Are We Ready for Personalized Therapy in Newly Diagnosed MM?

Faculty Presenter:
Brian G.M. Durie, MD

This activity is supported by educational grants from AbbVie; Amgen; Bristol-Myers Squibb; Celgene Corporation; Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Takeda Oncology.

Image: Copyright©2018 DNA Illustrations. All Rights Reserved
Faculty Presenter

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 disclosed that he has received consulting fees from Amgen, Celgene, Johnson & Johnson, and Takeda.
Patient Case Example

- A 55-year-old woman presented with bone pain and a whole-body low-dose CT scan showed multiple lytic lesions

- Additional testing revealed:
  - SPEP plus IFE revealed IgAk of 4.6 g/dL
  - Hemoglobin of 10.4 g/dL; WBC and platelets normal
  - Calcium and creatinine normal
  - Bone marrow shows 41% plasma cells
  - FISH testing shows trisomies of 3, 5, 9 and 15
  - Serum free light chain ratio (sFLC: involved/uninvolved) is 157
What treatment would you recommend for this patient?

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd)</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd)</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd)</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd)</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd)</td>
</tr>
</tbody>
</table>
Frontline Treatment of Myeloma

Newly Diagnosed MM*

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

Transplant Candidate
- VRd § x 3-4 cycles
- AutoSCT
  Maintenance
  (Len for std risk; Bortez for high risk)

VRd x 4 cycles Maintenance
Delayed ASCT

*Based on CALGB 100104, S0777, IFM-DFCI, CTN 0702 HOVON
§VTd/VCd if VRd not available

Rajkumar SV. 2016.
Induction Regimens for Patients Eligible for ASCT

![Graph showing response rates for different induction regimens. The regimens include VCD and VTd, with response rates indicated for both OR (OR) and ≥VGPR (≥VGPR). The graph compares various regimens such as VAD, Dex, CTD, Thal-Dex, VCD, Len-Dex, VTD, VRDC, RVD, and CRd.]
Treatment-naive MM without intent for immediate ASCT* (N = 525)

Stratifications: ISS; intent to transplant at progression

VRd†: Bortezomib Lenalidomide Dexamethasone (n = 264)
Eight 21-day cycles

Rd

Rd: Lenalidomide Dexamethasone (n = 261)
Six 28-day cycles

Len: 25 mg PO Until progression

Primary endpoint: PFS

*All patients received aspirin (325 mg/d). †Patients received HSV prophylaxis.
‡High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.

### SWOG 0777 Trial

#### Updated Response Results*

<table>
<thead>
<tr>
<th></th>
<th>VRd (n = 215)</th>
<th>Rd (n = 207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>24.2% (52)</td>
<td>12.1% (25)</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>50.7% (109)</td>
<td>41.1% (85)</td>
</tr>
<tr>
<td><strong>VGPR or better</strong></td>
<td><strong>74.9%</strong></td>
<td><strong>53.2%</strong></td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>15.3% (33)</td>
<td>25.6% (53)</td>
</tr>
<tr>
<td><strong>Overall Response Rate (ORR)</strong></td>
<td><strong>90.2% (194)</strong></td>
<td><strong>78.8% (163)</strong></td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>7.0% (15)</td>
<td>16.4% (34)</td>
</tr>
<tr>
<td>PD or death</td>
<td>2.8% (6)</td>
<td>4.8% (10)</td>
</tr>
</tbody>
</table>

*Both SWOG and IRC stratified Cochran-Mantel-Haenszel analyses indicated improved responses with RVd (odds ratio: 0.528, \( P = .006 \) [ITT]; odds ratio: 0.38, \( P = .001 \) [sensitivity analysis])

**Both SWOG and IRC assessments**

SWOG 0777: Progression-Free Survival

**CURRENT ELIGIBILITY (N = 460) – CURRENT DATA**

- **PFS**
  - 
  - Median in Months
    - **Rd**: 185 / 225, 29 (24, 37)
    - **VRd**: 167 / 235, 41 (33, 51)
  - *P-value = 0.003*

SWOG 0777: Overall Survival

CURRENT ELIGIBILITY (N = 460) – CURRENT DATA

VRd: 55% OS at 7 years

*P-value = 0.0114

Months from Registration

Deaths / N in Months
- Rd: 125 / 225, Median: 69 (59, 88)
- VRd: 102 / 235, NR

NR102 / 235 VRd

SWOG 0777: OS Landmarked at 12 Months (N = 357)

### Multivariate COX Proportional Hazards Model

**VRd Irrespective of Age**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n/N (%)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVd arm</td>
<td>235/460 (51%)</td>
<td>HR (0.77 (0.62, 0.95), 0.013</td>
<td>HR (0.75 (0.58, 0.98), 0.033)</td>
</tr>
<tr>
<td>ISS Stage III</td>
<td>155/460 (34%)</td>
<td>1.34 (1.01, 1.77), 0.041</td>
<td>1.98 (1.38, 2.86), &lt;.001</td>
</tr>
<tr>
<td>ISS Stage II</td>
<td>179/460 (39%)</td>
<td>1.12 (0.86, 1.47), 0.398</td>
<td>1.36 (0.95, 1.97), 0.096</td>
</tr>
<tr>
<td>Intent to Transplant</td>
<td>315/460 (68%)</td>
<td>0.95 (0.74, 1.23), 0.714</td>
<td>0.73 (0.54, 0.99), 0.043</td>
</tr>
<tr>
<td>Age &gt;= 65 yr</td>
<td>197/460 (43%)</td>
<td><strong>1.27 (1.00, 1.61), 0.048</strong></td>
<td><strong>1.63 (1.21, 2.19), 0.001</strong></td>
</tr>
</tbody>
</table>

HR- Hazard Ratio, 95% CI- 95% Confidence Interval, P-value from Score Chi-Square Test in Cox Regression
In 2018/2019:

Achievement of MRD undetected status at $10^{-6}$ is the goal of therapy.
True value of CR comes from the MRD status

**MRD- vs CR:** $P < .001$

- **CR vs nCR:** $P = .616$
- **nCR vs PR:** $P = .962$
- **PR vs <PR:** $P < .001$

**CR MRD negative**

- **MRD- vs CR:** $P < .001$
- **CR vs nCR:** $P = .594$
- **nCR vs PR:** $P = .912$
- **PR vs <PR:** $P = .024$

MRD approved by FDA and EMA as surrogate endpoint for myeloma

Trials included:
- IFM 2009
- EMN/Hovon
- MM05 [Heidelberg]
- STAMINA
- MRC
- Clarion
- CASTOR/POLLUX
- C16010
- IXA maintenance: C16019

FDA meeting December 11th, 2018
Patient Case Example

- A **76-year-old woman** presented with bone pain and a whole-body low-dose CT scan showed multiple lytic lesions.

- Additional testing revealed:
  - SPEP plus IFE revealed IgAk: 4.6 g/dL
  - Hemoglobin: 10.4 g/dL; WBC and platelets normal
  - Calcium and creatinine normal
  - Bone marrow shows 41% plasma cells
  - FISH testing shows trisomies of 3, 5, 9 and 15
  - Serum free light chain ratio (sFLC: involved/uninvolved) is 157
What treatment would you recommend for this patient?

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd), full dose or “lite”</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd), full dose or “lite”</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd), full dose or “lite”</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd), full dose or “lite”</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Daratumumab/lenalidomide/dexamethasone</td>
</tr>
</tbody>
</table>
Non-Transplant Candidate: Off-Study

- **t(11;14), t(6;14), Trisomies**
  - VRd for ~12 months;
  - If frail: Rd*
  - Rd for at least 1 year*, §

- **t(4;14), t(14;16), t(14;20), del(17p)**
  - VRd for ~12 months
  - Bortezomib-based maintenance until progression¶

---

*In patients treated initially with Rd, continuing treatment until progression is an options for patients responding well with low toxicities

§ Dex is usually discontinued after first year

¶Duration based on tolerance; consider risks and benefits for treatment beyond 3 years

---

**ALCYONE Study Design**

**VMP × 9 cycles (n = 356)**
- **Bortezomib**: 1.3 mg/m² SC  
  - Cycle 1: twice weekly  
  - Cycles 2-9: once weekly  
- **Melphalan**: 9 mg/m² PO on Days 1-4  
- **Prednisone**: 60 mg/m² PO on Days 1-4

**D-VMP × 9 cycles (n = 350)**
- **Daratumumab**: 10 mg/kg IV  
  - Cycle 1: once weekly  
  - Cycles 2-9: every 3 weeks  
- **Same VMP schedule**

**D Cycles 10+**
- **16 mg/kg IV**  
  - Every 4 weeks: until PD

**Key eligibility criteria:**
- Transplant-ineligible NDMM  
- ECOG 0-2  
- Creatinine clearance ≥40 mL/min  
- No peripheral neuropathy grade ≥2

**Stratification factors**
- ISS (I vs II vs III)  
- Region (EU vs other)  
- Age (≤75 vs ≥75 years)

**Primary endpoint:**
- PFS

**Secondary endpoints:**
- ORR  
- ≥VGPR rate  
- ≥CR rate  
- MRD (NGS; 10⁻⁶)  
- OS  
- Safety

**Follow-up for PD and survival**

**Statistical analyses**
- 360 PFS events: 85% power for 8-month PFS improvement  
- Interim analysis: ~216 PFS events

Mateos. NEJM. 2018; 378:518.
Efficacy: PFS

HR, 0.50
(95% CI, 0.38-0.65; P < 0.0001)

Median follow-up: 16.5 months
(range: 0.1-28.1)

Consistent PFS treatment benefit across subgroups

50% reduction in the risk of progression or death in patients receiving D-VMP

Mateos. NEJM. 2018; 378:518.
Efficacy: ORR and MRD (NGS; 10^{-5} Threshold)

VMP (n = 356) | D-VMP (n = 350)
---|---
PR | 24 | 20
VGPR | 25 | 29
CR | 7 | 18
sCR | 17 | 25

**ORR**
- VMP: 74%
- D-VMP: 91%

**MRD-negativity rate**
- VMP: 22%
- D-VMP: 6%

Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP
>3-fold higher MRD-negativity rate with D-VMP

Mateos. NEJM. 2018; 378:518.
Updates at ASH 2018

• LBA-2 Phase 3 dara/len/dex (dara Rd) versus len/dex (Rd)
  ➢ NDMM not eligible for transplant
Patient Case Example

- A 55-year-old woman presented with bone pain and a whole-body low-dose CT scan showed multiple lytic lesions.

- Additional testing revealed:
  - SPEP plus IFE revealed IgAk: 4.6 g/dL
  - Hemoglobin: 10.4 g/dL; WBC and platelets normal
  - Calcium and creatinine normal
  - Bone marrow shows 41% plasma cells
  - **FISH testing 1q+, 17p- and t(14;16)**
  - Serum free light chain ratio (SFLC: involved/uninvolved) is 157
What treatment would you recommend for this patient?

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Carfilzomib/lenalidomide/dexamethasone (KRd)</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>Carfilzomib/lenalidomide/dexamethasone (KRd)</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone (VRd)</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>Carfilzomib/lenalidomide/dexamethasone (KRd)</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Carfilzomib/lenalidomide/dexamethasone (KRd)</td>
</tr>
</tbody>
</table>
Controversies in 2018/2019

**Triplets:**
- KRd/KCd/KTd
- Dara-Rd or Vd or Cyd or Td
- IxaRd/IxaCyD/IxaTd (also combos with elotuzumab or pomalidomide if feasible)

**Four-drug combos:**
- Dara Rd + K or Ixa triplets
- Globally, Dara + VRd/VTd/VCd or VMP
Only 6/225 (3%) Relapses With VRd + ASCT (Spanish)

<table>
<thead>
<tr>
<th>Patient</th>
<th>359</th>
<th>454</th>
<th>502</th>
<th>635</th>
<th>751</th>
<th>767</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>III</td>
<td>III</td>
<td>I</td>
<td>III</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>FISH</td>
<td>1q+(59%)</td>
<td>del17p(22%)</td>
<td>1q+(50%) &amp; 1p-(61%)</td>
<td>1q+(85%) &amp; 1p-(89%)</td>
<td>NE</td>
<td>-</td>
</tr>
<tr>
<td>Bone-related plasmacytomas</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NE</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-protein</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>BMPCs (%)</td>
<td>4</td>
<td>3</td>
<td>46</td>
<td>1</td>
<td>58</td>
<td>4</td>
</tr>
<tr>
<td>Clonal PCs (%)</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Bone-related plasmacytomas</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NE</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Note: “Double hit” myeloma
- Double loss/mutation of p53 [17p-]
- ≥ 4 copies 1q21 [CKS1B]
Subclonal Mutational Patterns for 1q+

Single-cell exomes in an index case of amp1q21 multiple myeloma reveal more diverse mutanomes than the whole population

- RAS genes most frequently “co-mutated”
  - NRAS 19%
  - KRAS 16%
- 21 variant subclones
- 5 driver genes
  - ANK 3: ANKRIN membrane protein
  - AXIN 1: Wnt/β-catenin signaling
  - BRCA2: DNA repair
  - MAP4K3: cell signaling/c-Jun
  - Tripio: stat3 interacting

Increasing subclonal heterogeneity strongly supports early intervention

Pillars of Myeloma Therapy

- **Proteasome Inhibitors**
  - Bortezomib
  - Carfilzomib
  - Ixazomib

- **Immunomodulatory**
  - Thalidomide
  - Lenalidomide
  - Pomalidomide

- **Novel Immune Drugs**
  - Steroids
  - Elotuzumab

- **Monoclonal Antibodies**
  - Daratumumab
  - Elotuzumab
  - Isatuximab

- **Alkylators**
  - Melphalan, Cyclophosphamide

- **Other Conventional Chemo**
  - Bendamustine, DPACE...

- **Venetoclax**

- **Selinexor**

- **CAR T Cell Therapy?**
New Agents in Frontline Setting

- Daratumumab (or isatuximab): Add to create 4-drug combo?
- Venetoclax (or Mcl-1 inhibitions): Add if t(11;14) present?
- CAR T or BiTEs: Consider adding early in high risk and/or with suboptimal response?
PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels

- mPFS = 2.7 mo
- mPFS = 11.8 mo

Can CAR T Therapy Be Introduced Early?

- Can consider harvesting T-cells early!

- Potential of great efficiency **BUT** concerns about both short term and long-term toxicities.
Need New Response Criteria to Encompass Very Rapid Responses

• MRD assessment at 1, 3, 6 and 12 months

• Consider adding mass spec for M-component monitoring

• Define “sustained response” as endpoint
The Future of Myeloma Therapy

- **MGUS**
  - Low risk MGUS

- **HR SMM**
  - Low risk SMM
  - New HR SMM
  - 2/20/20
  - MDE

- **MM**
  - Ultra high risk
  - CRAB

- Monitor
- Treat as MM
Future of Myeloma Therapy in 2019 and Beyond

- **MGUS**
  - Low risk MGUS

- **SMM**
  - Low risk SMM
  - New HR SMM
  - 2/20/20

- **MM**
  - Standard or high risk
  - Ultra HR SMM
  - MM

- **Treat as MM**
  - Monitor
  - MDE
  - CRAB
Go Online for More Educational Programs on Myeloma!

**On-demand Webcast** of this symposium, including expert faculty commentary (IMF link below)

**Downloadable slides** from this symposium (IMF link below)

**Interactive Decision Support Tool** for myeloma, with personalized expert recommendations for your patients with myeloma

**Online programs** on caring for your patients with myeloma


[clinicaloptions.com/MyelomaTool](clinicaloptions.com/MyelomaTool)

[clinicaloptions.com/oncology/topics/Multiple-Myeloma](clinicaloptions.com/oncology/topics/Multiple-Myeloma)