Future research and Perspective in Multiple Myeloma

IFM

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Disclosures

- Honorarium, Grants/research support, and Consulting fees:
  Amgen, Celgene, Janssen, Takeda, Novartis, Sanofi, Merck, Pierre Fabre, Mundipharma, Karyopharm, Roche, Abbvie, Bristol-Myers Squibb, Gilead, Incyte, Carsgen
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
Rd (FIRST/IFM): Impact of depth of response on duration of response

- Median DOR was prolonged with Rd continuous vs Rd18 or MPT

CR, complete response; DOR, duration of response; MPT, melphalan-prednisone-thalidomide; PR, partial response; Rd, lenalidomide and low-dose dexamethasone; Rd18, Rd for 18 cycles; VGPR, very good partial response.

Bahlis N et al. Presented at EHA 2015
PFS OF ALCYONE AND MAIA TRIALS IN NSCT

**ALCYONE Trial**

- Median follow-up: 27.8 mos

**MAIA Trial**

- Median follow-up: 28 mos

References:
2. Facon et al LBA 2 ASH 2018
ABSTRACT 305

Efficacy and Feasibility of Dose/Schedule- Adjusted Rd-R Vs Continuous Rd in Elderly and Intermediate-Fit Newly Diagnosed Multiple Myeloma (NDMM) Patients: RV-MM-PI-0752 Phase 3 Randomized Study

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on behalf of co-investigators

1GIMEMA/European Myeloma Network, Italy; 2University of Torino - Currently Takeda Pharmaceuticals Co.

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STUDY DESIGN

**Primary endpoint:**
- EFS
  - Hematologic grade 4 AEs
  - Non-hematologic grade 3/4 AEs, including SPMs
  - LEN therapy discontinuation
  - PD
  - Death due to any cause

**Secondary endpoints:**
- PFS
- OS
- Response rate
- Incidence of dose reduction and discontinuation

- N=199 intermediate-fit patients

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*a Dose and schedule adopted in the FIRST trial in patients > 75 years.
EVENT FREE SURVIVAL

Median follow-up 25 months

Definition of the event**:- hematologic grade 4 AEs
- non-hematologic grade 3-4 AEs including SPM
- discontinuation of lenalidomide therapy
- disease progression
- death for any cause

Median EFS

<table>
<thead>
<tr>
<th>Group</th>
<th>Median EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd-R</td>
<td>9.3 months</td>
</tr>
<tr>
<td>Rd</td>
<td>6.6 months</td>
</tr>
</tbody>
</table>

Rd-R vs Rd: HR 0.72; CI 0.52-0.99; p=0.044

* Related to study drugs
Larocca A, et al. ASH 2018 [abstract 1305]. FOR CELGENE INTERNAL USE ONLY. NOT FOR DISTRIBUTION.
Study design: Rd DaraSC Frail

Active Treatment + PFS Follow-up Phase

Randomization 1:2

- Arm A: R-DaraSC
  - LEN + Dara SC continuously:
    - LENALIDOMIDE 25mg D1-21/28
    - DARATUMUMAB SC X mg/kg SC Q1Wk for 8 weeks
    - X mg/kg SC Q2Wk for 16 weeks
    - X mg/kg SC Q4Wk thereafter

- Arm B: Rd
  - LEN + Lo-DEX continuously:
    - LENALIDOMIDE 25mg D1-21/28
    - Lo-DEXAMETHASONE 20mg D1,8,15 & 22/28

PD or Unacceptable Toxicity

PD, OS and Subsequent anti-MM Tx

Randomization will be stratified by International Staging System (I vs II vs III) and age (<80 vs ≥80)

In Arm A Low Dose Dex (20mg/week) during Cycle 1 and 2 then Methylprednisolone (with SC Dara)
P-value (trend) : $p < 0.0001$

N at risk (events)

<table>
<thead>
<tr>
<th>N at risk</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-6}$</td>
<td>86 (0)</td>
<td>86 (0)</td>
<td>86 (0)</td>
<td>86 (0)</td>
<td>86 (5)</td>
<td>77 (3)</td>
<td>61 (5)</td>
<td>36 (0)</td>
<td>10</td>
</tr>
<tr>
<td>$10^{-5}$</td>
<td>29 (0)</td>
<td>29 (0)</td>
<td>29 (0)</td>
<td>29 (0)</td>
<td>28 (5)</td>
<td>22 (3)</td>
<td>16 (4)</td>
<td>4 (1)</td>
<td>1</td>
</tr>
<tr>
<td>$10^{-4}$</td>
<td>23 (0)</td>
<td>23 (0)</td>
<td>23 (0)</td>
<td>23 (1)</td>
<td>22 (3)</td>
<td>19 (2)</td>
<td>14 (5)</td>
<td>3 (0)</td>
<td>2</td>
</tr>
<tr>
<td>$10^{-3}$</td>
<td>40 (0)</td>
<td>40 (0)</td>
<td>40 (0)</td>
<td>40 (6)</td>
<td>33 (9)</td>
<td>23 (6)</td>
<td>15 (4)</td>
<td>4 (1)</td>
<td>2</td>
</tr>
</tbody>
</table>

Patients without progression (%)

40 40 40 33 23 15 4

Avet Loiseau et al. Submitted
In POLLUX, high-risk patients treated with daratumumab achieve MRD negativity and remain progression free.

**P = 0.0009. ***P = 0.0001.

*Percentage of patients within a given risk group and treatment arm.

ClinicalTrials.gov Identifiers: NCT02136134
IFM 2020 – eNDMM – FIT
Change of paradigm - MRD-adapted treatment = Prolonged PFS

Population: eNDMM NON Frail
Phase 3: Randomisée, ouvert, NON inferiorité (maxi 6 mois de difference, 45 – 50m)
Hypothèse: Traitement adapté à la MRD améliore la PFS, le cout global et la qualité de vie des patients
Primary end point: PFS
Secondary end point: PFS2; OS; DOR; Safety; QOL; Pheco, $10^{-5}$ MRD negativity
Exploratory objectives: MRD circ; clonal evol; ...

MRD/6m - ≥VGPR

AntiCD38-Rd

AntiCD38-Vlite-Rd x8

Str. Age, HR
Non Infériorité

PD

Arret 2 ans

AntiCD38-R

MRD
IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)

Randomize

- RVDx3
- Stratification ISS, FISH
- Systematic GEP, CGH
  → risk-adapted strategy

- RVDx3
- CY (3g/m2) MOBILIZATION
  Goal: 5x10^6 cells/kg
- CY (3g/m2)
  MOBILIZATION
  Goal: 5x10^6 cells/kg
- CY (3g/m2)
  MOBILIZATION
  Goal: 5x10^6 cells/kg

- Melphalan 200mg/m^2* + ASCT
- RVD x 2
- Revlimid 12 mos
- RVD x 5
- Revlimid 12 mos

SCT at relapse
MEL 200 mg/m2 if <65 yrs ,
>65 yrs 140mg/m2

Stratified Log-rank test : p=0.00019
Critical p-value : p=0.0152

Arm A - Conventional
Arm B - High dose

N at risk (events)
Conventional 350 (15) 332 (21) 309 (22) 285 (17) 259 (28) 212 (23) 128 (18) 59 (2) 18
High Dose 350 (17) 332 (21) 296 (36) 260 (28) 228 (34) 185 (24) 108 (18) 41 (5) 13

Attal et al. NEJM 2018
## Induction regimens IFM

<table>
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<tr>
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<tr>
<td>VD*</td>
<td>4</td>
<td>IFM2005</td>
<td>223</td>
<td>IFM2007</td>
<td>100</td>
<td>IFM2013</td>
<td>169</td>
<td>IFM2008</td>
<td>700</td>
<td>IFM2013</td>
<td>43</td>
<td></td>
<td></td>
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<tr>
<td>VTD°</td>
<td>3</td>
<td>IFM2013</td>
<td>169</td>
<td>IFM2013</td>
<td>169</td>
<td>IFM2008</td>
<td>31</td>
<td>IFM2009</td>
<td>31</td>
<td>IFM2013</td>
<td>43</td>
<td></td>
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<tr>
<td>VCD°</td>
<td>3</td>
<td>IFM2013</td>
<td>169</td>
<td>IFM2013</td>
<td>169</td>
<td>IFM2008</td>
<td>700</td>
<td>IFM2013</td>
<td>43</td>
<td>IFM2013</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRD**</td>
<td>3</td>
<td>IFM2008</td>
<td>31</td>
<td>IFM2008</td>
<td>31</td>
<td>IFM2009</td>
<td>700</td>
<td>IFM2013</td>
<td>43</td>
<td>IFM2013</td>
<td>46</td>
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<tr>
<td>VRD°°</td>
<td>3</td>
<td>IFM2008</td>
<td>31</td>
<td>IFM2008</td>
<td>31</td>
<td>IFM2009</td>
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<td>IFM2013</td>
<td>43</td>
<td>IFM2013</td>
<td>46</td>
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<tr>
<td>VRD°°°</td>
<td>3</td>
<td>IFM2008</td>
<td>31</td>
<td>IFM2008</td>
<td>31</td>
<td>IFM2009</td>
<td>700</td>
<td>IFM2013</td>
<td>43</td>
<td>IFM2013</td>
<td>46</td>
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<table>
<thead>
<tr>
<th>Response</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
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</thead>
<tbody>
<tr>
<td>≥ CR</td>
<td>2%</td>
<td>6%</td>
<td>12.0%</td>
</tr>
<tr>
<td></td>
<td>13.0%</td>
<td>8.9%</td>
<td>23.0%</td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td>37%</td>
<td>82%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>15%</td>
<td>36%</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>66.3%</td>
<td>56.2%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>37%</td>
<td>78%</td>
<td>85%</td>
</tr>
<tr>
<td>≥ PR</td>
<td>63%</td>
<td>79%</td>
<td>81%</td>
</tr>
<tr>
<td></td>
<td>88%</td>
<td>92.3%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>82%</td>
<td>93%</td>
<td>93%</td>
</tr>
</tbody>
</table>

°° Roussel et al. JCO 2014; °°° Attal et al. ASH2015; ***Roussel et al. ASH2016

Courtesy of Moreau P.
### IFM 2008: RESPONSE RATES (ITT)
**(VRD x 3 - Transplant - VRD x 2 - Rev 1 year)**

<table>
<thead>
<tr>
<th></th>
<th>After induction</th>
<th>After ASCT</th>
<th>After consolidation</th>
<th>After Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n=31</td>
<td>n=31</td>
<td>n=31</td>
<td>n=31</td>
</tr>
<tr>
<td>MRD negative</td>
<td>4/25 (16)</td>
<td>14/26 (54)</td>
<td>15/26 (58)</td>
<td>21/30 (70)</td>
</tr>
<tr>
<td>sCR + CR</td>
<td>7 (23)</td>
<td>14 (45)</td>
<td>15 (48)</td>
<td>18 (58)</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>18 (58)</td>
<td>21 (68)</td>
<td>26 (84)</td>
<td>26 (84)</td>
</tr>
</tbody>
</table>

Roussel et al. in preparation

Roussel et al.
CASSIOPEA-MMY3006 Study design

- **Induction**: VTD + DARA x 4 cycles
- **ASCT**: MEL 200/ASCT
- **Consolidation**: VTD + DARA x 2 cycles
- **Maintenance**: DARA until progression
- **Observation**

VTD, daratumumab.
<table>
<thead>
<tr>
<th>IFM 2019 : HR Trial</th>
<th>IFM 2019: Non-HR Trial (Phase III, n= 1 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomisation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Non-Adapted Therapy</strong></td>
<td><strong>Adapted Therapy</strong></td>
</tr>
<tr>
<td>PI+RD-MaBCD38 x 6</td>
<td>PI+RD-MaBCD38 x 6</td>
</tr>
<tr>
<td><strong>MRD1</strong></td>
<td><strong>MRD1</strong></td>
</tr>
<tr>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HDM</td>
<td>HDM</td>
</tr>
<tr>
<td><strong>M RD2</strong></td>
<td><strong>M RD2</strong></td>
</tr>
<tr>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HDM</td>
<td>HDM</td>
</tr>
<tr>
<td><strong>M RD2b</strong></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td></td>
</tr>
<tr>
<td>R-MaBCD38 2 years</td>
<td>Rev 2 years</td>
</tr>
<tr>
<td><strong>TEP</strong></td>
<td><strong>TEP</strong></td>
</tr>
<tr>
<td><strong>MRD3 (end of therapy)</strong></td>
<td><strong>MRD3 (end of therapy)</strong></td>
</tr>
<tr>
<td><strong>MRD 4, 5, 6 (each year)</strong></td>
<td><strong>MRD 4, 5, 6 (each year)</strong></td>
</tr>
</tbody>
</table>

**Phase II-PO:** 30% increase of PFS as compared with HR in the IFM 2009 trial

**PO:** MRD3 from 45% to 55% with adapted therapy.

**SO:** PFS, OS, Operational cure (ie: MRD3+4+5+6=Neg),

**Stringent-MRD (ie: MRD3 + TEP = Neg)**
Never give up!

Thank you for your attention