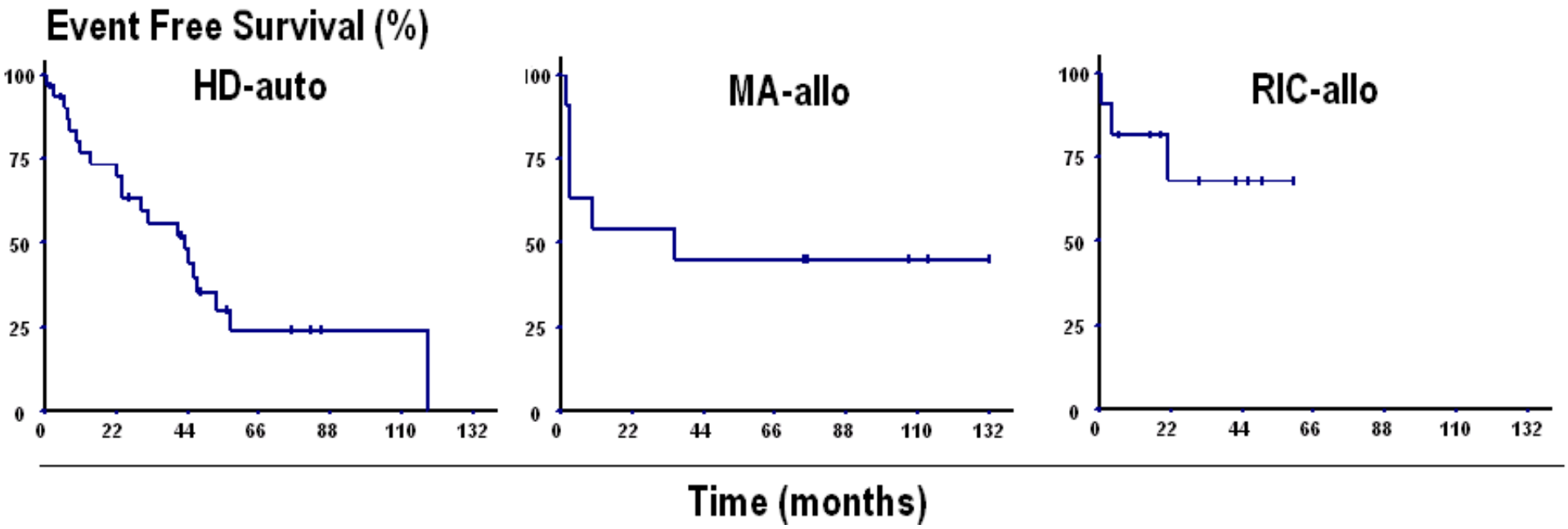
AUTO-SCT in WM
EBMT Registry

- Relapse 1,3,5 yrs: 20, 38, 55%
- PFS 1,3,5 yrs: 74, 54, 33%
- OS 1,3,5 yrs: 86, 75, 61%
- TRM about 8% Response 3 years

Kyriakou et al Kos June 2007

SCT French Experience

EFS=	**32**	**36**	**NR**
TRM=	**12.5%**	**36%**	**27%**
N=	**32**	**11**	**11**



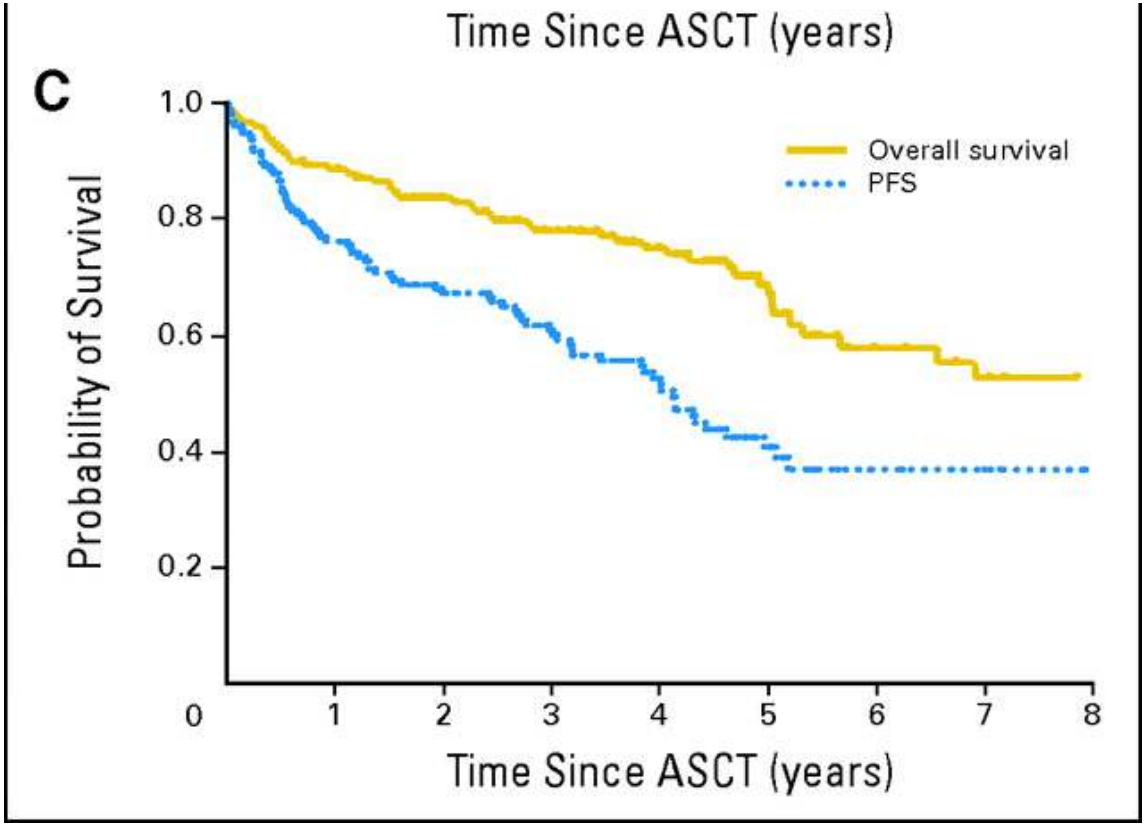
Kyriakou, C. et al. J Clin Oncol; 28:2227-2232 2010

Table 2. Post-Transplantation Outcome by Disease Status at the Time of ASCT

Outcome	Disease Status at ASCT				Total
	VGPR1	At Least VGPR2	Chemosensitive Disease	Chemorefractory Disease	
CR	10	3	21	0	34
VGPR	20	19	36	2	77
PR	0	0	18	5	23
No response (SD, progression)	4	0	11	3	18
N/E	0	0	2	1	3
N/A	0	0	3	0	3
Total	34	22	91	11	158

Abbreviations: ASCT, autologous stem-cell transplantation; VGPR, very good partial response; VGPR1, first VGPR; VGPR2, second VGPR; CR, complete remission; PR, partial remission; SD, stable disease; N/E, not evaluable; N/A, not available.

Kaplan-Meier plot of progression-free survival (PFS) and overall survival probabilities. ASCT, autologous stem-cell transplantation.



Kyriakou, C. et al. J Clin Oncol; 28:2227-2232 2010

Bendamustine

- 41 patients with WM, of whom 22 received bendamustine and rituximab and 19 received R-CHOP
- In both groups, the response rate was 95%
- The median PFS for R-CHOP was 36 mo Vs not reached with bendamustine and rituximab ($P<.0001$). At analysis, 4 relapses (18%) in the bendamustine and R group & 11 relapses (58%) in the R-CHOP group

Recommendations From the IVth IWWM for the Management of Newly Diagnosed Symptomatic WM Patients According to Specific Conditions

	Clinical condition	Panel Recommendation
Transplant candidate	**Cytopenias**	• **DRC** • **Rituximab –Thalidomide**
	High M-protein	• **R-CHOP** • **DRC**
Non-Transplant candidate	**Cytopenias**	• **DRC** • **Rituximab + thalidomide**
	High M-protein levels	• **nucleoside analogues + rituximab** • **nucleoside analogues + rituximab+ Cyclophosphamide**
	Comorbidities • **Low M-protein and cytopenias** • **Older age and slow progression**	• **Rituximab** • **Chlorambucil**

Dimopoulos MA et al. J Clin Oncol. 2009;27(1):120-126

How to treat

WALDENSTRÖMS MACROGLOBULINEMIA
(Mayo Clinic Consensus for Newly Diagnosed Disease):

- Bulky Disease
- Profound Cytopenias

(Hgb≤10 g/dL; Plts <100 x10^9/L)

- Constitutional symptoms
- Hyperviscosity Symptoms

Hgb< 11 g/dL or symptomatic

- Platelets< 120 x 10^9/L
- Neuropathy (IgM-related)
- WM associated hemolytic anemia or GN

- IgM MGUS
- Asymptomatic/ Smoldering Waldenstrom's
- Hgb ≥ 11 g/dL
- Platelets ≥120 x 10^9/L

Hyperviscosity

YES → Plasmapheresis

NO

msmart.org

Rituximab + *Alkylator

Rituximab + *Nucleoside analog

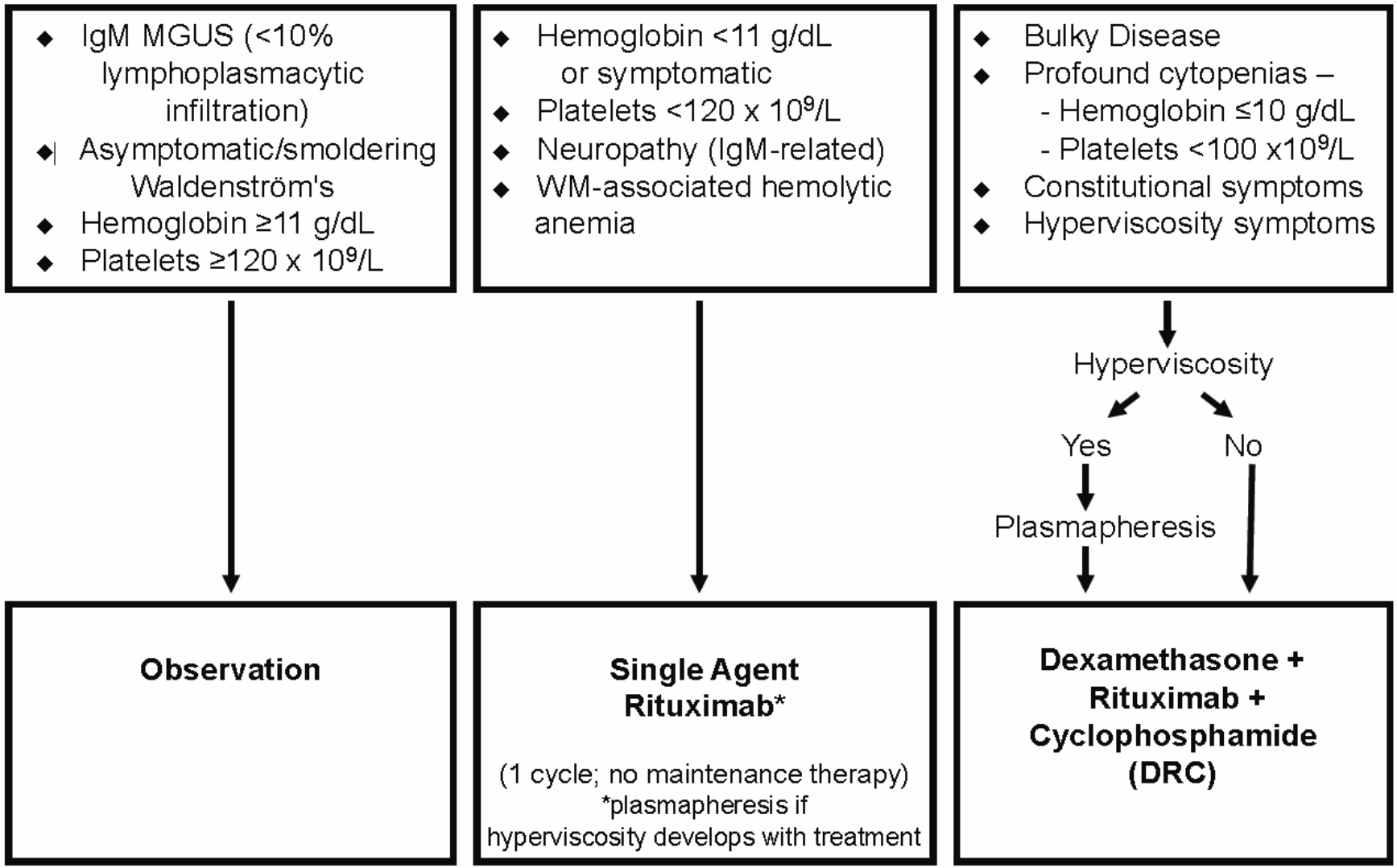
*(Avoid chlorambucil and nucleoside analogs in potential stem cell transplant candidates)

** Single Agent Rituximab (1 cycle; no maintenance therapy)

** plasmapheresis if hyperviscosity with treatment

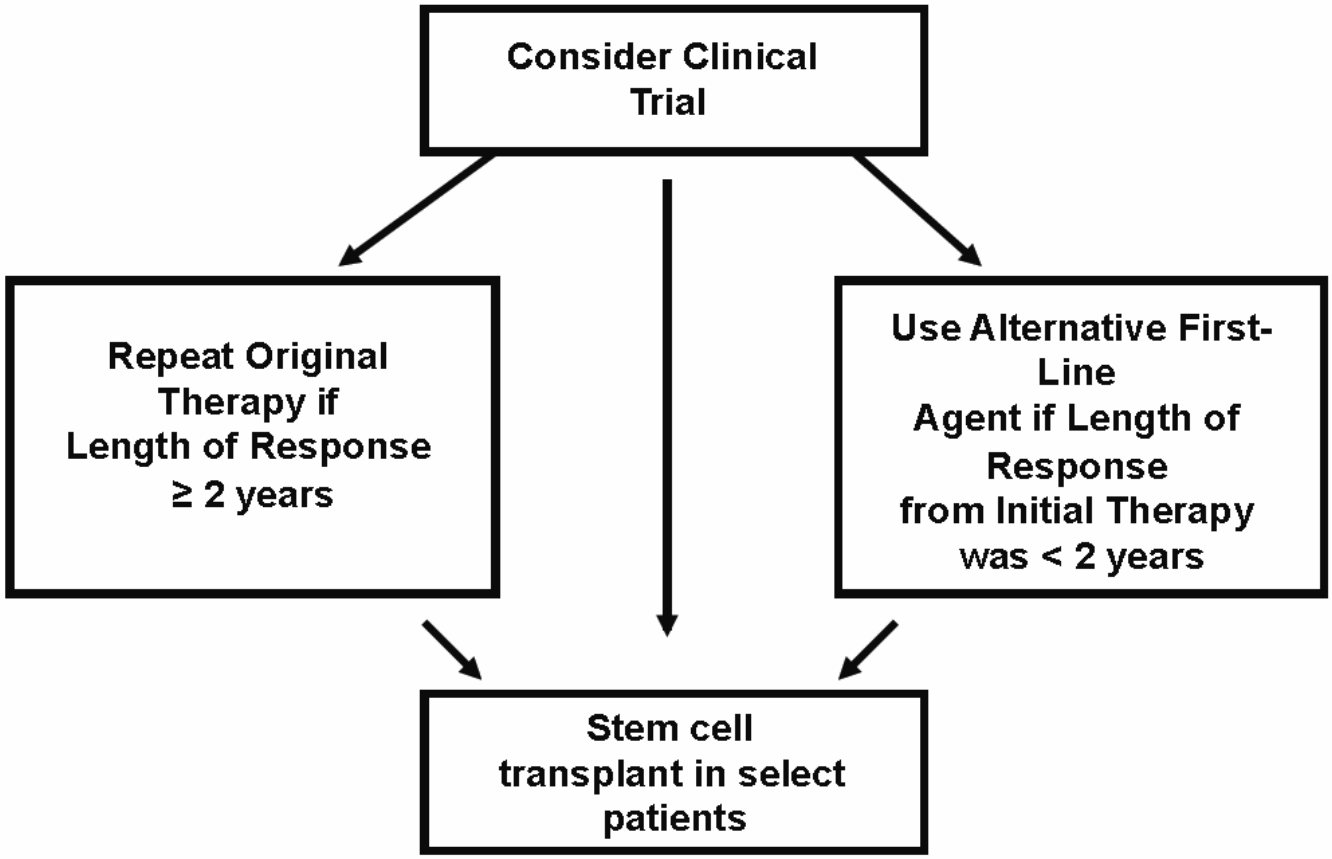
Observation

Consensus for Newly Diagnosed Waldenström's Macroglobulinemia



Ansell SM. Mayo Clinic Proc 2010;85:824-833

Waldenströms Macroglobulinemia Consensus for Salvage Therapy



Ansell SM. Mayo Clinic Proc 2010;85:824-833

Newly Diagnosed

Agent	Dosage	Route	Days	Cycle Length	Duration
Rituximab*	375 mg/m^2	IV	1	28 days	2 cycles beyond best response
Lenalidomide**	20mg	PO	1 thru 21**		
Cyclophosphamide	250 mg/m^2	PO	1, 8, 15		
Dexamethasone	40 mg	PO	1, 8, 15, 22		
Aspirin (see section 9.12 for alternatives)	325mg	PO	1 thru 28		

Relapsed Disease

Bortezomib 1.6 mg/m^2 IV day 1,8,15
Rituximab^2 375 mg/m^2 IV day 1,8,15,22
Dexamethasone 20 mg PO day 1,8,15
Temsirolimus 50 mg IV day 1,8,15,22

x 6 cycles

Agent	Dosage	Route	Days	Cycle Length	Duration
Rituximab*	375 mg/m^2	IV	1	28 days	Continue 2 cycles beyond best response or a maximum of 12 cycles
Cyclophosphamide	300 mg/m^2	PO	1, 8, 15, 22		
Bortezomib	1.3 mg/m^2	IV	1, 4, 8, 11		
Dexamethasone	40 mg	PO	1, 8, 15, 22		

R-CyBor-D

Phase I-II Everolimus Lenalidomide level 0 5mg qd & 10 mg qd