Welcome & Introductions

Myeloma
Update on Research and Treatment from the American Society of Hematology (ASH®) Annual Meeting

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Chair, Southwest Oncology Group Myeloma Committee

This program is not sponsored, sanctioned by, or part of the 55th Annual Meeting of the American Society of Hematology (ASH®)
Outline

• Disease biology
  • Asymptomatic myeloma
  • Non-transplant therapies
  • Induction before transplant
  • Options for therapy after transplant
  • Relapsed and/or refractory myeloma
  • Aspects of supportive care in myeloma

2013 ASH Abstract 529

Co-existent Hyperdiploidy does not Abrogate the Poor Prognosis Associated with Adverse Cytogenetics in Myeloma

Hyperdiploidy +/- Other Lesions

- Hyperdiploidy usually means good prognosis.

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Patient #s</th>
<th>PFS (Months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD w/o Adverse lesions</td>
<td>304</td>
<td>23</td>
<td>60.9</td>
</tr>
<tr>
<td>HD + Del 17p</td>
<td>20</td>
<td>19.1 (p=0.019)</td>
<td>35.2 (p=0.003)</td>
</tr>
<tr>
<td>HD + 1q+</td>
<td>142</td>
<td>15.4 (p&lt;0.001)</td>
<td>38.1 (p&lt;0.001)</td>
</tr>
<tr>
<td>HD + Adverse Translocation</td>
<td>9</td>
<td>15.4 (p=0.272)</td>
<td>40.1 (p=0.180)</td>
</tr>
<tr>
<td>HD + &gt;1 lesion</td>
<td>24</td>
<td>12.1 (p&lt;0.001)</td>
<td>19.9 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

- Hyperdiploidy overcome by poor risk lesions.

2013 ASH Abstract 689

Pomalidomide + Low-dose Dexamethasone in Relapsed or Refractory Multiple Myeloma with Deletion 17p and/or Translocation t(4;14)

Xavier Leleu, Lionel Karlin, Margaret Macro, Cyrille Hulin, Laurent Garderet, Murielle Roussel, Bertrand Arnulf, Brigitte Pegourie, Brigitte Kolb, Anne-Marie Stoppa, Sabine Brechiniac, Mauricette Michallet, Gerald Marit, Claire Mathiot, Anne Banos, Laurence Lacotte, Mourad Tiab, Mamoun Dib, Jean-Gabriel Fuzibet, Marie-Odile Petillon, Philippe Rodon, Marc Wetterwald, Bruno Royer, Laurence Legros, Lotfi Benboubker, Olivier Decaux, Denis Caillot, Martine Escoffre-Barbe, Jean Paul Fermand, Philippe Moreau, Michel Attal, Hervé Avet-Loiseau, and Thierry Facon
Pomalidomide and Deletion 17p

Time to Progression

- Response rate with pom/dex comparable in patients ± del 17p
- Pom may overcome this poor risk lesion

2013 ASH Abstract 123

Identification of Tight Junction Protein (TJP)-1 as a Modulator and Biomarker of Proteasome Inhibitor Sensitivity in Multiple Myeloma

Xing-Ding Zhang, Verrabhadran Baladandayuthapani, Heather Lin, George Mulligan, Bin Li, Dixie-Lee Esseltine, Lin Qi, Jian-Liang Xu, Walter Hunziker, Bart Barlogie, Saad Usmani, Qing Zhang, John Crowley, Bing-Zong Li, Hui-Han Wang, Jie-Xin Zhang, Isere Kuiatse, Jin-Le, Tang, Hua Wang, Richard Eric Davis, Wen-Cai Ma, Zhi-Qiang Wang, Lin Yang, and Robert Z. Orlowski
TJP1 Sensitizes to Bortezomib

- High TJP1 = Good response to bortezomib

<table>
<thead>
<tr>
<th></th>
<th>Median TTP (days)</th>
<th>L</th>
</tr>
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<tbody>
<tr>
<td>TJPI_202011_at</td>
<td>92</td>
<td>78</td>
</tr>
<tr>
<td>1\textsuperscript{st} tertile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} tertile</td>
<td>147</td>
<td>87</td>
</tr>
<tr>
<td>3\textsuperscript{rd} tertile</td>
<td>179</td>
<td>127</td>
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<tr>
<td>TJPI_214168_at</td>
<td>109</td>
<td>84</td>
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<tr>
<td>1\textsuperscript{st} tertile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} tertile</td>
<td>139</td>
<td>94</td>
</tr>
<tr>
<td>3\textsuperscript{rd} tertile</td>
<td>158</td>
<td>93</td>
</tr>
</tbody>
</table>

Outline

- Disease biology
- **Asymptomatic myeloma**
- Non-transplant therapies
- Induction before transplant
- Options for therapy after transplant
- Relapsed and/or refractory myeloma
- Aspects of supportive care in myeloma
Clinical and Correlative Pilot Study of Carfilzomib, Lenalidomide, and Dexamethasone Followed by Lenalidomide Extended Dosing (CRd – R) in High Risk Smoldering Multiple Myeloma Patients

Ola Landgren, Sham Mailankody, Mary Kwok, Elisabet E. Manasanch, Manisha Bhutani, Nishant Tageja, Dickran Kazandjian, Adriana Zingone, Rene Costello, Debra Burton, Yong Zhang, Peter Wu, George Carter, Marcia Mulquin, Diamond Zuchlinski, Irina Marie, Katherine R Calvo, Raul C. Braylan, Constance Yuan, Maryalice Stetler-Stevenson, Diane C Arthur, Liza Lindenberg, Karen Kurdziel, Peter Choyke, Seth M. Steinberg, Mark Roschewski, and Neha Korde

Study Design

- Each cycle is 28 days.
- Patients younger than 75 years underwent stem cell harvest after 4 cycles of CRd and continued therapy.
- C1D1/2 – Carfilzomib dose is 20 mg/m²
  - C1: 4 – Dex dose is 20 mg. C5-8 – Dex dose is 10 mg
- 8 cycles CRd Combination Therapy
  - Carfilzomib 20/36 mg/m², day 1, 2, 8, 9, 15, 16
  - Lenalidomide 25 mg/day, day 1-21
  - Dexamethasone 20/10 mg
  - day 1, 2, 8, 9, 15, 16, 22, 23

24 cycles Rev Extended Dosing
- Lenalidomide 10 mg/day, day 1-21
Response Rate and Quality

Toxicities

<table>
<thead>
<tr>
<th>Non-Hematologic</th>
<th>Grade 3/4, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte disturbances</td>
<td>3(25)</td>
</tr>
<tr>
<td>LFT elevation</td>
<td>2(17)</td>
</tr>
<tr>
<td>Rash/Pruritus</td>
<td>3(25)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>2(17)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1(8)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1(8)</td>
</tr>
<tr>
<td>Infections</td>
<td>1(8)</td>
</tr>
<tr>
<td>VTE</td>
<td>1(8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1(8)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1(8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Grade 3/4, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>5(42)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2(17)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1(8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3(25)</td>
</tr>
</tbody>
</table>
Outline

• Disease biology
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• **Non-transplant therapies**
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2013 ASH Abstract 2

**Initial Phase 3 Results of the FIRST (Frontline Investigation of Lenalidomide + Dexamethasone vs. Standard Thalidomide) Trial (MM-020/IFM 07 01) in Newly Diagnosed Multiple Myeloma Patients Ineligible for Stem Cell Transplantation**

Study Design

Randomization 1:1:1

Arm A
Continuous Rd
LEN + Lo-DEX Continuously
LENALIDOMIDE 25mg D1-21/28
Lo-DEX 40mg D1,8,15 & 22/28

Arm B
Rd18
LEN + Lo-DEX: 18 Cycles (72 wks)
LENALIDOMIDE 25mg D1-21/28
Lo-DEX 40mg D1,8,15 & 22/28

Arm C
MPT
MEL + PRED + THAL 12 Cycles (72 wks)
MELPHALAN 0.25mg/kg D1-4/42
PREDNISONE 2mg/kg D1-4/42
THALIDOMIDE 200mg D1-42/42

• Stratification by age, country and ISS stage

Progression-free Survival

Median PFS
Rd (n=535) 23.5 mos
Rd18 (n=541) 20.7 mos
MPT (n=547) 21.2 mos

Hazard ratio
Rd vs. MPT: 0.72; P = 0.00006
Rd vs. Rd18: 0.79; P = 0.00001
Rd18 vs. MPT: 1.03; P = 0.70349

Patients (%) 100 80 60 40 20 0
Time (months) 0 6 12 18 24 30 36 42 48 54 60

42% (Rd)
23% (Rd18)
23% (MPT)
Forest Plot of Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard ratio (HR) and 95% CI</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤ 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America and Pacific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS stage: I or II</td>
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<tr>
<td>ISS stage: III</td>
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<td></td>
</tr>
<tr>
<td>CrCl &lt; 30 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl 30 – 50 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl 50 – 80 ml/min</td>
<td></td>
<td></td>
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<tr>
<td>CrCl ≥ 80 ml/min</td>
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<td></td>
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<tr>
<td>ECOG PS Grade 0</td>
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<td></td>
</tr>
<tr>
<td>ECOG PS Grade 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG PS Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH ≤ 200 IU/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH &gt; 200 IU/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics High-risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics Non-high Risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ITT patients: 0.72 (0.61 - 0.85)

Favoring Rd Favoring MPT

Interim Analysis of Overall Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>4-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd (n=535)</td>
<td>59.4%</td>
</tr>
<tr>
<td>Rd18 (n=541)</td>
<td>55.7%</td>
</tr>
<tr>
<td>MPT (n=547)</td>
<td>51.4%</td>
</tr>
</tbody>
</table>

Hazard ratio: Rd vs. MPT: 0.78; P = 0.0186
Rd vs. Rd18: 0.90; P = 0.397
Rd18 vs. MPT: 0.88; P = 0.184
A Randomized Phase 3 Trial of Melphalan-Lenalidomide-Prednisone (MPR) or Cyclophosphamide-Prednisone-Lenalidomide (CPR) vs. Lenalidomide + Dexamethasone (Rd) in Elderly Newly Diagnosed Multiple Myeloma Patients

Antonio Palumbo, Valeria Magarotto, Sara Bringhen, Massimo Offidani, Giuseppe Pietrantuono, Anna Marina Liberati, Giulia Benevolo, Antonio Ledda, Milena Gilestro, Monica Galli, Francesca Patriarca, Mariella Genuardi, Nicola Giuliani, Renato Zambello, Adam Zdenek, Alessia La Fauzi, Paolo Corradini, Antonietta Pia Falcone, Caterina Musolino, Davide Rossi, Patrizia Caraffa, Pellegrino Musto, Federica Cavallo, Roman Hajek, and Mario Boccadoro

Study Design

- 660 patients have been randomized
- Symptomatic multiple myeloma patients not transplant-eligible

Reduction by age (>75 years): 1° Dexamethasone 20 mg/week; 2° Melphalan 0.13 mg/Kg; 3° Cyclophosphamide: 50 mg eod on days 1-21

* 59 CPR patients were treated with lower dose of Lenalidomide (10 mg) and Cyclophosphamide (50 mg eod) [Amaducci L, 2010, Asu]
Patient Outcomes

Median follow-up 26 months

- PFS
- OS

Rd vs MPR p=0.26 HR 0.858 (CI 0.655-1.123)
Rd vs CPR p=0.833 HR 0.985 (CI 0.853-1.137)
Rd vs MPR p=0.62 HR 1.115 (CI 0.726-1.711)
Rd vs CPR p=0.72 HR 0.956 (CI 0.748-1.223)

• Rd is the winner again!

2013 ASH Abstract 405

PFS2 in Elderly Patients with Newly Diagnosed Multiple Myeloma (NDMM): Results from the MM-015 Study

Meletios A. Dimopoulos, Maria Teresa Petrucci, Robin Foà, John V. Catalano, Martin Kropff, Zhinuan Yu, Lara Grote, Christian J. Jacques, and Antonio Palumbo
Emerging Concept: PFS2

<table>
<thead>
<tr>
<th></th>
<th>MPR-R (n = 152)</th>
<th>MPR (n = 153)</th>
<th>MP (n = 154)</th>
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</thead>
<tbody>
<tr>
<td>Any 2nd Line</td>
<td>81 (53)</td>
<td>18 (77)</td>
<td>126 (82)</td>
</tr>
<tr>
<td>LEN</td>
<td>24 (30)</td>
<td>70 (59)</td>
<td>91 (72)</td>
</tr>
<tr>
<td>BORT</td>
<td>40 (49)</td>
<td>32 (27)</td>
<td>27 (21)</td>
</tr>
<tr>
<td>THAL</td>
<td>11 (14)</td>
<td>9 (8)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>31 (38)</td>
<td>23 (20)</td>
<td>22 (18)</td>
</tr>
<tr>
<td>PFS2</td>
<td>39.7 mos.</td>
<td>28.5 mos.</td>
<td></td>
</tr>
</tbody>
</table>

- Len maintenance does not induce growth of more drug-resistant myeloma clones

2013 ASH Abstract 685

A Phase II Study With Carfilzomib, Cyclophosphamide and Dexamethasone (CCd) For Newly Diagnosed Multiple Myeloma

Sara Bringhen, Chiara Cerrato, Maria Teresa Petrucci, Mariella Genuardi, Fabiana Gentilini, Concetta Conticello, Stefania Oliva, Lucia Pantani, Massimo Offidani, Carmela Palladino, Giulia Benevolo, Vittorio Montefusco, Monica Astolfi, Oreste Villani, Agostina Siniscalchi, Alberto Rocci, Lorenzo De Paoli, Mario Boccadoro, Pieter Sonneveld, and Antonio Palumbo
Study Design

- Phase II
- Multicenter (10 centres)

1. Median follow-up, months (range): 18.1 (2.8-28.3)
2. CR/nCR orally
3. 36         36 36         36 36         36

Response Timecourse

- Like CyBorD, “CyCarD” is a good induction regimen for transplant-ineligible patients
Outline

- Disease biology
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- Aspects of supportive care in myeloma

2013 ASH Abstract 688

*Dose Escalation Phase 2 Trial of Carfilzomib Combined with Thalidomide and Low-Dose Dexamethasone in Newly Diagnosed, Transplant Eligible Patients with Multiple Myeloma: A Trial of the European Myeloma Network*

Pieter Sonneveld, Emilie Asselberg-Hacker, Sonja Zweegman, Bronno van der Holt, Marie Jose Kersten, Edo Vellenga, Marinus van Marwijk Kooy, Okke de Weerdt, Sarah Lonergan, Antonio Palumbo, and Henk Lokhorst
Study Design

induction
4 cycles
Carfilzomib 20/27mg/m² days 1, 2, 8, 9, 15, 16 of a 28 day cycle.
Thalidomide 200 mg days 1-28 of a 28 day cycle
Dexamethasone 40 mg days 1, 8, 15, 21 of a 28 day cycle

Intensification
1 cycle
HDM 200 mg/m² ASCT

Consolidation
4 cycles
Carfilzomib 27 mg/m² days 1, 2, 8, 9, 15, 16 of a 28 day cycle.
Thalidomide 50 mg days 1-28 of a 28 day cycle
Dexamethasone 40 mg days 1, 8, 15, 21 of a 28 day cycle

Response Data

<table>
<thead>
<tr>
<th>Carfilzomib dose</th>
<th>27 mg/m²</th>
<th>36 mg/m²</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>After Induction</td>
<td>sCR/CR</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>29</td>
<td>58</td>
<td>16</td>
</tr>
<tr>
<td>≥PR</td>
<td>46</td>
<td>92</td>
<td>19</td>
</tr>
<tr>
<td>After HDM</td>
<td>sCR/CR</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>34</td>
<td>68</td>
<td>16</td>
</tr>
<tr>
<td>≥PR</td>
<td>47</td>
<td>94</td>
<td>20</td>
</tr>
<tr>
<td>After Consol</td>
<td>sCR/CR</td>
<td>28</td>
<td>56</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>43</td>
<td>86</td>
<td>16</td>
</tr>
<tr>
<td>≥PR</td>
<td>47</td>
<td>94</td>
<td>20</td>
</tr>
</tbody>
</table>
Long-term Outcomes

- Carfilzomib-based regimen with thal is an excellent option prior to transplant
- Consolidation therapy deepens response further

2013 ASH Abstract 535

Twice-weekly Oral MLN9708 (Ixazomib Citrate), an Investigational Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma: Final Phase 1 Results and Phase 2 Data

Paul G. Richardson, Craig C Hofmeister, Cara A Rosenbaum, Myo Htut, David H. Vesole, Jesus Berdeja, Michaela Liedtke, Ajai Chari, Stephen D Smith, Daniel Lebovic, Deborah Berg, Eileen Liao, Neeraj Gupta, Alessandra Di Bacco, Jose Estevam, Ai-Min Hui and Rachid Baz
**Study Design**

Induction: up to 16 x 21-day treatment cycles

- Days 1, 4, 8, 11
- 21-day cycles

Induction:
- MLN9708
- Lenalidomide 25 mg, days 1–14

Maintenance:
- MLN9708
- *Dex* 20/10 mg cycles 1–8 / 9–16

All patients required thromboembolism prophylaxis with aspirin 81–325 mg QD or LMWH while receiving len-dex

**Response Data**

- **ORR 93%**
  - sCR/CR 11%
  - ≥VGPR 61%

- **ORR 95%**
  - sCR/CR 23%
  - ≥VGPR 71%

- **ORR 95%**
  - sCR/CR 29%
  - ≥VGPR 75%

Rates of rash, PN, and dose reductions appear lower in the parallel study using weekly MLN9708, with similar response rates and better convenience.

- Supports the use of weekly dosing in ongoing phase 3 trials
2013 ASH Abstract 538

Phase II Clinical and Correlative Study of Carfilzomib, Lenalidomide, and Dexamethasone Followed by Lenalidomide Extended Dosing (CRD-R) Induces High Rates of MRD Negativity in Newly Diagnosed Multiple Myeloma Patients

Neha Korde, Adriana Zingone, Mary L Kwok, Elisabet E. Manasanch, Manisha Bhutani, Nishant Tageja, Dickran Kazandjian, Sham Mailankody, Rene Costello, Yong Zhang, Debra Burton, George Carter, Peter Wu, Marcia Mulquin, Diamond Zuchlinski, Irina Marie, Katherine R Calvo, Raul C. Braylan, Mark Roschewski, Constance Yuan, Maryalice Stetler-Stevenson, Diane C Arthur, Liza Lindenberg, Karen Kurdziel, Pete Choyke, Seth M. Steinberg, and Ola Landgren

Study Design

8 cycles CRd Combination Therapy
Carfilzomib 20/36 mg/m², day 1, 2, 8, 9, 15, 16
Lenalidomide 25 mg/day, day 1-21
Dexamethasone 20/10 mg, day 1, 2, 8, 9, 15, 16, 22, 23

24 cycles Rev Extended Dosing
Lenalidomide 10 mg/day, day 1-21
Response Data

<table>
<thead>
<tr>
<th>Response</th>
<th>2 cycles n/N (%)</th>
<th>8 cycles n/N (%)</th>
<th>Best response n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥PR)</td>
<td>42/43 (98)</td>
<td>32/33 (97)</td>
<td>42/43 (98)</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>22/43 (51)</td>
<td>30/33 (91)</td>
<td>38/43 (88)</td>
</tr>
<tr>
<td>nCR/CR/sCR</td>
<td>7/43 (16)</td>
<td>24/33 (73)</td>
<td>29/43 (67)</td>
</tr>
<tr>
<td>CR/sCR</td>
<td>3/43 (7)</td>
<td>14/33 (42)</td>
<td>22/43 (51)</td>
</tr>
<tr>
<td>VGPR</td>
<td>15/43 (35)</td>
<td>6/33 (18)</td>
<td>9/43 (21)</td>
</tr>
<tr>
<td>PR</td>
<td>20/43 (47)</td>
<td>2/33 (6)</td>
<td>4/43 (9)</td>
</tr>
<tr>
<td>SD</td>
<td>1/43 (2)</td>
<td>1/33 (3)</td>
<td>1/43 (2)</td>
</tr>
</tbody>
</table>

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- Disease biology
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- Induction before transplant
- **Options for therapy after transplant**
- Relapsed and/or refractory myeloma
- Aspects of supportive care in myeloma
A Phase III Study of ASCT vs. Cyclophosphamide-Lenalidomide-Dexamethasone and Lenalidomide-Prednisone Maintenance vs. Lenalidomide Alone in Newly Diagnosed Myeloma Patients

Antonio Palumbo, Francesca Gay, Andrew Spencer, Francesco Di Raimondo, Adam Zdenek, Alessandra Larocca, Antonietta Pia Falcone, Lucio Catalano, Paola Finsinger, Scudla Vlastimil, Simona Aschero, Massimo Offidani, Anna Maria Liberati, Angelo Michele Carella, Maisnar Vladimir, Francesca Donato, Tommaso Caravita, Paolo Corradini, Roberto Ria, Stefano Pulini, Raffaella Stocchi, Concetta Conticello, Maria Teresa Petrucci, Roman Hajek, and Mario Boccadoro

Study Design

- 389 patients (younger than 65 years) randomized from 59 centers
- Patients: Symptomatic disease, organ damage, measurable disease

*Randomisation (2x2 design)*

- Rd
  - four 28-day courses

- CRD
  - six 28-day courses

- MEL 200
  - Two courses

- CRD vs MEL 200: RP maintenance vs R maintenance; Rd (R: 25 mg/d, days 1-21; d: 40 mg, days 1, 8, 15, 22); CRD (C: 300 mg/m², days 1, 8, 15; d: 40 mg/d, days 1, 8, 15, 22; R: 25 mg, d 1-21); MEL 200 (M: 200 mg/m², days 1-2); RP maint (R: 10 mg/day, days 1-21; P: 50 mg every other day); R maint (R: 10 mg/day, days 1-21); # One course MEL 200 if patients achieves VGPR after cycle 3.
- R: lenalidomide; MEL 200: melphalan 200 mg/m² and autologous stem cell transplant; CRD: cyclophosphamide-lenalidomide-dexamethasone; RP: lenalidomide-prednisone; NDMM: newly diagnosed multiple myeloma.
Primary Analysis

Progression-free survival

- Median PFS
  - CRD: 27 months
  - MEL200: Not reached

- HR 1.46, 95% CI 1.09-1.92, P = .012

Overall survival

- 3-year OS
  - CRD: 81%
  - MEL200: 84%

- HR 1.04, 95% CI 0.63-1.70, P = .891

- CRD, cyclophosphamide-lenalidomide-dexamethasone; MEL200, melphalan 200 mg/m²; PFS, progression-free survival; OS, overall survival

- Transplant still better than novel agents

Landmark Analysis

Progression-free survival

- 2-year PFS
  - RP maint.: 69%
  - R maint.: 58%

- HR 0.63, 95% CI 0.40-0.99, P = .045

Overall survival

- 2-year OS
  - RP maint.: 92%
  - R maint.: 90%

- HR 0.93, 95% CI 0.37-2.35, P = .879

- PFS, progression-free survival; OS, overall survival; R, lenalidomide; P, prednisone

- Longer follow-up needed to see if RP better than R
2013 ASH Abstract 406

Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma: Follow-up Analysis of the IFM 2005-02 Trial

Michel Attal, Valérie Lauwers-Cances, Gérald Marit, Denis Caillot, Thierry Facon, Cyrille Hulin, Philippe Moreau, Claire Mathiot, Murielle Roussel, Catherine Payen, Pascale Olivier, and Hervé Avet-Loiseau

Study Design

- Patients < 65 years, with non-progressive disease, ≤ 6 months after ASCT in first line
- Randomization: stratified according to Beta-2m, del13, VGPR
- Consolidation:
  - Arm A: Lenalidomide alone 25 mg/day p.o. days 1-21 of every 28 days for 2 months
  - 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...
Analysis After Relapse

- Primary analysis: len had better PFS, same OS
- At face value, current data suggest len may cause myeloma chemoresistance

Treatment After Relapse

- LESSON: Choice of 2nd line regimens make a big difference in outcomes
### 2013 ASH Abstract 407

**Lenalidomide Maintenance Therapy in Multiple Myeloma: A Meta-Analysis of Randomized Trials**


---

### Analysis After Relapse

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Hazard ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>IFM 05-02</td>
<td>1.060 0.820</td>
<td>1.375 0.664</td>
</tr>
<tr>
<td>CALGB 100104</td>
<td>0.610 0.424</td>
<td>0.878 0.008</td>
</tr>
<tr>
<td>MM-015</td>
<td>0.790 0.528</td>
<td>1.181 0.251</td>
</tr>
<tr>
<td>RV-MM-Pi209</td>
<td>0.620 0.417</td>
<td>0.923 0.018</td>
</tr>
<tr>
<td><strong>SUMMARY ESTIMATE</strong></td>
<td><strong>0.767 0.574</strong></td>
<td><strong>1.023 0.071</strong></td>
</tr>
</tbody>
</table>

Outcome: HR for death; Len vs. no maintenance
(<1 implies better outcome with Len)
Cochran Q=8.11 (p=0.044), I²=63%
2013 ASH Abstract 404

Bortezomib Induction and Maintenance Treatment Improves Survival in Patients with Newly Diagnosed Multiple Myeloma: Extended Follow-up of the HOVON-65/GMMG-HD4 Trial


Study Design

NDMM, TE, stg 18–65 y

Randomization

3 x VAD
CAD + GCSF
MEL 200 + PBSCT
In GMMG 2nd
MEL 200 + PBSCT
Thalidomide
maintenance
50 mg/day for
2 years

3 x PAD
CAD + GCSF
MEL 200 + PBSCT
In GMMG 2nd
MEL 200 + PBSCT
Bortezomib
Maintenance
1.3 mg/m²/2 weeks for 2
years

Allogeneic
Tx

Maintenance
1.3 mg/m²
Thalidomide
100 mg
Starting with Maintenance

- Bortezomib maintenance may be superior to thalidomide maintenance

Outline

- Disease biology
- Asymptomatic myeloma
- Non-transplant therapies
- Induction before transplant
- Options for therapy after transplant
- **Relapsed and/or refractory myeloma**
- Aspects of supportive care in myeloma
2013 ASH Abstract 283

Novel AKT Inhibitor Afuresertib in Combination with Bortezomib and Dexamethasone Demonstrates Favorable Safety Profile and Significant Clinical Activity in Patients with Relapsed/Refractory Multiple Myeloma

Peter M Voorhees, Andrew Spencer, Heather J. Sutherland, Michael E O'Dwyer, Shang-Yi Huang, Keith Stewart, Ajai Chari, Michael Rosenzweg, Ajay K. Nooka, Cara A Rosenbaum, Craig C Hofmeister, Deborah A Smith, Joyce M Antal, Ademi Santiago-Walker, Jennifer Gauvin, Joanna B Opalinska and Suzanne Trudel

Analysis After Relapse

<table>
<thead>
<tr>
<th>Dose Cohort</th>
<th>N</th>
<th>Best Unconfirmed Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NE</td>
</tr>
<tr>
<td>Part 1</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Part 2</td>
<td>37</td>
<td>7</td>
</tr>
<tr>
<td>PK/PD</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>
Activity by Prior Bortezomib Exposure

<table>
<thead>
<tr>
<th>Bortezomib Exposure</th>
<th>Naïve (n=13)</th>
<th>Relapsed (n=44)</th>
<th>Refractory (n=23)</th>
<th>Unk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>2/3 (67%)</td>
<td>10/18 (56%)</td>
<td>5/13 (38%)</td>
<td>-</td>
</tr>
<tr>
<td>Part 2</td>
<td>6/10 (60%)</td>
<td>17/26 (65%)</td>
<td>1/1 (100%)</td>
<td>-</td>
</tr>
<tr>
<td>PK/PD</td>
<td>NA</td>
<td>NA</td>
<td>4/9 (44%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Total</td>
<td>62%</td>
<td>61%</td>
<td>43%</td>
<td>1/10 (10%)</td>
</tr>
</tbody>
</table>

• Akt inhibition may be attractive in myeloma!

2013 ASH Abstract 284

SAR650984, a CD38 Monoclonal Antibody in Patients with Selected CD38+ Hematological Malignancies- Data from a Dose-Escalation Phase I Study

Thomas G Martin III, Stephen A. Strickland, Martha Glenn, Wei Zheng, Nikki Daskalakis, and Joseph R. Mikhael
Response Data

- Binds different epitope than daratumumab

2013 ASH Abstract 1986

Preliminary Safety and Efficacy Data of Daratumumab in Combination with Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma

Torben Plesner, Tobias Arkenau, Henk Lokhorst, Peter Gimsing, Jakub Krejcik, Charlotte Lemech, Monique C. Minnema, Ulrik Lassen, Andrew Cakana, Nikolai Constantin Brun, Linda Basse, Antonio Palumbo, and Paul G. Richardson
Response Data

Please note that patients in the 8 and 16 mg/kg cohorts have had less exposure and shorter follow-up.

<table>
<thead>
<tr>
<th>Change in response paraprotein (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 mg/kg</td>
</tr>
<tr>
<td>8 mg/kg</td>
</tr>
<tr>
<td>4 mg/kg</td>
</tr>
<tr>
<td>2 mg/kg</td>
</tr>
</tbody>
</table>

Patient number

<table>
<thead>
<tr>
<th>Time to response $&gt; PR$, weeks</th>
<th>2 mg/kg Pt no 1/2/3</th>
<th>4 mg/kg Pt no 4/3/6</th>
<th>8 mg/kg Pt no 7/8/9</th>
<th>16 mg/kg Pt no 10/11</th>
<th>Total (n=8) Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.1/2.1/4.1</td>
<td>4.3/2.0/2.1</td>
<td>4.0/ N/A /4.3</td>
<td>N/A</td>
<td>4.1 (2.0-4.3)</td>
</tr>
</tbody>
</table>

Adverse Events

<table>
<thead>
<tr>
<th>% of patients</th>
<th>2 mg/kg (N=3)</th>
<th>4 mg/kg (N=3)</th>
<th>8 mg/kg (N=4)</th>
<th>16 mg/kg (N=2)</th>
<th>Total (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>100</td>
<td>33</td>
<td>25</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>33</td>
<td>100</td>
<td>25</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>Constipation</td>
<td>100</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>67</td>
<td>25</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Fatigue</td>
<td>100</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Bone pain</td>
<td>33</td>
<td>33</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>33</td>
<td>67</td>
<td>0</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Anaemia</td>
<td>33</td>
<td>67</td>
<td>0</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>67</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>33</td>
<td>33</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
</tbody>
</table>
2013 ASH Abstract 690

Phase I/II Dose Expansion of a Multi-Center Trial of Carfilzomib and Pomalidomide with Dexamethasone (Car-Pom-d) in Patients with Relapsed/Refractory Multiple Myeloma


Response Data/Long-term Outcomes

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>N=79</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGPR</td>
<td>21 (27%)</td>
</tr>
<tr>
<td>PR</td>
<td>34 (43%)</td>
</tr>
<tr>
<td>MR</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

ORR = 70%

CBR = 83%
2013 ASH Abstract 285

Prolonged Survival and Improved Response Rates with ARRY-520 in Relapsed/Refractory Multiple Myeloma (RRMM) Patients with Low α-1 Acid Glycoprotein (AAG) Levels: Results From a Phase 2 Study


Mechanism of Action
Study Design

**Cohort 1: Filanesib Single-agent**
Filanesib 1.5 mg/m² q 2 weeks

```
1 2 1 2
G-CSF G-CSF
```

**Cohort 2: Filanesib + Dexamethasone Combination**
Filanesib 1.5 mg/m² q 2 weeks

```
1 2 1 2
G-CSF G-CSF
```
Dexamethasone 40 mg PO weekly

Response Data

<table>
<thead>
<tr>
<th></th>
<th>Filanesib Single-agent</th>
<th>Filanesib + Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>32</td>
<td>55</td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>5 (16%)</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>CBR (≥ MR)</td>
<td>7 (22%)</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Duration of Response (months)</td>
<td>8.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Time to Next Treatment (Months)</td>
<td>3.7</td>
<td>3.4</td>
</tr>
<tr>
<td>OS (months)</td>
<td>19.0</td>
<td>10.5</td>
</tr>
</tbody>
</table>
AAG and Outcomes

### Outline

- Disease biology
- Asymptomatic myeloma
- Non-transplant therapies
- Induction before transplant
- Options for therapy after transplant
- Relapsed and/or refractory myeloma
- Aspects of supportive care in myeloma
Thromboprophylaxis In Myeloma: A National Survey

Maeve P Crowley, Barry M Kevane, Joseph A Eustace, Susan O'Shea, and Oonagh M Gilligan

Study Findings

• Survey of hematologists treating myeloma patients in Ireland
• Only 48% used published guidelines to direct choice of prophylactic therapy
Malnutrition is Perceived Differently by Patients, Relatives and Physicians in Routine Hematology Practice. Subgroup Analysis of the French Cross-sectional Nutricancer 2012 Survey

Emmanuel Gyan, Bruno Raynard, Jean Lacau Saint Guily, François Goldwasser and Xavier Hebuterne

Study Findings

• Cross-sectional survey in 30 French hospitals of 213 pts with heme malignancies (15% myeloma)
• Prevalence of malnutrition according to the standard definition was 46%
  – Physicians identified malnutrition in 35%
    • Sensitivity 55, specificity 81%
  – Patients identified malnutrition in 18%
  – Relatives identified malnutrition in 14%
2013 ASH Abstract 1693

A Randomized Study of Music Therapy in Patients Undergoing Autologous Stem Cell Transplant: Decrease in Narcotic Medication use for Pain Control

Hien K. Duong, Debbie Bates, Lisa A. Rybicki, Matt Kalaycio, Steven Andresen, Ronald Sobecks, Lisa Gallagher, Robert M Dean, Brian T. Hill, Donna M Abounader, Melissa Yurch, Christina Ferraro, Shawnda Tench, Kelly Cherni, Gina Green, Joseph Kohuth, Vanessa Farrow, Heather Koniarczyk, Shannon Jarancik, Linda McLellan, Jane Dabney, Brad Pohlman, and Brian J. Bolwell

Study Findings

- 82 patients undergoing auto (40 with myeloma)
- Interactive music therapy with board-certified therapist
- Day +7: more nausea with music
- No difference in pain, but less narcotic use (24 vs. 73 mg morphine)
2013 ASH Abstract 2968

Frequency, Health Care Resource Use, and Costs Associated With Skeletal Related Events In US Patients With Multiple Myeloma

Emily Nash Smyth, Ilaria Conti, James Wooldridge, Lee Bowman, David Nelson, Jin Xie, and Daniel E Ball

Study Findings

• Population-based study of 1,112 pts with newly diagnosed myeloma
• 32% had inpatient episode related to an SRE
• Can occur at any time
  – At least as likely after diagnosis as before
Updates on Multiple Myeloma Therapy from ASH: Summary

Robert Z. Orlowski, Ph.D., M.D.
Director, Myeloma Section
Florence Maude Thomas Cancer Research Professor
Departments of Lymphoma/Myeloma & Experimental Therapeutics
Principal Investigator, MD Anderson SPORE in Multiple Myeloma
Chair, Southwest Oncology Group Myeloma Committee

Smoldering Myeloma

- New definitions coming for patients with ultra high risk disease; will be treated like myeloma
  - Presence of bony disease by PET, MRI
- Low risk smoldering myeloma will be treated be followed more like MGUS
- Remaining high risk and intermediate risk patients should enroll on well-designed clinical trials
  - ECOG E3A06 trial
Transplant-ineligible Myeloma

- Newer drugs being incorporated into up-front therapy, such as carfilzomib, ixazomib
- Greater acceptance of need for therapy continuation (maintenance) after induction to deepen response, prolong remission (Rd)
- High risk patients still don’t do as well, and should be treated differently vs. standard risk
  - High risk: SWOG S1211 (RVd ± Elotuzumab)
  - Standard risk: ECOG E1A11 (RVd vs. CRd)

Transplant Eligible Myeloma

- Newer drugs being incorporated into up-front therapy, such as carfilzomib, ixazomib
- Emerging role of consolidation post-transplant, and maintenance with multi-drug regimens, especially for high risk patients
- Importance of achieving and maintaining CR with immunofixation- MRD status, again especially for high risk patients
Relapsed and/or Refractory Myeloma

- Monoclonal antibodies with single-agent activity (daratumumab, SAR650984) or in combinations (these and elotuzumab) are attractive approaches
- Novel agents with new mechanisms of action (filanesib, afuresertib) will be entering registration studies
- Better molecular understanding of myeloma will allow us to personalize therapy

Importance of Clinical Trial Participation

- Access emerging novel agents not yet available outside of trials
- Advance knowledge about myeloma biology and myeloma therapy
- Speed the approval of new drugs and improve outcomes for all patients
- Bring us closer to a cure
MDACC Myeloma Center

• Referral Line: 1-855-MYELOMA (toll-free)
• Drs. Elisabet Manasanch, Robert Orlowski (rorlowsk@mdanderson.org), Jatin Shah, Sheeba Thomas, Michael Wang, Donna Weber
  – E-mail: myelomatrial@mdanderson.org
  – Twitter: @Myeloma_Doc

Question and Answer Session
Dr. Orlowski’s slides are available for download at www.LLS.org/programs
MYELOMA AND CAREGIVER ONLINE CHATS
• Every Tuesday evening from 8:00 PM – 10:00 PM ET
• Visit www.LLS.org/chat to register or for more information

The Leukemia & Lymphoma Society’s (LLS) Co-Pay Assistance Program offers financial assistance to qualified myeloma patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.
• WEBSITE: www.LLS.org/copay
• TOLL-FREE PHONE: (877) LLS-COPAY

For more information about myeloma and other LLS programs, please contact an LLS Information Specialist.
• TOLL-FREE PHONE: (800) 955-4572
• EMAIL: infocenter@LLS.org