Autologous Stem Cell Transplantation in Multiple Myeloma

Optimal Frontline Therapy and Maintenance Therapy

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ASCT in Myeloma

...... Where we were..

- **Induction**
  - VAD
    - Dexamethasone alone
    - Dexamethasone + thalidomide

- **Stem cell mobilization/collection**

- **High-dose melphalan + ASCT**

**Outcomes**

- Overall response rate: 80%
- CR/nCR rate: 20%
- Median PFS: 20-28 mos
- Median overall survival: 48-60 mos
Components of ASCT

- **INDUCTION**
- Stem cell mobilization/collection
- **High-dose therapy + ASCT**
- **CONSOLIDATION**
- **Maintenance Therapy**

Potential integration of novel agents
Considerations

- Many trials include pre- and post-ASCT therapy that may influence PFS/OS independently
  - Induction
  - High-dose therapy
  - Maintenance
- ASCT outcomes are influenced by biological factors
  - International Staging System
  - FISH cytogenetics
  - GEP
  - Other factors (LDH, plasma cell leukemia)
- Time of randomization
  - Before induction
  - After ASCT
    - Potentially selects better patients as ~ 15% have high-risk disease
## Survival after ASCT by FISH at PMH (N=126)

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>N (%)</th>
<th>Median OS (months)</th>
<th>Relative Risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 del</td>
<td>10 (8%)</td>
<td>14.7</td>
<td>4.5 (1.5-13.1)</td>
<td>0.0025</td>
</tr>
<tr>
<td>t(4:14)</td>
<td>15 (12%)</td>
<td>18.3</td>
<td>4.8 (1.8-12.7)</td>
<td>0.0005</td>
</tr>
<tr>
<td>t(11:14)</td>
<td>16 (13%)</td>
<td>37.2</td>
<td>1.5 (0.5-4.8)</td>
<td>0.5231</td>
</tr>
<tr>
<td>13q del</td>
<td>39 (31%)</td>
<td>34.4</td>
<td>2.3 (1.0-5.2)</td>
<td>0.0498</td>
</tr>
<tr>
<td>None</td>
<td>43 (34%)</td>
<td>NYR</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Chang et al. Bone Marrow Transplant 2005;36:793-796. NYR=not yet reached
Hypothesis:

Since patients in CR or nCR after ASCT have better outcomes, achievement of a deep response before ASCT should confer even better results.

Depth of response usually correlates with PFS and OS
Pre-ASCT Induction Therapy

Phase III Trials

- **Novel regimen vs VAD**
  - *HOVON-50*: **TAD** vs **VAD**
  - *IFM 2005-02*: **BD** vs **VAD**
  - *HOVON 65/GMMG-HD4*: **PAD** vs **VAD**
  - *MRC IX*: **CTD** vs **CVAD**

- **Novel regimen versus thalidomide + dexamethasone**
  - *GIMEMA MMY-3006*: **VTD** vs **thal + dex**
  - *PETHEMA*: **VTD** vs **VBCMP/VBAD/Vel** vs **thal + dex**

- **Novel regimen vs novel regimen**
  - *IFM 2007-02*: **vTD** vs **BD**
## Summary of Phase III ASCT Trials

<table>
<thead>
<tr>
<th>Study/Author</th>
<th>N</th>
<th>Induction regimen</th>
<th># ASCT</th>
<th>Consolidation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOVON-50 Lokhorst</td>
<td>536</td>
<td>TAD, VAD</td>
<td>1</td>
<td>--</td>
<td>Thal</td>
</tr>
<tr>
<td>MRC IX Morgan</td>
<td>1111</td>
<td>CTD, CVAD</td>
<td>1</td>
<td>--</td>
<td>+/- thal</td>
</tr>
<tr>
<td>IFM 2005-02 Harousseau</td>
<td>482</td>
<td>BD, VAD</td>
<td>1 or 2</td>
<td>+/- len</td>
<td>+/- len in some</td>
</tr>
<tr>
<td>HOVON 65/GMMG-HD4 Sonneveld</td>
<td>613</td>
<td>PAD, VAD</td>
<td>1 or 2</td>
<td>--</td>
<td>B 1.3 mg/m²</td>
</tr>
<tr>
<td>GIMEMA MMY-3006 Cavo</td>
<td>447</td>
<td>VTD, Thal + dex</td>
<td>2</td>
<td>VTD</td>
<td>Dex</td>
</tr>
<tr>
<td>PETHEMA/GEM Rosinol</td>
<td>306</td>
<td>Thal + dex, VTD, VBMCP/VBAD/Vel</td>
<td>1</td>
<td>--</td>
<td>IFN-α2b vs Thal vs Thal + B</td>
</tr>
<tr>
<td>IFM 2007-02 Moreau</td>
<td>199</td>
<td>BD, vTD</td>
<td>1 or 2</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Post Induction Results in Phase III Trials

<table>
<thead>
<tr>
<th>Study/Author</th>
<th>N</th>
<th>Induction regimen</th>
<th>Overall response rate (%)</th>
<th>≥VGPR (%)</th>
<th>CR/nCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOVON-50 Lokhorst</td>
<td>556</td>
<td>TAD VAD</td>
<td>71 / 57</td>
<td>37 / 18</td>
<td>3 / 2</td>
</tr>
<tr>
<td>MRC IX Morgan</td>
<td>1111</td>
<td>CTD CVAD</td>
<td>82 / 71</td>
<td>33 / 27</td>
<td>13 / 8</td>
</tr>
<tr>
<td>IFM 2005-02 Harousseau</td>
<td>482</td>
<td>BD VAD</td>
<td>78 / 63</td>
<td>38 / 15</td>
<td>15 / 6</td>
</tr>
<tr>
<td>HOVON 65/GMMG-HD4 Sonneveld</td>
<td>613</td>
<td>PAD VAD</td>
<td>83 / 59</td>
<td>42 / 11</td>
<td>15 / 5</td>
</tr>
<tr>
<td>GIMEMA MMY-3006 Cavo</td>
<td>447</td>
<td>VTD Thal + dex</td>
<td>93 / 79</td>
<td>62 / 28</td>
<td>31 / 11</td>
</tr>
<tr>
<td>PETHEMA/GEM Rosinol</td>
<td>386</td>
<td>VTD Thal + dex VBMCP/VBAD/B</td>
<td>82 / 75</td>
<td>60 / 36</td>
<td>35 / 22</td>
</tr>
<tr>
<td>IFM 2007-02 Moreau</td>
<td>199</td>
<td>vTD BD</td>
<td>88 / 81</td>
<td>49 / 36</td>
<td>31 / 22</td>
</tr>
</tbody>
</table>
### Post-ASCT Results in Phase III Trials

<table>
<thead>
<tr>
<th>Study/Author</th>
<th>Induction regimen</th>
<th>Overall response rate after ASCT (%)</th>
<th>≥VGPR (%)</th>
<th>CR/nCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOVON-50 Lokhorst</td>
<td>TAD VAD</td>
<td>84 (76)</td>
<td>54 (44)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>MRC IX Morgan</td>
<td>CTD CVAD</td>
<td>91 (90)</td>
<td>84 (62)</td>
<td>50 (37)</td>
</tr>
<tr>
<td>IFM 2005-02 Harousseau</td>
<td>BD VAD</td>
<td>80 (77)</td>
<td>54 (68*)</td>
<td>35 (39*)</td>
</tr>
<tr>
<td>HOVON 65/GMMG-HD4 Sonneveld</td>
<td>PAD VAD</td>
<td>--</td>
<td>61 (36)</td>
<td>30 (15)</td>
</tr>
<tr>
<td>GIMEMA MMY-3006 Cavo</td>
<td>VTD Thal + dex</td>
<td>93 (93*) (84*)</td>
<td>62 (82*)</td>
<td>31 (55*)</td>
</tr>
<tr>
<td>PETHEMA65 Rosinol</td>
<td>VTD Thal + dex</td>
<td>77 (58)</td>
<td>60 (29)</td>
<td>46+ (24+)</td>
</tr>
<tr>
<td></td>
<td>VBMCP/VBAD/B</td>
<td>73</td>
<td>58 (36)</td>
<td>46+ (38+)</td>
</tr>
<tr>
<td>IFM 2007-02 Moreau</td>
<td>nTD BD</td>
<td>89 (86)</td>
<td>58 (74)</td>
<td>61 (52)</td>
</tr>
</tbody>
</table>

*After 2 transplants. If performed  *IF negative CR
## Do Novel Induction Regimens Confer Better PFS/OS?

<table>
<thead>
<tr>
<th>Study/Author</th>
<th>Induction regimen</th>
<th>Median PFS (mos)</th>
<th>3 year PFS (%)</th>
<th>Median OS (mos)</th>
<th>3-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOVON-50 Lokhorst</td>
<td>TAD VAD</td>
<td>34 (25)</td>
<td>--</td>
<td>73 (60)</td>
<td>--</td>
</tr>
<tr>
<td>MRC IX Morgan</td>
<td>CTD CVAD</td>
<td>27 (25)</td>
<td>--</td>
<td>NYR (63)</td>
<td>--</td>
</tr>
<tr>
<td>IFM 2005-02 Harousseau</td>
<td>BD VAD</td>
<td>36 (30)</td>
<td>--</td>
<td>--</td>
<td>81% (77%)</td>
</tr>
<tr>
<td>HOVON 65/GMMG-D4 Sonneveld</td>
<td>PAD VAD</td>
<td>~34 (~24)</td>
<td>48% (42%)</td>
<td>--</td>
<td>78% (71%)</td>
</tr>
<tr>
<td>GIMEMA MMY-3006 Cavo</td>
<td>VTD Thal + dex</td>
<td>NYR NYR</td>
<td>68% (56%)</td>
<td>--</td>
<td>86% (84%)</td>
</tr>
<tr>
<td>PETHEMA/GEM Rosinol</td>
<td>VTD Thal + dex VBMCP/VBAD/B</td>
<td>NYR</td>
<td>--</td>
<td>--</td>
<td>~80% (~80%)</td>
</tr>
<tr>
<td>IFM 2007-02 Moreau</td>
<td>vTD BD</td>
<td>26 (30)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
Other Induction Regimens

- Many other phase I-II trials of 3- and 4-drug regimens
  - *ASCT not mandated in many studies*
  - *Examples:*
    - RVD (lenalidomide + bortezomib + dex)
    - RAD (lenalidomide + doxorubicin + dex)
    - CyBorD (weekly oral cyclophosphamide + bortezomib + dex)
    - EVOLUTION (CVD with intravenous cyclophosphamide +/- lenalidomide)
    - RVDD (lenalidomide + bortezomib + pegylated liposomal doxorubicin)
- RVD regimen selected for subsequent phase III trials
  - *Dana Farber/IFM trial of early vs delayed ASCT*
  - *CTN trial evaluating post-ASCT approaches*
  - *SWOG S0777 study of induction with lenalidomide + dex vs RVD, followed by len + dex until progression*
### 3- and 4-drug Bortezomib-based Induction Trials

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>N With ASCT</th>
<th>Response (%) Post-induction</th>
<th>Response Post-ASCT</th>
<th>PFS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥PR</td>
<td>≥VGPR</td>
<td>≥CR/CR</td>
</tr>
<tr>
<td>VDD¹</td>
<td>30</td>
<td>20</td>
<td>93</td>
<td>63</td>
<td>40</td>
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<tr>
<td>RVD²</td>
<td>66</td>
<td>28</td>
<td>100</td>
<td>67</td>
<td>40</td>
</tr>
<tr>
<td>RVDD³</td>
<td>68</td>
<td>24</td>
<td>96</td>
<td>58</td>
<td>30</td>
</tr>
<tr>
<td>VDR⁴</td>
<td>42</td>
<td>6</td>
<td>90</td>
<td>55</td>
<td>22</td>
</tr>
<tr>
<td>VDC⁴</td>
<td>31</td>
<td>5</td>
<td>87</td>
<td>41</td>
<td>6</td>
</tr>
<tr>
<td>VDCR⁴</td>
<td>33</td>
<td>3</td>
<td>94</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>VTDC⁵</td>
<td>48</td>
<td>27</td>
<td>96</td>
<td>--</td>
<td>44</td>
</tr>
<tr>
<td>VCD⁶</td>
<td>300</td>
<td>--</td>
<td>84</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>CyBor-D⁷</td>
<td>30</td>
<td>30</td>
<td>93</td>
<td>60</td>
<td>48</td>
</tr>
</tbody>
</table>

Induction with Lenalidomide + Dex

- E4A03: Lenalidomide + low-dose or high-dose dex\textsuperscript{1}
  - *High overall response rate after 4 cycles (68%-79%)*
  - *Oral regimen; excellent tolerance with weekly dex*
  - Stem cell collection issues can be addressed with optimal mobilization approaches
  - *Therapy after 4 cycles not mandated → bias for ASCT outcomes*

- What can be expected if **all** patients go to ASCT?

\textsuperscript{1}Rajkumar SV et al. Lancet Oncol 2010; 11: 29 - 37
Phase III Trial: MPR vs ASCT in Patients <65 Years of Age (N=402)

New Myeloma Pt Stratified by age and ISS

Len + dex x 4 cycles

CY + G-CSF mobilization

MPR x 6 cycles

N=202

N=200

Melphalan 200 mg/m² + ASCT x 2

25% CR; 60% >VGPR
2-year PFS 75%
2-year OS 97%
Regimens incorporating novel agents produce high remission rates before ASCT
- Unprecedented CR, nCR and VGPR rates.
- Toxicity is acceptable
- Stem cell procurement not significantly compromised

In general, highest response rates seen with 3-drug regimens containing bortezomib + IMiD

Remission rates increase further post-ASCT and are better than those seen with older regimens
Induction Regimens—Summary (2)

- Although it is difficult to isolate the effect of induction per se, post-transplant PFS is usually ~3 years with modern frontline therapy.

- Our PMH policy is to use weekly CyBorD (bortezomib 1.5 mg/m²/week + p.o. cyclophosphamide 300 mg/m²/week + dex) for 4 cycles¹
  - No significant neuropathy or myelosuppression
  - Cost advantages


Definitions of Post-ASCT Therapy

- **Maintenance therapy**—any treatment administered after the completion of induction therapy in patients whose disease is either responsive or non-progressive, with the goal of prolonging survival\(^1\)
  - *Steroids*
  - *Interferon-alpha*
  - *IMiDs (thalidomide, lenalidomide)*
  - *Bortezomib*

- **Consolidation therapy**—relatively intensive short-term post-ASCT therapy
  - *Total therapy programs (DPACE\(^2\), VTDPACE\(^3\), VRD\(^3\))*
  - *VTD=bortezomib + thalidomide + dex*
  - *RVD=lenalidomide + bortezomib + dex*
  - *Lenalidomide alone*
  - *Bortezomib alone*

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Post-ASCT Maintenance Therapy

**Phase III Trials**

- **Thalidomide**—7 trials
  - *NCIC results from MY.10 presented at ASH 2010*
  - *MRC IX results just published*
- **Bortezomib**
  - *HOVON MM 65/GMMG-HD4*
  - *Nordic Myeloma Study Group trial--ongoing*
- **Lenalidomide**—2 trials
  - *IFM 2005-02 with lenalidomide consolidation + maintenance*
  - *CALBG 100104 trial*

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<table>
<thead>
<tr>
<th><strong>Author/Year</strong></th>
<th><strong>N</strong></th>
<th><strong>Thalidomide dose (mg)/duration</strong></th>
<th><strong>PFS/ EFS</strong></th>
<th><strong>Overall Survival</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Attal/2006</td>
<td>597</td>
<td>Thal 200 (median dose) vs obs/progression</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spencer/2006</td>
<td>243</td>
<td>Thal 200 + pred vs pred/12 months</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Maiolino/2008</td>
<td>212</td>
<td>Thal 200 + dex vs dex/12 months</td>
<td>+</td>
<td>NS</td>
</tr>
<tr>
<td>Barlogie/2006*</td>
<td>668</td>
<td>Thal 400/progression</td>
<td>+</td>
<td>NS (+ in high-risk)</td>
</tr>
<tr>
<td>Lokhorst/2010*</td>
<td>550</td>
<td>Thal 50/ progression</td>
<td>+</td>
<td>NS</td>
</tr>
<tr>
<td>Stewart/2010</td>
<td>325</td>
<td>Thal 200 + pred vs obs/48 months</td>
<td>+</td>
<td>NS</td>
</tr>
<tr>
<td>Morgan/2011*</td>
<td>--</td>
<td>Thal 100/progression</td>
<td>+</td>
<td>+ (if optimal relapse Rx)</td>
</tr>
</tbody>
</table>

*Thalidomide also given as part of induction therapy
Results of MY-10

### Progression Free Survival by Therapy

- Median PFS 28 vs 17 mos
- HR = 1.81 (95% CI 1.39-2.36) 
  
- (p<0.0001)

### Overall Survival by Therapy

- Median OS NYR vs 5 yrs
- HR = 1.29 (95% CI 0.89-1.88)
  
- (p = 0.18)

#### However, QOL compromised:

- **Physical:** 34% vs. 21% worsened  
  
- (p=0.03)

- **Role:** 29% vs. 17%  
  
- (p=0.04)

- **Cognitive:** 54% vs. 41%  
  
- (p=0.01)

- **Global:** 40% vs. 26%  
  
- (p=0.01)

### Issues with tolerability

- **Median time to thal dose reduction:** 3.4 months

- **Median duration thal:** 16.1 months
MRC Myeloma IX Study: Phase III Trial

Induction randomization

- Older, less fit N=856
  - MP
  - CTDa
- Younger, fitter N=1114
  - CTD
  - C-VAD
  - HDM 200 mg/m²

Maintenance randomization

- 820 patients
- Thalidomide 50 mg/day increasing to 100 mg/day after 4 weeks if well tolerated
- No maintenance

- Factorial design
- Primary outcome measures: PFS and OS (determined using Cox model)
  - PFS and OS measured from maintenance randomization

CTD, cyclophosphamide + thalidomide + dexamethasone; CTDa, CTD attenuated (low-intensity); C-VAD, vincristine + doxorubicin + dexamethasone + cyclophosphamide; HDM, high-dose melphalan; MP, melphalan + prednisone.

MRC IX Trial Intensive Arm

**PFS**
- Thalidomide: median 30 months
- No thalidomide: median 23 months
- HR 1.42 (95% CI 1.22-1.73) (p<0.001)

**Overall Survival**
- Thalidomide: 3-year survival 75%
- No thalidomide: 3-year survival 80%
- $P=0.26$


# Phase III Trial: Bortezomib Consolidation vs Observation following ASCT

**Nordic Myeloma Study Group (n=370)**

**Bortezomib consolidation** (21 weeks: 2 cycles twice weekly + 4 cycles once weekly) vs **observation** starting 3 mos post-ASCT

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib (n=168)</th>
<th>Observation (n=162)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-ASCT</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/nCR (%)</td>
<td>20</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>≥VGPR (%)</td>
<td>39</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td><strong>Post-consolidation</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥VGPR (%)</td>
<td>70</td>
<td>58</td>
<td>0.01</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>27</td>
<td>20</td>
<td>0.02</td>
</tr>
<tr>
<td>Overall survival, 2 yr (%)</td>
<td>90</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

Grade 3/4 adverse events: Neutropenia 22%, thrombocytopenia 9%, neurologic pain 5%, sensory neuropathy 3%<sup>1</sup>

Primary end-point: time to relapse
Secondary end-points: CR rate, PFS, OS, feasibility of long-term lenalidomide

CALGB 100104: Study Design

Registration

< 70 years
≥ 2 cycles of Rx
≥ stable MM
≤ 6 months post-ASCT
< 1 year from Rx start
2 x 10^6 CD34 cells/kg

Restaging at day 90-100

ASCT with MEL 200 mg/m²

CR
PR
SD

Randomization

Lenalidomide
10 mg/day until progression

Placebo until progression

Stratified by:
β₂-microglobulin
IMiD during induction

McCarthy PL, et al. ASCO 2010; abstract #8017.
Summary of Phase III Trials of Lenalidomide Maintenance after ASCT

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>N</th>
<th>Pre-ASCT Induction</th>
<th># ASCT</th>
<th>PFS/TTP</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attal/2010 (IFM 2005-02)</td>
<td>614</td>
<td>VAD or BD</td>
<td>1 or 2</td>
<td>42 Lenalidomide Observation</td>
<td>60%* 81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(+ len x 2 mos)*</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCarthy/2010 (CALBG 100104)</td>
<td>568</td>
<td>Lenalidomide 32% Bortezomib 42% Thalidomide 16%</td>
<td>1</td>
<td>42.3 Lenalidomide Observation</td>
<td>~50%* 80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Lenalidomide consolidation x 2 months in all patients

Attal M, et al. ASCO 2010; abstract #8018; McCarthy PL, et al. ASCO 2010; abstract #8017.
Lenalidomide Maintenance

Effect on PFS

CALGB100104

Progression Free Survival (PFS)


IFM 2005-01

Event Free Survival (EFS)

Attal M, et al. ASCO 2010; abstract #8018.
Lenalidomide Maintenance

**Effect on Overall Survival**

**CALGB 100104**

Median follow-up of 28 mos.  \( P=0.018 \)

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

**IMF 2005-02**

No significant difference


Attal M, et al. ASCO 2010; abstract #8018.
### Significant Toxicity with Lenalidomide Maintenance Phase III Trials

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>IMF 2005-02</th>
<th></th>
<th>CALGB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Len</td>
<td>Placebo</td>
<td>Len</td>
<td>Placebo</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>43%</td>
<td>14%</td>
<td>43%</td>
<td>9%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12%</td>
<td>6%</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2%</td>
<td>0.1%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Documented Infection</td>
<td>10%</td>
<td>4%</td>
<td>16%</td>
<td>5%</td>
</tr>
<tr>
<td>Discontinuation of lenalidomide</td>
<td>6%</td>
<td>4%</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td>2° malignancy</td>
<td>N=23 (6.8%)</td>
<td>N=6 (1.6%)</td>
<td>N=18 (6.5%)</td>
<td>N=4 (2.6%)</td>
</tr>
</tbody>
</table>

Attal M, et al. ASCO 2010; abstract #8018; McCarthy PL, et al. ASCO 2010; abstract #8017; Attal M, personal communications; IMWG Feb 2011.
Secondary Cancers with Lenalidomide
Maintenance: Considerations

- Small increase in incidence, but.....
  - IFM study included skin cancers
  - CALGB study had several cases even before starting drug
- EMA released statement in Sept 2011
  - “The benefit-risk balance for lenalidomide remains positive within its approved patient population but advises doctors of the risk of new cancers as a result of treatment with the medicine”
  - 3.98 new cancers per every 100 patient-years with lenalidomide compared with 1.38 cases without lenalidomide in the approved population
  - Risk of secondary cancers was increased four-fold with the use of lenalidomide in newly diagnosed individuals
- Other factors likely contribute to these observations

Increased risk appears intrinsic to plasma cell disorders

Higher risk of MDS/AML and non-melanoma skin cancer in patients with myeloma and MGUS

Leukemogenic potential of conventional therapy

- Alkylating agents
  - Latency 5-10 years
  - Often with loss of all/part of chromosomes 5 and/or 7
- Topoisomerase II inhibitors (doxorubicin, etoposide)
  - Latency 1-5 years.
  - Often with translocation of 11q23.
- Concomitant XRT increases risk

Potential contribution of high-dose therapy + ASCT

- Low incidence MDS/AML with VAD induction and ASCT

FISH studies in Hodgkin’s and non-Hodgkin’s lymphoma indicate MDS changes present before ASCT in most cases

MDS-Associated Cytogenetic Abnormalities (CA) after High-Dose Melphalan and ASCT for Myeloma

- 105/3077 developed MDS CA
  - Transient in 72
  - MDS in 21; AML in 5
- Predictors
  - Age
  - Lower CD34+ cell yields
- Predictors for TT2 and TT3
  - Early onset MDS CA— longer time from dx and lower platelet count before ASCT
  - Late onset MDS CA— post-ASCT consolidation chemotherapy
  - No effect of thalidomide

Secondary Malignancies

Potential Factors

- Possible relationship to immunomodulatory effects of lenalidomide:
  - *Meta-analysis of 74 RCTs of anti-TNFα monoclonal antibody therapy showed relative risk of 2.09 for non-melanoma skin cancers and 0.99 for all other cancers*\(^1\)
  - *Risk of skin cancers and lymphoma is higher in organ transplant recipients*\(^2\)

- Updated analyses of secondary cancers in myeloma patients treated with ASCT, IMiDs and bortezomib--ASH 2011 abstracts #’s 678, 823, 996, 2933, 4087

Maintenance Therapy in Myeloma

Summary and Conclusions

- Maintenance with novel agents improves PFS
  - Toxicity issues are critical, particularly with thalidomide
  - PFS is 3½ years with lenalidomide maintenance
- Overall survival is significantly longer in some trials of:
  - Thalidomide maintenance
  - Lenalidomide maintenance
  - Bortezomib in induction and maintenance
- Consolidation improves responses and is under further evaluation
- Our current PMH policy: lenalidomide maintenance
- Post-ASCT therapy decisions will be influenced by:
  - Better understanding of 2o cancers
  - Outcome of subsequent therapy for myeloma progression
  - Identification of subgroups most likely to benefit
### Putting it all together......

**Phase III ASCT Trials: Best Reported Responses/Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Induction Rx</th>
<th>ASCT + Maintenance</th>
<th>≥ VGPR (CR+nCR) (%)</th>
<th>PFS (Median)</th>
<th>OS (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lokhorst(^1)</td>
<td>TAD</td>
<td>1 + thalidomide maintenance</td>
<td>66% (31%)</td>
<td>34 mos</td>
<td>73 mo</td>
</tr>
<tr>
<td>Harousseau(^2)</td>
<td>Bortezomib + Dex</td>
<td>1 or 2 (lenalidomide maintenance in some)</td>
<td>68% (39%)</td>
<td>36 mo</td>
<td>NYR 81% (3-year)</td>
</tr>
<tr>
<td>Cavo(^3)</td>
<td>VTD</td>
<td>2 + VTD consolidation + dex maintenance</td>
<td>89% (71%)</td>
<td>NYR</td>
<td>NYR</td>
</tr>
<tr>
<td>Sonneveld(^4)</td>
<td>PAD</td>
<td>1 or 2 + bortezomib maintenance</td>
<td>75% (50%)</td>
<td>~34 mos</td>
<td>NYR</td>
</tr>
</tbody>
</table>

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**Rosinol L, et al. PETHEMA update, ASH 2011 abstract #3962**
Putting it all together........

- Phase II trial IFM 2008 (n=31)

VRD X 3 → Mel 200 + ASCT → VRD X 2 → Len X 1 yr

Initial results

<table>
<thead>
<tr>
<th>Response after</th>
<th>≥ PR</th>
<th>≥VGPR</th>
<th>CR/sCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>97%</td>
<td>54%</td>
<td>28%</td>
</tr>
<tr>
<td>ASCT</td>
<td>94%</td>
<td>68%</td>
<td>35%</td>
</tr>
<tr>
<td>Consolidation</td>
<td>94%</td>
<td>89%</td>
<td>52%</td>
</tr>
</tbody>
</table>

Update: ASH 2011 abstract #1872

---

### Results of Trials of ASCT In Myeloma

**Subset Analysis of Patients with t(4;14)**

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>N</th>
<th>Induction</th>
<th># ASCT</th>
<th>Consolidation</th>
<th>Maintenance</th>
<th>PFS (months)</th>
<th>Overall Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 2004</td>
<td>16</td>
<td>VAD or dex</td>
<td>1</td>
<td>--</td>
<td>+/- thal</td>
<td>9.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Moreau 2007</td>
<td>100</td>
<td>VAD</td>
<td>2</td>
<td>--</td>
<td>+/- thal</td>
<td>21</td>
<td>41.4</td>
</tr>
<tr>
<td>Avet-Loiseau 2010</td>
<td>106</td>
<td>BD</td>
<td>1 or 2</td>
<td>+/- len ~ 30%</td>
<td>+/- len</td>
<td>28</td>
<td>63% (4 yrs)</td>
</tr>
<tr>
<td>Cavo 2010</td>
<td>110*</td>
<td>VTD</td>
<td>2</td>
<td>VTD</td>
<td>Dex</td>
<td>69% (3yr)</td>
<td>NA</td>
</tr>
<tr>
<td>Neben 2011</td>
<td>[26]</td>
<td>PAD</td>
<td>2</td>
<td>--</td>
<td>Bortezombib</td>
<td>25</td>
<td>66% (3 yrs)</td>
</tr>
<tr>
<td>Reece 2011</td>
<td>32</td>
<td>DBd</td>
<td>0</td>
<td>CyBorD x 8</td>
<td>Weekly dex</td>
<td>~24</td>
<td>~75% (2 yrs)</td>
</tr>
</tbody>
</table>

ASCT in Myeloma
Del17p (p53 deletion)

Total Therapy 2 vs 3¹

HOVON 65/GMMG-HD4²

Integration of novel agents with ASCT improves outcome
  - Benefit when added to induction, consolidation, maintenance

Improved response rates after newer frontline regimens
  - ≥ VGPR rates 65-89%; CR/nCR rates 31-71%

Median PFS has improved from 2 to 3 years
  - 3 ½ years with lenalidomide maintenance

Other strategies to optimize ASCT are ongoing
Overall survival benefit with novel agents harder to demonstrate, BUT significant advantage seen in 2 trials
- **HOVON 65/GMMG-HD4 trial -- bortezomib before/after ASCT**
- **CALGB 100104 trial -- lenalidomide maintenance**

Future decisions regarding maintenance/consolidation will likely be influenced by
- *Incidence of toxicities such as 2º malignancies*
- *Outcome after myeloma progression*
- *Subgroup analysis*
- *Better methods to assess MRD*