Multiple Myeloma Overview.
Treatment and challenges.

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Disclosure of Potential for Conflict of Interest

FINANCIAL DISCLOSURE


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Other: Employee of Cancercare Manitoba.
Epidemiology

- Myeloma is a disease of bone marrow plasma cells.
- It accounts for 1% of all cancers and 10% of haematological malignancies.
- In Canada 2,300 new cases/annum.
  - 1,300 males, 1,000 females. (1.4% of Cancers)
- In USA 14,600 new cases/annum
- In the England and Wales 2,0000 new cases/annum
- Black>Asians>Whites>Chinese.
- M:F=2:1
Spectrum of Plasma Cell Disorders at Mayo

Testing at diagnosis

• **Mandatory**
  - SPEP
  - UPEP
  - Quantitative IgGs
  - Biochemical profile
  - Cbc
  - Sβ2m
  - Skeletal survey
  - Bone Marrow
  - FISH

• **Permissible**
  - Plasma viscosity
  - cryoglobulinaemia
  - Amyloid stain
  - Clotting screen.
  - FLCR
  - MRI
  - PET
  - Image guided tissue biopsy
## Diagnostic Criteria

<table>
<thead>
<tr>
<th></th>
<th><strong>MGUS</strong></th>
<th><strong>SMM</strong></th>
<th><strong>MM</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M protein in serum $&lt;30g/l$</td>
<td>M protein $&gt;30g/l$</td>
<td>M protein in serum and/or urine. (No specific level required)</td>
</tr>
<tr>
<td></td>
<td>BMPCS $&lt;10%$ and low level of infiltration on trephine</td>
<td>BMPCS $&gt;10%$</td>
<td>BMPCS $&gt;10%$</td>
</tr>
<tr>
<td></td>
<td>No myeloma ROTI</td>
<td>No myeloma ROTI</td>
<td>Myeloma related organ or tissue impairment.</td>
</tr>
<tr>
<td></td>
<td>No evidence of other B cell LPD or light chain associated Amyloidosis or other tissue damage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Imaging in Myeloma

- Extended skeletal survey is imaging of choice.
- MRI for patients with bone pain and negative skeletal pain.
- Uninfused CT may be an alternative in cases with CKD.
- PET for plasmacytomas only at diagnosis. Role in monitoring unclear.
**18F-Fluoro-Deoxyglucose Positron Emission Tomography (FDG-PET)**

**Advantages**
- Higher sensitivity vs conventional radiography
- Detects 46% to 63% more lesions than WBXR
- Normalization of scans after treatment corresponds with a ≥ 90% decrease in M-protein

**Disadvantages**
- Less sensitive than MRI
  - Especially for diffuse disease

**MRI** = Magnetic resonance imaging; **WBXR** = Whole-body x-ray.

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Clinical Pathway for the Plasma Cell Dyscrasia (PCD)/Myeloma Clinic (DSG)

A. REFERRAL TO 1st APPOINTMENT:

New referral received at Central Referral Office (CRO) → DSG member Triages and Assigns Priority → Ref/ Clinic Clerk completes B/W, Imaging and other referrals

P1: 1st App within 14 working days
P2: 1st App within 1 Month
P3: 1st App anytime

Ref/ Clinic Nurse books App.

1st Appointment (PNP):

Physician:
- History/ Physical Procedures

Nurse:
- Eligibility for Tumor Banking
- Baseline Frailty
- HRQOL

Pharmacist:
- Medical Lists
- Allergies

2nd App. (NP)

TREATMENT

Procedures (Same day/ Other):
- Marrow
- Lumbar Puncture

Banking

Contact: referraloffice@cancercare.mb.ca
Fax 204 7860621, Tel 204 7862176.
### Active Therapy
- Quantitative paraprotein
- CBC
- Calcium
- Albumin
- Creatinine monthly

### Pre Transplant Disease Assessment
- Paraprotein assessment (serum, urine)
- Skeletal survey
- CBC
- Calcium
- Albumin
- Creatinine
- B2 microglobulin

### Post Transplant Disease Assessment (D100)
- See pre transplant disease assessment
- Bone marrow investigation if absence of monoclonal protein to determine complete remission status

### Surveillance*
- Q3 monthly assessment with quantitative paraprotein measurement
  - CBC, calcium, albumin, creatinine
- Skeletal survey annually
- Bone marrow examination as clinically indicated

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**BCSH guidelines 2011**
Presenting Features of MM

- M-protein S/U: 97%
- Anemia: 73%
- Lytic Bone Lesions: 66%
- Bone Pain: 58%
- Renal Insufficiency: 19%
- Hypercalcemia: 13%
- Minor or no abnormalities: 11%
- Hepatomegaly: 4%
- Amyloidosis: 4%
- Non-secretory (no S/U M-protein): 3%
Biology of response and relapse in MM: a case for disease control?

- **Asymptomatic**
  - MGUS or smouldering myeloma
  - Therapy
  - M protein (g/dL)

- **Symptomatic**
  - Active myeloma
  - Plateau remission
  - Relapse

- Therapy

- Refractory relapse

- ~31,500 cases annually in Europe

~21,500 deaths annually in Europe

Probability of progression among 1384 residents of southeastern Minnesota in whom monoclonal gammopathy of undetermined significance (MGUS) was diagnosed between 1964 and 1994.
Molecular pathogenesis of multiple myeloma

- Increased DNA labeling index
- Bone destruction
- Angiogenesis

1. Germinal Center B cell
2. MGUS
3. Smoldering Myeloma
4. Intra-medullary Myeloma
5. Extra-medullary Myeloma
6. Myeloma Cell Line

Karyotypic & epigenetic abnormalities

- Secondary (Ig) TLC
- NFκB activating mutations
- MAPK dysregulation: N, K-RAS, FGFR3
- PI3K dysregulation
- p18, RB inactivation
- MYC dysregulation
- p53 inactivation
Recurring Chromosomal Translocations in Multiple Myeloma
# Cytogenetics/FISH

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Patients/Total (%)</th>
<th>Median OS (months)</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17p13 del</td>
<td>18/168 (11)</td>
<td>15.1</td>
<td>8.7</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>26/153 (17)</td>
<td>18.8</td>
<td>8.2</td>
</tr>
<tr>
<td>T(4;14) + del 13</td>
<td>22/84 (26)</td>
<td>18.8</td>
<td>8.2</td>
</tr>
</tbody>
</table>

All new patients with MM and a potential for high dose therapy
Cancer in Manitoba Incidence 2005 Annual Statistical Report

Myeloma in Context

Incidence of Cancer in Manitoba: 2005

Cases

AML
Myeloma
CLL
Lymphoma
Prostate Cancer
Colorectal Cancer
Breast Cancer
Lung Cancer

CancerCare MANITOBA
Incidence Trend for Myeloma in 1956–2007

Count

90
80
70
60
50
40
30
20
10
0


Diagnosis Year

agegp

0–39 40–49 50–59

60–69 70+

All

CancerCare MANITOBA
<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;65</th>
<th>65-70</th>
<th>71-75</th>
<th>&gt;75</th>
<th>Total</th>
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<tbody>
<tr>
<td>2000</td>
<td>18</td>
<td>13</td>
<td>13</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>2001</td>
<td>19</td>
<td>19</td>
<td>13</td>
<td>23</td>
<td>74</td>
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<tr>
<td>2002</td>
<td>20</td>
<td>6</td>
<td>14</td>
<td>27</td>
<td>67</td>
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<td>2003</td>
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<td>8</td>
<td>6</td>
<td>30</td>
<td>64</td>
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<td>2004</td>
<td>16</td>
<td>7</td>
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<td>36</td>
<td>72</td>
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<tr>
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<td>22</td>
<td>11</td>
<td>6</td>
<td>33</td>
<td>72</td>
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<td>2006</td>
<td>20</td>
<td>6</td>
<td>5</td>
<td>31</td>
<td>62</td>
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<td>2007</td>
<td>22</td>
<td>10</td>
<td>11</td>
<td>26</td>
<td>69</td>
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<tr>
<td>2008</td>
<td>17</td>
<td>11</td>
<td>6</td>
<td>21</td>
<td>55</td>
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<tr>
<td>2009</td>
<td>20</td>
<td>8</td>
<td>11</td>
<td>13</td>
<td>52</td>
</tr>
<tr>
<td>2010</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>TOTAL</td>
<td>325</td>
<td>169</td>
<td>181</td>
<td>446</td>
<td>1121</td>
</tr>
</tbody>
</table>
Challenges in Manitoba…

• Delay in diagnosis
• “Fast moving target”
• Plethora of drugs (5 FDA considerations in 5-10 yrs).
  – What hierarchy?
• High cost drugs and intervention
  – Lenalidomide (CAD 7,000/month).
  – ASCT
• Variable care package throughout region
• “Piloting shared care model”
Initial therapy for MM
Relapse Free Interval from Plateau by MRC Response

\[ \chi^2 = 18.29, \text{ p}=0.0001 \]
High-dose versus conventional chemotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival</th>
<th>6 Year OS</th>
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<tbody>
<tr>
<td>Chemotherapy</td>
<td>42m</td>
<td>21%</td>
</tr>
<tr>
<td>ABMT</td>
<td>57m</td>
<td>43%</td>
</tr>
</tbody>
</table>
Paradigm shift in oncology evolution of a philosophy

1960s – 1990s

Empirical Approach

Non-specific cytotoxic agents

Molecular-based Approach

Targeted and selected biological agents

more effective, less toxic mechanism-based TxS
Milestones in myeloma therapy

- Melphalan and prednisolone: 1962
- Autologous SCT: 1996
- Thalidomide: 1999
- Velcade: 2003
- Revlimid: 2005
- ?????: 2009

VAD
Overall survival is improving with the advent of novel agents

Overall survival in 6-year intervals from time of diagnosis

- 2001–2006
- 1971–1976
- 1977–1982
- 1983–1988
- 1989–1994
- 1995–2000
- 2001–2006

Inhibition of angiogenic growth factor and basic fibroblast growth factor

Thalidomide 5

Inhibition of interleukin-6, tumour necrosis factor α, and interleukin-1β

Thalidomide 3

Induction of interleukin-2, and interferon-γ

CD8+ cells

Bone marrow blood vessel

Inhibition of angiogenic growth factor and basic fibroblast growth factor

Thalidomide 1

Alters profile of adhesion molecules

Intercellular adhesion molecule

Myeloma cells

Bone marrow stromal cells

Bone marrow

Myeloma

CD8+ cells

Inhibits growth and survival of tumour cells and/or BMSC’s

Thalidomide 4

Thalidomide 2

Thalidomide 5
### Thalidomide plus chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Regime</th>
<th>Response (%)</th>
<th>Type of dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kropff (2000)</td>
<td>14</td>
<td>HyperCDT</td>
<td>86</td>
<td>Advanced</td>
</tr>
<tr>
<td>Moehler (2000)</td>
<td>42</td>
<td>TCED</td>
<td>78</td>
<td>Advanced</td>
</tr>
<tr>
<td>Dimopoulos (2001)</td>
<td>24</td>
<td>TCD</td>
<td>50</td>
<td>Treated</td>
</tr>
<tr>
<td>Oakervee (2002a)</td>
<td>12</td>
<td>TVAD</td>
<td>100</td>
<td>De novo</td>
</tr>
<tr>
<td>Oakervee (2002b)</td>
<td>13</td>
<td>MPT</td>
<td>38</td>
<td>De novo</td>
</tr>
<tr>
<td>Oakervee (2002b)</td>
<td>9</td>
<td>MPT</td>
<td>44</td>
<td>Relapsed</td>
</tr>
<tr>
<td>Coleman (2001)</td>
<td>55(40)</td>
<td>BLT-D</td>
<td>93</td>
<td>Advanced</td>
</tr>
</tbody>
</table>
Deciding the dose……

"...say when..."
Managing toxicity

- Numbness 12%
- Drowsiness 34%
- Constipation 35%
- Rash 16%
- Thrombosis 15%
Lenalidomide: Pharmacologic Evolution

- More “potent” immunomodulator than thalidomide
  - Up to 50,000 times more potent inhibitor of TNFα
  - Increased stimulation of T-cell proliferation
  - Augmented stimulation of IL-2 and IFNγ production

Stirling D. Semin Oncol. 2001;28:602
MM-009 and MM-010: two phase III trials of Len + Dex in relapsed/refractory MM

**Inclusion criteria**
- ≤ 3 prior therapies
- No Dex resistance
- Normal hepatic and renal function

**Primary end-point**: TTP
**Secondary end-points**: OS, RR, safety, 1st skeletal-related event, PS

**Len** 25 mg days 1–21
**Placebo** days 22–28
**Dex** 40 mg days 1–4, 9–12, 17–20

(MM009: n=177, MM010: n=176)

× 4 courses

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

(MM009: n=176, MM010: n=175)

Continue until PD
Same, except Dex days 1–4

Stadtmauer et al: REVLIMID/dex improves OS to 42 months when used specifically in second-line

<table>
<thead>
<tr>
<th></th>
<th>Pooled MM-009/010 Follow Up (Dimopoulos)</th>
<th>2\textsuperscript{nd} line vs 3\textsuperscript{rd} line plus (Stadtmauer)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REVLIMID/Dex</td>
<td>2\textsuperscript{nd} line</td>
</tr>
<tr>
<td>ORR, %</td>
<td>60.6*</td>
<td>66.9</td>
</tr>
<tr>
<td>CR, %</td>
<td>15*</td>
<td>20.3</td>
</tr>
<tr>
<td>TTP, mos</td>
<td>13.4*</td>
<td>17.1</td>
</tr>
<tr>
<td>OS, mos</td>
<td>38*†</td>
<td>42</td>
</tr>
</tbody>
</table>

\(*p < 0.001; \# p = 0.03; \dagger p = 0.045\)
With Revlimid, quality of response improves over time

- First response can be seen quickly with lenalidomide + dexamethasone
  - median time to first response 2.1 months\(^1\)
- Response quality and the number of CRs increases over time!\(^{1,2}\)
  - median time to CR/nCR 5.1 months\(^1\)

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Number of responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>50</td>
</tr>
<tr>
<td>C4</td>
<td>40</td>
</tr>
<tr>
<td>C5</td>
<td>30</td>
</tr>
<tr>
<td>C6</td>
<td>20</td>
</tr>
<tr>
<td>C7</td>
<td>10</td>
</tr>
<tr>
<td>C8</td>
<td>0</td>
</tr>
<tr>
<td>C9</td>
<td>0</td>
</tr>
<tr>
<td>C10</td>
<td>0</td>
</tr>
<tr>
<td>C11</td>
<td>0</td>
</tr>
<tr>
<td>C12</td>
<td>0</td>
</tr>
<tr>
<td>C13</td>
<td>0</td>
</tr>
<tr>
<td>C14</td>
<td>0</td>
</tr>
<tr>
<td>C15</td>
<td>0</td>
</tr>
<tr>
<td>C16</td>
<td>0</td>
</tr>
<tr>
<td>C17</td>
<td>0</td>
</tr>
<tr>
<td>C18</td>
<td>0</td>
</tr>
<tr>
<td>C19</td>
<td>0</td>
</tr>
<tr>
<td>C20</td>
<td>0</td>
</tr>
</tbody>
</table>

CR = complete response; nCR = near CR; VGPR = very good partial response.

P value = <0.0001

Structural Similarities and Functional Differences Between IMiDs

- **Thalidomide**
  - Dose: 100-200 mg/d
  - Side Effects: Neuropathy, Constipation, Sedation, DVT

- **Lenalidomide**
  - Dose: 15-25 mg/d
  - Side Effects: Myelosuppression, Skin rash, DVT

- **Pomalidomide**
  - Dose: 1-4 mg/d
  - Side Effects: Myelosuppression, Fatigue, DVT
"...Apparently you collapsed when told the price of these..."
Key Elements: Registration

Physician Registers
- Confirmation of registration and Prescribers ID number
- Physician Resource Pack

Patient registration and informed consent
- Confirmation of registration and Patient ID number

Pharmacy Registers
- Confirmation of registration and Pharmacy ID number

Counselling and Informed consent
- Microsoft Word Document

Celgene Risk Management Centre
- Data-input
- Verification
- Risk management

Patient

Pharmacy
Treatment of transplant eligible patients <65yrs.
New Treatment Paradigm for Patients Who Are Eligible for Autotransplantation

Have novel agents incorporated into ASCT opened the doors for a risk-adapted strategy?
Concept of Consolidation and maintenance.

• **Consolidation**
  - Treatment intensification
  - Typically high dose
  - Multidrug treatment
  - Short duration

• **Maintenance.**
  - Treatment utility to prevent disease recurrence.
  - Lower drug doses
  - Usually single drug
  - Longer duration i.e. years
<table>
<thead>
<tr>
<th>Disease category</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR, stringent complete response</td>
<td>Normal free light chain (FLC) and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence</td>
</tr>
<tr>
<td>CR, complete response</td>
<td>Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow</td>
</tr>
<tr>
<td>VGPR, very good partial response</td>
<td>Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR • ≥90% reduction in serum M-protein AND urine M-protein &lt;100mg per 24hour</td>
</tr>
<tr>
<td>PR, partial response</td>
<td>≥50% reduction of serum M-protein AND reduction in 24h urinary M-protein by ≥90% OR to &lt;200mg per 24hour • If serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum FLC is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell % was ≥30% • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required</td>
</tr>
<tr>
<td>SD, stable disease</td>
<td>Not meeting criteria for CR, VGPR, PR or progressive disease</td>
</tr>
</tbody>
</table>
### Which induction regimen?

<table>
<thead>
<tr>
<th>Treatment Schedule</th>
<th>No of Patients</th>
<th>Pre -transplant</th>
<th>Post -transplant</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&gt;PR (%)</td>
<td>CR +nCR( %)</td>
<td>&gt;PR (%)</td>
</tr>
<tr>
<td>Thal-Dex vs. Dex</td>
<td>470</td>
<td>63 vs. 46</td>
<td>7.7 vs.2.6</td>
<td>-</td>
</tr>
<tr>
<td>CTD vs. CVAD</td>
<td>254</td>
<td>87 vs. 54</td>
<td>19 vs. 9</td>
<td>88 Vs 79</td>
</tr>
<tr>
<td>Len–Dex vs. Len–Dex</td>
<td>445</td>
<td>81 vs.75</td>
<td>17 vs.14</td>
<td>-</td>
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<td>Len –Dex vs. Dex</td>
<td>198</td>
<td>85 vs. 51</td>
<td>22 vs 4</td>
<td>-*</td>
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<td>Len-Cy-Dex</td>
<td>53</td>
<td>83</td>
<td>2</td>
<td>-</td>
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<tr>
<td>Len-Dex- Clarithromycin</td>
<td>72</td>
<td>90</td>
<td>46</td>
<td>-</td>
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<tr>
<td>Bortezomib-Dex</td>
<td>48</td>
<td>66</td>
<td>21</td>
<td>90</td>
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<tr>
<td>Bz- Dex vs. VAD</td>
<td>482</td>
<td>82 vs. 65</td>
<td>15 vs. 7</td>
<td>91 vs 91</td>
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<tr>
<td>Bz-Doxil-Dex</td>
<td>36</td>
<td>89</td>
<td>32</td>
<td>96</td>
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<tr>
<td>Bz-Thal-Dex</td>
<td>38</td>
<td>92</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Bz-AD vs. VAD</td>
<td>300</td>
<td>83 vs. 59</td>
<td>5 vs. 1</td>
<td>93 vs 80</td>
</tr>
<tr>
<td>Bz-DTPACE</td>
<td>12</td>
<td>83</td>
<td>17</td>
<td>92</td>
</tr>
<tr>
<td>VBMCP/VBAD-Bz vs. Thal-Dex vs. Bz-Thal-Dex</td>
<td>183</td>
<td>72 vs. 66 vs.80</td>
<td>28 vs. 12 vs. 41</td>
<td>97 vs. 97 vs. 97</td>
</tr>
</tbody>
</table>

- 4yr OS after 4 cycles and transplant: 92 in both arms
- regimes 3>2>1
- Novel agent induces more CR+ nCR

**Level 2A**

![CancerCare Manitoba](image)
All patients must be referred to BMT upon initiation of induction therapy

Transplant Algorithm

Plasma Cell Myeloma
Achieving PR or CR

Age < 70, KPS > 70

Yes

No

Successful collection of HPC aliquot (Cy2.5 g/m² + GCSF, 20L pheresis)

8 x 10⁶ CD34/kg (target)
2 x 10⁶ CD34/kg (min)

No SCT

AutoSCT: Mel 200 (CrCl ≥ 50, else Mel 140)

Age ≤ 60
PCL
Response: PR
See High Risk Algorithm

Clinical Relapse
See Salvage Algorithm

CancerCare
MANITOBA
Salvage Algorithm

MM and Relapse ≥ 18 mo after first ASCT
Response to reinduction: PR, CR

Age < 70, KPS > 70

Yes

2nd AutoSCT using Mel 200 (CrCl ≥ 50) else Mel 140

No

No Transplant

PR. Partial Response, CR. Complete Response (International Response Criteria)
PCL: Plasma Cell Leukemia, SCT: Stem Cell Transplant, Mel: Melphalan
META-ANALYSIS OF STUDIES INCLUDING A THALIDOMIDE MAINTENANCE REGIMEN

A

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Odds ratio (95% CI)</th>
<th>P-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM-9902</td>
<td>597</td>
<td>0.61 (0.33-1.13)</td>
<td>.040</td>
</tr>
<tr>
<td>Spencer et al.</td>
<td>243</td>
<td>0.43 (0.21-0.91)</td>
<td>.004</td>
</tr>
<tr>
<td>Total Therapy 2</td>
<td>668</td>
<td>0.82 (0.60-1.12)</td>
<td>.090</td>
</tr>
<tr>
<td>Ludwig et al.</td>
<td>128</td>
<td>0.93 (0.53-1.66)</td>
<td>.810</td>
</tr>
<tr>
<td>Myeloma IX</td>
<td>820</td>
<td>0.77 (0.55-1.07)</td>
<td>.040</td>
</tr>
<tr>
<td>All Studies</td>
<td>2456</td>
<td>0.75 (0.64-0.87)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

B

![Graph showing overall survival and differences between maintenance and no maintenance](CancerCare Manitoba)

### PHASE 3 STUDIES OF LENALIDOMIDE MAINTENANCE

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Median follow-up</th>
<th>PFS / TTP</th>
<th>OS</th>
<th>OS after relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 2005-02¹</td>
<td>Len consol - R Len</td>
<td>34 mo</td>
<td></td>
<td>44 mo</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>24 mo (P&lt;10⁻⁸)</td>
<td>No significant difference</td>
</tr>
<tr>
<td>CALGB 100104²</td>
<td>R Len</td>
<td>28 mo</td>
<td></td>
<td>48 mo</td>
<td>&gt; Len</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>31 mo (P&lt;0.0001)</td>
<td>NR</td>
</tr>
</tbody>
</table>

23 deaths in the lenalidomide arm and 39 deaths in the placebo arm.

ITT Analysis with a median follow-up from transplant of 28 months.

Follow-up to 04/17/2011

\( P = .018 \)

Treatment of non transplant eligible patients >70yrs.
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 comorbid conditions

  **Stratification** $\beta_2$-microglobulin, albumin, region

**VMP**
- Cycles 1–4
  - Bortezomib 1.3 mg/m$^2$ IV: d 1, 4, 8, 11, 22, 25, 29, 32
  - Melphalan 9 mg/m$^2$ and prednisone 60 mg/m$^2$: d 1–4
- Cycles 5–9
  - Bortezomib 1.3 mg/m$^2$ IV: d 1, 8, 22, 29
  - Melphalan 9 mg/m$^2$ and prednisone 60 mg/m$^2$: d 1–4

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

**MP**
- Cycles 1–9
  - Melphalan 9 mg/m$^2$ and prednisone 60 mg/m$^2$: d 1–4

- Primary end point: TTP

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

Updated Vista study

Median OS was 56.4 versus 43.1 months
Discontinuation of treatment because of adverse events was similar for the VMP and MP treatment groups (15% vs. 14%, respectively).
## MPT trials in published literature 2011

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Trial</th>
<th>Trial type</th>
<th>Age</th>
<th>Stage</th>
<th>Dose/Schedule</th>
<th>Cycle</th>
<th>1º endpoint</th>
<th>Results (MPTvs MP)</th>
<th>OS as a 2º endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wijermans 2010</td>
<td>HOVON 49 n=333</td>
<td>Randomized Open Label Multicenter Phase III</td>
<td>&gt; 65 years</td>
<td>Newly diagnosed Non-SCT eligible IB, II-III</td>
<td>M 0.25mg/kg d1-5 P 1mg/kg d1-5 +/-Thal 200mg OD</td>
<td>28d x 8 cycles</td>
<td>EFS</td>
<td>Median EFS: 13 vs 9mo (p&lt;0.001) At 2 years: 29% vs 10% EFS (p&lt;0.01)</td>
<td>OS: 40 vs 31mo (p=0.05)</td>
</tr>
<tr>
<td>Waage 2010</td>
<td>Nordic n=357</td>
<td>Randomized Double-blind Controlled Multicenter Phase III</td>
<td>Median 74 years</td>
<td>Newly diagnosed Non-SCT eligible DS I-III</td>
<td>M 0.25mg/kg d1-4 P 100mg d1-4 +/-Thal 400mg OD → 200mg maintenance</td>
<td>Q42d x 4 cycles</td>
<td>OS</td>
<td>Median OS: 29 vs 32 mo (p=0.16 Cox, p=0.35 log rank)</td>
<td></td>
</tr>
<tr>
<td>Hulin 2009</td>
<td>IFM 01/02 n=229</td>
<td>Randomized Controlled Multicenter Phase III</td>
<td>≥ 75 years</td>
<td>Newly diagnosed Non-SCT eligible DS II-III</td>
<td>M 0.2mg/kg d1-4 P 2mg/kg d1-4 +/-Thal 100mg OD</td>
<td>Q42d x 12 cycles</td>
<td>OS</td>
<td>Median OS: 44 vs 29 mo (HR 0.68, p=0.028)</td>
<td></td>
</tr>
<tr>
<td>Palumbo 2008 (Long-term follow-up data, median 38 mo)</td>
<td>GIMEMA n=255</td>
<td>Randomized Multicenter Open Label Unblinded</td>
<td>&gt; 65 years</td>
<td>Newly diagnosed Non-SCT eligible DS II-III</td>
<td>M 4mg/m² d1-7 P 40mg/m² d1-7 +/-Thal 100mg OD → 100mg maintenance</td>
<td>Q28d x 6 cycles</td>
<td>EFS</td>
<td>Median PFS: 21.8 vs. 14.5mo (HR 0.63, p&lt;0.001)</td>
<td>Median OS: 45 vs 47.6 mo (HR 1.04, p=0.79)</td>
</tr>
<tr>
<td>Facon 2007</td>
<td>IFM 99/06 n=321 (for MP &amp; MPT arms)</td>
<td>Randomized Multicenter</td>
<td>65-75 years</td>
<td>Newly diagnosed Non-SCT eligible DS II-III &amp; high-risk stage I</td>
<td>M 0.25mg/kg d1-4 P 2mg/kg d1-4 +/-Thal ≤ 400mg OD</td>
<td>Q42d x 12 cycles</td>
<td>OS</td>
<td>Median OS: 51.6 vs 33 mo (HR 0.59, p=0.0006)</td>
<td></td>
</tr>
<tr>
<td>Palumbo 2006 (Median fu = 16 mo)</td>
<td>GIMEMA n=255</td>
<td>Randomized Multicenter Open Label Unblinded</td>
<td>&gt; 65 years</td>
<td>Newly diagnosed Non-SCT eligible DS II-III</td>
<td>M 4mg/m² d1-7 P 40mg/m² d1-7 +/-Thal 100mg OD → 100mg maintenance</td>
<td>Q28d x 6 cycles</td>
<td>EFS</td>
<td>EFS @ 2 yrs: 54% vs. 27% (HR 0.51, p=0.0006)</td>
<td>OS @ 3 yrs: 80% vs. 64% (HR 0.68, p=0.19)</td>
</tr>
</tbody>
</table>
Phase III study: MPR in elderly patients with newly diagnosed MM

Induction (up to 9 28-day cycles)

- Arm A: MPR
  - R: 10 mg/day, days 1–21
  - M: 0.18 mg/kg, days 1–4
  - P: 2 mg/kg, days 1–4

- Arm B: MPR
  - R: 10 mg/day, days 1–21
  - M: 0.18 mg/kg, days 1–4
  - P: 2 mg/kg, days 1–4

- Arm C: MP
  - M: 0.18 mg/kg, days 1–4
  - P: 2 mg/kg, days 1–4

Maintenance

- MPR
  - R: 10 mg/d, days 1–21 every 28 days

- Placebo

Progression or unacceptable toxicity

Open label lenalidomide 25 mg/day +/- dex for eligible patients

M, melphalan; P, prednisone; R, lenalidomide

Palumbo et al. ASH 2010 (Abstract 622)
### Phase III Study: MPR in elderly patients

**Patients: n=459; > 65 yrs**

<table>
<thead>
<tr>
<th></th>
<th>MPR-R</th>
<th>MPR</th>
<th>MP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=152</td>
<td>N=153</td>
<td>N=154</td>
</tr>
<tr>
<td>Median age</td>
<td>71</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>&gt; 75 years</td>
<td>24%</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>65 - 75 years</td>
<td>76%</td>
<td>76%</td>
<td>75%</td>
</tr>
<tr>
<td>ISS stage I/ II/ III</td>
<td>18/33/49%</td>
<td>21/31/48%</td>
<td>18/31/51%</td>
</tr>
</tbody>
</table>

### Response data for patients 65 – 75 years

<table>
<thead>
<tr>
<th></th>
<th>MPR-R</th>
<th>MPR</th>
<th>MP</th>
<th>$P$ Value (MPR+R vs MP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>79%</td>
<td>47%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$\geq$ VGPR</td>
<td>35%</td>
<td>10%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to first response</td>
<td>2 months</td>
<td>3 months</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Analysis include data up to Feb 28, 2011
Median follow up of 30 mos

Palumbo et al. ASH 2010 (abstract 622); oral presentation: Palumbo et al., ASH 2011, Abstract 475
# Treatment Discontinuation in Phase III Trials of Novel-Agent-Based Therapies

<table>
<thead>
<tr>
<th>MPT vs MP trials(^1)-(^6)</th>
<th>VISTA trial: VMP vs MP(^7)</th>
<th>MM-015 study: MPR-R vs MPR vs MP(^8)</th>
<th>ECOG trial: RD vs Rd(^9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPT</td>
<td>MP</td>
<td>VMP</td>
<td>MP</td>
</tr>
<tr>
<td>15-52%</td>
<td>5-13%</td>
<td>34%*</td>
<td>14%</td>
</tr>
</tbody>
</table>

*19% discontinued bortezomib, but remained on MP.
†Includes MPR-R and MPR for the initial 9 cycles.
‡Only data for overall patient population available (age 35-87).

---

Summary of treatment in non transplant eligible

- VMP first line therapy in the elderly at CCMB.
- MPT probably equivalent.
- MPR in exceptional circumstances.
- Dose modifications and scheduling modifications to reduce toxicity.

Category 1 or 2A level of evidence.
Management of relapsed/ refractory disease.
Appendix I

Myeloma Treatment Algorithm Upfront

Transplant Candidate

Y → Specific Issues

N → Induction

2nd Transplant
If Relapse > 18 Months

Specific Issues

Y → Induction

N → Specific Issues

Y → Vel Based VD / PAD

N → Thal Based CTD

Vel Based VD / PAD

Thal Based CTD

PBSCH + HDM

>VGPR

Y → Observe

N → 12 Months Thal

12 Months Thal

Relapse R₁

REV Based RCD / RD

Specific Issues

Y → Vel Based VMP

N → Thal Based MPT

Vel Based VMP

Thal Based MPT

Relapse R₁

Clinical Choice As Appropriate CWAP

If Response >12 months Repeat Same Regime

Alternative Regime VMP → MPT

Relapse R₂

REV Based RCD / RD

OPD treatment
Revlimid/thalidomide
Renal failure
Velcade based
Neuropathy
Revlimid based
Thrombosis risk
Velcade based
Bad Bone disease
Velcade based
Adverse effects
Revlimid/switch class
High risk groups
Allogeneic transplant
Plasma cell Leukaemia

- PB Plasma cell count is $2 \times 10^9/$ml. or 20% of differential.
- Associated with adverse cytogenetics.
- Minimal bone lesions
  - Hypercalcemia
  - Organomegaly.
  - Lymphadenopathy
- Loss of CD56.
- Treatment of choice is $C_{750}BD$. 
Supportive care
# Thromboprophylaxis using ImiD based therapy

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Clinical Factors</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>· IMiD and previous personal history of VTE</td>
<td>· Prophylactic dose of LWMH</td>
</tr>
<tr>
<td></td>
<td>· IMiDs plus other therapy (high dose dexamethasone, doxorubicin or multiagent chemotherapy)</td>
<td>· Warfarin adjusted for INR 2-3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>· IMiD and any 2 VTE risk factors including (but not limited to):</td>
<td>Low bleeding risk</td>
</tr>
<tr>
<td></td>
<td>· Strong family history of VTE or known thrombophilia</td>
<td>· Prophylactic dose of LWMH or adjusted warfarin for INR 2-3 if bleeding risk is low</td>
</tr>
<tr>
<td></td>
<td>· Obesity</td>
<td>High bleeding risk</td>
</tr>
<tr>
<td></td>
<td>· Prolonged immobilization</td>
<td>· Prior uncontrolled bleed,</td>
</tr>
<tr>
<td></td>
<td>· Indwelling catheters</td>
<td>platelet count &lt; 80 x 109/L or difficult to control warfarin;</td>
</tr>
<tr>
<td></td>
<td>· Additional medication with VTE risk (estrogens, EPO)</td>
<td>reasonable to offer ECASA 81 mg OD</td>
</tr>
<tr>
<td></td>
<td>· Additional comorbidities that can increase risk (nephrotic syndrome, aggressive disease)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· high levels of paraprotein</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>· IMiD therapy is the only VTE risk factor</td>
<td>· ECASA*81 mg OD</td>
</tr>
</tbody>
</table>

*Enteric coated acetylsalicylic acid*
Skeletal-Related Events Are a Serious Problem for Patients With Multiple Myeloma


\[
\text{Total SREs: } 51\%
\]
\[
\text{Pathologic Fracture: } 37\%
\]
\[
\text{Radiation Therapy: } 34\%
\]
\[
\text{Surgical Intervention: } 4\%
\]
\[
\text{Spinal Cord Compression: } 2\%
\]

\(^a\) 21-month placebo cohort data (including osteolytic lesions) \(^2\) except for surgical intervention and spinal cord compression, for which only 9-month data are available from placebo arm of randomized study. \(^2\)

Myeloma Bone Disease

BP should be administered to all patients receiving chemotherapy.

Should not be administered to plasmacytomas of bone, MGUS or smoldering MM.

Pre-dental examination is recommended before starting BP.

BP therapy should be for 2 yrs at diagnosis and at relapse but can be continued at physician discretion if active SRE's.

BP therapy should be discontinued in cases of BONJ.

Receptor activator of nuclear factor-κB ligand (RANKL) acts to stimulate osteoclast formation and activity leading to bone erosion, whereas dickkopf1 (DKK1) appears to inhibit osteoblasts, thus preventing repair of the lesions.
Newly diagnosed or relapsed Multiple Myeloma Documented: Lytic bone lesion, fractures, osteopenia or osteoporosis and/or receiving chemotherapy

No bisphosphonate therapy

Dental evaluation

Pamidronate (Formulary Bisphosphonate)

CrCl > 30 mL/min

Pamidronate 90 mg IV in 500 mL NS over 4-6 hours q4 weeks

Pamidronate 90 mg IV in 250 mL NS over 2 hours q4 weeks

Contraindication to IV Zoledronic acid Yes

No

CrCl > 60

Yes

Zoledronic acid 4 mg IV in 100 mL NS or D5W over 15 minutes q3-4 weeks (Non Formulary Request Required)

Clodronate 1600 mg po OD 2 hours before or after a meal

Contraindication to oral Clodronate Yes

No Bisphosphonate

Contraindication to IV Zoledronic acid No

CrCl > 60

Yes

Zoledronic acid 4 mg IV in 100 mL NS or D5W over 15 minutes q3-4 weeks (Non Formulary Request Required)

Contraindication to oral Clodronate No

CrCl > 80

Yes

Clodronate 1600 mg po OD 2 hours before or after a meal

Discontinue bisphosphonate therapy:

- After 1 yr of therapy for patients who achieved CR or VGPR post transplantation and/or received a novel therapy combination and have no active bone disease
- After 2 yrs of therapy for patients who achieve less than VGPR and/or those without active bone disease
- In patients who develop osteonecrosis of the jaw

Note: For patients with continued active bone disease after 2 yrs of BP therapy, further BP use is recommended at the discretion of the treating physician
MRC Myeloma IX—ZOL Significantly Improved OS vs CLOa

Abbreviations: CLO, clodronate; ZOL, zoledronic acid.

*Log-rank, stratified by treatment pathway.

a Kaplan-Meier analysis adjusted for treatment pathway (intensive vs not).
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO 2005&lt;sup&gt;1&lt;/sup&gt;</td>
<td>“Long term”</td>
</tr>
</tbody>
</table>
| Mayo Clinic 2006<sup>2</sup> | Monthly for 2 years, then  
  • CR or stable plateau: discontinue  
  • Active disease: continue every 3 months |
| ASCO 2007<sup>3</sup>   | Monthly for 2 years; reinitiate at relapse                                        |
| IMWG 2007<sup>4</sup>   | Monthly for 1 year, then (up to 2 years)  
  • CR/VGPR and no bone disease: discontinue  
  • < VGPR and/or bone disease: continue  
  After 2 years:  
  • No active bone disease: discontinue  
  • Active bone disease: at own discretion |
| EMN 2009<sup>5</sup>    | Monthly for 1 year, then (up to 2 years)  
  • Continue at physician’s discretion  
  • If relapse, restart |
| NCCN 2012<sup>6</sup>   | Not addressed                                                                    |

CR = Complete response; VGPR = Very good partial response.

Vertebroplasty/ Balloon Kyphoplasty.

**Indications.**

- Conservative medical management has failed.
- Patients with acute Vertebral compression fractures.
- Localized pain in the spine.
- Loss of height or abnormal curvature.
- PMMA is used.
- For those with a posterior defect, consider balloon procedure.
- Best performed before Radiation therapy.
“I feel a lot better since I ran out of those pills you gave me.”
Recommended dose adjustments for bortezomib-based combinations

- Depending on age and comorbidities (heart, lung, kidney, liver)

<table>
<thead>
<tr>
<th>Bortezomib</th>
<th>&lt;65 years</th>
<th>65–75 years</th>
<th>&gt;75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.3 mg/m² twice weekly</td>
<td>1.3 mg/m² One cycle: twice weekly</td>
<td>1.3 mg/m² once weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Then: once weekly</td>
<td></td>
</tr>
</tbody>
</table>

If a Grade 3/4 AE occurs:
1. Discontinue therapy
2. Wait for toxicity to resolve to Grade 1
3. Restart at a lower dose

A Palumbo et al, ASH 2009
S Bringhen et al JCO 2010
IV and SC administration:

- IV injections were administered at a concentration of 1 mg/mL (3.5 mg in 3.5 mL normal [0.9%] saline) as a 3-to 5-second IV push

- SC injections were administered at a concentration of 2.5 mg/mL (3.5 mg in 1.4 mL of 0.9% saline)

- SC injection sites were the thighs or abdomen
  - Injection site was rotated for subsequent injections within a cycle
## Response After 8 Cycles (Bortezomib ± Dexamethasone)

<table>
<thead>
<tr>
<th>Response rate, %</th>
<th>Bortezomib IV ± dex (N=73)</th>
<th>Bortezomib SC ± dex (N=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (CR + PR)</strong></td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>CR*</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>PR</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>nCR</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>VGPR</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>≥VGPR (CR + nCR + VGPR)</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Response improvement (cycle 4 → 8) in patients who received dex, n/N (%)

- **PR → CR**
  - Bortezomib IV ± dex: 2/15 (13)
  - Bortezomib SC ± dex: 4/31 (13)

- **<PR → PR**
  - Bortezomib IV ± dex: 7/23 (30)
  - Bortezomib SC ± dex: 14/47 (30)

Data shown for the response-evaluable population

*CRs were confirmed by bone marrow assessment

**Pharmacokinetics**

- Bortezomib exposure following SC injection was equivalent to that following IV administration.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Bortezomib IV (N=14)</th>
<th>Bortezomib SC (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL), mean (SD)</td>
<td>223 (101)</td>
<td>20.4 (8.87)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (min), median (range)</td>
<td>2 (2–5)</td>
<td>30 (5-60)</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{last}}$ (ng.h/mL), mean (SD)</td>
<td>151 (42.9)</td>
<td>155 (56.8)</td>
</tr>
</tbody>
</table>

Treatment Guidelines: Gaps

- Lack of specific and consistent recommendations regarding
  - Treatment choices in patients with renal dysfunction
  - Treatment choices in patients with comorbidities that increase the risk of infections and peripheral neuropathy
  - Managing myelosuppression
  - Risk and management of thromboembolic events

- Lack of evidence-based data for sequencing of agents in maintenance and salvage settings
# Lenalidomide and GCSF

If ANC <500/µl

<table>
<thead>
<tr>
<th>ANC&gt;1000µl</th>
<th>ANC&lt;1000µl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resume Len at same dose level.</td>
<td>Aggressive disease</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Resume Len at same dose level with GCSF</td>
</tr>
</tbody>
</table>

Dimopoulous et al Leukaemia 2011
Horizon scanning
Target evolution

Old targets
- Hormones
- DNA
- Tubulin
- Topoisomerase

New targets
- Specific antigens
- Signal transduction
- Angiogenesis
- Apoptosis
- Cell cycle
- Proteasome

Future targets
- Genetic markers on individual patients
  - RAN/ZHX2/CHC1L
- GEP classification
Gene expression profiling in NDMM

HOVON-65/GMMG-HD4 trial

Novel Agents with Activity

- **HDAC inhibitors:** SAHA, LBH589, KD5170
- **Anti-angiogenesis agents:** Anti-VEGF
- **Monoclonal Antibodies:** Anti-CD138, Elotuzumab
- **Anti-growth factors:** Targeting IL6, IGF, IRF4
- **Hsp90 inhibitors:** Tanespimycin
- **Proteosome inhibitors:** Carfilzomib, NPI 0052.
- **Imids:** Pomalidomide.
Ongoing challenges...

- When to treat by identifying “high risk” patients?
- Which drugs are best used as first line treatment?
- Which drugs are best used for relapse?
- Which combinations of drugs work best together?
- Which combinations of drugs are least likely to cause serious side effects?
- Which drug for which patient?
- How to balance the books?
- What is the optimal supportive care?
Myeloma DSG-past and present