New Strategies for Multiple Myeloma Care: Next Steps for the Future

Friday, November 30, 2018
San Diego, California

Friday Satellite Symposium preceding the 60th ASH Annual Meeting & Exposition.

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.

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Chairman, International Myeloma Foundation  
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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.
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S. Vincent Rajkumar, MD, has no real or apparent conflicts of interest to disclose.
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Shaji Kumar, MD, has disclosed that he has consulted with payment to Mayo Clinic from AbbVie, Amgen, Celgene, Dr. Reddy’s Laboratory, Genentech, Janssen, Kite, MedImmune, Merck, Oncopeptides, and Takeda and funds for research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Kite, MedImmune, Merck, Novartis, Roche/Genentech, Sanofi, and Takeda.
Program Faculty

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

Jesús F. San-Miguel, MD, PhD
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Pamplona, Spain

Jesús F. San-Miguel, MD, PhD, has disclosed that he has received consulting fees from Amgen, Bristol-Myers Squibb, Celgene, Janssen, MSD, Novartis, Roche, Sanofi, and Takeda.
Symposium Format

Each topic discussion will include the following:

- Case presentation with interactive polling question(s) for the audience
- Presentation by faculty
- Panel discussion with expert recommendations
- Audience question and answer session
- Second audience vote on case question(s)
Agenda

- Risk stratification of plasma cell disorders
- Are we ready for personalized therapy in newly diagnosed MM?
- Considering the recent data on transplantation, consolidation, and maintenance after induction therapy
- Advances in the optimal choice of therapeutic strategies for patients with relapsed/refractory disease
- Proposed 2019 treatment algorithms for MM
Risk Stratification of Plasma Cell Disorders

Faculty Presenter:
S. Vincent Rajkumar, MD
Risk Stratification of Plasma Cell Disorders

S. Vincent Rajkumar
Professor of Medicine
Mayo Clinic

Scottsdale, Arizona  Rochester, Minnesota  Jacksonville, Florida
Disclosures

No conflicts to disclose
Patient Case Example

- A 54-year-old patient was found to have elevated monoclonal protein during work up for unexplained arthritis of 2 weeks’ duration
  - Arthritis has since resolved
  - M spike is 1.9 g/dL, IgG kappa

- Additional workup shows:
  - Serum free kappa is 5.0 mg/dL, serum free lambda is 1.0 mg/dL
  - CBC, calcium, creatinine are normal

- He has no additional symptoms
What would you recommend next for this patient?

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Bone marrow biopsy and bone imaging</td>
</tr>
<tr>
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</tr>
</tbody>
</table>
The patient undergoes bone marrow biopsy, which shows 8% plasma cells in bone marrow.

Bone imaging is negative.

He is watched annually for 3 years.

He now presents with an increase in M protein to 2.5 g/dL but has no symptoms:
- CBC, calcium, creatinine are normal.
- However, repeat bone marrow biopsy shows 25% plasma cells.
Which of the following are NOT consistent with high-risk smoldering myeloma?

<table>
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<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>3 focal lesions on MRI measuring 8-10 mm in size</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>3 focal lesions on MRI measuring 8-10 mm in size</td>
</tr>
<tr>
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<td>3 focal lesions on MRI measuring 8-10 mm in size</td>
</tr>
</tbody>
</table>
In a newly diagnosed patient with myeloma, which of the following indicates standard-risk disease?

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</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Trisomy 3, 5, 9, and 15</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
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<tr>
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<td>Jesús F. San-Miguel, MD, PhD</td>
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</tr>
</tbody>
</table>
Progression of MGUS to Myeloma

Primary Cytogenetic Abnormalities
- t(11;14)
- t(4;14)
- t(6;14)
- t(14;16)
- t(14;20)
- Trisomies

Secondary Cytogenetic Abnormalities
- 1q amp
- Del 17

Secondary Cytogenetic Abnormalities
- Myc translocations
- Del 17
- 1p del

Secondary Cytogenetic Abnormalities
- Relapsed Refractory MM
- Plasma Cell Leukemia
- Extra Medullary Disease

Trisomies/IgH Translocations
Establishment of the clone

Secondary Cytogenetic Abnormalities
Del(17p), Gain(1q)

Secondary Cytogenetic Abnormalities
Occur with progression

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

SV Vincent Rajkumar, Melatos A Dimopoulos, Antonio Palumbo, Jean-Blaise Ghiotto, Maria-Victoria Mateos, Shekili Kumar, Jerro Hillengass, Efstratios Konstantin, Paul Richardson, Ole Lindgren, Beatrice Poles, Angela Dispenza, Brendan Weis, Xavier Leleu, Sonya Zweegman, Sagol Lonial, Laura Rosini, Elena Zannagni, Sunil Jagannath, Orhan Sayar, Sigurdur V Kristinsson, Jo Cairns, Saad Z Usmeni, Juan José del puerto, Hans Erik Johnson, Marcel Bacsac, Michele Cavali, Heetnur Scharfe, Evangelos Tepos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

This International Myeloma Working Group consensus updates the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcemia, renal failure, anemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be
Revised IMWG Criteria for Myeloma

<table>
<thead>
<tr>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &lt; 10% BMPC <strong>AND</strong></td>
<td>• 10-60% BMPC <strong>OR</strong></td>
<td>• Clonal plasma cell disorder <strong>AND</strong></td>
</tr>
</tbody>
</table>
| • < 3 g/dL M protein | • ≥ 3 g/dL M protein | • 1 or more MDE
| • No MDE | • No MDE | • CRAB
| | | • ≥ 60% BMPC
| | | • ≥ 100 FLC ratio
| | | • > 1 MRI focal lesion

**MDE**= Myeloma Defining Events  
**CRAB**= Hypercalcemia, renal failure, anemia, or lytic bone lesions attributable to a clonal plasma cell disorder

MGUS
## Classification of MGUS

<table>
<thead>
<tr>
<th>Type of MGUS</th>
<th>Type of Progression</th>
<th>Risk of Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non IgM MGUS (IgG, IgA)</td>
<td>Myeloma, Plasmacytoma</td>
<td>1% per year</td>
</tr>
<tr>
<td>IgM MGUS</td>
<td>Waldenstrom Macroglobulinemia</td>
<td>1.5% per year</td>
</tr>
<tr>
<td>LC-MGUS</td>
<td>Light Chain Myeloma</td>
<td>Not known</td>
</tr>
</tbody>
</table>

All can progress to AL amyloidosis
Risk of Progression of MGUS

MGUS Risk Stratification: M spike size, M spike type, and FLC ratio

- All 3 factors abnormal
- Any 2 factors abnormal
- Any 1 factor abnormal
- Serum M-spike <1.5 gm/dL, IgG Subtype and normal FLC ratio

Workup of Suspected MGUS

Suspected MGUS

- Low risk (< 1.5 g/dL, IgG type, normal FLC ratio), or
- IgM < 1.5 g/dL, or
- Light chain MGUS with FLC ratio < 8

Uncomplicated*

Bone marrow biopsy and skeletal survey may be deferred

Presence of unexplained symptoms or laboratory features of concern

Bone marrow biopsy required; skeletal survey (low dose whole body CT or conventional radiographs) required in non-IgM patients

All other patients

*No unexplained symptoms or laboratory features concerning for serious plasma cell disorder.
Management of MGUS

All Patients with MGUS

Follow-up in 6 months

Stable

Possible progression

Risk stratification

Workup for lymphoplasmacytic malignancy

Low risk

Intermediate or high risk

No MGUS follow-up; usual medical care

Annual MGUS follow-up: CBC, calcium, creatinine, SPEP, FLC

No malignancy

Malignancy

Manage accordingly

Smoldering Multiple Myeloma

Robert A. Kyle, M.D., and Philip R. Greipp, M.D.

SMM vs MGUS

Smoldering Multiple Myeloma

High-Risk SMM

Low-risk SMM: 5%/yr risk of MM

25% per year risk of MM

MM

- >60% BMPC
- FLCr >100
- >1 MRI focal lesions
Len/Dex versus Observation in High Risk SMM: TTP

Freedom from Progression to Symptomatic Disease (%)

Hazard ratio for progression, 0.18
P<0.001

No. at Risk
Treatment group: 57, 57, 48, 38, 20, 14, 0
Observation group: 62, 49, 32, 21, 11, 3, 0

Len/Dex vs Observation in High-Risk SMM: OS

Hazard ratio for death, 0.31
P=0.03

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Treatment group</th>
<th>Observation group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>57</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>20</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>30</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>40</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>50</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

High-Risk SMM: Median TTP ~ 2 Years

≥ 10% PCs plus:

• SMM with M protein ≥ 3 g/dL

• Absence (< 5%) of normal PCs by immunophenotyping plus Immunoparesis

• Abnormal FLC ratio 8-100

• Del(17p), t(4;14), gain(1q21)

• IgA SMM

• Evolving pattern

• Increased circulating plasma cells

Mayo 20-2-20 Risk Stratification of SMM

BMPC > 20%, M protein > 2 g/dL, and FLC ratio (FLCr) > 20

2 or more (High Risk)

Any 1

None

Management of SMM

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 years)

Evolving SMM or many high-risk factors

Consider treat as myeloma

Low-Risk SMM
(~5% per year PD)

Clinical trials

Observation

SMM Trial Strategy

Conceptual/Regulatory
- Len v Obs
- Rd vs Obs
- Dara vs Obs

- Necessary trials

Strategic: Delay Progression
- DRd vs Rd
- KRd

- Survival benefit with early therapy

Strategic: ? Cure
- CESAR
- ASCENT

- ? Cure possible with early therapy
Multiple Myeloma
# Molecular Classification of Myeloma

<table>
<thead>
<tr>
<th>Trisomic MM</th>
<th>IgH Translocations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomies*</td>
<td>t(11;14) (CCND1)</td>
</tr>
<tr>
<td></td>
<td>t(6;14) (CCND3)</td>
</tr>
<tr>
<td></td>
<td>t(4;14) (FGFR3, MMSET)</td>
</tr>
<tr>
<td></td>
<td>t(14;16) (C-MAF)</td>
</tr>
<tr>
<td></td>
<td>t(14;20) (MAF-B)</td>
</tr>
</tbody>
</table>

*~10% have both trisomies and IgH translocations

The multiple myelomas – current concepts in cytogenetic classification and therapy

Shaji K. Kumar & S. Vincent Rajkumar

<table>
<thead>
<tr>
<th>Primary abnormalities</th>
<th>Secondary abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomies (~45%)</td>
<td>Monosomies</td>
</tr>
<tr>
<td>Odd-numbered chromosomes: 3, 5, 7, 9, 11, 15, 19, and 21</td>
<td>Chromosome 13</td>
</tr>
<tr>
<td>IgH translocations (~55%)</td>
<td>Chromosome 17</td>
</tr>
<tr>
<td>Translocations involving the IgH gene locus at 14q32</td>
<td>Chromosome 14</td>
</tr>
</tbody>
</table>

**Deletions**
- Chromosome 17p
- Chromosome 1p

**Amplification**
- Chromosome 1q gain or amplification

**Recurrent mutations**
- KRAS
- NRAS
- TP53
- DIS3
- FAM46C
- BRAF
- TRAF3
- ROBO1
- CYLD
- EGR1
- SP140
- FAT3
- CCND1

Cytogenetic Risk Stratification of Myeloma

- t(4;14) (FGFR3, MMSET)
- t(14;16) (C-MAF)
- t(14;20) (MAF-B)
- Trisomies*
- t(11;14) (CCND1)
- t(6;14) (CCND3)

Disease Aggressiveness

- del 17p, p53 mutations, gain 1q

- Double-Hit Myeloma = Any 2 high risk abnormalities
- Triple-Hit Myeloma = 3 or more high risk abnormalities
## Revised International Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Frequency (% of patients)</th>
<th>5-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serum albumin &gt;3.5</td>
<td>28%</td>
<td>82%</td>
</tr>
<tr>
<td>• Serum beta-2-microglobulin &lt;3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No high risk cytogenetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal LDH</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Neither stage I or III</td>
<td>62%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serum beta-2-microglobulin &gt;5.5 and</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>• High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated LDH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plasma Cell Leukemia
Plasma Cell Leukemia

PCL: ≥ 5% or more PCs on regular WBC differential

Summary

• New diagnostic criteria
• Molecular classification of MM
• Risk stratification systems for MGUS, SMM, MM are different
• New staging system for MM
Panel Discussion and Audience Q&A
Are We Ready for Personalized Therapy in Newly Diagnosed MM?

Faculty Presenter:
Brian G.M. Durie, MD
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

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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?

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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

**SWOG 0777 Trial**

**Treatment-naive MM without intent for immediate ASCT**

- **Stratifications:** ISS; intent to transplant at progression
- **R**
  - **VRd**: Bortezomib Lenalidomide Dexamethasone (n = 264)
    - Eight 21-day cycles
  - **Rd**: Lenalidomide Dexamethasone (n = 261)
    - Six 28-day cycles
  - **Rd**: 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.

# Updated Response Results*

<table>
<thead>
<tr>
<th>Response Category</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**

*Updated Response Results*

SWOG 0777: Progression-Free Survival

CURRENT ELIGIBILITY (N = 460) – CURRENT DATA

PFS

 Months from Registration

Events / N 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Deaths / N</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd</td>
<td>125 / 225</td>
<td>69 (59, 88)</td>
</tr>
<tr>
<td>VRd</td>
<td>102 / 235</td>
<td>NR</td>
</tr>
</tbody>
</table>

*P-value = 0.0114

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 HR (95% CI)</th>
<th>P-value</th>
<th>OS HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVd arm</td>
<td>235/460 (51%)</td>
<td>0.77 (0.62, 0.95)</td>
<td>0.013</td>
<td>0.75 (0.58, 0.98)</td>
<td>0.033</td>
</tr>
<tr>
<td>ISS Stage III</td>
<td>155/460 (34%)</td>
<td>1.34 (1.01, 1.77)</td>
<td>0.041</td>
<td>1.98 (1.38, 2.86)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ISS Stage II</td>
<td>179/460 (39%)</td>
<td>1.12 (0.86, 1.47)</td>
<td>0.398</td>
<td>1.36 (0.95, 1.97)</td>
<td>0.096</td>
</tr>
<tr>
<td>Intent to Transplant</td>
<td>315/460 (68%)</td>
<td>0.95 (0.74, 1.23)</td>
<td>0.714</td>
<td>0.73 (0.54, 0.99)</td>
<td>0.043</td>
</tr>
<tr>
<td><strong>Age &gt;= 65 yr</strong></td>
<td>197/460 (43%)</td>
<td><strong>1.27 (1.00, 1.61)</strong></td>
<td><strong>0.048</strong></td>
<td><strong>1.63 (1.21, 2.19)</strong></td>
<td><strong>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.
Concept to Influence Decisions

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: $P < .001$

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?

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Frontline Treatment of Myeloma

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: 16 mg/kg IV
  - Cycle 1: once weekly
  - Cycles 2-9: every 3 weeks
  - Same VMP schedule

Primary endpoint:
- PFS

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

Follow-up for PD and survival

1:1 Randomization (N = 706)

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

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

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

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

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)

**Diagram:**
- **VMP (n = 356)** vs. **D-VMP (n = 350)**
- **ORR**:
  - VMP: 74%
  - D-VMP: 91%
- **MRD-negativity rate**:
  - VMP: 6%
  - D-VMP: 22%

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

**Note:**
Mateos. NEJM. 2018; 378:518.
• 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
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Initial Treatment of Myeloma

Transplant Candidate: Off-Study

- t(11;14), t(6;14), Trisomies
  - Collect Stem Cells
  - AutoLOGous stem cell transplant (preferred)
  - Len maintenance for at least 2 years

- Del 17p
  - VRd x 4 cycles
  - Rd until progression

- t(4;14), t(14;16), t(14;20), Double or Triple Hit Myeloma
  - 4 cycles of VRd or KRd
  - Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
  - Carfilzomib or Bortezomib-based maintenance till progression

- t(4;14), t(14;16), t(14;20), Double or Triple Hit Myeloma
  - 4 cycles of KRd
  - Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
  - Carfilzomib or Bortezomib-based maintenance till progression

---

*If age >65 or >4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor
Duration based on tolerance; consider risks and benefits for treatment beyond 3 years
Continuing Rd for patients responding to Rd and with low toxicities

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>+</td>
<td>NE</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>
<tr>
<td>NE: not evaluated</td>
<td></td>
<td></td>
<td></td>
<td></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/βcatenin signaling
  - BRCA2: DNA repair
  - MAP4K3: cell signaling/c Jun
  - Tripio: stat3 interacting

Increasing subclonal heterogeneity strongly supports early intervention

Pillars of Myeloma Therapy

- Conventional Chemo (Bendamustine, DPACE...)
- Steroids
- Elotuzumab
- Doxorubicin, Panobinostat, Steroids
- Proteasome Inhibitors: Bortezomib, Carfilzomib, Ixazomib
- Immuno-modulatory: Thalidomide, Lenalidomide, Pomalidomide
- Alkylators: Melphalan, Cyclophosphamide
- Monoclonal Antibodies: Daratumumab, Elotuzumab, Isatuximab
- Novel Immune Drugs: Selinexor, Venetoclax
- 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 With BCMA (bb2121) CAR T

PFS at Inactive (50 \times 10^6) and Active (150–800 \times 10^6) Dose Levels

- 50 \times 10^6 \quad (n=3)
- 150–800 \times 10^6 \quad (n=18)

Events
- 3
- 10

mPFS (95\% CI), mo
- 2.7
- 11.8
  - (1.0–2.9)
  - (8.8–NE)

mPFS = 11.8 mo
mPFS = 2.7 mo

Patients at risk, n
- 50 \times 10^6
  - 3
  - 3
  - 2
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0
  - 0

- \geq 150 \times 10^6
  - 18
  - 18
  - 17
  - 17
  - 17
  - 17
  - 14
  - 14
  - 11
  - 11
  - 10
  - 6
  - 5
  - 5
  - 4
  - 3
  - 3
  - 2
  - 2
  - 0

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
  - High risk MGUS

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

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

- Monitor
- Treat as MM

[INTERNATIONAL MYELOMA FOUNDATION]
Panel Discussion and Audience Q&A
Considering the Recent Data on Transplantation, Consolidation, and Maintenance After Induction

*Faculty Presenters:*
Shaji Kumar, MD
Philippe Moreau, MD
Program Faculty

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

Shaji Kumar, MD, has disclosed that he has consulted with payment to Mayo Clinic from AbbVie, Amgen, Celgene, Dr. Reddy’s Laboratory, Genentech, Janssen, Kite, MedImmune, Merck, Oncopeptides, and Takeda and funds for research support from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Kite, MedImmune, Merck, Novartis, Roche-Genentech, Sanofi, and Takeda.
What’s next after induction?

The US Perspective
Patient Case Example

- A 53-year-old woman with no other health problems was diagnosed with myeloma when she presented with back pain and increasing fatigue.

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<th>Result</th>
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<td>Hemoglobin</td>
<td>10.8 g/dL</td>
</tr>
<tr>
<td>Serum Ca(^{2+})</td>
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</tr>
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<td>Serum creatinine</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum LDH</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum β(_{2})microglobulin</td>
<td>2.8 mg/dL</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>4.1 g/dL</td>
</tr>
</tbody>
</table>

- Serum protein electrophoresis: IgG\(\)K monoclonal protein of 3.2 g/dL
- 24-hour urine protein electrophoresis: 210 mg monoclonal protein, kappa light chain
Patient Case Example

- Whole-body low-dose CT showed multiple lytic lesions
- Bone marrow biopsy showed 40% plasma cell involvement, FISH showed no abnormality
- She was started on treatment with a combination of bortezomib, lenalidomide, and dexamethasone
- At the completion of 4 cycles of therapy:
  - Repeat bone marrow biopsy shows no MRD
  - Serum and urine immunofixation were both negative
What would you do next for this patient?

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<td>Above ULN</td>
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<td>Serum $\beta_2$microglobulin</td>
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Patient Case Example

- Whole-body low-dose CT showed multiple lytic lesions
- Bone marrow biopsy showed 40% plasma cell involvement, **FISH showed 17p deletion in > 50% of tumor cells**
- She was started on treatment with a combination of bortezomib, lenalidomide and dexamethasone
- At the completion of 4 cycles of therapy:
  - Repeat bone marrow biopsy shows no MRD
  - Serum and urine immunofixation were both negative
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Myeloma Treatment Paradigm

Induction followed by continuous therapy

GOAL
- Disease control and reversal of symptoms and signs
- Maximize disease control to provide most durable disease control, with eye on limiting long-term side effects

Tumor burden
Consolidation and Maintenance

• Stem cell transplantation (SCT): one or two?

• Post-transplantation consolidation?

• Post-transplantation maintenance?
When Do You Stop Induction Therapy?

Ideal Duration of Induction Prior to SCT?

- UK-based multicenter, open-label, parallel group, randomized controlled phase III trial

Induction 1
4 cycles if ASCT eligible;
6 cycles if ASCT ineligible

CRD
CTD

Max response*:
PR or MR

*Completed ≥ 4 cycles of IMiD-based induction.

Induction 2
Bortezomib
Cyclophosphamide
Dexamethasone
(n = 289)

No further induction therapy
(n = 294)

ASCT for eligible pts
(n = 367)

- Newly diagnosed MM pts (N = 583)

- Primary endpoints: PFS, OS
- Secondary endpoints: Improved response vs baseline, PI effect in high-risk pt group
Myeloma XI: Results

**Recommendation:** 4-6 cycles of induction and then transplant

**Median PFS, Mos (95% CI)**
- No CVD (n = 294): 20 (15-28) Mos
- CVD (n = 289): 30 (25-36) Mos

**HR:** 0.60 (95% CI: 0.48-0.75; log-rank \( P < .0001 \))

**3-Yr OS, % (95% CI)**
- No CVD (n = 294): 78.5 (72.3-84.6)
- CVD (n = 289): 77.3 (71.0-83.5)

**HR:** 0.97 (95% CI: 0.67-1.42; log-rank \( P = .8883 \))

Jackson. ASH 2016. Abstr 244.
Do We Still Need ASCT with Novel Drugs?

Hazard ratio for progression or death with high-dose melphalan, 0.44 (95% CI, 0.32–0.61); P<0.001

Hazard ratio for death with high-dose melphalan, 0.55 (95% CI, 0.32–0.93); P=0.02

Do We Still Need ASCT? IFM 2009

<table>
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<tr>
<td><strong>RVD 1</strong></td>
</tr>
<tr>
<td>Lenalidomide + Bortezomib + Dexamethasone</td>
</tr>
<tr>
<td><strong>Randomization (stratified on ISS and FISH)</strong></td>
</tr>
<tr>
<td>Arm A</td>
</tr>
<tr>
<td>RVD 2 and 3</td>
</tr>
<tr>
<td>PBSC Collection (cyclophosphamide and G-CSF)</td>
</tr>
<tr>
<td>RVD 4 to 8</td>
</tr>
<tr>
<td>Lenalidomide Maintenance 12 months (10-15 mg/day)</td>
</tr>
<tr>
<td>Arm B</td>
</tr>
<tr>
<td>RVD 2 and 3</td>
</tr>
<tr>
<td>PBSC Collection (cyclophosphamide and G-CSF)</td>
</tr>
<tr>
<td>ASCT HDM 200 mg/m²</td>
</tr>
<tr>
<td>RVD 4 and 5</td>
</tr>
<tr>
<td>Lenalidomide Maintenance 12 months (10-15 mg/day)</td>
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Attal. NEJM. 2017;376:1311.
# Deeper Responses With SCT

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<tr>
<th>Outcome</th>
<th>RVD-Alone Group (N = 350)</th>
<th>Transplantation Group (N = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response during the study, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>169 (48)</td>
<td>205 (59)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>101 (29)</td>
<td>102 (29)</td>
</tr>
<tr>
<td>Partial response</td>
<td>70 (20)</td>
<td>37 (11)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (3)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>169 (48)</td>
<td>205 (59)</td>
</tr>
<tr>
<td>Complete response or very good partial response, n (%)</td>
<td>270 (77)</td>
<td>307 (88)</td>
</tr>
<tr>
<td>Minimal residual disease not detected during study, n/total n with complete or very good partial response (%)</td>
<td>171/265 (65)</td>
<td>220/278 (79)</td>
</tr>
</tbody>
</table>

Attal. NEJM. 2017;376:1311.
Better PFS; Comparable OS

Recommendation: upfront SCT recommended, but a delayed approach is acceptable

Attal. NEJM. 2017;376:1311.
What Should Be Done Post ASCT?

• Consolidation with tandem ASCT?

• Non-transplant consolidation?

• Maintenance?
STaMINA Trial: BMT CTN 0702

N = 750 pts (250 in each arm)

Register and Randomize

MEL 200 mg/m² ASCT

Lenalidomide Maintenance **
N=257

VRD x 4*
N=254

Tandem ASCT
MEL 200mg/m²
Second ASCT

Lenalidomide Maintenance**
N=247

* Bortezomib 1.3 mg/m² days 1, 4, 8, 11
Lenalidomide 15 mg days 1-15
Dexamethasone 40 mg days 1, 8, 15
Every 21 days

** Lenalidomide x 3 years:
10 mg/d for 3 cycles, then 15 mg/d
Amendment in 2014 changed: lenalidomide maintenance until disease progression after report of CALGB 100104.
STaMINA Trial: Primary Endpoint—PFS

Recommendation: with VRd induction, no role for additional VRd consolidation

38-Month Estimate (95% CI)
- Auto/Auto: 56.5 (49.4-62.9)
- Auto/RVD: 56.7 (50.0-62.8)
- Auto/Maint: 52.2 (45.4-58.6)
Tandem ASCT: del(17p) ± t(4;14)

Kaplan-Meier survival estimates

Log rank test: 
\[ P = .0001 \]

HR: 0.22 (0.10-0.50) 
\[ P < .001 \]

Proportion Alive

EMN02: Single vs Tandem: High Risk Genetics

Recommendation: in high-risk patients, a discussion regarding tandem SCT is warranted

Lenalidomide Maintenance

McCarthy. JCO. 2017;35:3279.
Phase III HOVON-65/GMMG-HD4 Trial: Bortezomib Maintenance

**PFS**

- PAD/Bort (n = 413) 17
- VAD/Thal (n = 414) 10

HR: 0.77 (95% CI: 0.65-0.90)

**OS**

- PAD/Bort (n = 413) 48
- VAD/Thal (n = 414) 45

HR: 0.87 (95% CI: 0.71-1.04)

**Outcome, %**

- CR/nCR: PAD/Bort 50, VAD/Thal 35
- ≥ VGPR: PAD/Bort 75, VAD/Thal 56
- ORR: PAD/Bort 91, VAD/Thal 83

Recommendation: Lenalidomide maintenance should be considered for standard risk and bortezomib maintenance for high risk

Different strategy for HR? VRD Maintenance

Take Home Points

• In transplant-eligible patients: upfront transplant after 4-6 cycles of induction regardless of the depth of response is standard
  • Delayed SCT at first relapse is acceptable
• If VRd induction is used, additional consolidation with VRd is not recommended
• Tandem transplant is not standard approach
  • In high-risk MM, possibility of benefit should be discussed
• Lenalidomide maintenance recommended for all standard-risk MM and bortezomib based maintenance for high risk
  • del17p: VRd maintenance could be considered
Thank you

kumar.shaji@mayo.edu
What’s Next After Induction in Patients Eligible for ASCT?

The European Perspective

Pr Philippe Moreau
University Hospital, Nantes, France
Program 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.
Eligibility for ASCT

Yes  No

First option: VMP, Rd, VRD
Second option: VCD, MPT
Other options : BP, CTD, MP

Induction: 3-drug regimens
VTD
VCD
RVD
PAD

200 mg/m² Melphalan followed by ASCT

Maintenance
Lenalidomide

FRONTLINE THERAPY
ESMO guidelines
Moreau et al, Ann Oncol 2017
No Consolidation!

Single ASCT!

No Delayed ASCT!

≤ 65 Years or
Fit Patients ≤ 70 Years in Good Clinical Condition
In the context of novel-agent based therapy, frontline ASCT is the standard of care!

IFM 2009
EMN02
EMN02/HO95 MM Trial: Study Design

VCD induction x 3-4 cycles + PBSC collection

VMP x 4 cycles

Melphalan (HDM) 200mg/m² + single or double ASCT

VRD consolidation x 2 cycles

No consolidation

Maintenance Lenalidomide

PFS by randomization (VMP vs ASCT)

Median PFS:
ASCT: NR; VMP: 44.3 mos

HR: 0.76
(95% CI, 0.64-0.90), P=0.002

VMP | Number at risk |
--- | --- |
497 | 404 |
318 | 201 |
76 |

ASCT | Number at risk |
--- | --- |
695 | 597 |
480 | 299 |
110 |
IFM DFCI 2009 Trial
700 patients < 66 y,
Newly diagnosed symptomatic MM

3 RVD

5 RVD

MEL200 + ASCT

2 RVD

12 months of lenalidomide maintenance

Attal. NEJM. 2017;376:1311.
PROGRESSION-FREE SURVIVAL

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>RVD</th>
<th>Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>12</td>
<td>294</td>
<td>308</td>
</tr>
<tr>
<td>24</td>
<td>228</td>
<td>264</td>
</tr>
<tr>
<td>36</td>
<td>157</td>
<td>196</td>
</tr>
<tr>
<td>48</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

P<0.001

Attal. NEJM. 2017;376:1311.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Multivariate Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arm (B/A)</td>
<td>0.80</td>
<td>0.02</td>
</tr>
<tr>
<td>ISS II vs I</td>
<td>1.33</td>
<td>0.02</td>
</tr>
<tr>
<td>ISS III vs I</td>
<td>1.45</td>
<td>0.01</td>
</tr>
<tr>
<td>FISH (high risk/standard)</td>
<td>2.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CR</td>
<td>0.58</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MRD (FCM)</td>
<td>0.39</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Attal. NEJM. 2017;376:1311.
## IFM 2009: Best Response.

<table>
<thead>
<tr>
<th></th>
<th>RVD group N=350</th>
<th>Transplant group N=350</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>48%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>VGPR</td>
<td>29%</td>
<td>29%</td>
<td>0.004</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>&lt;PR</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>At least VGPR</td>
<td>77%</td>
<td>88%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRD neg by FCM , n (%)</td>
<td>171/265 (65%)</td>
<td>220/278 (80%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
IFM/DFCI 2009: OS According to MRD (FCM) (9/2015)

S2B

Patients (%)

P<0.001

Months of Follow-up

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>311</th>
<th>379</th>
<th>347</th>
<th>119</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD Negative</td>
<td>700</td>
<td>358</td>
<td>259</td>
<td>227</td>
<td>65</td>
<td>0</td>
</tr>
</tbody>
</table>

MRD Negative
MRD Positive
Overall survival at the start of maintenance NGS, $10^{-6}$

Overall survival after 12 months of maintenance NGS, $10^{-6}$

Perrot. Blood. 2018;[Epub].
Role of Induction

- Fast control of the disease
- Achieve high response rates (MRD neg?)
- Minimal toxicity
- Allow adequate stem cell harvest
VTD and VCD are widely used in Europe

VRD in US, less toxic, as effective : future in Europe following approval of Len ?
→ easily up to 6 cycles
Table 2. Response rate to induction therapy according to treatment arm

<table>
<thead>
<tr>
<th></th>
<th>QT + V, n = 129</th>
<th>TD, n = 127</th>
<th>VTD, n = 130</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, %</td>
<td>21*</td>
<td>12*</td>
<td>35*</td>
</tr>
<tr>
<td>VGPR, %</td>
<td>15</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>PR, %</td>
<td>39</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>SD, %</td>
<td>12</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>PD, %</td>
<td>12†</td>
<td>23</td>
<td>7‡</td>
</tr>
<tr>
<td>Early deaths, %</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*VTD vs QT + V, \( P = .01 \); VTD vs TD, \( P = .0001 \). †QT + V vs TD, \( P = .02 \). ‡VTD vs TD, \( P = .0004 \).

Median number of CD34+ cells: \( 3.8 \times 10^6 \)/kg
Pethema/GEM Phase 3 Study: VRD-GEM Induction 6 Cycles (N=455 Patients)

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Overall 455 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR + sCR)</td>
<td>176 (39)</td>
</tr>
<tr>
<td>VGPR</td>
<td>133 (29)</td>
</tr>
<tr>
<td>MRD negative, NGF, 3 x 10^{-6}, n = 320</td>
<td>35%</td>
</tr>
<tr>
<td>PR</td>
<td>77 (17)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>30 (6)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>30 (6)</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Early death</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>386 (85)</td>
</tr>
</tbody>
</table>

Median number of CD34+ cells (3 cycles) : 4.66x10^6/kg

### Toxicity

<table>
<thead>
<tr>
<th></th>
<th>VTD, n = 130</th>
<th>VRD, n = 455</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3-4 %</td>
<td>Grade 3-4 %</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>46</td>
<td>13</td>
</tr>
<tr>
<td>Grade 3</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation during induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Disease progression</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Kinetics of Response According to MRD, NGF/Euroflow (n=320), $10^{-6}$

<table>
<thead>
<tr>
<th></th>
<th>Induction (VRDx6)</th>
<th>HDT/ASCT</th>
<th>Consolidation (VRDx2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD negative</td>
<td>35%</td>
<td>54%</td>
<td>58%</td>
</tr>
<tr>
<td>MRD positive</td>
<td>65%</td>
<td>46%</td>
<td>42%</td>
</tr>
</tbody>
</table>

How to improve?

Future …
Newly diagnosed multiple myeloma patients eligible for autologous transplantation (ASCT)

Endpoints:
- Primary: VGPR
- Secondary: ORR, DoR, TTNT, OS, MRD

Study Schema:

Induction (4 cycles) One cycle = 28 days
- **Arm A: CRd**
  - Carfilzomib 36 mg/m² IV Days 1, 2, 8, 9, 15, 16
  - Lenalidomide 25 mg/day Days 1 - 21
  - Dexamethasone 20 mg PO Days 1, 2, 8, 9, 15, 16, 22, 23

- **Arm B: CCyd**
  - Carfilzomib 20/36 mg/m² IV Days 1, 2, 8, 9, 15, 16
  - Cyclophosphamide 300 mg/m² Days 1, 8, 15
  - Dexamethasone 20 mg PO Days 1, 2, 8, 9, 15, 16, 22, 23

Consolidation (4 cycles) One cycle = 28 days
- **Arm A: CRd**
  - Carfilzomib 36 mg/m² IV Days 1, 2, 8, 9, 15, 16
  - Lenalidomide 25 mg/day Days 1 - 21
  - Dexamethasone 20 mg PO Days 1, 2, 8, 9, 15, 16, 22, 23

- **Arm B: CCyd**
  - Carfilzomib 36 mg/m² IV Days 1, 2, 8, 9, 15, 16
  - Cyclophosphamide 300 mg/m² Days 1, 8, 15
  - Dexamethasone 20 mg PO Days 1, 2, 8, 9, 15, 16, 22, 23

Maintenance One cycle = 28 days
- **Arm A: CRd**
  - Carfilzomib 36 mg/m² IV Days 1, 2, 8, 9, 15, 16
  - Lenalidomide 25 mg/day Days 1 - 21
  - Dexamethasone 20 mg PO Days 1, 2, 8, 9, 15, 16, 22, 23

- **Arm B: CCyd**
  - Carfilzomib 36 mg/m² IV Days 1, 2, 8, 9, 15, 16
  - Cyclophosphamide 300 mg/m² Days 1, 8, 15
  - Dexamethasone 20 mg PO Days 1, 2, 8, 9, 15, 16, 22, 23

Total 12 Cycles

Abstract 121; Oral Dec. 1, 9:30 AM Gay et al
CASSIOPEIA – 1080 Patients – ASCO 2019

**Screening**
(-28 days)

**Randomize #1**

**Arm A**
- VTD 4 cycles

**Arm B**
- VTD + Dara 4 cycles

**Induction Phase**

**Stem cell mobilization, conditioning, and transplant**

**Consolidation Phase**

**Part 1**

**Arm A**
- VTD 2 cycles

**Subjects with PR or better**

**Randomize #2**

**Arm B**
- VTD + Dara 2 cycles

**Maintenance Phase**

**Part 2**

**Arm A**
- Observation until PD (maximum of 2 years)

**Dara Q8wks until PD (maximum of 2 years followed by observation until PD)**

**Follow-up**

NGF, NGS, PET
Daratumumab-VRd Trial in Transplant-Eligible NDMM
EMN017/HOVON158/MMY3014 Registration Trial

Induction 4 cycles
- VRd
  q 3 w
- VRd + Dara

Consolidation 2 cycles
- VRd
  q 3 w
- HDM + ASCT
- VRd + Dara
- Lenalidomide until PD

Maintenance
- Dara + Len 24m
- MRD pos
  Continue until PD
- MRD neg
  Stop after 1yr MDR negativity

Primary endpoint: PFS
Secondary endpoint: MRD \(10^{-5}\) by NGS after consolidation

Perseus, PI, P.Sonneveld
Role of Consolidation

- Short duration after ASCT
- Increased the depth of response (MRD neg)
- Reduced toxicity allowing maintenance
Tools and Issues

- Novel-agent based
- Second (tandem) ASCT

- Necessary?
- Best one?
- Optimal duration?
Double vs Single ASCT After Bortezomib-Based Induction

Cavo et al. ASH 2013
Abstract 767.

Cavo et al. ASH 2018
Abstract 124
Saturday, December 1, 2018: 9:30 AM
Retrospective trial
217 patients

VTD – auto
vs
VTD – auto - VTD

EMN02/HO95 MM Trial: Study Design

- **VCD induction x 3-4 cycles + PBSC collection**
- **VMP x 4 cycles**
- **Melphalan (HDM) 200 mg/m² + single or double ASCT**
- **VRD consolidation x 2 cycles**
- **No consolidation**
- **Maintenance lenalidomide**

PFS by Randomization (ASCT-1 vs ASCT-2)

HR: 0.71
(95% CI, 0.50-0.98), P=0.040

Number at risk
ASCT-008 173 135 84 25
ASCT-207 185 151 97 45

OS by Randomization (ASCT-1 vs ASCT-2)

OS probability

HR: 0.51
(95% CI, 0.31-0.86), P=0.011

88.3%
(84.4%; 93.7%)

81.5%
(78%; 87.5%)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>ASCT-008</th>
<th>ASCT-207</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>184</td>
<td>190</td>
</tr>
<tr>
<td>12</td>
<td>160</td>
<td>189</td>
</tr>
<tr>
<td>24</td>
<td>105</td>
<td>117</td>
</tr>
<tr>
<td>36</td>
<td>36</td>
<td>62</td>
</tr>
<tr>
<td>48</td>
<td>36</td>
<td>62</td>
</tr>
</tbody>
</table>

OS by Randomization in High-Risk Subgroups

High-risk cytogenetics

R-ISS II + III

Design of EMN02 Trial

Registration
Induction

Stem cell mobilization in all pts

Consolidation

Maintenance until relapse

Early or late ASCT, once or twice

MRD

HDM/ASCT at 1st relapse

4 × VCD + Stem cell apheresis

R1

4 × VMP

HDM 1/2

R2

2 × VRD None

Lenalidomide

Lenalidomide


Progression-Free Survival

HR = 0.78 (0.61-1.00)

no consolidation

VRD

Cox LR P=0.045 (adjusted for 1st random.)

At risk:

no consolidation: 435
VRD: 450

F

N

435
450
137
115
336
371
187
196
49
52

## Kinetics of Response According to MRD, NGF/Euroflow (n=320), $10^{-6}$

<table>
<thead>
<tr>
<th></th>
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<td>54%</td>
<td>58%</td>
</tr>
<tr>
<td>MRD positive</td>
<td>65%</td>
<td>46%</td>
<td>42%</td>
</tr>
</tbody>
</table>

BMT CTN 0702 Stem Cell Transplantation for Multiple Myeloma Incorporating Novel Agents: SCHEMA

N=750 pts (250 in each arm)

Register and Randomize → MEL 200mg/m²

 Lenalidomide Maintenance **

N=257

VRD x 4*

N=254

Lenalidomide Maintenance **

MEL 200mg/m²

N=247

Lenalidomide Maintenance **

*Bortezomib 1.3mg/m²
days 1, 4, 8, 11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg
days 1, 8, 15
Every 21 days

**Lenalidomide x 3 years:
10mg/d for 3 cycles, then 15 mg/d
Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104.
## Compliance with each intervention

<table>
<thead>
<tr>
<th></th>
<th>Auto/Auto (N=247)</th>
<th>Auto/RVD (N=254)</th>
<th>Auto/Maint (N=257)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Received 2nd Intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79 (32.0%)</td>
<td>30 (11.8%)</td>
<td>-</td>
</tr>
<tr>
<td>Yes</td>
<td>168 (68.0%)</td>
<td>224 (88.2%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Started maintenance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41 (16.6%)</td>
<td>43 (16.9%)</td>
<td>14 (5.4%)</td>
</tr>
<tr>
<td>Yes</td>
<td>206 (83.4%)</td>
<td>211 (83.1%)</td>
<td>243 (94.6%)</td>
</tr>
</tbody>
</table>
Progression-Free Survival – as treated/per protocol Analysis

38-Month Estimate and 95% CI
Auto/Auto: 61.8 (53.6, 68.9)
Auto/RVD: 57.8 (50.7, 64.2)
Auto/Maint: 52.2 (45.4, 58.6)

<table>
<thead>
<tr>
<th>N at risk</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto/Auto</td>
<td>247</td>
<td>149</td>
<td>121</td>
<td>70</td>
</tr>
<tr>
<td>Auto/RVD</td>
<td>254</td>
<td>195</td>
<td>160</td>
<td>91</td>
</tr>
<tr>
<td>Auto/Maint</td>
<td>257</td>
<td>212</td>
<td>157</td>
<td>79</td>
</tr>
</tbody>
</table>

Consolidation

- Necessary?
- Best one?
- Optimal duration?

Tandem ASCT in high risk
CASSIOPEIA – 1080 Patients – ASCO 2019

Screening
(≤28 days)

Randomize #1

Arm A
- VTD 4 cycles
- Stem cell mobilization, conditioning, and transplant
- VTD 2 cycles

Arm B
- VTD + Dara 4 cycles
- VTD + Dara 2 cycles

Induction Phase

Consolidation Phase

Subjects with PR or better

Randomize #2

Part 1

Observation until PD
(maximum of 2 years)

Part 2

Dara Q8wks until PD
(maximum of 2 years followed by observation until PD)

Maintenance Phase

Follow-up

Hovon
Sustained responses following ASCT are needed:

Impact of maintenance
Cytogenetic risk groups
Lenalidomide improved PFS regardless of cytogenetic risk

\[ t(4;14) \text{ and/or del}(17p) \text{ absent: HR 0.50} \]
\[ t(4;14) \text{ and/or del}(17p) \text{ present: HR 0.36} \]

Refer to Jackson. ASH 2017. Abstr 436.
TOURMALINE MM-3

- Ixazomib vs placebo, phase 3
- In patients responding to ASCT
- Randomization 3:2
- 656 patients
- D1,8,15 in 28-day cycles
- Primary endpoint: PFS

Dimopoulos. ASH 2018. Abstr 301; NCT02181413
Dimopoulos et al. ASH 2018; oral abstract 301. Sunday, December 2, 2018: 7:30 AM

**Median:** Ixazomib 26.5 months, Placebo 21.3 months

Log-rank test $p=0.002$

Hazard ratio (95% CI): 0.72 (0.582, 0.890)

Percentage of events: Ixazomib 50%, Placebo 60%

Median follow-up: 31 months
GEM14

Second trial as continuation of the previous one

- **Arm A**
  - Lena/dexa
  - Lena 15 mg/d x 21d
  - Dexamethasone 20 mg d 1-4 y 9-12

- **Arm B**
  - Lena/dexa + Ixazomib
  - Lena/dexa + Ixazomib 4 mg d 1,8,15

- MRD evaluation at 2 Yrs
  - MRD neg → Stop
  - MRD pos
    - Lena/dexa X 3 years

- MRD annual

NCT02253316.

The graph shows the progression-free survival (PFS) rates for different MRD (minimal residual disease) statuses. The x-axis represents time from diagnosis in months, while the y-axis shows the percentage of patients with progression-free survival.

- **MRD-negative, median PFS NR:** This group maintains a high survival rate throughout the graph.
- **MRD-positive \( \geq 2 \times 10^{-6} \) to \( <10^{-5} \), median PFS 40m:** The survival rate drops significantly compared to the MRD-negative group.
- **MRD-positive \( \geq 10^{-5} \) to \( <10^{-4} \), median PFS NR:** Similar to MRD-negative, this group also shows high survival.
- **MRD-positive \( \geq 10^{-4} \), median PFS 26m:** The survival rate is the lowest, with a median PFS of 26 months.

The table below shows the number at risk for each group at different time points:

<table>
<thead>
<tr>
<th>MRD Status</th>
<th>0 months</th>
<th>10 months</th>
<th>20 months</th>
<th>30 months</th>
<th>40 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-negative</td>
<td>225</td>
<td>224</td>
<td>177</td>
<td>86</td>
<td>4</td>
</tr>
<tr>
<td>MRD ( \geq 2 \times 10^{-6} ) to ( &lt;10^{-5} )</td>
<td>49</td>
<td>49</td>
<td>36</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>MRD ( \geq 10^{-5} ) to ( &lt;10^{-4} )</td>
<td>57</td>
<td>54</td>
<td>43</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>MRD ( \geq 10^{-4} )</td>
<td>127</td>
<td>84</td>
<td>57</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

*P < .001*
CASSIOPEIA – 1080 Patients – ASCO 2019

**Induction Phase**

- **Arm A**
  - VTD
  - 4 cycles
 - Stem cell mobilization, conditioning, and transplant
 - VTD
  - 2 cycles
 - Subjects with PR or better
 - Randomize #2

- **Arm B**
  - VTD + Dara
  - 4 cycles

**Consolidation Phase**

- VTD + Dara
  - 2 cycles

**Maintenance Phase**

- Dara Q8wks
  - until PD
  - (maximum of 2 years followed by observation until PD)

**Follow-up**
Conclusions: European Perspectives

- Frontline ASCT: standard of care
- VTD / VRD: best induction regimens prior to ASCT
- Optimal consolidation has to be defined (tandem in high risk)
- Consider the global strategy: induction/ ASCT / consolidation / maintenance
Panel Discussion and Audience Q&A
Patient Case Example, Repeat

- A 53-year-old woman with no other health problems was diagnosed with myeloma when she presented with back pain and increasing fatigue

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>10.8 g/dL</td>
</tr>
<tr>
<td>Serum Ca(^{2+})</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum LDH</td>
<td>Above ULN</td>
</tr>
<tr>
<td>Serum $\beta_{2}$microglobulin</td>
<td>7.1 mg/dL</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>4.1 g/dL</td>
</tr>
</tbody>
</table>

- Serum protein electrophoresis: IgGK monoclonal protein of 3.2 g/dL
- 24 hour urine protein electrophoresis: 210 mg monoclonal protein, kappa light chain
Patient Case Example, Continued

- Whole-body low-dose CT showed multiple lytic lesions
- Bone marrow biopsy showed 40% plasma cell involvement, **FISH showed 17p deletion in > 50% of tumor cells**
- She was started on treatment with a combination of bortezomib, lenalidomide, and dexamethasone
- At the completion of 4 cycles of therapy:
  - Repeat bone marrow biopsy shows no MRD
  - Serum and urine immunofixation were both negative
Now, what would you do next for this patient?

1. ASCT followed by RVD consolidation and lenalidomide maintenance
2. ASCT followed by RVD consolidation and PI-based maintenance
3. ASCT followed by lenalidomide maintenance
4. ASCT followed by PI-based maintenance
5. Tandem ASCT followed by RVD consolidation and lenalidomide maintenance
6. Tandem ASCT followed by RVD consolidation and PI-based maintenance
7. Uncertain
Advances in the Optimal Choice of Therapeutic Strategies for Patients With R/R Myeloma

Faculty Presenters:
Jesús F. San-Miguel, MD, PhD

Image: Copyright©2018 DNA Illustrations. All Rights Reserved
Program 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, MSD, Novartis, Roche, Sanofi, and Takeda.
Therapeutic Strategies at Relapse in Multiple Myeloma

Jesus San-Miguel
Universidad Navarra
Patient Case Example

- A 66-year-old woman was diagnosed with IgG lambda **R-ISS stage II** myeloma
  - BM showed 60% PC with **1q gain plus t(4;14)**
  - MC: 43 g/L; **Hb: 10.3 g/dL**, creatinine: 1.2 mg/dL; calcium: 9.2 mg/dL
  - She had extensive **bony disease**
- She was treated **VTD + ASCT + lenalidomide for 2 years** and achieved **sCR**
- **After 4 years**, she **relapsed**
<table>
<thead>
<tr>
<th>Faculty</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
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</tr>
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</tr>
<tr>
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<td>Daratumumab/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Rescue treatment followed by second ASCT</td>
</tr>
</tbody>
</table>
Late relapse (> 3-4 years post ASCT)
- **Aggressive relapse**: Reinduction (VRD/KRD +/- Dara) + 2nd ASCT
- **Biochemical relapse**: Repeat the initial approach or same as above

Early relapse (< 1 year post ASCT)

- "**Overcome drug resistance**"
  Combination of non cross-resistant agents
  VRD (KRD)-PACE + Dara $\rightarrow$ RIC-Allo/CAR-T

Intermediate relapse (1-3 years post ASCT)

- "**Prolong survival until curative treatments are developed**"
  Sequential novel agent combinations: Dara + PomDex.....KRD...
A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II MM
- BM showed 1q gain plus t(4;14) with extensive bony disease
- She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR
- After 4 years, she relapsed

She refused 2nd ASCT (70 years, with hypertension) and was treated with VCD x 8 cycles and achieved CR

She relapsed 10 months later
# How would you treat this patient?

<table>
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<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Daratumumab/lenalidomide/dexamethasone</td>
</tr>
</tbody>
</table>
# Lenalidomide-Based Regimens: Efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>POLLUX (n=569)</th>
<th>ASPIRE (n=792)</th>
<th>ELOQUENT-2 (n=646)</th>
<th>TOURMALINE-MM1 (n=722)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS HR (▲ m)</strong></td>
<td>DaraRd vs Rd</td>
<td>KRd vs Rd</td>
<td>ERd vs Rd</td>
<td>IRd vs Rd</td>
</tr>
<tr>
<td></td>
<td>0.44 (▲ 27)</td>
<td>0.67 (▲ 8.7 m)</td>
<td>0.71 (▲ 4.5 m)</td>
<td>0.74 (▲ 5.9 m)</td>
</tr>
<tr>
<td></td>
<td>44.5 vs 17.5 m</td>
<td>26.3 vs 17.6 m</td>
<td>19.4 vs 14.9 m</td>
<td>20.6 vs 14.7 m</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>93</td>
<td>87</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td><strong>≥ CR, %</strong></td>
<td>51</td>
<td>32</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td><strong>OS HR (95% CI)</strong></td>
<td>0.63</td>
<td>0.79 (▲ 8 m)</td>
<td>0.78 (▲ 4.1 m)</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>48 vs 40 m</td>
<td>43.7 vs 39.6 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High Risk: m (HR)</strong></td>
<td>22.6 (0.64)</td>
<td>23 (0.70)</td>
<td>19 (0.60)</td>
<td>21 (0.54)</td>
</tr>
</tbody>
</table>

This table is provided for ease of viewing information from multiple trials with different patient populations. Direct comparison across trials is not intended and should not be inferred.

DOR, duration of response; NE, not evaluated.

Patient Case Example

- A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II MM
  - BM showed **1q gain plus t(4;14)** with extensive **bony disease**
  - She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR
  - After 4 years, she relapsed

- She refused 2nd ASCT (70 years, with hypertension) and was treated
  with VCD x 8 cycles and achieved CR

- She relapsed 10 months later

- She began tx with **lenalidomide/dexamethasone** until progression
  - On cycle 5, she was already in VGPR and maintained her response for
    15 months before relapse
How would you treat this patient?

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</tr>
</thead>
<tbody>
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<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Daratumumab/bortezomib/dexamethasone</td>
</tr>
<tr>
<td>Efficacy</td>
<td>ENDEAVOR (n=929)</td>
</tr>
<tr>
<td>----------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>PFS HR</strong></td>
<td>Kd vs Vd ³</td>
</tr>
<tr>
<td>PFS HR</td>
<td>0.53 (▲ 9.3 m)</td>
</tr>
<tr>
<td>18.7 vs 9.4 m</td>
<td>16.7 vs 7.1 m</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>77</td>
</tr>
<tr>
<td><strong>≥ CR, %</strong></td>
<td>13</td>
</tr>
<tr>
<td><strong>OS HR (95% CI)</strong></td>
<td>0.79 (▲ 7.6 m)</td>
</tr>
<tr>
<td>47.6 vs 40 m</td>
<td>47.6 vs 40 m</td>
</tr>
<tr>
<td><strong>Len Refract</strong></td>
<td>24% (8.6m)</td>
</tr>
<tr>
<td><strong>High Risk: m (HR)</strong></td>
<td>8.8 (0.73)</td>
</tr>
</tbody>
</table>

Patient Case Example

- A 66-year-old woman was diagnosed with IgG lambda R-ISS stage II MM
  - BM showed $1q$ gain plus $t(4;14)$ with extensive bony disease
  - She was treated VTD + ASCT + lenalidomide for 2 years and achieved sCR but relapsed after 4 years
- She refused 2nd ASCT (70 years, with hypertension) and was treated with VCD x 8 cycles and achieved CR
  - She relapsed 10 months later
- She began tx with lenalidomide/dexamethasone until progression
  - She achieved VGPR but relapsed 15 months later
- She received Dara-Vd and achieved PR on C2 but progressed with extramedullary disease on C8
How would you treat this patient now?

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Carfilzomib/pomalidomide/dexamethasone</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>Elotuzumab/pomalidomide/dexamethasone</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>Clinical trial with BCMA CAR T-cell therapy</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>Carfilzomib/pomalidomide/dexamethasone</td>
</tr>
<tr>
<td>Jesús F. San-Miguel, MD, PhD</td>
<td>Elotuzumab/pomalidomide/dexamethasone</td>
</tr>
</tbody>
</table>
## Treatment at 3rd/subsequent relapses

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Poma – Dexa</strong>&lt;sup&gt;1&lt;/sup&gt; <em>(backbone)</em></td>
<td>31%</td>
<td>4 m</td>
<td>13.1 m</td>
</tr>
<tr>
<td>PCyDex (ORR 65%; PFS 9.5 m)&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EloPom Dex (ORR:53%, PFS 10.2 m)&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Daratumumab</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>31%</td>
<td>4m</td>
<td>20.1 m</td>
</tr>
<tr>
<td>DaraCfzDex *</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CfzPomDex n=(60) EMN011<sup>7</sup>**
- ORR: 87% (31%CR)
- PFS: 18m

**DaraPomDex (ORR 60%, PFS 8.8m)**
- IxaPomDex (ORR 55%)<sup>4</sup>

**DaraCfzDex n=85 (60% Len Ref)**<sup>6</sup>
- ORR: 86% (81%)
- PFS: 71% at 12m (14.1m)

---

Elotuzumab-Poma-Dexa vs Poma-Dex in RRMM: Phase 2 Randomized ELOQUENT-3 Trial – Efficacy (N = 117)

**KEY INCLUSION**
- ≥ 2 prior regimens
- Prior IMID and PI treatment
- Refractory to last line
- Refractory to Len and a PI

POM: 4 mg days 1-21; 40 mg (20 of >75y) weekly
ELO: 10 mg/kg/w C1&C2; >C3: 20mg/kg/ 4 w

- Median number of prior lines: 3 (2 – 8)
- Prior exposure to: BORT (100%), CFZ (21%), LEN (99%)
- Refractory to: PI 80%, LEN 87%, double refractory (70%)

**Safety Epd vs Pd:** Grade 3-4 neutropenia: 13% vs 27% // Anemia: 10% vs 20% // Infections any grade: 65% vs 65%.

*Safety was consistent with prior reports of ELO and POM*

Dimopoulos MA et al. NEJM 2018, 379:1811-22
XPO1-Inhibitor Selinexor in RRMM. Summary of Phase I data

First-in-class, oral Selective Inhibitor of Nuclear Export (SINE) that inhibits XPO1 and activates tumor suppressor proteins & reduces oncoproteins

- Cancer cells (and MM) overexpress XPO1, causing increased export of tumor suppressors and growth regulatory proteins from the nucleus
- Selinexor inhibit XPO1 mediated nuclear-cytoplasmic transport by transiently binding to XPO1 cargo binding site.
- Accumulation of Tumor suppressors in the nucleus amplifies the natural apoptotic function in cancer cells with damaged DNA.

Tai et al. Leukemia 2014

PHASE I OF SELINEXOR PLUS/MINUS DEX IN RRMM

- Single agent (oral:3-45 mg twice/ w).... 17% MR, Chen et al. ASH 2014
  Main AEs: Anorexia, nausea/vomiting, fatigue, thrombocytopenia.

- +Dex (n=122) (STORM)................................. 26% ORR (Pent a-Refct) PFS: 3,7m Vogl et al. JCO 2018, Chari ASH 2018 (Abs 598)
  AEs: nausea 73%, vomiting 49%, anorexia 49%, thrombocytopenia 73% /59% gr 3-4)

- + Bortz/dex (n=42)................................. 63% (43% in Btz Rfct) (PFS: 9 (6,1)m ) Bahlis NJ, Blood 2018, (PH III BOSTON trial ongoing)
  AEs: anorexia 33%, nausea 67%, Thrombocytopenia 17%

- + Pom/dex (n=24)................................. 65% % in Pom Naive/Len R (29% in Pom/Len Rft). Chen et al, ASH 2017

- + Dara/dex (n=25)................................. 74% % in double Rft. Gasparetto et al, ASH 2018, Abs 599)
Venetoclax (bcl-2 inhibitor) in RRMM. Summary of Ph1 data

- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor, induces cell death in multiple myeloma (MM) cell lines and primary samples, particularly those positive for the translocation t(11;14), which correlates with higher ratios of BCL2 to MCL1 and BCL2 to BCL2L1 (BCL-XL) mRNA.

- **Monotherapy** (n=66) (61% double Ref) .......... ORR 21% (40% in t(11;14)) DOR: 9.7m
  
  G 3-4 AEs: thrombocytopenia (26%) & neutropenia (21%)

- **+Btz/Dex** (n=66) .................................. ORR 67% (90% in BTz sensitive & 94% in BCL2 high)
  
  G3-4 AEs: Thrombocytopenia (29%), anemia (15%), neutropenia (14%),

- **+Cfz/Dex** (n=42) (33% double Ref)...............ORR 78% (PFS: 5.7m. The VGPR in t(11,14): 88%)
Melflufen

- Melflufen is a highly lipophilic alkylator, belonging to the **novel class of Peptidase Enhanced Compounds**, consisting of melphalan + 4-fluoro-L-phenylalanine.

- Intracellular amino-peptidases that are overexpressed in most malignant cells, will rapidly cleave melflufen releasing the hydrophilic, active metabolite melphalan.

- In vitro, equimolar treatment of tumor cells with melphalan and melflufen, results in a 20-50 fold higher intracellular concentration.

**Melflufen 40 mg iv every 28 days + Dex 40 mg weekly**

**Phase II O-12-M1 trial**

RRMM pts ≥ 2 lines and refr. to last line.

n = 45; 4 (2-14) lines; 64% double refr.; 53% Alkylator refr.

**ORR 31% .......... 5 VGPR & 9 PR 36% in Alkylator refr.**

PFS: 5,7m ; OS: 20M

G3/4 AEs: Thromboc. (58%), Neutrop(51%), Anemia: 42%

*Blood 2017, 130: 3150*

**Phase II Horizon trial**

RRMM pts ≥ 2 lines and 89% double Ref

n = 62 6 (3-11) lines; Alkylator refr. 58%; Pom & Dara Refr: 56%

**ORR 32% .......... PFS: 5,7M; OS: 20,7M**

G3/4 rel. TEAEs: Thromboc. (45%), Neutropenia (39%), Anemia: 21%

*Richardson P. ASH 2018 (Abst 600)*
Four Major Targets for Cancer Immunotherapy

- **Direct targeting of surface tumor antigens:**
  - Monoclonal antibodies

- **Boosting immune effectors:**
  - Adoptive cell therapy

- **Overcoming inhibitory immune suppression:**
  - Immunomodulators: IMiDs, checkpoint inhibitors

- **Activating tumor specific immunity:**
  - Vaccines

IMiD, immunomodulatory drugs.
Bispecific T-cell engagers: BCMA–CD3 Phase I trials

- AMG 420: 35 pts: (Topp et al ASH 2018, 1010)
  28% ORR (6CR). 83% ORR at MTD (including MRD-)
  SAE: 49% (infections); CRS (3 cases).

Conjugated mAb:
GSK2857916: BCMA – MMAF*
AMG 224: BCMA – DM1
STRO-001: CD74-DBCO

*35 patients (Trudel S, et al. Blood 2017;130:741)
ORR: 60% (43% previous data) PFS: 7.9m
63% corneal events most G1-2

MMAF, monomethyl auristatin F; DM1, maytansinoid N(2')-deacetyl-N(2')(3-mercaptop-1-oxopropyl)-maytansine.
Adoptive Cell Therapy: Genetically Modified T-Cell Therapy

TCR engineered T-cells

<table>
<thead>
<tr>
<th>TCR engineered T-cells</th>
<th>CAR T-cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA - restricted</td>
<td>Antigen recognition is independent of MHC molecule</td>
</tr>
<tr>
<td>Potential recognition of intracellular antigens</td>
<td>Only extracellular proteins can be recognized (like mAb)</td>
</tr>
<tr>
<td>TCR-mediated activation</td>
<td>Possibility to insert other genes</td>
</tr>
</tbody>
</table>

HLA, human leukocyte antigen; mAb, monoclonal antibody; MHC, major histocompatibility complex; TCR, T-cell receptor; CAR, Chimeric antigen receptor (CAR) T-cells

## BCMA CAR T-Cells in MM

<table>
<thead>
<tr>
<th>Trial site</th>
<th>ScFv</th>
<th>Co-s domain</th>
<th>Gene transfer</th>
<th>Conditioning therapy</th>
<th>T-cell dose CAR+ T-cells/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>11D5-3</td>
<td>CD28</td>
<td>Y- retroviral</td>
<td>Cy 300 mg/m² x3 + Flu 30 mg/m² x3</td>
<td>0.3–9.0 x 10⁶</td>
</tr>
<tr>
<td>Bluebird Celgene, Cellgene</td>
<td>NR, murine</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>Cy 300 mg/m² x3 + Flu 30 mg/m² x3</td>
<td>50, 150, 450 and 800 x 10⁶</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>NR, human</td>
<td>4-1BB</td>
<td>Lentiviral</td>
<td>None or Cy 1.5 g/m²</td>
<td>10–50 x 10⁶ or 100–500 x 10⁶</td>
</tr>
<tr>
<td>Nanjing Legend Biotech</td>
<td>NR</td>
<td>NR</td>
<td>Lentiviral</td>
<td>Cy 300 mg/m² x3</td>
<td>1.5–7.0 x 10⁶</td>
</tr>
<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>NR, human</td>
<td>4-1BB</td>
<td>Y- retroviral</td>
<td>Cy 3000 mg/m² or Cy 300 mg/m² x 3 + Flu 30 mg/m² x3</td>
<td>1x10⁶</td>
</tr>
</tbody>
</table>

This slide is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

ScFv, single-chain fragment variable.
# BCMA CAR T-cell Therapies for MM

<table>
<thead>
<tr>
<th>Group/company</th>
<th>Anti-BCMA CAR(^1) NCT02215967</th>
<th>Bb2121(^2) NCT02658929</th>
<th>CART-BCMA(^3) NCT02546167</th>
<th>LCAR-B38M(^4) NCT03090659</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>16 patients at 9x10(^6)/kg dose level</td>
<td>22 (&gt;150 x 10(^6) cells)</td>
<td>21 (3 cohorts): 9 (10-500 x 10(^6), No Cyt) 5 (10–50 x 10(^6), Cyt) 7 (500-500 x 10(^6), Cyt)</td>
<td>57</td>
</tr>
<tr>
<td>BCMA expression required?</td>
<td>Yes</td>
<td>Yes; ≥ 50% BCMA expression</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Median prior lines of therapy</td>
<td>7</td>
<td>7</td>
<td>7 (3–11)</td>
<td>3</td>
</tr>
<tr>
<td>Reported efficacy</td>
<td>ORR 14/16 (81%) 11/14 (79%) MRD- (50% sCR/CR) EFS: 7.2 months</td>
<td>86.4% ≥VGPR</td>
<td>#1: 67% (1 sCR, 1VGPR) #2: (40%) 1 PR, 1 MR both PD #3: (83%) 1 CR, 3 PR, 1 MR</td>
<td>ORR: 88% CR: 74% MRD-: 93% of CR PFS: 15m</td>
</tr>
<tr>
<td>Safety data</td>
<td>CRS all grades:100%, 37%G3-4</td>
<td>CRS all grades: 63% 2 events of CRS grade ≥3 resolved within 24 hours</td>
<td>CRS: 17 pts (grade 3: 32%) Neurotoxicity: 3 (2 grade 4) 1 death – PD candidaemia</td>
<td>Transient CRS (5.7%, G3) No neurotoxicity</td>
</tr>
</tbody>
</table>

Safety Concerns Regarding CAR T-Cell Therapy

CRS is the most common toxicity triggered by the activation of T-cells and bystander immune cells → release of cytokines and chemokines: IFN-γ, soluble IL-2R, IL-6, etc.

- Off target effects (B-cell aplasia)
- Tumour lysis syndrome
- CRS 40–100% (severe ~20–30%)
- Neurological toxicities (CRES)
- HLH/MAS
- GVHD

CRS, cytokine release syndrome (Tocilizumab & Corticosteroids)  CRES, CAR T-cell-related encephalopathy syndrome,   GVHD, graft-versus-host disease, HLH, haemophagocytic lymphohistiocytosis, MAS, macrophage activation syndrome.
## Improvements of CAR T-Cell Therapies

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Potential Improvements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunological rejection &amp; safety</strong></td>
<td>• <strong>Humanised</strong> CARs to reduce immunogenicity</td>
</tr>
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<td></td>
<td>• <strong>Allogeneic CAR T</strong>: Gene editing (CRISPR/Cas9) of normal donor T-cells to remove naive TCR (to avoid GVHD) and transfection with a CAR with post-conditioning vaccination to improve memory</td>
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<td></td>
<td>• <strong>Safety marker gene</strong> to extinguish the CAR-T activity.</td>
</tr>
<tr>
<td><strong>Immune system limitations</strong></td>
<td>• <strong>Rational combination strategies</strong>: Checkpoint inhibitors, IMiDs, BTK inhibitors</td>
</tr>
<tr>
<td><strong>Efficacy &amp; antigen escape</strong></td>
<td>• <strong>Bi-specific CAR</strong> (e.g. CD19, CD123, BCMA, SLAMF7)</td>
</tr>
<tr>
<td></td>
<td>• Use of <strong>specific T-cell subpopulations</strong> (from naive to <strong>central memory</strong> and to terminal effector T-cells)</td>
</tr>
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<td></td>
<td>• <strong>APRIL</strong> as the <strong>natural</strong> BCMA/TACI ligand instead of the Ab (anti-BCMA)</td>
</tr>
<tr>
<td></td>
<td>• <strong>Antibody-Coupled T-Cell Receptor (ACTR)</strong>: engages antibody to direct T-cell attack against many different Ags</td>
</tr>
<tr>
<td></td>
<td>• <strong>Armored CAR</strong> (<strong>2nd gene that generate a cytokine</strong>: i.e. IL12)</td>
</tr>
</tbody>
</table>

AICD, activation-induced cell death, ScFv, single-chain fragment variable, TRAC, T-cell receptor α constant.

Conclusions

• The discovery and development of new therapies addressing a variety of therapeutic targets is already changing the natural history of MM.

• The understanding of the mechanisms of progression and immune-surveillance escape as well as the manipulation of autologous immune cells and gene editing are opening new frontiers in the treatment of advanced or difficult-to-treat MM.

• The combination of different class of drugs with complementary immunological strategies and earlier in the natural history of the disease may offer the future possibility of long-term control or even disease eradication in some subsets of patients.
For Christmas I want a dragon!

Be realistic.

Ok I want my paper to be accepted without revisions.

What color do you want your dragon?

Red.
Panel Discussion and Audience Q&A
Proposed 2019 Treatment Algorithm for MM
Myeloma: 2019 Algorithms

S. Vincent Rajkumar
Professor of Medicine
Mayo Clinic

Scottsdale, Arizona
Rochester, Minnesota
Jacksonville, Florida
2019 Algorithms

• Clinical Trials preferred
• Only commercially available options
• Assumes all drugs available
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 years)
- Evolving, or
Many high risk factors
- Consider Treat as Myeloma

Low Risk SMM
(~5% per year PD)
- Clinical Trials
- Observation

Rajkumar SV, Landgren O, Mateos MV. Blood 2015
Myeloma: Frontline Treatment

**Newly Diagnosed MM***

**Not Transplant Candidate**
- VRd x 8-12 cycles §
- R or Rd maintenance

**Transplant Candidate**
- VRd § x 3-4 cycles

§ VTd/VCd if VRd not available

R (If frail)

- AutoSCT Maintenance (Len for std risk; Bortez for high risk)
- VRd x 4 cycles
- Delayed ASCT

*Based on CALGB 100104, S0777, IFM-DFCI, CTN 0702 HOVON

Rajkumar SV. 2019.
Myeloma: First Relapse

First Relapse

Not Refractory to Lenalidomide *

DRd

K Rd
Frail: IRd, ERd

Refractory to Lenalidomide

DVd, DPd

VCd, KPd, EPd
Frail: Pd, IPd

*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

First-Relapse Options

• Any first relapse options that have not been tried
  (2 new drugs; triplet preferred)

Additional Options

• VDT-PACE like regimens
• Melphalan
• Venetoclax (t11;14)
• Bendamustine-based regimens
• Adding Panobinostat
• Quadruplet regimens

Rajkumar SV. 2019.
Final Thoughts and Audience Questions
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

myeloma.org/videos/new-strategies-multiple-myeloma-care-next-steps-future
clinicaloptions.com/MyelomaTool
clinicaloptions.com/oncology/topics/Multiple-Myeloma