18th International Myeloma Workshop
September 9th, 2021

„Maintenance strategies for MM“

Prof. Dr. med. Hartmut Goldschmidt
Multiple Myeloma Section
Medical Clinic V, University Hospital and the
National Center for Tumor Diseases (NCT) Heidelberg
Disclosures

Prof. Dr. med. Hartmut Goldschmidt

University Hospital Heidelberg, Medical Clinic V and National Center for Tumor Diseases (NCT), Heidelberg

Disclosures

- Honoraria
  - Amgen, BMS, Celgene, Chugai, GSK, Janssen, Novartis, Omnia Med Deutschland, Sanofi

- Consulting or advisory role
  - Adaptive Biotechnology, Amgen, BMS, Celgene, Millennium Pharmaceuticals Inc., Molecular Partners AG Zürich, Janssen, Sanofi, Takeda

- Research funding
  - Amgen, BMS, Celgene, Chugai, Janssen, Incyte, Merck Sharp and Dohme (MSD), Molecular Partners AG Zürich, Mundipharma, Novartis, Sanofi, Takeda

- Travel, accommodations, expenses
  - Amgen, BMS, Celgene, Chugai, GSK, Janssen, Novartis, Takeda, Omnia Med Deutschland, Sanofi
Drugs before and after ABSCT in the Early Days of HDT

Induction:
- VAD
- MP

ABSCT 1x:
- Mel 200

Consolidation 2nd ABSCT:
- Mel 200

Maintenance:
- Nothing
- Alpha-IFN

Adapted from Einsele, DGHO Slides 2012
PFS and OS With Lenalidomide Maintenance After ASCT in MM: Meta-analysis of 3 Phase III Trials

- Median PFS, Mos (95% CI):
  - Lenalidomide: 52.8 (45.1-62.6)
  - Observation: 23.5 (21.0-26.2)

- Median OS, Mos (95% CI):
  - Lenalidomide: NE (NE-NE)
  - Observation: 86.0 (79.8-96.0)

- HR: 0.75 (95% CI: 0.63-0.90); P = .001

- 7-yr OS: 62%
- 5-yr OS: 50%

- Median follow-up: 80 mos

- Patients at Risk, n:
  - Len maintenance: 605, 499, 428, 353, 293, 244, 191, 131, 83, 28, 5
  - Observation: 603, 419, 275, 179, 125, 90, 71, 52, 30, 9, 0

McCarthy, JCO. 2017;35:3279.
Meta-analysis of Lenalidomide maintenance therapy: Overall survival - subgroup analysis

- 3 studies included: IFM 2005-02; CALGB 100104 (Alliance); GIMEMA-RVMM-PI-209

<table>
<thead>
<tr>
<th></th>
<th>LEN (^a)</th>
<th>CONTROL (^a)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 60 yrs</td>
<td>372</td>
<td>375</td>
</tr>
<tr>
<td></td>
<td>≥ 60 yrs</td>
<td>233</td>
<td>229</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>322</td>
<td>349</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>283</td>
<td>255</td>
</tr>
<tr>
<td>ISS stage</td>
<td>I or II</td>
<td>411</td>
<td>440</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>113</td>
<td>90</td>
</tr>
<tr>
<td>Response after ASCT</td>
<td>CR/VGPR</td>
<td>66</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>PR/SD/PD</td>
<td>320</td>
<td>339</td>
</tr>
<tr>
<td>Prior induction therapy</td>
<td>LEN</td>
<td>218</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td>Non-LEN</td>
<td>147</td>
<td>146</td>
</tr>
<tr>
<td>Adverse-risk cytogenetics (^b)</td>
<td>Yes</td>
<td>56</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>231</td>
<td>243</td>
</tr>
<tr>
<td>CrCl after ASCT (^c)</td>
<td>&lt; 50 mL/min</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>≥ 50 mL/min</td>
<td>379</td>
<td>404</td>
</tr>
</tbody>
</table>

Phase III Myeloma XI Trial: PFS With Len Maintenance in ASCT-Eligible Patients by Cytogenetic Risk

- High risk: presence of either t(4;14), t(14;16), t(14;20), del 17p, or gain 1q
- Ultrahigh risk: presence of more than 1 of these lesions
- Standard risk: absence of these lesions

GMMG MM5-Trial CR: Landmark (after cons.) PFS + OS

HR = 1.84 (95% CI: 1.08 - 3.13) p = 0.02

HR = 1.80 (95% CI: 0.74 - 4.36) p = 0.19

Heidelberg University Hospital | Maintenance strategies for MM - 18th International Myeloma Workshop | September 2021 | Prof. Dr. med. Hartmut Goldschmidt
Multiple Myeloma:
First Line Treatment - EHA/ESMO Guidelines 2021

Eligibility for autologous stem cell transplantation (ASCT)

YES

Induction
First option: VRD, DaraVTD
Other options: VTD, VCD, PAD

200 mg/m² melphalan followed by ASCT

Lenalidomide maintenance

NO

First option: VRD, DaraVMP, DaraRd
Second option: VMP, Rd, VCD, VD

Figure 1. Frontline therapy for Myeloma

Dimopoulos et al. 2021
ORIGINAL ARTICLE

Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial

H Goldschmidt¹,², HM Lokhorst³, EK Mai¹, B van der Holt⁴, IW Blau⁵, S Zweegman⁶, KC Weisel⁷, E Vellenga⁸, M Pfurtschuh⁹, MJ Kersten¹⁰, C Scheid¹¹, S Croockewit¹², R Raymakers¹³, D Hose¹, A Potamianou¹⁴, A Jauch¹⁵, J Hillengass¹, M Stevens-Kroef¹⁶, MS Raab¹, A Broijl¹⁷, HW Lindemann¹⁸, GMJ Bos¹⁹, P Brossart²⁰, M van Marwijk Kooy²¹, P Ypma²², U Duehsen²³, RM Schaafsma²⁴, U Bertsch¹, T Hielscher²⁵, Le Jarari²⁶, HJ Salwender²⁷ and P Sonneveld¹⁷

Sonneveld et al., JCO 2013
Goldschmidt et al., Leukemia 2018
HOVON 65/GMMGHD4: OS by Treatment Arm Subgroup with del(17/17p)

VAD

Cumulative percentage

0 25 50 75 100

At risk:

no del(17p) del(17p)

N 159 69 22 20

D 133 105 82 2

p<0.001

PAD

Cumulative percentage

0 25 50 75 100

At risk:

no del(17p) del(17p)

N 153 64 17 8

D 128 106 88 8

p=0.5

Neben et al., Blood 2012

Goldschmidt et al., Leukemia 2017

Heidelberg University Hospital | Maintenance strategies for MM • 18th International Myeloma Workshop | September 2021 | Prof. Dr. med. Hartmut Goldschmidt
Mayo Clinic Off-Study Treatment Algorithm for Transplant-Eligible Myeloma Patients

mSMART – Off-Study
Transplant Eligible

- t(11;14), t(6;14), Trisomies
  - 4 cycles of VRd
    - Collect Stem Cells
      - Autologous stem cell transplant (preferred)
        - VRd x 4 cycles
          - Len maintenance

- Del 17p, Gain 1q
  - 4 cycles of Dara-VRd
    - Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
  - Double or Triple Hit Myeloma
    - 4 cycles Dara-VRd
      - Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT

- t(4;14), t(14;16),

---

* If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor; ** Duration usually until progression based on tolerance

VRd, Bortezomib, lenalidomide, dexamethasone; Dara, daratumumab

Patients who completed consolidation and achieved ≥PR were re-randomized 1:1 to DARA 16 mg/kg IV every 8 weeks or OBS (no maintenance) for 2 years.
DARA Significantly Improved PFS From Second Randomization vs OBS

Median follow-up: 35.4 months from second randomization

HR 0.53 (95% CI 0.42–0.68)  
P<0.0001
### Increasing Number of New Drugs Before and After ABSCT

<table>
<thead>
<tr>
<th>Induction</th>
<th>ABSCT 1/2x</th>
<th>Consolidation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>Mel 200</td>
<td>Bortezomib</td>
<td>IMID</td>
</tr>
<tr>
<td>TAD</td>
<td>Mel 200</td>
<td>Len 25</td>
<td>PI</td>
</tr>
<tr>
<td>VD</td>
<td></td>
<td>VTD</td>
<td>Antibodies</td>
</tr>
<tr>
<td>VCD + Ab</td>
<td></td>
<td>VRD</td>
<td>Combinations</td>
</tr>
<tr>
<td>VTD + Ab</td>
<td></td>
<td>KRD</td>
<td>M-STOP</td>
</tr>
<tr>
<td>VRD</td>
<td></td>
<td>+ Ab</td>
<td></td>
</tr>
<tr>
<td>KRD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Len-Dex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRD + Ab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRD + Ab</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Einsele, DGHO Slides 2012
Final analysis of survival outcomes in first trial PFS

- Results remain consistent nearly 3 yrs after the original analysis of the primary endpoint, PFS:
  - Rd continuous significantly improved PFS vs MPT ($P < .00001$)

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mos</th>
<th>4-yr PFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd continuous</td>
<td>26.0</td>
<td>32.6</td>
</tr>
<tr>
<td>Rd18</td>
<td>21.0</td>
<td>14.3</td>
</tr>
<tr>
<td>MPT</td>
<td>21.9</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Final analysis of survival outcomes in first trial OS

HR (95% CI)
Rd continuous vs MPT: 0.78 (0.67-0.92), P = .0023

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, mos</th>
<th>4-yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd continuous</td>
<td>59.1</td>
<td>59.0</td>
</tr>
<tr>
<td>Rd18</td>
<td>62.3</td>
<td>58.0</td>
</tr>
<tr>
<td>MPT</td>
<td>49.1</td>
<td>51.7</td>
</tr>
</tbody>
</table>

- Rd continuous significantly extended OS vs MPT (P = .0023) and resulted in similar OS vs Rd18
- In patients achieving ≥ VGPR, median OS was 79.5 mos with Rd continuous, 55.7 mos with MPT, and 80.1 mos with Rd18
MAIA Trial: OS

D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible.

D-Rd: median, NR
Rd: median, NR

HR, 0.68; 95% CI, 0.53-0.86;
P = 0.0013a

*P = 0.0013 is statistically significant, crossing the prespecified stopping boundary of P = 0.0414.
Mayo Clinic Off-Study Treatment Algorithm for Transplant-Ineligible Myeloma Patients

**mSMART – Off-Study**

**Transplant Ineligible**

- **t(11;14), t(6;14), Trisomies**
  - VRd for ~12 months followed by Len maintenance*;
    - or
    - DRd²
- **t(4;14), t(14;16), t(14;20), Del 17p**
  - VRd for ~12 months
  - Bortezomib-based maintenance till progression*²

* Duration is usually until progression, based on tolerance

VRd, Bortezomib, lenalidomide, dexamethasone; DRd, daratumumab, lenalidomide, dexamethasone

<table>
<thead>
<tr>
<th>Study</th>
<th>NCT number</th>
<th>Phase</th>
<th>Maintenance/continuous treatment regimens</th>
<th>N</th>
<th>Primary endpoint</th>
<th>Estimated 1st completion data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-ASCT maintenance therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENO1001444</td>
<td>NCT03540504</td>
<td>3</td>
<td>Ixazomib-Rd vs. Rd</td>
<td>316</td>
<td>PFS</td>
<td>Not known</td>
</tr>
<tr>
<td>MM-015</td>
<td>NCT03554716</td>
<td>2</td>
<td>Ixazomib vs. R</td>
<td>240</td>
<td>MRD</td>
<td>November 2019</td>
</tr>
<tr>
<td>NCI-01-020</td>
<td>NCT03289017</td>
<td>2</td>
<td>Ixazomib-Rd vs. R</td>
<td>86</td>
<td>MRD</td>
<td>March 2020</td>
</tr>
<tr>
<td>ATLAS</td>
<td>NCT03092929</td>
<td>3</td>
<td>Carfilzomib-Rd vs. R</td>
<td>180</td>
<td>PFS</td>
<td>March 2019</td>
</tr>
<tr>
<td>FORTE</td>
<td>NCT02056413</td>
<td>2</td>
<td>Carfilzomib-R vs. R</td>
<td>477</td>
<td>s/dVRP rate post-induction</td>
<td>October 2016</td>
</tr>
<tr>
<td>Castor</td>
<td>NCT0254183</td>
<td>2</td>
<td>Daratumumab vs. observation</td>
<td>1085</td>
<td>PFS</td>
<td>August 2022</td>
</tr>
<tr>
<td>EAP118</td>
<td>NCT03890317</td>
<td>2</td>
<td>Daratumumab-ixazomib vs. ixazomib</td>
<td>400</td>
<td>MRD-reg, rate</td>
<td>February 2022</td>
</tr>
<tr>
<td>AURGA/MM-3031</td>
<td>NCT0399163</td>
<td>3</td>
<td>Daratumumab-R vs. R</td>
<td>314</td>
<td>SABR rate at 12 months</td>
<td>May 2021</td>
</tr>
<tr>
<td>GBRF14-MM-2004</td>
<td>NCT02867472</td>
<td>2</td>
<td>Daratumumab-R vs. R</td>
<td>222</td>
<td>s/dVRP rate post-consolidation</td>
<td>January 2019</td>
</tr>
<tr>
<td>DraiMar</td>
<td>SWOG19183</td>
<td>3</td>
<td>Daratumumab-R vs. R</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>GWMH-066</td>
<td>NCT03443922</td>
<td>3</td>
<td>Elotuzumab-R vs. R</td>
<td>564</td>
<td>PFS</td>
<td>June 2020</td>
</tr>
<tr>
<td>GWMH-067</td>
<td>NCT03671777</td>
<td>3</td>
<td>Isatuximab-R vs. R</td>
<td>662</td>
<td>PFS</td>
<td>May 2025</td>
</tr>
<tr>
<td>Continuous frontline therapy, non-ASCT setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOURMALINE-MM2</td>
<td>NCT0195514</td>
<td>3</td>
<td>Ixazomib-Rd vs. placebo-Rd</td>
<td>701</td>
<td>PFS</td>
<td>February 2018</td>
</tr>
<tr>
<td>COBRA</td>
<td>NCT02029804</td>
<td>3</td>
<td>Carfilzomib-Rd vs. VdRd</td>
<td>250</td>
<td>PFS</td>
<td>December 2021</td>
</tr>
<tr>
<td>GENO1917FT</td>
<td>NCT03742973</td>
<td>3</td>
<td>Daratumumab plus carfilzomib-Rd vs. carfilzomib-Rd vs. VMl-Rd</td>
<td>300</td>
<td>CR rate</td>
<td>October 2020</td>
</tr>
<tr>
<td>Pioneer</td>
<td>NCT03740675</td>
<td>3</td>
<td>Daratumumab-VdRd-daratumumab-R vs. VdRd-R</td>
<td>690</td>
<td>PFS</td>
<td>May 2029</td>
</tr>
<tr>
<td>MMY3019</td>
<td>NCT03620041</td>
<td>3</td>
<td>Daratumumab-VdRd-daratumumab-Rd vs. VdRd-Rd</td>
<td>350</td>
<td>MRD-reg</td>
<td>March 2024</td>
</tr>
<tr>
<td>ELOLENT-1</td>
<td>NCT0335399</td>
<td>3</td>
<td>Elotuzumab-Rd vs. Rd</td>
<td>750</td>
<td>PFS</td>
<td>May 2019</td>
</tr>
<tr>
<td>SWOG 5211</td>
<td>NCT039871</td>
<td>3</td>
<td>Elotuzumab-VdRd vs. VdRd</td>
<td>122</td>
<td>PFS</td>
<td>May 2019</td>
</tr>
<tr>
<td>IMROZ</td>
<td>NCT03319667</td>
<td>3</td>
<td>Isatuximab-VdRd-isatuximab-Rd vs. VdRd-Rd</td>
<td>440</td>
<td>PFS</td>
<td>December 2023</td>
</tr>
<tr>
<td>Post-induction maintenance therapy, non-ASCT setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOURMALINE-MM4</td>
<td>NCT0352529</td>
<td>3</td>
<td>Ixazomib vs. placebo</td>
<td>706</td>
<td>PFS</td>
<td>August 2019</td>
</tr>
<tr>
<td>Ovoa continuation</td>
<td>NCT03474913</td>
<td>3</td>
<td>Ixazomib-Rd vs. placebo-Rd</td>
<td>105</td>
<td>PFS</td>
<td>December 2024</td>
</tr>
<tr>
<td>Myeloma XIV (FITNESS)</td>
<td>NCT03720041</td>
<td>3</td>
<td>Ixazomib-R vs. placebo-R (post-ASCT)</td>
<td>740</td>
<td>PFS</td>
<td>December 2024</td>
</tr>
<tr>
<td>X4601</td>
<td>NCT0373269</td>
<td>2</td>
<td>Ixazomib-R vs. ixazomib</td>
<td>52</td>
<td>PFS, AE</td>
<td>December 2023</td>
</tr>
<tr>
<td>AGMT-M01-3</td>
<td>NCT02861811</td>
<td>2</td>
<td>Carfilzomib vs. observation</td>
<td>146</td>
<td>Post-induction CR</td>
<td>September 2023</td>
</tr>
</tbody>
</table>


1Data reported from inclusion/exclusion/consolidation phase, not yet reported from the randomized maintenance phase of the study.
2Not reported from randomization/consolidation phase, not yet reported from the randomized maintenance phase of the study.
3Information from https://www.mmcommunity.org/risk/3mm-18/.
4Information from https://www.mmcommunity.org/risk/3mm-18/.
Multiple Myeloma - Heidelberg Center
20 Years ABSCT (n = 1486 pts)

Overall survival of patients
with autologous stem cell transplantations in Heidelberg (since 9.6.1992)

Hillengaß et al., J Cancer Res Clin Oncol. 2013
Regulatory differences and clonal evolution in RRMM

Clonal composition (pre treatment)
- pre2
- pre1

Clonal composition (post treatment)
- post

scATAC-seq clustering
- post clone
- pre2 clone
- pre1 clone

NFKB2 activity

By courtesy of A. Poos, N. Prokoph, M. Raab, K. Rippe, N. Weinhold
Presentation at ASH 2020 and manuscript in preparation
Thank you for your attention!