THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History

My WM is Back:

Treatment Options for Relapsed Waldenström macroglobulinemia

Sheeba Thomas, MD

Reasons to Treat Relapsed WM

History

- Fever > 101 F
- Drenching Night Sweats
- Weight Loss
- Severe Neuropathy
- Severe Fatigue

Physical

- Fundoscopic exam
- Lymphadenopathy
- Organomegaly
- Neuropathy

Other Diseases/Signs

- Amyloidosis
- Kidney Impairment
- Cryoglobulinemia
- Transformation

Monoclonal Protein

- IgM by Densitometry
- No Certain Level

Rising

Other Tests

- Hemoglobin $\leq$ 10g/dL
- Platelets < 100 x 10^9/L due to WM
- Bulky lymph nodes/liver/spleen
- Hyperviscosity with signs (~>4 cp)

Kyle, Semin Oncol, 2003

Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

Conventional Chemotherapy

- Cyclophosphamide
- Bendamustine
- Fludarabine
- Cladribine

Stem Cell Transplant

- Autologous SCT
- Allogeneic SCT

Monoclonal Antibodies

- Rituximab
- Ofatumumab
- Alemtuzumab

BTK inhibitor

- Ibrutinib

mTOR inhibitor

- Everolimus

Proteasome inhibitors

- Bortezomib
- Carfilzomib

Immunomodulators

- Thalidomide
- Lenalidomide
- ? Pomalidomide

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Treatment Decision Considerations

- Disease related
  - Slow vs. rapid progression
  - Neuropathy
  - Cranial nerve involvement
- Patient related
  - Performance status
  - Kidney/Liver function
  - Blood counts
  - Other medical conditions
  - Convenience/Practical considerations
- Treatment related
  - Length of response to prior therapy (>12 months)
  - Prior drug exposure (relapsed/progressive disease on therapy)
  - Ongoing side effects from prior therapy

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Monoclonal Antibodies

- **Rituximab**
- **Ofatumumab**

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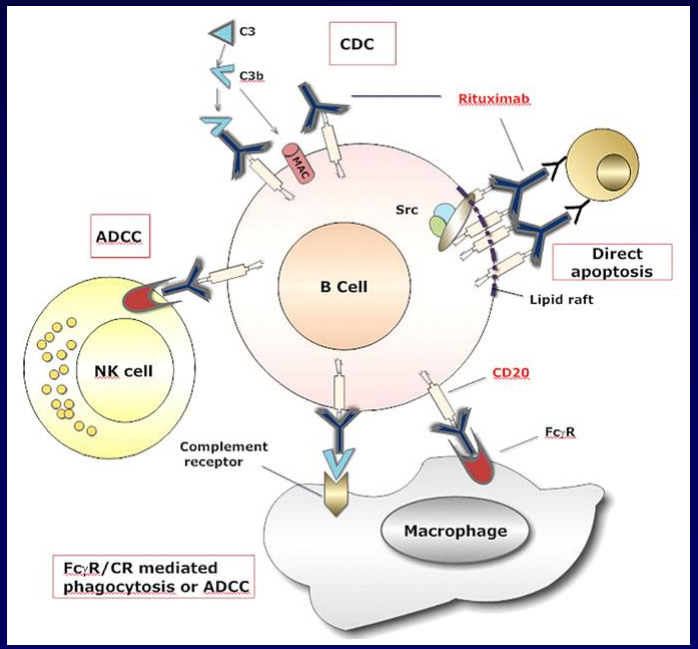
Rituximab: Backbone of Treatment

Multicenter Phase 2 Trial of Rituximab for Waldenström Macroglobulinemia (WM): An Eastern Cooperative Oncology Group Study (E3A98)

- N = 35 previously treated patients (none with prior rituximab)
- Regimen: Weekly rituximab x 4 doses
- Partial Response rate = 20%



Jaglowski S et al. Blood 2010 116(19) 3705-14

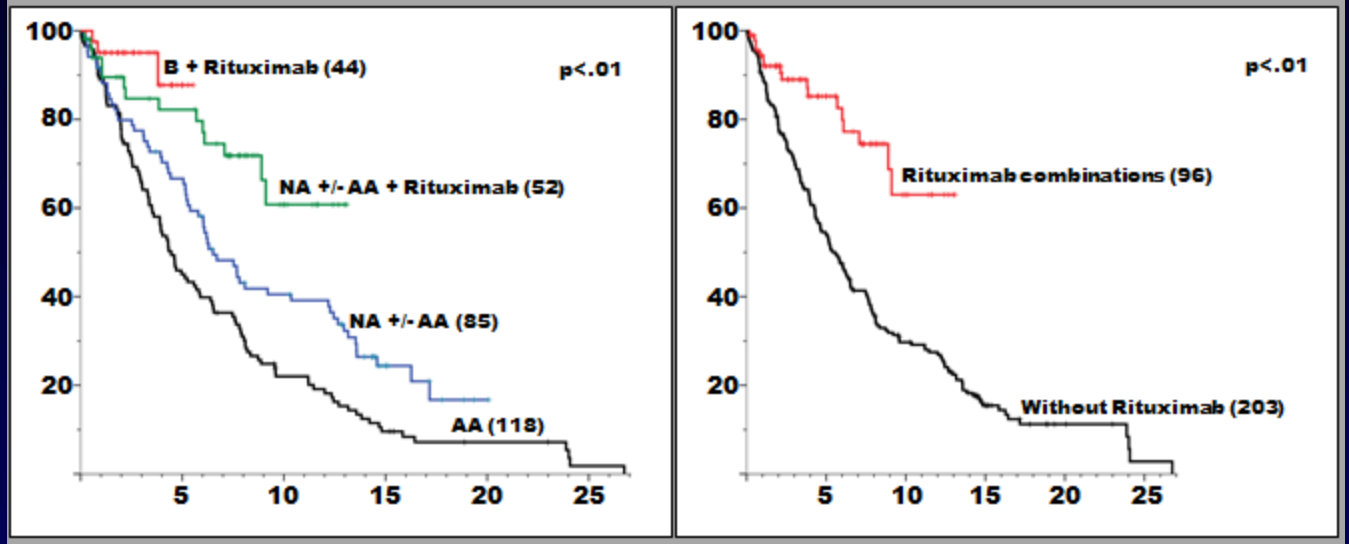
Gertz M et al. Leukemia and Lymphoma 2004 Oct;45(10):2047-55

Impact of Rituximab on the Treatment of Waldenström's Macroglobulinemia

Sheeba K. Thomas, M.D., Kay B. Delasalle, B.S., Jatin J. Shah, M.D., Michael Wang, M.D., Robert Z. Orlowski, M.D., Ph.D., Raymond Alexanian, M.D., Donna M. Weber, M.D

Department of Lymphoma/Myeloma, The University of Texas M. D. Anderson Cancer Center

Overall Survival



Retrospective evaluation of 312 pts. who received primary therapy with:

- **Alkylating agents (AA)**
  CHOP, CVP, melphalan-prednisone, chlorambucil-prednisone
- **Nucleoside analogs (NA) +/- AA**
  2CdA, 2CdA + prednisone, 2CdA + cyclophosphamide
- **NA +/- AA + Rituximab**
  2CdA + rituximab, 2CdA + cyclophosphamide + rituximab
- **Bortezomib (B) + Rituximab**
  +/- dexamethasone

Regimen	Median OS (yrs)
AA alone	4.5
NA +/- AA	6.5
NA +/- AA + Rituximab	Not reached
B + Rituximab	Not reached
Rituximab combinations	>13
Without rituximab	5.6

Thomas et al. ASH Annual Meeting Abstracts 2012

Rituximab Intolerance: Ofatumumab in Relapsed WM

- **Fully human monoclonal anti-CD20 antibody**

Regimen	Median Prior Rx	No. Evaluable	Major Response Rate
A) OFA 300 mg wk 1 and **1000** mg wks 2–4 **or** B) OFA 300 mg wk 1 and **2000** mg wks 2–5	3 (1-5)	28	57%

Treatment A - lower response rate if had prior rituximab

Treatment B - equal response regardless of prior rituximab or other prior therapy

* 2 patients developed an IgM flare

Furman et al. ASH Annual Meeting Abstracts 2011

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Dexamethasone-Rituximab-Cyclophosphamide

Author	Regimen (28 day cycle)	No. Evaluable*	Major Response Rate	2 year Progression Free Survival
Dimopoulos et al. 2007	Dexamethasone 20mg Rituximab 375mg/m2 Cyclophosphamide 100mg/m2	72	74%	67% (all patients) 80% (responders)

* All patients were previously untreated for Waldenstrom's

Dimopoulos MA et al. J Clin Oncol. 2007 Aug 1;25(22):3344-9.

Bendamustine +/- Rituximab

Regimen (28 day cycle)	Median Prior Rx	No. Evaluable	Major (Complete) Response Rate	Progression Free Survival (months)
Bendamustine-Rituximab	0	22	93 (40)*	69.5
vs.				
R-CHOP		19	91 (30)*	28.1

* Response rate is for all patients on study – includes different types of low grade lymphomas

Bendamustine-Rituximab	**2 (1-9)**	**24**	**79**	**13.2 (all)**
Bendamustine-Ofatumumab		**2**	**100**	
Bendamustine		**4**	**100**	

Rummel MJ, J Clin Oncol. 2005 May 20; 23(15):3383-9. Treon et al. Clin Lymphoma Myeloma Leuk. 2011 Feb;11(1):133-5

Cladribine +/- Rituximab in Relapsed WM

Author	Regimen	No. Evaluable	Major (Complete) Response Rate	Time to Treatment Failure	% MDS/AML or Transformation
Dimopoulos et al.	Cladribine X 2 cycles	20	40%	Not reported	Not Reported
Laszlo et al.	Cladribine-Rituximab x 4 cycles	13	84.6%	Not Reached (50 mos of follow-up)	0

Dimopoulos et al. Ann Int Med 1993 Feb 1;118(3):195-8.

Laszlo et al. Clin Lymphoma Myeloma Leuk. 2011 Feb;11(1):130-2

Cladribine (2-CdA) Retreatment Sensitivity

	2-CdA	2-CdA/Cy	Total
No. Patients			
Total	16	38	
Relapsed	12	19	
Retreated	10	13	23
Response	8	10	**18** (78%)
Remission Duration (median # mos.)			
First	23.5	37.7	
Second	24	30	

Weber DM et al. Semin Oncol 2003 30(2):243-7

Fludarabine Based Therapy

Author	Regimen (28 day cycle)	No. Evaluable	Major Response Rate	Long Term Outcome
LeBlond et al. 2001	Fludarabine	45	30%	Duration of Response = 19 months
Dhodapkar et al.	Fludarabine 30mg/m2 x 5 days } x 4-8 cycles	64	33%	Estimated 5 year PFS = 41%
Treon et al.	Fludarabine x 6 cycles Rituximab x 8 infusions	16	81%	Time to progression = 33.4 months

LeBlond et al. Blood 2001, Blood 98(9)
Dhodapkar et al. Semin Oncol 2003;30(2):220-5. Treon et al. Blood. 2009 Apr 16;113(16):3673-8

2nd Cancers after Cladribine/Fludarabine

Treon et al. Fludarabine + Rituximab (n=43 patients)

- Median follow-up of 40.3 months:
  - 2nd cancers seen in 8

Rakhitt et al. Cladribine alone, + Cyclophosphamide, or + Cyclophosphamide-Rituximab (n=111 patients)

- 10 patients (9%) had transformation to large cell lymphoma.
  - 4 pts had transformation of disease within 13 months.
- An additional 13 pts (12%) developed a second cancer.
  - Median time to 2nd cancer was 85.5 months

Leleu et al. (n= 193 patients with Nucleoside Analog exposure; 136 without NA exposure)

- 12 patients (6.2%) had transformation or t-MDS/AML in NA treated group
- 1 patient (0.4%) had transformation in the non-NA treated group ($P < .001$)

Treon et al. Blood 2009 Apr 16;113(16):3673-8 Rakhitt R et al. ASH Annual Meeting Abstracts 2008 Leleu X et al. JCO 2009; 27(2): 250-255

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Stem Cell Transplantation

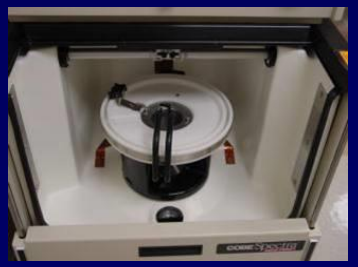
Autologous

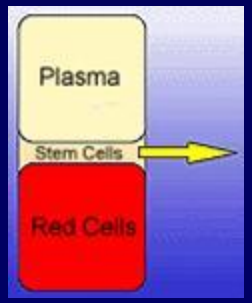
Stem cell collection
from patient

Allogeneic

Stem cell collection
from donor

Stem Cell Collection





High Dose Chemotherapy

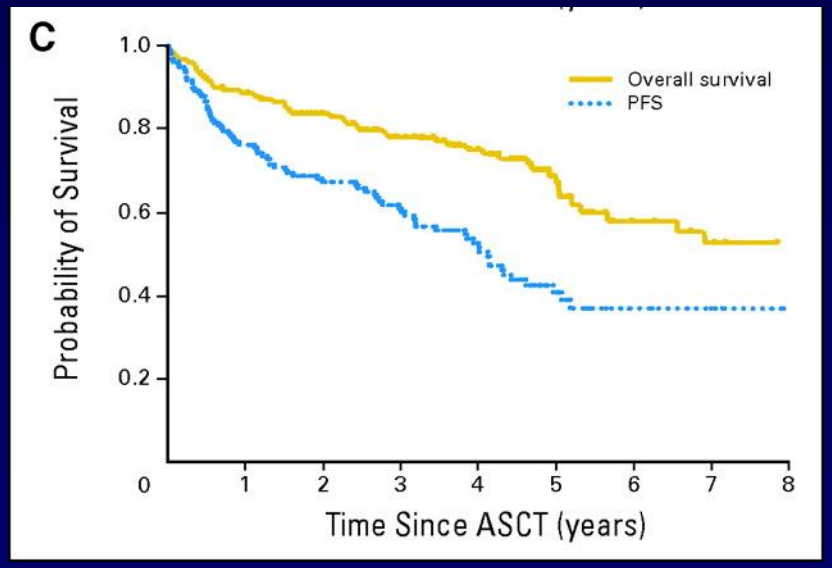
- To destroy the cancer cells in your body
- Varied chemotherapy drugs can be used.
- 24-72 hours for the chemotherapy to clear from your body before infusing the stem cells.
- The amount of time between your last dose of chemotherapy and your transplant is determined by what drugs you receive.

Photo courtesy of www.msnbc.msn.com

Stem Cell Transplantation

Autologous Stem Cell Transplant in Relapsed WM

	Transplant Dates	No. Evaluable	Median time from diagnosis to ASCT	Median Prior Rx	Major (Complete) Response Rate	Estimated 5 year PFS Rate
EBMT registry	1/1991-12/2005	75	1.7 yrs (0.3-20.3)	3	87 (22)%	40%



Factors predicting longer PFS:

- Having <3 prior therapies for WM
- Having chemosensitive disease at time of transplant

8.4% incidence of 2nd cancers at 5 years

Kyriakou C et al. J Clin Oncol 2010 May 1;28(13):2227-32

Allogeneic Stem Cell Transplant

Review of EBMT registry from 1/1998-12/2005

- 86 patients (Myeloablative Conditioning, 37pts; Reduced Intensity Conditioning, 49 pts)
- Median time from diagnosis to Allo SCT = 37 months
- Median Age = 49 yrs (23-64 yrs)

Conditioning Regimen	Major Response Rate (%)	Estimated 5 Year Progression Free Survival	Estimated 5 Year Overall Survival	Incidence of Graft vs. Host Disease
Myeloablative	76%	56%	62%	61%
Reduced Intensity		49%	64%	33%

47 patients had ≥ 3 prior therapies

59 patients (69%) had chemotherapy-sensitive disease at the time of alloSCT.
8 patients had relapsed after prior autologous stem cell transplant

Non-Relapse Mortality Rate: 33% MAC; 23% RIC

Kyriakou C et al. J Clin Oncol 2010;28(33):4926-34

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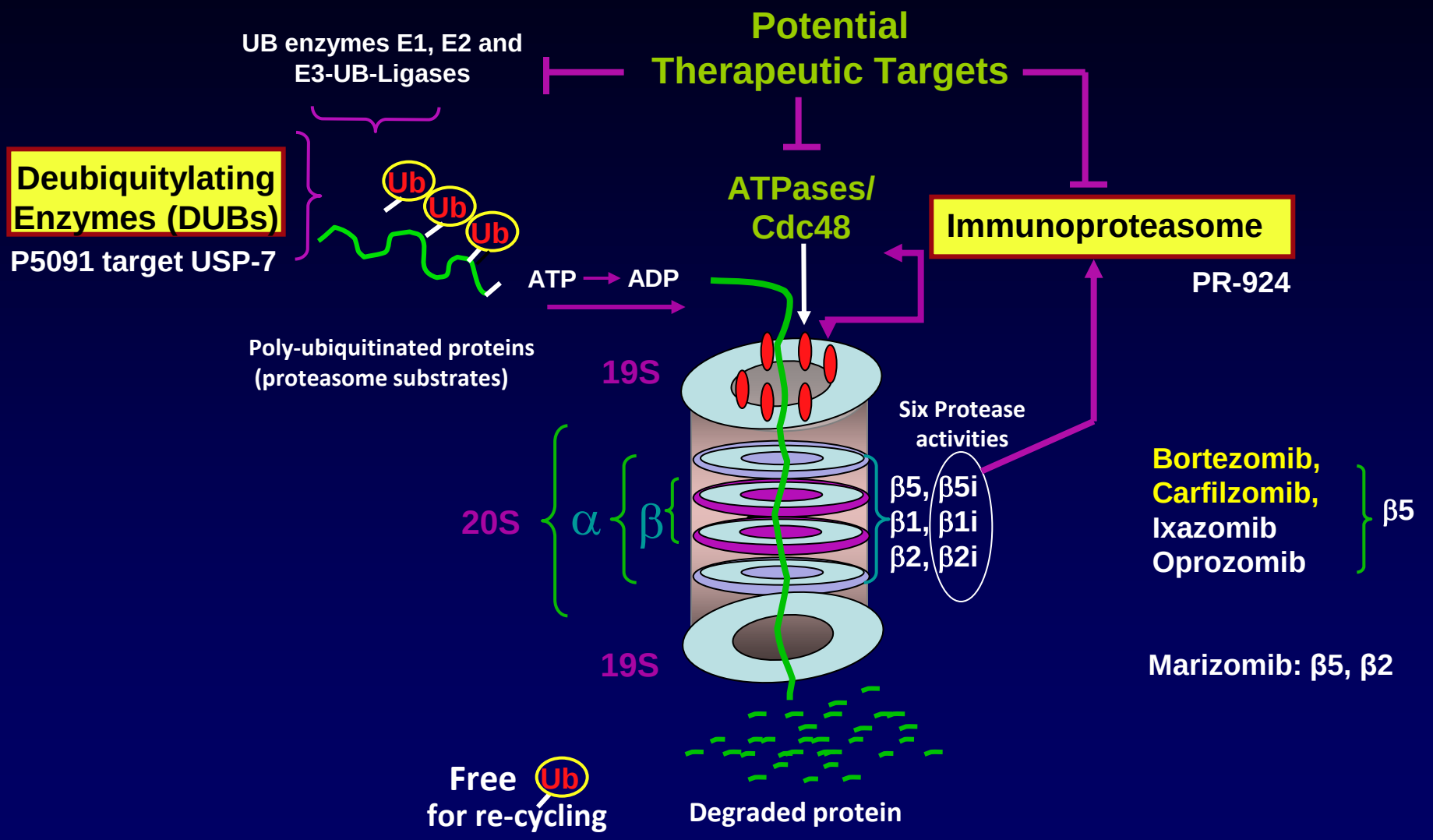
Proteasome: Present and Future Therapies



Anderson KC et al. *J Clin Oncol 30:445-452. © 2012*

Bortezomib +/- Rituximab in Relapsed WM

Author	Regimen	No. Evaluable	Major (Complete) Response Rate	Median Time to Progression/ Progression Free Survival
Chen et al.	Bortezomib 1.3 mg/m^2 iv twice weekly	15	27%	16.3 months *all patients
Treon et al.	Bortezomib 1.3 mg/m^2 iv twice weekly } x 8	27	48%	7.9 months
Dimopoulos et al.	Bortezomib 1.3 mg/m^2 iv twice weekly } x 4	10	60%	>11 months (estimate)
Ghobrial et al.	Bortezomib 1.6 mg/m^2 iv Rituximab 375 mg/m^2 } x 6	37	51 (5)%	15.6 months (Range = 11-21 mos.)

Chen et al. J Clin Oncol 2007 vol. 25 (12) 1570-1575.

Treon et al. Clin Cancer Res 2007 Jun 1;13(11):3320-5.

Ghobrial et al. J Clin Oncol 2010 Mar 10;28(8):1422-8.

Recommendations for Treating Relapsed WM

Clinical Trial of a Novel Agent is a Priority

Proteasome inhibitor-based

Carfilzomib

- Low rates of neuropathy

Side Effects to Consider

- Fatigue
- Nausea
- Low blood counts
- Kidney impairment
- - seen less commonly now
- Heart problems

Lonial et al. *Clin Cancer Res*. 2011;17(6):1264-1277;
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Immunomodulators in WM

- **Thalidomide**
  - Thalidomide alone: ≥ PR of 25%
  - Thalidomide + steroids and/or clarithromycin: ≥ PR of 25-83%.
  - Thalidomide + Rituximab (Phase II Study): ≥ PR of 64%.
    - 25-44% of patients developed ≥ Grade 2 peripheral neuropathy

- **Lenalidomide**
  - Lenalidomide + Rituximab (Phase II Study): ≥ PR of 25%
    - 56% of patients developed ≥ Grade 2 anemia

Coleman et al. Semin Oncol. 2003 Apr;30(2):270-4.
Treon et al., Clinical Cancer Research 2009 Jan 1;15(1):355-60

Dimopoulos et al. Semin Oncol 2003 Apr;30(2):265-9.
Treon et al. Blood 2008 Dec 1;112(12):4452-7.

Considerations for Thalidomide in Relapsed WM

Clinical Trial of a Novel Agent is a Priority

Immunomodulator-based

Thalidomide-based

- Low blood counts
- Impaired Kidney Function

Side Effects to Consider

- Sleepiness (>12%)
- Blood Clot risk (with steroids)
- Neuropathy (> 44%)
- Constipation
- Birth defects
- Rash

Lonial et al. *Clin Cancer Res*. 2011;17(6):1264-1277
NCCN Clinical Practice Guidelines in Oncology, v.3.2015
Guglielmeli et al. Br J Haemat 2010; 152: 108-21.

Considerations for Lenalidomide in Relapsed WM

Clinical Trial of a Novel Agent is a Priority

Immunomodulator-based

Lenalidomide

- Underlying peripheral neuropathy
- Adjust dose if kidney function impaired

Side Effects to Consider

- Blood Clot risk (with steroids)
- Constipation or Diarrhea
- Birth defects
- Can lower blood counts
- Rash

Lonial et al. *Clin Cancer Res*. 2011;17(6):1264-1277;
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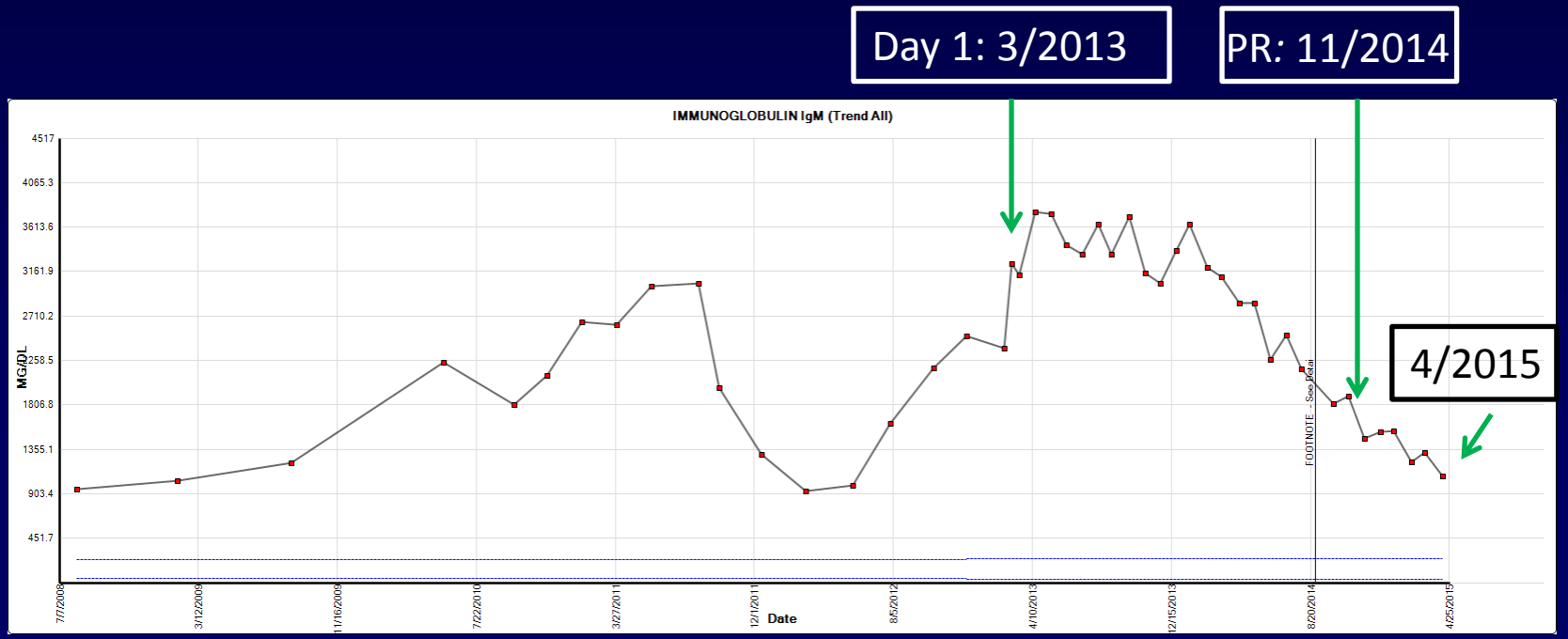
Phase I Trial Of Pomalidomide

Author	Regimen (28 day cycle)	No. Evaluable*	Major Response Rate (%)	Time on Therapy
Thomas et al.	Pomalidomide 1mg 2mg	6 3	1/6 Not tolerable	2 years, 1 month +



Thomas et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 8536)

Recommendations for Treating Relapsed WM

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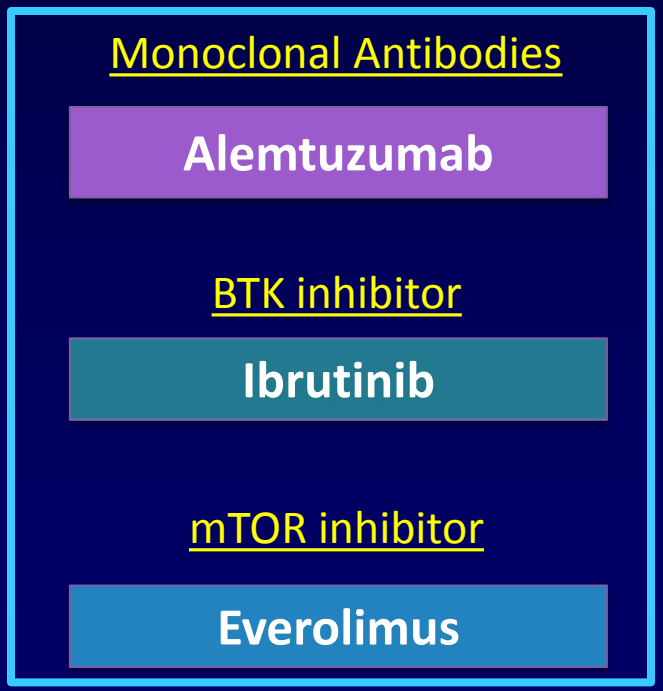

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Alemtuzumab in Relapsed WM

- Humanized monoclonal antibody to CD 52

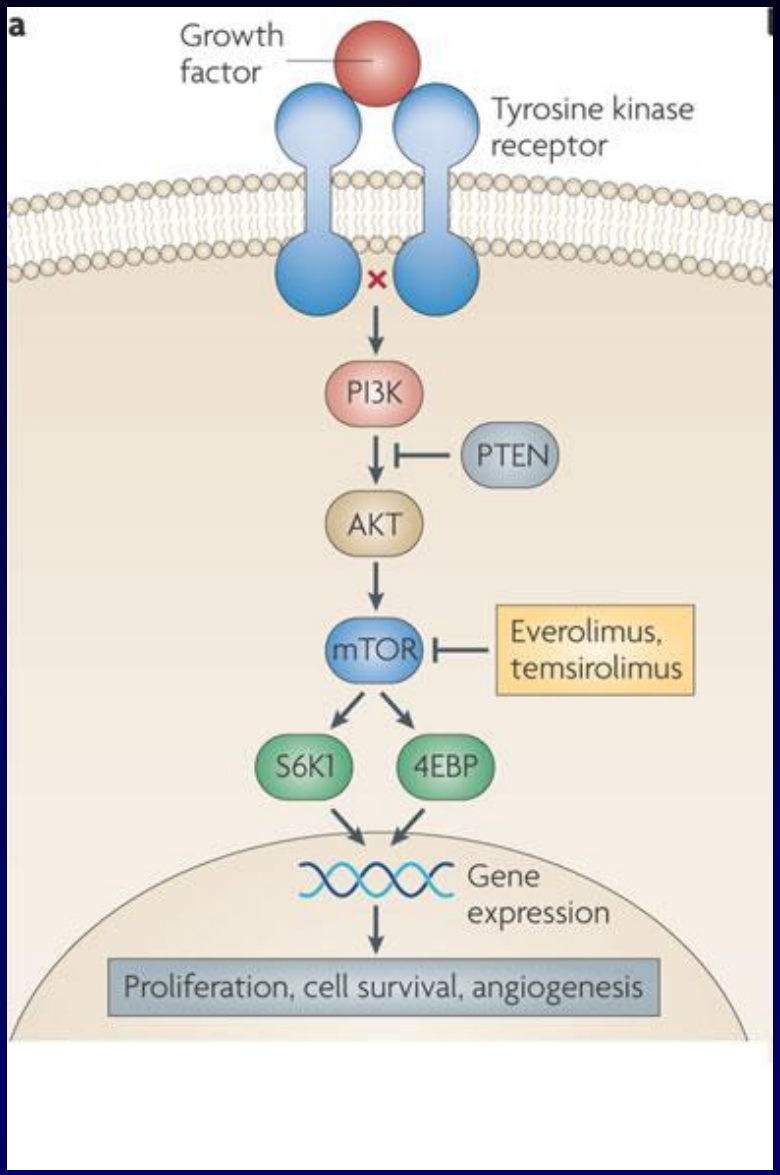
Regimen	No. Evaluable	Median Prior Rx	Major Response Rate	Median Time to Progression
30 mg iv 3x/week for up to 12 wks	23	2 **46% refractory to last therapy**	36%	14.5 months

Toxicities of Note:

- Cytomegalovirus reactivation occurred in 18%, leading to 3 deaths
- New-onset autoimmune thrombocytopenia in 14% (4 pts), leading to 1 death

Treon et al. Blood 2011 118(2):276–281

Everolimus in Relapsed WM

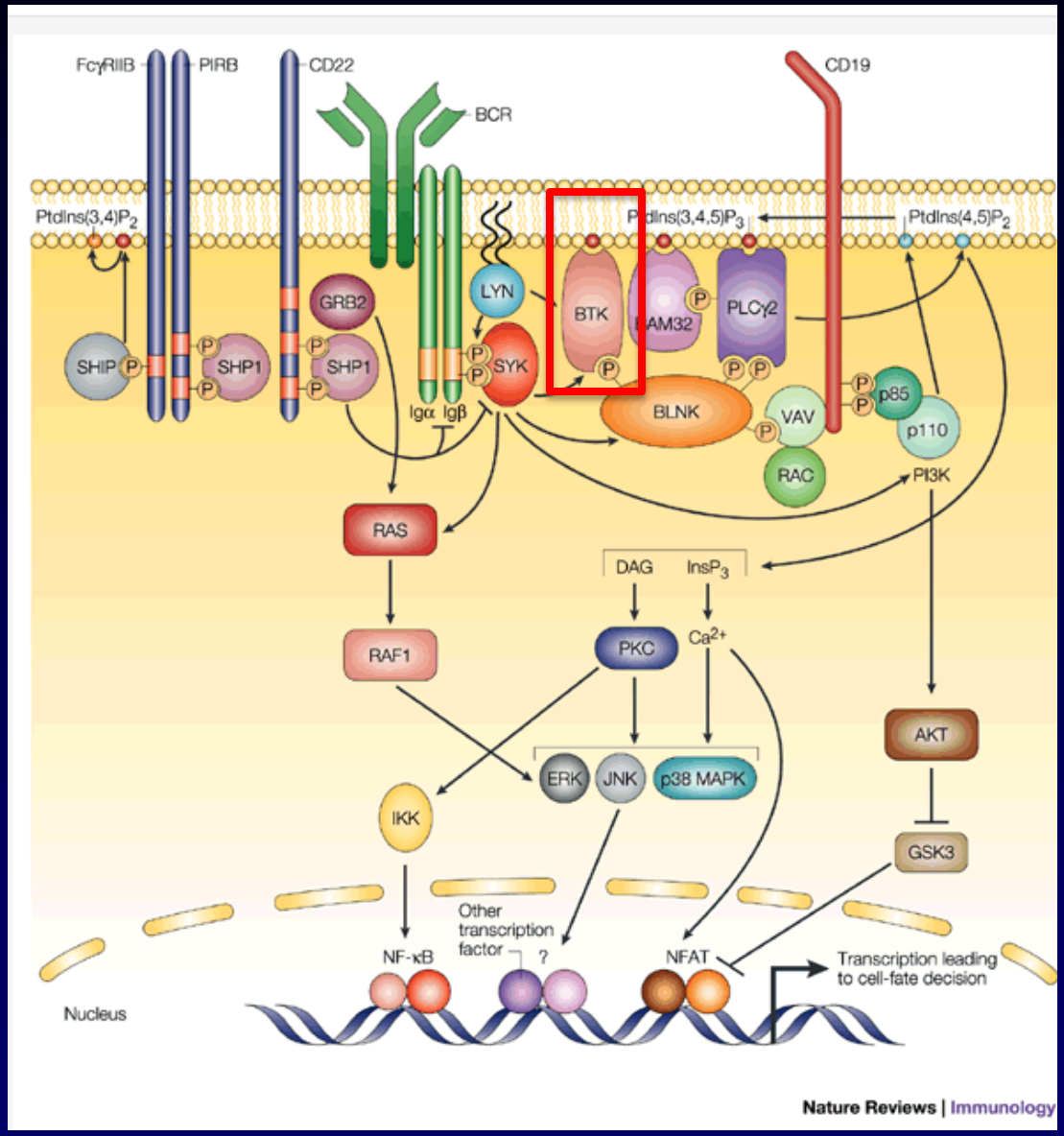


Regimen	No. Evaluable	Major Response Rate	Median Progression Free Survival
Everolimus 10mg/day	60	50%	21 months

Toxicities
Lung Toxicity (5%) Mouth Sores (8%) Diarrhea (5%) Fatigue (8%) Grade 3-4 toxicity rate = 67% - Mostly low blood counts

Atkins et al. Nature Reviews Drug Discovery 2009; 8, 535-536.
Ghobrial et al. Am J. Hematol 2014 Mar;89(3):237-42.

Ibrutinib in Relapsed WM



Niiro H et al. 2002 Nature Reviews Immunology 2, 945-956

Ibrutinib in Relapsed WM

Author	Regimen (28 day cycle)	No. Evaluable	Median Prior Rx	Major Response Rate (%)	Median Time to Response
Treon et al. 2015	Ibrutinib 420mg/day	63	2 (1-6)	57.1	4 weeks

- Attainment of major responses was impacted by mutations in CXCR4
- MRR was 77% for pts with wild-type CXCR4 vs. 30% in those with WHIM-like CXCR4 mutations

Side Effects:

Low platelets (14%)
Low neutrophils (22%)
Pneumonia (8%)
Bleeding events – bloody nose, bleeding after procedures (6%)
Atrial Fibrillation (5%) – all in pts w/history of intermittent afib
- resolved after stopping drug; drug was later resumed uneventfully

Treon et al. NEJM 2015 Apr 9;372(15):1430-40

Ibrutinib in Relapsed WM

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Available Trials for Relapsed WM on Clinical Trials.Gov

Clinical Trial of a Novel Agent is a Priority

- Carfilzomib-Rituximab-Dexamethasone
- Oprozomib
- BTK inhibitors
  - Ibrutinib + Rituximab
  - ACP196
- TLR antagonists – IMO 8400

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