Treatment Advances in Multiple Myeloma: Expert Perspectives on Translating Clinical Data to Practice

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San Diego, California

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Jesús F. San-Miguel, MD, PhD, has disclosed that he has received consulting fees, honoraria, and fees for non-CME/CE services received directly from a commercial interest or their agents (eg, advisory board) from Amgen, Bristol-Myers Squibb, Celgene, Janssen, MSD, and Novartis.
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Bruno Paiva, PhD, has disclosed that he has received consulting fees from Celgene, Janssen, Merck, Novartis, and Takeda; funds for research support from Celgene and EngMab; and other honorarium for lectures from Amgen, Celgene, Janssen, and Takeda.
How Should We Use Maintenance for Patients in Clinical Practice?

Moderator
Brian G.M. Durie, MD

Faculty Presenters
Jesús F. San-Miguel, MD, PhD
Bruno Paiva, PhD
Pt Case Example

- 65-yr-old male presents with:
  - 60% BM PCs
  - 3.5 IgG-K M-spike (no immune paresis)
  - High LDH
  - ISS III
  - t(4;14), no del(17p)

- He enrolled in the phase III SWOG S0777 trial and was randomized to receive eight 21-day cycles of VRd

- The pt is in CR at the end of induction

- MRD was assessed after induction and was positive ($10^{-5}$)
What would you recommend now?

A. Observation
B. Lenalidomide maintenance for up to 2 yrs
C. Lenalidomide maintenance until progression
D. Bortezomib maintenance for up to 2 yrs
E. ASCT followed by lenalidomide maintenance
F. ASCT followed by bortezomib maintenance
G. Unsure
# Expert Recommendations

<table>
<thead>
<tr>
<th>Expert</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>ASCT followed by lenalidomide maintenance</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>ASCT followed by lenalidomide maintenance</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>ASCT followed by lenalidomide maintenance</td>
</tr>
<tr>
<td>Bruno Paiva, PhD</td>
<td>ASCT followed by lenalidomide maintenance</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>ASCT followed by bortezomib maintenance</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>ASCT followed by lenalidomide maintenance</td>
</tr>
</tbody>
</table>
Role of Maintenance Therapy in Multiple Myeloma

Jesus San-Miguel, MD, PhD

University of Navarra, Spain
What is the goal of consolidation or maintenance therapy??

Consolidation
- **Improve** response/deeper following therapy
  - By administration of treatment for a *limited period*

Maintenance
- **Maintain** response achieved following therapy
  - By administration of treatment for a *prolonged period*
Role of Maintenance Therapy in Multiple Myeloma

- Young, transplant candidate pts
- Elderly pts

*Maintenance is not a new concept ......in the 90’s IFN was used following ASCT and pulses of MP to maintain the response*
Maintenance Treatment With Thalidomide*

- 6 randomized trials have compared thalidomide ± pred vs nothing or pamidronate or prednisone or IFN
  - > PFS in all 6 trials……… but improved OS in only 3
    - Meta-analysis: modest benefit in PFS and OS (± 6 m)

Caveats: Role in CR, duration of maintenance, toxicity, outcome after relapse

1. Spencer A et al. IMWG 2013 Kyoto
## Maintenance With Bortezomib-Based Therapy

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Median f/u</th>
<th>Results</th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥ nCR</td>
<td>≥ VGPR</td>
<td>PFS</td>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>PAD/HDM/ bortezomib[1] vs VAD/HDM/ thalidomide</td>
<td>41 m</td>
<td>49%*</td>
<td>76%*</td>
<td>35 m*</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Median not</td>
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<td></td>
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<td></td>
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<td>reached</td>
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<tr>
<td></td>
<td></td>
<td>HR: 0.77</td>
<td>(0.60-1.00)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .049</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction/HDM/ bort + thal vs thal vs IFN x 3 yrs[2]</td>
<td>24 m</td>
<td>74%</td>
<td></td>
<td>50.6 m**</td>
<td>78% @ 5 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40.3 m</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32.5 m</td>
<td>70%</td>
</tr>
</tbody>
</table>

*Significant difference between arms

**Median fw 58.6 m, P = .03

IfN: 3 MU/sc 3 times a wk. Thal: 100 mg/day. Bort: one cycle/3 mos.

Lenalidomide vs Placebo After ASCT: PFS From Randomization

**IFM 2005-02**
- **OS:** 75% at 5 yrs in both arms
- 2nd Malignancies: 6.5% vs 2%
- PFS
  - Len: 46 m
  - Placebo: 24 m
  - *P* < 10^{-8}

**CALGB 100104**
- Median OS: 76 vs NR, *P* = .001
- 2nd Malignancies: 8 vs 3%
- PFS
  - Len: 53 m
  - Placebo: 26 m
  - *P* < 10^{-8}

**GIMEMA MM-RV-209**
- 4-yr OS: 80% vs 62%, *P* = .02
- PFS
  - Len: 37 m
  - Placebo: 26 m

**References**
26% reduction in risk of death, representing an estimated 2.5-yr increase in median survival.\(^a\)

<table>
<thead>
<tr>
<th>Survival Probability</th>
<th>Overall Survival, mos</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1209</td>
</tr>
<tr>
<td>LENALIDOMIDE</td>
<td>CONTROL</td>
</tr>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>NE (NE-NE)</td>
</tr>
<tr>
<td>86.0 (79.8-96.0)</td>
<td>50%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.74 (0.62-0.89)</td>
</tr>
<tr>
<td>P = .001</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Median for lenalidomide treatment arm was extrapolated to be 116 mos based on median of the control arm and HR (median: 86 mos; HR: 0.74).

Overall Survival: Subgroup Analysis

Myeloma XI: Trial Design

Intensive Pathway

Randomize 1:1
CTD, RCD

Assess Response

NC + PD, CR + VGPR, PR + MR

CTD, cyclophosphamide (500mg p.o. D1,8,15), thalidomide (100-200mg p.o. daily), dexamethasone (40mg p.o. D1-4, 12-15); CTDa, cyclophosphamide (500mg p.o. D1,8,15, 22), thalidomide (50-200mg p.o. daily), dexamethasone (20mg p.o. D1-4, 15-18); MR, minimal response; NC, no change; PD, progressive disease; PR, partial response; RCD, cyclophosphamide (500mg p.o. D1,8,15, 22), lenalidomide (25mg p.o. D1-21), dexamethasone (40mg p.o. D1-4, 12-15); RCDa, cyclophosphamide (500mg p.o. D1,8,15, 22), lenalidomide (25mg p.o. D1-21), dexamethasone (20mg p.o. D1-4, 15-18), VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response.

CVD

Assess Response

High-Dose Melphalan & ASCT

Maintenance Randomization**

No maintenance, Lenalidomide 10 mg maintenance, Lenalidomide 10 mg + Vorinostat 300 mg maintenance

Non-Intensive Pathway

Randomize 1:1
CTDa, RCDa

Assess Response

NC + PD, CR + VGPR, PR + MR

CTDa, cyclophosphamide (500mg p.o. D1,8), lenalidomide (25mg p.o. D1-21), dexamethasone (20mg p.o. D1-4, 15-18), VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response.

CVD

Assess Response

Nothing CVD

Assess Response

Maintenance Randomization**

No maintenance, Lenalidomide 10 mg maintenance, Lenalidomide 10 mg + Vorinostat 300 mg maintenance

ASH2016 abstracts

**Pts entered into the RCD arm and assessed as NC or PD at the end of RCD induction are not eligible for the maintenance randomisation.

ASCT, autologous stem cell transplant; CR, complete response; CTD, cyclophosphamide (500mg p.o. D1,8,15), thalidomide (100-200mg p.o. daily), dexamethasone (40mg p.o. D1-4, 12-15); CTDa, cyclophosphamide (500mg p.o. D1,8,15, 22), thalidomide (50-200mg p.o. daily), dexamethasone (20mg p.o. D1-4, 15-18); MR, minimal response; NC, no change; PD, progressive disease; PR, partial response; RCD, cyclophosphamide (500mg p.o. D1,8,15, 22), lenalidomide (25mg p.o. D1-21), dexamethasone (40mg p.o. D1-4, 12-15); RCDa, cyclophosphamide (500mg p.o. D1,8), lenalidomide (25mg p.o. D1-21), dexamethasone (20mg p.o. D1-4, 15-18), VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response.

1. Rev (15.07.2014) Myeloma X1 Trial Protocol v5
Myeloma XI: PFS Len Maintenance vs No Maintenance

Median Follow-up: 26 mos

- Primary endpoint maintenance comparison: PFS and OS
- Len maintenance doubles PFS vs no maintenance: 55% reduction in the risk of progression or death
  - Median PFS 37 vs 19 mos (HR: 0.45 [95% CI: 0.39-0.52], \( P < .0001 \))
- Significant improvement in PFS was observed in each pathway and across subgroups
- Main grade 3/4 AEs: neutropenia (35%), thrombocytopenia (7.4%), anaemia (4.4%), PN (1.4%)
- SPMs: Hematologic incidence 0.3% vs 0.9%; slight excess in older pts, mostly noninvasive and did not impact outcome benefit demonstrated

![Graph showing PFS comparison between Len maintenance and No maintenance in Post-ASCT and NSCT settings.](image-url)
### 4 Independent Phase III Clinical Trials Investigated Lenalidomide Maintenance Post-ASCT

<table>
<thead>
<tr>
<th>Coop trial</th>
<th>PFS Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM2005-02[^1]\</td>
<td>0.50</td>
</tr>
<tr>
<td>CALGB 100104[^2]\</td>
<td>0.48</td>
</tr>
<tr>
<td>GIMEMA RV-209[^3]\</td>
<td>0.44</td>
</tr>
<tr>
<td>Myeloma XI[^4]\</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Elderly MM Patients

- Is there any role for maintenance therapy?
## Thalidomide: Effect of Maintenance on PFS/OS

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>N</th>
<th>CR (IF–)</th>
<th>TTP PFS/EFS</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palumbo (Blood 2008;112:3107)</td>
<td>MPT (T maint.)</td>
<td>129</td>
<td>16%</td>
<td>21.8 m</td>
<td>NS: 45 m vs 47.6 m</td>
</tr>
<tr>
<td></td>
<td>MP (no maint.)</td>
<td>126</td>
<td>4%</td>
<td>14.5 m</td>
<td>P = .79</td>
</tr>
<tr>
<td>Wijermans (JCO 2010;28:3160)</td>
<td>MPT (T maint.)</td>
<td>165</td>
<td>2%</td>
<td>13 m</td>
<td>40 m vs 31 m</td>
</tr>
<tr>
<td></td>
<td>MP (no maint.)</td>
<td>168</td>
<td>2%</td>
<td>9 m</td>
<td>P = .05</td>
</tr>
<tr>
<td>Waage A (Blood 2010;116:1405)</td>
<td>MPT (T maint.)</td>
<td>363</td>
<td>13%</td>
<td>15 m</td>
<td>NS: 29 m vs 32 m</td>
</tr>
<tr>
<td></td>
<td>MP (no maint.)</td>
<td>363</td>
<td>4%</td>
<td>14 m</td>
<td>P = .35</td>
</tr>
</tbody>
</table>

- **Thal-IFN vs IFN alone after induction with Thal/Dex or MP:**
  Benefit in PFS but not in OS (Ludwig H. Haematologica 2010)

- **Thal vs no maintenance after induction with CTDa or MP:**
  Benefit in PFS (11m vs 9 m) but not in OS (Morgan G. Blood 2012)

*Duration of Thal maintenance therapy short, due to toxicity.*
**Influence of Maintenance: VMPT + VT vs VMP**

CR (IF−) after VMPT->VT increased **up to 42%** (maintenance)

- VMPT
- VT continuous therapy

- VMPT-VT

- VMP

<table>
<thead>
<tr>
<th></th>
<th>4-years OS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMPT-VT</td>
<td>67%</td>
<td>Not reached</td>
</tr>
<tr>
<td>VMP</td>
<td>55%</td>
<td>54.2 months</td>
</tr>
</tbody>
</table>

HR 0.63, 95% CI, 0.46-0.88, p = .006

**Median PFS: 37 m**

*P < .0001  HR: 0.48*

**Bortezomib ± Thalidomide Maintenance**

*Modified VMP vs VTP Followed by Maintenance With VT or VP in Newly Diagnosed Elderly Pts With MM (GEM2005)*

CR (IF−) increased from 24% (after induction) up to 42% (maintenance)

**PFS**

- VT: 39 m
- VP: 32 m
- Proportion of Pts $P=0.1$

**OS**

- VT: Not reached
- VP: 60 m
- 5-y OS: 69%

**VISTA:**

- PFS 21 m
- 5-y OS: 46%

Lenalidomide Maintenance

**MM-015: MPR-R vs MPR vs MP**

- **MPR-R**: Median PFS 31 mos
- **MPR**: Median PFS 14 mos
- **MP**: Median PFS 13 mos

No differences were observed so far in OS

**FIRST Trial: Len/Dex (18 Cycles or Continuous) vs MPT**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd (n = 535)</td>
<td>26 mos</td>
<td>59 mos</td>
</tr>
<tr>
<td>Rd18 (n = 541)</td>
<td>21 mos</td>
<td>62 mos</td>
</tr>
<tr>
<td>MPT (n = 547)</td>
<td>21.9 mos</td>
<td>49 mos</td>
</tr>
</tbody>
</table>

**Median follow-up 67 mos, data cutoff 21 Jan 2016**

**PFS:** Rd continuous vs MPT: HR 0.69 (0.59-0.79) \( P < .00001 \)

**OS:** Rd continuous vs MPT: HR 0.78 (0.67-0.92) \( P = .0023 \)

- **SPM, %**
  - Solid tumour: 6.0, 6.9, 5.9
  - Haematological: 0.8, 0.4, 6.2

**Hazard ratio**

- Rd vs MPT: 0.78; \( P = 0.002 \)
- Rd vs Rd18: 0.91; \( P = 0.305 \)
- Rd18 vs MPT: 0.83; \( P = 0.034 \)

VMP (x9) + Len/Dex (x9): PFS and OS

GEM/Pethema GEM2010 Trial

Median follow-up: 30 months (9-43)

**PFS**
- Sequential: 32m
- Alternating: 34 m

**OS**
- Sequential: 72% at 3 yrs
- Alternating: 74% at 3 yrs

VISTA: 21m
FIRST: 26m (cont Rd); 21 m (Rd18)

VISTA: 68% at 3 yrs
FIRST: 70% (cont Rd), 66% at (Rd18) 3 yrs

Lenalidomide single agent

**Len vs Len+Dex:** To determine which of the dual mechanisms of lenalidomide action, antitumoral and immunomodulatory, is more effective at maintaining the response.

- Len + PI (Ixazomib / Carfilzomib)
- Len + PI + anti-CD38 or Elo??
- Len + PD-L1 inhibition

Optimal Maintenance Treatment: Number of Agents and Duration

One, two, three drugs???
## Maintenance Therapy After ASCT: Future

<table>
<thead>
<tr>
<th>Study</th>
<th>Len x 1 yr vs len until DP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM/DFCI 2009¹</td>
<td>ECOG-ACRIN E1A11²</td>
</tr>
<tr>
<td>ECOG-ACRIN E1A11²</td>
<td>Len x 2 yr vs len until DP</td>
</tr>
<tr>
<td>Myeloma XI³</td>
<td>Len vs len + vorinostat vs no maintenance</td>
</tr>
<tr>
<td>PETHEMA GEM 2014⁴</td>
<td>Len vs len + ixazomib x 2 yrs (MRD+ Pts cont x 3y)</td>
</tr>
<tr>
<td>SWOG⁷</td>
<td>Len vs len + ixazomib until DP</td>
</tr>
<tr>
<td>GMMG-HD6⁵</td>
<td>Len-dex vs len-dex + elotuzumab</td>
</tr>
<tr>
<td>GIMEMA⁶</td>
<td>Len vs len + carfilzomib</td>
</tr>
<tr>
<td>BMT CTN 1401⁸</td>
<td>Len vs len + vaccination</td>
</tr>
<tr>
<td>AFT-40⁹</td>
<td>Len vs len + durvalumab vs len + daratumumab vs len + ACY241</td>
</tr>
<tr>
<td>TOURMALINE-MM3¹⁰</td>
<td>Ixazomib for up to 2 yrs vs placebo</td>
</tr>
<tr>
<td>HOVON 131 MM-IFM 2015-01¹¹</td>
<td>Daratumumab vs placebo</td>
</tr>
</tbody>
</table>

GEM 2017 for Fit, Elderly Pts: VMP/Rd vs KRd +/- Dara

**Induction**
- VMP/Rd
- KRd +/- Dara

**Consolidation**
- 18 cycles
- DaraRd (x4)
- (except Dara arm)

**Maintenance**
- MRD+ R
- MRD- R
- X
- DR

- Genetic risk stratification
- Screening of displasia
- Circulating tumor cells
- Immune profiling
- FACS-sorting

- MRD monitoring
- PET/CT (if CR)
- Immune profiling
- FACS-sorting

- MRD monitoring
- PET/CT (if CR)
- Immune profiling
- FACS-sorting

- MRD monitoring
- PET/CT (if CR)
- Immune profiling
- Screening of displasia
How Should We Monitor Patients During Maintenance Therapy?

Bruno Paiva, PhD
The true value of CR relies on the MRD status, and CR without MRD is no better than PR

Progression-free survival (%)

Time from response assessment (mos)

MRD– (n=316) median PFS: 58 mos
CR (n=128) median PFS: 24 mos
nCR (n=96) median PFS: 21 mos
PR (n=199) median PFS: 26 mos
< PR (38) median PFS: 9 mos

MRD– vs CR: *P* <.001
CR vs nCR: *P* =.127

Overall survival (%)

Time from response assessment (mos)

MRD– (n=316) median OS: 145 mos
CR (n=128) median OS: 59 mos
nCR (n=96) median OS: 63 mos
PR (n=199) median OS: 59 mos
< PR (38) median OS: 32 mos

MRD– vs CR: *P* <.001
CR vs nCR: *P* =.657
Clinical benefit after CR vs MRD negativity among pts with high-risk cytogenetics

### Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.62</td>
<td>0.53-0.72</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Transplant eligible</td>
<td>0.65</td>
<td>0.55-0.78</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Transplant ineligible</td>
<td>0.58</td>
<td>0.42-0.82</td>
<td>.002</td>
</tr>
<tr>
<td>ISS I</td>
<td>0.59</td>
<td>0.44-0.79</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ISS II</td>
<td>0.72</td>
<td>0.57-0.91</td>
<td>.005</td>
</tr>
<tr>
<td>ISS III</td>
<td>0.55</td>
<td>0.39-0.77</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Standard-risk FISH</td>
<td>0.66</td>
<td>0.50-0.87</td>
<td>.004</td>
</tr>
<tr>
<td>High-risk FISH</td>
<td>0.76</td>
<td>0.44-1.32</td>
<td>.330</td>
</tr>
</tbody>
</table>

**Reduced risk after CR**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.37</td>
<td>0.29-0.47</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Transplant eligible</td>
<td>0.34</td>
<td>0.26-0.45</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Transplant ineligible</td>
<td>0.53</td>
<td>0.34-0.82</td>
<td>.004</td>
</tr>
<tr>
<td>ISS I</td>
<td>0.26</td>
<td>0.16-0.43</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ISS II</td>
<td>0.46</td>
<td>0.32-0.65</td>
<td>&lt; .001</td>
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<td>0.46</td>
<td>0.29-0.75</td>
<td>.002</td>
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<tr>
<td>Standard-risk FISH</td>
<td>0.39</td>
<td>0.28-0.55</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>High-risk FISH</td>
<td>0.35</td>
<td>0.19-0.66</td>
<td>.001</td>
</tr>
</tbody>
</table>

**Reduced risk after MRD**

Lahuerta JJ, et al. *manuscript under review*
Can persistent MRD after induction be controlled with further treatment?

Median time on maintenance in the Phase III Trial SWOG S0777: 385 days

What is the meaning of persistent MRD after maintenance therapy

![Graph showing MRD at postmaintenance](Image)

**P value (trend) < .0001**
MRD+ pts have different outcomes according to their cytogenetic profile

Clinical impact of mutations in selected genes: Myeloma XI trial

Prognostic value of immune reconstitution in patients with persistent MRD

Single 8-color combination (CD45, CD138, CD38, CD56, CD27, CD19, CD117, CD81):
Enumeration of 15 different BM cell populations

Individual patient immune signatures

Patients with favorable immune profile are characterized by an increased compartment of mature B-cells

As presented at ASH 2015.
Need for integrated next-generation immunophenotypic and sequencing techniques for new concepts in risk stratification toward precision medicine
Next-generation prognostication for precision medicine in multiple myeloma

Prediction of outcomes based on big datasets

Genetic landscape

MRD monitoring

Immune profiling

Time-to-progression (%)
Which maintenance strategies are effective in patients with persistent MRD?
Next-generation MRD-negative patients: favorable outcome, but need to check for PB contamination

**Progression-Free Survival (%)**

<table>
<thead>
<tr>
<th>Cell Population</th>
<th>% Normal BM Cells (Range)</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast cells</td>
<td>0.006% (0.002-0.03)</td>
<td>0.002%</td>
<td>0.0006%</td>
</tr>
<tr>
<td>Erythroblasts</td>
<td>6.4% (2-11.5)</td>
<td>8.01%</td>
<td>5.1%</td>
</tr>
<tr>
<td>CD19⁻ nPC</td>
<td>0.05% (0.003-0.2)</td>
<td>0.004%</td>
<td>0.004%</td>
</tr>
<tr>
<td>CD19⁻/CD19⁺ nPC ratio</td>
<td>0.6% (0.08-1.1)</td>
<td>0.3%</td>
<td>0.08%</td>
</tr>
<tr>
<td>CD27⁺ B-cell precursors</td>
<td>0.08% (0.004-0.4)</td>
<td>0.0001%</td>
<td>0.003%</td>
</tr>
<tr>
<td>CD27⁻ B-cell precursors</td>
<td>0.4% (0.05-2.2)</td>
<td>0.001%</td>
<td>0.01%</td>
</tr>
<tr>
<td>CD27⁺/CD27⁻ B-cell precursor ratio</td>
<td>0.2% (0.04-1)</td>
<td>0.09%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Mature B-cells</td>
<td>1.6% (0.6-3.5)</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>B-cell precursor/mature B-cell ratio</td>
<td>0.2% (0.03-1.1)</td>
<td>0.02%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Myeloid precursors</td>
<td>1.8% (0.2-3.6)</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

NGF, next-generation flow.

Flores-Montero J, et al. *manuscript under review.*
Myeloma is a patchy disease: need for continuous monitoring

Treatment stages

Diagnosis
CR
MRD+ 0.06%

Induction
MRD−

HDT/ASCT
MRD−

Consolidation
MRD+ 0.003%
PFS for patients with negative PET-CT and negative MRD by flow (47.7% of pts) vs others premaintenance

$P = .02$

## IMWG Criteria for MRD in Multiple Myeloma

<table>
<thead>
<tr>
<th>MRD Negativity Criteria (Requires CR)</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sustained MRD-negative</strong></td>
<td>MRD negative in the marrow (NGF or NGS) and by imaging as defined below, confirmed one yr apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD negative at 5 yrs, etc)</td>
</tr>
<tr>
<td><strong>Imaging MRD-negative</strong></td>
<td>MRD negative as defined below (NGF or NGS) PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT</td>
</tr>
<tr>
<td><strong>Flow MRD-negative</strong></td>
<td>Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10⁵ nucleated cells or higher</td>
</tr>
<tr>
<td><strong>Sequencing MRD-negative</strong></td>
<td>Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10⁵ nucleated cells or higher</td>
</tr>
</tbody>
</table>

Go Online for More CCO Coverage of Multiple Myeloma!

Capsule Summaries of all the key data

Additional CME-certified slideset on multiple myeloma with expert faculty commentary on all the key studies

Online Treatment Decision Aid with recommendations from 5 experts for your individual patients with myeloma

myeloma.org/videos/ASH-Satellite-Symposium-2016
clinicaloptions.com/oncology
clinicaloptions.com/MyelomaTool