Approaches To Achieve the Best Possible Outcomes in Myeloma

Friday, December 6, 2019
1:00 PM – 4:00 PM
Orlando, Florida

Supported by educational grants from Celgene Corporation, Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, Karyopharm Therapeutics Inc., Oncopeptides, Takeda Oncology, and The Binding Site.

Friday Satellite Symposium preceding the 61st ASH Annual Meeting & Exposition.
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.
Shaji Kumar, MD, has disclosed that he has received consulting fees paid to his institution from AbbVie, Amgen, Celgene, Genentech, Janssen, Kite, MedImmune, Merck, and Takeda and funds for research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Kite, MedImmune, Merck, Novartis, Roche/Genentech, Sanofi, and Takeda.
Faculty

**Thomas G. Martin, MD**  
*Clinical Professor of Medicine, Associate Director, Myeloma Program*  
University of California, San Francisco Medical Center  
San Francisco, California

**Thomas G. Martin, MD** has disclosed that he has received consulting fees from Legend Biotech and funds for research support from Amgen, Johnson & Johnson – Janssen, Sanofi, and Seattle Genetics.
Faculty

Philippe Moreau, MD
*Professor of Clinical Hematology*
*Head, Hematology Department*
University Hospital Hôtel-Dieu
Nantes, France

*Philippe Moreau, MD,* has disclosed that he has received consulting fees from AbbVie, Amgen, Celgene, Janssen, and Takeda.
Faculty

S. Vincent Rajkumar, MD
Edward W. and Betty Knight Scripps Professor of Medicine
Mayo Clinic
Rochester, Minnesota

S. Vincent Rajkumar, MD, has no real or apparent conflicts of interest to disclose.
Faculty

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

Jesús F. San-Miguel, MD, PhD, has disclosed that he has received consulting fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Merck Sharp & Dohme, Novartis, Roche, Sanofi, and Takeda.
Learning Objectives

At the conclusion of this activity, participants should be able to:

- Initiate treatment for appropriate patients based on an accurate diagnosis of monoclonal gammopathy of undetermined significance, smoldering MM, or active MM
- Create individualized treatment strategies for patients with newly diagnosed MM through consideration of the available clinical data as well as risk assessment, age, comorbidities, and patient preferences
- Select safe and effective maintenance therapy for patients with MM based on risk and response to induction therapy
- Evaluate the efficacy and safety of combination regimens to individualize therapeutic strategies for patients with MM at first relapse
- Plan appropriate treatment strategies using all available agents and classes to provide efficacious combination therapies to heavily pretreated patients with relapsed/refractory MM
- Employ novel agents and clinical trial participation as part of clinical care strategies for MM
Agenda

- Diagnosis and Risk Stratification of Plasma Cell Disorders - Jesús F. San-Miguel, MD, PhD
- Evolution of Upfront Therapy for the Transplantation-Ineligible Patient - Shaji Kumar, MD
- Upfront Therapy for the ASCT-Eligible Patient: Advances in Induction, ASCT, Consolidation, and Maintenance Therapy - Philippe Moreau, MD
- The Current Therapeutic Landscape for Relapsed or Refractory MM: Which Combinations to Use and When? - S. Vincent Rajkumar, MD
- Future Directions: A New Era of Promising Treatments for MM - Thomas G. Martin, MD
- Proposed 2020 treatment algorithms for MM
Case Discussion 2—Evolution of Upfront Therapy for the Transplantation-Ineligible Patient

Shaji Kumar, MD
Department of Hematology
Mayo Clinic
Rochester, Minnesota
Shaji Kumar, MD
Department of Hematology
Mayo Clinic
Rochester, Minnesota

Shaji Kumar, MD, has disclosed that he has received consulting fees paid to his institution from AbbVie, Amgen, Celgene, Genentech, Janssen, Kite, MedImmune, Merck, and Takeda and funds for research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Kite, MedImmune, Merck, Novartis, Roche/Genentech, Sanofi, and Takeda.
Patient Case Example

- A 75-year-old male presented with increasing back pain that was associated with radiculopathy involving the right lower extremity
- MRI showed multiple enhancing destructive lesions in the lumbar spine, sacrum, pelvis, right iliac bone, destructive lesion in L1 vertebra and L3 vertebra
- Initial lab evaluation showed elevated total protein at 10, and creatinine of 1.4
- Additional workup showed:
  - Hemoglobin: 12.0 g/dL
  - Calcium: normal
  - Serum M-spike: 3.2 g/dL, IgG kappa
  - IgG: 3350 mg/dL
  - FLC: kappa 655 mg/L, lambda 4.3 mg/L
  - Bone marrow plasma cells: 60%
  - β₂-microglobulin: 6.9 µg/mL
  - Albumin: 3.6 g/dL
  - Plasma cell FISH: trisomy 7, 11, 14
  - Conventional cytogenetics: normal
In your current clinical practice, which of the following would you recommend for initial therapy?

<table>
<thead>
<tr>
<th>Expert Recommendations</th>
<th>Initial Therapy Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>Bortezomib/lenalidomide/dexamethasone</td>
</tr>
</tbody>
</table>
| Thomas G. Martin, MD    | Bortezomib/lenalidomide/dexamethasone  
                          | Daratumumab/lenalidomide/dexamethasone *(once SQ dara available)* |
| Philippe Moreau, MD     | Lenalidomide/dexamethasone |
| S. Vincent Rajkumar, MD | Bortezomib/lenalidomide/dexamethasone |
| Jesus San-Miguel, MD    | Daratumumab/bortezomib/melphalan/prednisone *(already approved)*  
                          | Daratumumab/lenalidomide/dexamethasone *(not yet approved)* |
Evolution of Upfront Therapy for the ASCT-Ineligible Patient

Shaji Kumar, M.D.
Professor of Medicine
Chair, Myeloma, Amyloid, Dysproteinemia Group
Mayo Clinic

Scottsdale, Arizona  Rochester, Minnesota  Jacksonville, Florida
Myeloma Treatment Paradigm

SCT Eligible

SCT Ineligible

Diagnosis & Risk Stratification

Induction

Consolidation (ASCT)

Maintenance

Induction Followed by Continuous Therapy

Tumor Burden

Who are these patients?
Transplant Eligibility...Who? When?

• Has been primarily based on age...patients included in the initial trials
  – Presence of comorbidities...ability to tolerate the procedure
  – Functional status...frailty
  – Access to healthcare
  – Increasingly patient choice as more options arrive

• Decision made at time of diagnosis → decision regarding initial Rx
  – Less of an issue now as treatment approaches converge
Why Is Age an Important Issue?

• Comorbidities
  – Hypertension, ischemic heart disease, diabetes
  – Renal insufficiency
  – Osteoporosis
  – Psychological issues

• Frailty

• Altered drug metabolism

• Limited social support, financial issues

• Limited independence/mobility
The Start: Melphalan + Prednisone

27 randomized trials

- Allocated CCT (% ± SD)
- Allocated MP (% ± SD)

Can we make MP better?
Do we need melphalan?
How long should we treat?
CAN WE IMPROVE MP?
## MP vs MPT

<table>
<thead>
<tr>
<th></th>
<th>GIMEMA&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>IFM 99-06&lt;sup&gt;3&lt;/sup&gt;</th>
<th>IFM 01-01&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Nordic&lt;sup&gt;5&lt;/sup&gt;</th>
<th>HOVON&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP</td>
<td>15</td>
<td>18</td>
<td>19</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>MPT</td>
<td>22</td>
<td>28</td>
<td>24</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>P value</td>
<td>0.0004</td>
<td>&lt; 0.0001</td>
<td>0.001</td>
<td>NS</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td><strong>Median OS, months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP</td>
<td>48</td>
<td>33</td>
<td>29</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>MPT</td>
<td>45</td>
<td>52</td>
<td>44</td>
<td>29</td>
<td>40</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>0.0006</td>
<td>0.028</td>
<td>NS</td>
<td>0.05</td>
</tr>
</tbody>
</table>

†Significant.

In 4 of 5 studies, MPT was superior to MP in terms of PFS

In 2 of 5 studies, MPT was superior to MP in terms of OS

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VISTA Trial: MPV vs MP

San Miguel et al. JCO 2013;31:448-455
Key eligibility criteria:
- ASCT-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)

VMP × 9 cycles (n = 356)
Bortezomib: 1.3 mg/m² SC
Cycle 1: twice weekly on Wk 1, 2, 4, and 5
Cycles 2-9: once weekly on Wk 1, 2, 4, and 5
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: 16 mg/kg IV
Cycle 1: once weekly
Cycles 2-9: every 3 weeks
Same VMP schedule

Follow-up for PD and survival

Primary endpoint:
- PFS

Secondary endpoints:
- ORR
- ≥VGPR rate
- ≥CR rate
- MRD (NGS; 10⁻⁵)
- OS
- Safety

Statistical analyses
- 360 PFS events: 85% power for 27.6% lower risk of disease progression or death
- Interim analysis: ~231 PFS events
ALCYONE: Dara-VMP vs VMP

**Table**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Daratumumab Group (N=350)</th>
<th>Control Group (N=356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with response</td>
<td>318</td>
<td>263</td>
</tr>
<tr>
<td>Rate — % (95% CI)</td>
<td>90.9 (87.3–93.7)</td>
<td>73.9 (69.0–78.4)</td>
</tr>
<tr>
<td>Best overall response — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response or better</td>
<td>149 (42.6)</td>
<td>87 (24.4)</td>
</tr>
<tr>
<td>Stringent complete response‡</td>
<td>63 (18.0)</td>
<td>25 (7.0)</td>
</tr>
<tr>
<td>Complete response</td>
<td>86 (24.6)</td>
<td>62 (17.4)</td>
</tr>
<tr>
<td>Very good partial response or better</td>
<td>249 (71.1)</td>
<td>177 (49.7)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>100 (28.6)</td>
<td>90 (25.3)</td>
</tr>
<tr>
<td>Partial response</td>
<td>69 (19.7)</td>
<td>86 (24.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>20 (5.7)</td>
<td>76 (21.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Response could not be evaluated</td>
<td>12 (3.4)</td>
<td>15 (4.2)</td>
</tr>
<tr>
<td>Negative status for minimal residual disease — no. (%)‡</td>
<td>78 (22.3)</td>
<td>22 (6.2)</td>
</tr>
</tbody>
</table>

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859 Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Patients with Transplant–Ineligible Newly Diagnosed Multiple Myeloma: Overall Survival in Alcyone

Program: Oral and Poster Abstracts
Type: Oral
Session: 653. Myeloma: Therapy, excluding Transplantation: Improving the Outcomes of Newly Diagnosed Multiple Myeloma

Hematology Disease Topics & Pathways:
Diseases, antibodies, Adult, Biological, multiple myeloma, Therapies, Study Population, Plasma Cell Disorders, Lymphoid Malignancies

Monday, December 9, 2019: 4:30 PM
Hall E2, Level 2 (Orange County Convention Center)

Maria–Victoria Mateos¹, Michele Cavo²*, Joan Bladé, MD, PhD³, Meletios A. Dimopoulos, MD⁴, Kenshi Suzuki, MD, PhD⁵, Andrzej Jakubowiak, MD, PhD⁶, Stefan Knop⁷*, Chantal Doyen, MD⁸, Paulo Lucio, MD, PhD⁹*, Zsolt Nagy, MD, PhD¹⁰*, Ludek Pour, MD¹¹*, Mark Cook, MBChB, PhD¹², Sebastian Grosicki, MD, PhD¹³, Andre H Crepaldi, MD¹⁴*, Anna Marina Liberati¹⁵, Philip Campbell, MBBS, FRACP, FRCPA¹⁶, Tatiana Shelekhova¹⁷*, Sung–Soo Yoon, MD, PhD¹⁸, Genadi Iosava, MD¹⁹*, Tomoaki Fujisaki, MD, PhD²⁰*, Mantta Garg, MD, FRCP, FRCPath²¹*, Maria Krevvata, PhD²²*, Jianping Wang²³*, Anupa Kudva, MD²⁴*, Jon Ukropec, PhD²⁴, Susan Wroblewski, PhD²⁵*, Rachel Kobos, MD²⁶ and Jesus San–Miguel, MD, PhD²⁷
DO WE NEED MELPHALAN?
RD (Continuous or 18 Cycles) vs MPT

S0777: VRd vs Rd

<table>
<thead>
<tr>
<th>Events</th>
<th>Median, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRd</td>
<td>137/242, 43 (39–52)</td>
</tr>
<tr>
<td>Rd</td>
<td>166/229, 30 (25–39)</td>
</tr>
</tbody>
</table>

One-sided p = 0.0018 (two-sided p = 0.0037)

<table>
<thead>
<tr>
<th>Deaths</th>
<th>Median, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRd</td>
<td>76/242, 75 (65–NR)</td>
</tr>
<tr>
<td>Rd</td>
<td>100/229, 64 (56–NR)</td>
</tr>
</tbody>
</table>

Two-sided p = 0.0250

RVD Lite

Induction (cycles 1–9)
Repeat q35 days × 9 cycles

- Lenalidomide 15 mg po days 1–21
- Bortezomib 1·3 mg/m² sc* days 1, 8, 15, 22
- Dexamethasone 20 mg po days 1, 2, 8, 9, 15, 16, 22, 23 (patients ≤75 years)
- Dexamethasone 20 mg po days 1, 8, 15, 22 (patients >75 years)

Consolidation (cycles 10–15)
Repeat q28 days × 6 cycles

- Lenalidomide 15 mg po days 1–21 (or last tolerated dose as of cycle 9)
- Bortezomib 1·3 mg/m² sc on days 1, 15 (or last tolerated dose as of cycle 9)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total = 50</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stringent complete response</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Complete response</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Partial response</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Minimal response</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Not evaluable*</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>43</td>
<td>86</td>
</tr>
<tr>
<td>Very good partial response or better</td>
<td>33</td>
<td>66</td>
</tr>
</tbody>
</table>

* The first 10 patients received bortezomib intravenously for cycle 1 only followed by subcutaneous administration. Subsequent patients received bortezomib subcutaneously.

MAIA: Daratumumab Len-Dex vs Len Dex

Key eligibility criteria:
- Transplant-ineligible NDMM
- ECOG 0-2
- Creatinine clearance ≥30 mL/min

1:1 Randomization

D-Rd (n = 368)
- Daratumumab (16 mg/kg IV) Cycles 1-2: QW, Cycles 3-6: Q2W, Cycles 7+: Q4W until PD
- Lenalidomide: 25 mg PO daily on Days 1-21 until PD
- Dexamethasone: 40 mg PO or IV weekly until PD

Primary endpoint:
- PFS

Key secondary endpoints:
- ≥CR rate
- ≥VGPR rate
- MRD-negative rate (NGS; 10^-5)
- ORR
- OS
- Safety

Rd (n = 369)
- Lenalidomide: 25 mg PO daily on Days 1-21 until PD
- Dexamethasone: 40 mg PO or IV weekly until PD

Cycle: 28 days
- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)

MAIA: Daratumumab+Rd vs Rd


Progression-free Survival (%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Daratumumab Group (N = 368)</th>
<th>Control Group (N = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response — no. (%) [95% CI]</td>
<td>342 (92.9 [89.8–95.3])</td>
<td>300 (81.3 [76.9–85.1])</td>
</tr>
<tr>
<td>Best overall response — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response or better</td>
<td>175 (47.6)</td>
<td>92 (24.9)</td>
</tr>
<tr>
<td>Stringent complete response;‡</td>
<td>112 (30.4)</td>
<td>46 (12.5)</td>
</tr>
<tr>
<td>Complete response</td>
<td>63 (17.1)</td>
<td>46 (12.5)</td>
</tr>
<tr>
<td>Very good partial response or better</td>
<td>292 (79.3)</td>
<td>196 (53.1)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>117 (31.8)</td>
<td>104 (28.2)</td>
</tr>
<tr>
<td>Partial response</td>
<td>50 (13.6)</td>
<td>104 (28.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11 (3.0)</td>
<td>56 (15.2)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Response could not be evaluated</td>
<td>14 (3.8)</td>
<td>13 (3.5)</td>
</tr>
<tr>
<td>Negative status for minimal residual disease — no. (%)‡</td>
<td>89 (24.2)</td>
<td>27 (7.3)</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death, 0.56 (95% CI, 0.43–0.73) P<0.001

Months since Randomization
Continuous Therapy vs Fixed Duration

**Progression-Free Survival (probability)**
- CT: 417, 219, 9
- FDT: 410, 308, 13

HR, 0.47; 95% CI, 0.40 to 0.56; P < .001

**Overall Survival (probability)**
- CT: 417, 111
- FDT: 410, 143

HR, 0.69; 95% CI, 0.54 to 0.88; P = .003
Shorter Duration of Dex

Primary endpoint: Event-free Survival (EFS)

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

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd-R</td>
<td>101</td>
<td>9.3 months</td>
</tr>
<tr>
<td>Rd</td>
<td>98</td>
<td>6.6 months</td>
</tr>
</tbody>
</table>

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

• Ongoing debate
• Improves PFS, effect on OS not consistent
• Increased toxicity, especially long term
• Quality-of-life impact
• Cost of care
Conclusions

• Melphalan not necessary as part of initial therapy
• VRd or Dara-Rd are preferred regimens for initial therapy
• VRd for high-risk patients
• Rd in elderly, frail patients
• Continuous therapy until progression, if well tolerated, is reasonable
• Dose modifications for age and frailty important
• Early discontinuation of dexamethasone important
• Careful monitoring for toxicity important
THANK YOU

kumar.shaji@mayo.edu