TREATMENT FOR NON-TRANSPLANT ELIGIBLE MULTIPLE MYELOMA

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OUTLINE

- Overview of treatment for non-transplant eligible MM
- Current TMWG Guideline
- Update in non-transplant eligible MM induction treatment
Overview of treatment for non-transplant eligible MM

Current TMWG Guideline

Update in non-transplant eligible MM induction treatment
Multiple myeloma predominantly affects elderly patients

The elderly multiple myeloma population is highly heterogeneous

- Biologic, genetic prognostic disease-related factors and age are insufficient to explain different disease and treatment outcome
GERIATRIC ASSESSMENT PREDICTS SURVIVAL IN ELDERLY MM: IMWG

# Geriatric Assessment

- **Score**
- 0: Fit
- 1: Intermediate fitness
- ≥ 2: Frail

![Score Table](image)

www.myelomafrailtyscorecalculator.net

ADL: Activity of Daily Living
IADL: Lawton Instrumental Activity of Daily Living
CCI: Charlson Comorbidity Index

Consideration of treatment adjustment based on patient fitness

**Patient risk factors**

- Age >75 years
- Mild, moderately, or severely frail (patients who need help with either household tasks, personal care, or are completely dependent)
- Comorbidities (pulmonary, renal, cardiac, and hepatic dysfunction)

Preferably with (a) IMWG-frailty index\(^1\) and/or (b) R-MCI\(^2\) define fit, intermediate-fit, and frail patients, in order to consider to adapt antmyeloma therapy; fit level 0, intermediate fit level -1, and frail level -2.

**Frailty index risk factors**

<table>
<thead>
<tr>
<th>IMWG frailty index(^1)</th>
<th>0</th>
<th>1</th>
<th>1 + occurrence of grade 3–4 hematological AE</th>
<th>≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-MCI(^2)</td>
<td>1–3</td>
<td>4–6</td>
<td>7–9</td>
<td></td>
</tr>
<tr>
<td>Dose level</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
<td>-2</td>
</tr>
</tbody>
</table>

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\(^2\) [http://www.myelomacomorbidityindex.org/en_about.html](http://www.myelomacomorbidityindex.org/en_about.html).

IMWG, International Myeloma Working Group; R-MCI, Revised Myeloma Comorbidity Index

<table>
<thead>
<tr>
<th>Treatment doses</th>
<th>Level 0</th>
<th>Level -1</th>
<th>Level -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>2 mg/kg days 1–4 of a 4–6 week cycle</td>
<td>1 mg/kg days 1–4 of a 4–6 week cycle</td>
<td>0.3–0.5 mg/kg days 1–4 of a 4–6 week cycle</td>
</tr>
<tr>
<td></td>
<td>60 mg/m² days 1–4 of a 6 week cycle</td>
<td>30 mg/m² days 1–4 of a 6 week cycle</td>
<td>10–15 mg/m² days 1–4 of a 6 week cycle</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg day 1, 8, 15, 22 of a 28-day cycle</td>
<td>20 mg day 1, 8, 15, 22 of a 28-day cycle</td>
<td>10 mg day 1, 8, 15, 22 of a 28-day cycle</td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.25 mg/kg days 1–4 of a 4–6 week cycle</td>
<td>0.18 mg/kg days 1–4 of a 4–6 week cycle</td>
<td>0.13 mg/kg days 1–4 of a 4–6 week cycle</td>
</tr>
<tr>
<td></td>
<td>9 mg/m² days 1–4 of a 6 week cycle</td>
<td>7.5 mg/m² days 1–4 of a 6 week cycle</td>
<td>5 mg/m² days 1–4 of a 6 week cycle</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>100 (–200) mg/day</td>
<td>50 (–100) mg/day</td>
<td>50 mg qod (–50 mg/day)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg days 1–21 of a 28-day cycle</td>
<td>15 mg days 1–21 of a 28-day cycle</td>
<td>10 mg days 1–21 of a 28-day cycle</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>4 mg days 1–21 of a 28-day cycle</td>
<td>3 mg days 1–21 of a 28-day cycle</td>
<td>2 mg days 1–21 of a 28-day cycle</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² twice weekly Day 1, 4, 8, 11 every 3 weeks</td>
<td>1.3 mg/m² once weekly Day 1, 8, 15, 22 every 5 weeks</td>
<td>1.0 mg/m² once weekly Day 1, 8, 15, 22 every 5 weeks</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>20 mg/m² day 1, 2, 8, 9, 15, 16 cycle 1, 27 mg/m² cycle 2 every 3 weeks</td>
<td>20 mg/m² cycle 1 → 27 mg/m² cycle 2, day 1, 8, 15, every 3 weeks</td>
<td>20 mg/m² day 1, 8, 15, every 4 (5) weeks</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>4 mg day 1, 8, 15, every 4 weeks</td>
<td>3 mg day 1, 8, 15, every 4 weeks</td>
<td>2.3 mg day 1, 8, 15, every 4 weeks</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>16 mg/kg bw cycle 1–8: weekly; cycle 9–24: day 1+15, from week 25: every 4 weeks</td>
<td>16 mg/kg bw cycle 1–8: weekly; cycle 9–24: day 1+15, from week 25: every 4 weeks</td>
<td>16 mg/kg bw cycle 1–8: weekly; cycle 9–24: day 1+15, from week 25: every 4 weeks</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>10 mg/kg day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15</td>
<td>10 mg/kg bw day 1, 8, 15, 22, cycle 1+2, from cycle 3: day 1+15</td>
<td>10 mg/kg bw day 1, 8, 15, 22 cycle 1+2, from cycle 3: day 1+15</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>20 mg day 1, 3, 5, 8, 10, 12 every 4 weeks</td>
<td>15 mg day 1, 3, 5, 8, 10, 12 every 4 weeks</td>
<td>10 mg day 1, 3, 5, 8, 10, 12 every 5 weeks</td>
</tr>
</tbody>
</table>
## Parameters to consider in decision-making process in frail patients with MM

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Medical History</th>
<th>Criteria to start treatment</th>
<th>Disease characteristic</th>
<th>Goal of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Cardio-vascular disease</td>
<td>Myeloma-defining events: CRAB or Biomarkers of malignancy</td>
<td>Cytogenetics Stage (ISS) Tumor aggressiveness</td>
<td>Response (CR) Disease control Quality of life</td>
</tr>
<tr>
<td>Functional and independence status (ADL and IADL) Comorbidity (CCI) Psychosocial status</td>
<td>Thromboembolism Diabetes Renal impairment Peripheral neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADL, Activity of Daily Living; CCI, Charlson comorbidity index; CR, complete response; IADL, Instrumental Activity of Daily Living; ISS, International Staging System;
TREATMENT FOR NON-TRANSPLANT ELIGIBLE MM: OVERVIEW

**DISEASE BIOLOGY:**
- Cytogenetics
- ISS stage

**ENVIRONMENTAL FACTORS:**
- Access to care
- Social support

**PATIENT FACTORS:**
- Comorbidities
- Functional status
- Goals of care

**Individualized treatment**

**Disease response**

**Toxicity of therapy**

**DURATION OF SURVIVIAL**

**QUALITY OF LIFE**

Overview of treatment for non-transplant eligible MM

Current TMWG Guideline

Update in non-transplant eligible MM induction treatment
Newly diagnosed non-transplant candidate myeloma

Induction therapy x 3-4 cycles

Response $\geq$ PR
- Continue therapy to reach a treatment plateau (treatment should be continued for at least 2 cycles beyond best response) or as in the clinical trial
- Follow up and monitor disease status q 3 mo

Stable/progressive disease
- Salvage therapy
- Consider maintenance therapy

Overview of treatment of non-transplant eligible MM
FIXED DURATION THERAPY (FDT) VS CONTINUOUS THERAPY (CT) IN MM

Trials included: 2 MPR-R, 1 VMPT-VT

FIXED DURATION THERAPY (FDT) VS CONTINUOUS THERAPY (CT) IN MM

OS

Non-novel agent-based regimen

- Melphalan-prednisolone (MP) (+)
- Cyclophosphamide-dexamethasone (CyD) (+)
- Pulse dexamethasone (+)
ATTENUATED CTD VS MP IN ELDERLY MM

CTDa: higher rates of thromboembolic events, constipation, infection, and neuropathy than MP

Novel agent-based regimen

- Melphalan-prednisolone-thalidomide (MPT) (+)
- Melphalan-prednisolone-bortezomib (VMP) (+)
- Bortezomib-dexamethasone (VD) (+)
- Continuous lenalidomide-dexamethasone (Rd) (+/-)
MPT VS MP IN ELDERLY MM

Progression–free survival

<table>
<thead>
<tr>
<th>Study</th>
<th>MPT:E/N</th>
<th>MP:E/N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM–I</td>
<td>97/125</td>
<td>176/196</td>
<td>0.50 (0.39, 0.65)</td>
</tr>
<tr>
<td>IFM–II</td>
<td>87/113</td>
<td>103/116</td>
<td>0.61 (0.46, 0.82)</td>
</tr>
<tr>
<td>GIMEMA</td>
<td>111/167</td>
<td>125/164</td>
<td>0.62 (0.48, 0.80)</td>
</tr>
<tr>
<td>TMSG</td>
<td>30/57</td>
<td>31/57</td>
<td>0.70 (0.42, 1.17)</td>
</tr>
<tr>
<td>HOVON</td>
<td>139/165</td>
<td>150/168</td>
<td>0.79 (0.62, 1.00)</td>
</tr>
<tr>
<td>NMSG</td>
<td>134/182</td>
<td>138/175</td>
<td>0.89 (0.70, 1.13)</td>
</tr>
</tbody>
</table>

Overall (I–squared = 60.9%, p = 0.026) 0.68 (0.56, 0.81)

Favours MPT  Favours MP
MPT VS MP IN ELDERLY MM

Overall survival

<table>
<thead>
<tr>
<th>Study</th>
<th>MPT: E/N</th>
<th>MP: E/N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM–I</td>
<td>67/125</td>
<td>133/196</td>
<td>0.61 (0.45, 0.81)</td>
</tr>
<tr>
<td>IFM–II</td>
<td>58/113</td>
<td>76/116</td>
<td>0.68 (0.48, 0.96)</td>
</tr>
<tr>
<td>HOVON</td>
<td>86/165</td>
<td>104/168</td>
<td>0.75 (0.57, 1.00)</td>
</tr>
<tr>
<td>TMSG</td>
<td>20/57</td>
<td>21/57</td>
<td>0.86 (0.46, 1.60)</td>
</tr>
<tr>
<td>GIMEMA</td>
<td>77/167</td>
<td>69/164</td>
<td>1.06 (0.76, 1.46)</td>
</tr>
<tr>
<td>NMSG</td>
<td>109/182</td>
<td>101/175</td>
<td>1.12 (0.85, 1.47)</td>
</tr>
<tr>
<td>Overall (I-squared = 61.3%, p = 0.024)</td>
<td></td>
<td></td>
<td>0.82 (0.66, 1.03)</td>
</tr>
</tbody>
</table>

Favours MPT   Favours MP

Time to next therapy was longer with VMP than with MP (median 30.7 vs 20.5 months; P=0.001)

UPFRONT TRIAL: VD VS VMP VS VTP

PFS

<table>
<thead>
<tr>
<th></th>
<th>Events, n (%)</th>
<th>Median PFS, months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD</td>
<td>168</td>
<td>96 (57)</td>
<td>14.7</td>
</tr>
<tr>
<td>VTD</td>
<td>167</td>
<td>78 (47)</td>
<td>15.4</td>
</tr>
<tr>
<td>VMP</td>
<td>167</td>
<td>91 (54)</td>
<td>17.3</td>
</tr>
</tbody>
</table>

OS

<table>
<thead>
<tr>
<th></th>
<th>Events, n (%)</th>
<th>Median OS, months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD</td>
<td>168</td>
<td>68 (40)</td>
<td>49.8</td>
</tr>
<tr>
<td>VTD</td>
<td>167</td>
<td>62 (37)</td>
<td>51.5</td>
</tr>
<tr>
<td>VMP</td>
<td>167</td>
<td>66 (40)</td>
<td>53.1</td>
</tr>
</tbody>
</table>

FIRST TRIAL:
CONTINUOUS RD VS RD18 VS MPT12

A Progression-free Survival

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>54</td>
<td>5</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>535</th>
<th>400</th>
<th>319</th>
<th>265</th>
<th>218</th>
<th>168</th>
<th>105</th>
<th>55</th>
<th>19</th>
<th>2</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous Ld</td>
<td>535</td>
<td>400</td>
<td>319</td>
<td>265</td>
<td>218</td>
<td>168</td>
<td>105</td>
<td>55</td>
<td>19</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ld18</td>
<td>541</td>
<td>391</td>
<td>319</td>
<td>265</td>
<td>167</td>
<td>108</td>
<td>56</td>
<td>30</td>
<td>7</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>MPT</td>
<td>547</td>
<td>380</td>
<td>304</td>
<td>244</td>
<td>170</td>
<td>116</td>
<td>58</td>
<td>28</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Median Progression-free Survival (mo)

- Continuous Ld: 25.5
- Ld (N=535)
- Ld18 (N=541): 20.7
- MPT (N=547): 21.2

Hazard ratio:
- Continuous Ld vs. MPT, 0.72; P<0.001
- Continuous Ld vs. Ld18, 0.70; P<0.001

2 Facon T. J Clin Oncol 2015; Abstract 8524.
FIRST TRIAL: CONTINUOUS RD VS RD18 VS MPT12

![Graph showing overall survival and number at risk](image)

- **4-Yr Overall Survival (%)**
  - Continuous Ld (N=535) 59
  - Ld18 (N=541) 56
  - MPT (N=547) 51

- **Hazard ratio**
  - Continuous Ld vs. MPT, 0.78; P=0.02
  - Continuous Ld vs. Ld18, 0.90; P=0.31

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Continuous Ld</th>
<th>Ld18</th>
<th>MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>535</td>
<td>541</td>
<td>547</td>
</tr>
<tr>
<td>12 months</td>
<td>488</td>
<td>505</td>
<td>484</td>
</tr>
<tr>
<td>18 months</td>
<td>457</td>
<td>465</td>
<td>448</td>
</tr>
<tr>
<td>24 months</td>
<td>433</td>
<td>425</td>
<td>418</td>
</tr>
<tr>
<td>36 months</td>
<td>403</td>
<td>393</td>
<td>375</td>
</tr>
<tr>
<td>42 months</td>
<td>338</td>
<td>324</td>
<td>312</td>
</tr>
<tr>
<td>48 months</td>
<td>224</td>
<td>209</td>
<td>205</td>
</tr>
<tr>
<td>54 months</td>
<td>121</td>
<td>124</td>
<td>106</td>
</tr>
<tr>
<td>60 months</td>
<td>43</td>
<td>44</td>
<td>30</td>
</tr>
<tr>
<td>59 months</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>60 months</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

MPR/CPR vs RD induction then R vs RP maintenance
### MPR/CPR VS RD INDUCTION THEN R VS RP MAINTENANCE

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MPR (n= 211)</th>
<th>CPR (n=220)</th>
<th>Rd (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>71%</td>
<td>68%</td>
<td>74%</td>
</tr>
<tr>
<td>CR</td>
<td>3%</td>
<td>0.5%</td>
<td>3%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>24 mo</td>
<td>20 mo</td>
<td>21 mo</td>
</tr>
<tr>
<td>4-year OS</td>
<td>65%</td>
<td>68%</td>
<td>58%</td>
</tr>
<tr>
<td>Grade ≥3 hematological AE</td>
<td>68%</td>
<td>32%</td>
<td>29%</td>
</tr>
<tr>
<td>Grade ≥3 extra-hematologic AE</td>
<td>31%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Second primary malignancies</td>
<td>1.5%</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Thalidomide maintenance only in non-high risk cytogenetics (+/-)
Bortezomib maintenance (+/-)
Lenalidomide maintenance (+/-)
THALIDOMIDE MAINTENANCE: MRC MYELOMA IX

PFS

OS

THALIDOMIDE MAINTENANCE: MRC MYELOMA IX

- **Adverse iFISH:** gain(1q), t(4;14), t(14;16), t(14;20), del(17p)

**Morgan GJ. Blood 2012;119:7-15.**
UPFRONT STUDY: VD VS VTD VS VMP
THEN BORTEZOMIB MAINTENANCE

**A**

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Median PFS, months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD 168</td>
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<td>14.7</td>
</tr>
<tr>
<td>VTD 167</td>
<td>78 (47)</td>
<td>15.4</td>
</tr>
<tr>
<td>VMP 167</td>
<td>91 (54)</td>
<td>17.3</td>
</tr>
</tbody>
</table>

**B**

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Median OS, months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD 168</td>
<td>68 (40)</td>
<td>49.8</td>
</tr>
<tr>
<td>VTD 167</td>
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<td>51.5</td>
</tr>
<tr>
<td>VMP 167</td>
<td>66 (40)</td>
<td>53.1</td>
</tr>
</tbody>
</table>

VMP (VISTA Trial) 24 months
VMP (VISTA Trial) 56.4 months

VT OR VP MAINTENANCE AFTER VMP OR VTP

VMP (VISTA Trial) 24 months

VMP (VISTA Trial) 56.4 months

1 Mateos MV. Blood 2012;120:2581-8.
MPR-R VS MPR VS MP IN ELDERLY MM

A  Progression-free Survival

- MPR-R
- MPR
- MP

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

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>MPR-R</th>
<th>MPR</th>
<th>MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>152</td>
<td>153</td>
<td>154</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>115</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
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<td>85</td>
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<td>3</td>
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<td>4</td>
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<td>27</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
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<td>6</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

B  Overall Survival

- MPR-R
- MPR
- MP

Hazard ratio
- MPR-R vs. MPR: 0.79; P=0.25
- MPR-R vs. MP: 0.95; P=0.81

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>MPR-R</th>
<th>MPR</th>
<th>MP</th>
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<tr>
<td>0</td>
<td>152</td>
<td>153</td>
<td>154</td>
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<tr>
<td>1</td>
<td>130</td>
<td>134</td>
<td>134</td>
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<tr>
<td>2</td>
<td>117</td>
<td>108</td>
<td>117</td>
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<tr>
<td>3</td>
<td>82</td>
<td>79</td>
<td>84</td>
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<tr>
<td>4</td>
<td>27</td>
<td>18</td>
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<tr>
<td>5</td>
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<td>0</td>
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</table>

MPR-R VS MPT-T IN ELDERLY MM ECOG E1A06 TRIAL

Stewart AK. Blood 2015;126:1294-301.

PFS

OS

p = 0.186

p = 0.476
MPR-R VS MPT-T IN ELDERLY MM HOVON87/NMSG18 TRIAL

PFS

OS

A

% progression free

0 10 20 30 40 50 60 70 80 90 100

months

0 12 24 36 48

At risk:

MPT-T 318
MPR-R 319

N 243 232
F 227 138

Cox LR P=0.12 (adjusted for ISS)

B

% survival

0 10 20 30 40 50 60 70 80 90 100

months

0 12 24 36 48

At risk:

MPT-T 318
MPR-R 319

N 130 117
D 271 288

Cox LR P=0.13 (adjusted for ISS)

Zweegman S. Blood 2016;127:1109-16.
MPR/CPR VS RD THEN R VS RP MAINTENANCE IN ELDERLY MM

**A**

PFS

- MPR vs Rd HR 0.805 (95% CI 0.631-1.027) $P = .081$
- MPR vs CPR HR 0.797 (95% CI 0.626-1.015) $P = .066$
- CPR vs Rd HR 1.005 (95% CI 0.895-1.127) $P = .938$

**B**

OS

- MPR vs Rd HR 1.016 (95% CI 0.721-1.431) $P = .927$
- MPR vs CPR HR 0.862 (95% CI 0.607-1.222) $P = .404$
- CPR vs Rd HR 0.934 (95% CI 0.784-1.114) $P = .448$
OUTLINE

- Overview of treatment for non-transplant eligible MM
- Current TMWG Guideline
- Update in non-transplant eligible MM induction treatment
Bortezomib and lenalidomide-based regimen
- VRd
- CyBorD
- VMP and Rd alternate or sequential
VRD VS RD IN NON-TRANSPLANT ELIGIBLE MM

PFS
- Median 43 months (VRd) vs 30 months (Rd)

OS
- Median 75 months (VRd) vs 64 months (Rd)

ORR (CR rate)
- VRd 81.5% (15.7%) vs Rd 71.5% (8.4%)

Age > 65 years
- VRd 48% vs Rd 38%

Primary therapy for non-transplant candidates

Preferred regimens
- Bortezomib/lenalidomide/dexamethasone (1)
- Lenalidomide/low-dose dexamethasone* (1)
- Bortezomib/cyclophosphamide/dexamethasone** (2A)

Other regimens
- Carfilzomib/lenalidomide/dexamethasone (2A)
- Carfilzomib/cyclophosphamide/dexamethasone (2A)
- Ixazomib/lenalidomide/dexamethasone (2A)

Useful in certain circumstances
- Bortezomib/dexamethasone* (2A)

*Elderly or frail patients may be treated with doublet regimens
**Preferred initial treatment in patients with AKI
Maintenance therapy

Preferred regimens
   ▪ Lenalidomide

Other recommended regimens
   ▪ Bortezomib
PHASE II STUDY OF CY-BOR-D IN NEWLY DIAGNOSED MM

- 63 patients with mean age of 60 (38–75) years
- 14 patients (22%) did not have undergone ASCT
- ORR 89% with ≥VPPR 62%
  - For patients completed 4 cycles: ORR 93% (≥VGPR 67%)
- Median PFS 40.0 months
- 5-year PFS 42% and OS 70%

## BORTEZOMIB-BASED INDUCTION IN NON-TRANSPLANT ELIGIBLE MM: RETROSPECTIVE SINGLE CENTER STUDY

<table>
<thead>
<tr>
<th></th>
<th>CyBorD (n = 42)</th>
<th>VMP (n = 42)</th>
<th>VD (n = 38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>76</td>
<td>73</td>
<td>77</td>
<td></td>
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<tr>
<td>Overall response rate (≥PR)</td>
<td>95.2%</td>
<td>80.9%</td>
<td>76.3%</td>
<td>0.031</td>
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<tr>
<td>≥Very good partial response</td>
<td>76.1%</td>
<td>52.3%</td>
<td>26.3%</td>
<td>0.001</td>
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<tr>
<td>Progression</td>
<td>33.3%</td>
<td>80.9%</td>
<td>78.9%</td>
<td>0.001</td>
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<tr>
<td>Median PFS (months)</td>
<td>22.4</td>
<td>17.5</td>
<td>10.1</td>
<td>0.04</td>
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<tr>
<td>Median OS (months)</td>
<td>38</td>
<td>43.2</td>
<td>37.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Median OS and PFS was longer for patients receiving continuous therapy more than 12 cycles
- OS 56.8 vs. 31 months, p = 0.01
- PFS 21.1 vs. 11.1 months, p = 0.009

SEQUENTIAL VS ALTERNATING ADMINISTRATION OF VMP AND RD IN ELDERLY MM

**Sequential scheme**

- VMP x 9 cycles
- Rd x 9 cycles

**Alternating scheme**

- MPV Rd MPV Rd MPV Rd MPV Rd MPV Rd MPV Rd MPV Rd

**VMP**

- One-6 week cycle
  - Bortezomib 1.3 mg/m²
  - Melphalan 9 mg/m²
  - Prednisone 60 mg/m²
  - Days: 1 2 3 4 8 11 22 25 29 32 33-42
  - Rest period

- Eight-4 week cycles
  - Bortezomib 1.3 mg/m²
  - Melphalan 9 mg/m²
  - Prednisone 60 mg/m²
  - Days: 1 2 3 4 8 15 22 23-28
  - Rest period

**Rd**

- Nine-4 week cycles
  - Lenalidomide 25 mg days 1-21
  - Dexamethasone 40 mg weekly

SEQUENTIAL VS ALTERNATING ADMINISTRATION OF VMP AND RD IN ELDERLY MM

Median PFS: VMP (VISTA) 24 months, Rd (FIRST) 25.5 months

UPDATE IN INDUCTION TREATMENT OF NON-TRANSPLANT ELIGIBLE MM

- Bortezomib and lenalidomide-based regimen
- Carfilzomib-based regimen
## CARFILZOMIB INDUCTION IN NON-TRANSPLANT ELIGIBLE MM

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Response rate</th>
<th>Survival outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMP¹</td>
<td>44</td>
<td>ORR 90%, VGPR 58%, CR 12%</td>
<td>Median PFS 21 months, 3-year OS 80%</td>
</tr>
<tr>
<td>CRd²</td>
<td>23</td>
<td>nCR 82% after 8 cycles, 100% after 16 cycles, sCR 35% after 8 cycles, 78% after 16 cycles</td>
<td>3-year PFS 79.6%, 3-year OS 100%</td>
</tr>
<tr>
<td>CCyd³</td>
<td>58</td>
<td>ORR 95%, VGPR 71% after 9 cycles, nCR 49%, sCR 20%</td>
<td>2-year PFS 76%, 2-year OS 87%</td>
</tr>
</tbody>
</table>

CMP: carfilzomib-melphalan-prednisolone; CRd: carfilzomib-lenalidomide-dexamethasone; CCyd: carfilzomib-cyclophosphamide-dexamethasone

UPDATE IN INDUCTION TREATMENT OF NON-TRANSPLANT ELIGIBLE MM

- Bortezomib and lenalidomide-based regimen
- Carfilzomib-based regimen
- Ixazomib-based regimen
IRD-IXAZIMIB MAINTENANCE IN NEWLY DIAGNOSED MM

- **Phase 1/2 study**: 65 patients (median age 66 years)

- 1-year PFS and OS 88 and 94%, respectively
- Grade 3-4 peripheral neuropathy 6%

Primary therapy for non-transplant candidates

Preferred regimens
- Bortezomib/lenalidomide/dexamethasone (1)
- Lenalidomide/low-dose dexamethasone* (1)
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**Preferred initial treatment in patients with AKI
UPDATE IN INDUCTION TREATMENT OF NON-TRANSPLANT ELIGIBLE MM

- Bortezomib and lenalidomide-based regimen
- Carfilzomib-based regimen
- Ixazomib-based regimen
- Elotuzumab-based regimen
Phase I study: only safety data available

VRd-Elo induction for 8 cycles then dose-attenuated VRd-Elo maintenance

Median patient age 67 years (range 56–79)

The most common AEs

- Fatigue (100%)
- Peripheral sensory neuropathy (83%)
- Edema (83%)
- Lymphopenia (66%) with 1 DLT (grade 4 lymphopenia)
- Leukopenia (50%)

UPDATE IN INDUCTION TREATMENT OF NON-TRANSPLANT ELIGIBLE MM

- Bortezomib and lenalidomide-based regimen
- Carfilzomib-based regimen
- Ixazomib-based regimen
- Elotuzumab-based regimen
- Daratumumab-based regimen
Phase III ALCYONE study: 706 patients

Receive 9 cycles of

- Daratumumab combined with VMP then daratumumab once every 4 weeks until PD
- VMP alone

The study met primary endpoint of improving PFS at a preplanned interim analysis

- Median PFS NR vs. 18.1 months
  (HR = 0.50, 95% CI 0.38–0.65; P < 0.0001)

Data will be presented in ASH 2017

Treatment of elderly MM should be individualized based on patient’s factor (including frailty) and disease’s factor.

Continuous therapy is now recommended more than fixed-duration therapy.

New combination with novel agents are promising for treatment of elderly MM.
CONCLUSIONS

- Treatment of elderly MM should be individualized based on patient’s factor (including frailty) and disease’s factor
- Continuous therapy is now recommended more than fixed-duration therapy
- New combination with novel agents are promising for treatment of elderly MM

Balance between efficacy and toxicity
THANK YOU FOR YOUR ATTENTION