Optimizing treatment of MM with novel agents

Antonio Palumbo, MD
Division of Hematology
University of Torino
Torino, Italy
OS From Time of Diagnosis in 6-yr Intervals Based on Date of Diagnosis

Younger Patients
Novel agents as induction therapy for patients eligible for a transplant

Conventional
- VAD
- ID
- CY + Dex

Thalidomide
- Thal + Dex
- TAD vs VAD
- CTD

Bortezomib
- Vel + Dex
- PAD
- VCD

Lenalidomide
- RD
- Rd

Stem cell harvest
- High-dose melphalan
- Stem cell infusion
IFM2005/01 Study: Bortezomib-Dex vs Vincristine-Doxorubicin-Dex (VAD)

Primary analysis: post-induction response in VAD vs Bortezomib-Dex

Randomization stratified by $\beta_2$-microglobulin level ($>3\text{mg/L vs } \leq 3\text{mg/L}$) and presence of chromosome 13 abnormalities (by FISH analysis)

- **A1**
  - VAD x 4
  - DCEP x 2
  - Melphalan 200mg/m² + ASCT

- **A2**
  - VAD x 4
  - DCEP x 2
  - Melphalan 200mg/m² + ASCT

- **B1**
  - Bortezomib-Dex x 4
  - Melphalan 200mg/m² + ASCT

- **B2**
  - Bortezomib-Dex x 4
  - DCEP x 2
  - Melphalan 200mg/m² + ASCT

**Induction**
**Consolidation**
**Transplant 1**

Second ASCT or RIC allo if <VGPR

Harousseau et al. ASH 2007 (abstract 450); ASCO 2008 (abstract 8505)
### Bortezomib-Dex vs VAD: Responses
Evaluatable patients (Intention-to-Treat (ITT) Analysis)

<table>
<thead>
<tr>
<th></th>
<th>VAD</th>
<th>Bortezomib-Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=219</td>
<td>n=223</td>
</tr>
<tr>
<td><strong>Response after induction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + nCR</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>16%</td>
<td>39%</td>
</tr>
<tr>
<td>≥PR</td>
<td>65%</td>
<td>82%</td>
</tr>
<tr>
<td><strong>Response after first ASCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + nCR</td>
<td>22%</td>
<td>40%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>44%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Response after second ASCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥VGPR</td>
<td>47%</td>
<td>68%</td>
</tr>
</tbody>
</table>

Harousseau et al. ASH 2008
Bortezomib-Thalidomide-Dex (VTD) vs Thalidomide-Dex (TD) (GIMEMA study)

Randomization

Induction
- Bortezomib-Thal-Dex
- Thal-Dex

Induction
- Thal-Dex

PBSC collection
- CTX

Transplantation
- MEL 200
- MEL 200

Consolidation
- Bortezomib-Thal-Dex

Consolidation
- Thal-Dex

Maintenance
- Dex

# Response Rates

<table>
<thead>
<tr>
<th></th>
<th>VTD (%)</th>
<th>TD (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response after induction (n=399)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>21</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR/nCR</td>
<td>33</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \geq ) VGPR</td>
<td>61</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \geq ) PR</td>
<td>92</td>
<td>78.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression</td>
<td>0</td>
<td>4.5</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Responses after ASCT (n=250)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>41</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR/nCR</td>
<td>54</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \geq ) VGPR</td>
<td>75</td>
<td>53</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Superiority of VTD over TD maintained across all sub-group analyses according to standard prognostic factors, including \( \beta_2 \)-m, albumin, stage (ISS), Hb, PLTs, bone marrow PC, M protein isotype, LDH, CRP

_Cavo et al. ASH 2008 (abstract 158); Cavo et al. ASH 2008 (abstract 1662)_
Phase 3: PAD vs VAD as induction treatment
HOVON 65 MM / GMMG-HD4 study

MM Stage II or III, Age 18–65

Randomization

3 x VAD
CAD + GCSF
MEL 200 + PBSCT
Depending on local policy for patients ≥PR
MEL 200 + PBSCT
Thalidomide 50 mg/day for 2 years maintenance

3 x PAD
CAD + GCSF
MEL 200 + PBSCT
Depending on local policy for patients ≥PR
MEL 200 + PBSCT
Allogeneic Tx
Bortezomib 1.3 mg/m² / 2 weeks for 2 years maintenance

Sonneveld et al. ASH 2008 (abstract 653)
### Phase 3: PAD vs VAD as induction treatment

**Response data**

<table>
<thead>
<tr>
<th>Response after induction</th>
<th>PAD (n=150)</th>
<th>VAD (n=150)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/nCR</td>
<td>5%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>42%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>≥ PR</td>
<td>83%</td>
<td>59%</td>
<td></td>
</tr>
</tbody>
</table>

**Responses after first ASCT**

<table>
<thead>
<tr>
<th></th>
<th>PAD (n=150)</th>
<th>VAD (n=150)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/nCR</td>
<td>23%</td>
<td>9%</td>
<td>0.0015</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>80%</td>
<td>50%</td>
<td>0.0019</td>
</tr>
<tr>
<td>≥ PR</td>
<td>93%</td>
<td>80%</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

Sonneveld *et al.* ASH 2008 (abstract 653)
Phase I/II trial of RVD in newly diagnosed MM: trial design and response

Non-randomized, open-label, dose-comparison study

21-Day cycle (maximum 8 cycles)

EBMT response | Patients, %
--- | ---
CR | 26
CR or nCR | 44
≥ VGPR | 74
≥ PR | 100

n = 66 response-evaluable patients; response rates independent of del(13q), t(4;14).

RVD = lenalidomide, bortezomib, dexamethasone.

After a median follow-up of 8 months, median time to progression, progression-free survival, and overall survival were not reached.

The most common adverse events included haematological events and hyperglycaemia.

**EVOLUTION: a phase I study of RVD + cyclophosphamide (RVCD)**

Non-randomized, open-label, dose-comparison study

Day 1 4 8 11 14 15 21

<table>
<thead>
<tr>
<th>Day</th>
<th>B</th>
<th>B</th>
<th>B</th>
<th>B</th>
<th>D</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EBMT response**

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>20</td>
</tr>
<tr>
<td>CR or nCR</td>
<td>36</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>68</td>
</tr>
<tr>
<td>≥ PR</td>
<td>100</td>
</tr>
</tbody>
</table>

25 patients, median age 61 years


B = bortezomib 1.3 mg/m²
D = dexamethasone 40 mg
C = cyclophosphamide 100–500 mg/m²

Lenalidomide 15 mg/day

8 cycles
Therapeutic Algorithm
Level of Evidence 1b (≥ 1 Randomized Trial)

Diagnosis

< 65 years

VD > VAD 1 randomized trial
VTD > VAD 1 randomized trial
Rd > RD 1 randomized trial
PAD Induction, MEL-100, Len/Prednisone Consolidation, and Len Maintenance in Elderly Patients With Newly Diagnosed MM

PAD → MEL-100 → LP → L

PBSC Mobilization (Cyclophosphamide + G-CSF) → MEL-100 ASCT → LP → L

4 cycles 2 cycles 2 cycles 4 cycles

PAD = bortezomib + pegylated doxorubicin + dexamethasone; MEL-100 = melphalan 100 mg/m²; LP = lenalidomide + prednisone; L = lenalidomide

21-day cycle
1 B 4 B 8 B 11 B 21
B = bortezomib 1.3 mg/m²; PLD = pegylated doxorubicin 30 mg/m²; Dex = dexamethasone 40 mg/d *Dex days 1–4, 8–11, 15–18 on cycle 1

28-day cycle
1
Lenalidomide 25 mg/d
Prednisone 50 mg/every other day

28-day cycle
1
Lenalidomide 10 mg/d

Palumbo A et al. Blood. 2008;112:65 [abstract 159]; updated results presented at: 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA
Role of Maintenance After Autologous Transplant

* Per protocol

Consolidation vs maintenance
CLINICAL IMPACT OF VTD CONSOLIDATION STATUS CHANGES DURING CONSOLIDATION:

11 VGPR → CR
3 VGPR → nCR
4 nCR → CR
1PR → PD

Response at study entry (evaluable 39 pts.)
- CR: 64%
- nCR: 13%
- VGPR: 23%

Response after VTD consolidation (evaluable 27 pts.)
- CR: 66%
- nCR: 15%
- VGPR: 4%
- PD: 15%
### VTD: progression-free survival of patients

**PCR negative or positive**

<table>
<thead>
<tr>
<th>Treatment phase</th>
<th>evaluable pts</th>
<th>PCR-neg pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>After ASCT</td>
<td>40</td>
<td>2(5%) (one transient)</td>
</tr>
<tr>
<td>After VTD 4 courses</td>
<td>29</td>
<td>6(21%) (all true MR)</td>
</tr>
</tbody>
</table>

![Graph showing progression-free survival](image)
ASCT vs mini ALLO
Outcome according to presence of HLA-identical siblings (n=162), Median follow up from diagnosis: 45 months, range 21-90

**Overall survival**

- HLA-Id sibling: YES n=80
- HLA-Id sibling: NO

**Event free survival**

- p=0.01
- p=0.02

_B. Bruno et al NEJM 2007_
Elderly Patients
Autologous Stem Cell Transplant in Elderly Patients

Survival Advantage
Age <65 years

Tandem MEL200

Survival Advantage
Age 65-70 years

Tandem MEL100

Survival Advantage
Age 65-75 years

Tandem MEL100

NO Survival Advantage
Age 65-75 years

Tandem MEL100
VMP: The Current Standard of Care in Transplant Ineligible Patients

52% reduced risk of progression
~36% reduced risk of death


VMP = bortezomib/melphalan/prednisone
# VMP: Twice-weekly or weekly infusion?

<table>
<thead>
<tr>
<th></th>
<th>VMP biweekly (N=42)</th>
<th>VMP Mix (N=19)</th>
<th>VMP weekly (N=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>27%</td>
<td>23%</td>
<td>20%</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>14%</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>12%</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>24%</td>
<td>22%</td>
<td>10%</td>
</tr>
</tbody>
</table>
# MPT: The Current Standard of Care in Elderly Patients

## MP-Thal vs MP Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Median PFS, Months</th>
<th>PFS P Value</th>
<th>Median OS, Months</th>
<th>OS P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 1</td>
<td>27.5 vs 17.8</td>
<td>&lt;.0001</td>
<td>51.6 vs 33.2</td>
<td>.0006</td>
</tr>
<tr>
<td>GIMEMA 2</td>
<td>N/A</td>
<td>.0006</td>
<td>N/A</td>
<td>NS</td>
</tr>
<tr>
<td>IFM 3</td>
<td>24.1 vs 19</td>
<td>.001</td>
<td>45.3 vs 27.7</td>
<td>.03</td>
</tr>
<tr>
<td>Nordic 4</td>
<td>16 vs 14</td>
<td>NS</td>
<td>29 vs 33</td>
<td>NS</td>
</tr>
<tr>
<td>Hovon 5</td>
<td>N/A</td>
<td>&lt;.001</td>
<td>N/A</td>
<td>NS</td>
</tr>
</tbody>
</table>

N/A= not available; N.S.= not significant

Low Molecular Weight Heparin vs Warfarin vs ASA Prophylaxis for Thalidomide Regimens

Study Design

Thalidomide regimens (950 pts) Random

ASA
Aspirin 100 mg/day

WAR
Warfarin 1.25 mg/day

LMWH
Enoxaparin 40 mg/day

No Prophylaxis

Rates of VTE

MPT (melphalan/prednisone/thalidomide) vs MPR (melphalan/prednisone/lenalidomide)

**MPT**

Best response

- n = 129*
- CR: 16
- VGPR: 21
- PR: 40
- MR: 5
- SD: 5
- PD: 8
- Patients (%): 37%

**MPR**

Best response

- n = 32^*
- CR: 24
- VGPR: 29
- PR: 33
- MR: 1
- SD: 0
- Patients (%): 53%

**MPR**

Overall survival


VMPT vs VMP
Best Response

VMPT
N=221
Median No. of cycles 5

VMP
N=229
Median No. of cycles 5

% of patients

51%*

42%*

§ P < 0.0001
* P = 0.06

CR
VGPR
PR
SD
PD

CR
VGPR
PR
SD
PD

§
Therapeutic Algorithm
Level of Evidence 1b (> 1 Randomized Trial)

Diagnosis

> 65 years

- MPT > MP: 5 randomized trials
- MPV > MP: 1 randomized trial
- MPR > MP: under evaluation
Risk stratification
Risk stratification in multiple myeloma

- **Some important factors in risk stratification**
  - **Advanced age**
    - Advanced age associated with poor outcome with conventional treatments\(^1\)
  - **Cytogenetic abnormalities**
    - With conventional treatments, a number of chromosomal abnormalities are associated with poor prognosis\(^2\)
  - **Renal impairment/failure**
    - A frequent complication in multiple myeloma

---

Age-Adjusted Therapy

65-75 years
- 36%
- Full dose chemotherapy

75-101 years
- 33%
- Reduced-dose chemotherapy

25-64 years
- 31%
- Autologous transplant

Regione Piemonte, Assessorato Sanità 2006,15
## Age-Adjusted Doses

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

If a grade 3-4 AE occurs: 1. discontinue therapy; 2. wait for grade 1 AE; 3. restart at a lower dose

*Lenalidomide plus melphalan starting dose 10 mg/d

Recommendations by A. Palumbo.
Cytogenetic abnormalities
Bortezomib induction regimens in patients with cytogenetic abnormalities

<table>
<thead>
<tr>
<th></th>
<th>≥VGPR (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bortezomib-dex vs VAD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del (13) (FISH)</td>
<td>n=101</td>
<td>n=103</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>47%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>t(4;14) and/or del(17p)</td>
<td>n=40</td>
<td>n=29</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CR + nCR (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTD vs TD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del (13)</td>
<td>39%</td>
<td>12%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>t(4;14) and/or del(17p)</td>
<td>40%</td>
<td>8.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>del(17p)</td>
<td>27%</td>
<td>0</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Bortezomib induction regimens are effective in terms of response rate in high-risk subgroups, including patients with del (13), t(4;14), and del (17p)

Harousseau et al. ASH 2008 (joint ASH/ASCO symposium)
Cavo et al. ASH 2008 (Abstract 1662)
Retrospective analysis: Lenalidomide/Dex in patients with cytogenetic abnormalities

- **Patients** (n=207) with relapsed/refractory MM
  - 41% del (13), 14% t(4;14), 7% del (17p)

- **Results**

<table>
<thead>
<tr>
<th></th>
<th>del (13)</th>
<th>No del (13)</th>
<th><em>P</em></th>
<th>t(4;14)</th>
<th>No t(4;14)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>43%</td>
<td>71%</td>
<td>&lt;0.001</td>
<td>39%</td>
<td>62%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>5 months</td>
<td>12.5 months</td>
<td>&lt;0.001</td>
<td>5.5 months</td>
<td>10.6 months</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>10.4 months</td>
<td>17.4 months</td>
<td>0.001</td>
<td>9.4 months</td>
<td>15.4 months</td>
<td>0.005</td>
</tr>
</tbody>
</table>

- Hemoglobin (<10 g/dL), progression on thalidomide, and del (13) identified as independent predictors of reduced PFS

Avet Loiseau *et al*. ASH 2008 (Abstract 3685)
Renal impairment in MM
Renal impairment is a frequent complication in MM

• When is fast action needed?
  – Patient with deteriorating renal function with imminent requirement for dialysis
  – Patient with acute renal dysfunction on dialysis

• How should such a patient be managed?
  – Supportive care
  – Fast acting myeloma therapy to remove disease burden
    - Which agent would you choose?
Bortezomib results in reversal of renal failure in a significant proportion of patients

<table>
<thead>
<tr>
<th>Study details</th>
<th>n</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>15</td>
<td>Reversal of renal failure in 80% of patients</td>
<td>Kastritis <em>Haematologica</em> 2007;92:546–549</td>
</tr>
<tr>
<td>Pilot study</td>
<td>8</td>
<td>Reversal of renal failure in 5 out of 8 patients</td>
<td>Ludwig <em>Haematologica</em> 2007;92:1411–1414</td>
</tr>
<tr>
<td>Phase 2</td>
<td>20</td>
<td>Reversal of renal failure in 40%</td>
<td>Roussou <em>Leuk Lymphoma</em> 2008;49:890–895</td>
</tr>
<tr>
<td>Retrospective analysis</td>
<td>64</td>
<td>Reversal of renal impairment in 47%</td>
<td>Gentile ASH 2008 (Abstract 3681)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>40</td>
<td>Significant renal response in 43%</td>
<td>Ludwig et al. ASH 2008 (Abstract 3682)</td>
</tr>
</tbody>
</table>
# IMiDs in patients with renal impairment/failure

## Thalidomide
- Small amount cleared by kidneys\(^1\)
- Pharmacokinetics similar in patients with and without renal failure\(^2\)
- **Use feasible in renal failure**
  - Efficacy and tolerability similar to patients with normal renal function\(^3,4\)
  - Recovery of renal function in most responsive patients

## Lenalidomide
- Primarily **excreted by kidneys**
- Subanalysis of Phase III Len/dex trials\(^5\)
  - Patients with moderate or severe renal impairment respond equally well
- **Increased myelosuppression** in patients with high creatinine levels\(^5,6\)
- **Dose reduction mandatory**\(^7,8\)

---

**IMiDs, immunomodulatory derivatives**

7. Revlimid SmPC January 2009
Salvage therapy
Bortezomib vs Dexamethasone in relapsed MM

Time to progression ($n = 669$)  
78% improvement in median TTP with bortezomib

1-year survival ($n = 669$)

Bortezomib 1.3 mg/m² IV push  
Days 1, 4, 8, 11 Q3W cycle, 8 cycles

Richardson et al. NEJM 2005
Bortezomib + CAELYX vs Bortezomib Monotherapy: Study Design

**Study Design**
- Relapsed or refractory MM
- Phase III, multicenter (123 participating centers)

**Eligibility**
- 2+ lines of therapy
- Bortezomib-naïve
- ECOG 0-1

**Stratify**
- $\beta_2$ microglobulin ($\leq 2.5$, $> 2.5$ but $\leq 5.5$, $> 5.5$)
- Response vs progression to prior treatment

- N = 646
- Bortezomib 1.3 mg/m² days 1, 4, 8, 11 every 21 days
- Bortezomib as above + CAELYX 30 mg/m² on day 4
- Treat until progression, unacceptable toxicity or max. of 8 cycles (unless disease still responding)

Primary endpoint: TTP
Secondary: OS, ORR, safety

Time-to-Progression

P = 0.000004
HR = (95% CI): 1.82 (1.41 to 2.35)

Overall Survival

Survival Rate at 15 months:
CAELYX + Bortezomib: 76%
Bortezomib: 65%


P = 0.0476
HR = (95% CI): 1.406 (1.002 to 1.972)
Len/Dex vs Dex in Relapsed MM (MM09-MM010)

Lenalidomide 25 mg d 1–21
Dex 40 mg d 1–4, 9–12, 17–20

TTP

Survival

Proportion of patients without progression

Time to tumour progression (months)

Cumulative survival

Time (weeks)

Treatment Strategies
Therapeutic Algorithm

COMBINATION

Diagnosis

30 months

Combination regimen

SINGLE

1° Relapse

15 months

Single non cross-resistant agent

SINGLE

2° Relapse

7 months

Single non cross-resistant agent

SINGLE

3° Relapse

3 months

Single n c-res agent
## Therapeutic Algorithm

<table>
<thead>
<tr>
<th></th>
<th>Patients &lt; 65 years</th>
<th>Patients &gt; 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td><strong>Autologous transplant (high-dose melphalan)</strong></td>
<td><strong>Oral melphalan (low-dose melphalan)</strong></td>
</tr>
<tr>
<td>1° Relapse</td>
<td><strong>Dexamethasone</strong></td>
<td><strong>Dexamethasone</strong></td>
</tr>
<tr>
<td>2° Relapse</td>
<td><strong>Doxorubicin</strong></td>
<td><strong>Doxorubicin</strong></td>
</tr>
<tr>
<td>3° Relapse</td>
<td><strong>Cyclophosphamide</strong></td>
<td><strong>Cyclophosphamide</strong></td>
</tr>
</tbody>
</table>
## Possible Therapeutic Algorithm

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Old drug backbone</th>
<th>New drug backbone</th>
<th>Adding new compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>LEN-DEX</td>
<td>VEL-DEX</td>
<td>THAL-DEX</td>
</tr>
<tr>
<td>1° Relapse</td>
<td>BORT-DEX</td>
<td>VEL-DEX DOXORUBICIN</td>
<td>THAL-DEX MELPHALAN</td>
</tr>
<tr>
<td>2° Relapse</td>
<td>THAL-DEX</td>
<td>VEL-DEX MELPHALAN</td>
<td>THAL-DEX MELPHALAN BORTEZOMIB</td>
</tr>
<tr>
<td>3° Relapse</td>
<td></td>
<td>VEL-DEX CYCLOPHOSP.</td>
<td></td>
</tr>
</tbody>
</table>