The Map of Current Treatment Options for Waldenström Macroglobulinemia

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DISCLOSURES

Relevant Financial Relationship(s)
Mayo Clinic receives funding to conduct research

Off Label Usage
Yes
Everolimus, bortezomib, bendamustine, carfilzomib........
Objectives

• Review indications for therapy
• Understand the different drug classes
• Be aware of potential side effects of therapy
• Review treatment options
  • Newly diagnosed
  • Relapsed disease
• Discuss the role of stem cell transplantation
IgM M-protein

**IgM MGUS**
- <10% LP cells
- IgM <3gm

**Smoldering WM**
- >10% LP cells
- IgM >3gm
- No symptoms/signs

**WM**
- >10% LP cells
- Anemia
- Hyperviscosity
- Organomegaly

**IgM Myeloma**
- Lytic lesions
- CD20+ PC
- t(11;14)
WM Treatment

• The first question - Is there a need to treat?
• Second - What treatment to use?
• There is no IgM threshold that mandates starting therapy
• Conversely, a low IgM doesn’t mean treatment is not needed
• Delaying therapy may allow a better treatment – less toxic, more effective
## Indications for Therapy

### Table 1. Indications for initiation of therapy in patients with WM

<table>
<thead>
<tr>
<th>Clinical indications for initiation of therapy</th>
<th>Laboratory indications for initiation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent fever, night sweats, weight loss, fatigue</td>
<td>Symptomatic cryoglobulinemia</td>
</tr>
<tr>
<td>Hyperviscosity</td>
<td>Cold agglutinin anemia</td>
</tr>
<tr>
<td>Lympadenopathy which is either symptomatic or bulky (≥5 cm in maximum diameter)</td>
<td>Immune hemolytic anemia and/or thrombocytopenia</td>
</tr>
<tr>
<td>Symptomatic hepatomegaly and/or splenomegaly</td>
<td>Nephropathy related to WM</td>
</tr>
<tr>
<td>Symptomatic organomegaly and/or organ or tissue infiltration</td>
<td>Amyloidosis related to WM</td>
</tr>
<tr>
<td>Peripheral neuropathy due to WM</td>
<td>Hemoglobin ≤10 g/dL</td>
</tr>
<tr>
<td></td>
<td>Platelet count &lt;100 × 10⁹/L</td>
</tr>
</tbody>
</table>
Considerations before choosing a treatment regimen

- Confirm a need to treat
- Is the patient a candidate for stem cell transplant?
  - Avoid purine nucleosides (PNA’s)(Fludarabine)
- Comorbidities?
  - Peripheral neuropathy
  - Heart disease
  - Diabetes
- Urgency to treat?
  - Hyperviscosity
IgM

- Pentamer
- Intravascular
- Disease effects:
  - Hyperviscosity
  - Cold agglutinin
  - Cryoglobulin
  - Neuropathy
  - Amyloidosis
Hyperviscosity Syndrome

- Associated with Waldenström macroglobulinemia, rarely IgA or IgM multiple myeloma

30% WM have hyperviscosity symptoms:
- Neurologic – confusion, blurry vision, diplopia, HA, vertigo, ataxia, stroke, coma
- Oronasal bleeding
- Heart failure

- Serum viscosity >4 cP (1.8 normal)
  - Measure viscosity if M-spike >4g/dL

Br J Haematol. 2001;115(3):575
Hyperviscosity Syndrome - Treatment

- Plasmapheresis
  - Removes the IgM from the plasma
- Therapy to stop the production of IgM
## Treatment Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>IgM absent, marrow and nodes normal</td>
</tr>
<tr>
<td>VGPR</td>
<td>≥90% reduction in IgM</td>
</tr>
<tr>
<td>PR</td>
<td>≥50% reduction in IgM</td>
</tr>
<tr>
<td>MR</td>
<td>25-50% reduction in IgM</td>
</tr>
<tr>
<td>SD</td>
<td>&lt;25% reduction in IgM</td>
</tr>
<tr>
<td>PD</td>
<td>≥25% increase in IgM</td>
</tr>
</tbody>
</table>

**Overall response (ORR) = MR or better**  
**Major response (MRR) = PR or better**
# Drug Classes in WM

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Alkylators</th>
<th>Proteasome Inhibitors</th>
<th>Steroids</th>
<th>Purine Nucleosides</th>
<th>Kinase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Cyclophosphamide</td>
<td>Bortezomib</td>
<td>Prednisone</td>
<td>Fludarabine</td>
<td>Ibrutinib</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>Chlorambucil</td>
<td>Carfilzomib</td>
<td>Dexamethasone</td>
<td>Cladribine</td>
<td>Idelalisib</td>
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<tr>
<td>Obinutuzumab</td>
<td>Bendamustine</td>
<td>Ixazomib</td>
<td>Pentostatin</td>
<td></td>
<td>Everolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oprozomib</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Antibody Therapy

• Targets the CD20 surface antigen on WM cells
  • **Rituximab (Rituxan)**
  • Ofatumumab (Arzerra), Obinutuzumab (Gazyva)

• Response slow, may be inadequate as single agent
  • except perhaps for P. neuropathy, cryoglobulinemia, hemolytic anemia

• Side effects
  • Infusion reaction: fever, chills, itching, hives
  • Low gammaglobulin levels can occur with long term use (maintenance) and may contribute to infection

• Can see IgM flare when used alone
  • May need plasmapheresis
Chlorambucil (Leukeran)

• Alkylator, oral
• Used to treat Hodgkin and non-Hodgkin lymphoma, chronic lymphocytic leukemia
• Can combine with rituximab and other antibodies (Ofatumumab, Obinutuzumab)
• Side effects: Nausea, low blood counts
• Can also damage bone marrow and lead to leukemia with prolonged use
Cyclophosphamide (Cytoxan)

• Alkylator – oral or IV administration
• Very useful drug for many types of lymphoma
• Usually combined with rituximab (R) and a steroid:
  • **DRC** = Dexamethasone + rituximab
  • **R-CVP** = Vincristine + prednisone + rituximab
  • **R-CHOP** = adriamycin + vincristine + prednisone + rituximab
• Can cause: low blood counts, hair loss, nausea, vomiting, diarrhea
• Risk of bone marrow damage and leukemia with prolonged use
**Bendamustine (Treanda)**

- Alkylator with anti-metabolite activity (Bifunctional)
- FDA approved 2008 for relapsed indolent non-Hodgkin lymphoma and CLL
- IV infusion over 15-30 minutes X 2 days every month
- Usually combined with rituximab = B-R or BR
- Well tolerated:
  - Rash, fever, fatigue, low blood counts, nausea, HA, diarrhea
  - No hair loss, neuropathy
Bortezomib (Velcade)

- Proteasome inhibitor
- Subcutaneous injection vs. IV, and
- Once weekly vs. twice weekly
  
  Tolerated better – less neuropathy

- Side effects: peripheral neuropathy, diarrhea, constipation, fatigue, low platelet count
Carfilzomib (Kyprolis)

• Second generation proteasome inhibitor
• Less neurotoxicity
• Intravenous infusion twice weekly

• CaRD (CFZ + Rituximab + Dexamethasone)
  • 87% ORR
  • 67% Major response

Blood 2013, abst 757
Purine Nucleoside Analogs

• Fludarabine (Fludara)
  • IV daily X 5 days every 4 weeks
  • Combined with rituximab (FR), cyclophosphamide (FCR)
  • Common side effects: nausea, fatigue, low blood counts, infection, fever, damage to stem cells
  • Risk of MDS/leukemia

• Cladribine (2-CDA)(Leustatin)
  • IV daily X 5 days or continuous IV every month
  • Combined with rituximab, cyclophosphamide
  • Rash, Nausea, diarrhea, constipation, low blood counts, fatigue
Ibrutinib
Bruton Tyrosine Kinase Inhibitor

- FDA approved for *relapsed* mantle cell lymphoma (65% response) November 2013

- FDA approved for *relapsed or high risk* CLL with 17p deletion February 2014

- FDA approved for WM February 2015 – *new or relapsed disease*!
Ibrutinib in WM

Phase II trial
N = 63
460 mg daily
Med prior treat = 2
TTR = 1.2 months
DOR not reached

The response rate based on independent review committee assessment was 61.9% (95% CI: 48.8, 73.9)\(^1\)
No patients had a complete response (CR)\(^1\)

ASH 2014, #122

Response rate = CR+VGPR+PR
VGPR = very good partial response
PR = partial response
Adapted from response criteria developed by the International Workshop on WM.
Rate of Response to Ibrutinib in Patients with Waldenström's Macroglobulinemia, According to Mutation Status.

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>Mutated MYD88 and Wild-Type CXCR4 (N=36)</th>
<th>Mutated MYD88 and CXCR4 WHIM (N=21)</th>
<th>Wild-Type MYD88 and CXCR4 (N=5)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>100</td>
<td>85.7</td>
<td>60</td>
<td>0.005</td>
</tr>
<tr>
<td>Major</td>
<td>91.7</td>
<td>61.9</td>
<td>0</td>
<td>&lt;0.001</td>
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</tbody>
</table>

* Responses were assessed in 62 previously treated patients with Waldenström’s macroglobulinemia for whom both MYD88 and CXCR4 mutation status had been determined. MYD88 status was determined by means of Sanger sequencing of the entire gene. CXCR4 mutation status was determined by means of Sanger sequencing and allele-specific polymerase-chain-reaction assay for CXCR4 S338X C→G and C→A mutations in CD19-selected bone marrow cells. A major response was defined as a partial or very good partial response. No complete responses were observed. WHIM denotes warts, hypogammaglobulinemia, infections, and myelokathexis.

† P values are for the overall comparison among the three groups and were calculated with the use of Fisher’s exact test.
Ibrutinib - Side Effects

**Serious**
- Neutropenia
- Thrombocytopenia
- Infection
- Atrial Fibrillation
- Significant bleeding - 6%
  (Any bleeding - 50%)

**Common > 10% of patients**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>37</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
</tr>
<tr>
<td>Rash</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>21</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16</td>
</tr>
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</table>
Ibrutinib in Rituximab-Refractory Patients with Waldenström's Macroglobulinemia

- Ibrutinib showed ORR of 90% in Ph II trial in WM – FDA approval
- International open-label multicenter trial with Ibrutinib for *rituximab refractory* WM
- Dose 420 mg/d
- ORR 84%, ≥PR 65%

<table>
<thead>
<tr>
<th>Grade 3-4 AE’s</th>
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<tbody>
<tr>
<td>Neutropenia</td>
<td>13%</td>
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<tr>
<td>Anemia</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
</tr>
<tr>
<td>T’penia</td>
<td>6%</td>
</tr>
<tr>
<td>HTN</td>
<td>6%</td>
</tr>
</tbody>
</table>

Figure: Median hemoglobin and IgM levels during early follow-up

Blood 2015;126:#2745
Idelalisib

- PI3 kinase inhibitor
- Oral medicine
- FDA approved for relapsed CLL, Follicular lymphoma and SLL.
- Side effects:
  - pneumonitis, diarrhea, fever, rash, low WBC, liver inflammation
- Ph II trial, n=125, 10 WM
  - ORR 56%, 70% in WM

ASH2014 abst # 1708
Mature Follow up from a Phase 2 Study of PI3K-Delta Inhibitor Idelalisib in Patients with Double (Rituximab and Alkylating agent)-Refractory Indolent B-Cell Non-Hodgkin Lymphoma (iNHL)

<table>
<thead>
<tr>
<th></th>
<th>N = 125</th>
<th>ORR %</th>
<th>CR %</th>
<th>PFS months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL n =72</td>
<td>54</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>SLL n =28</td>
<td>61</td>
<td>4</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>MZL n =15</td>
<td>47</td>
<td>7</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>LPL n =10</td>
<td>70</td>
<td>0</td>
<td>22.2</td>
<td></td>
</tr>
</tbody>
</table>

Gopal. ASH2014, abst#1708
Everolimus

- mTOR inhibitor
- Oral daily dosing
- Relapsed WM, dose 10 mg po daily
- ORR 50 %
- Gr 3 AE 56% (fatigue, diarrhea, mouth sores)
- Median PFS 21 mo

Ghobrial. AJHem, 2014
WM – Treatment Combinations

• Combinations with rituximab (R)
  • R-Thalidomide, R-Bendamustine, R-bortezomib,
• Combinations with alkylators
  • R-CVP, R-CP, DRC, R-CHOP
• Purine nucleoside combos
  • R-Flu, R-Cladribine
  • FCR, Cladribine-Cyclo-R, PCR
Dexamethasone + Rituximab + Cyclophosphamide (DRC)

- Dex 20mg IV day 1
- Rituximab 375 mg/m² Day 1
- Cyclo 100 mg/m² po BID days 1-5
- N = 72

- ORR 83% CR 7%, PR 67%, MR 9%
- OS at 2 yrs 81%

Gr 3/4 AE 15%

Dimopoulos M A et al. JCO 2007;25:3344-3349
StiL: Bendamustine + Rituximab vs CHOP-R in Frontline NHL

Patients with frontline iNHL or MCL
(N = 549)

CHOP-R q3w x 6
(n = 253)

Bendamustine-Rituximab q4w x 6
(n = 261)

Rituximab 375 mg/m² on Day 1; bendamustine 90 mg/m² on Days 1-2 q28 days or standard CHOP q21 days x 6

Bendamustine-Rituximab

- StiL trial: B-R vs R-CHOP \textit{frontline} Rx
  - WM (n=41)
  - ORR 95% in both arms
  - Progression-free survival longer for B-R
    - 70 vs 28 months
  - B-R less toxic than R-CHOP
    - Less hair loss, neuropathy, infection

- B-R +/- R maintenance trial
  - Awaiting results

Rummel. Lancet 2013, ASH abst 2012
Bendamustine + Rituximab for Relapsed WM

- Retrospective, 14 Italian centers
- 71 pts
  - Rituximab 375 mg/m² day 1
  - Bendamustine 70-90 mg/m² days 1, 2
  - Up to 6 cycles q 28 days
- ORR 80.3%
  - most were PR

ASH 2014 #3072
Long-Term Outcome of Bortezomib, Dexamethasone and Rituximab in Untreated Waldenstrom’s Macroglobulinemia

- **BDR** = BTZ 1.3mg/m2 and Dex 40mg IV days 1, 4, 8, 11.
  Rituximab 375 mg/m2 day 11 q 21 days. - 4 cycles then
  Maintenance was 1 cycle q 3 months X 4

- N= 23
- ORR 94%
- OS 95%, PFS 57% at 5 years
- Grade 2 toxicities – Neuropathy in 16/23 (69%), neutropenia 56%
- 60% discontinued BTZ

(Need a less toxic regimen)

Median serum immunoglobulin M (IgM) levels at baseline (BL), and after each cycle of induction (C1 to C4) and maintenance (M1 to M4) therapy in patients treated with bortezomib, dexamethasone, and rituximab.

Treon S P et al. JCO 2009;27:3830-3835

©2009 by American Society of Clinical Oncology
BDR in Newly Diagnosed Patients with WM

- BTZ 1.3mg/m2 IV days 1,4,8,11 then weekly BTZ 1.6 mg/m2 q 5 weeks for 4 more cycles with Rituximab and dexamethasone weekly cycle 2 and cycle 5.
  (8 total doses of rituximab and dexamethasone)
- No maintenance given
- ORR 85%
  - 3% CR, 7% VGPR, 58% PR
- TTNT 73 mo, Med PFS 43 mo, med DOR 64.5, OS 66% at 7yrs

“Chemo-free”
Fixed duration of therapy
Durable responses

Blood 2017;129:456
Overall survival rates

Overall survival rates by ISSWM

Cyclophosphamide, bortezomib, and dexamethasone combination in Waldenstrom macroglobulinemia

- ORR (MR or better) 14 (93%)
- MRR (PR or better) 8 (53%)
Bortezomib, Cyclophosphamide and Rituximab (BCR)

- BCR vs. FCR - randomized trial
- Newly diagnosed WM
- BCR less toxic

<table>
<thead>
<tr>
<th></th>
<th>BCR</th>
<th>FCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>98%</td>
<td>82%</td>
</tr>
<tr>
<td>MRR</td>
<td>79%</td>
<td>76%</td>
</tr>
</tbody>
</table>
Fludarabine + Rituximab

- N = 43, 0-1 prior therapies (63% no prior Rx)
- Rituximab weekly X 8 + Flu 25mg/m² days 1-5 weeks 5, 9, 13, 19, 23, 27
- Results:
  - CR 5%
  - VGPR 33%
  - PR 21%
  - MR 9%

ORR = 95.3%
TTP 51.2 mo

Gr 3 AE
- 63% neutropenia
- 16% T’penia
- Death 5%
- tNHL 7%
- MDS/AML 7%

Treon. Blood 2009;113:3673
Maintenance Therapy

• Rituximab commonly used as maintenance in low grade B-cell lymphoma
  • IV every 2-3 months for ~2 years

• Shown to improve time in remission (PFS) but not overall survival (OS)

• Risks include low blood counts, low gammaglobulin levels, increased infections and more trips to the clinic or hospital.

• There is inadequate data in WM to recommend this for all patients
Regimen Efficacy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR</th>
<th>MRR</th>
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</thead>
<tbody>
<tr>
<td>Chlorambucil</td>
<td>-</td>
<td>36%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>53%</td>
<td>35%</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>95%</td>
<td>-</td>
</tr>
<tr>
<td>BR</td>
<td>95%</td>
<td>-</td>
</tr>
<tr>
<td>BDR</td>
<td>85-96%</td>
<td>83-68%</td>
</tr>
<tr>
<td>FCR</td>
<td>79%</td>
<td>74%</td>
</tr>
<tr>
<td>BCR</td>
<td>98%</td>
<td>79%</td>
</tr>
<tr>
<td>CaRD</td>
<td>87%</td>
<td>67%</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>91%</td>
<td>73%</td>
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<tr>
<td>Everolimus</td>
<td>73%</td>
<td>50%</td>
</tr>
<tr>
<td>DRC</td>
<td>83%</td>
<td>74%</td>
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<tr>
<td>FR</td>
<td>94-96%</td>
<td>89-82%</td>
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</tbody>
</table>

Adapted from Kapoor et al, JAMA Oncol, 2017
Many Treatment Options
Treatment of Waldenström Macroglobulinemia
Mayo Consensus

Scottsdale, Arizona | Rochester, Minnesota | Jacksonville, Florida
**Consensus for Newly Diagnosed Waldenström Macroglobulinemia**

- IgM MGUS (<10% lymphoplasmacytic infiltration)
- Asymptomatic/smoldering Waldenström’s
- Hemoglobin ≥11 g/dL
- Platelets ≥120 x 10⁹/L

- Hemoglobin <11 g/dL or symptomatic
- Platelets <120 x 10⁹/L
- IgM-related neuropathy
- WM-associated hemolytic anemia
- Symptomatic cryoglobulinemia

- Bulky Disease
- Profound cytopenias –
  - Hemoglobin ≤10 g/dL
  - Platelets <100 x 10⁹/L
- Constitutional symptoms
- Hyperviscosity symptoms

---

**Hyperviscosity symptoms**

- Yes
  - Plasmapheresis
- No

**Bendamustine + Rituximab (BR)**
  - x 4-6 cycles
  - No rituximab maintenance therapy

**Single Agent Rituximab**
  - (1 cycle; no maintenance therapy)
  - *plasmapheresis if hyperviscosity develops with treatment

**Observation**

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*Dexamethasone + Rituximab + Cyclophosphamide (DRC)* x 6 cycles is an alternative if the disease burden is low

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*Mayo Clinic*

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v4 Revised April 2015
Repeat Original Therapy

Autologous stem cell transplant in select patients

**Waldenström Macroglobulinemia Consensus for Salvage Therapy**

**Time to next therapy**

≥ 3 years from previous therapy

**Yes**

Repeat Original Therapy

**No**

- Ibrutinib monotherapy*
- BDR if preexisting PN < Grade 2*
- BR*
- DRC*

---

*If not previously used.

For multiply relapsed or refractory disease, in addition to the regimens listed above, consider nucleoside analog (cladribine or fludarabine)-based regimens or everolimus as alternatives.

**DRC** = Dexamethasone + Rituximab + Cyclophosphamide

**BR** = Bendamustine + Rituximab

**BDR** = Bortezomib (weekly), Dexamethasone + Rituximab

**PN** = peripheral neuropathy

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v4 Revised April 2015
Mayo Guidelines

• We avoid bortezomib (Velcade) up front because of neuropathy risk

• We don’t recommend Ibrutinib in the newly diagnosed setting as there is no long term followup data and its ongoing therapy where the only end is toxicity or progression of disease

• We avoid PNA’s (Fludarabine) in frontline due to high risk of MDS and leukemia

• Retreating with the initial regimen at the time of relapse reasonable if duration of the remission was >3 years. If not, Stem cell transplant or second line regimen best.

• Clinical trials can be considered at all points on the map
Role of Stem Cell Transplantation in Waldenstrom Macroglobulinemia

• Why consider autologous SCT?
  
  • Current therapy not curative
  • Alkylators and PNA’s increase risk of MDS/AML
  • Novel agents do have toxicities
  • MM and indolent NHL benefit from SCT
  • Data suggest long term PFS
  • Auto SCT has low mortality
  • Allo SCT associated with higher mortality

Gertz, Reeder, Kyle, Ansell. Bone Marrow Transplantation (2012) 47, 1147 -- 1153
Select Summary of Trials of Autologous Transplantation

<table>
<thead>
<tr>
<th>Reference</th>
<th>#</th>
<th>Regimen</th>
<th>#</th>
<th>Response</th>
<th>RFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>44</td>
<td>24</td>
<td>Mel 200</td>
<td>10</td>
<td>PR14</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Mel or Cy + TBI</td>
<td>9</td>
<td>CR10</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Other</td>
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<tr>
<td>45</td>
<td>17</td>
<td>Mel or Cy + TBI</td>
<td>13</td>
<td>PR8</td>
<td>9 Progression</td>
<td>6 dead median 11.5 mo.</td>
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<tr>
<td></td>
<td></td>
<td>BEAM</td>
<td>3</td>
<td>VGPR 7</td>
<td>Median 10 mo.</td>
<td>11 alive median 25+ mo.</td>
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<tr>
<td></td>
<td></td>
<td>Mel 180</td>
<td>2</td>
<td>CR2</td>
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<td></td>
<td></td>
<td>Other</td>
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</tr>
<tr>
<td>46</td>
<td>10</td>
<td>TBI + other</td>
<td>3</td>
<td></td>
<td>65% @ 3 yr.</td>
<td>70% @ 3 yr.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bu + Cy + other</td>
<td>2</td>
<td></td>
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<td></td>
<td>Other</td>
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<td>48</td>
<td>32</td>
<td>BEAM</td>
<td>13</td>
<td></td>
<td>Median 32 mo.</td>
<td>58% @ 5 yr.</td>
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<td>Mel or Cy + TBI</td>
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<td>Other</td>
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</tr>
<tr>
<td>49</td>
<td>9</td>
<td>Mel 200</td>
<td>3</td>
<td>PR 5</td>
<td>43% @ 4 yr.</td>
<td>73% @ 4 yr.</td>
</tr>
<tr>
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<td>BEAM</td>
<td>5</td>
<td>VGPR 1</td>
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<td></td>
<td></td>
<td>Cy + TBI</td>
<td>1</td>
<td>CR3</td>
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<tr>
<td>50</td>
<td>158</td>
<td>TBI + other</td>
<td>45</td>
<td>PR 23</td>
<td>39.7% @ 5 yr.</td>
<td>68.5% @ 5 yr.</td>
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<tr>
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<td>BEAM</td>
<td>46</td>
<td>VGPR 77</td>
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<td></td>
<td>Other</td>
<td>67</td>
<td>CR 34</td>
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</tr>
</tbody>
</table>

Gertz, Reeder, Kyle, Ansell. Bone Marrow Transplantation (2012) 47, 1147 -- 1153
Autologous SCT in WM

• Retrospective 1995 – 2011, EBMT database
• N = 615
• Median age 53
• Time to SCT 19 months
• NRM 7%

• OS at 5yr 65%
• 71% if in 1\textsuperscript{st} and 63% if in 2\textsuperscript{nd} or later remission

ASH 2014 #678
Stem Cell Transplantation in WM - Summary

• Auto SCT can be expected to produce deep and durable responses with low transplant mortality
• Avoid PNA’s if potential for SCT (age <70)
• Consider PBSC collection in first remission or plateau
• Cryopreserved stem cells can be used at time of relapse
• Allogeneic SCT an option for patients with refractory disease

Gertz, Reeder, Kyle, Ansell. Bone Marrow Transplantation (2012) 47, 1147 -- 1153
Clinical Trials considered at all decision points
WM – Treatment Summary

- Asymptomatic WM may be observed without therapy
- Symptomatic patients require therapy to reduce the lymphoma burden
- Bendamustine + Rituximab is our preferred initial regimen
  - Bortezomib + Rituximab + dexamethasone (BDR) an option but concern of neuropathy
  - DRC an option if low tumor burden
- Hyperviscosity is managed with plasmapheresis and therapy to decrease the IgM production
- Auto SCT should be considered an option for relapsed disease
- Ibrutinib an excellent drug best used as option at relapse
- Maintenance therapy – need more data
Survival Improved

A graph showing survival rates over time for different age groups. The x-axis represents the period of diagnosis, and the y-axis represents the 5-year relative survival. The legend indicates the following age groups: 20-39 years (blue), 40-59 years (red), 60-79 years (green), and 80+ years (orange).