Initial Therapy for Multiple Myeloma

IMF Patient and Family Seminar
August 2015

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Associate Professor of Medicine, Mayo Clinic Arizona

Objectives

1. Explain when to initiate treatment in myeloma and how it has recently changed
2. Describe the role of risk stratification and its potential effect on treatment
3. Formulate an individualized treatment approach in patients ineligible for transplant
4. Appreciate that initial therapies between ineligible and eligible patients are now very similar
Managing myeloma: the components

Transplant Eligible Patients
- Initial Therapy
- Consolidation
- Maintenance
- Treatment of Relapsed disease

Transplant Ineligible patients
- Consolidation/Maintenance/Continued therapy

Supportive Care

Previous Disease Definitions

<table>
<thead>
<tr>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &lt;10% BMPC AND</td>
<td>• ≥10% BMPC OR</td>
<td>• Clonal PCPD</td>
</tr>
<tr>
<td>• &lt;3gm/dL M protein AND</td>
<td>• ≥3 gm/dL M protein AND</td>
<td>• CRAB</td>
</tr>
<tr>
<td>• No CRAB</td>
<td>• No CRAB</td>
<td></td>
</tr>
</tbody>
</table>

CRAB = Hypercalcemia, renal failure, anemia, or lytic bone lesions attributable to a clonal plasma cell disorder

**Revised IMWG Criteria**

<table>
<thead>
<tr>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &lt;10% BMPC AND &lt;3gm/dL M protein AND No MDE</td>
<td>• ≥10-60% BMPC OR ≥3 gm/dL S. M protein OR ≥500 mg/24h Ur. M protein AND No MDE</td>
<td>• PCPD, AND 1 or more MDE CRAB ≥60% BMPC ≥100 FLC ratio &gt;1 MRI focal lesion</td>
</tr>
</tbody>
</table>

CRAB= Hypercalcemia, renal failure, anemia, or lytic bone lesions attributable to a clonal plasma cell disorder  
MDE= Myeloma Defining Events


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**Ultra High Risk SMM = Active Myeloma**

Not CRAB but now SLiM CRAB

- **S** (60% Plasmacytosis)
- **Li** (Light chains I/U >100)
- **M** (MRI 1 or more focal lesion)
- **C** (calcium elevation)
- **R** (renal insufficiency)
- **A** (anemia)
- **B** (bone disease)

Treatment Options for Newly Diagnosed Patients

**Autologous stem cell transplant candidate?**

- **YES**
  - **Front-line induction therapy** (3-4 cycles)
    - Dexamethasone + Lenalidomide and/or Bortezomib-based regimen
    - Bortezomib plus Lenalidomide
    - Carfilzomib based regimen
    - Clinical trial
  - Autologous transplant
  - Continue induction until relapse; consider delayed transplant upon relapse

- **NO**
  - **Front-line therapy**
    - Revlimid-low-dose dexamethasone
    - Bortezomib-MP, Lenalidomide-MP or MP-Thalidomide (9-12 cycles)
    - Any of the regimens listed as options for transplant candidates
  - Clinical trial

**Response to Front-Line Therapy**
Continue with either: (a) observation, (b) maintenance therapy

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**Randomized Trials in ASCT Ineligible**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>N</th>
<th>CR, %</th>
<th>≥PR, %</th>
<th>Median PFS/EFS, mo</th>
<th>Overall survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 93-01</td>
<td>Dex</td>
<td>127</td>
<td>1</td>
<td>42</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>IFM 93-01</td>
<td>Dex+IFN</td>
<td>121</td>
<td>1</td>
<td>43</td>
<td>15</td>
<td>32</td>
</tr>
<tr>
<td>IFM 93-01</td>
<td>MP</td>
<td>122</td>
<td>1</td>
<td>41</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>Ludwig, 2005</td>
<td>Thal-Dex</td>
<td>142</td>
<td>2</td>
<td>60</td>
<td>17</td>
<td>2-yr 61%</td>
</tr>
<tr>
<td>Ludwig, 2005</td>
<td>MP</td>
<td>141</td>
<td>2</td>
<td>52</td>
<td>21</td>
<td>2-yr 70%</td>
</tr>
<tr>
<td>Trial-MM 005</td>
<td>Thal-Dex</td>
<td>240</td>
<td>6</td>
<td>63</td>
<td>15</td>
<td>2-yr 69%</td>
</tr>
<tr>
<td>Trial-MM 005</td>
<td>Dex</td>
<td>235</td>
<td>6</td>
<td>46</td>
<td>6</td>
<td>2-yr 83%</td>
</tr>
<tr>
<td>E1409P2</td>
<td>RD</td>
<td>71</td>
<td>74</td>
<td>22</td>
<td>2-yr 90%</td>
<td></td>
</tr>
<tr>
<td>FIRST (ASH 2013)</td>
<td>RDMP</td>
<td>535</td>
<td>15</td>
<td>75</td>
<td>25</td>
<td>3-yr 70%</td>
</tr>
<tr>
<td>FIRST (ASH 2013)</td>
<td>MP</td>
<td>541</td>
<td>14</td>
<td>73</td>
<td>21</td>
<td>3-yr 66%</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>MP</td>
<td>609</td>
<td>23</td>
<td>59</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>MRC IX non-intense</td>
<td>CTDox</td>
<td>419</td>
<td>13</td>
<td>64</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>VISTA</td>
<td>VMP</td>
<td>344</td>
<td>30</td>
<td>71</td>
<td>24</td>
<td>3-yr 62%</td>
</tr>
<tr>
<td>PHEMA</td>
<td>VMP</td>
<td>338</td>
<td>4</td>
<td>35</td>
<td>17</td>
<td>3-yr 64%</td>
</tr>
<tr>
<td>VMP</td>
<td>VIP</td>
<td>130</td>
<td>20</td>
<td>80</td>
<td>34</td>
<td>3-yr 74%</td>
</tr>
<tr>
<td>VMP + VT</td>
<td>VMP</td>
<td>257</td>
<td>24</td>
<td>81</td>
<td>3-yr 41%</td>
<td>3-yr 67%</td>
</tr>
<tr>
<td>VMP + VT</td>
<td>VMP+VT</td>
<td>284</td>
<td>38</td>
<td>69</td>
<td>3-yr 56%</td>
<td>3-yr 80%</td>
</tr>
<tr>
<td>MM 016</td>
<td>MPR-R</td>
<td>152</td>
<td>33</td>
<td>77</td>
<td>31</td>
<td>3-yr 70%</td>
</tr>
<tr>
<td>MM 016</td>
<td>MPR</td>
<td>153</td>
<td>33</td>
<td>68</td>
<td>14</td>
<td>3-yr 62%</td>
</tr>
<tr>
<td>MM 016</td>
<td>MP</td>
<td>154</td>
<td>12</td>
<td>50</td>
<td>13</td>
<td>3-yr 66%</td>
</tr>
</tbody>
</table>

*Secondary randomization to either VT or VP. Complete response + very good partial response ≤ p < 0.001 ≤ p < 0.01 ≤ p = 0.03
3-Year Overall Survival Rates

<table>
<thead>
<tr>
<th>Trial</th>
<th>3-Year Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISTA Trial</td>
<td></td>
</tr>
<tr>
<td>MM-015 Trial</td>
<td></td>
</tr>
<tr>
<td>FIRST Trial</td>
<td></td>
</tr>
<tr>
<td>PETHEMA/GEM Trial</td>
<td></td>
</tr>
<tr>
<td>VMPT vs VMP Trial</td>
<td></td>
</tr>
</tbody>
</table>

Transplant Ineligible/Elderly

- MP is no longer the standard of care
- MP-T and MP-V
  - Higher responses
  - More rapid responses
  - Improve survival over MP alone
- Maintenance therapy (or continuous long term therapy) may improve responses and long term outcome
- Newer options without melphalan are emerging…
Initial Therapy Options as a Non-Transplant Candidate

Until recently, the most common initial therapy was melphalan and prednisone (MP)

**Option MP + Bortezomib**
- 71% ORR
- 30% CR

**Option MP + Thalidomide**
- 76% ORR
- 28% CR/nCR

**Option MP + Lenalidomide**
- 100% ORR
- 13% CR/nCR

Combining new agents with MP offer improved response rates and survival over MP alone

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**VISTA OS (ITT)**

![Graph showing overall survival with Bortezomib and Control]

BUT wait!!

- For many reasons, most initial therapy strategies will no longer use Melphalan…

Why Melphalan may no longer standard of initial care in elderly patients

1. Novel agents are equivalent if not superior to MP+novel agent
2. MP+ results in greater short term toxicity
3. As survival is extended in myeloma, using melphalan upfront is not desirable due to marrow toxicity
4. Melphalan can lead to increased second primary malignancies
Summary of Trends in Elderly Patients

1. Novel agent use
2. Less use of melphalan
3. Longer therapy
4. Improved survival

Goals of Induction Therapy

- High response rate
- Rapid response
- Durable response
- Improve performance status

Questions
- Does it depend upon cytogenetics or prognostic factors?
- What if you don’t achieve a CR?
First Line Therapy – Transplant Ineligible

- Most agree that at least a proteasome inhibitor (bortezomib or carfilzomib) OR an Imid (thalidomide, lenalidomide) – or possibly both together are needed
- Most will also add a steroid (dexamethasone) as they boost response to either
- Sometimes other agents may be added like cyclophosphamide

Lenalidomide Based Combinations

- Lenalidomide – dexamethasone
- Lenalidomide – cyclophosphamide – dexamethasone
Bortezomib Based Combinations

- Bortezomib – dexamethasone
- Cyclophosphamide – bortezomib – dexamethasone (CyBorD)
- Bortezomib – thalidomide - dexamethasone
- Bortezomib – Lenalidomide - dexamethasone

Other Combinations

- Carfilzomib Based
  - Carfilzomib – lenalidomide – dex
- Thalidomide Based
  - Thalidomide - dexamethasone
What is the advantage of using Combinations?

• Better depth of response
• Pre-transplant depth of response correlates with improved outcomes
• Attack tumor cell from multiple different mechanisms which reduces resistance
• Synergy from combinations that are not seen with each agent alone.

So how do we choose??

• Risk Status
• Rapidity of response needed
• Kidney Function
• Other conditions – diabetes, heart disease…
• Patient preference
• Institutional preference
• Cost
• Clinical trial availability
Increasing depth of response in myeloma with newer drugs

At least VGPR after 4 cycles induction in newly diagnosed MM

RD or CyBoRD
$100,000 per year

VRD or KRD
$250,000 per year

KRD - Dythelfield Haematologica 99(9) e162-4 2014
KCd – Bringhen Blood 124(1) 63-69 2014
VCD – Khan Br J Haematol 156(3) 326-333 2012
TD & VTD – Cavo Blood 2012
RD – Rajkumar Lancet Oncol 11(1) 29-37

K – Carfilzomib
C – Cyclophosphamide
V – Bortezomib
R – Lenalidomide
A – Doxorubicin
D – Dexamethasone

FIRST Trial: Study Design

Screening

Active Treatment + PFS Follow-up Phase

LT Follow-Up

- Stratification: age, country and ISS stage

ISS, International Staging System; LT, long-term; PD, progressive disease; OS, overall survival

FIRST Trial: Final PFS
Continuous Rd  the risk of PFS events (PD or death) by 28% vs. MPT

Median PFS
Rd (n= 535) 25.5 mos
Rd18 (n= 541) 20.7 mos
MPT (n= 547) 21.2 mos

Hazard ratio
Rd vs. MPT: 0.72; P = 0.00006
Rd vs. Rd18: 0.70; P = 0.00001
Rd18 vs. MPT: 1.03; P = 0.70349

FIRST Trial: Overall Survival Interim Analysis
574 deaths (35% of ITT)

4-year OS
Rd (n= 535) 59.4%
Rd18 (n= 541) 55.7%
MPT (n= 547) 51.4%

Hazard ratio
Rd vs. MPT: 0.78; P = 0.0168 († 22% risk of death with Rd)
Rd vs. Rd18: 0.90; P = 0.307
Rd18 vs. MPT: 0.88; P = 0.184

The pre-specified boundary (p<0.0096) was not crossed for Rd_continuous vs MPT_18 months
**MM015 Progression Free Survival**

- **Progression-free Survival**

- **Hazard ratio**
  - MPR-R vs. MPR: 0.49; P<0.001
  - MPR-R vs. MP: 0.40; P<0.001

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR-R</td>
<td>152</td>
<td>115</td>
<td>89</td>
<td>70</td>
<td>49</td>
<td>31</td>
<td>16</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>MPR</td>
<td>153</td>
<td>120</td>
<td>90</td>
<td>40</td>
<td>27</td>
<td>10</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MP</td>
<td>154</td>
<td>111</td>
<td>83</td>
<td>42</td>
<td>29</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


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**Age-Adjusted Dose Reduction in Patients**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age &lt;65 Yr</th>
<th>Age 65-75 Yr</th>
<th>Age &gt;75 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>Dose of 40 mg/day given orally on days 1-14, 15-18 every 4 wk, or 40 mg/day given orally on days 1, 8, 15, 22 every 4 wk&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Dose of 40 mg/day given orally on days 1, 8, 15, 22 every 4 wk&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Dose of 20 mg/day given orally on days 1, 8, 15, 22 every 4 wk&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Dose of 0.25 mg/kg given orally on days 1-4 every 6 wk&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Dose of 0.25 mg/kg given orally on days 1-4 every 6 wk&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Dose of 0.18 mg/kg given orally on days 1-4 every 6 wk&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Dose of 100 mg/m² given orally on days 1, 8, 15, 22 every 4 wk&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Dose of 100 mg/m² given orally on days 1, 8, 15, 22 every 4 wk&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Dose of 50 mg/day given orally on days 1-2 every 4 wk&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Dose of 100 mg/m² given orally on days 1, 8, 15, 22 every 4 wk&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Dose of 100 mg/m²&lt;sup&gt;14&lt;/sup&gt; or 200 mg/m²&lt;sup&gt;15&lt;/sup&gt; given orally continuously</td>
<td>Dose of 50 mg/day&lt;sup&gt;16&lt;/sup&gt; to 100 mg/day&lt;sup&gt;16&lt;/sup&gt; given orally continuously</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Dose of 25 mg/day given orally on days 1-21 every 4 wk&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Dose of 15-25 mg/day given orally on days 1-21 every 4 wk&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Dose of 15-25 mg/day given orally on days 1-21 every 4 wk&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Dose of 1.3 mg/m² given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Dose of 1.3 mg/m² given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Dose of 1.0-1.3 mg/m² given as bolus intravenous infusion on days 1, 4, 8, 11 every 5 wk&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Subcutaneous bortezomib causes less neuropathy

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>SC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pts</td>
<td>74</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td>Response rate (8 cycles)</td>
<td>52%</td>
<td>52%</td>
<td>NS</td>
</tr>
<tr>
<td>PFS</td>
<td>8.0m</td>
<td>10.2m</td>
<td>NS</td>
</tr>
<tr>
<td>1-year OS</td>
<td>73%</td>
<td>77%</td>
<td>NS</td>
</tr>
<tr>
<td>Gr 3/4 Neuropathy</td>
<td>16%</td>
<td>6%</td>
<td>$P&lt;0.024$</td>
</tr>
</tbody>
</table>

296 patients treated with VD for 8 cycles (6 months)

Moreau et al, Lancet Oncol 2011

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**Carfilzomib, Lenalidomide, dexamethasone (KRD)**

NIH CRd-R Phase II Trial
CRd x 8 cycle then 24 cycles of Len Maint

<table>
<thead>
<tr>
<th>Response</th>
<th>2 cycles n/N (%)</th>
<th>8 cycles n/N (%)</th>
<th>*Best response n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (&gt;PR)</td>
<td>42/43 (98)</td>
<td>32/33 (97)</td>
<td>42/43 (98)</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>22/43 (51)</td>
<td>30/33 (91)</td>
<td>23/43 (68)</td>
</tr>
<tr>
<td>nCR/CR/sCR</td>
<td>7/43 (16)</td>
<td>24/33 (73)</td>
<td>29/43 (67)</td>
</tr>
<tr>
<td>CR/sCR</td>
<td>3/43 (7)</td>
<td>14/33 (42)</td>
<td>22/43 (51)</td>
</tr>
<tr>
<td>VGPR</td>
<td>15/43 (35)</td>
<td>6/33 (18)</td>
<td>9/43 (21)</td>
</tr>
<tr>
<td>PR</td>
<td>29/43 (47)</td>
<td>2/33 (6)</td>
<td>4/43 (9)</td>
</tr>
<tr>
<td>SD</td>
<td>1/43 (2)</td>
<td>1/33 (3)</td>
<td>1/43 (2)</td>
</tr>
</tbody>
</table>

Among 27 nCR/sCR* patients assessed by flow, all 27 are MRD negative
Response rates based on FISH/cytogenetics are non-differential

Korde et al, ASH 2013, Abstract #538
Most commonly used regimens

- Lenalidomide – Dexamethasone
- Bortezomib – Dexamethasone (plus or minus cyclophosphamide)
- Bortezomib-lenalidomide-dexamethasone

Take home pearls

1. Don’t mix lenalidomide & alkylators
2. Don’t use melphalan in most
3. Don’t interfere with QOL
4. Avoid high doses of steroids
5. Don’t ask patients to drive too much
### mSMART Transplant Ineligible

<table>
<thead>
<tr>
<th>Standard-Risk</th>
<th>Intermediate-Risk</th>
<th>High-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomies only</td>
<td>t(11;14), t(6:14), Trisomies + IgH</td>
<td>t(4;14)</td>
</tr>
<tr>
<td>Rd, b</td>
<td>Weekly CyBorD for ~12 months c</td>
<td>Del 17p, t(14;16), t(14;20)</td>
</tr>
<tr>
<td>Until progression d</td>
<td>Followed by observation</td>
<td>Bor-based therapy maintenance for minimum of 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bor as maintenance for minimum of 1 year</td>
</tr>
</tbody>
</table>

*In patients treated with Rd, continuing treatment is an option for patients responding well with low toxicities; Dex is usually discontinued after first year.

*b Bortezomib containing regimens preferred in renal failure or if rapid response needed

*c CyBorD is considered a less toxic variation of VBp; VBp can be used as alternative

*d Continuing Rd for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year

**Clinical trials strongly recommended as the first option


### More to Come!

**Classes of Agents in Development for Myeloma**

1. **Oral Proteasome Inhibitors** – ixazomib (MLN 9708), oprozomib
2. **Monoclonal antibodies**
   a. SLAMF7 (Signaling Lymphocytic Activation Molecule F7) (formerly CS-1) – elotuzumab
   b. Anti CD38 – daratumumab, SAR650984
   c. Anti CD 138 – indatuximab, ravatansine
3. **KSP Inhibitors** – filanesib
4. **Histone Deacetylase Inhibitors** – panobinostat, ACY-1215
5. **Akt inhibitors - afuresertib**
6. **BCL Family Inhibitors** – ABT-199
7. **CDK inhibitors - dinaciclib**
8. **Nuclear Transport – CRM/XPO1 - selinexor**
9. **IAP antagonists – LCL161**
10. **PIM kinase inhibitors – LGH447**
11. **Bromodomain and Extra-Terminal (BET) inhibitors- GS0525762**
12. **Immune Therapies – programmed cell death protein 1 (pd1), programmed death-ligand 1 (pd1)**
Anti CD 38 Monoclonal Antibodies

• Nostalgia for Milan 2014… IMWG prior to EHA

• Most promising agents for myeloma voted upon (1 vote each)

• 80% selected anti CD MoAbs - Daratumumab or SAR 650984 (= Isatuximab)

• Both have significant single agent and in combination activity

• Will this be the “rituximab” of Myeloma??

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MMY1001 (NCT01998971): Phase lb study of daratumumab + backbone treatments

• VD: bortezomib (1.3 mg/m²) twice weekly x 4 cycles, then once weekly x 14 cycles/dexamethasone (20 mg)a
  • Newly diagnosed; n = 6

• VMP: bortezomib (1.3 mg/m²) twice weekly x 1 cycle, then once weekly x 8 cycles/melphalan (9 mg/m²)/prednisone (60 mg/m²)b
  • Newly diagnosed, transplant ineligible; n = 12

• VTD: bortezomib (1.3 mg/m²) twice weekly x 4 cycles, then once weekly x 14 cycles)/thalidomide (100 mg daily x 21 days)/dexamethasone (20 mg)a
  • Newly diagnosed; n = 12

• POM-D: pomalidomide (4 mg once daily)/dexamethasone (40 mg)c
  • Relapsed/refractory, 22 lines of therapy, including 2 consecutive cycles of lenalidomide and bortezomib; n = 50 subjects maximum

aDaratumumab once weekly x 2 cycles, then once every 3 weeks x 16 cycles or until transplantation.
bDaratumumab once weekly x 1 cycle, then every 3 weeks x 8 cycles.
cDaratumumab once weekly x 2 cycles, then once every 2 weeks x 4 cycles, then once every 4 weeks x 7 cycles or until disease progression; dexamethasone 20 mg if age >75 y.

**MMY1001: Efficacy**

- **ORR:**
  - 100% in newly diagnosed group
  - 50% in the relapsed group

V, bortezomib; D, dexamethasone; DARA, daratumumab; M, melphalan; P, prednisone; T, thalidomide; POM, pomalidomide.
sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; PD, progressive disease.

*VGPR confirmed, †VGPR repeat assessment pending.

All patients treated with DARA 16 mg/kg.

---

**Treatment sequence in Myeloma**

**Now**

<table>
<thead>
<tr>
<th>VD Rev/Dex</th>
<th>SCT</th>
<th>Nothing</th>
</tr>
</thead>
<tbody>
<tr>
<td>CyBorD</td>
<td></td>
<td>Thalidomide?</td>
</tr>
<tr>
<td>VTD</td>
<td></td>
<td>Bortezomib</td>
</tr>
<tr>
<td>VRD</td>
<td></td>
<td>Lenalidomide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bortezomib</th>
<th>Lenalidomide</th>
<th>Thalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib</td>
<td>Pomalidomide</td>
<td>Panobinostat</td>
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</table>

**New**

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidation</th>
<th>Post consolidation</th>
<th>Rescue</th>
</tr>
</thead>
<tbody>
<tr>
<td>“more” induction</td>
<td>Lenalidomide 2 mths</td>
<td>? Ixazomib</td>
<td>Ixazomib/Oprozomib</td>
</tr>
</tbody>
</table>

Monoclonal Ab (CD38) Elotuzumab Bendamustine

+++
Improvement in OS in MM

Shaji Kumar Unpublished data

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