Multiple Myeloma: Improving the Outcome in resource limited settings

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## Trend of Myeloma (ASR): All ages

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Male</strong></td>
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<tr>
<td>Chennai</td>
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<td>0.8</td>
<td>1.0</td>
<td>0.8</td>
<td>1.6</td>
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<tr>
<td>Bangalore</td>
<td>0.9</td>
<td>0.7</td>
<td>1.0</td>
<td>-</td>
<td>1.8</td>
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<td>Mumbai</td>
<td>0.8</td>
<td>1.2</td>
<td>1.2</td>
<td>1.4</td>
<td>1.5</td>
<td>1.6</td>
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<tr>
<td>Delhi</td>
<td>-</td>
<td>-</td>
<td>1.9</td>
<td>2.4</td>
<td>2.0</td>
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<tr>
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<td>0.6</td>
<td>0.7</td>
<td>-</td>
<td>1.4</td>
<td>1.4</td>
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<tr>
<td>Mumbai</td>
<td>0.9</td>
<td>0.9</td>
<td>1.1</td>
<td>0.9</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Delhi</td>
<td>-</td>
<td>-</td>
<td>1.1</td>
<td>1.8</td>
<td>1.2</td>
<td>1.4</td>
</tr>
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**Plasma cell dyscrasias**  
(1995-2011), n=714

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>%</th>
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<tr>
<td>MGUS</td>
<td>04</td>
<td>0.6</td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>20</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Multiple myeloma</strong></td>
<td>607</td>
<td>85.0</td>
</tr>
<tr>
<td>Plasma cell Leukemia</td>
<td>05</td>
<td>0.7</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>40</td>
<td>5.6</td>
</tr>
<tr>
<td>Waldenstrom’s</td>
<td>11</td>
<td>1.5</td>
</tr>
<tr>
<td>POEMS syndrome</td>
<td>25</td>
<td>3.5</td>
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<tr>
<td>Others</td>
<td>02</td>
<td>0.3</td>
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</table>
### Clinical Presentation

<table>
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<tr>
<th></th>
<th>AIIMS (n=607)</th>
<th>USA : Kyle (n=1027)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>54</td>
<td>66</td>
</tr>
<tr>
<td>Age&lt;40yrs, %</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Asymptomatic, %</td>
<td>&lt;1%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Bone Pains, %</td>
<td>95.3</td>
<td>68</td>
</tr>
<tr>
<td>Anemia (&lt;10g%)</td>
<td>62.2</td>
<td>35</td>
</tr>
<tr>
<td>s. Creatinine ≥ 2mg%</td>
<td>31.8</td>
<td>19</td>
</tr>
<tr>
<td>ISS stage III</td>
<td>40%</td>
<td>30%</td>
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</tbody>
</table>

### Conventional cytogenetics

<table>
<thead>
<tr>
<th>Total Samples analyzed</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metaphase obtained in sample*</td>
<td>53 (58%)</td>
</tr>
<tr>
<td>Normal Karyotype (46XX/46XY)</td>
<td>32 (35%)</td>
</tr>
<tr>
<td>Abnormal Karyotype</td>
<td>21 (23%)</td>
</tr>
<tr>
<td>Hyper diploid</td>
<td>16 (18%)</td>
</tr>
<tr>
<td>Hypo diploid</td>
<td>5 (5%)</td>
</tr>
</tbody>
</table>

![Normal](image1.png) ![Hypo](image2.png) ![Hyper](image3.png)

- Normal
- Hypo
- Hyper
### Interphase FISH

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>del 13q14</td>
<td>51/90 (56%)</td>
</tr>
<tr>
<td>del 17p13</td>
<td>13/160 (8.1%)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>12/75 (16%)</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>1/160 (0.63%)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>1/47 (2.1%)</td>
</tr>
</tbody>
</table>
Interaction of MM Cells with the BM Microenvironment


VEGF  
VEGF  

bFGF  

Bone Marrow  
Vessels  

Bone Marrow  
Stromal Cells  

IL-6  
TNFα  
IL-1β  

ICAM-1  

CD8+ T Cells  
NK Cells  

IL-2  
IFNγ  

PBMC  

## ELISA: New Vs Relapse

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=26)</th>
<th>Newly diagnosed (n=80)</th>
<th>Relapse/refractory (n=22)</th>
<th>Global P-value (K-Wallis test)</th>
<th>Global P-value (Mann Whitney test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF (pg/ml)</td>
<td>236.1±191.1</td>
<td>338.0±260.1</td>
<td>478.8±380.4</td>
<td>0.06</td>
<td>1 vs 2= 0.07 2 vs 3= 0.26 1 vs 3= 0.03</td>
</tr>
<tr>
<td></td>
<td>220.4 (28.8-688.6)</td>
<td>247.5 (22.8-1089.1)</td>
<td>321.7 (61.5-1049.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>1.8±1.5 (0.09-5.64)</td>
<td>12.1±16.2 (0.06-80.4)</td>
<td>15.0±12.5 (0.7-41.3)</td>
<td>0.0001</td>
<td>1 vs 2= 0.0000 2 vs 3= 0.15 1 vs 3= 0.001</td>
</tr>
<tr>
<td></td>
<td>1.4 (0.09-5.64)</td>
<td>6.7 (0.06-80.4)</td>
<td>13.7 (0.7-41.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>1.4±1.6 (4.3-5.1)</td>
<td>20.7±20.7 (1.3-85.8)</td>
<td>11.4±15.3 (1.7-62.4)</td>
<td>0.0001</td>
<td>1 vs 2= 0.000 2 vs 3= 0.10 1 vs 3= 0.000</td>
</tr>
<tr>
<td></td>
<td>1.2 (-4.3-5.1)</td>
<td>10.3 (1.3-85.8)</td>
<td>8.4 (1.7-62.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAFF (pg/ml)</td>
<td>447.4±282.0 (78.1-987.4)</td>
<td>1339.1±796.5 (277.7-3841.7)</td>
<td>1625.4±707.5 (431.2-3021.4)</td>
<td>0.0001</td>
<td>1 vs 2= 0.0000 2 vs 3= 0.04 1 vs 3= 0.000</td>
</tr>
<tr>
<td></td>
<td>343.9 (78.1-987.4)</td>
<td>1149.4 (277.7-3841.7)</td>
<td>1676.5 (431.2-3021.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RANKL (pmol/l)</td>
<td>2.49±2.6 (0.2-9.2)</td>
<td>28.6±19.4 (2.6-80.9)</td>
<td>22.6±10.4 (4.0-37.6)</td>
<td>0.0001</td>
<td>1 vs 2= 0.0000 2 vs 3= 0.52 1 vs 3= 0.0000</td>
</tr>
<tr>
<td></td>
<td>1.3 (0.2-9.2)</td>
<td>22.8 (2.6-80.9)</td>
<td>23.4 (4.0-37.6)</td>
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</tbody>
</table>

Mean ± SD; Median (Range) values of the measured parameters in multiple myeloma patients and controls.
Pre and Post- treatment cytokines levels (n=37)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF (pg/ml)</td>
<td>393.1 ± 291.7</td>
<td>327.6 ± 290.0</td>
<td>0.23</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>17.7 ± 25.4</td>
<td>7.6 ± 7.8</td>
<td>0.03</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>21.8 ± 22.2</td>
<td>16.2 ± 18.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BAFF (pg/ml)</td>
<td>1436.6 ± 943.4</td>
<td>1191.8 ± 1052.2</td>
<td>0.07</td>
</tr>
<tr>
<td>RANKL (pmol/l)</td>
<td>30.0 ± 18.2</td>
<td>19.4 ± 20.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Mean ± SD values for serum cytokines levels of newly diagnosed MM patients before and after treatment. (n=37)

*p- values were calculated using Wilcoxon rank-sum (Mann-Whitney) test and Wilcoxon signed-rank test for paired samples.*
Mean ± SD; Median (Range) values of the measured parameters in serum (PB) and plasma (BM) of 45 multiple myeloma patients and controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum</th>
<th>Plasma</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF (pg/ml)</td>
<td>353.2±259.8 307.0 (32.1-1089.1)</td>
<td>108.7±101.5 76.5 (1.6-334.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>10.4±15.1 6.6 (0.6-80.4)</td>
<td>16.8±16.7 10.0 (0.5-70.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>18.1±20.9 8.1 (1.8-85.8)</td>
<td>13.7±17.5 8.3 (0.4-89.9)</td>
<td>0.49</td>
</tr>
<tr>
<td>BAFF (pg/ml)</td>
<td>1345.8±830.4 1119.3 (277.7-3841.7)</td>
<td>539.8±224.4 553.6 (161.1-990.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RANKL (pmol/l)</td>
<td>27.3±17.5 24.3 (5.0-80.9)</td>
<td>23.5±20.4 14.6 (2.1-73.2)</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Optimal induction therapy
# Thal-dexa vs Len-dexa: Phase 3 study
(April, 2009 – Sept. 2014)

<table>
<thead>
<tr>
<th></th>
<th>Len-dexa</th>
<th>Thal-dexa</th>
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<tbody>
<tr>
<td><strong>Median Age</strong></td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td><strong>M:F</strong></td>
<td>77:30</td>
<td>63:36</td>
</tr>
<tr>
<td><strong>ISS Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>II</td>
<td>37%</td>
<td>33%</td>
</tr>
<tr>
<td>III</td>
<td>39%</td>
<td>42%</td>
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Clin Lymphoma, Myeloma & Leukemia, IMW 2015 a
Thal-dexa vs Len-dexa: A Phase 3 study
Response rate: Intent to treat analysis

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>Len/dexa N=100</th>
<th>Thal/dexa N=96</th>
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<tbody>
<tr>
<td>sCR</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Complete (CR)</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Very good partial</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Partial</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>sCR+CR+VGPR+PR</td>
<td>68%</td>
<td>67%</td>
</tr>
<tr>
<td>Stable</td>
<td>19</td>
<td>18</td>
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<tr>
<td>Prog. dis.</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>6</td>
<td>3</td>
</tr>
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</table>

Clin Lymphoma, Myeloma & Leukemia, 2015a
Thalidomide + dexamethasone Vs Lenalidomide + dexamethasone: A phase III Randomized study

**OS**

**PFS**

**PFS responders vs non-responders**
Bortezomib, Lenalidomide and low-dose dexamethasone (VRD) versus Lenalidomide and low-dose dexamethasone (Ld) for Newly-Diagnosed Multiple myeloma: A Randomized Phase III study

Mookerjee A et al. Blood 2017, 130:866
## Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VRD n=70</th>
<th>Rd n=65</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age</td>
<td>56 (31-70)</td>
<td>52 (28-69)</td>
<td>0.24</td>
</tr>
<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>43</td>
<td>0.21</td>
</tr>
<tr>
<td>ISS</td>
<td></td>
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</tr>
<tr>
<td>I</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>49</td>
<td>42</td>
<td>0.4</td>
</tr>
<tr>
<td>RISS I/II/III</td>
<td>2/9/53</td>
<td>7/13/43</td>
<td>0.22</td>
</tr>
<tr>
<td>DSS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IIIA</td>
<td>52</td>
<td>50</td>
<td>0.85</td>
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<tr>
<td>IIIB</td>
<td>13</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>IIA &amp; IA</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Myeloma subtype</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IgG</td>
<td>44</td>
<td>36</td>
<td>0.31</td>
</tr>
<tr>
<td>IgA</td>
<td>12</td>
<td>11</td>
<td>11.0</td>
</tr>
<tr>
<td>Light chain</td>
<td>14</td>
<td>18</td>
<td>0.24</td>
</tr>
<tr>
<td>Serum LDH (&gt;normal)</td>
<td>25 (44.6%)</td>
<td>31 (52.5%)</td>
<td>0.46</td>
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</table>
**Response rate at the end of 4 cycles**

<table>
<thead>
<tr>
<th>Category</th>
<th>VRd n (%)</th>
<th>Rd n(%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent CR</td>
<td>14 (18.9%)</td>
<td>12 (17.4%)</td>
<td>0.83</td>
</tr>
<tr>
<td>CR</td>
<td>7 (9.5%)</td>
<td>9 (13%)</td>
<td>0.60</td>
</tr>
<tr>
<td>sCR+ CR</td>
<td>21 (28.4%)</td>
<td>21 (30.4%)</td>
<td>0.86</td>
</tr>
<tr>
<td>VGPR</td>
<td>8 (10.8%)</td>
<td>9 (13%)</td>
<td>0.80</td>
</tr>
<tr>
<td>sCR+CR+VGPR</td>
<td>29 (39.2%)</td>
<td>30 (43.4%)</td>
<td>0.62</td>
</tr>
<tr>
<td>PR</td>
<td>29 (39.2%)</td>
<td>21 (30.4%)</td>
<td>0.30</td>
</tr>
<tr>
<td>sCR+CR+VGPR+PR</td>
<td>58 (78.4%)</td>
<td>51 (73.8%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3 (4.1%)</td>
<td>1 (1.4%)</td>
<td>0.62</td>
</tr>
<tr>
<td>PD/NR or death</td>
<td>5 (6.8%)</td>
<td>6 (8.6%)</td>
<td>0.76</td>
</tr>
</tbody>
</table>
OS: VRd or Rd

Kaplan-Meier survival estimates

Number at risk
- Regimen = 1: 70
- Regimen = 2: 65

Time since randomization in months

Probability
- Regimen = VRd
- Regimen = Ld

p = 0.21
PFS : VRd or Rd

Kaplan-Meier survival estimates

- Probability
  - 0.00
  - 0.25
  - 0.50
  - 0.75
  - 1.00

- Number at risk
  - regimen = 1: 70
  - regimen = 2: 65

- Time since randomization in months
  - 0
  - 10
  - 20
  - 30
  - 40

- Number at risk
  - 59
  - 30
  - 6
  - 0

- Kaplan-Meier survival estimates
  - p=0.17

- Graph:
  - regimen = VRd
  - regimen = Ld
Autologous
Stem cell Transplantation
Treatment Algorithm

- Age ≤65 Yrs
- Induction therapy 4 cycles

Response evaluation

- CR/VGPR
  - Stem cell Transplant

- PR
  - 2 more cycles
  - CR/VGPR

- No /min
  - 2nd line Tt
  - Good response
  - Transplant
# ASCT for Plasma cell disorders

**December, 2016 (n=375)**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma</td>
<td>349</td>
</tr>
<tr>
<td>Plasma cell leukemia</td>
<td>05</td>
</tr>
<tr>
<td>POEMS syndrome</td>
<td>08</td>
</tr>
<tr>
<td>AL Amyloidosis</td>
<td>08</td>
</tr>
<tr>
<td>2\textsuperscript{nd} transplant</td>
<td>05 (auto-3, allo-2)</td>
</tr>
</tbody>
</table>
ASCT: Results (till Dec. 2016)

- Total no of Pts: 349
- Median Age: 53 (29 to 68 Y)
- M:F: 67.6% : 32.4%
- ISS III: 34.7%
- DSS IIIB: 24.4%
- Pre Tx status
  - Chemo-sensitive: 83.4%
  - Resistant: 16.6%
Stem cell Mobilization

- G-CSF 10 mcg/kg x 5 d
- PB : CD 34+, on d 4
- Conditioning
  - Melphalan : 200 mg/m2
  - Renal failure : 140-150mg/m2

PB CD34+ value of <20/µl predict for poor mobilization
- Sensitivity 93%
- Specificity 91%
- (PPV 71% & NPV 98%)
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</thead>
<tbody>
<tr>
<td><strong>CR (IF -ve)</strong></td>
<td>36.1</td>
<td>42.9</td>
<td>58.3</td>
<td>60.0</td>
</tr>
<tr>
<td><strong>VG PR</strong></td>
<td>29.6</td>
<td>24.5</td>
<td>18.8</td>
<td>17.5</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>13.9</td>
<td>15.6</td>
<td>12.5</td>
<td>12.7</td>
</tr>
<tr>
<td><strong>Stable</strong></td>
<td>9.4</td>
<td>8.2</td>
<td>3.7</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Died</strong></td>
<td>11.0</td>
<td>8.8</td>
<td>6.6</td>
<td>5.7</td>
</tr>
</tbody>
</table>

1. BMT 43: 481-89, 2009  
3. Cancer Medicine 2014  
5. BMT 2017
Median Follow up:
71.5 months (59.5 to 83.8)

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>91.0 mon.</td>
<td>68.6 to 113.4</td>
</tr>
<tr>
<td>Progression-free</td>
<td>37.0 mon.</td>
<td>28.7 to 45.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>5 Yr</th>
<th>10 Yr</th>
<th>15 Yr</th>
<th>20 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>61.5%</td>
<td>41.6%</td>
<td>26.0%</td>
<td>20.8%</td>
</tr>
<tr>
<td>PFS</td>
<td>38.7%</td>
<td>25.7%</td>
<td>9.8%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>
## CR as Predictor of OS

<table>
<thead>
<tr>
<th>Status</th>
<th>No of Pts</th>
<th>Median (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>209</td>
<td>174</td>
<td>124.8-223.2</td>
</tr>
<tr>
<td>VGPR</td>
<td>61</td>
<td>54.0</td>
<td>26.5-81.5</td>
</tr>
<tr>
<td>PR</td>
<td>44</td>
<td>48.0</td>
<td>23.1-72.9</td>
</tr>
<tr>
<td>Stable</td>
<td>14</td>
<td>12.0</td>
<td>7.3-16.7</td>
</tr>
</tbody>
</table>
Survival according to Response

Overall Survival

Progression free Survival

CR
VGPR
PR

Cum Survival

Months since transplant

Cum Survival
Consolidation: Schema
(A prospective study)

TWO 28-day Cycles of VRd

ASCT D + 100

Response evaluation

Bortezomib 1.3/mg² S/C Wkly
Len 15 mg/day PO d 1-15
Dexa 40 mg/wk d1,8,15,22

Response assessment

Followed by maintenance therapy
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Median Age</td>
<td>52 year (32-66Y)</td>
</tr>
<tr>
<td>2 Males</td>
<td>26 (63.4%)</td>
</tr>
<tr>
<td>3 Subtype</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>23 (56.0%)</td>
</tr>
<tr>
<td>IgA</td>
<td>05 (12.0%)</td>
</tr>
<tr>
<td>Light Chain</td>
<td>13 (32.0%)</td>
</tr>
<tr>
<td>4 ISS Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>07 (17.1%)</td>
</tr>
<tr>
<td>II</td>
<td>11 (26.8%)</td>
</tr>
<tr>
<td>III</td>
<td>23 (56.1%)</td>
</tr>
<tr>
<td>5 No of lines of Rx</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30 (73.2%)</td>
</tr>
<tr>
<td>2</td>
<td>10 (24.4%)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>01 (2.4%)</td>
</tr>
<tr>
<td>6 Extramedullary disease</td>
<td>15 (36.6%)</td>
</tr>
<tr>
<td>7 Pre-Tx status</td>
<td></td>
</tr>
<tr>
<td>Chemo-sensitive (CR15, VGPR 10, PR10)</td>
<td>35 (85.4%)</td>
</tr>
<tr>
<td>Chemo-resistant disease (SD1, PD5)</td>
<td>06 (14.6%)</td>
</tr>
</tbody>
</table>
End Points

- Response rate: day +100, d+180
- MRD: by multicolour flow cytometry on day +100, and Day +180.
  - MRD defined as +ve
  - If a discrete population of phenotypically aberrant plasma cells comprising >50 events identified in the 500,000-event file (0.01% limit of detection)
- Toxicity by CTC criteria version 4.03
### Response rate (n=41)

<table>
<thead>
<tr>
<th>Response</th>
<th>Prior to Tx</th>
<th>Post Tx d+100</th>
<th>Post consolidation Day +180</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>15(36%)</td>
<td>32(78.0%)</td>
<td>39(95.0%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>10(24.4%)</td>
<td>7(17.1%)</td>
<td>1(2.5%)</td>
</tr>
<tr>
<td>PR</td>
<td>10(24.4%)</td>
<td>2(4.9%)</td>
<td>-</td>
</tr>
<tr>
<td>Stable</td>
<td>1(2.4%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prog Dis</td>
<td>5(12.2%)</td>
<td></td>
<td>1(2.5%)</td>
</tr>
<tr>
<td>MRD negative</td>
<td></td>
<td>21(52.5%)</td>
<td>31(77.5%)</td>
</tr>
</tbody>
</table>
Survival

Progression Free survival

Overall Survival

- Median Follow up = 11.1 months  
  Median PFS and OS = Not reached
- Estimated one year PFS and OS is 87% and 94%, respectively
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1 /2 N (%)</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>2 (4.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Infection, H1N1</td>
<td>2 (4.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (4.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (9.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>3 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6(14.6%)</td>
<td>0</td>
</tr>
</tbody>
</table>
## Relapses, n= 5

<table>
<thead>
<tr>
<th>SN</th>
<th>Stage ISS</th>
<th>Response at ASCT</th>
<th>Day 100 Response</th>
<th>Day 100 MRD</th>
<th>Day 180 RESPONSE</th>
<th>Day 180 MRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>III</td>
<td>VGPR</td>
<td>sCR</td>
<td>NEG</td>
<td>sCR</td>
<td>NEG</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>PD</td>
<td>CR</td>
<td>NEG</td>
<td>VGPR</td>
<td>NEG</td>
</tr>
<tr>
<td>4</td>
<td>III</td>
<td>PD</td>
<td>VGPR</td>
<td>POS</td>
<td>PD</td>
<td>POS</td>
</tr>
<tr>
<td>5</td>
<td>II</td>
<td>CR</td>
<td>CR</td>
<td>POS</td>
<td>CR</td>
<td>POS</td>
</tr>
<tr>
<td>6</td>
<td>III</td>
<td>VGPR</td>
<td>CR</td>
<td>NEG</td>
<td>sCR</td>
<td>NEG</td>
</tr>
</tbody>
</table>
Conclusion

Consolidation with two cycles of VRd improves Response rate and MRD negativity rate post-Tx
Maintenance therapy

- Maintenance therapy for 2 years or more
  - Thalidomide 50 mg / day
  - Lenalidomide 10 mg/day for 21 d q 4wk
  - Bortezomib 2 mg SC twice a month
Summary

Induction: Optimum response
Early Transplant

CR
nCR, VGPR

Maintenance: Prolonged Survival

Cure?
Acknowledgements

- Clinical Team and Lab, Medical Oncology, Lab Oncology
- Biochemistry
- DBT: Govt of India, for research grant
- Patients and their Families
Thank you
Multiple myeloma
## Frequency of del 13q14 by FISH

*n = 90*

<table>
<thead>
<tr>
<th>Probe</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB-1 (del 13q14)</td>
<td>51/90 (56%)</td>
</tr>
</tbody>
</table>

Control:C2

RB-1 gene(13q14) only one copy

(Rakesh Verma et al. 2010 (Blood 2010,116:4987a))
## IgH translocations by FISH (n=90)

<table>
<thead>
<tr>
<th>Probe</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgH (14q32)</td>
<td>75/90 (83%)</td>
</tr>
<tr>
<td>PCR for t(4;14)</td>
<td>12/75 (16%)</td>
</tr>
</tbody>
</table>

Rakesh Verma et al. 2010 (Blood 2010,116:4987a)
# Myeloma: Newer drugs

<table>
<thead>
<tr>
<th></th>
<th>Before 2000</th>
<th>After 2000</th>
<th>2012-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Thalidomide</td>
<td>Carfilzomib</td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>Lenalidomide</td>
<td>Pomalidomide</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Bortezomib</td>
<td>Monoclonal antibodies</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Liposomal doxorubicin</td>
<td>Anti-IL-6R (siltuximab)</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>HDAC inhibitors (Vorinostat)</td>
<td>Anti-CD38 (daratumumab)</td>
<td></td>
</tr>
<tr>
<td>BCNU</td>
<td></td>
<td>CS1 (elotuzumab)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ixazomib (oral PSI)</td>
<td></td>
</tr>
</tbody>
</table>
### Response to transplant: AIIMS Experience

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (IF -ve)</td>
<td>36.1</td>
<td>42.9</td>
<td>58.3</td>
<td>60.0</td>
</tr>
<tr>
<td>VG PR</td>
<td>29.6</td>
<td>24.5</td>
<td>18.8</td>
<td>17.5</td>
</tr>
<tr>
<td>PR</td>
<td>13.9</td>
<td>15.6</td>
<td>12.5</td>
<td>12.7</td>
</tr>
<tr>
<td>Stable</td>
<td>9.4</td>
<td>8.2</td>
<td>3.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Died</td>
<td>11.0</td>
<td>8.8</td>
<td>6.6</td>
<td>5.7</td>
</tr>
</tbody>
</table>

## Tx related complications

<table>
<thead>
<tr>
<th>Period</th>
<th>No of transplants</th>
<th>D100 mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993-2000</td>
<td>40</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>2001-2005</td>
<td>45</td>
<td>4 (8.8%)</td>
</tr>
<tr>
<td>2005-2010</td>
<td>76</td>
<td>3 (3.9%)</td>
</tr>
<tr>
<td>2011-2015</td>
<td>153</td>
<td>6 (3.9%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>314</strong></td>
<td><strong>18 (5.73%)</strong></td>
</tr>
</tbody>
</table>
## Characteristics: Relapse and Non-relapse cohort

<table>
<thead>
<tr>
<th>SN</th>
<th>Variable</th>
<th>Non Relapse (n=36)</th>
<th>Relapse (n=5)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>23</td>
<td>03</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>13</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MM subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgG k</td>
<td>18</td>
<td>05</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>IgA</td>
<td>05</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Light Chain MM</td>
<td>13</td>
<td>00</td>
<td></td>
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<tr>
<td>3</td>
<td>ISS stage</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>07</td>
<td>00</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>09</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>20</td>
<td>03</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No lines of therapy</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>27</td>
<td>03</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>08</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;3</td>
<td>01</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Extra medullary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td>No</td>
<td>23</td>
<td>03</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>13</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Interval from diagnosis to ASCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;12MONTHS</td>
<td>19</td>
<td>03</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>&gt;12 MONTHS</td>
<td>17</td>
<td>02</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>MRD d100 (n=40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>21</td>
<td>00</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>14</td>
<td>05</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MRD d180 (n=40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>30</td>
<td>01</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>05</td>
<td>04</td>
<td></td>
</tr>
</tbody>
</table>
Thank You!!!
Consolidation Therapy

- Distinct course of therapy aimed at increasing the depth of response.
- Limited no of cycles of single agent or combination, or of a second Tx step.\(^4,2,5\)
- Achievement of CR and in particular a MRD negative state post Tx is associated with prolonged PFS.\(^1,2,3,4,5\)

4. Roussel et al. *JCO*.2013.54.8164
5. Mellqvist et al. *BLOOD*, 6 JUNE 2013
## Myeloma: Cytogenetics

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Cytogenetics</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk (25%)</td>
<td>t (4;14)</td>
<td>24.7 months</td>
</tr>
<tr>
<td></td>
<td>t (14;16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-17p13</td>
<td></td>
</tr>
<tr>
<td>Intermediate (17%)</td>
<td>-13q14</td>
<td>42.3 months</td>
</tr>
<tr>
<td>Good Risk (58%)</td>
<td>All others</td>
<td>50.5 months</td>
</tr>
</tbody>
</table>

- Hyperdiploidy - Good, Hypodiploidy - poor risk

Fonesca et al. Blood 2003;101:4569-75