Treatment Strategies for Transplant-ineligible NDMM Patients

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Multiple Myeloma affects primarily elderly patients

SEER: New MM Cases by Age Group

Myeloma is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis

69

Period estimates of 10-year survival of patients with MM by major age groups in defined calendar periods from 1984-1986 to 2002-2004

Brenner et al; Blood 2008; 111:2521-26
Dexamethasone-based Regimens vs. MP for Elderly NDMM Patients (IFM 95-01)

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Refresher on MPT and VMP data
A journey back in time...

MPT: melphalan, prednisone, thalidomide  VMP: bortezomib, melphalan, prednisone
MPT becomes a standard of care

Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial


Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials

Peter M. Fayers, Antonio Palumbo, Cyrille Hulin, Anders Waage, Pierre Wijermans, Meral Beksaç, Sara Bringhen, Jean-Yves Mary, Peter Gimsing, Fabian Termorshuizen, Rauf Haznedar, Tommaso Caravita, Philippe Moreau, Ingemar Turessson, Pellegrino Musto, Lotfi Benboubker, Martijn Schaafisma, Pieter Sonneveld, Thierry Facon and on behalf of the Nordic Myeloma Study Group, Italian Multiple Myeloma Network, Turkish Myeloma Study Group, Hemato-Oncologie voor Volwassenen Nederland, Intergroupe Francophone du Myélome, and European Myeloma Network

VMP becomes a standard of care

Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma

Jesús F. San Miguel, M.D., Ph.D., Rudolf Schlag, M.D., Nuriet K. Khuageva, M.D., Ph.D., Meletios A. Dimopoulos, M.D., Ofer Shpilberg, M.D., Ph.D., Martin Kropff, M.D., Ivan Spicka, M.D., Ph.D., Maria T. Petrucci, M.D., Antonio Palumbo, M.D., Olga S. Samoilova, M.D., Ph.D., Anna Dmoszynska, M.D., Ph.D., Kudrat M. Abdulkadyrov, M.D., Ph.D., Rik Schots, M.D., Ph.D., Bin Jiang, M.D., Maria-Victoria Mateos, M.D., Ph.D., Kenneth C. Anderson, M.D., Dixie L. Esseltine, M.D., Kevin Liu, Ph.D., Andrew Cakana, M.D., Helgi van de Velde, M.D., Ph.D., and Paul G. Richardson, M.D., for the VISTA Trial Investigators*

Both VMP and MPT are recognised standards of care in TNE NDMM patients

2014: IMWG guidelines

“Recommended treatments for patients not eligible for high-dose therapy, or in case the transplant procedure is not available, include MPT, MPV and CTD"

2014: EMN guidelines

“Bortezomib-melphalan-prednisone or melphalan-prednisone-thalidomide are the standards of care for transplant-ineligible patients"

2014: NCCN guidelines

“MPT and VMP are 2 of the five preferred primary regimens for non-transplant candidates with multiple myeloma”

Back to present day

The benefits of continuous therapy in elderly patients
FIRST Trial: Study Design (Ph3 Pivotal Trial)

- **Primary endpoint:** PFS (Rd vs. MPT)
- **Key secondary endpoints:** OS, QoL, TTF, Time to 2nd AMT, DOR, Safety

**RANDOMIZATION (N = 1,623)**

- **Arm A**
  - Continuous Rd
  - LEN + Lo-DEX continuously
    - LENALIDOMIDE 25 mg D1-21/28
    - LoDEX 40 mg D1,8,15 & 22/28
  - (n = 535)

- **Arm B**
  - Rd18
  - LEN + Lo-DEX 18 cycles (72 wks)
    - LENALIDOMIDE 25 mg D1-21/28
    - LoDEX 40 mg D1,8,15 & 22/28
  - (n = 541)

- **Arm C**
  - MPT
  - MEL + PRED + THAL 12 cycles\(^1\) (72 wks)
    - MELPHALAN 0.25 mg/kg D1-4/42
    - PREDNISONE 2 mg/kg D1-4/42
    - THALIDOMIDE 200 mg D1-42/42
  - (n = 547)

**Screening**

**Active Tx + PFS follow-up phase**

- PD, OS and subsequent anti-MM Tx

**Long-term follow-up**

- PD or unacceptable toxicity

- AMT, anti-myeloma treatment; D, days; DOR, duration of response; LoDEX, low-dose dexamethasone; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pts, patients; QoL, quality of life; TTF, time to treatment failure, TX, treatment; wks, weeks.


FIRST Trial: 1,623 Patients Worldwide

246 centers in 18 countries, in partnership with the IFM

North America
Canada  251
United States  60

Europe
Austria  41
Belgium  52
France  459
Germany  97
Greece  86
Italy  148
Portugal  27
Spain  87
Sweden  19
Switzerland  26
United Kingdom  72

Asia
China  47
S. Korea  56
Taiwan  11

Asia Pacific
Australia  72
New Zealand  12

IFM, Intergroupe Francophone du Myelome
FIRST Trial: Final PFS and Interim OS

**Final PFS**

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<th>Median PFS (mos)</th>
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</tr>
<tr>
<td>Rd18 (n = 541)</td>
<td>20.7</td>
</tr>
<tr>
<td>MPT (n = 547)</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Hazard ratio:
- Rd vs. MPT: 0.72; \( P = 0.00006 \)
- Rd vs. Rd18: 0.70; \( P = 0.00001 \)
- Rd18 vs. MPT: 1.03; \( P = 0.70349 \)

**Interim OS**

<table>
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<tr>
<th>Treatment</th>
<th>4-year OS (%)</th>
</tr>
</thead>
<tbody>
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<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; \( P = 0.0168 \)
- Rd vs. Rd18: 0.90; \( P = 0.307 \)
- Rd18 vs. MPT: 0.88; \( P = 0.184 \)

# FIRST Trial: Safety – Selected Grade 3–4 TEAEs

<table>
<thead>
<tr>
<th></th>
<th>Continuous Rd (n=532)</th>
<th>Rd 18 (n=540)</th>
<th>MPT (n=541)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematological (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>18.2</td>
<td>15.7</td>
<td>18.9</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27.8</td>
<td>26.5</td>
<td>44.9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8.3</td>
<td>8.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.1</td>
<td>3.0</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Non-hematological (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>28.9</td>
<td>21.9</td>
<td>17.2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8.1</td>
<td>8.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.9</td>
<td>3.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.3</td>
<td>1.9</td>
<td>5.4</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>1.1</td>
<td>0.4</td>
<td>9.4</td>
</tr>
<tr>
<td>DVT and/or PE</td>
<td>7.9</td>
<td>5.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Cataract</td>
<td>5.8</td>
<td>2.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Severity of AEs graded according to NCI CTCAE v3.0.
DVT, deep-vein thrombosis; PE, pulmonary embolism; TEAEs, treatment-emerging adverse events.

FIRST Trial - Age Analysis: PFS

**Age ≤ 75 yrs**

<table>
<thead>
<tr>
<th></th>
<th>Median (mos)</th>
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<tr>
<td>Rd</td>
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**Age > 75 yrs**

<table>
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<tr>
<td>Rd</td>
<td>21.2</td>
</tr>
<tr>
<td>Rd18</td>
<td>19.4</td>
</tr>
<tr>
<td>MPT</td>
<td>19.2</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI)
- Rd vs. MPT: $0.68 (0.56–0.83)$
- Rd vs. Rd18: $0.68 (0.55–0.83)$
- Rd18 vs. MPT: $1.01 (0.84–1.21)$

- 46% (Rd)
- 25% (Rd18)
- 23% (MPT)

- 35% (Rd)
- 19% (Rd18)
- 22% (MPT)

**Abbreviations**
- mos, months; MPT, melphalan-prednisone-thalidomide; PFS, progression-free survival; pts, patients; Rd, lenalidomide and low-dose dexamethasone; Rd18, Rd for 18 cycles; yrs, years.

**FIRST Trial - Age Analysis: OS Interim Analysis**

#### Age ≤ 75 yrs

<table>
<thead>
<tr>
<th></th>
<th>3-yr OS</th>
</tr>
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<tbody>
<tr>
<td>Rd</td>
<td>74%</td>
</tr>
<tr>
<td>Rd18</td>
<td>70%</td>
</tr>
<tr>
<td>MPT</td>
<td>67%</td>
</tr>
</tbody>
</table>

**Hazard ratio (95% CI)**
- Rd vs. MPT: 0.77 (0.59–1.01)
- Rd vs. Rd18: 0.88 (0.67–1.16)
- Rd18 vs. MPT: 0.88 (0.68–1.14)

#### Age > 75 yrs

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<thead>
<tr>
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<th>3-yr OS</th>
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<tbody>
<tr>
<td>Rd</td>
<td>63%</td>
</tr>
<tr>
<td>Rd18</td>
<td>58%</td>
</tr>
<tr>
<td>MPT</td>
<td>54%</td>
</tr>
</tbody>
</table>

**Hazard ratio (95% CI)**
- Rd vs. MPT: 0.80 (0.59–1.09)
- Rd vs. Rd18: 0.94 (0.69–1.29)
- Rd18 vs. MPT: 0.85 (0.63–1.15)

**Graphs**
- Pts (% vs. OS (mos))
- Hazard ratio (95% CI)

**Legend**
- Rd: lenalidomide and low-dose dexamethasone
- Rd18: Rd for 18 cycles
- MPT: melphalan-prednisone-thalidomide

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mos, months; MPT, melphalan-prednisone-thalidomide; OS, overall survival; pts, patients; Rd, lenalidomide and low-dose dexamethasone; Rd18, Rd for 18 cycles; yrs, years.

Nominal $P$ values are presented for multiplicity assessments which need to be taken into consideration before making clinical interpretations.

HR, hazard ratio; mos, months; MPT, melphalan-prednisone-thalidomide; PFS, progression-free survival; Rd, lenalidomide plus low-dose dexamethasone; Rd18, Rd for 18 cycles; RI, renal impairment; IRAC, Independent Response Adjudication Committee

First Trial: EORTC QLQ-MY20 Results

- Rd resulted in a significant reduction in patient-reported Side Effects of Tx vs. MPT at most time points

EORTC, European Organisation for Research and Treatment of Cancer; Mo, month; MPT, melphalan, prednisone, thalidomide; Rd, lenalidomide plus low-dose dexamethasone; Tx, treatment.

PFS: FIRST and MM-015 Trials

**FIRST Trial: PFS**
(Median follow-up 37 mos)

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**MM-015: PFS**
(Median follow-up 30 mos)

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<th>Treatment</th>
<th>Median PFS (mos)</th>
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<tr>
<td>MPR-R (n = 152)</td>
<td>31</td>
</tr>
<tr>
<td>MPR (n = 153)</td>
<td>14</td>
</tr>
<tr>
<td>MP (n = 154)</td>
<td>13</td>
</tr>
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**Hazard ratio**
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- Rd vs. Rd18: 0.70; \( P = 0.00001 \)
- Rd18 vs. MPT: 1.03; \( P = 0.70349 \)

- MPR-R vs. MPR: 0.49; \( P < 0.001 \)
- MPR-R vs. MP: 0.40; \( P < 0.001 \)

20 February 2015

REVLIMID® (Lenalidomide) Approved by the European Commission for the Treatment of Adult Patients with Previously Untreated Multiple Myeloma who are Not Eligible for Transplant

Oral REVLIMID is approved for treatment until disease progression

BOUDRY, Switzerland--(BUSINESS WIRE)-- Celgene International Sàrl, a wholly owned subsidiary of Celgene Corporation (NASDAQ: CELG), today announced that the European Commission (EC) has approved REVLIMID® (lenalidomide) for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

The REVLIMID Marketing Authorisation has been updated to include this new indication in multiple myeloma, building upon the already approved indication of REVLIMID in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

• (continuous) Lenalidomide in combination with
  – Low-dose dexamethasone (Rd) based on FIRST trial
  – Melphalan and prednisone (MPR-R) based on MM-015 trial

• FDA approval in same week (18 February)
Why is IFM 2007-01/MM020/FIRST an important trial? (among others)

Design: Continuous (CT) vs. Fixed Duration Therapy (FDT)
- the FIRST trial compared the same regimen (Rd) given either as CT or FDT
Alkylator-free vs. Alkylator-containing
- without being designed to assess the role of alkylating agents

Result: Continuous Rd > MPT

Conclusion: A dual paradigm changing study
- in a disease where alkylators and FDT have been the standard of care for decades
A practice changing study
- establishing continuous Rd as a new standard of care
## Maintenance treatment with bortezomib in elderly patients with MM

<table>
<thead>
<tr>
<th>Group</th>
<th>Median follow-up (months)</th>
<th>Median PFS (months)</th>
<th>5-year OS</th>
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<tr>
<td>VMP-VT/VP(^1)</td>
<td>46</td>
<td>35</td>
<td>58%</td>
</tr>
<tr>
<td>VMPT-VT(^2)</td>
<td>54</td>
<td>35.3*</td>
<td>61%*</td>
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*significant difference versus no maintenance

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\(^1\)Mateos et al. Blood 2012; 120: 2581-2588

\(^2\)Palumbo et al. JCO 2014, Epub 21 January
What is the next step forward?
Treatment of NDMM in Elderly Patients – Landscape and Perspectives

 alternating regimens\(^6\) \(?\)

MP \(<\) MPT \(<\) Rd

MPR-R \(<\) # MPT-T

VMP # Vd

VMP-Daratumumab\(^1\)

Rd-MLN 9708\(^2\)
Rd-Elotuzumab\(^3\)
Rd-Daratumumab\(^4\)

MP-Carfilzomib\(^5\)

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Challenges and perspectives with transplant-ineligible patients – Conclusion 1

• During the past 10 years significant progress has been made in the management of transplant-ineligible MM patients
  – Median PFS has increased from 10–15 to 25–30 months
  – Median OS has increased from 30 to approx. 60 months

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4-year OS
- Rd (n= 535) 59.4%
- Rd18 (n= 541) 55.7%
- MPT (n= 547) 51.4%

During the past 10 years significant progress has been made in the management of transplant-ineligible MM patients.
- Median PFS has increased from 10–15 to 25–30 months
- Median OS has increased from 30 to approx. 60 months
革命尚未成功
同志仍须努力
孙文