TREATMENT OF MULTIPLE MYELOMA CURRENT STATUS AND FUTURE DIRECTIONS

Jean-Luc HAROUSSEAU
Nantes
TREATMENT OF MM

1960
- Melphalan

1970
- MP

1980
- First reports on High-dose Tt 1983
- VAD 1984

1990
- ASCT>CC 1996
- Thalidomide 1999

2000
- Double ASCT > single 2003
- Bortezomib 2004, Lenalidomide 2005
**CONVENTIONAL CHEMOTHERAPY**

**Gold Standard : MP**

- Melphalan + Prednisolone (per os 1 4-day course every 4 to 6 weeks)
- Introduced in the early sixties
- No significant improvement with the addition of other agents
- < 50% PR, very rare CR

→ **Standard > 65 years unfit for ASCT**

**High-dose dexamethasone (VAD)**

- More rapidly active but more toxic (infections)
- Less toxic for stem cells

→ **Standard ≤ 65 years as induction prior to ASCT**
## CONVENTIONAL CHEMOTHERAPY (CC) vs ASCT RANDOMIZED STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts</th>
<th>Age</th>
<th>CR Rate</th>
<th>Median EFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM90 (N Engl J Med 96)</td>
<td>200</td>
<td>≤ 65</td>
<td>5 vs 22**</td>
<td>18 vs 28**</td>
<td>44 vs 57**</td>
</tr>
<tr>
<td>MRC7 (N Engl J Med 03)</td>
<td>401</td>
<td>≤ 65</td>
<td>8 vs 44**</td>
<td>19 vs 31**</td>
<td>42 vs 54**</td>
</tr>
<tr>
<td>Italian MMSG (Blood 04)</td>
<td>194</td>
<td>50-70</td>
<td>6 vs 25**</td>
<td>16 vs 28**</td>
<td>42 vs 58+**</td>
</tr>
</tbody>
</table>

*2 courses of IDM (100mg/m²)*

**Significant
SWOG 9321

### Progression-Free Survival

- **HDCTX+PBSC prior to Autol BMT**
- **HDCTX+PBSC prior to chemo**

<table>
<thead>
<tr>
<th>Events / N</th>
<th>7-Year Estimate</th>
<th>Logrank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>210 / 261</td>
<td>17% (12.22)</td>
<td>.16</td>
</tr>
</tbody>
</table>

- **HDCTX+PBSC prior to Autol BMT**
- **HDCTX+PBSC prior to chemo**

<table>
<thead>
<tr>
<th>Deaths / N</th>
<th>7-Year Estimate</th>
<th>Logrank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>151 / 261</td>
<td>38% (31.45)</td>
<td>.78</td>
</tr>
</tbody>
</table>

### Overall Survival

- **HDCTX+PBSC prior to Autol BMT**
- **HDCTX+PBSC prior to chemo**

<table>
<thead>
<tr>
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<td>151 / 261</td>
<td>38% (31.45)</td>
<td>.78</td>
</tr>
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</table>
Comparison of IFM 90 and US Intergroup trials

Chemotherapy better in US study

<table>
<thead>
<tr>
<th></th>
<th>IFM 90</th>
<th>S9321</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>200</td>
<td>516</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AUTO</th>
<th>CR rate (%)</th>
<th>22*</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7-yr EFS (%)</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>7-yr OS (%)</td>
<td>43</td>
<td>37</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHEMO</th>
<th>CR rate (%)</th>
<th>5</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7-yr EFS (%)</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>7-yr OS (%)</td>
<td>27</td>
<td>42</td>
</tr>
</tbody>
</table>

* Assessed by electrophoresis only
IFM 90: Survival according to response

- ≥ 90% (n = 51)
- ≥ 50% (n = 81)
- < 50% (n = 46)
Randomized studies comparing ASCT and CC

Conclusions

- OS improvement is related to CR rate increase
- ASCT is superior to most standard CC regimens but when results of CC are improved, the benefit of ASCT is no more significant
- The comparison of ASCT with standard CC is no longer an issue since results of ASCT have improved in the past 10 years
CC vs ASCT

- ASCT is the standard of care in younger patients (up to 65 years of age)

- OS improvement is related to CR achievement

- ASCT is superior to CC when it increases CR rate

- HDM is superior to conventional doses of Melphalan and is the best way to administer alkylating agents
# Improvement of ASCT results in the past 10 years

## IFM Experience

<table>
<thead>
<tr>
<th></th>
<th>IFM 90</th>
<th>IFM 99</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>200</td>
<td>1064</td>
</tr>
<tr>
<td><strong>Single ASCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + VGPR</td>
<td>38 %</td>
<td>54.5%</td>
</tr>
<tr>
<td>Med EFS</td>
<td>28 M</td>
<td>36 M</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>52 %</td>
<td>62 %</td>
</tr>
<tr>
<td>Med OS</td>
<td>57 M</td>
<td>NR at 66 M</td>
</tr>
</tbody>
</table>
IFM 94

EFS
Survival

Overall

A: single transplant (N=199)
B: double transplant (N=200)

median
30 months

median
25 months

20%
B

42%
B

21%
A

p < 0.03

p < 0.01
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts</th>
<th>Age</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 94 (N Engl J Med 03)</td>
<td>399</td>
<td>&lt; 61</td>
<td>EFS and OS</td>
</tr>
<tr>
<td>MAG 95 (Sydney 05)</td>
<td>227</td>
<td>&lt; 56</td>
<td>OS</td>
</tr>
<tr>
<td>Bologna (Sydney 05)</td>
<td>220</td>
<td>&lt; 61</td>
<td>EFS</td>
</tr>
<tr>
<td>GMMG (Sydney 05)</td>
<td>261</td>
<td>&lt; 66</td>
<td>EFS</td>
</tr>
<tr>
<td>Hovon (Sydney 05)</td>
<td>303</td>
<td>&lt; 66</td>
<td>CR and EFS</td>
</tr>
</tbody>
</table>
The only factor predicting the impact of the 2nd ASCT is the result of the first.

\[ \text{VGPR or CR } p = 0.7 \quad (n=46) \]

\[ \text{<VGPR } p < 0.001 \quad (n=128) \]
DOUBLE ASCT WITH MORE INTENSIVE 2ND HDT IMPROVES THE OUTCOME OF POOR-RISK MM
Historical Comparison in pts with high B2 and del 13
ROLE OF CONSOLIDATION IN TT2
Barlogie Blood 2006

TT2 without Thalidomide (n=345) vs TT1 (n=231)

- Identical CR rate (43% vs 41%)
- Superior 5-yr EFS: 43% vs 28% (p<.001)
- Trend for improved SV: 62% vs 57%
- TT2>TT1 in pts without cytogenetic abnormalities (2/3)

- Role of consolidation with DCEP?
Cytogenetic + $\beta$2m model

OS

- No t(4;14), no del(17p), $\beta$2m<4, no del(13) 155 pts
- No t(4;14), no del(17p), $\beta$2m<4, del(13)+ 110 pts
- No t(4;14), no del(17p), $\beta$2m>4, no del(13) 74 pts
- No t(4;14), no del(17p), $\beta$2m>4, del(13)+ 69 pts
- t(4;14) or del(17p)>60%, $\beta$2m<4 63 pts
- t(4;14) or del(17p)>60%, $\beta$2m>4 42 pts
Inhibition of angiogenesis in BM milieu

Inhibition of cytokine circuits

Enhanced host immune response

Apoptosis (growth arrest)

Inhibition of MM cell adhesion to BMSC

Thal/IMiDs

IL-2, IFN-γ↑

NK/CTL

Targeting the Myeloma Cell in Its BM Microenvironment

Host microenvironment
THALIDOMIDE ALONE IN RELAPSED MM

RESULTS

- Reduction in paraprotein of ≥ 25%: 40-80%
- Partial remission in 10-50% of patients and CR possible in some heavily pretreated pts
- Optimal daily dose (IFM study 100 vs 400): 400 more toxic and no SV benefit if Dex added if no response at 3 m
- Early onset of response and maximal response within 2-4 months
THALIDOMIDE + DEXAMETHASONE

- Synergy in preclinical studies

- Lower doses of Thalidomide
  → better tolerance of Thal but more infectious complications and risk of DVT

- More effective?
  - 65-80% response rate in relapsed / refractory MM
  - As first salvage therapy improves the outcome as compared to CC: median PFS 17m vs 11 (p=.002)
  SV at 3 yr 60% vs 26% (p=.001) (Palumbo 2004)

- Currently used as frontline therapy
Bortezomib (VELCADE™)

- Adhesion
- Cytokine
- Angiogenesis

↓ Adhesion

↓ Cytokine
- TNFα
- IGF-I
- VEGF
- IL-6

↓ Angiogenesis
- BM vessels

↓ Adhesion

↓ Cytokine

↓ Angiogenesis
- BM vessels

IL-6, VEGF

Intracellular level

FAS

Block activation

IκB/NFκB

↓ Apoptosis inhibitors (IAP, FLICE)

↓ MAPK

PI3K

Increased apoptosis

Decreased proliferation

Inhibition DNA-repair effectors

Disruption of unfolded protein response

Updated APEX efficacy data
Response rates

ORR with bortezomib improved from 38% to 43%

**Updated analysis**
- 43% Response %
  - 27% PR
  - 7% nCR
  - 9% CR

**Primary analysis**
- 38% Response %
  - 25% PR
  - 7% nCR
  - 6% CR
  - 18% with Dex
  - <1% nCR

*Richardson et al. Blood 2005;106 (Abstract 2547); Poster at ASH 2005*
Lenalidomide + Dex vs Dexamethasone (MM-009/010)

**Time to Progression**

- MM-009 Len/Dex (15.0 m)
- MM-009 Dex alone (5.1 m)
- MM-010 Len/Dex (11.3 m)
- MM-010 Dex alone (4.7 m)

### Overall Survival

- MM-009: 29.6 months vs 20.2 months, p=0.01
- MM-010: Not reached vs 20.6 months, p=0.03

*Cut-off date: June 2005.*

Weber D. Presented at ASCO Annual Meeting; 2005 May 13–17; Orlando, FL.

Dimopoulos M, et al. Presented at ASH Annual Meeting; Dec 10–13, 2005; Atlanta, GA.
Updated APEX survival data

- Superior survival for bortezomib
  - Median OS: bortezomib 29.8 months vs 23.7 months for high-dose Dex ($P=0.0272$)
  - 1-year survival rate: 80% vs 67% ($P=0.0002$)

Richardson et al. Blood 2005;106 (Abstract 2547); Poster at ASH 2005
Revlimid™ (Lenalidomide) (CC-5013)

Actimid™ (CC-4047)

Thalidomide
MM-009/010: Response

Response Rate (%)

Len/dex
Len/dex
Dex
Dex

009
010
009
010

61.2%*
57.9%
22.8%*
21.7%

34.7%
44.3%
18.7%
17.7%

26.5%
13.6%
4.1%
4.0%

1 Blade criteria
IF, immunofixation

*P<0.001
MM- 009/010 Time to Progression

- 009 Len/Dex
- 009 Dex alone
- 010 Len/Dex
- 010 Dex alone

P < 0.000001
The future role of transplantation in multiple myeloma
## Thal-based regimens prior to ASCT

<table>
<thead>
<tr>
<th></th>
<th>Randomized trial&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Historical comparison&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dex n=100</td>
<td>Thal/De VAD n=100</td>
</tr>
<tr>
<td>Response rate</td>
<td>41</td>
<td>63</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + nCR (%)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>DVT (%)</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Early death</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>1</sup> Rajkumar et al. JCO 2006;24:431–6  
<sup>2</sup> Cavo et al. Blood. 2005;106:35–9
Stem cell collection in 45 patients (median 2 collections required [range 1–4])

Well tolerated: AEs mainly grade 1/2 (1 grade 4 GI)

PN: 6% grade 3 and 8% grade 2

Results form basis for IFM Phase III trial of bortezomib + dex vs VAD

Harousseau et al. Haematologica 2005;90(Suppl 1):148 (Abstract P0.724), Presented at IMW, Sydney, 2005
IFM 2005-01

STUDY SCHEMA

Accrual Goal = 480

RANDOMIZE

Δ1
VAD: Four 28-day cycles
Δ1
VAD: Four 28-day cycles
Followed by DCEP: Two 28-day cycles

1st ASCT

EVALUATE

* CR
nCR
PR
MR
SD
2nd ASCT

* Evaluation based on modified Blood and Marrow Transplantation (EBMT) criteria.¹

¹ Not a complete list of inclusion and exclusion criteria. Before making a decision regarding trial enrollment, please consult the complete list in the trial summary.
Integrating bortezomib into induction regimen may result in superior CR rates compared with conventional induction regimen

Conventional SCT vs BORTEZOMIB INDUCTION REGIMENT

Conventional SCT
Attal 1996, Morgan 2003

Bortezomib induction regimen

- Conventional SCT
  - CR + nCR: 22%
  - CR + nCR + VGPR: 38%

- Bortezomib induction regimen
  - Bortez + dex: 19%
  - PAD: 44%
  - Reduced-dose PAD: 52%
  - VTD: 57%
  - VDT-PACE: 81%

Harousseau et al. Haematologica 2005;90(Suppl 1):148 (Abstract P0.724)
Badros et al. Blood 2005;106 (Abstract 2747)
Wang et al. Blood 2005;106 (Abstract 784)
Pts ≤ 65 y ; 0/1 adverse prognostic factors (Δ13, β2m)

VAD
VAD
VAD

SC collection

HDM140 + AT

HDM200 + AT

Control

Pamidronate

Pamidronate + Thalidomide

IFM 99-02 - M. ATTAL Blood 2006
IFM 99 02: Response Rate $\geq 90\%$.

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>After VAD</td>
<td>15%</td>
<td>15%</td>
<td>16%</td>
<td>NS</td>
</tr>
<tr>
<td>At Random</td>
<td>45%</td>
<td>47%</td>
<td>50%</td>
<td>NS</td>
</tr>
<tr>
<td>After Random</td>
<td>55%</td>
<td>57%</td>
<td>68%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

NS indicates no significant difference.
IFM 99 02: EFS from Diagnosis

P < 0.003
IFM 99 02: Overall Survival according to Thal (Arm B versus Arm C).

Arm C

Arm B

P < 0.01
ROLE OF THALIDOMIDE *(Barlogie NEJM 2006)*

- 668 pts randomized to receive or not Thal during inductionTX, consolidation and maintenance

- CR 62% vs 43% (p<0.001)

- 5-year EFS 56% vs 44% (p=0.01)

- No difference in OS due to shorter SV after relapse 1.1 yr vs 2.7 yr (p=0.001)

- 30% DVT and 27 % PN
# Differences between the thalidomide arms of IFM 99/02 and Total Therapy 2

<table>
<thead>
<tr>
<th></th>
<th>TT2</th>
<th>IFM 99/02</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of Treatment</strong></td>
<td>From the beginning until disease progression or side effects</td>
<td>After double ASCT until disease progression or side-effects</td>
</tr>
<tr>
<td><strong>DVT</strong></td>
<td>30% (Thal + chemo)</td>
<td>2% (Thal alone)</td>
</tr>
<tr>
<td><strong>PN &gt; 2</strong></td>
<td>27% (longer duration ?)</td>
<td>7%</td>
</tr>
<tr>
<td><strong>SV after Relapse</strong></td>
<td>&lt; control arm (selection of identical to control arm resistant clones ?)</td>
<td></td>
</tr>
</tbody>
</table>

- Optimal dose and duration of Thalidomide treatment?
- Other agents are current evaluated (Bortezomib, Lenalidomide)
Update on recent developments for elderly patients with newly diagnosed multiple myeloma
Newly diagnosed MM 65-75 years

**Arm A**
- MP 1
- MP 2
- MP 3

**Arm B**
- Arm A
- Thalidomide ≤ 400 mg/d

**Arm C**
- VAD 1
- VAD 2
- Cyclophosphamide 3g/m²
- + G-CSF
- + PBSC harvest
- MEL 100 mg/m²
- + PBSC + G-CSF

Clodronate for all pts
- MEL 100 mg/m²
- + PBSC + G-CSF
### Response to treatment in the IFM 99-06 trial
#### Second interim analysis

<table>
<thead>
<tr>
<th>Category of response</th>
<th>% of patients (at 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MP</td>
</tr>
<tr>
<td>Complete response</td>
<td>3</td>
</tr>
<tr>
<td>≥ 90%</td>
<td>8</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>34</td>
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</tbody>
</table>
PROGRESSION-FREE SURVIVAL ACCORDING TO TREATMENT

<table>
<thead>
<tr>
<th>Treatment</th>
<th># at risk</th>
<th>Survival time median ± se (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP</td>
<td>191</td>
<td>17.1 ± 1.4</td>
</tr>
<tr>
<td>MP+Thal</td>
<td>124</td>
<td>27.6 ± 3.6</td>
</tr>
<tr>
<td>Int.</td>
<td>121</td>
<td>19.0 ± 1.2</td>
</tr>
</tbody>
</table>

P < 0.0001
OVERALL SURVIVAL ACCORDING TO TREATMENT

Time from inclusion (month)

<table>
<thead>
<tr>
<th>O/N Survival time</th>
<th>Median±se month</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP 86/191</td>
<td>30.3 ± 5.5</td>
</tr>
<tr>
<td>MP+Thal 34/124</td>
<td>not reached at 56.</td>
</tr>
<tr>
<td>Int. 52/121</td>
<td>38.6 ± 4.7</td>
</tr>
</tbody>
</table>

P = 0.0039

# at risk
191 150 120 97 69 49 34 22 13 6 MP
124 105 88 73 61 47 35 22 9 1 MP+Thal
121 95 77 68 52 44 28 17 11 6 Int.
## MP vs MPT in older patients

<table>
<thead>
<tr>
<th></th>
<th>Palumbo et al (1)</th>
<th>Facon et al (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>47</td>
<td>76</td>
</tr>
<tr>
<td>CR rate (%)</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>13.6</td>
<td>29.2</td>
</tr>
<tr>
<td>3-yr OS</td>
<td>64</td>
<td>80</td>
</tr>
<tr>
<td><strong>MPT</strong></td>
<td></td>
<td></td>
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<tr>
<td>N=129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>CR rate (%)</td>
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<td>80</td>
<td>65</td>
</tr>
<tr>
<td>N=191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>81</td>
<td>40</td>
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<tr>
<td>CR rate (%)</td>
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<td>2</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>29.5</td>
<td>17</td>
</tr>
<tr>
<td>3-yr OS</td>
<td>65</td>
<td>48</td>
</tr>
<tr>
<td>N=124</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Lancet 2006  
(2) ASCO 2006
MPV response rates (n=53)
Analysis of best response achieved

1st cycle MPV

Best response: median 5 cycles (2–9)

Mateos et al. Blood 2005;106 (Abstract 786); Presented at ASH 2005
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of pts</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 90</td>
<td>100</td>
<td>Med 28 m</td>
<td>Med 57 m</td>
</tr>
<tr>
<td>(Single ASCT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFM 99 06</td>
<td>124</td>
<td>Med 28 m</td>
<td>NR at 56 m</td>
</tr>
<tr>
<td>(MPT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFM 99 02-04</td>
<td>1064</td>
<td>Med 36m</td>
<td>NR at 66 m</td>
</tr>
<tr>
<td>(Double ASCT Thal in some pts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT 2 Thal arm</td>
<td>334</td>
<td>5-yr 56%</td>
<td>5-yr 62 %</td>
</tr>
<tr>
<td>(Double ASCT)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Combination Therapy with novel agents (MPT, MPV, MPR, VTD…) will probably:

- yield CR rates comparable to those achieved with single ASCT
- be superior to CC (MP)
- improve the outcome of older patients who are not candidate to ASCT
- NOT replace ASCT in younger patients since ASCT results have already improved
ALLOGENEIC SC TRANSPLANTATION
WHAT WE KNOW

- High transplant-related mortality
- Short-term retrospective comparisons are in favor of autologous SCT

BUT

- Durable CR (including molecular remissions) : the only curative treatment ?
- Remissions with DLI : GVM effect
- Better results if better supportive care and earlier transplantation (Gahrton 2001)
Transplant related mortality: EBMT retrospective study

Cumulative Incidence

Time (Months)

RIC n=321

Standard n=196

p=0.001

EBMT retrospective study Crawley, Prag 2005
Relapse: EBMT retrospective study

RIC n=321
Standard n=196

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Cumulative Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>1.0</td>
</tr>
<tr>
<td>24</td>
<td>0.8</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

p=0.001
Disease-free survival

Survival probability vs. Time (Months)

- RIC n=321
- Standard n=196

Statistical significance: p=0.009
### Auto-allo tandem transplantation

<table>
<thead>
<tr>
<th></th>
<th><strong>Maloney</strong></th>
<th><strong>Kröger</strong></th>
<th><strong>Carella</strong></th>
<th><strong>Bruno</strong></th>
<th><strong>Seok</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GvHD II – IV</strong></td>
<td>38.5 %</td>
<td>32 %</td>
<td>44 %</td>
<td>36 %</td>
<td>33 %</td>
</tr>
<tr>
<td><strong>Acute GvHD III – IV</strong></td>
<td>8 %</td>
<td>6 %</td>
<td>18 %</td>
<td>11 %</td>
<td>8 %</td>
</tr>
<tr>
<td><strong>Chronic GvHD</strong></td>
<td>64 %</td>
<td>28 %</td>
<td>37 %</td>
<td>31 %</td>
<td>50 %</td>
</tr>
<tr>
<td><strong>Complete remission</strong></td>
<td>52 %</td>
<td>55 %</td>
<td>62 %</td>
<td>58 %</td>
<td>83 %</td>
</tr>
<tr>
<td><strong>Median follow-up (months)</strong></td>
<td>18</td>
<td>16</td>
<td>30</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td><strong>Estimated overall survival</strong></td>
<td>78 % (2 yrs)</td>
<td>70 % (3 yrs)</td>
<td>62 % (3 yrs)</td>
<td>n. d.</td>
<td>100 % (2 yrs)</td>
</tr>
<tr>
<td><strong>Estimated progression-free survival</strong></td>
<td>55 % (2 yrs)</td>
<td>54 % (3 yrs)</td>
<td>56 % (3 yrs)</td>
<td>n. d.</td>
<td>100 % (2 yrs)</td>
</tr>
<tr>
<td><strong>Treatment-related mortality at day 100</strong></td>
<td>0 %</td>
<td>6 %</td>
<td>0 %</td>
<td>2 %</td>
<td>0 %</td>
</tr>
<tr>
<td><strong>Treatment-related mortality at one year</strong></td>
<td>17 %</td>
<td>11 %</td>
<td>6 %</td>
<td>16 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>
Cumulative Incidence of Progression (Maloney 11/05)

N=52
EVENT-FREE SURVIVAL
PROTOCOL COMPLETED

IFM 99-04, 166 patients
2.5% TRM

IFM 99-03, 46 patients
CR+VGPR: from 47% to 62% after RIC
24% Gr II aGVH
11% TRM
but 26 relapses 17 DLI
5 responses in early rel

\[ p = 0.35 \]
OVERALL SURVIVAL IFM99-03 VS 99-04

$p = .27$

IFM 99-04, 219 patients
IFM 99-03, 65 patients

Probability of Survival vs months
IS THERE A ROLE OF ALLO IN MM?

- **NOT IN GOOD RISK MM**
  - Results of current treatments do not justify the risk of 10-15% 1-year TRM and 30-40% CGVHD
  - Specially with the introduction of novel agents which already challenge Autologous SCT!

- In most studies follow-up is still short but relapse appears to be a major concern

- In poor risk MM
  - Auto/RIC ALLO not > tandem Auto
  - High relapse rate

**ONLY IN CLINICAL TRIALS**
Bortezomib in the treatment of relapsed MM
Higher response rates with second-line treatment compared with later therapy.

Sonneveld et al. Haematologica 2005;90(Suppl 1):146 (Abstract PO.721); Poster at IMW 2005
Best response achieved after longer duration of bortezomib therapy

Time to maximal serum M-protein reduction in patients responding to bortezomib

Approximately 20% of patients responding to bortezomib achieved maximal M-protein reduction in cycle 8 or later
# Bortezomib dose modification for the management of PN

<table>
<thead>
<tr>
<th>Severity of PN signs/symptoms</th>
<th>Modification of dose and regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paresthesia and/or loss of reflexes without pain or loss of function)</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 <strong>with pain</strong> or grade 2 (interfering with function but not with ADL)</td>
<td>Reduce bortezomib to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 2 with pain or <strong>grade 3</strong> (interfering with ADL)</td>
<td>Withhold bortezomib until toxicity resolves then reinitiate at 0.7 mg/m² and administer once per week</td>
</tr>
<tr>
<td>Grade 4 (permanent sensory loss interfering with function)</td>
<td>Discontinue bortezomib</td>
</tr>
</tbody>
</table>
## Bortezomib Combination Regimens in Relapsed Multiple Myeloma

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Evaluable Patients (n)</th>
<th>CR/nCR</th>
<th>PR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berenson (ASH 2005)</td>
<td>Bortezomib + Arsenic Trioxide + Ascorbic Acid</td>
<td>21</td>
<td>10%</td>
<td>10%</td>
<td>19%</td>
</tr>
<tr>
<td>Reece (ASH 2005)</td>
<td>Bortezomib + Cyclophosphamide + Prednisone</td>
<td>20</td>
<td>15%</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>Popat (ASH 2005)</td>
<td>Bortezomib + Low-dose Melphalan + Dexamethasone</td>
<td>21</td>
<td>5%</td>
<td>48%</td>
<td>52%</td>
</tr>
<tr>
<td>Palumbo (ASH 2005)</td>
<td>Bortezomib + Melphalan + Prednisone + Thalidomide</td>
<td>29</td>
<td>28%</td>
<td>41%</td>
<td>69%</td>
</tr>
<tr>
<td>Kropff (ASH 2005)</td>
<td>Bortezomib + Dexamethasone + Cyclophosphamide</td>
<td>50</td>
<td>12%</td>
<td>70%</td>
<td>82%</td>
</tr>
<tr>
<td>Terpos (ASH 2005)</td>
<td>Bortezomib + Melphalan + Dexamethasone + Thalidomide</td>
<td>36</td>
<td>42%</td>
<td>17%</td>
<td>58%</td>
</tr>
</tbody>
</table>
### Bortezomib Combination Regimens in Relapsed Multiple Myeloma

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Evaluable Patients (n)</th>
<th>CR/nCR</th>
<th>PR</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlowski (Blood 2005)</td>
<td>Bortezomib + Doxil®</td>
<td>22</td>
<td>36%</td>
<td>36%</td>
<td>73%</td>
</tr>
<tr>
<td>Berenson (JCO 2006)</td>
<td>Bortezomib + Melphalan</td>
<td>34</td>
<td>15%</td>
<td>32%</td>
<td>47%</td>
</tr>
<tr>
<td>Zangari (ASH 2005)</td>
<td>Bortezomib + Thalidomide +/- Dexamethasone</td>
<td>85</td>
<td>16%</td>
<td>39%</td>
<td>55%</td>
</tr>
<tr>
<td>Chanan-Khan (IMW 2005)</td>
<td>Bortezomib + Doxil + Thalidomide</td>
<td>16</td>
<td>25%</td>
<td>38%</td>
<td>63%</td>
</tr>
<tr>
<td>Hollmig (ASH 2004)</td>
<td>Bortezomib + Doxorubicin + Thalidomide + Dexamethasone</td>
<td>16</td>
<td>25%</td>
<td>38%</td>
<td>63%</td>
</tr>
<tr>
<td>Richardson (ASH 2005)</td>
<td>Bortezomib + Lenalidomide</td>
<td>21</td>
<td>10%</td>
<td>43%</td>
<td>52%</td>
</tr>
</tbody>
</table>
Novel Therapies Targeting the Myeloma Cell in Its BM Microenvironment

**Targeting MM Cell**
- 17AAG, TRAIL, SAHA, IGF1R Inhibitors, FTI (e.g., R11577), telomestatin, epothilone B, oblimersen sodium, rituximab, CD40 MoAb

**Targeting BM Microenvironment**
- IKK inhibitors (e.g., PS-1145), P38-MAPK inhibitors (SC 469)

**Targeting MM Cell BM Microenvironment**
- Thalidomide, lenalidomide, bortezomib, AS$_2$O$_3$, PTK787, FTI (e.g., R11577), 2ME2, LPAAT inhibitors
Combinations With Bortezomib

- Phase I-II
  - Liposomal doxorubicin\(^1\)
  - Low-dose melphalan\(^2\)
  - Thalidomide ± Dex\(^3\)

- New trials
  - Lenalidomide
  - Dexamethasone + low-dose po cyclophosphamide
  - Dexamethasone + liposomal doxorubicin
  - As\(_2\)O\(_3\)
  - 17- AAG (KOS 953)
  - Scios 469 (P38 MAPK inhibition)
  - FTI inhibitors

2. Yang et al. ASH 2003; Abstract 826.
**Gene Microarray Identifies Molecular Mechanism of Bortezomib Anti-MM Activity and Potential Pathways of Resistance**

- **Caspase cascade**
  - $\uparrow$ pro-caspases -9, -7 and -5
  - $\uparrow$ Fas (Apo-1, CD95)
  - $\uparrow$ DR5 Apo2L/TRAIL receptor
  - $\uparrow$ Fas (transmembrane)
  - $\downarrow$ soluble (decoy) Fas (alt. Splicing)
  - $\downarrow$ Toso (negative Fas regulator)
  - $\downarrow$ Caspase inhibitors

- **IGF signaling**
  - IGF-1
  - $\downarrow$ IGF-1R
  - $\downarrow$ insulin receptor substrate-1 (IRS-1)

- **$I\kappa B$**
  - $I\kappa B$ kinase-alpha, $\uparrow I\kappa B$ kinase-gamma

- **Ubiquitin/Potchaseome pathway**
  - $\uparrow$ Ubiquitin
  - $\uparrow$ p40.5, p44.5, p55, p58
  - $\uparrow$ HsN3, HsC7-I, HsC10-II
  - $\uparrow$ p112, p97,
  - $\uparrow$ Nin1p, HC5, HC8,
  - $\uparrow$ POH1, X, Y, Z,

- **Molecular Chaperones**
  - $\uparrow$ hsp90
  - $\uparrow$ hsp70
  - $\uparrow$ hsp40
  - $\uparrow$ hsp28
  - $\uparrow$ hsp32 (heme oxygenase-1)
  - $\uparrow$ heat shock protein apg-1
  - $\uparrow$ mitochondrial hsp75

*Mitsiades et al. Proc Natl Acad Sci (USA) 2002; 99: 14374*
The Hsp90 Inhibitor 17-AAG Prolongs Survival in a SCID/NOD Mouse Model of Diffuse Multiple Myeloma

Control cohort

17-AAG-treated cohort

Graph:
- Control cohort:
- 17-AAG-treated cohort:
- Log-rank test,
  \( P < 0.0001 \)

Time (days):
- 0
- 25
- 50
- 75
- 100
- 125
- 150
- 175
- 2

Percent surviving:
- 100
- 80
- 60
- 40
- 20
Bortezomib + Hsp-90 inhibitor augments MM cell death*

Bortezomib combined with an Hsp-90 inhibitor is much more cytotoxic than either agent alone.

*2002: clinical trial 2003

Mitsiades et al. Proc Natl Acad Sci USA 2002;99:14374–9
Combination of Bortezomib + Lenalidomide

THALIDOMIDE IN COMBINATION IN NEWLY DIAGNOSED PATIENTS

with conventional chemotherapy

- TCD
- DVdT
- MP T

with novel agents (bortezomib)

- TVD, TT3
- MPVT
Bortezomib-associated PN is reversible in the majority of patients (APEX)

- Incidence of PN (37% 124/331)
  - 10% grade 1
  - 18% grade 2
  - 8% grade 3
  - <1% grade 4

- 64% (58/91) of patients with ≥grade 2 PN experienced improvement or resolution
  - 55% (50/91) had complete resolution (return to baseline)
  - 9% (8/91) experienced improvement by at least 1 CTC grade
  - Median time to improvement/resolution:
    - 110 days from diagnosis
## THALIDOMIDE ALONE

TOXICITY IS RELATED TO THE DAILY DOSE

Incidence of grade ≤ 2 adverse effects *(Singhal 1999)*

<table>
<thead>
<tr>
<th>Condition</th>
<th>200 mg (N = 83)</th>
<th>400 mg (N = 72)</th>
<th>600 mg (N = 57)</th>
<th>800 mg (N = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>35</td>
<td>44</td>
<td>44</td>
<td>59</td>
</tr>
<tr>
<td>Weakness/Fatigue</td>
<td>29</td>
<td>31</td>
<td>39</td>
<td>48</td>
</tr>
<tr>
<td>Somnolence</td>
<td>34</td>
<td>43</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>Tingling/Numbness</td>
<td>12</td>
<td>14</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17</td>
<td>25</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>Rash</td>
<td>16</td>
<td>18</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Mood changes</td>
<td>16</td>
<td>24</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Incoordination</td>
<td>16</td>
<td>17</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Tremor</td>
<td>10</td>
<td>13</td>
<td>19</td>
<td>22</td>
</tr>
</tbody>
</table>
PERIPHERAL NEUROPATHY

- Clinical symptoms: mostly sensitive neuropathy
  - Numbness, paresthesia
  - Pain in the hands or arms, feet or legs
- Electrophysiologic studies
  - Mostly axonal damage
- Incidence
  - 28% overall (Glasmacher 2005)
  - Up to 75% in patients with prolonged treatments (Tosi 2004)
  - Role of previous Tx and previous neuropathy
- Prognosis
  - Grade > II 6% overall (27.5% in patients treated > 1yr)
  - Can be irreversible if Tx not promptly withdrawn
DEEP VEIN THROMBOSIS

- Clinical manifestations
  At the site of CVL or at distant sites
  Including pulmonary embolism

- Date of onset: median time 42 D

- Incidence (FDA report + clinical studies)

<table>
<thead>
<tr>
<th>Thal alone</th>
<th>Thal + Dex</th>
<th>Thal + Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
<td>10 – 15%</td>
<td>up to 30%</td>
</tr>
</tbody>
</table>
Bortezomib in Relapsed MM

- **Phase II SUMMIT, CREST**
  - Basis for initial approval for treatment of relapsed/refractory MM in 2003 (USA) and 2004 (Europe)

- **Phase III APEX**
  - Sub-analysis confirmed significant efficacy in patients who had received only 1 prior line of therapy compared with those who had received more than one line of prior therapy
  - 2005: bortezomib approved for treatment of patients with MM who have received at least 1 prior therapy (USA and Europe)
APEX: Peripheral Neuropathy (PN)

- 69% of 310 pts on Bortezomib reported symptoms of PN at baseline (FACT/GOG-Ntx score >0)

- PN reported in:
  - Bortezomib 36% (≥ Grade 3 = 8%)
  - Dex 9% (≥ Grade 3 < 1%)

- Baseline FACT/GOG-Ntx score directly correlated with development of ≥ Grade 3 PN

- PN ≥ Grade 2 improved or resolved in 51% of pts
  - Median time to improvement or resolution from first onset = 107 d (~ 3.5 mos)
Lenalidomide Phase 1 Trial in Relapsed Multiple Myeloma

Results

- Dose-limiting toxicities of **myelosuppression** in all patients treated with 50-mg dose after day 28
- **MTD 25 mg** in this patient population
- No somnolence, constipation, or neuropathy at any dose
- Stable disease or response in 79% of patients
  - 71%: ≥25% decrease in M protein
  - 8%: stable disease

MTD, maximal tolerated dose

## MM- 009/010 Grade 3/4
### Hematologic Toxicity

<table>
<thead>
<tr>
<th></th>
<th>MM-009</th>
<th></th>
<th>MM-010</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Len/De</td>
<td>Dex</td>
<td>Len/De</td>
<td>Dex</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>N = 171</td>
<td>x</td>
<td>N = 175</td>
</tr>
<tr>
<td>Neutropenia, %</td>
<td>30.0</td>
<td>3.5</td>
<td>17.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>2.9</td>
<td>0</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10.6</td>
<td>6.4</td>
<td>9.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>10.6</td>
<td>3.5</td>
<td>4.5</td>
<td>4.0</td>
</tr>
</tbody>
</table>
## MM-009/010 Grade 3/4 Other Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>MM-009 Len/Dex</th>
<th>MM-009 Dex</th>
<th>MM-010 Len/Dex</th>
<th>MM-010 Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 170</td>
<td>N = 171</td>
<td>N = 176</td>
<td>N = 175</td>
</tr>
<tr>
<td>DVT/PE, %</td>
<td>15.3</td>
<td>3.5</td>
<td>8.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>4.7</td>
<td>0</td>
<td>0.6</td>
<td>1.7</td>
</tr>
<tr>
<td>CHF</td>
<td>2.4</td>
<td>0</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.8</td>
<td>0</td>
<td>1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.4</td>
<td>0</td>
<td>2.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.9</td>
<td>4.7</td>
<td>6.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2.9</td>
<td>1.2</td>
<td>1.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>
1. Is ASCT still superior to CC?
2. Are tandem ASCT superior to single ASCT?
3. What is the best induction TT prior to ASCT?
4. What is the role of consolidation/maintenance?
5. Will novel agents replace ASCT?
# AUTOLOGOUS STEM CELL TRANSPLANTATION

1. Is ASCT still superior to CC?

2. Are tandem ASCT superior to single ASCT?

3. What is the best induction Tt prior to ASCT?

4. What is the role of consolidation/maintenance?

5. Will novel agents replace ASCT?
IFM 94: OVERALL SURVIVAL

A: single transplant (N=199)  42%

B: double transplant (N=200)  21%

p < 0.01
IFM 94: EFS

A: single transplant (N=199)
B: double transplant (N=200)

p < 0.03

median 25 months
median 30 months

20%
10%
The only factor predicting the impact of the 2nd ASCT is the result of the first.

- VGPR or CR: $p = 0.7$ (n=46)
- <VGPR: $p < 0.001$ (n=128)
1. Is ASCT still superior to CC?

2. Are tandem ASCT superior to single ASCT?

3. What is the best induction TT prior to ASCT?

4. What is the role of consolidation/maintenance?

5. Will novel agents replace ASCT?
INDUCTION TREATMENT

CONCLUSION

1) Bortezomib-containing regimens appear to increase the CR rate prior to ASCT

2) However we still don’t know whether a higher CR rate prior to ASCT
   - will result in a higher overall CR rate (Barlogie 06, Goldschmidt ASH 05)
   - will improve OS
1. Is ASCT still superior to CC?
2. Are tandem ASCT superior to single ASCT?
3. What is the best induction TT prior to ASCT?
4. What is the role of consolidation/maintenance?
5. Will novel agents replace ASCT?
IFM 99 02: EFS According to Response at Random

Response at Random ≥ 90%

Response at Random < 90%

P < 0.0003
The most common toxicities were: neuropathy (68%), fatigue (34%), constipation (20%), neutropenia (7%), and cardiac (4%).

The incidence of DVT was not increased in the Thal arm (4%).

39% of patients had to discontinue Thal for drug-related AE.

Neuropathy was the main reason for discontinuation.

Median duration of Thal: 15 m (1-51).

Mean dosage of Thal: 200 mg / d (50-400).
1. Is ASCT still superior to CC?
2. Are tandem ASCT superior to single ASCT?
3. What is the best induction TT prior to ASCT?
4. What is the role of consolidation/maintenance?
5. Will novel agents replace ASCT?
## COMPARISON OF IFM 90 / IFM 94 AND IFM99 TRIALS

<table>
<thead>
<tr>
<th></th>
<th>IFM90 N = 200</th>
<th>IFM94* N = 399</th>
<th>IFM99 N = 1064</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT</td>
<td>Auto</td>
<td>Single</td>
</tr>
<tr>
<td>Med EFS</td>
<td>18</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>5y SV</td>
<td>12%</td>
<td>52%</td>
<td>38%</td>
</tr>
</tbody>
</table>

* *patients < 60 years*
CONCLUSIONS

- Novel agents already improve OS when used in relapsed MM
- Novel agents are changing the standard of care in older patients
- Novel agents improve the results of ASCT and are even challenging ASCT in younger patients
- Patients without unfavorable prognostic factors already obtain prolonged EFS but patients with high B2M and unfavorable cytogenetics need other approaches
DE NOVO MM, < 65 years, \( \beta 2M > 3 \text{mg/l} \) AND D13

VAD x 4

Stem cell collection

ASCT n°1 : HDM 200

HLA-sibling donor available

Mini-allo

Bu 4 Fluda 25X5
ATG 2.5/KG X5

IFM9903 trial N=65

No donor available

ASCT n°2

HDM 220 +/- anti-IL6

IFM9904 trial N=219
Comparison with TT1  *Barlogie, ASCO 2005*

- 668 pts compared to 231 pts treated with TT1
- CR and near CR 66% vs 43% (p < 0.001)
- 4-yr EFS and OS: 62% and 69%
- TT2 > TT1 in pts without cytogenetic abnormalities (2/3)
- Benefit even in the non Thal arm
DE NOVO MM, < 65 years, β2M > 3mg/l AND D13

VAD x 4

Stem cell collection

ASCT n°1 : HDM 200

HLA-sibling donor available
Mini-allo
Bu 4 Fluda 25X5
ATG 2.5/KG X5
IFM9903 trial N=65

No donor available
ASCT n°2
HDM 220 +/- anti-IL6
IFM9904 trial N=219
IFM 99-03 / 99-04

- ≤ 65 years
- β2 mic > 3 mg/l + Δ13 (FISH)

VAD x 3

SC collection

HDM200 + ASCT

HLA id sibling
IFM 99-03
ATG + Bu + F
Allo BMT

No HLA id sibling
IFM 99-04
HDM 220 + Anti IL6
Auto SCT
IFM 99-04 P MOREAU BLOOD 2006
RESPONSE RATE

No difference between the 2 arms
IFM 99-04

median : 39 months

median : 30 months

OS

EFS
DOUBLE ASCT WITH MORE INTENSIVE 2ND HDT IMPROVES THE OUTCOME OF POOR-RISK MM

Historical Comparison

**EFS**
- Med 33
- 166 PTS
- Med 15
- 33 PTS

**OS**
- Med 47
- 166 PTS
- Med 25
- 33 PTS
EFS intent-to-treat: IFM 99-03 VS 99-04

Probability of Survival

99-04 N=220
99-03 N=64

p = 0.70
HOW TO IMPROVE ASCT

- Double ASCT
- Further increase of dose-intensity
- Integrating novel agents in the ASCT paradigm
Patients with newly diagnosed MM ≤ 65 y.o.

<table>
<thead>
<tr>
<th>A1</th>
<th>A2</th>
<th>B1</th>
<th>B2</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAD</td>
<td>Vel/Dex</td>
<td>VAD</td>
<td>Vel/Dex</td>
</tr>
<tr>
<td>VAD</td>
<td>Vel/Dex</td>
<td>VAD</td>
<td>Vel/Dex</td>
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<tr>
<td>VAD</td>
<td>Vel/Dex</td>
<td>VAD</td>
<td>Vel/Dex</td>
</tr>
<tr>
<td>VAD*</td>
<td>Vel/Dex*</td>
<td>VAD*</td>
<td>Vel/Dex*</td>
</tr>
</tbody>
</table>

1st ASCT

DCEP

1st ASCT

DCEP

2nd ASCT if < CR within 3 months

* SC collection
IS THERE A ROLE FOR ALLO IN MM?

- Probably not in good risk patients = results of current treatments do not justify the risk, (specially with the introduction of novel agents)

- In poor risk MM results do not appear to be > Tandem Auto → evaluate other preparative regimens and GVH prophylaxis

- Follow-up is still short but relapse appears to be a major concern with miniallo

- Role of Novel Agents in reducing the risk of relapse post-RIC allo SCT?
IFM 2005

**Induction trial (IFM 2005-01)**

VAD  
Dex/Vel  
VAD  
Dex/Vel  
DCEP  
DCEP

**Autologous Transplantation**

Mel 200 + CSP

If response within 3 months < 90% : Second ASCT  
Or RIC Allo if HLA id donor and 1 adverse pc factor

Patients with <90% response after 2 ASCT : 3 months of THAL

**Maintenance trial (IFM 2005-02)**

Revlimid VS  
Placebo
Thalidomide/Lenalidomide Target

**MM Cells in the BM Microenvironment**

- **A. Lenalidomide/IMID**
- **B. Lenalidomide/IMID**
- **C. Lenalidomide/IMID**
- **D. Lenalidomide/IMID**
- **E. Lenalidomide/IMiD**

**Regulatory Cytokines:**
- IL-6
- TNFα
- IL-1β
- IL-2
- IFNγ

**Bone Marrow Stromal Cells:**
- ICAM-1
- VEGF
- bFGF

**Bone Marrow Vessels:**
- CD8+ T Cells
- NK Cells

**References:**
### MPV: treatment schedule

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>8</th>
<th>11</th>
<th>22</th>
<th>25</th>
<th>29</th>
<th>32</th>
<th>33–42</th>
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<tbody>
<tr>
<td><strong>Four 6-week cycles</strong></td>
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<td>Bortezomib</td>
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<tr>
<td>Melphalan 9 mg/m²</td>
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<tr>
<td>Prednisone 60 mg/m²</td>
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<tr>
<td><strong>Five 5-week cycles</strong></td>
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<td>Bortezomib</td>
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<td>Melphalan 9 mg/m²</td>
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<td>Prednisone 60 mg/m²</td>
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</tbody>
</table>

*Total = 49 weeks of treatment*

Mateos et al. *Blood* 2005;106 (Abstract 786); Presented at ASH 2005
TRAITEMENT DU MYELOME MULTIPLE

Un pronostic redoutable

- Maladie peu sensible aux chimiothérapies
  Alkylants (Melphalan)
  Corticoïdes (Dexaméthasone)
- Pronostic constamment fatal
  Médiane survie longtemps estimée à 3 ans

Une maladie douloureuse et invalidante

- Atteinte osseuse
- Anémie

Progrès récents
- nouvelles stratégies
- nouveaux traitements
LES MODALITES THERAPEUTIQUES

- Alkylants (Melphalan)
- Corticoïdes (Dexaméthasone hautes doses)
- Interféron
- Traitement intensif + greffe
- Thalidomide
- Velcade®
- Autres traitements en développement (analogues Thalidomide)
INTERFERON
L’ESPOIR DECU

- N’est plus utilisé en combinaison avec la chimio
- En entretien après chimio conventionnelle
  (méta-analyse de 12 essais randomisés)
  - 6 mois prolongation de SV sans progression
  - 7 mois prolongation de SV globale
  Mais effect secondaires
côt
- En entretien après autogreffe ?
1. **Stem cell collection**
   - Collect enough SC to perform 2 ASCT
   - In newly diagnosed patients this objective is easily reached with G-CSF alone (10\(\mu\)g/kg) or with Cyclophosphamide + G-CSF (5\(\mu\)g/kg)

2. **Conditioning regimen**
   - IFM 95: HDM 200 at least as effective and better tolerated compared to HDM140 + TBI

3. **Source of SC**
   - No evidence that CD34+ selected PBSC are superior to unselected PBSC (3 randomized trials)
LE TRAITEMENT INTENSIF

Rôle de l’IFM

- Essai IFM 90 (patients ≤ 65 A)
  - Autogreffe > chimio conventionnelle (tx réponse, SSE, SV globale)
  - Impact de la RC sur la survie

- Confirmation 7 ans plus tard par l’essai anglais
CC vs ASCT

FACTS

- Standard of care in patients up to the age of 65
- Should not be restricted to patients responding to initial CT (Pethema)
- Survival benefit is related to CR achievement
### CC vs ASCT
#### RANDOMIZED STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>Nb of pts</th>
<th>Age</th>
<th>CR rate</th>
<th>Median EFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM90 (NEJM 96)</td>
<td>200</td>
<td>≤ 65</td>
<td>5 vs 22**</td>
<td>18 vs 28**</td>
<td>44 vs 57**</td>
</tr>
<tr>
<td>MRC7 (NEJM 03)</td>
<td>401</td>
<td>≤ 65</td>
<td>8 vs 44**</td>
<td>19 vs 31**</td>
<td>42 vs 54**</td>
</tr>
<tr>
<td>Italian MMSG (Blood 04)</td>
<td>194</td>
<td>50-70</td>
<td>6 vs 25**</td>
<td>16 vs 28**</td>
<td>42 vs 58+**</td>
</tr>
<tr>
<td>MAG 91 (ASH 99)</td>
<td>190</td>
<td>55-65</td>
<td>-</td>
<td>19 vs 25**</td>
<td>45 vs 42</td>
</tr>
<tr>
<td>PETHEMA* (ASH 03)</td>
<td>164</td>
<td>≤ 65</td>
<td>11 vs 30**</td>
<td>34 vs 42</td>
<td>67 vs 65</td>
</tr>
<tr>
<td>US Intergroup (ASH 04)</td>
<td>516</td>
<td>-</td>
<td>15 vs 17</td>
<td>21 vs 25</td>
<td>53 vs 62</td>
</tr>
</tbody>
</table>

* only in patients responding to initial CC
** significant
IFM 90: Survival according to response

- ≥ 90% (n = 51)
- ≥ 50% (n = 81)
- < 50% (n = 46)
IFM 94

Newly diagnosed patients ≤ 60 years

First randomisation: single versus double
- VAD
- VAD
- VAD

Second randomisation: BM versus PBSC

- VAD
- Mel (140) + TBI
- BM
- PBSC

- VAD
- Mel (140) + PBSC
- BM
- PBSC

- VAD
- Mel (140) + TBI
- BM
- PBSC

VAD: 
VAD
VAD
Mel (140) + TBI
BM
PBSC
IFM 94 : EFS

p < 0.03

A: single transplant (N=199)
B: double transplant (N=200)
IFM 94: OVERALL SURVIVAL

A: single transplant (N=199)
B: double transplant (N=200)

p < 0.01
## SINGLE vs DOUBLE ASCT RANDOMIZED STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>Nb of pts</th>
<th>Age</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 94 (NEJM 03)</td>
<td>399</td>
<td>&lt; 61</td>
<td>EFS and OS</td>
</tr>
<tr>
<td>MAG 95 (Turin 04)</td>
<td>227</td>
<td>&lt; 56</td>
<td>No difference</td>
</tr>
<tr>
<td>Bologna (Turin 04)</td>
<td>220</td>
<td>&lt; 61</td>
<td>EFS</td>
</tr>
<tr>
<td>GMMG (Turin 04)</td>
<td>261</td>
<td>&lt; 66</td>
<td>EFS</td>
</tr>
<tr>
<td>Hovon (Turin 04)</td>
<td>303</td>
<td>&lt; 66</td>
<td>CR and EFS</td>
</tr>
</tbody>
</table>
Lokhorst (J C Oncol 2003;21:1728-33)

- 53 patients with an HLA identical sibling

- Median age 48 y (31-56)

- Variable T-cell depletion (1-7 x 10^5/kg) + cyclosporine

- Induction treatment
  
  VAD alone  5
  1 IDM  26
  2 IDM  22
T-CELL DEPLETED SCT FOR FIRST-LINE TREATMENT RESULTS

- A GVHD > 2  \( \frac{24}{53} \) (43%)
- C GVHD 43% (30% extensive)
- 100 day TRM 34%
- 89% response rate
  19% CR rate
- median PFS 17 Mo
median OS 25 Mo
only 3 pts in continuing CR
Objective

- To ensure engraftment and reduce TRM with immunosuppressive treatment while harnessing GVM effect
- DFS and OS are related to disease status at Tx (high relapse rate in advanced patients)

AUTO SCT followed by mini-allo
### AUTOLOGOUS SCT FOLLOWED BY MINI-ALLO

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Med Age</th>
<th>Rel/Ref</th>
<th>Auto</th>
<th>Mini Allo</th>
<th>Immuno Suppression</th>
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<tr>
<td>Maloney</td>
<td>54</td>
<td>52</td>
<td>48%</td>
<td>HDM200</td>
<td>LD TBI</td>
<td>MM + CYA</td>
</tr>
<tr>
<td><em>Blood 2003</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Badros</td>
<td>31*</td>
<td>56</td>
<td>55%</td>
<td>30 Prior ASCT</td>
<td>HDM100 or M/F/LD TBI</td>
<td>CYA + MPDN</td>
</tr>
<tr>
<td><em>Blood 2002</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kroger</td>
<td>47**</td>
<td>52</td>
<td>None</td>
<td>HDM200</td>
<td>M/F/ATG</td>
<td>CYA + MTX</td>
</tr>
<tr>
<td><em>Turin 2004</em></td>
<td></td>
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</tr>
</tbody>
</table>

* 6 unrelated
** 23 unrelated donors
All front-line
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Chimer</th>
<th>CR</th>
<th>AGVH</th>
<th>100 d TRM</th>
<th>M F-up</th>
<th>cGVH</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maloney Blood 2003</td>
<td>54</td>
<td>100%</td>
<td>52%</td>
<td>36.5%</td>
<td>2%</td>
<td>18m</td>
<td>46%</td>
<td>2-yr OS 78% 2-yr PFS 55%</td>
</tr>
<tr>
<td>Badros Blood 2002</td>
<td>31**</td>
<td>89%</td>
<td>61%</td>
<td>58%</td>
<td>10%</td>
<td>6 m</td>
<td>36%</td>
<td>1 yr EFS 86%</td>
</tr>
<tr>
<td>Kroger Turin 2004</td>
<td>47</td>
<td>100%</td>
<td>55%</td>
<td>32%</td>
<td>6%</td>
<td>15 m</td>
<td>32%</td>
<td>3-yr OS 70% 3-yr EFS 54%***</td>
</tr>
</tbody>
</table>

* 1 DLI  ** 18 DLI  *** Unrelated:66% vs related 47%
THALIDOMIDE
RENAISSANCE D’UN VIEUX TRAITEMENT

- Sédatif retiré de la pharmacopée en 1962 pour ses effets tératogènes
- Toujours utilisé dans certaines formes de lèpre et certains troubles dysimmunitaires
- Considéré comme antiangiogénique

→ Nouvelle arme dans le MM
Thalidomide alone

- Pionnering work by the Little Rock group in heavily pretreated patients
- Initial results confirmed by a number of Phase II studies (in relapsed / refractory patients)
  - 30-80% responses
  - rapid responses
  - toxicity: optimal dosage?
  - with the usual dosage (400mg/D) side effects are manageable but long-term toxicity is a concern (peripheral neuropathy) in many patients
THALIDOMIDE + DEXAMETHASONE

- Synergy in preclinical studies

- Lower doses of Thalidomide → better tolerance

- More effective?
  - 65-80% response rate in relapsed / refractory MM
  - As first salvage therapy improves the outcome as compared to CC: median PFS 17m vs 11 (p=.002)
  - SV at 3 yr 60% vs 26% (p=.001) (Palumbo 2004)

- Currently used as frontline therapy
THALIDOMIDE + CHEMOTHERAPY

- Thalidomide: no hematological toxicity
- Synergy in preclinical studies
- Effective in relapsed/refractory patients (TCD, DT - PACE) but high incidence of DVT
- Currently tested as frontline therapy
BORTEZOMIB IN MM

Richardson (SUMMIT 025 Phase II trial)

- Velcade 1.3mg/m² IV on days 1, 4, 8 and 11
  21 D cycles (max 8 cycles)

- 202 pts heavily pretreated
  - median number of prior regimens: 6
  - 64% prior stem cell transplant
  - 83% prior Thal TX

- 91% refractory to the last prior TX
SUMMIT RESULTS

- 35% overall response (CR + PR + MR)
- 10% CR
- Response independent of prior therapy
- Median SV 16 months
- Median TTP 7 months
- 74 pts with SD/PD received PS341 + Dex
  → 24% improved response
### Summit Results

#### Toxicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>All grades (0%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>55</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>31</td>
<td>12</td>
</tr>
</tbody>
</table>
VELCADE APEX TRIAL

- Multicenter international Phase III randomized trial
- 669 pts enrolled at 94 centers
- Relapsed or refractory MM (after 1-3 lines Tt)
- Velcade vs Dexamethasone
- Companion study: Velcade for patients progressing with Dex
- Primary end point: time to progression
APEX TRIAL
RESULTS

- Median time to progression significantly improved 6.2 m vs 3.5 m (p < 0.0001)

- CR + PR : 38% vs 18% (p < 0.0001)

- CR : 6% vs 1% (p = 0.0001)

- OS and 1-year significantly improved
VELCADE IN MM
ONGOING AND FUTURE STUDIES

- In combination with
  • Dexamethasone
  • Chemo - MP
    - Doxil
  • Thalidomide

- In frontline therapy
  • Older patients
  • Prior to SCT
ACTIMID

Phase I *(J Clin Oncol 2004)*

- 24 relapsed / refractory pts

- oral, dose-escalation (1, 2, 5, 10mg / D)

- 67% RR, 54% PR, 17% CR

- MTD : 2 mg/d

- dose limiting toxicity : neutropenia

- 3 DVT
SUMMARY
YOUNGER PATIENTS (<65yo)

Standard of care

- Induction: Dex based regimen
- Collection of SC: enough SC to perform 2 ASCT
- Consolidation: double ASCT
YOUNGER PATIENTS (< 65 yo)

QUESTIONS TO BE ADDRESSED

- **Stratification according to initial prognostic factors**

- Double ASCT for all pts or only for selected pts (less than 90% response after initial CT ?)

- Induction: how to improve the CR rate prior to ASCT
  - add Thal
  - other novel agents

- Maintenance therapy

- Place of allogeneic SCT
PROGNOSTIC FACTORS IN NEWLY DIAGNOSED PATIENTS

Initial characteristics

- IgA
- CRP, Albumin
- β2 M, LDH
- cytogenetics ++

Treatment related

- response to initial CT
- achievement of CR
Overall survival according to the number of unfavorable prognostic factors ($\beta 2m \geq 2.5$ mg/L, $\Delta 13$)

<table>
<thead>
<tr>
<th># factors</th>
<th>O/N</th>
<th>Survival time median ± se (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2/22</td>
<td>$&gt;111.$</td>
</tr>
<tr>
<td>1</td>
<td>29/55</td>
<td>47.3 ± 4.6</td>
</tr>
<tr>
<td>2</td>
<td>22/33</td>
<td>25.3 ± 3.2</td>
</tr>
</tbody>
</table>

$P < .0001$
YOUNGER PATIENTS (< 65 yo) QUESTIONS TO BE ADDRESSED

- Stratification according to initial prognostic factors
- Double ASCT for all pts or only for selected pts (less than 90% response after initial CT?)
- Induction: how to improve the CR rate prior to ASCT
  - add Thal
  - other novel agents
- Maintenance therapy
- Place of allogeneic SCT
IFM 94:
OS IF RESPONSE TO 1st GRAFT < 90%

p < 0.001

(n=128) B
(n=84) A
YOUNGER PATIENTS (< 65 yo)

QUESTIONS TO BE ADDRESSED

- Stratification according to initial prognostic factors
- Double ASCT for all pts or only for selected pts (less than 90% response after initial CT ?)
- **Induction**: how to improve the CR rate prior to ASCT
  - add Thal
  - other novel agents
- Maintenance therapy
- Place of allogeneic SCT
THAL/DEX FOR NEWLY DIAGNOSED MM RANDOMIZED PHASE III ECOG TRIAL

Rajkumar et al (ASCO 2004)

Thal 200mg/D
+ Dex 40mg/D days 1-4, 9-12, 17-20
Dex 40mg/D days 1-4, 9-12, 17-20
x 4 cycles
<table>
<thead>
<tr>
<th></th>
<th>THAL/DEX N=100</th>
<th>Dex N=101</th>
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</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>68%</td>
<td>46%</td>
</tr>
<tr>
<td>Med-time to response</td>
<td>1.1 m</td>
<td>1.1 m</td>
</tr>
<tr>
<td>CR</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Successful harvest</td>
<td>91%</td>
<td>100%</td>
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</table>
**ECOG E1A00**

**PRELIMINARY RESULTS**

**TOXICITY**

<table>
<thead>
<tr>
<th></th>
<th>THAL/DEX</th>
<th>Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity ≥ 4</td>
<td>33%</td>
<td>15%</td>
</tr>
<tr>
<td>DVT</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>Death within 4 months</td>
<td>7%</td>
<td>11%</td>
</tr>
</tbody>
</table>
YOUNGER PATIENTS (< 65 yo)  
QUESTIONS TO BE ADDRESSED

- Stratification according to initial prognostic factors
- Double ASCT for all pts or only for selected pts (less than 90% response after initial CT ?)
- Induction : how to improve the CR rate prior to ASCT  
  • add Thal  
  • other novel agents
- Maintenance therapy
- Place of allogeneic SCT
- Patients < 65 years
- 0 or 1 adverse prognostic factors (chr 13, β2 M)

VAD
VAD
VAD
SC collection

HDM140 + AT

HDM200 + AT

Control

Pamidronate

Pamidronate + Thalidomide
IFM 99 02 : EFS ACCORDING TO THAL

p<0.02
YOUNGER PATIENTS (< 65 yo)

QUESTIONS TO BE ADDRESSED

- Stratification according to initial prognostic factors
- Double ASCT for all pts or only for selected pts (less than 90% response after initial CT ?)
- Induction: how to improve the CR rate prior to ASCT
  - add Thal
  - other novel agents
- Maintenance therapy
- Place of allogeneic SCT
Transplant related mortality: EBMT retrospective study

Crawley, Prag 2005
IFM 99
03 / 04
PRELIMINARY RESULTS (1)

From 10/99 to 01/02

150 PTS

45 IFM 99-03
29 (64%)
Mini Allo SCT

105 IFM 99-04
73 (69%)
Double ASCT
EFS
INTENT TO TREAT ANALYSIS

Probability of Survival

P = 0.06

Double ASCT
N = 105

Mini Allo SCT
N = 45
SURVIVAL
INTENT TO TREAT ANALYSIS

Double ASCT
N = 105

Mini Allo SCT
N = 45

P = 0.36
**MINI ALLO-SCT**
**THE ROLE OF CHROMOSOME 13 DELETION**

*Kroger Blood 2004*

<table>
<thead>
<tr>
<th></th>
<th>13q- N = 31</th>
<th>No 13q- N = 37</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yr SV</td>
<td>18%</td>
<td>67%</td>
<td>0.03</td>
</tr>
<tr>
<td>2 yr EFS</td>
<td>18%</td>
<td>42%</td>
<td>0.03</td>
</tr>
<tr>
<td>Cumulative incidence of relapse</td>
<td>77%</td>
<td>44%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1-yr TRM</td>
<td>18%</td>
<td>24%</td>
<td>0.4</td>
</tr>
</tbody>
</table>
PROGNOSTIC FACTORS
RISK GROUPS

IFM (*Facon 2001*)

\[ \beta_2 \text{M + chr 13 abnormalities (FISH)} \]

<table>
<thead>
<tr>
<th>Nb adverse PF</th>
<th>0 (20%)</th>
<th>1 (50%)</th>
<th>2 (30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median SV</td>
<td>111 m</td>
<td>47 m</td>
<td>25 m</td>
</tr>
</tbody>
</table>
ALLOGENEIC SCT

Main question: for all patients up to the age of 65 with an HLA identical sibling?

YES
- Only in a prospective trial comparing double autologous SCT and autologous SCT + mini allo

NO
- Good prognosis ($\beta_2m < 3$, no hypodiploidy, no chr13 abn): no indication since a high incidence of prolonged EFS is achieved with double auto
- Poor prognosis ($\beta_2m > 3$ and chr13 abno)
  → Phase II trial (Maxi BMT, MUD)
- Intermediate: clinical trial testing auto + mini allo
OLDER PATIENTS > 65 yo

- Results with MP are not satisfactory
- Other approaches are clearly needed
  - intermediate dose Melphalan + ASCT
  - Thal + MP
  - PS 341 + MP
OLDER PATIENTS
MEL 100 + ASCT

Palumbo et al (Blood 2004)

Pts 50-70 yo
De novo MM

M 6mg/m²/D D1-7
P 60mg/m²/D D1-7
2 DAV → CTX 3g/m² + G-CSF
→ Mel 100 + G-CSF + ASCT + ASCT

Maintenance therapy in both arms:
αIFN 3M IU x 3/wk
+ Dex 40mg D1-4 every 2 months

SC collection
<table>
<thead>
<tr>
<th></th>
<th>No Pts</th>
<th>CR %</th>
<th>CR+ VGPR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palumbo</td>
<td>95</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Attal IFM 94</td>
<td>399</td>
<td>NA</td>
<td>12</td>
</tr>
<tr>
<td>Moreau</td>
<td>399</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Lenhoff</td>
<td>274</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>Barlogie</td>
<td>231</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Segeren</td>
<td>379</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Cavo</td>
<td>100</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>
### TREATMENT SCHEDULES

<table>
<thead>
<tr>
<th>Treatment Schedule</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan 4 mg/m² 7 days/month for 6 courses</td>
<td>+</td>
</tr>
<tr>
<td>Prednisone 40 mg/m² 7 days/month for 6 courses</td>
<td>+</td>
</tr>
<tr>
<td>Thalidomide 100mg/d continuously until relapse</td>
<td>or</td>
</tr>
<tr>
<td>Melphalan 4 mg/m² 7 days/month for 6 courses</td>
<td>+</td>
</tr>
<tr>
<td>Prednisone 40 mg/m² 7 days/month for 6 courses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MPT N = 49</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>CR + near CR</td>
<td>39%*</td>
</tr>
<tr>
<td>Response rate (&gt;50%)</td>
<td>79.5%</td>
</tr>
</tbody>
</table>

* 24.5% CR (negative IF)
## Adverse Events

<table>
<thead>
<tr>
<th>WHO (grade)</th>
<th>MPT 1-2</th>
<th>MPT 3-4</th>
<th>MP 1-2</th>
<th>MP 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic (%)</td>
<td>35</td>
<td>22</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Constipation (%)</td>
<td>27</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neurologic (%)</td>
<td>31</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infection (%)</td>
<td>16</td>
<td>12</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Thromboemb. (%)</td>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Early death (%)</td>
<td>4</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
TRAITEMENTS DE SUPPORT

- Diphosphonates
  Clodronate
  Pamidronate
  Zolédronate

- EPO
Therapeutic options

- supportive care
- repeat initial CT
- use another CT regimen
- ASCT
- Thalidomide (+/- Dex)
- other novel agents
ALLOGENEIC SC TRANSPLANTATION
WHAT WE KNOW

- High transplant-related mortality
- Short-term retrospective comparisons are in favor of autologous SCT

BUT

- Durable CR (including molecular remissions): the only curative treatment?
- Remissions with DLI: GVM effect
- Better results if better supportive care and earlier transplantation (Gahrton 2001)
- Possibly the only curative treatment of MM

- Balance between GVH and GVM

- High TRM

- Better results if performed upfront

- Encouraging preliminary results with autologous SCT followed by mini allo (Maloney, Kroger)

- However inferior results with mini allo in patients with poor risk disease (chr 13) (Kroger, IFM 99)
INTERFERON

- No longer used in combination with CT

- Maintenance therapy (meta-analysis of 12 randomized trials)
  - 6 months prolongation of PFS
  - 7 months prolongation of OS
THERAPEUTIC POSSIBILITIES

- Alkylating agents
- High-dose corticoids
- Interferon
- High-dose therapy
- Thalidomide
- Novel agents
## IFM 94 TRIAL

### RESPONSE RATE

<table>
<thead>
<tr>
<th></th>
<th>Single TX N = 199</th>
<th>Double TX N = 200</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDM 140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>-</td>
<td>77</td>
</tr>
<tr>
<td>CR</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>CR + VGPR</td>
<td>-</td>
<td>26</td>
</tr>
<tr>
<td>HDM 140 + TBI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>CR</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>VGPR + CR</td>
<td>42</td>
<td>50</td>
</tr>
</tbody>
</table>

**p = 0.15**
PLACE de l’AUTOGREFFE

Rôle de l’IFM

- Essai IFM 90 (patients ≤ 65 A)
  - Autogreffe > chimio conventionnelle (tx réponse, SSE, SV globale)
  - Impact de la RC sur la survie

- Confirmation 7 ans plus tard par l’essai anglais
ALKYLATING AGENTS

- MP has been the standard regimen for decades
- 50% PR
  CR very rare
  Maximum responses may take several months
- No survival benefit for combination CT vs MP
- Should be avoided if ASCT is planned

Standard in elderly patients
HIGH-DOSE STEROIDS

- **VAD (or VAMP):**
  - Initially used in pts refractory to alkylating agents
  - 60-80% PR in newly diagnosed pts (10% CR)
  - Rapid response
  - No damage to SC

- **Dex is responsible for much of the efficacy of VAD (or VAMP)**

  Standard induction TT in younger pts
IMiDs

- **Immunomodulating drugs**
  - inhibit NF-kB and activate Caspase-8
  - inhibit adhesion of MM cells to BM stromal cells
  - inhibit secretion of cytokines
  - inhibit angiogenesis
  - decrease MM cell proliferation

- 2 compounds are in clinical development (Revimid and Actimid)
Progress in the treatment of MM over the past 40 years

- 1962: Prednisone + melphalan
- 1980s: Supportive care
- 1999: First report on thalidomide
- 2000s: Tandem ASCT
- 2002 onward: Lenalidomide clinical trials
- 2002: Bortezomib phase I trials published
- April 2005: Bortezomib approved for second-line in Europe
- From 1980s: Myeloablation + ASCT
- Melphalan

Bortezomib EU licence 2004
- Occurrence of GVHD is the major predictive factor for response after DLI in MM (Lockhorst Blood 2002)

  → Targets for GVH and GVM are the same?

- With standard myeloablative regimens TRM remains too high even when used early

  → Select patients

  → Use strategy to reduce TRM while harnessing GVM
THALIDOMIDE ALONE IN RELAPSED MM RESULTS

- Reduction in paraprotein of ≥ 25%: 40-80%
- Partial remission in 10-50% of patients
- CR and VGPR possible even in heavily pretreated patients
- Early onset of response 4-12 weeks
- Maximal response within 2-4 months
Bortezomib-associated PN is reversible in the majority of patients (APEX)

- Incidence of PN (37% 124/331)
  - 10% grade 1
  - 18% grade 2
  - 8% grade 3
  - <1% grade 4

- 64% (58/91) of patients with ≥grade 2 PN experienced improvement or resolution
  - 55% (50/91) had complete resolution (return to baseline)
  - 9% (8/91) experienced improvement by at least 1 CTC grade
  - Median time to improvement/resolution: 110 days from diagnosis
# Reports of peripheral neuropathy

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib</th>
<th>Thalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1/2</td>
<td>29%</td>
<td>Grade 1/2</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>8%</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td><strong>Predominantly sensory</strong></td>
<td></td>
<td>Mostly sensory neuropathy</td>
</tr>
<tr>
<td><strong>Not all patients will develop PN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Can be managed with dose modification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bortezomib-induced PN is reversible in majority of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thalidomide-induced PN can be irreversible</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Presented at ASH 2005*

Naina et al. *Blood* 2005;106 (Abstract 3475)  

San Miguel et al. *Blood* 2005;106 (Abstract 366);
# VISTA

International randomized, open-label, phase III trial in patients with previously untreated MM

<table>
<thead>
<tr>
<th>Arm A: MPV</th>
<th>Arm B: MP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V</strong> 1.3 mg/m²</td>
<td><strong>V</strong> 1.3 mg/m²</td>
</tr>
<tr>
<td>days 1, 4, 8, 11, 22, 25, 29, 32</td>
<td>days 1, 8, 22, 29</td>
</tr>
<tr>
<td>4 cycles</td>
<td>5 cycles</td>
</tr>
</tbody>
</table>

Arm B: MP

<table>
<thead>
<tr>
<th>V</th>
<th>M</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3 mg/m²</td>
<td>9 mg/m²</td>
<td>60 mg/m²</td>
</tr>
<tr>
<td>days 1, 2, 3, 4</td>
<td>for 9 cycles</td>
<td></td>
</tr>
</tbody>
</table>

Cycle = 6 weeks
### THALIDOMIDE IN COMBINATION WITH CHEMOTHERAPY IN PREVIOUSLY TREATED PATIENTS

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Study/Year</th>
<th>Nb of pts</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD</td>
<td>Kropff 2001</td>
<td>40</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Dimopoulos 2004</td>
<td>53</td>
<td>60%</td>
</tr>
<tr>
<td>TCED</td>
<td>Mochler 2001</td>
<td>56</td>
<td>86%</td>
</tr>
<tr>
<td>MPT</td>
<td>Palumbo 2006</td>
<td>24</td>
<td>58%</td>
</tr>
<tr>
<td>MDT</td>
<td>Srlkavic 2000</td>
<td>21</td>
<td>81%</td>
</tr>
<tr>
<td>DT PACE</td>
<td>Barlogie 2001</td>
<td>135</td>
<td>54%</td>
</tr>
<tr>
<td>TD CEP</td>
<td>Barlogie 2001</td>
<td>38</td>
<td>36%</td>
</tr>
</tbody>
</table>
### IFM 90 Trial

200 patients ≤ 65 y.o.

<table>
<thead>
<tr>
<th></th>
<th>CC N=100</th>
<th>HDT N=100</th>
<th>p. Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate</strong> (CR + VGPR)</td>
<td>38%</td>
<td>14%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Median EFS</strong></td>
<td>18 m</td>
<td>28 m</td>
<td></td>
</tr>
<tr>
<td><strong>7-year EFS</strong></td>
<td>8%</td>
<td>16%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>44 m</td>
<td>57 m</td>
<td></td>
</tr>
<tr>
<td><strong>7-year OS</strong></td>
<td>25%</td>
<td>43%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
THALIDOMIDE IN COMBINATION WITH DEXAMETHASONE IN MM NEWLY DIAGNOSED PATIENTS

- Active in indolent / smoldering MM
  - Mayo Clinic 29 pts 34% PR
  - MDACC 28 pts 36% PR

- Active in previously untreated patients with symptomatic MM
  - Mayo Clinic (JCO 2002) 50 pts 64% PR
  - MDACC (JCO 2003) 40 pts 72% PR
APEX: bortezomib vs dex

- International, randomized, open-label Phase III study in relapsed MM
  - 669 patients enrolled at 93 centers
  - 42% North America, 58% Europe/Israel

**Treatment plan**

<table>
<thead>
<tr>
<th>Bortezomib</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 cycles</td>
<td>4 cycles</td>
</tr>
<tr>
<td>1.3 mg/m² IV push</td>
<td>40 mg PO</td>
</tr>
<tr>
<td>days 1, 4, 8, 11 q3w cycle</td>
<td>days 1–4, 9–12, 17–20 q5w cycle</td>
</tr>
<tr>
<td>3 cycles</td>
<td>5 cycles</td>
</tr>
<tr>
<td>1.3 mg/m² IV push</td>
<td>40 mg PO</td>
</tr>
<tr>
<td>days 1, 8, 15, 22 q5w cycle</td>
<td>days 1–4 q4w cycle</td>
</tr>
<tr>
<td>273 treatment days</td>
<td>280 treatment days</td>
</tr>
</tbody>
</table>

Phase 2 Trial of Lenalidomide With or Without Dexamethasone in Relapsed/Refractory Myeloma

**Cohort 1**
- 30 mg/q.d. (3 wk on, 1 wk off q 28 days × 6 cycles)
- 15 mg/b.i.d. (3 wk on, 1 wk off q 28 days × 6 cycles)

**OR**

**Cohort 2**
- 30 mg/q.d. (3 wk on, 1 wk off q 28 days × 6 cycles)

PD or SD after cycle 2, 4

**Treatment Scheme**

**PD or SD**

Dex @ 40 mg days 1–4 q 14 days

N=70

PD, progressive disease; SD, stable disease

Updated APEX efficacy data
Response rates

ORR with bortezomib improved from 38% to 43%

Updated analysis

<table>
<thead>
<tr>
<th>Response %</th>
<th>Bortezomib</th>
<th>Bortezomib</th>
<th>Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>43%</td>
<td>27% PR</td>
<td>25% PR</td>
<td>16% PR</td>
</tr>
<tr>
<td></td>
<td>7% nCR</td>
<td>7% nCR</td>
<td>&lt;1% nCR</td>
</tr>
<tr>
<td></td>
<td>9% CR</td>
<td>6% CR</td>
<td></td>
</tr>
</tbody>
</table>

Primary analysis

\( P < 0.0001 \)
Updated APEX survival data

- Superior survival for bortezomib
  - Median OS: bortezomib 29.8 months vs 23.7 months for high-dose Dex ($P=0.0272$)
  - 1-year survival rate: 80% vs 67% ($P=0.0002$)

Richardson et al. Blood 2005;106 (Abstract 2547); Poster at ASH 2005
TOTAL THERAPY II

4 phases of treatment (Barlogie NEJM 2006)

- intensive induction treatment (VAD, DCEP, CAD, DCEP) + THAL throughout
- double ASCT (HDM 200)
- consolidation CT (DCEP / CAD)
- maintenance treatment (IFN + Dex)