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

Friday, December 2, 2016
San Diego, California

This program is supported by educational grants from Amgen, Celgene Corporation, Karyopharm, Takeda Oncology, and The Binding Site.
Program Director

Brian G.M. Durie, MD
Medical Director, AMyC
Co-Chair Myeloma Committee, SWOG
Chairman, International Myeloma Foundation
Specialist in Multiple Myeloma and Related Disorders
Cedars-Sinai Outpatient Cancer Center
Los Angeles, California

Brian G.M. Durie, MD, has no real or apparent conflicts of interest to disclose.
Faculty

Jesús F. San-Miguel, MD, PhD  
*Director of Clinical and Transnational Medicine*  
Clinica Universidad de Navarra  
Universidad de Navarra  
Pamplona, Spain

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.
Faculty

Bruno Paiva, PhD
Department of Hematology and Immunology
Flow Cytometry Core - CIMA LAB Diagnostics
University of Navarra
Pamplona, Spain

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
<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
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*

What is the goal of consolidation or maintenance therapy??
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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥ nCR</td>
</tr>
<tr>
<td>PAD/HDM/ bortezomib[1]</td>
<td></td>
<td>49%*</td>
</tr>
<tr>
<td>vs</td>
<td>41 m</td>
<td></td>
</tr>
<tr>
<td>VAD/HDM/ thalidomide</td>
<td></td>
<td>34%</td>
</tr>
<tr>
<td>Induction/HDM/ bort + thal vs thal vs IFN x 3 yrs[2]</td>
<td>24 m</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant difference between arms

**Median f/u 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
- **PFS**
  - Len: 46 m
  - Placebo: 24 m
  - 
P \(< 10^{-8}

**OS:** 75% at 5 yrs in both arms

2nd Malignancies: 6.5% vs 2%


### CALGB 100104
- **PFS**
  - Len: 53 m
  - Placebo: 26 m
  - 
P \(< 10^{-8}

**Median OS:** 76 vs NR, \(P = .001

2nd Malignancies: 8 vs 3%


### GIMEMA MM-RV-209
- **PFS**
  - Len: 37 m
  - Placebo: 26 m

**4-yr OS:** 80% vs 62%, \(P = .02

Meta-Analysis of Overall Survival With Lenalidomide Maintenance: Median Follow-up of 80 mos

26% reduction in risk of death, representing an estimated 2.5-yr increase in median survival

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).


HR, hazard ratio; NE, not estimable; OS, overall survival.
Overall Survival: Subgroup Analysis


*Number of pts. a Cytogenetic data were available only for the IFM and GIMEMA studies. b CrCl post-ASCT data were available only for the CALGB and IFM studies.

ASCT, autologous stem cell transplant; CR, complete response; CrCl, creatinine clearance; HR, hazard ratio; ISS, International Staging System; LEN, lenalidomide; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.
Myeloma XI: Trial Design

Intensive Pathway

Randomize 1:1
CTD  RCD
Assess Response
NC + PD  CR + VGPR  PR + MR
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
CVD
Assess Response
CVD
Maintenance Randomization
No maintenance  Lenalidomide 10 mg maintenance  Lenalidomide 10 mg + Vorinostat 300 mg maintenance

**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

VCD, Bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response.

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), lenalidomide (25mg p.o. D1-21), dexamethasone (40mg p.o. D1-4, 12-15); RCD, cyclophosphamide (500mg p.o. D1,8,15), lenalidomide (25mg p.o. D1-21), dexamethasone (20mg p.o. D1-4, 15-18); VCD, Bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response.

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%), thrombocytopaenia (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

---

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\textsuperscript{[1]}</td>
<td>0.50</td>
</tr>
<tr>
<td>CALGB 100104\textsuperscript{[2]}</td>
<td>0.48</td>
</tr>
<tr>
<td>GIMEMA RV-209\textsuperscript{[3]}</td>
<td>0.44</td>
</tr>
<tr>
<td>Myeloma XI\textsuperscript{[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 P = .79</td>
</tr>
<tr>
<td></td>
<td>MP (no maint.)</td>
<td>126</td>
<td>4%</td>
<td>14.5 m</td>
<td></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 P = .05</td>
</tr>
<tr>
<td></td>
<td>MP (no maint.)</td>
<td>168</td>
<td>2%</td>
<td>9 m</td>
<td></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 P = .35</td>
</tr>
<tr>
<td></td>
<td>MP (no maint.)</td>
<td></td>
<td>4%</td>
<td>14 m</td>
<td></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)

- Median PFS: 37 m (VMPT-VT)
- HR: 0.48
- CR (IF–) after VMPT→VT increased up to 42%

4-y OS: 67%

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

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

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)

VISTA: PFS 21m

VT: 39m

VP: 32m

$P = 0.1$

VISTA: 5-y OS: 46%

VT: Not reached 5-y OS: 69%

VP: 60m

$P = 0.1$

Lenalidomide Maintenance

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


No differences were observed so far in OS

**Median PFS**

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

**HR**

- **MPR-R vs MP**: HR 0.49, \(P < .001\)
- **MPR vs MP**: HR 0.40, \(P < .001\)
**FIRST Trial:** Len/Dex (18 Cycles or Continuous) vs MPT

### Median PFS

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd (n = 535)</td>
<td>26</td>
</tr>
<tr>
<td>Rd18 (n = 541)</td>
<td>21</td>
</tr>
<tr>
<td>MPT (n = 547)</td>
<td>21.9</td>
</tr>
</tbody>
</table>

### Median OS

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd (n = 535)</td>
<td>59</td>
</tr>
<tr>
<td>Rd18 (n = 541)</td>
<td>62</td>
</tr>
<tr>
<td>MPT (n = 547)</td>
<td>49</td>
</tr>
</tbody>
</table>

### Hazard ratios

- **Rd vs MPT:** HR 0.69 (0.59-0.79) \( P < 0.00001 \)
- **Rd vs Rd18:** HR 0.70 (0.60-0.81) \( P = 0.0001 \)
- **Rd18 vs MPT:** HR 1.03 (0.86-1.23) \( P = 0.70349 \)

### PFS: Rd continuous vs MPT
- HR 0.69 (0.59-0.79) \( P < 0.00001 \)

### OS: Rd continuous vs MPT
- HR 0.78 (0.67-0.92) \( P = 0.0023 \)

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

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
- p=NS

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

**VISTA**
- 68% at 3 yrs

**FIRST**
- 70% (cont Rd), 66% at (Rd18) 3 yrs

Optimal Maintenance Treatment: Number of Agents and Duration

One, two, three drugs???

- 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
## Maintenance Therapy After ASCT: Future

<table>
<thead>
<tr>
<th>Study</th>
<th>Group Compared</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM/DFCI 2009</td>
<td>Len x 1 yr vs len until DP</td>
<td></td>
</tr>
<tr>
<td>ECOG-ACRIN E1A11</td>
<td>Len x 2 yr vs len until DP</td>
<td></td>
</tr>
<tr>
<td>Myeloma XI</td>
<td>Len vs len + vorinostat vs no maintenance</td>
<td></td>
</tr>
<tr>
<td>PETHEMA GEM 2014</td>
<td>Len vs len + ixazomib x 2 yrs (MRD+ Pts cont x 3y)</td>
<td></td>
</tr>
<tr>
<td>SWOG</td>
<td>Len vs len+ ixazomib until DP</td>
<td></td>
</tr>
<tr>
<td>GMMG-HD6</td>
<td>Len-dex vs len-dex + elotuzumab</td>
<td></td>
</tr>
<tr>
<td>GIMEMA</td>
<td>Len vs len + carfilzomib</td>
<td></td>
</tr>
<tr>
<td>BMT CTN 1401</td>
<td>Len vs len + vaccination</td>
<td></td>
</tr>
<tr>
<td>AFT-40</td>
<td>Len vs len + durvalumab vs len + daratumumab vs len + ACY241</td>
<td></td>
</tr>
<tr>
<td>TOURMALINE-MM3</td>
<td>Ixazomib for up to 2 yrs vs placebo</td>
<td></td>
</tr>
<tr>
<td>HOVON 131 MM-IFM 2015-01</td>
<td>Daratumumab vs placebo</td>
<td></td>
</tr>
</tbody>
</table>

1. NCT01208662 at www.clinicaltrials.gov
2. NCT01863850 at www.clinicaltrials.gov
3. NCT01554852 at www.clinicaltrials.gov
4. NCT0206144 at www.clinicaltrials.gov
5. NCT02495922 at www.clinicaltrials.gov
6. NCT02203643 at www.clinicaltrials.gov
7. SWOG S1606 study
8. NCT02728102 at www.clinicaltrials.gov
9. Alliance study proposal
10. NCT02181413 at www.clinicaltrials.gov
11. NCT02541383 at www.clinicaltrials.gov
GEM 2017 for Fit, Elderly Pts: VMP/Rd vs KRd +/- Dara

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

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

**Maintenance**
- 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
- FACS-sorting
- Screening of dysplasia

- Genetic risk stratification
- Screening of dysplasia
- Circulating tumor cells
- Immune profiling
- FACS-sorting
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
Clinical benefit after CR vs MRD negativity among pts with high-risk cytogenetics

**Overall Survival**

**CR**

<table>
<thead>
<tr>
<th>Subgroup</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>

**MRD**

<table>
<thead>
<tr>
<th>Subgroup</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>
</tr>
<tr>
<td>ISS III</td>
<td>0.46</td>
<td>0.29-0.75</td>
<td>.002</td>
</tr>
<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>
Can persistent MRD after induction be controlled with further treatment?

**Time from MRD assessment at cycle 9 (months)**

- **MRD− (n=25)**, median TTP: NR
- **CR & MRD+ (n=22)**, median TTP: NR
- **<CR & MRD+ (n=80)**, median TTP: 15m

**Time to progression (%)**

- **MRD− (n=25)**, 3y OS: 83%
- **CR & MRD+ (n=22)**, 3y OS: 53%
- **<CR & MRD+ (n=80)**, 3y OS: 58%

**Overall survival (%)**

- **MRD− (n=25)**, 3y OS: 83%
- **CR & MRD+ (n=22)**, 3y OS: 53%
- **<CR & MRD+ (n=80)**, 3y OS: 58%

*Paiva B et al. Blood 2016;127(25):3165-74*
What is the meaning of persistent MRD after maintenance therapy

MRD at postmaintenance

Pts Without Progression (%)

Mos Since Randomization

P value (trend) < .0001

$10^{-5} - 10^{-6}$
MRD+ pts have different outcomes according to their cytogenetic profile

Clinical impact of mutations in selected genes: Myeloma XI trial

- **ZFHX4**
  - Nonintensive (n = 103)
  - Intensive (n = 132)
  - Assess response
  - CTDa (n = 99)
  - CRD (n = 129)
  - Randomly assign
  - NC + PD (n = 60)
  - PR + MR (n = 33)
  - CVD (n = 14)
  - Assess response
  - Randomly assign (n = 60)
  - Assess response
  - NC + PD (n = 10)
  - PR + MR (n = 13)
  - CVD (n = 10)
  - Assess response
  - Randomly assign (n = 25)
  - Assess response
  - Nonmutated (n = 448)
  - Mutated (n = 18)
  - P-value: 0.001

- **IRF4**
  - Assess response
  - Randomly assign (n = 60)
  - Assess response
  - NC + PD (n = 10)
  - Assess response
  - Randomly assign (n = 25)
  - Assess response
  - Nonmutated (n = 448)
  - Mutated (n = 18)
  - P-value: 0.001

- **EGFR1**
  - Assess response
  - Randomly assign (n = 60)
  - Assess response
  - NC + PD (n = 10)
  - Assess response
  - Randomly assign (n = 25)
  - Assess response
  - Nonmutated (n = 447)
  - Mutated (n = 16)
  - P-value: 0.04

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’s 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

- Genetic landscape
- MRD monitoring
- Immune profiling
  - T-cells
  - NK cells
  - B-cells

Prediction of outcomes based on big datasets
Which maintenance strategies are effective in patients with persistent MRD?
Next-generation MRD-negative patients: favorable outcome, but need to check for PB contamination

<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><strong>0.0001%</strong></td>
<td><strong>0.003%</strong></td>
</tr>
<tr>
<td>CD27- B-cell precursors</td>
<td>0.4% (0.05-2.2)</td>
<td><strong>0.001%</strong></td>
<td><strong>0.01%</strong></td>
</tr>
<tr>
<td>CD27+/CD27- B-cell precursor ratio</td>
<td>0.2% (0.04-1)</td>
<td><strong>0.09%</strong></td>
<td>0.3%</td>
</tr>
<tr>
<td>Mature B-cells</td>
<td>1.6% (0.6-3.5)</td>
<td><strong>0.2%</strong></td>
<td><strong>0.1%</strong></td>
</tr>
<tr>
<td>B-cell precursor/mature B-cell ratio</td>
<td>0.2% (0.03-1.1)</td>
<td><strong>0.02%</strong></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.*

---

Progression-Free Survival (%)

<table>
<thead>
<tr>
<th>Time From MRD Assessment (Mos)</th>
<th>NGF- (n=37), 75% PFS: NR</th>
<th>NGF+ (n=42), 75% PFS: 10 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>15</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>20</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>25</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>30</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

*P = .01*
Myeloma is a patchy disease: need for continuous monitoring

Diagnosis

CR
MRD+ 0.06%

Induction
MRD–

HDT/ASCT
MRD–

Consolidation
MRD+ 0.003%

Treatment stages
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>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained MRD-negative</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 (e.g., MRD negative at 5 yrs, etc)</td>
</tr>
<tr>
<td>Imaging MRD-negative</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>Flow MRD-negative</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 $10^5$ nucleated cells or higher</td>
</tr>
<tr>
<td>Sequencing MRD-negative</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 $10^5$ 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