Waldenstrom's Macroglobulinemia: Bortezomib (Velcade®) based therapy

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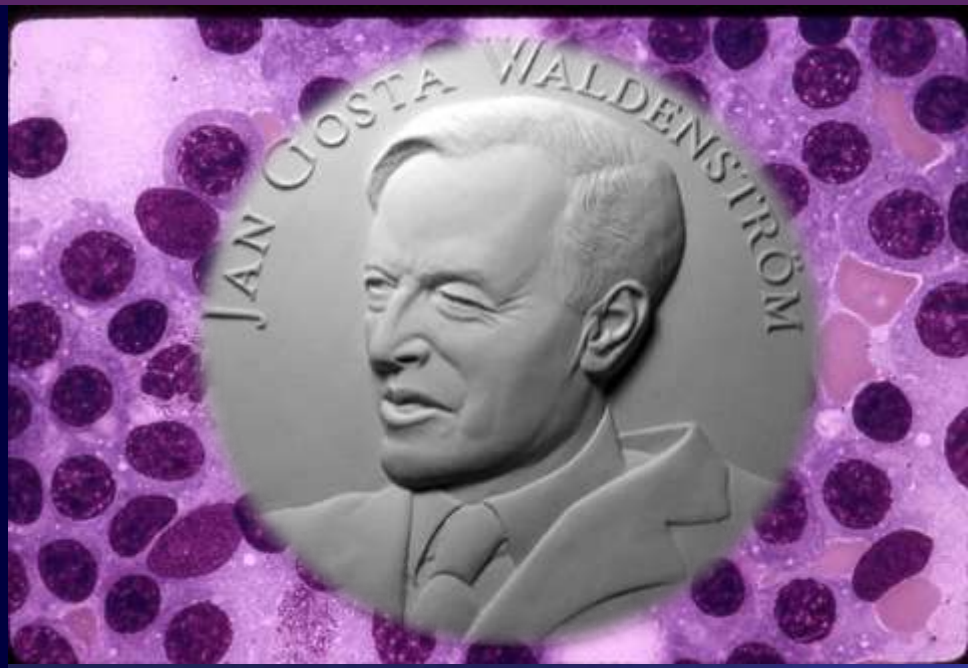
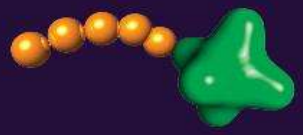


Bortezomib (Velcade®) is a proteasome inhibitor

Inhibition of the proteasome by VELCADE prevents the degradation of intracellular proteins, affecting multiple signaling cascades within cells, in both normal and non-tumor cells.

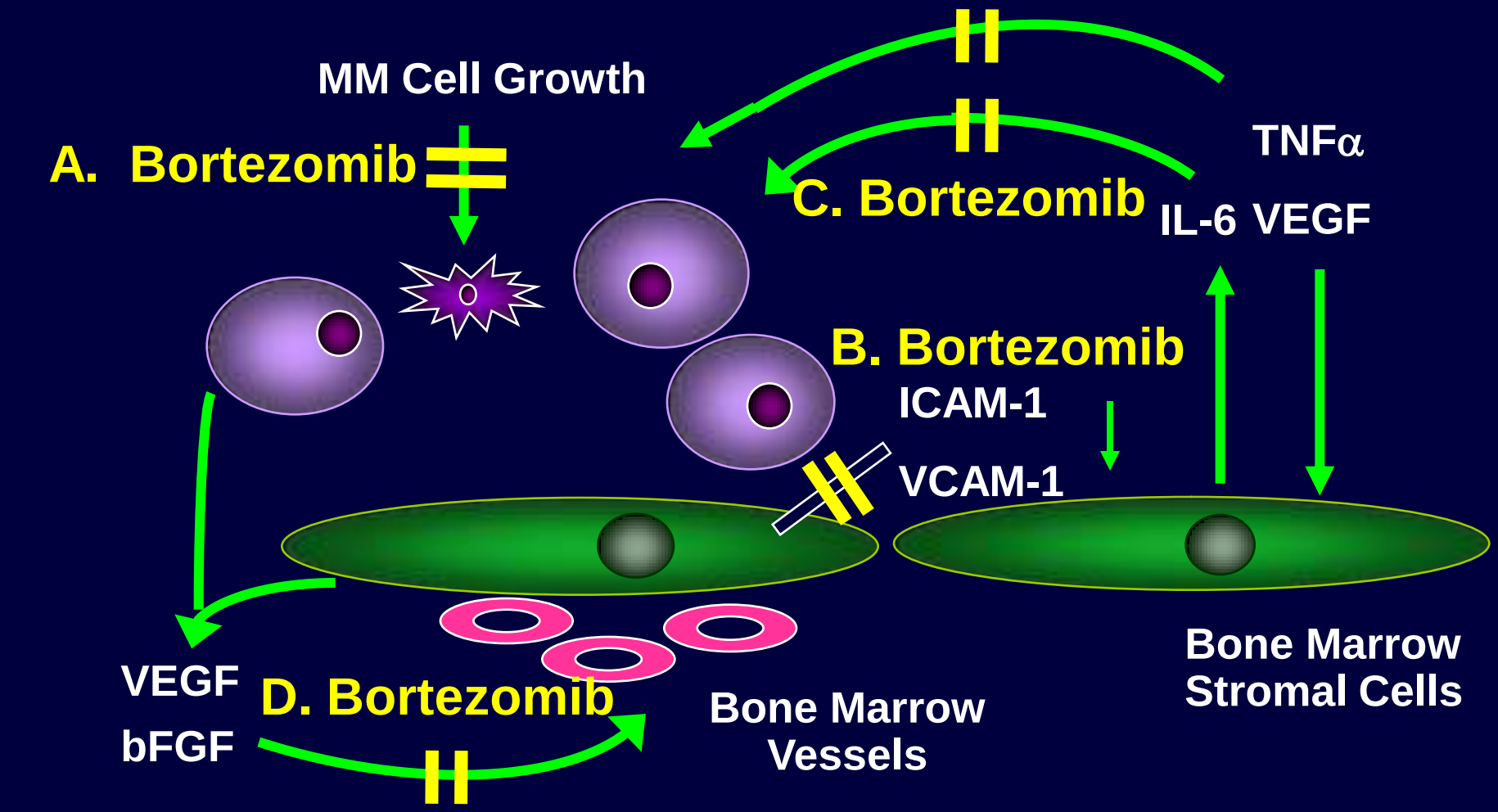


VELCADE

Proteasome

1. Adams J, Palombella VJ, Sausville EA, et al. *Cancer Res.* 1999;59:2615-2622; 2. Adams J, Palombella VJ, Elliot P. *Invest New Drugs*. 2000;18:109-121; 3. Glickman MH and Ciechanover A. *Physiol Rev.* 2002;82:373-428; *Sci Am.* 2001;284:63-73; 4. Baumeister W, Walz J, Zühl F, et al. *Cell*. 1998; 92:367-380.

Bortezomib Targets the BM Microenvironment



Hideshima et al. Cancer Res 61: 3071, 2001

Hideshima et al. Oncogene 20: 4519, 2001

Mitsiades et al. Blood 99: 4079, 2002

Hideshima et al. J Biol Chem 277: 16639, 2002

Overview of Bortezomib

- Stem cell sparing agent;
- IV drug, given as a push over 3-5 seconds;
- Need to space out doses by at least 72 hours to avoid GI toxicity;
- Typically 6-8 cycles administered;
- Each cycle involves giving drug on days 1,4,8,11 out of a 3 week cycle (i.e. Mon, Thu, Mon, Thu, then off for one week).

- Main side effects:

  Reversible peripheral sensory neuropathy: numbness, tingling, burning, pain;

  Decreased platelet count
- Neuropathy is usually reversible and patients can benefit with Lyrica®.
- Approved by the FDA for Myeloma and relapsed/refractory MCL.

Bortezomib Monotherapy in WM

Study	N	# Cycles*	ORR	PR
WMCTG	27	6	85%	44%
NCI-Canada	27	6	78%	41%
Dimopoulos	10	6	60%	60%

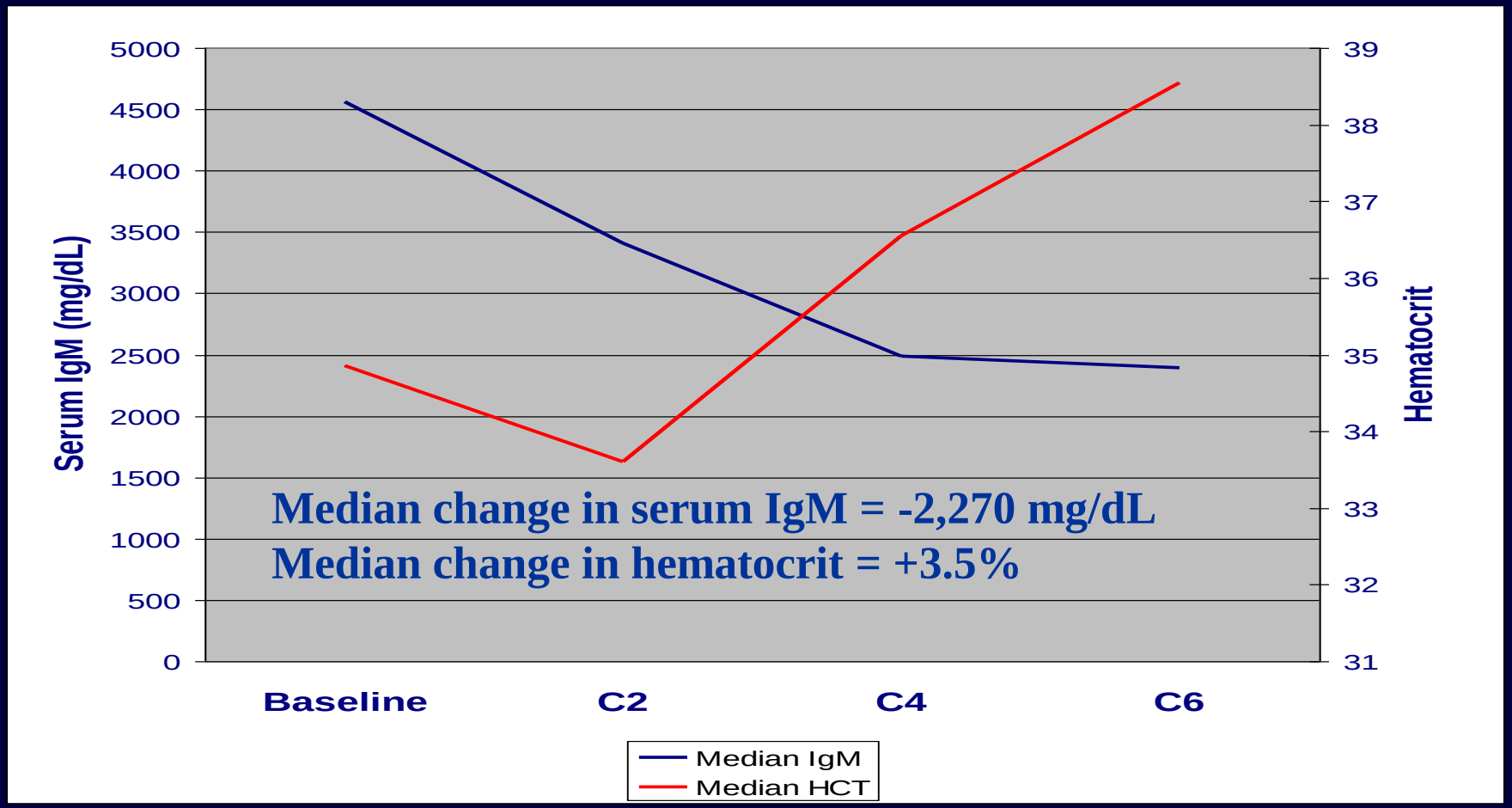
*Median number of cycles given.

- 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.

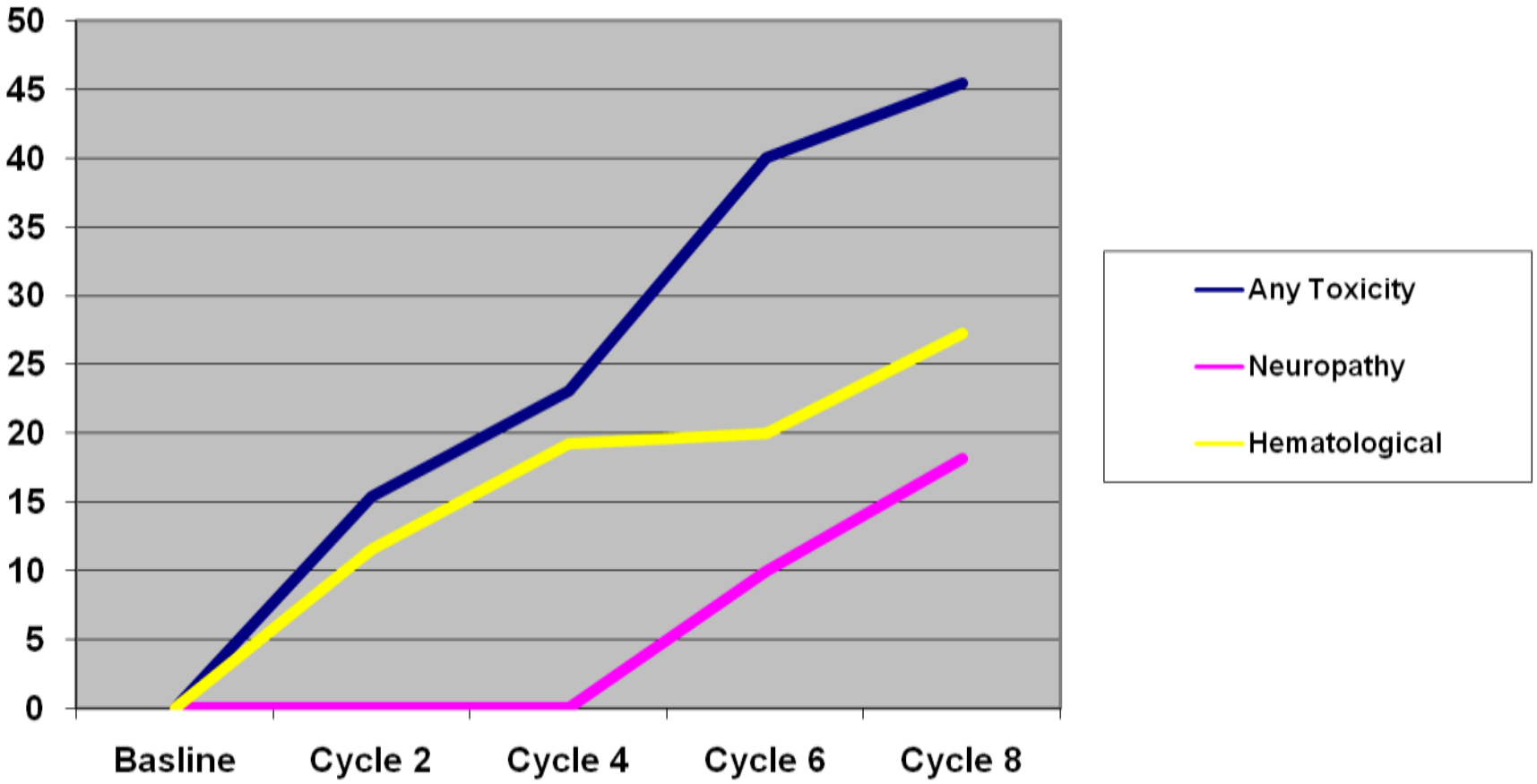
Treon SP, et al. Clin Cancer Res 2007 13;3105-3106. Chen et al. Hematologica 2005;90 (S1):155.

Paraprotein and Hematological Response



Treon et al, Clin Cancer Res 2007

Percent of patients on active therapy experiencing toxicities ≥ grade 3 per cycle.



Paraprotein and BM Responses

Patient	Change in sIgM	Change in BM
1*	**-39.44%**	**-15.79%**
2	-45.87%	-28.57%
3	-65.94%	-75.00%
4	-64.86%	-50.00%
5	-58.84%	-60.00%
6*	**-56.65%**	**-11.11%**
7	-51.85%	-72.73%
8*	**-72.42%**	**+92.00%**
9	-45.70%	-57.10%
10	-42.30%	-78.50%

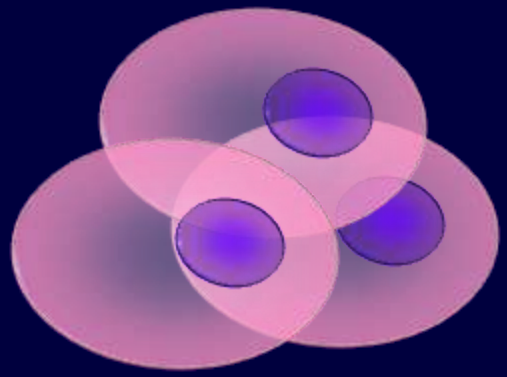
Median change in BM Involvement: -53.60%

sIgM, secretory immunoglobulins M.

Treon SP. et al. ASH 2006. Abstract 2765.

Updated Recommendations for Salvage Therapy of WM

- *Re-use or alternative use of a frontline agent*
- *CHOP, CVP, CAP alone or with rituximab*
- *Bortezomib*
- *Alemtuzumab*
- *Thalidomide ± steroids, rituximab*
- *Autologous transplantation*



Κως 2007

Dimopoulos et al, JCO 2009

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

BDR in Waldenstrom's Macroglobulinemia: Patient Characteristics

Median Age	65	(46-78)
Prior therapies	0	(0)
Median BM Involvement	55%	(20-90)
Median IgM	4830 mg/dL	(458-9950)
Median Hct	29.8%	(19.5-37)
Median B2M	3.26mg/L	(1-7.1)

N=23

Treon et al, JCO 2009

BDR Response Assessment

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

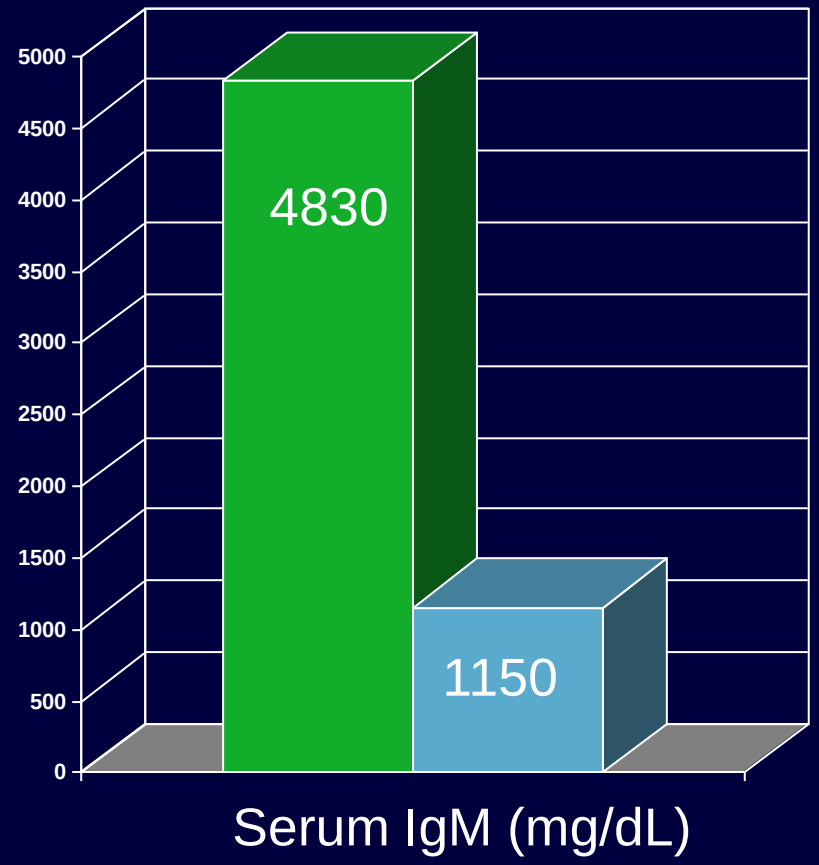
83%

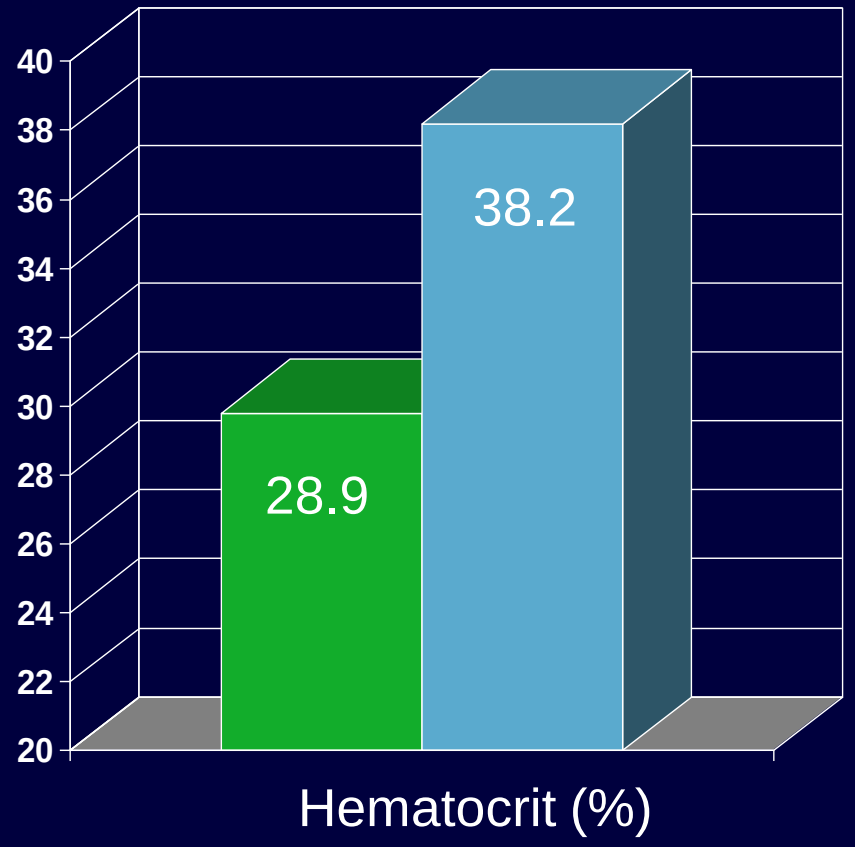
95.6%

- 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. ASCO 2008.

Paraprotein and Hematological Response





Treon et al, ASCO 2008

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);

BDR in WM: Adverse Events

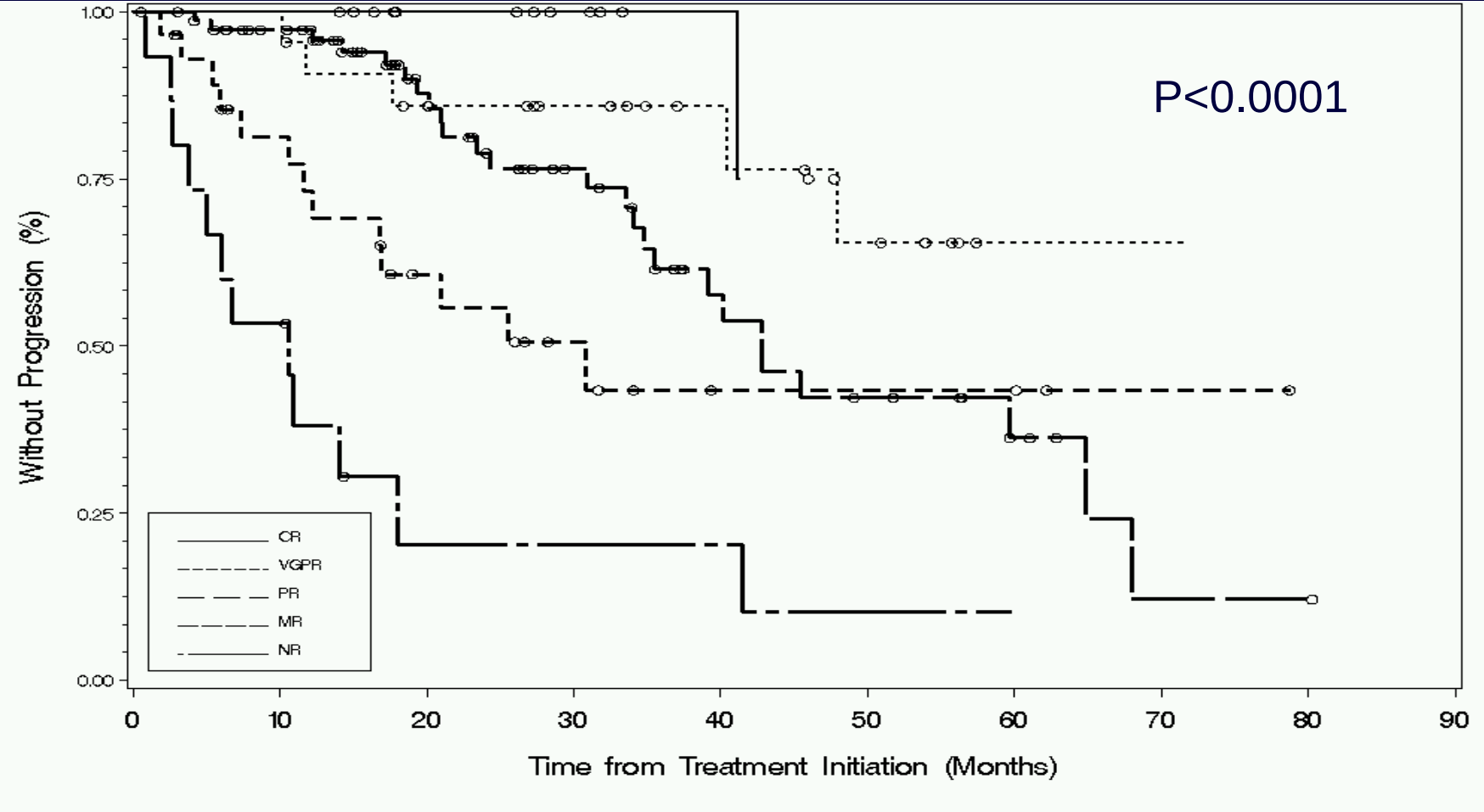
- Grade ≥ 2 toxicities
  - Neuroparasthesias (69%); grade 3 (30%)
  - Neutropenia (30%)
  - Thrombocytopenia (9%)

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

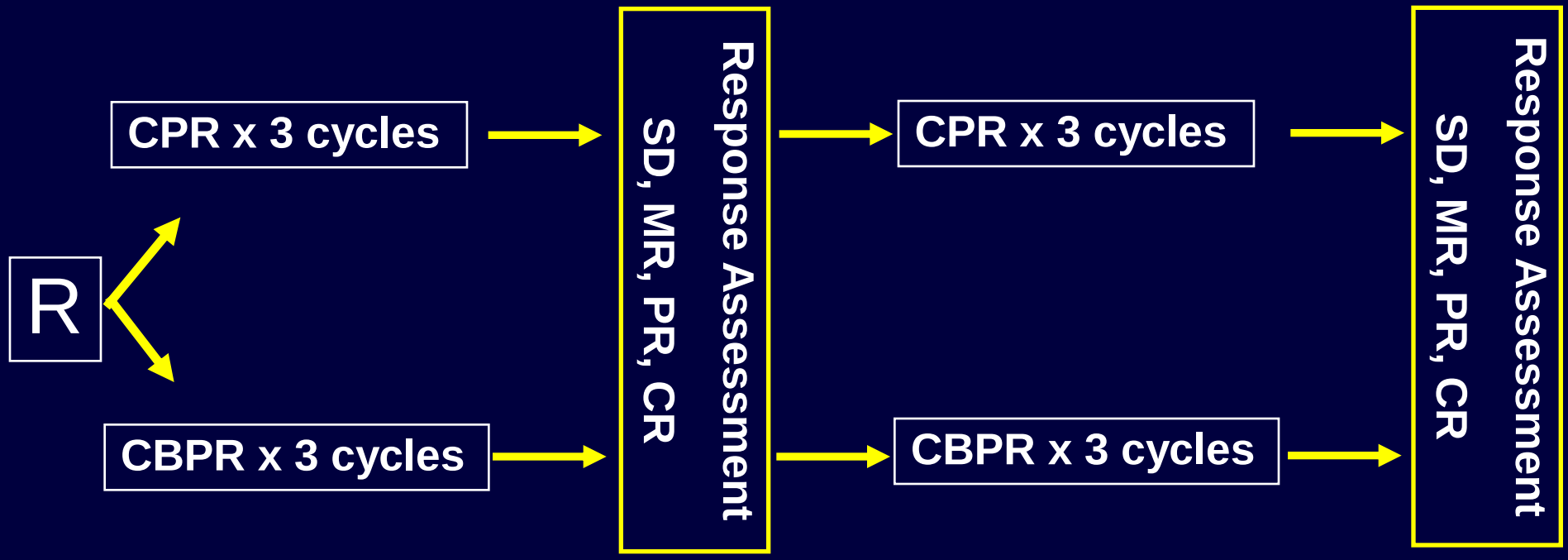
- Among first 7 patients on study, 4 developed herpes zoster outbreak prompting initiation of valtrex at 1 gm po qD. Only one subsequent herpes zoster outbreak occurred in a patient who did not fill her script for valtrex.

Treon et al, JCO 2009.

Response status correlates with progression free survival in WM.



Randomized study of CPR vs. CBPR 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

Summary

- Bortezomib is an active agent in the treatment of WM, with rapid onset of response;
- ORR of 60-80% are observed in WM patients with relapsed/refractory disease;
- In primary therapy, the combination of bortezomib, dexamethasone and rituximab (BDR) leads to high ORR (95%) and CR (22%) rates;

Summary

- Bortezomib may counteract the IgM related flare associated with rituximab;
- Bortezomib based therapy may be particularly suited for patients presenting with hyperviscosity;
- Reversible peripheral neuropathy is the main concern with bortezomib, and altered schedules of administration may decrease neuropathy;
- Herpes zoster prophylaxis is advised with BDR.