Therapiesequenz bei der Therapie des Multiplen Myeloms

Hartmut Goldschmidt
Visiting Professor of the University of Belgrade
Sektion Multiples Myelom
Medizinische Klinik V, Universität Heidelberg
Nationales Centrum für Tumorerkrankungen Heidelberg
Progress in Therapeutic Options

1950-1960s
- MP
- RTX
- STEROIDS

1970-1980s
- ALLO
- ASCT
- HDC
- VAD
- STEROIDS
- RTX
- MP

1990s
- THAL
- BISPH
- Mini-ALLO
- ASCT
- HDC
- VAD
- STEROIDS
- RTX
- MP

2000s
- THAL
- BISPH
- Mini-ALLO
- ASCT
- HDC
- VAD
- STEROIDS
- RTX
- MP

New Targets
- Hsp90
- Proteasome
- Aggresome
- HDAC
- Akt
- XBP-1
- Nitric oxide
- Muc-1
- MEK
- NF-kB
- STAT3
- Telomerase
- Natural products

Agent
- KOS 953
- PR171, NPI0052
- Tubacin
- LBH
- Perifosine
- XBP-1 peptide
- JSK
- NM3
- AZD6244
- NPI1387
- WP1066
- Enzastaurin
- SCIO469
- GRN 163L
- EGCG

Palliation
- Cure
- Chronic illness

BTZ = Bortezomib
BISPH = Bisphosphonates
THAL = Thalidomide
ASCT = Stem cell transplantation
HDC = High-dose chemotherapy
MP = Melphalan + Prednisone
PLD = Pegylated liposomal doxorubicin

Munshi 2009
Which level of response is necessary?

Depth of response is related to TTP

- Treatment initiation
- Progression

MR
PR
VGPR/ nCR
CR
sCR
Molecular/Flow CR

Time

Response in MM

More sensitive techniques required to detect depth of response beyond CR

• Bone marrow level
  - Clonality of PC and k:λ FLC ratio → STRINGENT CR (sCR) ¹
  - Multiparametric flow cytometry → IMMUNOPHENOTYPIC CR ²
  - Qualitative and quantitative RT-PCR → MOLECULAR CR ³,⁴

• Outside bone marrow
  - MRI ⁵
  - PET-CT ⁶

¹. Durie et al, Leukemia 2006;20:1467-1473
². Paiva et al, Blood 2008;112:4017-4023
⁴. Ladetto et al, J Clin Oncol 2010;28:2077-2084
⁵. Barlogie, Blood 2006; 108:2134
Overview of studies showing an association between depth of response and outcome
## Impact of CR/VGPR

### Correlation of best response und OS in patients with newly diagnosed MM, treated with HDT

<table>
<thead>
<tr>
<th>Prospective Study</th>
<th>Comparison</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM90</td>
<td>CR/VGPR vs. PR vs. other</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>MRC VII</td>
<td>CR vs. PR vs. MR</td>
<td>0.00002</td>
</tr>
<tr>
<td>TT1</td>
<td>CR vs. PR</td>
<td>0.2496</td>
</tr>
<tr>
<td>TT2</td>
<td>CR vs. PR/NR</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IFM94-02</td>
<td>Maximal response</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFM99C</td>
<td>CR/VGPR vs. PR</td>
<td>&lt;0.0000</td>
</tr>
<tr>
<td>NMSG 5/94</td>
<td>CR vs. PR/NR</td>
<td>0.38</td>
</tr>
<tr>
<td>Bologna</td>
<td>≥ VGPR vs. other</td>
<td>0.002</td>
</tr>
<tr>
<td>GMA</td>
<td>CR/MRD vs. other</td>
<td>0.22</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>CR/VGPR vs. PR vs. other</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Adapted from Van de Velde H et al. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Haematologica 2007; 92:1399-1406
Impact of CR/VGPR

OS Heidelberg Cohort

Kaplan Meier Plot - OS - CR/nCR

years since first auto. resp.

0.0 0.2 0.4 0.6 0.8 1.0

CR/nCR

other
Impact of CR/VGPR

OS Heidelberg Cohort

[Graph showing survival data with different outcomes labeled as "sustained nCR/CR", "lost nCR/CR", and "no nCR/CR". The x-axis represents years from a 3-year landmark after first auto. tpi., and the y-axis shows survival probability.]
Impact of CR in VISTA:VMP group

Time to next treatment

Treatment-free interval

CR correlates with long-term PFS and OS in elderly patients treated with novel agents

- Retrospective analysis:
  - 3 randomized trials of GIMEMA and HOVON groups (n=1175)
- First-line treatment
  MP (n=332), MPT (n=332), VMP (n=257), VMPT-VT (n=254)

**Impact of CR/VGPR**

PFS

- CR
- VGPR
- PR

P<0.001

OS

- CR
- VGPR
- PR

P<0.001

Impact of post-ASCT MRD detected by flow cytometry on clinical outcomes

**PFS**
- MRD negative (n=94)
  - Median: 71 months
  - 62% at 5 years
- MRD positive (n=53)
  - Median: 37 months
  - 30% at 5 years

**OS**
- MRD negative (n=94)
  - Medians: not reached
- MRD positive (n=53)
  - 59% at 5 years

Paiva et al. Blood 2008;112(10):4017–4023
VTD consolidation: long-term follow up

- Impact of MRD detection by RQ-PCR on late recurrences and OS
- Median follow-up: 65 months; n=39

**Probability of PFS**

- SMR
- No SMR

<table>
<thead>
<tr>
<th>Probability of PFS</th>
<th>Probability of OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr PFS 82% vs 44%, p=0.009</td>
<td>5 yr OS 100% vs 74%, p=0.012</td>
</tr>
</tbody>
</table>

**SMR:** Standard molecular remission (MRD negativity on two consecutive samples by RQ-PCR)

- No patient with full molecular remission or SMR has died
- Dynamic increase in molecular tumor burden predicts late disease relapses before clinical recurrence

Ladetto *et al.* ASH 2011 (Abstract 827), oral presentation
How to improve ASCT - the role of new drugs
Phase 2 EVOLUTION study: Response rates at 4 cycles and overall

Kumar et al. Haematologica 2011; 96 (s1): S100 (Abstract P-234); poster presentation at IMW 2011
Improving the response quality / Increasing CR rate after SCT

**Induction**
- Vel-Dex (VD)
- Vel-Cyclo-Dex (VCD)
- Vel-ADM-Dex (PAD)
- VRD
- VTD
- Len-Dex
- RAD

**Consolidation**
- VTD
- VRD
- Bortezomib
- Len 25

**Maintenance**
- Thalidomide
  - IMF 99/02
- Lenalidomide
  - IMF 2005-02, CALGB
- Bortezomib
  - Hovon/GMMG
  - DSMM XI
  - PETHEMA/GEM
### Impact of VTD consolidation post-ASCT

<table>
<thead>
<tr>
<th>Study details</th>
<th>Results</th>
</tr>
</thead>
</table>
| • n=39 in ≥VGPR after ASCT<sup>1</sup>  
• treated with 4 cycles VTD | Median follow up: 42 months:  
No relapse in patients with molecular remission |
| • Molecular substudy of GIMEMA trial: VTD vs TD induction and consolidation<sup>2</sup>  
• n=67 with ≥nCR after ASCT, treated with two 35-day cycles VTD or TD | Significant increase in molecular remissions and reduction in tumor burden with VTD versus TD |
| • n=46 ≥PR after HDM<sup>3</sup>  
• treated with 2 cycles vtD (bortezomib 1mg/m<sup>2</sup> twice/week, thal 100 mg/d, dex 40 mg/d once/wk) | Improvement of response in 39% post-consolidation |

<sup>1</sup>Ladetto et al. J Clin Oncol 2010; 28(12): 2077-2084  
<sup>2</sup>Terragna et al. Haematologica 2011; 96 (s1): S96 (Abstract P-224); poster presentation at IMW 2011  
<sup>3</sup>Roussel et al. ASH 2010 (Abstract 3041), poster presentation
**IFM 2005-02: Study design**

**Phase III randomized, placebo-controlled trial**  
N= 614 patients, from 78 centers, enrolled between 7/2006 and 8/2008

Patients < 65 years, with non-progressive disease, ≤ 6 months after ASCT in first line

Randomization: stratified according to Beta-2m, del13, VGPR

**Consolidation:**  
**Lenalidomide alone** 25 mg/day p.o.  
days 1-21 of every 28 days for 2 months

**Arm A=**  
Placebo  
(N=307)  
until relapse

**Arm B=**  
Lenalidomide  
(N=307)  
10-15 mg/d until relapse

**Primary end-point:** PFS.  
**Secondary end-points:** CR rate, TTP, OS, feasibility of long-term lenalidomide....

ASCT = autologous stem cell transplant. IFM = Intergroupe Francophone du Myélome.
PFS according to Response Pre-Consolidation

PR or SD

HR = 0.37 - CI 95% [0.25-0.58]

VGPR or CR

HR = 0.54 - CI 95% [0.37-0.78]

p < 10^{-5}

p = 0.001
## Incidence of secondary malignancies

<table>
<thead>
<tr>
<th>Hematological malignancies (n)</th>
<th>Solid tumors (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Len</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td><strong>IFM 2005-01</strong>¹</td>
<td></td>
</tr>
<tr>
<td>Len (n=307)</td>
<td>11</td>
</tr>
<tr>
<td>Placebo (n=307)</td>
<td>5 AML/MDS</td>
</tr>
<tr>
<td></td>
<td>2 ALL</td>
</tr>
<tr>
<td></td>
<td>4 HL</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CALGB 100104</strong>²*</td>
<td></td>
</tr>
<tr>
<td>Len (n=231)</td>
<td>8</td>
</tr>
<tr>
<td>Placebo (n=229)</td>
<td>6 AML/MDS</td>
</tr>
<tr>
<td></td>
<td>1 ALL</td>
</tr>
<tr>
<td></td>
<td>1 HL</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*3 hematological and 4 solid tumors occurred before randomization

¹Attal et al. Haematologica 2011; 96 (s1): S23; oral presentation at IMW 2011
²McCarthy et al. Haematologica 2011; 96 (s1): S23; oral presentation at IMW 2011
Comparison of ASCT with new drugs based conventional therapy
Melphalan/prednisone/lenalidomide (MPR) versus high-dose melphalan and autologous transplantation (MEL200) in newly diagnosed multiple myeloma (MM) patients: a phase III study

A. Palumbo et al.

Boccadoro et al. J Clin Oncol 2011;29 (suppl) (Abstract 8020); poster presentation at ASCO 2011
Palumbo et al. Haematologica 2011;96(s2):214 (Abstract 508); oral presentation at EHA 2011
Phase 3: MPR versus tandem ASCT

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

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

Maintenance
- No maintenance
- Maintenance
  - Len 10 mg/d, d 1-21
  - 28-d course until relapse

Primary end point: PFS

Boccadoro et al. J Clin Oncol 2011;29 (suppl) (Abstract 8020); poster presentation at ASCO 2011
Palumbo et al. Haematologica 2011;96(s2):214 (Abstract 508); oral presentation at EHA 2011
Results: Efficacy

- Median follow up 26 months

<table>
<thead>
<tr>
<th></th>
<th>MPR (n=202)</th>
<th>MEL 200 (n=200)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>20%</td>
<td>25%</td>
<td>0.55</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>60%</td>
<td>62%</td>
<td>0.8</td>
</tr>
<tr>
<td>≥PR</td>
<td>95%</td>
<td>96%</td>
<td>0.77</td>
</tr>
<tr>
<td>Median PFS</td>
<td>25.26 months</td>
<td>Not reached</td>
<td>0.0002</td>
</tr>
<tr>
<td>2-year PFS</td>
<td>54%</td>
<td>73%</td>
<td>n/a</td>
</tr>
<tr>
<td>2-year OS</td>
<td>87%</td>
<td>90%</td>
<td>0.19</td>
</tr>
</tbody>
</table>

- 49.4% reduced risk of progression with MEL 200

*References*

Boccadoro et al. J Clin Oncol 2011;29 (suppl) (Abstract 8020); poster presentation at ASCO 2011
Palumbo et al. Haematologica 2011;96(s2):214 (Abstract 508); oral presentation at EHA 2011
IFM/DFCI 2009 study
Newly diagnosed MM patients (SCT candidates)

Randomize, stratification ISS & FISH

- VRD x 3
- CY (3g/m^2) MOBILIZATION
  Goal: 5 x 10^6 cells/kg
- Melphalan 200mg/m^2* + ASCT
- VRD x 2
- Lenalidomide 12 mos

Induction

- VRD x 3
- CY (3g/m^2) MOBILIZATION
  Goal: 5 x 10^6 cells/kg

Collection

Consolidation

Maintenance

SCT at relapse
MEL 200 mg/m^2 if <65 yrs, ≥65 yrs 140mg/m^2

http://www.clinicaltrials.gov/ct2/show/NCT01208662?term=nct01208662&rank=1
Novel agents alone versus intensive therapy + novel agents: European Intergroup trial (HOVON 95 MM, 2009-017903-28, EMN02)

3 x CVD + Stem cell apheresis

Registration
Induction
Stem cell mobilization in all pts

R1

4 x VMP
HDM 1/2

R2

2 x VRD
none

Consolidation

Maintenance until relapse

Lenalidomide

Lenalidomide

HDM/ASCT at relapse

Results of GMMG/HOVON
Normal: 2 homologous chromosomes → 2 Spots

Additional copy of 11q23

Staining of intracytoplasmatic kappa-light chains

del(13)(q14)
**FISH based risk score**
(Translocations t(4;14) and t(14;16), deletions 13q14 and 17p13, gain 1q21)

**Overall Survival**
Neben et al., Haematoligica 2010

**Progression-free Survival**

<table>
<thead>
<tr>
<th>Favorable:</th>
<th>NONE of the following aberrations del 13q, del 17p, +1q21, t(4;14), t(14;16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate:</td>
<td>del 13q and / or +1q21</td>
</tr>
<tr>
<td>Poor:</td>
<td>del 17p and / or t(4;14), and / or t(14;16)</td>
</tr>
</tbody>
</table>
Mobilisation & Leukapherese

Randomisation

MM St. II oder III, Alter 18-65

3 x VAD

CAD

Mobilisation & Leukapherese

B2MG >3 mg/l / ungünstige Prognose gemäß FISH, HLA-sib donor

3 x PAD

CAD

MEL 200 + PBSCT

MEL 200 + PBSCT

Thalidomid 50 mg pro Tag

Allogene Transplantation

MEL 200 + PBSCT

MEL 200 + PBSCT

Bortezomib 1,3 mg/m² alle 2 Wo

Bortezomib 1,3 mg/m² 2 mal pro Woche

(MM: Multiples Myelom; B2MG: Beta-2-Mikroglobulin; FISH: Fluoreszenz-in situ-Hybridisierung; HLA-sib donor: HLA-identischer Familienspender; MEL 200: Melphalan 200mg/m²; PBSCT: autologe periphere Blutstammzell-Transplantation)

Ungünstige Prognose gemäß FISH: t(4:14) / del17p13 o. del13q14 (ohne t(11;14))

GMMG-HD4 / HOVON-65 Studie
## Multivariate Cox regression analysis

<table>
<thead>
<tr>
<th>PFS (allo censored)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>t</strong></td>
<td><strong>t</strong></td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td><strong>HR</strong></td>
</tr>
<tr>
<td><strong>p</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td>Arm</td>
<td>Arm</td>
</tr>
<tr>
<td>0.74</td>
<td>0.70</td>
</tr>
<tr>
<td>.002</td>
<td>.013</td>
</tr>
<tr>
<td>WHO</td>
<td>WHO</td>
</tr>
<tr>
<td>1.22</td>
<td>1.49</td>
</tr>
<tr>
<td>.005</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IgA</td>
<td>IgA</td>
</tr>
<tr>
<td>1.62</td>
<td>1.82</td>
</tr>
<tr>
<td>.002</td>
<td>.01</td>
</tr>
<tr>
<td>IgG</td>
<td>IgG</td>
</tr>
<tr>
<td>1.33</td>
<td>1.71</td>
</tr>
<tr>
<td>.041</td>
<td>.008</td>
</tr>
<tr>
<td>LDH</td>
<td>LDH</td>
</tr>
<tr>
<td>1.25</td>
<td>1.59</td>
</tr>
<tr>
<td>.10</td>
<td>.006</td>
</tr>
<tr>
<td>ISS</td>
<td>ISS</td>
</tr>
<tr>
<td>1.25</td>
<td>1.47</td>
</tr>
<tr>
<td>.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>13q-</td>
<td>13q-</td>
</tr>
<tr>
<td>1.43</td>
<td>1.62</td>
</tr>
<tr>
<td>.001</td>
<td>.002</td>
</tr>
<tr>
<td>SG</td>
<td>SG</td>
</tr>
<tr>
<td>0.81</td>
<td>0.73</td>
</tr>
<tr>
<td>.039</td>
<td>.031</td>
</tr>
</tbody>
</table>
Kidney Function

Overall survival

Cumulative percentage

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>A; cr&lt;=176</td>
<td>328</td>
<td>89</td>
</tr>
<tr>
<td>A; cr&gt;176</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>B; cr&lt;=176</td>
<td>336</td>
<td>83</td>
</tr>
<tr>
<td>B; cr&gt;176</td>
<td>34</td>
<td>10</td>
</tr>
</tbody>
</table>

Logrank: $P < .001$

At risk:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>A; cr&lt;=176</td>
<td>328</td>
<td>291</td>
<td>269</td>
<td>163</td>
</tr>
<tr>
<td>A; cr&gt;176</td>
<td>44</td>
<td>28</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>B; cr&lt;=176</td>
<td>336</td>
<td>307</td>
<td>280</td>
<td>176</td>
</tr>
<tr>
<td>B; cr&gt;176</td>
<td>34</td>
<td>28</td>
<td>25</td>
<td>15</td>
</tr>
</tbody>
</table>

C. Scheid et al., ASH 2010
Comparison between both study arms HD4 Deletion 17p13

- **Progression-free survival (%):**
  - del (17p), arm A (without Bortezomib)
  - no del (17p), arm A (without Bortezomib)
  - del (17p), arm B (with Bortezomib)
  - no del (17p), arm B (with Bortezomib)

- **Overall survival (%):**
  - del (17p), arm A (without Bortezomib)
  - no del (17p), arm A (without Bortezomib)
  - del (17p), arm B (with Bortezomib)
  - no del (17p), arm B (with Bortezomib)
**MEL 100 and new drugs**

**PAD vs PAD→MEL-100 vs PAD→MEL-100→LP vs PAD→MEL-100→LP→L: Response Rate***

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD (n=102)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD 4 Cycles</td>
<td>13</td>
<td>47</td>
<td>36</td>
<td>3</td>
<td>1</td>
<td>60%</td>
</tr>
<tr>
<td>PAD→MEL-100 (n=77)</td>
<td>43</td>
<td>44</td>
<td>30</td>
<td>3</td>
<td>1</td>
<td>87%</td>
</tr>
<tr>
<td>PAD→MEL-100→LP (n=56)</td>
<td>59</td>
<td>30</td>
<td>9</td>
<td>0</td>
<td>2</td>
<td>89%</td>
</tr>
<tr>
<td>PAD→MEL-100→LP→L (n=40)</td>
<td></td>
<td>22</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>95%</td>
</tr>
</tbody>
</table>

*Per protocol

Palumbo A et al. *Blood*. 2008;112:65 [abstract 159]; updated results presented at: 50th ASH Annual Meeting; December 6–9, 2008; San Francisco, CA
PBSCT Mobilization

Induction 1)
- 3 x PAd
- A1 + B1
- 3 x VCD
- A2 + B2

Mobilization
- CAD + leukapheresis

PBSCT
- HDM + TPL

2. PBSCT (if no CR)
- HDM + TPL

Consolidation
- 2 x R

Maintenance
- Free light chain (FLC) + MRD diagn. every 3 months
- Lenalidomide for 2 years
- if no CR

1) Risk assessment within first 4 weeks; high risk patients proposed to go off protocol and in an experimental phase II trial (allogeneic transplantation)
2) PAd = Bortezomib (PS-341, Velcade) 1.3mg/m² d1,4,8,11; Adriamycin 9mg/m², d1-4; Dexamethasone 20mg, d1-4, d9-12, d17-20
3) VCD = Bortezomib (PS-341, Velcade) 1.3mg/m² d1,4,8,11; Cyclophosphamide 900mg/m², d1, Dexamethasone 40mg, d1-2, d4-5, d8-9, d11-12
4) CAD = Cyclophosphamide 1g/m² d1; Adriamycin 15mg/m², d1-4; Dexamethasone 40mg, d1-4;
5) HDM + TPL = High Dose Melphalan 200mg/m² and autologous stem cell transplantation
6) Rd = Lenalidomide (Revlimid) 15mg/d, d1-21; Dexamethasone 20 mg/die d1-4, 8, 15, 22;
7) Lenalidomide 10mg/d
8) MRD = minimal residual disease
9) randomization to one of four treatment strategies A1, B1, A2, B2: A1= PAd induction, lenalidomide maintenance for 2 years; B1= PAd induction, lenalidomide maintenance if no CR; A2= VCD induction, lenalidomide maintenance for 2 years; B2 = VCD induction, lenalidomide maintenance if no CR
OS GMMG-HD2 vs HD3/HD4

Overall Survival
ITT

OS Probability
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

years since first HDM

0 1 2 3 4 5 6 7 8

HD2
HD3/HD4
Participating and associated sites
Thank you for your attention!

Multiple Myeloma: Thank You