Current Landscape of Multiple Myeloma Management with a Focus on Novel Therapies

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Historical Perspective of Multiple Myeloma Therapies

- **1962**: High-dose melphalan
- **1983**: Oral melphalan and prednisone
- **1984**: ABMT
- **1986**: VAD
- **1996**: High-dose therapy with autologous stem cell support
- **1999**: Bisphosphonates
- **2000+**: Thalidomide, Proteasome inhibitors, Other immuno-modulatory agents

References:

MULTIPLE MYELOMA
...not just one disease!

- Risk stratification
- Individualization of treatment

3 decades

Drach J, ASH 2012
Importance of Interaction Between Plasma Cells and Bone Marrow for Development of Myeloma

Natural History of Multiple Myeloma: Nearly All Pts Experience Relapse

Novel Agents: Changing the Treatment Landscape of MM (2003-2013)

- Bortezomib, lenalidomide/dex, thalidomide/dex, bortezomib + liposomal doxorubicin, bortezomib + MP, bortezomib/dex, carfilzomib/dex, pomalidomide/dex

- Targeting MM in the BM microenvironment to overcome conventional drug resistance in vitro, in vivo

- Effective in relapsed/refractory MM

- Effective as induction/first-line therapy

- Emerging role of transplant/maintenance
Continued Improvement in Survival Since the Introduction of Novel Agents

- 1,056 pts grouped into 2001–2005 and 2006–2010 cohorts
- Survival improved over time, particularly in pts aged > 65 years (p = 0.001)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Median OS, years</td>
<td>4.6</td>
<td>NR</td>
<td>0.001</td>
</tr>
<tr>
<td>1-year survival, %</td>
<td>83</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>5-year estimated OS, %</td>
<td>Overall</td>
<td>&lt; 65 years</td>
<td>&gt; 65 years</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>63</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>73</td>
<td>NS</td>
</tr>
</tbody>
</table>

Progress and Challenges in the Treatment of MM

- **Progress**
  - Better understanding of disease biology
  - Significant improvements in outcome due to availability of new effective therapies
    - Potential for MM to become a chronic disease in some pts
  - Learnings in the management of adverse events, comorbidities, handling of novel agents

- **Challenges**
  - MM remains incurable in majority of pts
  - Increasing symptom burden due to disease and cumulative effects of treatments
  - Managing balance of disease control and quality of life
Advances in the Understanding of the Biology of MM
Initiation and Progression of MM

Initiation

Germinal centre
Post-germinal-centre B cell

Progression

Bone marrow
MGUS
Smouldering myeloma
Myeloma
Peripheral blood
Plasma cell leukaemia

Inherited variants
Primary genetic events:
- IGH@ translocations
- Hyperdiploidy

Secondary genetic events:
- Copy number abnormalities
- DNA hypomethylation
- Acquired mutations

Competition selection for bone marrow niche

Clonal advantage

Migration and founder effect

Tumour cell diversity

Genetic lesions
Clonal Architecture at Diagnosis and Relapse: Clonal Tides Instead of Linear Evolution

![Diagram showing clonal architecture at diagnosis and relapse.](image-url)

Bahlis et al. Blood 2012;120:1077-1086
Rational Combination Strategies in Relapsed Refractory MM

Lonial S, Mitsiades CS, Richardson PG. Clin Cancer Res 2011;17:1264-1277
Incorporating Novel Agents Into Treatment Strategies for Young Pts
Frontline Treatment

Candidate for ASCT?

Yes

Induction

Bort-based
Bort/dex, VTD, PAD, TT3, VCD, VRD

IMiD-based
Thal/dex, TAD, CTD, VTD, TT3, Rd, VRD

Stem cell harvest
High-dose melphalan
Stem cell infusion

≥VGPR

Yes

No TX

Consolidation
Thal, VTD, len?

No

Consolidation
Thal, other combo?

No

2nd SCT

Consolidation
Thal, other combo?

Yes

Bort based
• VMP

IMiD-based
MPT, CTDa, Rd, MPR

No

Consolidation
Thal, other combo?

Elderly and frail

Low-dose tx
MPT, bort, MP, dex, len/dex, CDTa, cyc/pred

Fit or frail?

Fit

Specific complication

Yes

Renal: bort-based
VTE/PE: bort-based
Poor-risk cytogenetics: bort or len-based
PN: len-based

No

IMiD-based
MPT, CTDa, Rd, MPR

Elderly and frail

Low-dose tx
MPT, bort, MP, dex, len/dex, CDTa, cyc/pred

Fit or frail?

No

Stem cell harvest
High-dose melphalan
Stem cell infusion

≥VGPR

Yes

No TX

Consolidation
Thal, VTD, len?

No

2nd SCT

Consolidation
Thal, other combo?

Combinations in the Upfront Treatment of MM

Stewart AK, Richardson PG, San Miguel JF  *Blood* 2009
Novel Agent-based Induction Therapies

<table>
<thead>
<tr>
<th>2-drug combinations</th>
<th>3-drug combinations</th>
<th>4-drug combinations</th>
<th>New agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide-based</td>
<td>Lenalidomide-based</td>
<td>Bortezomib-based</td>
<td>Bortezomib + IMiD-based</td>
</tr>
<tr>
<td>TD</td>
<td>RD</td>
<td>VD</td>
<td></td>
</tr>
<tr>
<td>Rd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAD</td>
<td>RAD</td>
<td>PAD</td>
<td>VTD</td>
</tr>
<tr>
<td>CTD</td>
<td>RCD</td>
<td>VCD</td>
<td>RVD</td>
</tr>
<tr>
<td>BiRD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*CfzTD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CfzRd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>**RId</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>***R2V2</td>
</tr>
</tbody>
</table>

* Cfz: carfilzomib; ***R2V2: RVD + vori; **RId: lenalidomide, ixazomib (mln 9708), dex
Impact of Upfront New Drug-containing Regimens in the Setting of High-dose Therapy

Recommended Induction Regimens: EU Perspective

Induction with

3-drug regimens
Bortezomib/dex + IMiD/alklyator/anthracycline
VTD* / VRD
VCD
PAD*
CTD*

2-drug regimens
Bortezomib/dex*
RD/Rd

Stem cell harvest (G-CSF, Chemo?)
High-dose melphalan (1? 2?)
→ Stem cell infusion

Strong preference for 3-drug regimens

*Data available from Phase III randomized clinical trials

Ludwig et al. The Oncologist 2012; 17(5):592-606
Consolidation and Maintenance: Questions / Considerations

- Do novel agents containing consolidation regimens improve the depth of response?

- Does the administration of consolidation or maintenance therapy result in an improvement in overall outcome, i.e. PFS, OS?

- What is the impact of prolonged therapy regarding tolerability, quality of life, treatment at relapse?
Novel Agent-containing Consolidation Therapy Improves Depth of Response and Prolongs PFS

- **Bortezomib monotherapy (Nordic Myeloma Study Group [NMSG 15/05] trial)**
  - Significant improvement in PFS with bortezomib consolidation compared to control: 27 versus 20 mos, p=0.037

- **VTD versus TD (GIMEMA trial)**
  - VTD consolidation significantly increased CR and CR/nCR rates versus TD
  - Median PFS significantly longer for VTD versus TD: 56 versus 42 mos, p=0.001

Mellqvist et al. Haematologica 2011; 96 (s1): S31 (Abstract O-11); oral presentation at IMW 2011
Cavo et al. ASH 2012 (Abstract 4210), poster presentation
## Lenalidomide and Bortezomib/
Lenalidomide-based Consolidation

### Study details

**IFM 2005-02**
- Len consolidation (2 mos)
- Maintenance randomization: Len vs placebo

**IFM 2008**
- VRD induction
- ASCT
- VRD consolidation (2 cycles)
- Len maintenance

### Response data

<table>
<thead>
<tr>
<th>n=572</th>
<th>Pre-consolidation</th>
<th>Post-consolidation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR (IF⁻)</td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>≥ VGPR</td>
<td>58%</td>
<td>67%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n=31</th>
<th>Post-induction</th>
<th>Post-ASCT</th>
<th>Post-consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sCR</td>
<td>17%</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>VGPR</td>
<td>39%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Consolidation: upgraded response in 26%

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1Attal et al. Haematologica 2011; 96 (s1): S23; oral presentation at IMW 2011
2Roussel et al. ASH 2011 (Abstract 1872), poster presentation
## Thalidomide Maintenance Therapy

<table>
<thead>
<tr>
<th></th>
<th>Significant improvement in PFS with maintenance therapy</th>
<th>Significant improvement in OS with maintenance therapy</th>
<th>Survival after relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>Yes</td>
<td>Yes (3 yrs follow up)</td>
<td>Similar in all groups</td>
</tr>
<tr>
<td>Attal</td>
<td>Yes</td>
<td>Yes (@ 39 m), but OS advantage disappeared with longer follow-up (5.7 yrs)</td>
<td>Similar in all groups</td>
</tr>
<tr>
<td>Barlogie</td>
<td>Yes</td>
<td>Yes (7.2 yrs follow-up)</td>
<td>Reduced OS after thal exposure</td>
</tr>
<tr>
<td>Lokhorst</td>
<td>Yes</td>
<td>No</td>
<td>Reduced OS after thal exposure</td>
</tr>
<tr>
<td>Morgan</td>
<td>Yes</td>
<td>No</td>
<td>Reduced OS after thal exposure</td>
</tr>
<tr>
<td>Stewart</td>
<td>Yes</td>
<td>No</td>
<td>Reduced OS after thal exposure</td>
</tr>
</tbody>
</table>

# Lenalidomide Maintenance Therapy

<table>
<thead>
<tr>
<th>Study details</th>
<th>n</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 2005-02(^1)</td>
<td>307</td>
<td>Lenalidomide</td>
<td>PFS 41 mos, 4-yr OS 73%</td>
</tr>
<tr>
<td>Median follow-up:</td>
<td>307</td>
<td>Placebo</td>
<td>23 mos, p&lt;0.001, 75%, p=ns</td>
</tr>
<tr>
<td>45 mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB 100104(^2)</td>
<td>231</td>
<td>Lenalidomide</td>
<td>TTP 46 mos, Deaths n=35</td>
</tr>
<tr>
<td>Median follow-up:</td>
<td>229</td>
<td>Placebo</td>
<td>27 mos, p&lt;0.001, n=53, p=0.03</td>
</tr>
<tr>
<td>34 mos</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Occurrence of secondary primary malignancies (SPMs) requires monitoring

Phase 3: PAD vs VAD Induction, HDM and Bortezomib or Thalidomide Maintenance
HOVON 65 MM / GMMG-HD4 Study

PFS

Progression-Free Survival (%)

Time (months)

OS

Overall Survival (%)

Time (months)

Post-ASCT Maintenance: VT versus Thal Versus Interferon alfa2b (PETHEMA/GEM study)

Median follow-up: 34.9 mos

PFS from maintenance

<table>
<thead>
<tr>
<th></th>
<th>IFN</th>
<th>Thal</th>
<th>VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>90</td>
<td>87</td>
<td>89</td>
</tr>
</tbody>
</table>

**PFS**

- **overall group**: Significant benefit for VT, p=0.0009
- **pts with high-risk MM**: PFS poor for all arms
- **pts with standard-risk MM**: Significant benefit with VT, p=0.02

**OS**

- **overall group**: No significant difference between arms, p=0.47
- **pts with high-risk MM**: Poor for all arms

IFN: Interferon-α2b

Rosinol et al. ASH 2012 (Abstract 334), oral presentation
Second Primary Malignancies (SPMs)

- **Lenalidomide**\(^1\)-\(^5\)
  - Increase in SPMs with maintenance noted
  - Benefit-risk balance remains positive
  - Risk of SPMs must be taken into account before initiating treatment

- **Bortezomib**\(^6,7\)
  - No increased risk of SPM with bortezomib maintenance observed (PAD induction, HDM, bortezomib maintenance [HOVON/GMMG study])
  - No increased risk of SPMs with addition of bortezomib to MP

4. Palumbo et al. ASH 2011; Abstract 996
What is the Role of Transplantation in MM in the Era of Novel Agents?

Could ASCT be Delayed for Some Pts?
Early Versus Delayed ASCT after IMiD-based Induction Therapy

Retrospective analysis

- Patients (n=290)
- Treatment
  - TD or RD induction
  - Early ASCT: ASCT within 2 months of SC harvest and 12 months of diagnosis (n=173)
  - Delayed ASCT: ASCT > 12 months after diagnosis (n=112; n=42 at current report)
- Results
  - 4-year OS: 73% in both groups
  - TTP: early ASCT 20 months, delayed ASCT 16 months, p=ns

Benefit of early transplantation in ECOG trial

Post-hoc retrospective analysis

• Patients < 65 years, who survived first four cycles of therapy

• Results
  – OS at 3-years
    • Early ASCT: 94%
    • Continued protocol therapy (RD or Rd): 78%

  – However, no randomized comparison

Siegel et al. Blood 2010; 116(21); Abstract 38; oral presentation at ASH 2010
Phase 3: MPR versus Tandem ASCT

Induction

n=402
Rd (four 28-d cycles)
Lenalidomide 25 mg/d, d1-21
Low-dose dex 40mg/d, d 1,8,15,22

Randomize

Consolidation

n=202
MPR (six 28-d cycles)
Melphalan 0.18 mg/kg/d, d 1-4
Prednisone 2 mg/kg/d, d 1-4
Len 10 mg/d, d 1-21

Randomize

Maintenance

n=200
MEL 200
Tandem Mel 200mg /m² plus stem cell support

Randomize

No maintenance

Maintenance
Len 10 mg/d, d 1-21
28-d course until relapse

Primary end point: PFS

Palumbo et al. ASH 2011 (Abstract 3069), poster presentation
Phase 3: MPR versus Tandem ASCT

- Pts (n=402) with newly diagnosed MM
- Treatment
  - Len / low-dose dex induction
  - Randomization: MPR vs tandem ASCT
  - Randomization: Maintenance Len until PD vs no maintenance
- Median follow up 26 mos

<table>
<thead>
<tr>
<th></th>
<th>MPR (n=202)</th>
<th>MEL 200 (n=200)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>20%</td>
<td>25%</td>
<td>0.49</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>60%</td>
<td>58%</td>
<td>0.24</td>
</tr>
<tr>
<td>2-yr PFS</td>
<td>54%</td>
<td>73%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-yr OS</td>
<td>87%</td>
<td>90%</td>
<td>0.19</td>
</tr>
<tr>
<td>Gr 3/4 neutropenia</td>
<td>55%</td>
<td>89%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gr 3/4 infections</td>
<td>0%</td>
<td>17%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gr 3/4 GI toxicity</td>
<td>0%</td>
<td>21%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DVT</td>
<td>2.44%</td>
<td>1.13%</td>
<td>0.43</td>
</tr>
<tr>
<td>Second tumors</td>
<td>0.5%</td>
<td>1.5%</td>
<td>0.12</td>
</tr>
</tbody>
</table>
IFM/DFCI 2009 Phase 3 Study
Newly Diagnosed MM (SCT candidates; n=1000)

Randomize

- RVDx3

Induction

- CY (3g/m2)
- MOBILIZATION
  - Goal: $5 \times 10^6$ cells/kg

- Melphalan
  - 200mg/m$^2$ +
  - ASCT

- RVD x 2

Collection

- RVDx3

- CY (3g/m2)
- MOBILIZATION
  - Goal: $5 \times 10^6$ cells/kg

Consolidation

- RVD x 5

Maintenance

- Lenalidomide

- SCT at relapse
Novel Agents Alone versus Intensive Therapy + Novel Agents: European Intergroup Trial

Registration
Induction
Stem cell mobilization in all pts

Consolidation
Maintenance until relapse

Incorporating Novel Agents into Treatment Strategies for Elderly Pts
Progress in the Treatment of Elderly Pts with MM
Novel Agent Combinations: PFS and OS Data

<table>
<thead>
<tr>
<th>Combination</th>
<th>Median PFS (mos)</th>
<th>Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP&lt;sup&gt;1&lt;/sup&gt;</td>
<td>11–20</td>
<td>29</td>
</tr>
<tr>
<td>BP&lt;sup&gt;2&lt;/sup&gt;</td>
<td>14*</td>
<td>32</td>
</tr>
<tr>
<td>MPT&lt;sup&gt;3-8&lt;/sup&gt;</td>
<td>15–27.5</td>
<td>29–51.6</td>
</tr>
<tr>
<td>CTDa&lt;sup&gt;9&lt;/sup&gt;</td>
<td>13</td>
<td>33.2</td>
</tr>
<tr>
<td>VMP&lt;sup&gt;10,11,14&lt;/sup&gt;</td>
<td>21.7–27.4</td>
<td>56.4</td>
</tr>
<tr>
<td>MPR-R&lt;sup&gt;12&lt;/sup&gt;</td>
<td>31</td>
<td>N/A</td>
</tr>
<tr>
<td>VMP-VT/VP&lt;sup&gt;13&lt;/sup&gt;</td>
<td>35</td>
<td>74% (3-yr OS)</td>
</tr>
<tr>
<td>VMPT-VT&lt;sup&gt;14&lt;/sup&gt;</td>
<td>35.3</td>
<td>61% (5-yr OS)</td>
</tr>
</tbody>
</table>

*TTF: time to treatment failure

<sup>1</sup>MTCG. J Clin Oncol 1998;16(12):3832-42
<sup>3</sup>Palumbo et al. Blood 2008; 112:3107–3114
<sup>4</sup>Facon et al. Lancet 2007; 370:1209–1218
<sup>6</sup>Waage et al. Blood 2010; 116:1405-12
<sup>7</sup>Wijermans et al. J Clin Oncol 2010; 28:3160-6
<sup>9</sup>Morgan et al. Blood 2011;118:1231-8
<sup>11</sup>San Miguel et al. ASH 2011 (Abstract 476), oral presentation
<sup>13</sup>Mateos et al. Blood 2012;120(13):2581-8
<sup>14</sup>Palumbo et al. ASH 2012 (Abstract 200), oral presentation
### VMPT vs VMP in Elderly Patients With Newly Diagnosed MM

<table>
<thead>
<tr>
<th></th>
<th>VMP (N=253)</th>
<th>VMPT → VT (N=250)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>81%</td>
<td>89%</td>
<td>0.01</td>
</tr>
<tr>
<td>CR</td>
<td>24%</td>
<td>38%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFS @ 3 years</td>
<td>32%</td>
<td>51%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS @ 3 years</td>
<td>89%</td>
<td>89%</td>
<td>0.77</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>PN*</td>
<td>5%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Discontinuations</td>
<td>17%</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>

*PN reduction moving from twice weekly to weekly: 14% vs 2%, and discontinuations due to PN 16% vs 4%*
# Maintenance with VMPT-VT Improves Survival vs. VMP in Transplant-Ineligible NDMM

<table>
<thead>
<tr>
<th>5-Year OS, %</th>
<th>VMPT-VT</th>
<th>VMP</th>
<th>HR (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>59.3</td>
<td>45.9</td>
<td>0.74 (.04)</td>
</tr>
<tr>
<td>Aged &lt; 75 years</td>
<td>67.8</td>
<td>49.9</td>
<td>0.63 (.01)</td>
</tr>
<tr>
<td>Patients in CR</td>
<td>81.4</td>
<td>48.2</td>
<td>0.38 (.006)</td>
</tr>
</tbody>
</table>

Panel A. All patients

Panel B. Patients aged 65-75

Panel C. Patients achieving CR after induction

Palumbo et al, ASH 2012
What have we Learnt regarding the Management of Novel Agent Combos in the Elderly Population?

• Heterogeneous group
  – Fit versus frail
  – Comorbidities
  – Disability

• Treatment tolerability key issue
  – Phase 3 trial Thal/dex vs MP in elderly pts: toxic effects of therapy much greater in pts aged >75 yrs\(^1\)

• Need to tailor treatment according to patient status / preference
  – Dose reduction / modification
  – Schedule changes

\(^1\)Ludwig et al. Blood 2009;113(15):3435-42
Considerations when Treating Elderly Pts

- **Decrease in functional capacity**: performance status, activities of daily living, cognitive function
- **Comorbidity** (renal, pulmonary, hepatic, cardiac, bone marrow insufficiency, polyneuropathy)
- **Disability**
- **Frailty** (weakness, poor endurance, weight loss, low physical activity, slow gait speed)
- **Increased prevalence of unfavorable prognostic factors** ($\beta_2M \geq 3.5 \mu g/mL$, albumin $< 3.5 \text{ g/dL}$, Hb $< 10 \text{ g/dL}$, ISS stage III)$^1$
- **Polypharmacy**
- **Decreased capacity to tolerate toxicity**

Ludwig et al. J Clin Oncol 2010;28(9):1599-605
Recommendations

• **Assess**
  – Biological age
  – Comorbidities
  – Frailty (‘full go’, ‘slow go’, very slow or no go’)
  – Disability
    → Degree of functional impairment

• **Select most appropriate drug regimen**
  – Adapt doses if required

• **Optimize supportive care**
  – Bisphosphonates, antibiotics, antivirals, anticoagulants, growth factors, pain control
Strategies to Improve Tolerability

- Need to tailor treatment according to patient status / preference
  - Dose reduction / modification
  - Schedule changes
  - Route of administration, e.g. subcutaneous bortezomib
Improving Tolerability with Dose Reduction

- **VD versus vtD as induction treatment prior to ASCT**
  - Significantly reduced incidence of PN with vtD
    - Grade ≥ 2 PN: 34% VD arm vs 14% vtD (P=0.001)

- **Low-dose versus high-dose thalidomide for advanced MM**
  - 100 mg/d better tolerated than 400 mg/d
    - Significantly lower rates of high-grade somnolence, constipation, nausea/vomiting and PN

- **Len 15 mg / Dex 20 for relapsed MM > 75 yrs of age**
  - 45 pts, ORR : 65%, PFS 14 mos

## Dose Adjustment Recommendations for the Treatment of Frail Elderly Pts

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose level  0</th>
<th>Dose level  – 1</th>
<th>Dose level  – 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² twice / wk d 1,4,8,11 / 3 wks</td>
<td>1.3 mg/m² once / wk d 1,8,15,22 / 5 wks</td>
<td>1.0 mg/m² once / wk d 1,8,15,22 / 5 wks</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>100 mg/d</td>
<td>50 mg/d</td>
<td>50 mg qod</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg/d d 1-21 / 4 wks</td>
<td>15 mg/d d 1-21 / 4 wks</td>
<td>10 mg/d d 1-21 / 4 wks</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg/d d 1,8,15,22 / 4 wk</td>
<td>20 mg/d d 1,8,15,22 / 4 wk</td>
<td>10 mg/d d 1,8,15,22 / 4 wk</td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.25 mg/kg d 1-4 / 4-6 wks</td>
<td>0.18 mg/kg d 1-4 / 4-6 wks</td>
<td>0.13 mg/kg d 1-4 / 4-6 wks</td>
</tr>
<tr>
<td>Prednisone</td>
<td>50 mg qod</td>
<td>25 mg qod</td>
<td>12.5 mg qod</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>100 mg/d d 1-21 / 4 wks</td>
<td>50 mg/d d 1-21 / 4 wks</td>
<td>50 mg qod d 1-21 / 4 wks</td>
</tr>
</tbody>
</table>

**Bortezomib 1x Versus 2x per Week**
Reduction in toxicity and discontinuation of therapy without loss of efficacy

<table>
<thead>
<tr>
<th>Study details</th>
<th>Efficacy</th>
<th>Grade 3/4 Sensory PN</th>
<th>Discont. due to PN</th>
<th>Discont. due to AEs overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
<td>Median PFS</td>
<td>3-yr OS</td>
<td></td>
</tr>
<tr>
<td><strong>VMP with twice-wkly bortezomib administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VISTA&lt;sup&gt;1-3,7&lt;/sup&gt;</td>
<td>30%</td>
<td>21.7m</td>
<td>68.5%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>VMP with once-wkly bortezomib administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIMEMA&lt;sup&gt;4,5,7&lt;/sup&gt;</td>
<td>23%</td>
<td>27m</td>
<td>87%</td>
<td>2%</td>
</tr>
<tr>
<td>PETHEMA/GEM&lt;sup&gt;6,7&lt;/sup&gt;</td>
<td>20%</td>
<td>34m</td>
<td>74%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*3% discontinued VMP; 11% selectively discontinued bortezomib due to PN

1. San Miguel et al. NEJM 2008; 359: 906-917
7. Mateos et al. Haematologica 2011; 96 (s1): S81 (Abstract P-175); poster presentation at IMW 2011
## Bortezomib IV Versus SC

- 222 pts with relapsed and/or refractory MM
- Bortezomib given at conventional dose and scheme

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib IV (n=73)</th>
<th>Bortezomib SC (n=145)</th>
</tr>
</thead>
</table>
| **Primary endpoint: response after 4 / 8cycles**
  (single agent bortezomib or +/-dex) |                      |                        |
| ORR              | 42% / 52%             | 42% / 52%              |
| CR               | 8% / 12%              | 6% / 10%               |
| TTP              | 9.4 m                 | 10.4 m                 |

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bortezomib IV</th>
<th>Bortezomib SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade ≥3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peripheral Neuropathy</strong></td>
<td>53%</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*P=0.04 and 0.03

Comparable pharmakokinetic data

Arnulf et al. Haematologica 2012;97(12):1925-8
Treatment at Relapse
Clinical Factors When Choosing Therapy for Relapsed Disease

- Comorbid conditions
- Previous therapy
- Time from previous therapy
- Mode of drug administration
- Risk profile
- Potential role of second ASCT or allo-SCT

Consider ASCT

Considering frontline treatment with novel agent?

Yes

Repeat or change frontline treatment

No

Use novel agent

Repeat remission after:
- Long remission
- No toxicity concerns from first-line tx

Switch class after:
- Short remission
- Toxicity concern from previous line

IMiDs® based
- Len + Dex
- Thal ± Dex
- CTD

Bort based
- Bort ± Dex
- Bort/PegLD
- VCD

Bort + IMiDs® based
- VMPT
- VRD

Considerations in case of special complications:

Renal Impairment:
- Bortezomib based
- Thalidomide based
- Lenalidomide based (dose modification)

Current or recent VTE or CV event:
- Bortezomib based
- Lenalidomide based

Treatment related PN:
- Lenalidomide based

Frontline consisted of:

Thal-based regimen (eg, MPT, CTD)

Bort-based regimen (eg, MPV, VD)

Dual Refractory Disease

Pts Relapsing and Refractory to Bortezomib and Thalidomide or Lenalidomide

Median EFS 5 mos
Median OS 9 mos

N = 286

### Preferred Regimens

- Repeat primary induction therapy (if relapse at > 6 mo)
- Bortezomib (cat. 1)
- Bortezomib / dex
- Bortezomib / lenalidomide / dex
- Bortezomib / liposomal doxorubicin (cat. 1)
- Bortezomib / thalidomide / dex
- Carfilzomib
- Cyclophosphamide / bortezomib / dex
- Cyclophosphamide / lenalidomide / dex
- Dex / cyclophosphamide / etoposide / cisplatin (DCEP)
- Dex / thalidomide / cisplatin / doxorubicin / cyclophosphamide / etoposide (DT-PACE) ± bortezomib (VTD-PACE)
- High-dose cyclophosphamide
- Lenalidomide / dex (cat. 1)
- Pomalidomide / dex
- Thalidomide / dex

### Other Regimens

- Bendamustine
- Bortezomib / vorinostat
- Lenalidomide / bendamustine / dex

---

*Consideration for appropriate regimen is based on the context of clinical relapse.

1 Indicated for patients who have received at least two prior therapies including bortezomib and an IMiD and have demonstrated disease progression on or within 60 days of completion of the last therapy.

2 Consider single agent lenalidomide, pomalidomide, or thalidomide for steroid-intolerant individuals.

[http://www.nccn.org](http://www.nccn.org)
## Selected Novel Agents Currently Available and/or Under Investigation for RR MM

<table>
<thead>
<tr>
<th>Class</th>
<th>First generation</th>
<th>Next generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunomodulatory drugs</td>
<td>Lenalidomide (p.o.)</td>
<td>Pomalidomide (p.o.)</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>Bortezomib (i.v./s.c.)</td>
<td>Carfilzomib (i.v.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marizomib [NPI-0052] (i.v.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ixazomib [MLN9708] (p.o.)</td>
</tr>
<tr>
<td>Others including:</td>
<td>Elotuzumab, Daratumumab</td>
<td></td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>Vorinostat, Panobinostat, Romidepsin, AC1215</td>
<td></td>
</tr>
<tr>
<td>HDAC Inhibitors</td>
<td>Bendamustine, others (TH 302, melflufen)</td>
<td></td>
</tr>
<tr>
<td>Alkylating Agents</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pomalidomide in Myeloma

MM cells

Bone Marrow Stromal Cells

Bone Marrow Vessels

Dendritic Cells

NK Cells

NK-T Cells

LeBlanc R et al. Blood 103: 1787, 2004

VEGF
bFGF

ICAM-1

IL-6
TNFα
IL-1β

PI3K
PKCζ
NFAT

CD28

IL-2

CD8+ T Cells

IFNγ

IL-2

NK Cells

NK-T Cells
Pomalidomide: Background

- Pomalidomide is a distinct oral immunomodulatory drug with significant anti-myeloma activity *in vitro*\(^1,2\)
- Pomalidomide has demonstrated promising activity in patients with relapsed/refractory multiple myeloma\(^3\)
- When combined with low-dose dexamethasone, Pomalidomide has clinical efficacy in RRMM patients previously treated with lenalidomide and/or bortezomib\(^4-6\)

---

Phase 2 Trial of Pomalidomide + Low-Dose Dex (MM-002): Study Design

- **Primary endpoint:** PFS
- **Secondary endpoints:** ORR, DoR, OS, and safety

*Pts aged > 75 yrs had a DEX starting dose of 20 mg/wk.

Pomalidomide + Low-Dose Dex (MM-002): Response Rates

- Median number of cycles received: 5 (range: 1–28)
- Disease control (≥ SD) was observed in 81% of patients

Updated data presented at ASH 2012.
Pomalidomide + Low-Dose Dex (MM-002): Survival Outcomes

- There was no significant difference in OS:
  - POM + LoDEX: 16.5 mos; POM*: 13.6 mos (HR = 0.92; p = 0.609)

Updated data presented at ASH 2012.

* LoDEX added for 64 patients (59%).
Phase 3 trial of Pomalidomide + Low-Dose Dex versus High-Dose Dex (MM-003)

- Primary endpoint: PFS
- Key secondary endpoints: OS, ORR (≥ PR), DoR, safety

N = 455
- Age ≥ 18 yrs
- ≥ 2 prior therapies
- Refractory to last treatment
- Refractory, intolerant or relapsed ≤ 6 mos (if ≥ PR) to BORT and LEN

POM + LoDEX (n = 302):
POM: 4 mg, d1–21
LoDEX: 40 mg (≤ 75 y) or 20 mg (> 75 y), d1, 8, 15, 22
28-day cycles

HiDEX (n = 153):
HiDEX: 40 mg (≤ 75 y) or 20 mg (> 75 y)
d1–4, 9–12, 17–20
28-day cycles

Follow-up for OS and SPM until 5 years post-enrollment

Companion trial MM-003C
POM 21/28 days

Updated data presented at ASH 2012.
Pomalidomide + Low-dose Dex (MM-003): Progression-Free Survival

**ITT population**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEX (n = 302)</td>
<td>3.6 months</td>
</tr>
<tr>
<td>HiDEX (n = 153)</td>
<td>1.8 months</td>
</tr>
</tbody>
</table>

HR = 0.45  
*p < 0.001*

**LEN- and BORT-refractory**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEX (n = 221)</td>
<td>3.2 months</td>
</tr>
<tr>
<td>HiDEX (n = 108)</td>
<td>1.7 months</td>
</tr>
</tbody>
</table>

HR = 0.48  
*p < 0.001*

Updated data presented at ASH 2012.

ITT: intent-to-treat.
Pomalidomide + Low-Dose Dex (MM-003): overall survival

ITT population*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEX (n = 302)</td>
<td>NR (11.1–NE)</td>
<td>0.53</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HiDEX (n = 153)</td>
<td>7.8 months (5.4–9.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LEN- and BORT-refractory*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEX (n = 221)</td>
<td>NR (8.5–NE)</td>
<td>0.56</td>
<td>0.003</td>
</tr>
<tr>
<td>HiDEX (n = 108)</td>
<td>7.4 months (4.3–9.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Updated data presented at ASH 2012.

* 29% of pts received POM after progressing on HiDEX. ITT: intent-to-treat
Carfilzomib: A Novel Proteasome (Chymotryptic) Inhibitor

- Novel chemical class with highly selective irreversible proteasome binding
- Minimal neurotoxicity in animals
- Durable responses in relapsed and relapsed, refractory MM (ORR 23%) with reduced neuropathy (G1-2 15%, G3 1%)
- Carfilzomib Lenalidomide Dex versus Lenalidomide Dex ongoing (phase III trial for new drug approval – ASPIRE Study)
- Escalating dose trials in relapsed MM and combination trial with Len Dex as initial therapy promising (CRd in ND MM: ORR 94%, Jakubowiak et al, Blood 2012)

Efficacy Results of Carfilzomib in RRMM Across Phase 2 Studies (Response Rate)

Direct comparisons across studies are not possible, given differences in study design and patient populations.

Safety Profile of Carfilzomib from the 003-A1 Study

Incidence and severity of treatment-emergent adverse events (≥ 25%) and carfilzomib-related adverse events (n = 266)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>All grades, n (%)</th>
<th>Grades 3 or 4, n (%)</th>
<th>All grades carfilzomib-related, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>122 (46)</td>
<td>63 (24)</td>
<td>59 (22)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>103 (39)</td>
<td>77 (29)</td>
<td>77 (29)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>62 (23)</td>
<td>52 (20)</td>
<td>44 (17)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>48 (18)</td>
<td>29 (11)</td>
<td>40 (15)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>37 (14)</td>
<td>18 (6.8)</td>
<td>31 (12)</td>
</tr>
<tr>
<td>Non-haematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>130 (49)</td>
<td>20 (7.5)</td>
<td>98 (37)</td>
</tr>
</tbody>
</table>

- Other important toxicities included transient renal impairment and shortness of breath as well as hypertension and rare cases of significant cardiac dysfunction

Novel Proteasome Inhibitors Show *in vitro* and *in vivo* Activity

Marizomib and Ixazomib: 2nd generation proteasome inhibitors with promising activity in RRMM:

- **Marizomib (NPI-0052):**
  - induces apoptosis in cell lines resistant to conventional and bortezomib-based therapies
  - in animal models, NPI-0052 was well tolerated and prolonged survival
  - active in RRMM patients (ORR ~ 25% at MTD +/- dex)

- **Ixazomib (MLN9708):**
  - shows selective anti-MM activity in cell lines and an animal model
  - is currently being tested in clinical trials, with promising activity, esp. in combination, and has favourable tolerability

Ixazomib (MLN9708), lenalidomide and dexamethasone ("RId") : Study design

- **Phase 1**: oral MLN9708 dose-escalation
  - Standard 3+3 schema, 33% dose increments, based on cycle 1 dose-limiting toxicities (DLTs)
- **Phase 2**: oral MLN9708 at the RP2D from phase 1
- Stem cell collection allowed after 3 cycles, with autologous stem cell transplantation (ASCT) deferred until after 6 cycles
- MLN9708 maintenance continued until progression or unacceptable toxicity
- Mandatory thromboprophylaxis with aspirin or low-molecular-weight heparin

Kumar S. et al, ASH 2012
Best percent change in M-protein from baseline in response-evaluable patients

- 48% of pts achieved 100% reduction in M-protein
- Reductions were seen at multiple dose levels

Kumar S. et al, ASH 2012
Progression-free survival

- 4 of 65 pts have progressed or died
- Estimated 1-year progression-free survival probability: 93%

Kumar S. et al, ASH 2012
MAb-Based Therapeutic Targeting of Myeloma

**Antibody-dependent Cellular cytotoxicity (ADCC)**

- Effector cells: MM
- **ADCC**
- FcR

**Complement-dependent Cytotoxicity (CDC)**

- CDC
- C1q

**Apoptosis/growth arrest via targeting signaling pathways**

- MM

**MAb-Based Therapeutic Targeting of Myeloma**

- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb®5592 (HM1.24)
- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

Tai & Anderson Bone Marrow Research 2011
Phase II: Elotuzumab + Len + Low-Dose Dex in Rel/Ref MM (Study 1703)

• Phase 2: Pts (n=73) with relapsed and/or refractory MM with 1-3 prior therapies were randomized to elotuzumab 10 or 20 mg/kg IV combined with
  – Lenalidomide 25 mg PO
  – Low-dose dexamethasone 40 mg PO

• Endpoints
  – Primary: ORR (≥PR per IMWG Criteria)
  – Key secondary endpoints: PFS and safety

Len/dex: lenalidomide plus low dose dexamethasone
†Progression defined by IMWG Criteria.
Efficacy: Maximum Percent Reduction in Serum M Protein*

- 10 mg/kg Elotuzumab (n=36)
- 20 mg/kg Elotuzumab (n=29)†

*Maximum percentage decrease from baseline to 60 d after permanent discontinuation of elotuzumab or start of new line of MM therapy.

†Eight pts without measurable disease (baseline and all on-study serum M-protein levels <0.5 g/dL) were not included.

Richardson et al. ASH 2012
At a median follow-up of 20.8 mos, median PFS has not been reached in the 10 mg/kg arm.

- Preliminary median PFS of 26.9 mos was reported in the abstract; after 2.7 mos of additional follow-up, no new PD or death reported. These pts had an increased PFS duration, and in the updated analysis, median PFS was not yet reached.
Conclusions

• Elotuzumab plus lenalidomide and low-dose dexamethasone has a high ORR in relapsed and relapsed/refractory MM
  – 82% for all pts (91% in pts who had received only 1 prior therapy)
  – 92% for pts treated with elotuzumab 10 mg/kg
• At a median follow-up of 14.1 mos, the median PFS was not reached
  – PFS rate was 65% to 75%
• The combination was generally well tolerated
  – Most common Grade 3/4 treatment-emergent AEs were neutropenia (16%), thrombocytopenia (16%), and lymphopenia (16%)
  – Premedication regimen decreased incidence and mitigated severity of infusion reactions*

*Richardson et al. ASH 2012
DARATUMUMAB, A CD38 MONOCLONAL ANTIBODY IN PATIENTS WITH MULTIPLE MYELOMA - DATA FROM A DOSE-ESCALATION PHASE I/II STUDY

Torben Plesner, Henk Lokhorst, Peter Gimsing, Hareth Nahi, Steen Lisby, Paul Richardson

Vejle Hospital, Denmark; University Medical Center Utrecht, Netherlands; Copenhagen University Hospital, Denmark; Karolinska Institutet, Stockholm, Sweden; Genmab A/S, Copenhagen, Denmark; Dana-Farber Cancer Institute, Boston, MA, USA

ASH 2012, IMW 2013
Daratumumab: A Human CD38 mAb with Broad-Spectrum Killing Activity

CD38 molecule

CD38 is expressed on multiple myeloma, various leukemias (B-CLL, AML, B-ALL, plasma cell leukemia), NHL including DLBCL

1. CD38 molecule

Human CD38 antibody generated in transgenic mice

2. Human CD38 antibody

Potent
- CDC, ADCC & ADCP
- Inhibition of CD38 enzymatic activity
- Apoptosis after cross-linking
- In vivo efficacy: active at very low doses in mouse models

3. Potency

Currently in two clinical trials for multiple myeloma

4. Clinical Trials

Effectively kills CD38+ tumor cells, e.g. in multiple myeloma

Enhanced killing in combination with other novel agents

5. Therapeutic Efficacy
Daratumumab Trial Design

Part 1

Open label, weekly i.v. infusion, 8 weeks

Dose-escalation: 3+3 scheme*

0.005 → 0.05 → 0.1 → 0.5 → 1.0 → 2.0 → 4.0 → 8.0 → 16.0 → 24.0 mg/kg

Part 2

Open label, single arm, i.v. infusion

weekly: 8 weeks

every other week: 16 weeks

every fourth week: up to 96 weeks

8 mg/kg, 16 patients

*: - start with pre-dose at 10% of the full dose, max 10 mg
- three weeks’ delay after first full dose
- governed by independent data monitoring committee
Phase I/II Dose-Escalation Study: Daratumumab
Brief Summary of Results

- Favorable safety profile as monotherapy in relapsed or rel/ref MM

- Promising single-agent activity:
  - ORR 13%
  - CBR 31%

CBR: clinical benefit rate

Plesner et al. ASH 2012 (Abstract 73), oral presentation
Daratumumab Response
Maximal Change in Paraprotein

A: serum M-component
B: urine M-component
C: FLC

Relative change in paraprotein from baseline (%)

Patient number

< 1 mg/kg  2 mg/kg  4 mg/kg  8 mg/kg  16 mg/kg  24 mg/kg
Cytogenetics, Risk and Novel Therapies

Summary

- Treatment regimens incorporating the novel agents show promising results in MM patients with unfavorable prognostic factors
- **Cytogenetic abnormalities**
  - Lenalidomide: some activity in del(13) and t(4;14) del(17p) still a poor prognostic feature
  - Bortezomib effective in patients with del(13), t(4;14)
  - Bortezomib-based therapy for t(4;14)
  - Optimal treatment approach for patients with del(17p) still unclear, but bortezomib appears key and needs to be prolonged
Gene Profiles Correlated With Response to Bortezomib

- Response (CR + PR + MR)
- Nonresponse (SD + PD)

- Fc alpha receptor
- Hrk activator of apoptosis
- Cullin 4A
- Hsp 90, 27
- Programmed cell death 10
- Cancer/testis antigen 2
- Ubiquitin carrier protein

MMRF Identified Mutations in Myeloma
19 patients each with newly diagnosed and relapsed MM

- **Protein homeostasis**: 42% including FAM46C, RPL10, RPS6KA1, EIF3B, XBP1, LRRK2

- **NF-κB signaling**: 10 point mutations, 4 additional structural re-arrangements affecting coding

- **IRF-4, Blimp-1**: 2 mutations each

- **Histone methylating enzymes**: WHSC1, UTX, MLL

- **BRAF**: 4% activating mutations

Integrated Genomic Profiling Over Time for Personalized Medicine in Multiple Myeloma

Munshi NC, Avet-Loiseau H. Clin Cancer Res 2011;17:1234-1242
Summary / Conclusions

- Novel agent combinations targeting the tumor cell and microenvironment have markedly improved response rates, EFS and OS
- Numerous trials ongoing to develop strategies to optimally incorporate novel agents (consolidation, maintenance, sequencing…)
- Substantial progress in management of complications and AEs
- Future goals:
  - Tailored approach to therapy:
    - Identify groups of pts in whom multi-drug combinations are required versus pts in whom doublets/triplets as sequences should be used
    - Use of gene expression profiling, proteomics
    - Risk adaptation
Ongoing MM Collaborative Model for Rapid Translation From Bench to Bedside

- Nine new FDA-approved drugs/combos in last 10 yrs
Improving Outcome in MM: The Impact of Novel Therapies

>> 68 yr old gentleman artist, DSS3a IgGk MM, B2M 4.0 (ISS 2)
Ch 13 del+; t 11,14 neg; CD 20 + (NB …no SCT!)

1998 (diagnosed at age 53 yrs to present)

- VAD ~ PD
- HD Cyclophosphamide ~ PD
- Thalidomide ~ PR (6 mos)
- IFN ~ PD
- Rituxan ~ PD
- Bortezomib ~ PR (SUMMIT) (12 mos)
- 2 ME 2 ~ SD (36 mos)
- Lenalidomide ~ PR (44 mos)
- Marizomib ~ SD (6 mos)
- Bortezomib + lenalidomide ~ PR (24 mos)
- Bortezomib + anti-Baff MoAb ~ PR (14 mos+)
- Next steps – DARA MoAb, POM/dex, CFLZ/dex ….
Look: I’m not here to make a fashion statement: just to get some sun and avoid the sharks.
How to Tell if Your Boat is Too Small...

Sitting in a 3.8-metre sea kayak and watching a four-metre great white approach you is a fairly tense experience.
APEX/ SUMMIT/CREST/ VISTA/ Combination Studies Investigators: Sponsors including Celgene; Millenium; J & J; Novartis; BMS; Keryx; Merck
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Agura E.
Alexanian R.
Alsina M.
Andre M.
Attal M.
Avigan D.
Barlogie B.
Baccarani M.
Bahlis N.
Barbui T.
Barton, K.
Belch A.
Beksac M
Bensinger W.
Ben-YehudD.
Berdeja J.
Berenson, J.
Bjorkstrand
Bladé J.
Boccadoro, M.
Boe F.
Bourhis J.
Bron D.
Catlett J.
Moreau P.
Landau H.
Morgan G.
Palumbo A.
Davies F.
Kumar S.

Cavenagh J.
Cavet J.
Chanan-Khan A.
Coiffier B.
Comenzo, R.
Cook, G.
Craddock, C.
Dearden C.
Delforge M.
Densmore J.
Dispienzeri, A
Dimopoulos, T
Doyen C.
Durk H.
Durie, B
Ehninger G.
Einsele H.
Engelhardt M.
Facon T.
Fay J.
Fehrenbacher
Feremans W.
Fermand JP.
Fernandez H.
Fonseca, R
Giguere J.
Glass J.
Goldschmidt H.
Gordon P.
Gramatzki M.
Gruber A.
Gyan E.
Hamm J.
Hassoun H.
Hegewisch-Becker C.
Hideshima T.
Huber C.
Hulin C.
Hussein M.
Ifthikharuddin J.
Irwin D.
Jackson G.
Jagannath S.
Jagasia M.
Jakubowiak A.
Joshua D.
Klein A.
Kobbe G.
Kovacs M.
Krishnan A.
Kropff M.
Kuter D
Lacy M.
Lenhoff S.
Limentani S.
Lokhorst H.
Lonial S.
Ludwig H.
Mandelli F.
Marie J.P.
Marsden G.J.
Martin T.
Mason J.
Mateos S.
Mavromatis B.
Mitsiades, C.
Morris C.
Morrison V.
Niesviesky R.
Nowrousian M.
Orlowski R.
Pecora A.
Phelan J.
Posada J.
Prince M
Rahemtulla A.
Rai K.
Rajkumar V.

Reece D.
Richardson P.
Rowe J.M.
Schiller R.
Schmidt W.
Schuster M.
Sezer O.
Shadduck R.
Shustik C.
Siegel D.
Singhal S.
Sonneveld P.
Sotto J.J.
Stadtmauer E.
Stewart, K
Tarantolo S.
Van Droogenbroeck V.
Van Oers M.H.
Vellenga E.
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United Nations Against Myeloma: Jerome Lipper and Lebow Bench to Bedside Research Team


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