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

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San Diego, California

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Where Are We Now and Where Are We Going With the Care of Patients With MM?

Moderator
Brian G.M. Durie, MD

Panel Discussion
When Should Treatment Be Initiated?

Potential New Myeloma or Smoldering Myeloma

Any Myeloma Defining Events?
- CRAB,
- > 60% PC,
- FLC > 100,
- MRI > 1 focal

Treat as Myeloma

No Myeloma Defining Events (SMM)

High Risk SMM
(Median TTP ~ 2 Yrs)

Evolving, or Many High-Risk Factors

Consider Treating as Myeloma

Clinical Trials

Low Risk SMM
(~5 % per Yr PD)

Observation

**Myeloma: Frontline Treatment**

- **Not Transplant Candidate**
  - VRd
  - Rd (if frail, age ≥75)*

- **Transplant Candidate**
  - VRd x 3-4 cycles
  - **Auto SCT Maintenance**
    - (Len for std risk; Bortez for high risk)
  - VRd x4 cycles
    - Maintenance
    - Delayed Transplant

*Based on CALGB 100104, S0777, IFM-DFCI, CTN 0702, HOVON
VTd/VCd if VRd not available
Double vs Single Autologous Stem Cell Transplantation After Bortezomib-Based Induction Regimens for Multiple Myeloma: An Integrated Analysis of Patient-Level Data From Phase European III Studies

OS for Pts With High-Risk Cytogenetics and Who Failed CR After Bort-Based Induction

Log rank test: $P = .0001$

HR: 0.22 (0.10-0.50) $P < .001$

Double ASCT 76%

Single ASCT 33%
Role of Transplant

Late Breaking Abstract #LBA-1 [Tuesday 7:30 am]

- BMT CTN 0702 staMINA Trial
- PI: Ed Stadtmauer
- 758 patients
- Stratification:
  - Cytogenetic risk
  - B2-M
  - Center

No differences in PFS/ OS/ PD

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OS</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACM</td>
<td>57%</td>
<td>86%</td>
<td>42%</td>
</tr>
<tr>
<td>TAM</td>
<td>56%</td>
<td>82%</td>
<td>42%</td>
</tr>
<tr>
<td>AM</td>
<td>52%</td>
<td>83%</td>
<td>47%</td>
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</tbody>
</table>

## Co-Morbidity Assessment

### Patient Status Assessment

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
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<tbody>
<tr>
<td>Age</td>
<td>0-2</td>
</tr>
<tr>
<td>Charlson</td>
<td>0-1</td>
</tr>
<tr>
<td>ADL</td>
<td>0-1</td>
</tr>
<tr>
<td>IADL</td>
<td>0-1</td>
</tr>
</tbody>
</table>

### Fit, Unfit, Frail

- **Fit**: Additive total score = 0
- **Unfit**: Additive total score = 1
- **Frail**: Additive total score ≥ 2

### Pharmacologic Management

**Go-Go**
- Full-dose

**Moderate-Go**
- Reduced-dose

**Slow-Go**
- Further reduced dose

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Level 0</th>
<th>Dose Level -1</th>
<th>Dose Level -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>25 mg/d</td>
<td>15 mg/d</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m²/wk</td>
<td>1.0 mg/m²/wk</td>
<td>1.3 mg/m²/2wk</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg/wk</td>
<td>20 mg/wk</td>
<td>10 mg/wk</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>300 mg/m² d 1,8,15</td>
<td>50 mg/d</td>
<td>50 mg/qod</td>
</tr>
</tbody>
</table>

Which maintenance strategies are effective in patients with persistent MRD?
GEM 2017 Fit, Elderly Patients: VMP/Rd vs KRd +/- Dara

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

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

**Maintenance**
- DR
  - MRD+
  - MRD-
  - 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

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

- MRD monitoring
- PET/CT (if CR)
- Immune profiling
- FACS-sorting
- Screening of displasia
# Maintenance Therapy After ASCT: Future

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparator</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM/DFCI 2009¹</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 XI²</td>
<td>Len vs len + vorinostat vs no maintenance</td>
<td></td>
</tr>
<tr>
<td>PETHEMA GEM 2014⁴</td>
<td>Len vs len + ixazomib x 2 yrs (MRD+ pts cont x 3y)</td>
<td></td>
</tr>
<tr>
<td>SWOG⁷</td>
<td>Len vs len + ixazomib until DP</td>
<td></td>
</tr>
<tr>
<td>GMMG-HD6⁵</td>
<td>Len-dex vs len-dex + elotuzumab</td>
<td></td>
</tr>
<tr>
<td>GIMEMA⁶</td>
<td>Len vs len + carfilzomib</td>
<td></td>
</tr>
<tr>
<td>BMT CTN 1401⁸</td>
<td>Len vs len + vaccination</td>
<td></td>
</tr>
<tr>
<td>AFT-40⁹</td>
<td>Len vs len + durvalumab vs len + daratumumab vs len + ACY241</td>
<td></td>
</tr>
<tr>
<td>TOURMALINE-MM3⁰</td>
<td>Ixazomib for up to 2 yrs vs placebo</td>
<td></td>
</tr>
<tr>
<td>HOVON 131 MM-IFM 2015-01¹¹</td>
<td>Daratumumab vs placebo</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Results of New Regimens for the Treatment of Relapsed Multiple Myeloma.*

<table>
<thead>
<tr>
<th>Trial and Regimen†</th>
<th>Complete Response % of patients</th>
<th>Median Progression-free Survival mo</th>
<th>Hazard Ratio for Disease Progression or Death (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lenalidomide-based regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOURMALINE-MM1⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide–dexamethasone</td>
<td>7</td>
<td>14.7</td>
<td>0.74 (0.59–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ixazomib–lenalidomide–dexamethasone</td>
<td>12</td>
<td>20.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELOQUENT-2⁷</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide–dexamethasone</td>
<td>7</td>
<td>14.9</td>
<td>0.70 (0.57–0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elotuzumab–lenalidomide–dexamethasone</td>
<td>4</td>
<td>19.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPIRE⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide–dexamethasone</td>
<td>14</td>
<td>17.6</td>
<td>0.69 (0.57–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carfilzomib–lenalidomide–dexamethasone</td>
<td>32</td>
<td>26.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POLLUX¹⁰</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide–dexamethasone</td>
<td>19</td>
<td>18.4</td>
<td>0.37 (0.27–0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daratumumab–lenalidomide–dexamethasone</td>
<td>43</td>
<td>NR</td>
<td></td>
<td></td>
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<tr>
<td><strong>Bortezomib-based regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANORAMA¹⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib–dexamethasone</td>
<td>6</td>
<td>8.1</td>
<td>0.63 (0.52–0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Panobinostat–bortezomib–dexamethasone</td>
<td>11</td>
<td>12.0</td>
<td></td>
<td></td>
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<tr>
<td>CASTOR³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib–dexamethasone</td>
<td>9</td>
<td>7.2</td>
<td>0.39 (0.28–0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daratumumab–bortezomib–dexamethasone</td>
<td>19</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Myeloma: First Relapse

*Relapse occurring while off all therapy, or while on small doses of single-agent lenalidomide, or on bortezomib maintenance

¶Consider salvage auto transplant in eligible patients
Myeloma: Second or higher relapse

Preferred Options

- Any first relapse options that have not been tried
- Pom-based regimens (KPd, DPd, etc)
- Preferably include Dara

Additional Options

- VDT-PACE
- Bendamustine-based regimens
- Adding Panobinostat
New Myeloma Therapy
Combination With HIV drug

Abstract #487 [Sunday 4:30pm]

- St Gallen, Switzerland team
- Phase II trial with 34 patients; resistant to bortezomib
- Nelfinavir (NFV): oral protease inhibitor; overcomes bortezomib resistance
- Combo = NFV + bortezomib/dex; well tolerated
- Relapse/refractory patients with median 5 lines of therapy
- ORR (PR or better) = 65%

Figure 1. Maximum relative change in serum-M protein or serum free light chain concentration in individual evaluable patients.
Venetoclax: BCL-2 Inhibitor Therapy

Abstract #488 [Sunday 4:45pm]

- Shaji Kumar; phase I study
- 66 patients; relapse/refractory disease
- Acceptable safety profile

Philippe Moreau; phase Ib study

66 patients; relapse/refractory disease

Dan Vogl; phase II

79 patients:

- 48 – quad (4) refractory: len/pom/bortez/carfilz
- 31 – penta (5) refractory: + dara → “unmet need group”

ORR (≥ partial response) = 21% (quad); 20% (penta)

Median DOR = 5 months

OS = 9.3 months

Main AEs: platelets ↓; GI; fatigue

Abstract #491 [Sunday 5:30pm]

“STORM” Trial

Selinexor/Bortezomib/Dex Combo

**Abstract #977 [Monday 3:45pm]**

- Nizar Bahlis; phase I/II
- 22 patients with refractory MM; combination well tolerated

Table 1: Best Response by Prior Proteasome Inhibitor (PI) Treatment Status

<table>
<thead>
<tr>
<th>Prior PI Status</th>
<th>N</th>
<th>ORR, n (%)</th>
<th>CR, n (%)</th>
<th>VGPR, n (%)</th>
<th>PR, n (%)</th>
<th>MR, n (%)</th>
<th>SD, n (%)</th>
<th>PD, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory (7 Bort, 2 Car, 2 Ixa)</td>
<td>12</td>
<td>7 (58)</td>
<td>1 (9)</td>
<td>---</td>
<td>6 (50)</td>
<td>3 (25)</td>
<td>1 (8)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Bort Exposed</td>
<td>7</td>
<td>7 (100)</td>
<td>---</td>
<td>5 (71)</td>
<td>2 (29)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Also, Abstract #330: Selinexor/Pom/Dex

Abstract #973: Selinexor/Car/Dex
Abstract #974 [Monday 3:00pm]

- Alfred Garfall; U Penn Team; pilot study
- 10 patients treated with CTL019 CAR T-cells post-ASCT; safe

### Table of Patient Characteristics

<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>Sex</th>
<th>Prognostic &amp; Clinical Features</th>
<th>OS (months)</th>
<th>VGPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48F</td>
<td>F</td>
<td>Complex karyotype</td>
<td>10</td>
<td>VGPR</td>
</tr>
<tr>
<td>2</td>
<td>58M</td>
<td>M</td>
<td>Complex karyotype</td>
<td>7</td>
<td>PD</td>
</tr>
<tr>
<td>3</td>
<td>66F</td>
<td>F</td>
<td>Palmar cell leukemia</td>
<td>3</td>
<td>VGPR</td>
</tr>
<tr>
<td>5</td>
<td>54F</td>
<td>F</td>
<td>t(6;14), +1q</td>
<td>7</td>
<td>VGPR</td>
</tr>
<tr>
<td>6</td>
<td>53M</td>
<td>M</td>
<td>BRCA1 V600E mutation</td>
<td>2</td>
<td>VGPR</td>
</tr>
<tr>
<td>7</td>
<td>62F</td>
<td>F</td>
<td>NA</td>
<td>5</td>
<td>VGPR</td>
</tr>
<tr>
<td>8</td>
<td>57F</td>
<td>F</td>
<td>t(6;14), +1q</td>
<td>4</td>
<td>PR</td>
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<tr>
<td>9</td>
<td>62M</td>
<td>M</td>
<td>t(6;14), +1q</td>
<td>4</td>
<td>PD</td>
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<tr>
<td>10</td>
<td>59F</td>
<td>F</td>
<td>del(17p), +1q</td>
<td>10</td>
<td>PR</td>
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<td>12</td>
<td>50M</td>
<td>M</td>
<td>NA</td>
<td>6</td>
<td>VGPR</td>
</tr>
</tbody>
</table>

3 long VGPRs

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