Treatment of elderly patients with multiple myeloma
Improved survival in multiple myeloma and the impact of novel therapies

Kumar et al. Blood 2008;111:2516–2520
MM patients not eligible for transplantation

1. Treatment available (evidence based)

2. Suggestions (ongoing trials)

3. Frail patients
Phase III: Thal/dex vs MP in newly diagnosed MM

- Higher mortality during first year with Thal/dex 28% vs 16%, \( P=0.014 \)
- No significant difference in OS between two maintenance arms
  - Thal/IFN vs IFN: 53.1 months vs not reached, \( P=0.49 \)

<table>
<thead>
<tr>
<th></th>
<th>Thal/dex (n=145)</th>
<th>MP (n=143)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>( \geq ) VGPR</td>
<td>26%</td>
<td>13%</td>
<td>0.0066</td>
</tr>
<tr>
<td>( \geq ) PR</td>
<td>68%</td>
<td>50%</td>
<td>0.0023</td>
</tr>
<tr>
<td>TTP</td>
<td>21.2 months</td>
<td>29.1 months</td>
<td>0.2</td>
</tr>
<tr>
<td>PFS</td>
<td>16.7 months</td>
<td>20.7 months</td>
<td>0.1</td>
</tr>
<tr>
<td>OS</td>
<td>41.5 months</td>
<td>49.3 months</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Overall survival in patients \( \geq 75 \) years old

- Higher mortality during first year with Thal/dex 28% vs 16%, \( P=0.014 \)
- No significant difference in OS between two maintenance arms
  - Thal/IFN vs IFN: 53.1 months vs not reached, \( P=0.49 \)

Gimema: Italian Myeloma Network

Prospective Randomized Trial
Newly Diagnosed MM Patients
Age >65 years

Melphalan Prednisone, Thalidomide (MPT)

versus

Melphalan Prednisone (MP)
MPT vs MP in Elderly Patients with Multiple Myeloma: Event-Free Survival and Overall Survival

**EFS**

49% ↓ in risk of event for MPT

**OS**

65% ↓ in risk of death at >9 mo for MPT

Adapted with permission from Palumbo A et al. *Lancet*. 2006;367:825
RESPONSE TO THERAPY

% CR + VGPR

30
20
10

5% ~5-10%

MP

THALIDOMIDE BORTEZOMIB LENALIDOMIDE

~30-40%

MP + T OR B OR L

DIVISIONE UNIVERSITARIA DI EMATOLOGIA AZIENDA OSPEDALIERA SAN GIOVANNI TORINO, ITALY
## Summary of five MPT Phase III trials conducted in the upfront setting

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>CR+PR (%)</th>
<th>CR (%)</th>
<th>PFS/EFS/TTP</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thal/MP vs MP</td>
<td>129</td>
<td>76</td>
<td>16</td>
<td>21.8 m</td>
<td>45 m</td>
<td>Palumbo et al. Blood 2008; 112:3107–3114</td>
</tr>
<tr>
<td></td>
<td>126</td>
<td>48</td>
<td>4</td>
<td>14.5 m</td>
<td>47.6 m</td>
<td></td>
</tr>
<tr>
<td>Thal/MP vs MP</td>
<td>191</td>
<td>76</td>
<td>13</td>
<td>27.5 m</td>
<td>51.6 m</td>
<td>Facon, et al. Lancet 2007; 370:1209–1218</td>
</tr>
<tr>
<td></td>
<td>124</td>
<td>35</td>
<td>2</td>
<td>17.8 m</td>
<td>33.2 m</td>
<td></td>
</tr>
<tr>
<td>Thal/MP vs MP (&gt;75 y)</td>
<td>113</td>
<td>62</td>
<td>7</td>
<td>24.1 m</td>
<td>44 m</td>
<td>Hulin, et al. JCO 2009 [Epub]</td>
</tr>
<tr>
<td></td>
<td>116</td>
<td>31</td>
<td>1</td>
<td>18.5 m</td>
<td>29.1 m</td>
<td></td>
</tr>
<tr>
<td>Thal/MP* vs MP</td>
<td>363</td>
<td>42</td>
<td>6†</td>
<td>20 m</td>
<td>29 m</td>
<td>Gulbrandsen et al. EHA 2008 (Abstract 209)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>3†</td>
<td>18 m</td>
<td>33 m</td>
<td></td>
</tr>
<tr>
<td>Thal/MP vs MP</td>
<td>152</td>
<td>66</td>
<td>2</td>
<td>EFS 13 m vs 9 m</td>
<td>37 m</td>
<td>Wijermans et al. IMW 2009 (Abstract 116)</td>
</tr>
<tr>
<td></td>
<td>149</td>
<td>47</td>
<td>2</td>
<td>PFS 14 m vs 10 m</td>
<td>30 m</td>
<td></td>
</tr>
</tbody>
</table>

In 5/5 studies, MPT was superior to MP in terms of PFS and/or TTP.
In 2/5 studies, MPT was superior to MP in terms of OS.
VISTA: VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone

- Randomized, international, phase III trial of VMP vs MP in previously untreated patients with symptomatic MM who were not candidates for HDT-ASCT due to age (≥65 yrs) or co-morbid conditions
- Stratification: β₂-microglobulin, albumin, region

**VMP**
- Cycles 1–4
  - Bortezomib 1.3 mg/m² IV: d 1,4,8,11,22,25,29,32
  - Melphalan 9 mg/m² and prednisone 60 mg/m²: d 1–4
- Cycles 5–9
  - Bortezomib 1.3 mg/m² IV: d 1,8,22,29
  - Melphalan 9 mg/m² and prednisone 60 mg/m²: d 1–4

**MP**
- Cycles 1–9
  - Melphalan 9 mg/m² and prednisone 60 mg/m²: d 1–4

9 x 6-week cycles (54 weeks) in both arms

- Primary end point: TTP
- Secondary end points: CR rate, ORR, time to response, DOR, time to next therapy (TNT), OS, QoL (PRO)

**VISTA: Response data**

**Responses according to EBMT criteria**

<table>
<thead>
<tr>
<th></th>
<th>VMP (n=337)</th>
<th>MP (n=331)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥PR)</td>
<td>71%</td>
<td>35%</td>
<td>&lt;10^-6</td>
</tr>
<tr>
<td>CR</td>
<td>30%</td>
<td>4%</td>
<td>&lt;10^-6</td>
</tr>
<tr>
<td>PR</td>
<td>40%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td>9%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>18%</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

**Time to response and duration of response**

<table>
<thead>
<tr>
<th></th>
<th>VMP</th>
<th>MP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to response, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to first response*</td>
<td>1.4</td>
<td>4.2</td>
<td>&lt;10^-10</td>
</tr>
<tr>
<td>Time to CR*</td>
<td>4.2</td>
<td>5.3</td>
<td>&lt;10^-10</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All responders</td>
<td>19.9</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>Patients achieving CR</td>
<td>24.0</td>
<td>12.8</td>
<td></td>
</tr>
</tbody>
</table>

*Medians shown for responding patients; p-values based on total study population


Phase III VISTA: VMP vs MP

Efficacy

Time to progression
52% reduced risk of progression on VMP

Overall survival
~36% reduced risk of death on VMP

- 43% of MP patients received bortezomib upon progression
- Analysis bortezomib >4 cycles: OS at 1 and 2 years: 98.5% and 89%
- Treatment-related death: 2% in both arms

San Miguel et al. ASH 2008 (abstract 650); oral presentation
Therapeutic Algorithm
Level of Evidence 1b (> 1 Randomized Trial)

**Diagnosis**

> 65 years

TD = MP

1 randomized trial

MPT > MP

5 randomized trials *

MPV > MP

1 randomized trial *

MPR ? MP

ASH 2009


* Approved by EMEA
MM patients not eligible for transplantation

1. Treatment available (evidence based)

2. Suggestions (ongoing trials)

3. Frail patients
Phase 1/2: MPR in newly diagnosed MM

- Patients (n=21) median age 69 years

- Treatment:
  - 9 four-week cycles of MPR at MTD:
    - Melphalan 0.18 mg/kg d 1-4
    - Prednisone 2 mg/Kg d 1-4
    - Lenalidomide 10 mg d 1-21
    - Maintenance lenalidomide 10 mg/day for 21 days every 4 weeks

- Results
  - Response data
    - $\geq$ VGPR 47.6%
    - $\geq$ PR 81%
  - Median follow-up 29.5 months:
    - Median TTP 28.5 months
    - Median PFS 28.5 months
    - 2-year OS 90.5%

Palumbo et al. ASH 2008 (abstract 2768); IMW 2009 (abstract 74)
Prospective Randomized Trial
Newly Diagnosed MM Patients
Age >65 years

Melphalan, Prednisone, Lenalidomide (MPR)

versus

Melphalan Prednisone (MP)
Phase III MRC trial: MP vs CTDa

- Patients (n=856)
- Treatment
  - Initial randomization: MP vs CTDa (thal at 100mg/day; dex at 20mg)
  - Maintenance randomization: low-dose thal vs no maintenance
- Results

<table>
<thead>
<tr>
<th></th>
<th>CTDa</th>
<th>MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>82.5%</td>
<td>48.7%</td>
</tr>
<tr>
<td>CR</td>
<td>22.5%</td>
<td>6.2%</td>
</tr>
</tbody>
</table>

- No significant difference in OS between patients receiving thal maintenance vs no maintenance
  - Non-significant benefit seen in terms of PFS
  - Thal maintenance appears to be disadvantageous in patients with 17p-

Owen et al. IMW 2009 (abstract 547), data from abstract
Bortezomib, Melphalan, Prednisone and Thalidomide (VMPT) versus Bortezomib, Melphalan, Prednisone (VMP) in elderly newly diagnosed myeloma patients

Prospective, randomized, phase III study by the Italian Myeloma Network (GIMEMA)

Palumbo et Al. Oral 128 Dic 6 4,55 PM
Study Design

- 511 Patients (≥ 65 years) randomized from 58 Italian Centres
- Protocol amended to change bortezomib from biweekly to weekly infusions

**VMP**
- Cycles 1-9
- Bortezomib 1.3mg/m² IV: days 1, 8, 15, 22*
- Melphalan 9mg/m² and prednisone 60mg/m² days 1-4

**VMPT**
- Cycles 1-9
- Bortezomib 1.3mg/m² IV: days 1, 8, 15, 22*
- Melphalan 9mg/m² and prednisone 60mg/m² days 1-4
- Thalidomide 50mg/day continuously

9 x 5-week cycles in both arms

**NO MAINTENANCE**

Until Relapse

**MAINTENANCE**
- Bortezomib 1.3mg/m² IV: days 1, 15
- Thalidomide 50mg/day continuously

* 64 VMP patients and 71 VMPT patients were treated with twice-weekly infusions of bortezomib

Palumbo et al. EHA 2009: Abstract 472 (Oral presentation)
Best Response

- Median number of cycles in each treatment arm: 5

<table>
<thead>
<tr>
<th></th>
<th>VMPT group (n=221)</th>
<th>VMP group (n=229)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>84%</td>
<td>78%</td>
<td>-</td>
</tr>
<tr>
<td>CR</td>
<td>35%</td>
<td>21%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VGPR</td>
<td>16%</td>
<td>21%</td>
<td>-</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>51%</td>
<td>42%</td>
<td>0.06</td>
</tr>
<tr>
<td>PR</td>
<td>33%</td>
<td>36%</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>9%</td>
<td>18%</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>1%</td>
<td>1%</td>
<td>-</td>
</tr>
</tbody>
</table>

Palumbo et al. EHA 2009: Abstract 472 (Oral presentation)
### Efficacy and toxicity

**Bortezomib twice-weekly versus bortezomib once-weekly infusion**

<table>
<thead>
<tr>
<th></th>
<th>VMPT</th>
<th>VMP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>twice weekly (n=71)</td>
<td>weekly (n=150)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>38%</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Grade 3-4 Peripheral neuropathy</strong></td>
<td>18%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Dose reduction</strong>*</td>
<td>42%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Discontinuation</strong>*</td>
<td>10%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Due to peripheral neuropathy

25 VMPT and 19 VMP patients received both twice- and once-weekly bortezomib

Palumbo et al. EHA 2009: Abstract 472 (Oral presentation)
### Overview of Phase 3 trials in elderly patients with newly diagnosed MM - toxicity

Grade ≥3 toxicity with regimens with novel agents

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>Infections</th>
<th>DVT</th>
<th>PN</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>MPT</td>
<td>129</td>
<td>10%</td>
<td>12%</td>
<td>6%</td>
<td>Palumbo et al. Blood 2008</td>
</tr>
<tr>
<td>MPT</td>
<td>191</td>
<td>17%</td>
<td>12%</td>
<td>8%</td>
<td>Facon et al. Lancet 2007</td>
</tr>
<tr>
<td>VMP VISTA</td>
<td>344</td>
<td>10%</td>
<td>1%</td>
<td>14%</td>
<td>San Miguel VISTA</td>
</tr>
<tr>
<td>VMP PETHEMA</td>
<td>130</td>
<td>na</td>
<td>1%</td>
<td>5%</td>
<td>Mateos ASH 08 (abs 651)</td>
</tr>
<tr>
<td>VMP GIMEMA</td>
<td>116</td>
<td>7%</td>
<td>na</td>
<td>2%</td>
<td>Palumbo ASH 08 (abs 652)</td>
</tr>
</tbody>
</table>

Other relevant toxicities: GI (stipsis, diarrhoea), psychiatric disorders
445 pts

- Len + Dex (RD) x 4 cycles
- Len + Low dose Dex (Rd) x 4 cycles

@ 4 months
Pts can go off study

Less than PR

Thal + Dex x 4 cycles

CR/PR/Stable
Overall Survival: Age ≥65

Logrank p=0.0178

<table>
<thead>
<tr>
<th></th>
<th>No. of Subjects</th>
<th>Event (%)</th>
<th>Censored (%)</th>
<th>Median (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>119</td>
<td>28% (33)</td>
<td>72% (86)</td>
<td>NA (26.94 NA)</td>
</tr>
<tr>
<td>B</td>
<td>114</td>
<td>15% (17)</td>
<td>85% (97)</td>
<td>NA (NA NA)</td>
</tr>
</tbody>
</table>
MM patients not eligible for transplantation

1. Treatment available (evidence based)
2. Suggestions (ongoing trials)
3. Frail patients
Multiple Myeloma

ASL TORINO: 902,000 people

INCIDENCE:
1974: 5.9/100,000
2002: 8.9/100,000

Median age at diagnosis: 69.4 years

65-75 years: 36%
25-64 years: 31%
75-101 years: 33%

Regione Piemonte, Assessorato Sanità 2006
# Early Discontinuation

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>Starting</th>
<th>Early Discontinuation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doses</td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td><strong>MPT¹</strong> Thalidomide</td>
<td>400 mg/d</td>
<td>200 mg/d</td>
<td>45% in 52% pts</td>
</tr>
<tr>
<td><strong>MPT²</strong> Thalidomide</td>
<td>100 mg/d</td>
<td>100 mg/d</td>
<td>41%</td>
</tr>
<tr>
<td><strong>VISTA³</strong> Bortezomib</td>
<td>1.3mg/m²</td>
<td>1.3mg/m²</td>
<td>34%</td>
</tr>
</tbody>
</table>

# Suggested dose reductions

<table>
<thead>
<tr>
<th></th>
<th>65-75 Years</th>
<th>&gt;75 Years</th>
<th>Further Dose Reduction</th>
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</thead>
<tbody>
<tr>
<td><strong>Dexamethasone</strong> weekly</td>
<td>40 mg</td>
<td>20 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td><strong>Melphalan</strong> days 1-4</td>
<td>0.25 mg/kg</td>
<td>0.18 mg/kg</td>
<td>0.13 mg/kg</td>
</tr>
<tr>
<td><strong>Thalidomide</strong> per day</td>
<td>200 mg</td>
<td>100 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td><strong>Lenalidomide</strong>* days 1-21</td>
<td>25 mg</td>
<td>15 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td><strong>Bortezomib</strong></td>
<td>1.3 mg/m²</td>
<td>1.3 mg/m²</td>
<td>1.0 mg/m²</td>
</tr>
</tbody>
</table>

*Note: Lenalidomide dosing is given on a body surface area basis.*
Principal investigators

Clinical studies: A Palumbo

Immunol: M. Massaia
Lab: P. Omedè
Allo transplant: B. Bruno
Mol Biol: M. Ladetto

Investigators: S. Bringhen, F. Cavallo, P. Falco, L. Giaccone,
I. Avonto, F. Gay, M. Gilestro M, A. Larocca, M. Rotta, M. Ruggeri, R. Sorasio, V. Magarotto,
M. Coscia, F. Fiore

Trial office: Marangon Tiziana
Bono Antonella, Fiorillo Antonella, Fornaro Maria Jose, Leotta Federica, Tigano Elena

Fondazione Neoplasie Sangue Onlus (FO.NE.SA.): Perocchio Bruna

GIMEMA - MYELOMA WORKING PARTY