Current Management of Multiple Myeloma

December 2012
Kevin Song MD FRCPC
Leukemia/BMT Program of B.C.
## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honoraria</td>
<td>Celgene, Janssen, Novartis</td>
</tr>
<tr>
<td>Speaker</td>
<td>Celgene, Janssen</td>
</tr>
<tr>
<td>Research Support</td>
<td>Celgene</td>
</tr>
<tr>
<td>Stocks</td>
<td>None</td>
</tr>
</tbody>
</table>
Outline of Talk

• Biology
  – Cytogenetic testing
• Stem cell transplant
• Pharmacotherapy
  – Advent of new agents
    • In the relapse setting
    • In the initial treatment setting
    • Other area of possible integration
  – Future therapies
Epidemiology

- 2000 new Canadian patient with myeloma in 2007
- 207 new patients in BC in 2005
- 169 patients died of myeloma in 2004
- 500-1000 patients with myeloma in BC
- Myeloma is considered incurable
- Improvement in treatment has resulted in increase survival

bccancer.bc.ca/HPI/CancerStatistics
Multiple Myeloma Biology
Development of Myeloma Cells

Ig gene changes leading to MM

VDJ rearrangement  
Somatic mutation  
Class switching

Stem cell  
Pre-B cell  
B-cell  
Oncogenic Event

Cell surface markers

Hideshima T, Anderson K. Nat Rev Cancer. 2002;2:927
<table>
<thead>
<tr>
<th>Genomic aberration</th>
<th>Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(13)</td>
<td>48 %</td>
</tr>
<tr>
<td>t(11;14)(q13;q32)</td>
<td>21 %</td>
</tr>
<tr>
<td>t(4;14)(p16;q32)</td>
<td>14 %</td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>39 %</td>
</tr>
<tr>
<td>MYC translocations</td>
<td>13 %</td>
</tr>
<tr>
<td>del(17p)</td>
<td>11 %</td>
</tr>
</tbody>
</table>
Genetic abnormalities and survival in MM: the experience of the IFM

Black - lacking del(13), t(4;14), and del(17p), and low β2-M.
Blue - del(13) but lacking t(4;14) and del(17p) and low β2-M

Green – lacking del(13), t(4;14) and del(17p) but with a high β2-M
Red - del(13) lacking both t(4;14) and del(17p) with a high β2-M
Gray - either a t(4;14) or a del(17p) and low β2-M
Pink - t(4;14) or del(17p) and high β2-M
Standard Tests in BC

• All Labs
  – FISH t(4;14)
  – FISH del (17p)
  – FISH t(14;16)
Gene expression profiling

oligoneucleotide microarrays assessing 6800 genes

• clustering analysis reveals patterns of expression based on disease
Traditional Treatment

• **Alkylators** (Melphalan, Cyclophosphamide)
  – covalently bond alkyl groups to cellular molecules
  – crosslink DNA, strand breakage, cell death
  – side-effect; myelosuppression, secondary neoplasia

• **Corticosteroids** (Prednisone, Decadron)
  – binds to steroid receptors causing apoptosis
  – no myelosuppression
Combination chemotherapy versus melphalan & prednisone (6633 patients, 27 studies)

Response rate
Melphalan/prednisone: 53%
Response rate combination chemotherapy: 60%

Myeloma Trialists’ Collaborative Group. JCO 1998
Randomized Trial of Autologous Bone Marrow Transplantation and Chemotherapy in Myeloma (Attal NEJM 1996)

• 200 patients randomized to conventional chemo vs. high dose chemo and Autologous BMT

• Age less than 65 and good organ function

• High dose therapy - Melphalan 140mg/m² and radiation

Table 2. Response Rates According to Treatment Group.*

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Conventional Dose (N = 100)</th>
<th>High Dose (N = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Very good partial</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Partial</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Minimal</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>25</td>
<td>12</td>
</tr>
</tbody>
</table>
Results of High Dose Treatment with Autologous Transplantation

[Graphs showing event-free and overall survival rates for conventional and high dose treatments over different months]
Allogeneic Stem Cell Transplant

• High dose chemotherapy to eliminate as much myeloma as possible
• Stem cells infused from donor
  – Adverse effect - Graft vs. Host Disease
  – Benefit - ? *Graft vs. Myeloma effect*
• Difficulties with therapy
  – limited to younger age (≤ 55)
  – donors are not readily available
  – treatment related mortality ~ 40%
  – benefit is presumed and not proven
Myeloablative AlloSCT for myeloma (Vancouver)

Event Free Survival

Overall Survival

Kuruvilla BBMT 2007
Reduced Intensity Allogeneic Stem Cell Transplants

- Conditioning chemoradiotherapy is much less than standard transplants and designed to be immunosuppressive not myeloablative
- HLA identical allogeneic stem cells are infused into the recipient
- Further donor lymphocytes (DLI) may be infused weeks or months later to promote chimerism
- Early results suggest it is less toxic than standard allotransplants, efficacy unknown
<table>
<thead>
<tr>
<th>Author</th>
<th>No. Pts</th>
<th>CR rate</th>
<th>EFS mths</th>
<th>OS mths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garban</td>
<td>219 vs 65</td>
<td>36 vs. 33 (p= NS)</td>
<td>32 vs. 35 (p=NS)</td>
<td>56 vs. 34 (p=0.017)</td>
</tr>
<tr>
<td>Bruno</td>
<td>82 vs 80</td>
<td>26 vs. 55 (p=0.004)</td>
<td>29 vs. 35 (p=0.008)</td>
<td>56 vs. NR (p=0.009)</td>
</tr>
<tr>
<td>Blade</td>
<td>85 vs 26</td>
<td>10 vs 35 (p=0.01)</td>
<td>48 vs. NR (p=NS)</td>
<td>80 vs. NR (p=NS)</td>
</tr>
<tr>
<td>Krishnan</td>
<td>156 vs 366</td>
<td>NS at 3 years</td>
<td>NS at 3 years</td>
<td>NS at 3 years</td>
</tr>
</tbody>
</table>

• Garban *Blood* 2006  
• Bruno *NEJM* 2007  
• Bladé *Blood* 2007  
• Krishnan *Lancet Oncol* 2011
Myeloma Therapy

Transplant eligible

Induction

ASCT

Observe ......

Relapse Therapy

Dex based

MEL-200

Limited options
History of Thalidomide

• Used in late 1950s in Europe as sedative
  – Good sleep quality and low risk of fatal overdose
• Also used for “morning sickness” associated with pregnancy
• Teratogenicity
  – >10,000 malformed children born
  – Malformation of limbs (dysmyel<a href="http://cerhr.niehs.nih.gov/gerpub/topics/thalidomide2-ccae">ia, phocomelia, radial aplasia), digestive tract, heart, eyes, ears, kidney, nervous system,

Rajkumar SV. *Oncology.* 2000;14(suppl 13):11
http://cerhr.niehs.nih.gov/gerpub/topics/thalidomide2-ccae
Immunomodulatory Agents (IMIDS)

Structurally similar, but functionally different—both qualitatively and quantitatively

- **Thalidomide**
  - 100-200 mg/d
  - Neuropathy
  - Constipation
  - Sedation
  - DVT

- **Lenalidomide**
  - 15-25 mg/d
  - Myelosuppression
  - Skin rash
  - DVT

- **Pomalidomide**
  - 1-4 mg/d

Stewart AK. Hematology 2009
Lenalidomide (Revlimid®)

- More “potent” immunomodulator than thalidomide
  - Up to 50,000 times more potent inhibitor of TNF\(\alpha\)
  - 200- to 1000-fold in cytokine modulation
  - Increased stimulation of T-cell proliferation
  - Augmented stimulation of IL-2 and IFN\(\gamma\) production
- Fewer side effects: no significant constipation, neuropathy, or sedation
- ? teratogenic

Protocol Lenalidomide (Target n=302/trial)

Lenalidomide 25 mg, d 1–21
Placebo, d 22–28
Dex 40 mg, d 1–4, 9–12, 17–20

× 4 COURSES

Placebo, d 1–28
Dex 40 mg, d 1–4, 9–12, 17–20

Same except Dex, d 1–4
Continue until PD

North America (MM009) 354 pts
International (MM010): 351 pts
Median time to progression (months)

<table>
<thead>
<tr>
<th></th>
<th>Len/Dex</th>
<th>Placebo/Dex</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM-009</td>
<td>11.1</td>
<td>4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MM-010</td>
<td>11.3</td>
<td>4.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*`P-value from log-rank test.

Weber et al. NEJM 2007
Dimopoulos et al. NEJM 2007
Proteosome Inhibition

NF_κβ = Bad

I_κβ = Good
Overall and 1-Year Survival

P = .0272
Subcutaneous administration of bortezomib

- Studies were initiated based on a medication administration error
- Initial study was a phase 1 study which examined pharmacokinetics and pharmacodynamics (Moreau et al. Haematologica 2008)
- Phase 3 study performed based on results of phase 1 study (Moreau et al. Lancet Oncology 2011)
- Efficacy remains the same
- Reduced neuropathy and GI effects
## Bortezomib as a Backbone

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>ORR</th>
<th>Time-to event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steroids alone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jagannath 2006</td>
<td>BTZ, DEX</td>
<td>18-33%</td>
<td>TTP 7 mos OS 17 mos</td>
</tr>
<tr>
<td><strong>Alkylators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reece 2006*</td>
<td>BTZ, CY, Pred</td>
<td>93%</td>
<td>NA</td>
</tr>
<tr>
<td>Berenson 2006</td>
<td>BTZ, Melphalan</td>
<td>68%</td>
<td>PFS 8 mos</td>
</tr>
<tr>
<td><strong>Thalidomide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zangari 2005*</td>
<td>BTZ, Thal (DEX added)</td>
<td>55%</td>
<td>EFS 9 mos</td>
</tr>
<tr>
<td><strong>Doxorubicin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlowski 2007</td>
<td>BTZ, PLD (Doxil)</td>
<td>44%</td>
<td>TTP 9.3 mos</td>
</tr>
<tr>
<td>Lee 2007*</td>
<td>DXR, DEX (PAD) followed by TD</td>
<td>92.8%</td>
<td>1 yr PFS 66.8%</td>
</tr>
<tr>
<td><strong>Multiple agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palumbo 2007</td>
<td>BTZ, Melphalan, Prednisone, Thal (VMPT)</td>
<td>67%</td>
<td>1 yr PFS 61%</td>
</tr>
<tr>
<td>Chanan-Khan 2006*</td>
<td>Thal, PLD (VDT)</td>
<td>65%</td>
<td>PFS 10.9 mos OS 15.7 mos</td>
</tr>
</tbody>
</table>

* Abstract form only
Classes of medications

- Alkylators (Cyclophosphamide and Melphalan)
- Corticosteroids (Dexamethasone, Prednisone)
- Immunomodulatory Drugs (thalidomide, lenalidomide)
- Proteosome inhibitors (bortezomib)
Impact of Novel Agents on the Outcome in Post ASCT Relapsed/refractory Disease (n=387)
Front-Line Therapy

Transplant ineligible
VISTA: VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone

- Phase III trial: untreated patients with symptomatic Myeloma not candidates for ASCT

<table>
<thead>
<tr>
<th>682 Patients</th>
<th>Randomization 1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age 71 Years</td>
<td></td>
</tr>
</tbody>
</table>

Induction: 6-Week Cycles

- Cycles 1-4
  - **VMP Bi-Weekly**
    - V: 1.3 mg/m² IV, d 1, 4, 8, 11, 22, 25, 29, 32
    - M: 9 mg/m² po, d 1-4
    - P: 60 mg/m² po, d 1-4
  - **VMP Weekly**
    - V: 1.3 mg/m² IV, d 1, 8, 22, 29
    - M: 9 mg/m² po, d 1-4
    - P: 60 mg/m² po, d 1-4

median OS was 56.4 versus 43.1 months
# VMP: Twice Weekly Compared to Weekly Bortezomib

## Comparison of efficacy and tolerability of different VMP schedules

<table>
<thead>
<tr>
<th></th>
<th>VISTA trial</th>
<th>GIMEMA trial: VMPT+VT vs VMP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>VMP (twice weekly)</td>
</tr>
<tr>
<td>CR</td>
<td>30%</td>
<td>27%</td>
</tr>
<tr>
<td>2-year PFS</td>
<td>48%</td>
<td>56%</td>
</tr>
<tr>
<td>3-year OS</td>
<td>69%</td>
<td>89%</td>
</tr>
<tr>
<td>Total planned dose</td>
<td>67.6 mg/m²</td>
<td>67.6 mg/m²</td>
</tr>
<tr>
<td>Total delivered dose</td>
<td>na</td>
<td>40.1 mg/m²</td>
</tr>
<tr>
<td>Hematologic events</td>
<td></td>
<td>45%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>37%</td>
<td>26%</td>
</tr>
<tr>
<td>Gastrointestinal events</td>
<td>19%</td>
<td>11%</td>
</tr>
<tr>
<td>Systemic events</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Dermatologic events</td>
<td>7%</td>
<td>2%</td>
</tr>
</tbody>
</table>

*Bringhen et al. Blood 2010; 116:4745-4753*
VMP: Twice Weekly Compared to Weekly Bortezomib

- Comparison of peripheral neuropathy (PN) with different VMP schedules

<table>
<thead>
<tr>
<th>sensory PN</th>
<th>VISTA trial</th>
<th>GIMEMA trial: VMPT+VT vs VMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Discontinuation due to PN</td>
<td>15%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Survival
bortezomib: twice weekly vs once weekly

Progression-free survival
Overall survival

Bringhen et al. Blood 2010
MPT versus MP in newly diagnosed patients ≥ 75 years with MM

Melphalan & Prednisone 12 (6 week) cycles + Placebo

Randomize 1:1

Melphalan & Prednisone 12 (6 week) cycles + Thalidomide 100mg daily for 72 weeks

- 232 patient enrolled
- Median age 79

MPT versus MP in newly diagnosed patients ≥ 75 years with MM

**Progression Free Survival**

- Median PFS 24 mo vs 18 mo

**Overall Survival**

- Median OS 44 mo vs 29 mo

Meta-analysis: MPT vs MP
Overall Survival

<table>
<thead>
<tr>
<th>STUDY</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 99/06</td>
<td>1.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>GIMEMA MPT</td>
<td>1.0</td>
<td>0.81</td>
</tr>
<tr>
<td>IFM 01/01</td>
<td>1.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HOVON 49</td>
<td>1.2</td>
<td>0.16</td>
</tr>
<tr>
<td>NMSG</td>
<td>0.9</td>
<td>0.40</td>
</tr>
<tr>
<td>OVERALL</td>
<td>1.2</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Cochran's Q=12.3 (p=0.02); I²=67%
Outcome: hazard ratio for death

Kapoor et al. ASH 2009 Abstract 615
MR vs MPR vs MPR-R

N=459, 82 centers in Europe, Australia and Israel

Stratified by age (≤ 75 vs. > 75 years) and stage (ISS 1,2 vs. 3)

M, melphalan; P, prednisone; R, lenalidomide; PBO, placebo.

Palumbo et al. ASH 2009 (Abstract 613)
Progression Free Survival

Len maintenance started

Palumbo NEJM 2012
Overall Survival

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

Palumbo NEJM 2012
Len/dex indefinite vs Len/dex for 18 months vs MPT in newly diagnosed transplant ineligible MM (1500 pts)
Front-Line Therapy

Transplant Eligible
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**
# Phase 3: bortezomib-dex vs VAD

## IFM 2005-01 Study

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>VAD</th>
<th>VD</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥VGPR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>16%</td>
<td>39%</td>
</tr>
<tr>
<td>ASCT1</td>
<td>37%</td>
<td>54%</td>
</tr>
<tr>
<td>ASCT2</td>
<td>47%</td>
<td>68%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>VAD</th>
<th>VD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS in all patients</td>
<td>30 months</td>
<td>36 months</td>
<td>0.057</td>
</tr>
<tr>
<td>PFS in patients with ISS 2 &amp; 3</td>
<td>23 months</td>
<td>33 months</td>
<td>0.006</td>
</tr>
<tr>
<td>PFS in patients with t(4;14) +/- del17p</td>
<td>24 months</td>
<td>33 months</td>
<td>0.113</td>
</tr>
</tbody>
</table>

Harousseau et al. ASH 2009 (abstract 353)
(A) Progression-free survival and (B) overall survival

(A) Progression-free survival

- VAD: 128 events (52.9%) / 242; median, 29.7 (95% CI, 26.2 to 37.1)
- Bortezomib plus dexamethasone: 110 events (45.8%) / 240; median, 36.0 (95% CI, 32.5 to 41.0)

Log-rank $P = .0643$

$P = .057$ if adjusted for initial stratification factors

(B) Overall survival

- VAD: 45 deaths (18.6%) / 242; median not reached
- Bortezomib plus dexamethasone: 40 deaths (16.7%) / 240; median not reached

Log-rank $P = .5079$

$P = .572$ if adjusted for initial stratification factors
Combination Treatments Up Front Setting

Stewart A K et al. Blood 2009;114:5436-5443
**Phase 2 EVOLUTION study: VDR vs VDC vs VDCR**

<table>
<thead>
<tr>
<th><strong>Randomize</strong></th>
<th><strong>Induction: 8 x 21 day cycles</strong></th>
<th><strong>Maintenance: 4 x 42 day cycles</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>VDR</td>
<td>Bortezomib 1.3 mg/m² d1, 4, 8, 11</td>
<td>Bortezomib 1.3 mg/m² d1, 8, 15, 22</td>
</tr>
<tr>
<td></td>
<td>Dex 40 mg d1, 4, 8, 15, 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rev 25 mg d1-14</td>
<td></td>
</tr>
<tr>
<td>VDC</td>
<td>Bortezomib 1.3 mg/m² d1, 4, 8, 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dex 40 mg d1, 4, 8, 15, 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cy 500 mg/m² d1, 8</td>
<td></td>
</tr>
<tr>
<td>VDCR</td>
<td>Bortezomib 1.3 mg/m² d1, 4, 8, 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dex 40 mg d1, 4, 8, 15, 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cy 500 mg/m² d1, 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rev 15 mg d1-15</td>
<td></td>
</tr>
</tbody>
</table>

Pts received prophylactic antibiotics, acyclovir, transfusion support, and anti-coagulants as required

Eligible patients wishing to undergo HDT-ASCT could undergo SC collection any time after cycle 2 and ASCT any time after cycle 4

Kumar *et al.* ASH 2009 (abstract 127)
To date, 6 pts have undergone ASCT in the VDR arm, 5 in the VDC arm, and 3 in the VDCR arm

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>VDR</th>
<th>VDC</th>
<th>VDCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable pts</td>
<td>42</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>Response Rates, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>90</td>
<td>87</td>
<td>94</td>
</tr>
<tr>
<td>CR (sCR)</td>
<td>12</td>
<td>6</td>
<td>15 (3)</td>
</tr>
<tr>
<td>VGPR* (nCR)</td>
<td>33 (10)</td>
<td>35</td>
<td>42 (3)</td>
</tr>
<tr>
<td>PR</td>
<td>45</td>
<td>45</td>
<td>36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety, %</th>
<th>VDR</th>
<th>VDC</th>
<th>VDCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>95</td>
<td>97</td>
<td>88</td>
</tr>
<tr>
<td>SAEs</td>
<td>24</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>≥Gr 3</td>
<td>67</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Grade 3/4 AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5/5</td>
<td>28/13</td>
<td>23/9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5/2</td>
<td>9/0</td>
<td>5/0</td>
</tr>
<tr>
<td>DVT</td>
<td>0</td>
<td>0</td>
<td>2/0</td>
</tr>
</tbody>
</table>

*Pts categorized as VGPR include those with no measureable M-protein who have not yet had follow-up bone marrow assessments to confirm CR/nCR status

Kumar et al. ASH 2009 (abstract 127)
Continuous Therapy

Transplant eligible

- Induction
- ASCT
- Consolidation/Maintenance
- Relapse Rx

Bortezomib + MEL-200 Various options

Transplant ineligible

- Induction
- Maintenance & Relapse therapy

VMP / MPT Various options
Thalidomide maintenance studies in the transplant setting

- 6/6 studies showed significant improvement in PFS
- 2/6 studies showed significant improvement in OS

Considerations
- Toxicity of thalidomide
- Short survival following relapse in some studies
Lenalidomide As Consolidation and Maintenance After Autologous Stem Cell Transplant (IFM 2005-02)

- Patients ≤ 6 months after ASCT in first line
- Consolidation: Lenalidomide
  - Lenalidomide
    10 -15 mg/day, continuous dosing until relapse
  - Placebo until relapse

Randomization:

Attal NEJM 2012
Lenalidomide Maintenance post ASCT IFM

Attal NEJM 2012
## IFM 2005-02: OS From Randomization

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=307</th>
<th>Lenalidomide n=307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>73</td>
<td>79</td>
</tr>
<tr>
<td>3-yrs post randomization</td>
<td>84%</td>
<td>80%</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Attal NEJM 2012
Lenalidomide Versus Placebo Maintenance Therapy Following Single ASCT (CALGB 100104):

Randomization:

- **Lenalidomide**: 10 mg/day, continuous dosing until relapse
- **Placebo**: until relapse

Patients ≤ 6 months after ASCT in first line

McCarthy NEJM 2012
Lenalidomide Maintenance post ASCT CALGB

McCarthy NEJM 2012
Lenalidomide Maintenance post ASCT CALGB

- Overall Survival better on maintenance arm (15% vs 23% death at follow-up)
- More hematological side-effect (anemia, neutropenia, thrombocytopenia), fatigue, rash, diarrhea
- Second malignancies

McCarthy NEJM 2012
Phase III: PAD vs VAD induction
HOVON 65 MM / GMMG-HD4 study

MM Stage II or III, Age 18–65 n=744, median age 57

Randomization

n=373
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 n=371
CAD + GCSF
MEL 200 + PBSCT
Depending on local policy for patients ≥PR
MEL 200 + PBSCT
Bortezomib 1.3 mg/m² / 2 weeks for 2 years maintenance

PAD:
Bortezomib: 1.3 mg/m², days 1,4,8,11
Doxorubicin: 9 mg/m², days 1-4
Dex 40 mg, days 1-4, 9-12, 17-20

Sonneveld et al. ASH 2010 (Abstract 40)
PAD vs VAD (bortezomib maintenance)

Sonneveld JCO 2012
Summary

- Paradigm shift in the treatment on newly diagnose myeloma
- Key backbone agents:
  - thalidomide, bortezomib, lenalidomide
- Individualized approach is needed
- More data needed
- Cost of drugs remain a major issue
<table>
<thead>
<tr>
<th>Investigational Agents in MM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMD-3100</strong></td>
</tr>
<tr>
<td>Amifostine</td>
</tr>
<tr>
<td>Aplidin</td>
</tr>
<tr>
<td>Atiprimod</td>
</tr>
<tr>
<td>Belinostat</td>
</tr>
<tr>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Cetuximab</td>
</tr>
<tr>
<td>CNTO 328</td>
</tr>
<tr>
<td>CYT997</td>
</tr>
<tr>
<td>Darinaparsin</td>
</tr>
<tr>
<td>Dasatinib</td>
</tr>
<tr>
<td>Deforolimus</td>
</tr>
<tr>
<td>Denosumab</td>
</tr>
<tr>
<td>Depsipeptide</td>
</tr>
<tr>
<td>Eltrombopag</td>
</tr>
<tr>
<td>Everolimus</td>
</tr>
<tr>
<td>Gallium nitrate</td>
</tr>
<tr>
<td>LBH589</td>
</tr>
<tr>
<td>Leteprinim, potassium</td>
</tr>
<tr>
<td>Mapatumumab</td>
</tr>
<tr>
<td>Motexafin gadolinium</td>
</tr>
<tr>
<td>Oblimersen</td>
</tr>
<tr>
<td>Perifosine</td>
</tr>
<tr>
<td>PTK787</td>
</tr>
<tr>
<td>SC10-469</td>
</tr>
<tr>
<td>Sorafenib</td>
</tr>
<tr>
<td>Tenespinmycin</td>
</tr>
<tr>
<td>Temsirolimus</td>
</tr>
<tr>
<td>VEGF Trap</td>
</tr>
<tr>
<td>Velafermin</td>
</tr>
<tr>
<td>XL999</td>
</tr>
</tbody>
</table>

Adapted with permission from The International Myeloma Foundation, Myeloma Matrix Part I. Available at: http://myeloma.org/main.jsp?source=link&source_link_id=728&type=article&tab_id=4&menu_id=0&id=735
Just Around the Corner

- Carfilzomib (proteosome inhibitor)
  - Recent FDA approval
- Pomalidomide (iMiD)
  - Recent submission to the FDA
- Antibody therapy?
  - Elotuzumab
  - Daratumumab
## Impact of New Drugs on Survival in BC

<table>
<thead>
<tr>
<th>Date of Diagnosis</th>
<th>% alive at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 2003</td>
<td>50%</td>
</tr>
<tr>
<td>2003 and beyond</td>
<td>70%</td>
</tr>
</tbody>
</table>
Post-Relapse Survival
Pre and post 2004:
Survival benefit is from post-relapse treatment

Venner et al. ASH 2009 (abstract 2872)
Conclusions

- Improved Survival with newer agents
- Initial introduction of new agents is in the relapsed/refractory setting
- Strong support for moving newer agents to initial treatment
- Newer agents are being investigated
- Cost of drugs remain a concern (access?)
- Myeloma still remains incurable and patients require a lot of care.