Waldenström’s macroglobulinemia: Genetic Basis and Therapy.

Steve Treon MD, MA, PhD
Dana Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts, United States
Waldenström’s Macroglobulinemia – first described by Jan Gosta Waldenström in 1944.
Waldenström’s macroglobulinemia: Similar but Different to Myeloma.
Genetic Predisposition
Familial disease predisposition in WM

- N=1076 consecutive patients with clinicopathological diagnosis of WM
- 26.1% of WM patients have a first or second degree relative with a B-cell LPD.

Distribution of B-cell LPD in relatives of 281 Familial WM patients.

Treon et al, ASH 2011.
WM Familial Genomics Project

IRB Approved Registry. Over 800 individuals, 187 families enrolled. Detailed familial history for cancer and autoimmune disorders collected, updated biannually. CBCD, quantitative Igs, SPEP, serum, buccal and PB DNA collected on all participants.
Impact of familial status in rituximab-naïve patients receiving a rituximab containing regimen.

Response to Therapy

Overall Major VGPR/CR
Sporadic Familial

93.9 74.8 23.2 75 55.6 16.7

p=0.029 p=0.032 P<0.001

Treon et al, ASH 2011
Familial Disease Is Associated with shorter PFS and Time to Next Therapy

PFS

<table>
<thead>
<tr>
<th>No familial disease</th>
<th>Familial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent without progression</td>
<td>Percent without progression</td>
</tr>
<tr>
<td>Months</td>
<td>Months</td>
</tr>
</tbody>
</table>

\[ p=0.015 \]

TTNT

<table>
<thead>
<tr>
<th>No familial disease</th>
<th>Familial disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent without progression</td>
<td>Percent without progression</td>
</tr>
<tr>
<td>Months</td>
<td>Months</td>
</tr>
</tbody>
</table>

\[ p=0.024 \]

Treon et al, ASH 2011
Familial Disease Status in WM is an Independent Prognostic for PFS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Disease</td>
<td>1</td>
<td>-0.59016</td>
<td>0.27386</td>
<td>4.6438</td>
<td>0.0312</td>
<td>0.554</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>-0.02276</td>
<td>0.01320</td>
<td>2.9712</td>
<td>0.0848</td>
<td>0.977</td>
</tr>
<tr>
<td>sIgM</td>
<td>1</td>
<td>0.0000498</td>
<td>0.0000573</td>
<td>0.7538</td>
<td>0.3853</td>
<td>1.000</td>
</tr>
<tr>
<td>sB₂M</td>
<td>1</td>
<td>0.13171</td>
<td>0.05077</td>
<td>6.7293</td>
<td>0.0095</td>
<td>1.141</td>
</tr>
<tr>
<td>Hgb</td>
<td>1</td>
<td>0.08309</td>
<td>0.07579</td>
<td>1.2018</td>
<td>0.2730</td>
<td>1.087</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Disease</td>
<td>1</td>
<td>-0.66490</td>
<td>0.26764</td>
<td>6.1717</td>
<td>0.0130</td>
<td>0.514</td>
</tr>
<tr>
<td>IPSS</td>
<td>1</td>
<td>0.20736</td>
<td>0.15232</td>
<td>1.8531</td>
<td>0.1734</td>
<td>1.230</td>
</tr>
</tbody>
</table>
Does the type treatment impact response for familial patients?

N=36

Non-Bortezomib

Bortezomib

ORR

Major

VGPR/CR

Treon et al, ASH 2011
Is there a common genetic predisposition with other cancers in WM patients?
## Other Cancers in WM Patients

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Sporadic</th>
<th>Familial, Mixed B-cell</th>
<th>Familial, WM Only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=</strong></td>
<td>924</td>
<td>685</td>
<td>194</td>
<td>45</td>
</tr>
<tr>
<td><strong>Prostate (Males)</strong></td>
<td><strong>54 (9.42%)</strong></td>
<td><strong>47 (10.7%)</strong></td>
<td>5 (4.59%)</td>
<td>1 (4.00%)</td>
</tr>
<tr>
<td><strong>Breast (Females)</strong></td>
<td><strong>28 (8.00%)</strong></td>
<td><strong>22 (9.13%)</strong></td>
<td>6 (6.67%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td><strong>Skin (Non-Melanoma)</strong></td>
<td><strong>66 (7.14%)</strong></td>
<td><strong>56 (8.18%)</strong></td>
<td>10 (5.15%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td><strong>26 (2.81%)</strong></td>
<td><strong>16 (2.33%)</strong></td>
<td>8 (4.12%)</td>
<td>2 (4.44%)</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td><strong>20 (2.16%)</strong></td>
<td><strong>15 (2.19%)</strong></td>
<td>4 (2.06%)</td>
<td>1 (2.22%)</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td><strong>14 (1.40%)</strong></td>
<td><strong>5 (0.73%)</strong></td>
<td><strong>8 (4.12%)</strong></td>
<td>1 (2.22%)</td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
<td><strong>10 (1.08%)</strong></td>
<td><strong>10 (1.46%)</strong></td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td><strong>GYN</strong></td>
<td><strong>10 (1.08%)</strong></td>
<td><strong>8 (1.16%)</strong></td>
<td><strong>2 (1.03%)</strong></td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>273 (29.6%)</strong></td>
<td><strong>212 (31.4%)</strong></td>
<td><strong>53 (25.8%)</strong></td>
<td><strong>8 (17.77%)</strong></td>
</tr>
</tbody>
</table>

Hanzis et al, CLML 2011
Consensus Panel Recommendations for Initiation of Therapy in WM

- Hb \( \leq 10 \) g/dL on basis of disease
- PLT <100,000 mm\(^3\) on basis of disease
- Symptomatic hyperviscosity (>4.0 cp)
- Moderate to severe peripheral neuropathy
- Symptomatic cryoglobulinemia, cold agglutininemia, amyloidosis, or symptomatic autoimmune-related events on the basis of disease

Natural Killer Cell

Fc receptor

Fc

CD20-Directed Rituximab Monoclonal Antibody

CD20

WM cell

Fab
Serum IgM Levels Following Rituximab in Patients With WM

$P$ denotes patient-required plasmapheresis for hyperviscosity.

Bystander Release of IL-6 by Monocytes May Account for the Rituximab IgM Flare

- +monocytes
- +rituximab
- +anti-IL6 beads

<table>
<thead>
<tr>
<th>IgM (ng/ml)</th>
<th>1200</th>
<th>1400</th>
<th>1600</th>
<th>1800</th>
<th>2000</th>
<th>2200</th>
<th>2400</th>
<th>2600</th>
</tr>
</thead>
<tbody>
<tr>
<td>+monocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+rituximab</td>
<td>2500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+anti-IL6</td>
<td>2300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagram:
- Rituximab
- IVIg
- FcγRIIA
- Monocytes
- IL-6
- IL-6R
- WM-LPC
- IgM
### Primary Therapy of WM with Rituximab-Based Options

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab x 4</td>
<td>25-30%</td>
<td>0%</td>
</tr>
<tr>
<td>Rituximab x 8</td>
<td>40-45%</td>
<td>0%</td>
</tr>
<tr>
<td>Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, RCD</td>
<td>70-80%</td>
<td>8-10%</td>
</tr>
<tr>
<td>Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R</td>
<td>70-90%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Rituximab/thalidomide</td>
<td>70%</td>
<td>5%</td>
</tr>
<tr>
<td>Rituximab/bortezomib i.e. BDR, VR</td>
<td>70-90%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Rituximab/bendamustine</td>
<td>90%</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Disease Transformation and MDS/AML Following Nucleoside Analogue in WM

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Median F/U (mo)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leleu et al, JCO 2009¹</td>
<td>Prev treated with NA vs. non-NA or untreated</td>
<td>439</td>
<td>60</td>
<td>Histologic Transformation (8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MDS/AML (5%)</td>
</tr>
<tr>
<td>Tamburini et al, Leukemia</td>
<td>Firstline with Fludara/Cyclo</td>
<td>49</td>
<td>41</td>
<td>Histologic Transformation (10%)</td>
</tr>
<tr>
<td>2005²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leblond, JCO 1998³</td>
<td>Previously treated with Fludara</td>
<td>71</td>
<td>34</td>
<td>Histologic Transformation (10%)</td>
</tr>
<tr>
<td>Rakkhit et al, ASH 2008⁴</td>
<td>Untreated; 2CDA based therapy</td>
<td>111</td>
<td>NA</td>
<td>Histologic Transformation (9%)</td>
</tr>
</tbody>
</table>

Advances in the Biology of Waldenstrom’s Macroglobulinemia

Revlimid-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.

## Phase I Study of Pomalidomide, Dexamethasone, and Rituximab (PDR) in WM

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomalidomide</td>
<td>0.5, 1, 2 mg QD</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg wkly IV</td>
<td>Pre-rituximab</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m²/wk</td>
<td>W1-4; W12-15</td>
</tr>
</tbody>
</table>

- Aggravated Anemia less pronounced
- Complete remission in first dose cohort
- IgM flare is potentiated
Proteasome Inhibitors
New Proteasome Inhibitors

Bortezomib/Carfilzomib

MLNM4924
Bortezomib Combination Therapy in WM

• **Primary**
  
  Bortezomib (1.3 mg/m²/biwkly)/Dexamethasone/Rituximab  
  ORR 95%; CR 22%; TTP >4 yrs; 30% Grade 3 PN  
  Bortezomib (1.6 mg/m²/wk)/Rituximab  
  ORR 92%; CR 8%; 80% 1 Y PFS; No Grade 3 PN

• **Salvage**
  
  Bortezomib (1.6 mg/m²/wk)/Rituximab  
  ORR 81%; CR 5%; TTP 12 months; 5% Grade 3 PN.  
  Bortezomib (randomized wkly vs biwkly)/Rituximab  
  ORR 80%; CR 0%; TTP ?; 0% Grade 3 PN.

vs. 10-12% in MM!

---

Bortezomib-Based Rituximab Therapy

- Twice A Week
  - CR/VGPR
  - PFS (?)
  - Time to Response
  - Rituximab IgM Flare

- Once A Week
  - Neuropathy
Neuropathy Data for Carfilzomib in MM (Pooled Data from 003/004 Studies)

<table>
<thead>
<tr>
<th>Prior history of neuropathy</th>
<th>N=201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related to prior treatment</td>
<td>155 (78%)</td>
</tr>
<tr>
<td></td>
<td>122 (61%)</td>
</tr>
</tbody>
</table>

Neuropathy symptoms at baseline: 109 (54%)

Incidence of treatment-emergent PN in 003 / 004:

- Grade 1: 9.5% (4.5% unrelated, 4.0% drug-related)
- Grade 2: 6.0% (4.0% unrelated, 2.0% drug-related)
- Grade 3: 1.5% (1.0% unrelated, 0.5% drug-related)
- Grade 4: 0%

Only 1 patient had drug discontinued for PN (study 004; BTZ-treated arm).

Primary Therapy of WM with Carfilzomib, Rituximab, Dex (CARD)

<table>
<thead>
<tr>
<th>Induction Cycle 1 q21 days</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1,2,8,9</td>
<td>Carfilzomib 20 mg/m² IV; Dexamethasone 20 mg IV.</td>
</tr>
<tr>
<td>Days 2,9</td>
<td>Rituximab 375 mg/m²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Induction Cycle 2-6 q21 days</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1,2,8,9</td>
<td>Carfilzomib 36 mg/m² IV; Dexamethasone 20 mg IV.</td>
</tr>
<tr>
<td>Days 2,9</td>
<td>Rituximab 375 mg/m²</td>
</tr>
</tbody>
</table>

2 months

<table>
<thead>
<tr>
<th>Maintenance Cycles 1-8 q 2 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1,2</td>
<td>Carfilzomib 36 mg/m² IV; Dexamethasone 20 mg IV.</td>
</tr>
<tr>
<td>Days 2</td>
<td>Rituximab 375 mg/m²</td>
</tr>
</tbody>
</table>
Bendamustine in WM

Bendamustine

Nitrogen mustard

Cyclophosphamide

Carboxylic acid

Benzimidazole ring

Cladribine

Cyclophosphamide

Cladribine
PFS: Benda-R vs CHOP-R in Frontline WM

Rummel M, et al. Presented at: Third International Pt Physic Summit on WM; May 1-3, 2009; Boston, Massachusetts, United States.
Bendamustine in Relapsed/Refractory WM

- ORR 83%
- PFS 13.2 mos.

To Maintain or Not to Maintain?
PFS in rituximab naïve WM patients who were observed or given maintenance rituximab therapy.

N=248

Infectious Events in WM Patients Who Underwent Observation or Maintenance Rituximab Therapy

Other Options for relapsed/refractory patients.
Everolimus 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 response:
  - NR (3-22+ mos)
- Grade ≥3 thrombocytopenia, pneumonitis, mucositis, and hyperglycemia.

IgM Discordance to WM BM Disease Involvement is Common With RAD001

7 non-responders by serial BM biopsies despite reductions in sIgM.
“Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided.”

*Phillipus Aureolus Paracelsus*
Campath in WM

• CD52 widely expressed on WM and BM Mast cells.

• **UK Study (n=7):**
  - ORR 86%; 1 CR;
  - 2 deaths due to Opportunistic Infections.

• **Multicenter study by WMCTG (n=28):**
  - ORR 75%; Major RR: 36% (1 CR);
  - TTP 14.5 months;
  - Cytopenias, CMV (3 deaths); Late ITP (1 death).

Novel Directions
B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation.

Bruton’s Tyrosine Kinase (Btk) is an essential element of the BCR signaling pathway.

Inhibitors of Btk block BCR signaling and induce apoptosis.

*Nat Rev Imm 2:945*
Preclinical Studies of PCI-32765 in WM.

- p<0.03 for all comparisons to untreated controls.

**Annexin V**

- BCWM.1
- MWCL-1

**UnRx**
- BTK-(pY223)
- IKBα-(pS32)

**+PCI-32765**
- total BTK
- total ERK1/2
- total IKBα
## PCI-32765 Clinical Experience

<table>
<thead>
<tr>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>ORR % ITT</th>
<th>ORR % Eval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL/SLL</td>
<td>16</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>69%</td>
</tr>
<tr>
<td>FL</td>
<td>16</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>25%</td>
</tr>
<tr>
<td>MCL</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td></td>
<td>78%</td>
</tr>
<tr>
<td>DLBCL</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td>29%</td>
</tr>
<tr>
<td>MZL/MLT</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td>25%</td>
</tr>
<tr>
<td>WM</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>56</td>
<td>5</td>
<td>22</td>
<td>11</td>
<td>10</td>
<td>6</td>
<td>48%</td>
</tr>
</tbody>
</table>

Most Frequently Observed Toxicities: fatigue, diarrhea, nausea, myalgia, headache, and pneumonia. No apparent hepatic or renal toxicities. No evidence of cumulative hematologic toxicity.

Advani et al. ASCO 2010
PCI 327625 in Relapsed/Refractory WM

Screening

Registration

560 mg po qD
PCI-32765

Progressive Disease (PD) or Unacceptable Toxicity

Stop PCI-32765

Event Monitoring

Stable Disease or Response
Continue x 24 four week cycles
(maximum)

Event Monitoring
WHOLE GENOME SEQUENCING IN WM

3,000,000,000 DNA molecules

Paired Sequencing from same individuals

NORMAL

WM

www.jayon.co.uk
Whole Genome Sequencing in 30 patients with WM

• 27 of 30 (90%) patients had a somatic mutation in MYD88 (L265P).

• Confirmed by Sanger sequencing.

Treon et al, ASH 2011.
Sanger sequencing for MYD88 L265P in expanded cohorts of WM, MGUS, MM, and MZL Patients.

<table>
<thead>
<tr>
<th></th>
<th>N=</th>
<th>MYD88 L265P</th>
<th>Homozygous (% of L265P pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM</td>
<td>54</td>
<td>49* (90.7%)</td>
<td>5 (10.2%)</td>
</tr>
<tr>
<td>IgM MGUS</td>
<td>10</td>
<td>1** (10.0%)a</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>MM</td>
<td>10</td>
<td>0 (0.0%)b</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>MZL</td>
<td>46</td>
<td>3 (6.5%)c</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Healthy Donors</td>
<td>15</td>
<td>0 (0.0%)d</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

* Identified in both CD19+ and CD138+ selected BM LPC for 14 WM pts.
** Absence confirmed for 7 negative MGUS pts by cloning and sequencing of at least 100 clones. 1 positive patient progressing.
Knockdown of MYD88 induces apoptosis in L265P expressing BCWM.1 and MWCL.1 WM cells.

**Lentiviral MYD88 Knockdown**

**Over-expression**

**LentiVector**

**BCWM.1**

- Over-expression
  - Myd88
  - Scbl Myd88

**MWCL.1**

- Over-expression
  - Myd88
  - Scbl Myd88

**MYD88 WT**

- Annexin V Staining

**MYD88 L265P**

- Annexin V Staining

**Annexin V Staining**
Disruption of MYD88 signaling induces apoptosis of MYD88 L265P expressing WM cells.

**MYD88 Homodimer Peptide Inhibitor**

**IRAKe 1/IRAKe 4 Kinase Inhibitor**

A. Untreated | Control peptide | MYD88 Inhibitory peptide

BCWM.1

- 18.6%
- 28.9%
- 78.7%

MWCL-1

- 15.6%
- 15.1%
- 56.0%

B. Vehicle Control | IRAKe 1/4 inhibitor

BCWM.1

- 15.4%
- 13.0%
- 26.2%

MWCL-1

- 10.1%
- 10.8%
- 20.5%

Guang Yang Abstract 597
Disruption of MYD88 signaling induces apoptosis of MYD88 L265P expressing patient BM LPC.
IkBα phosphorylation after knock-down of MYD88 or use of MYD88/IRAK signal inhibitors.
Take Home

- Familial predisposition is common in WM and impacts therapy.
- Bendamustine, bortezomib, cyclophosphamide, and thalidomide–based rituximab therapies are active, and can be used for symptomatic WM.
- Use of nucleoside analogues should be carefully weighed against other options.
- Better categorical responses are associated with improved PFS in rituximab treated patients, and reflect FCGR3A polymorphisms.
- WGS has revealed a somatic mutation in MYD88 in 91% of WM patients and represents a novel target for therapy of WM.
“Do not go where the path may lead, go instead where there is no path and leave a trail”

Ralph Waldo Emerson