Considering the Recent Data on Transplantation, Consolidation, and Maintenance After Induction

Faculty Presenters:
Shaji Kumar, MD
Philippe Moreau, MD

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

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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.
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.
What’s next after induction?

The US Perspective

Shaji Kumar, MD
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.

<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>Normal</td>
</tr>
<tr>
<td>Serum β₂ 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?

<table>
<thead>
<tr>
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<tr>
<td>Brian G.M. Durie, MD</td>
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<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>
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</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

- 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?

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<tr>
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<tr>
<td>Philippe Moreau, MD</td>
<td>Tandem ASCT followed by RVD consolidation and PI-based maintenance</td>
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<td>Tandem ASCT followed by RVD consolidation and lenalidomide maintenance</td>
</tr>
</tbody>
</table>
Myeloma Treatment Paradigm

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

Diagnosis & risk stratification

SCT
- Eligible
- Ineligible

Induction
- Induction followed by continuous therapy

Consolidation

Maintenance

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

- Newly diagnosed MM pts (N = 583)
  - 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)

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

Jackson. ASH 2016. Abstr 244.
Myeloma XI: Results

Recommendation: 4-6 cycles of induction and then transplant

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

Probability of PFS (%)

- High-dose melphalan
- MPR

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

Probability of 4-Yr OS (%)

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>
<thead>
<tr>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RVD 1</strong></td>
</tr>
<tr>
<td>Lenalidomide + Bortezomib + Dexamethasone</td>
</tr>
</tbody>
</table>

**Randomization (stratified on ISS and FISH)**

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD 2 and 3</td>
<td>RVD 2 and 3</td>
</tr>
<tr>
<td>PBSC Collection (cyclophosphamide and G-CSF)</td>
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</tr>
<tr>
<td>RVD 4 to 8</td>
<td><strong>ASCT</strong></td>
</tr>
<tr>
<td>Lenalidomide Maintenance 12 months (10-15 mg/day)</td>
<td>HDM 200 mg/m²</td>
</tr>
<tr>
<td></td>
<td>RVD 4 and 5</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide Maintenance 12 months (10-15 mg/day)</td>
</tr>
</tbody>
</table>

Attal. NEJM. 2017;376:1311.
## Deeper Responses With SCT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RVD-Alone Group (N = 350)</th>
<th>Transplantation Group (N = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best response during the study, n (%)</strong></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><strong>Complete response, n (%)</strong></td>
<td>169 (48)</td>
<td>205 (59)</td>
</tr>
<tr>
<td><strong>Complete response or very good partial response, n (%)</strong></td>
<td>270 (77)</td>
<td>307 (88)</td>
</tr>
<tr>
<td><strong>Minimal residual disease not detected during study, n/total n with complete or very good partial response (%)</strong></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?
Register and Randomize

MEL 200 mg/m²
ASCT

Lenalidomide Maintenance **
N=257

VRD x 4*
N=254

Tandem ASCT
MEL 200 mg/m²
Second ASCT
N=247

Lenalidomide Maintenance**

* 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) $P < .001$

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): 96-Mo PFS, 17%
- **VAD/Thal** (n = 414): 96-Mo PFS, 10%

**HR:** 0.77 (95% CI: 0.65-0.90)  
**P** = .001

**OS**

- **PAD/Bort** (n = 413): 96-Mo OS, 48%
- **VAD/Thal** (n = 414): 96-Mo OS, 45%

**HR:** 0.87 (95% CI: 0.71-1.04)  
**P** = .22

**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
Eligibility for ASCT

Yes

Induction: 3-drug regimens
- VTD
- VCD
- RVD
- PAD

200 mg/m² Melphalan followed by ASCT

Maintenance
- Lenalidomide

No

First option: VMP, Rd, VRD

Second option: VCD, MPT

Other options: BP, CTD, MP

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!
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

R1

R2

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

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMP</td>
<td>497</td>
<td>404</td>
<td>318</td>
<td>201</td>
<td>76</td>
</tr>
<tr>
<td>ASCT</td>
<td>695</td>
<td>597</td>
<td>480</td>
<td>299</td>
<td>110</td>
</tr>
</tbody>
</table>

IFM DFCI 2009 Trial
700 patients < 66y,
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

Attal. NEJM. 2017;376:1311.
## IFM 2009: PFS, Prognostic Factors

<table>
<thead>
<tr>
<th>Multivariate Analysis</th>
<th>aHR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment arm (B/A)</strong></td>
<td>0.80</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>ISS II vs I</strong></td>
<td>1.33</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>ISS III vs I</strong></td>
<td>1.45</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>FISH (high risk/standard)</strong></td>
<td>2.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>0.58</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>MRD (FCM)</strong></td>
<td>0.39</td>
<td>&lt; 0.001</td>
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Attal. NEJM. 2017;376:1311.
IFM 2009: Best Response.

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

S2B

![Graph showing OS according to MRD](image)

- MRD Negative
- MRD Positive

<table>
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<tr>
<th>Months of Follow-up</th>
<th>No. at Risk</th>
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<tr>
<td></td>
<td>MRD Negative</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>311</td>
</tr>
<tr>
<td>24</td>
<td>379</td>
</tr>
<tr>
<td>36</td>
<td>347</td>
</tr>
<tr>
<td>48</td>
<td>119</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
</tr>
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P < 0.001
Overall survival at the start of maintenance NGS, $10^{-6}$

Overall survival after 12 months of maintenance NGS, $10^{-6}$
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>
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<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: \(3.8 \times 10^6/\text{kg}\)
Pethema/GEM Phase 3 Study: VRD-GEM Induction 6 Cycles (N=455 Patients)

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Overall n (%)</th>
</tr>
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<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><strong>Overall response rate</strong></td>
<td><strong>386 (85)</strong></td>
</tr>
<tr>
<td><strong>Median number of CD34+ cells (3 cycles)</strong></td>
<td><strong>4.66x10^6/kg</strong></td>
</tr>
</tbody>
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# 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/m^2 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/m^2 IV Days 1, 2, 8, 9, 15, 16
- Cyclophosphamide 300 mg/m^2 Days 1, 8, 15
- Dexamethasone 20 mg PO Days 1, 2, 8, 9, 15, 16, 22, 23

Arm C: CRd
- Carfilzomib 36 mg/m^2 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

Consolidation (4 cycles) One cycle = 28 days

Arm A: CRd
- Carfilzomib 36 mg/m^2 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/m^2 IV Days 1, 2, 8, 9, 15, 16
- Cyclophosphamide 300 mg/m^2 Days 1, 8, 15
- Dexamethasone 20 mg PO Days 1, 2, 8, 9, 15, 16, 22, 23

Maintenance One cycle = 28 days

Lenalidomide 10 mg Days 1-21

To Progression or Intolerance

Lenalidomide 10 mg Days 1-21
Carfilzomib 27 mg/m^2 IV Days 1, 2, 15, 16

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
- VTD 2 cycles

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

**Induction Phase**

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

**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**

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

**Induction**
- 4 cycles
  - VRd q 3 w
  - VRd + Dara
  - HDM + ASCT

**Consolidation**
- 2 cycles
  - VRd q 3 w
  - VRd + Dara
  - Dara + Len 24m

**Maintenance**
- Lenalidomide until PD
- 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

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

OS probability

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>
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<tr>
<td>24</td>
<td>105</td>
<td>117</td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

81.5% (76% ; 87.5%)

88.3% (84.4% ; 93.7%)

OS by Randomization in High-Risk Subgroups

High-risk cytogenetics

OS probability

<table>
<thead>
<tr>
<th>Months</th>
<th>ASCT-1</th>
<th>ASCT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>24</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>36</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>48</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

HR: 0.52
(95% CI, 0.28-0.98), P=0.042

Number at risk
<table>
<thead>
<tr>
<th>ASCT-1</th>
<th>ASCT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

R-ISS II + III

OS probability

<table>
<thead>
<tr>
<th>Months</th>
<th>ASCT-1</th>
<th>ASCT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>24</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>36</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>48</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

HR: 0.48
(95% CI, 0.27-0.86), P=0.013

Number at risk
<table>
<thead>
<tr>
<th>ASCT-1</th>
<th>ASCT-2</th>
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<td>31</td>
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<tr>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>92</td>
<td>92</td>
</tr>
</tbody>
</table>

Design of EMN02 Trial

Registration
Induction

Stem cell mobilization in all pts

Consolidation

Maintenance until relapse

Early or late ASCT, once or twice

R1

4 × VCD + Stem cell apheresis

HDM 1/2

R2

4 × VMP

2 × VRD

None

Lenalidomide

Lenalidomide

HDM/ASCT at 1st relapse

Progression-Free Survival

- **HR = 0.78 (0.61-1.00)**

- **At risk:**
  - No consolidation: 435
  - VRD: 450

- **Progression-Free Survival**

## 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>

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**

VRD x 4* → MEL 200mg/m² → Lenalidomide Maintenance**

N=257
N=254
N=247

* 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></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Received 2nd Intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79</td>
<td>32.0</td>
<td>30</td>
</tr>
<tr>
<td>Yes</td>
<td>168</td>
<td>68.0</td>
<td>224</td>
</tr>
<tr>
<td>Started maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41</td>
<td>16.6</td>
<td>43</td>
</tr>
<tr>
<td>Yes</td>
<td>206</td>
<td>83.4</td>
<td>211</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)

N at risk
Auto/Auto 247
Auto/RVD 254
Auto/Maint 257

Months from Randomization
0 12 24 38
0 0.2 0.4 0.6 0.8 1.0
Consolidation

- Necessary?
- Best one?
- Optimal duration?

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

Following screening (≤28 days), patients are randomized to either Arm A or Arm B.

**Induction Phase**

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

**Consolidation Phase**

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

**Randomize #2**

- Subjects with PR or better proceed to Part 2.

**Part 2**

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

**Maintenance Phase**

Follow-up
Sustained responses following ASCT are needed:

Impact of maintenance
Cytogenetic risk groups

Lenalidomide improved PFS regardless of cytogenetic risk

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

Probability of PFS

Ixazomib

Placebo

Time (months) from randomization

Number of patients at risk
Ixazomib 395 363 340 311 279 255 238 213 187 135 93 56 35 9 3 0
Placebo 261 238 210 195 174 153 130 117 100 69 46 32 15 3 0 0
Second trial as continuation of the previous one

Arm A
Lena/dexa
Lena 15 mg/d x 21d
Dexa 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.

Progression-free survival (%)

- **MRD-negative, median PFS NR**
- **MRD-positive $\geq 2 \times 10^{-6}$ to $< 10^{-5}$, median PFS 40m**
- **MRD-positive $10^{-5}$ to $< 10^{-4}$, median PFS NR**
- **MRD-positive $\geq 10^{-4}$, median PFS 26m**

$P < .001$

**Number at risk**

<table>
<thead>
<tr>
<th>MRD Status</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-neg</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 $10^{-5}$ 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>
CASSIOPEIA – 1080 Patients – ASCO 2019

Screening
(-28 days)

Randomize #1

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
VTD + Dara
2 cycles

Induction Phase

Consolidation Phase

Part 1

Part 2
Observation until PD
(maximum of 2 years)

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

Follow-up

Maintenance Phase
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
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