Individualized Approaches to Frontline Treatment Selection

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

- What patient and disease factors guide therapy decisions?
  - Impact of age, performance status, and comorbidities on therapy selections
  - When to use 3-drug vs 4-drug regimens?
- Current therapeutic options for transplant eligible and ineligible patients
  - Triplet therapies
  - Quad therapies
- New therapeutic strategies for transplantation, consolidation, and maintenance
Patient Case Example: 73-Year-Old Male

Presents with:
- Bone pain
- Anemia Hb: 10.2 g/dL
- Serum electrophoresis: M-spike: 4.2 g/dL; IF: IgG K
- Bone marrow aspirate: 30% plasma cells
- Cytogenetics (FISH): t(11;14)
- Low-dose whole-body CT: diffuse bone lesions, spine
- Creatinine: 0.9 mg/dL; β2-M: 2.5 mg/L, albumin 3.8 g/dL, LDH < normal

→ symptomatic multiple myeloma, ISS1, R-ISS1
Presurvey 2: In your current clinical practice, what would you recommend for this patient?

1. Rd until progression
2. VRD x 8 followed by Rd until PD
3. VRD lite followed by R until PD
4. VMP-daratumumab x 9 followed by daratumumab until PD
5. Rd + daratumumab, until PD
6. VRD x 4 → ASCT prepared by mel 200 → len maintenance until PD
7. Uncertain
## Expert Recommendations

<table>
<thead>
<tr>
<th>Expert Recommendations</th>
<th>Treatment Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian G.M. Durie, MD</td>
<td>Rd + daratumumab, until PD</td>
</tr>
<tr>
<td>Shaji Kumar, MD</td>
<td>Rd + daratumumab, until PD</td>
</tr>
<tr>
<td>Thomas G. Martin, MD</td>
<td>RVd x 4 → ASCT → Len maintenance</td>
</tr>
<tr>
<td>Philippe Moreau, MD</td>
<td>Rd + daratumumab, until PD</td>
</tr>
<tr>
<td>S. Vincent Rajkumar, MD</td>
<td>VRD x 8 → Rd until PD</td>
</tr>
<tr>
<td>Jesús San-Miguel, MD</td>
<td>Rd + daratumumab, until PD Dara + VMP with bortez maintenance</td>
</tr>
</tbody>
</table>
Phase III Trials in NDMM Not Eligible for ASCT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>n</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vista¹</td>
<td>VMP</td>
<td>344</td>
<td>24 (TTP)</td>
<td>56.4</td>
</tr>
</tbody>
</table>

## Phase III Trials in NDMM Not Eligible for ASCT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>n</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vista¹</td>
<td>VMP</td>
<td>344</td>
<td>24 (TTP)</td>
<td>56.4</td>
</tr>
<tr>
<td>FIRST²</td>
<td>Rd cont</td>
<td>535</td>
<td>26</td>
<td>59.1</td>
</tr>
</tbody>
</table>

**SWOG 0777 Trial**

Treatment-naïve MM without intent for immediate ASCT* (N = 525)

Stratifications: ISS, intent to transplant at progression

---

**VRd†:**
Bortezomib
Lenalidomide
Dexamethasone (n = 264)

Eight 21-day cycles

---

**Rd:**
Lenalidomide
Dexamethasone (n = 261)

Six 28-day cycles

Len: 25 mg PO until progression

---

**Rd**

---

**Primary endpoint:** PFS

---

*All high-risk 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.

Carfilzomib, lenalidomide, and dexamethasone (KRd) versus bortezomib, lenalidomide, and dexamethasone (VRd) for initial therapy of newly diagnosed multiple myeloma: results of ENDURANCE (E1A11) phase 3 trial

Shaji K. Kumar, Susanna J. Jacobus, Adam D. Cohen, Matthias Weiss, Natalie Scott Callander, Avina A. Singh, Terri L. Parker, Alexander Menter, Alex Yang, Benjamin Marshall Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Seth Rosenberg, Jeffrey A. Zonder, Edward Anthony Faber, Sagar Lonial, Paul G. Richardson, Robert Z. Orlowski, Lynne I. Wagner, S. Vincent Rajkumar
2nd interim analysis of PFS (Jan 2020):
298 PFS events (75% of 399 planned)

Median (95% CI) estimated follow up of 15 (13-18) months

For patients ≥ 70 years, median PFS (95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months

With censoring at SCT or alternative therapy: Median PFS (95% CI) for VRd = 31.7 (28.5-44.6) and KRd = 32.8 (27.2-37.5) months
# Phase III Trials in NDMM Not Eligible for ASCT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>n</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vista¹</td>
<td>VMP</td>
<td>344</td>
<td>24 (TTP)</td>
<td>56.4</td>
</tr>
<tr>
<td>FIRST²</td>
<td>Rd cont</td>
<td>535</td>
<td>26</td>
<td>59.1</td>
</tr>
<tr>
<td>SWOG777³</td>
<td>VRD</td>
<td>242*</td>
<td>43</td>
<td>75</td>
</tr>
<tr>
<td>SWOG777³</td>
<td>VRD</td>
<td>91**</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>Endurance⁴</td>
<td>VRD</td>
<td>542 #</td>
<td>34.4</td>
<td>3-year:84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>167 ##</td>
<td>37</td>
<td>NA</td>
</tr>
</tbody>
</table>

*: median age: 64; ** > 65 years; # median age 65; ## > 70 years

D-VMP continued to demonstrate a significant PFS benefit with extended follow up

• Median (range) follow-up: 40.1 (0-52.1) months

Phase III ALCYONE Trial: PFS with Dara + VMP vs VMP in NDMM

- Daratumumab monotherapy phase
- 42-month PFS
- HR, 0.42; 95% CI, 0.34-0.51; \( P < 0.0001 \)

D-VMP: median 36.4
VMP: median 19.3

Phase III Trials in NDMM Not Eligible for ASCT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>n</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vista(^1)</td>
<td>VMP</td>
<td>344</td>
<td>24 (TTP)</td>
<td>56.4</td>
</tr>
<tr>
<td>FIRST(^2)</td>
<td>Rd cont</td>
<td>535</td>
<td>26</td>
<td>59.1</td>
</tr>
<tr>
<td>SWOG777(^3)</td>
<td>VRD</td>
<td>242*</td>
<td>43</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>91**</td>
<td>65</td>
</tr>
<tr>
<td>Endurance(^4)</td>
<td>VRD</td>
<td>542 #</td>
<td>34.4</td>
<td>3-year: 84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>167 ##</td>
<td>37</td>
<td>NA</td>
</tr>
<tr>
<td>Alcyone(^5)</td>
<td>VMP-Dara</td>
<td>356</td>
<td>36.4</td>
<td>42-Mo: 75%</td>
</tr>
</tbody>
</table>

*: median age: 64; ** > 65 years; # median age 65; ## > 70 years

## Phase III Trials in NDMM Not Eligible for ASCT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>n</th>
<th>mPFS</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vista(^1)</td>
<td>VMP</td>
<td>344</td>
<td>24 (TTP)</td>
<td>56.4</td>
</tr>
<tr>
<td>FIRST(^2)</td>
<td>Rd cont</td>
<td>535</td>
<td>26</td>
<td>59.1</td>
</tr>
<tr>
<td>SWOG777(^3)</td>
<td>VRD</td>
<td>242*</td>
<td>43</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>91**</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>Endurance(^4)</td>
<td>VRD</td>
<td>542 #</td>
<td>34.4</td>
<td>3-year: 84% NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>167 ##</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Alcyone(^5)</td>
<td>VMP-Dara</td>
<td>356</td>
<td>36.4</td>
<td>42-Mo: 75%</td>
</tr>
<tr>
<td>MAIA(^6)</td>
<td>Rd-Dara</td>
<td>368</td>
<td>30-Mo: 71%</td>
<td>Immature</td>
</tr>
</tbody>
</table>

*: median age: 64; ** > 65 years; # median age 65; ## > 70 years

---

ASH2020 – Kumar et al – MAIA Follow-up: 4 years

Median NR (55+ ?) vs 34 mos

Overview of Median PFS in Recent Phase III Trials in Patients Not Eligible for ASCT

Direct comparison between trials is not intended and should not be inferred. HR, hazard ratio; NR, not reached; NSCT, non-stem cell transplant; PFS, progression-free survival; Rd, lenalidomide, low-dose dexamethasone; RdD, daratumumab, lenalidomide, dexamethasone; RVd, lenalidomide, bortezomib and dexamethasone; VMP, bortezomib, melphalan, prednisone.

Accumulative Lines of Therapy Received by Age at Diagnosis: Best Therapy Should Be Used Upfront in Elderly Patients

- <70 years, n = 165
- 70+ years, n = 174
PFS and OS by Frailty Level in the FIRST Study

Category Score

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>• ≤ 75 years</td>
<td>0</td>
</tr>
<tr>
<td>• 76-80 years</td>
<td>1</td>
</tr>
<tr>
<td>• &gt; 80 years</td>
<td>2</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td></td>
</tr>
<tr>
<td>• ≤ 1</td>
<td>0</td>
</tr>
<tr>
<td>• &gt; 1</td>
<td>1</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>• 0</td>
<td>0</td>
</tr>
<tr>
<td>• 1</td>
<td>1</td>
</tr>
<tr>
<td>• ≥ 2</td>
<td>2</td>
</tr>
<tr>
<td>Sum of scores</td>
<td></td>
</tr>
<tr>
<td>• Non-frail</td>
<td>0-1</td>
</tr>
<tr>
<td>• Frail</td>
<td>≥ 2</td>
</tr>
</tbody>
</table>

Facon. Leukemia. 2020;34:224.
Modified RVd (RVd-lite) in Transplant-Ineligible MM

NDMM
Ineligible for ASCT

**Induction**

RVd-lite
- R: 15 mg days 1–21
- V: 1.3 mg/m² SC³ weekly
- d: 20 mgᵇ
- 9 x 35-day cycles

**Consolidation**

RV
- R: 15 mgᶜ days 1–21
- V: 1.3 mg/m²ᵇ SC days 1, 15
- 6 x 28-day cycles

**Maintenance**

Rᵈ until PD or unacceptable side-effects

---

**Baseline characteristics, %**

<table>
<thead>
<tr>
<th></th>
<th>N = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>73 (65–91)</td>
</tr>
<tr>
<td>ISS stage at diagnosis</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>38</td>
</tr>
<tr>
<td>II</td>
<td>34</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
</tr>
<tr>
<td>ECOG PS score</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
</tr>
</tbody>
</table>

** Responses**

- ≥ CR was 44% (ITT population, N = 50)
- ORR was 86%, ≥ VGPR was 66% for patients evaluable for responseᵃ after 4 cycles (n = 46)
- Median TTR was 1.1 months
- Grade 3/4 peripheral neuropathy was 2%, neutropenia was 14%

**Survival (probability)**

- Median follow-up: 30 months
- Median PFS: 35.1 months

---

ᵃ The first 10 patients received BORT IV for cycle 1 only followed by SC administration. Subsequent patients received BORT SC. ᵇ Days 1, 2, 8, 9, 15, 16, 22, 23 for patients ≤ 75 years; days 1, 8, 15, 22 for patients > 75 years. ᶜ Or last tolerated dose as of cycle 9. ᵈ Optional. ⁶% of patients received < 4 cycles of therapy and were therefore not evaluable. MR, minimal response; TTR, time to response.
Eligibility for ASCT

**Yes**

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

200 mg/m² Melphalan followed by ASCT

Maintenance
- Lenalidomide

...”< 66 years Or fit patients < 70 years in good clinical condition”…

**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
Multiple Myeloma, Version 1.2020

Featured Updates to the NCCN Guidelines

Shaji K. Kumar, MD; Natalie S. Callander, MD; Jens Hillengass, MD; Michaela Liedtke, MD; Muhamed Baljevic, MD; Erica Campagnaro, MD; Jorge J. Castillo, MD; Jason C. Chandler, MD; Robert F. Cornell, MD, MPH; Caitlin Costello, MD; Yvonne Efebe, MD, MPH; Matthew Faiman, MD; Alfred Garfall, MD; Kelly Godby, MD; Leona Holmberg, MD, PhD; Myo Htut, MD; Carol Ann Huff, MD; Yubin Kang, MD; Ola Landgren, MD, PhD; Ehsan Malek, MD; Thomas Martin, MD; James Omel, MD; Noopur Raje, MD; Douglas Sborov, MD, MSc; Seema Singhal, MD; Keith Stockel-Goldstein, MD; Carlyn Tan, MD; Donna Weber, MD; Alyse Johnson-Chilla, MD; Jennifer Keller, MSS; and Rashmi Kumar, PhD

Response after primary therapy

OR

Autologous stem cell transplant (category 1)

Continuous myeloma therapy or maintenance therapy

OR

Allogeneic stem cell transplant, under certain circumstances

JNCCN.org | Volume 17 Issue 10 October 2019
INDUCTION

ASCT prepared by melphalan 200 mg/m²

(Consolidation)

Maintenance
Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to autologous transplantation in multiple myeloma

Laura Rosiñol, Albert Oriol, Rafael Rios, Anna Sureda, María-Jesús Blanchard, Miguel Teodoro Hernández, Rafael Martínez-Martínez, Jose M Moraleda, Isidro Jarque, Juan Bargay, Mercedes Gironella, Felippe de Arriba, Luis Palomera, Yolanda González-Montes, Josep Martí, Isabel Krsnik, Jose M Argüinano, María-Esther Gonzalez, Ana Pilar Gonzalez, Luis Felipe Casado, Lucia Lopez-Anglada, Bruno Paiva, Maria-Victoria Mateos, Jesus San Miguel, Juan-José Lahuerta and Joan Bladé
VGPR or better in the 426 patients
Who initiated cycle 6

Response rates in the ITT
N = 458

Median number of CD34+ cells (3 cycles) : $4.66 \times 10^6$/kg

CASSIOPEIA Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017

**Key eligibility criteria:**
- Transplant-eligible NDMM
- 18-65 years
- ECOG 0-2

**Induction**

**D-VTd**
- D: 16 mg/kg IV QW Cycles 1-2, Q2W Cycles 3-4
- V: 1.3 mg/m² SC Days 1, 4, 8, 11
- T: 100 mg/day PO
d: 20-40 mg IV/PO<sup>a</sup>

**VTd**
- VTd administered as in the D-VTd arm

4 Cycles of 28 days

**Consolidation**

**D-VTd**
- D: 16 mg/kg IV Q2W
- V: 1.3 mg/m² SC Days 1, 4, 8, 11
- T: 100 mg/day PO
d: 20 mg IV/PO<sup>a</sup>

**VTd**
- VTd administered as in the D-VTd arm

2 Cycles of 28 days

**Maintenance**

**D monotherapy**
- D 16 mg/kg IV Q8W until PD (2 years maximum, then observation until PD)

**Observation**
- (2 years maximum)

**Follow-up**

**Part 1**

4 Cycles of 28 days

**Part 2**

2 Cycles of 28 days

---

Efficacy: Response Rates Over Time

65% VGPR or better

D-VTd

Patients (%)

Post-induction | Post-ASCT | Post-consolidation
---|---|---
SD/PD/NE | PR | VGPR | CR | sCR

VTd

Patients (%)

Post-induction | Post-ASCT | Post-consolidation
---|---|---
SD/PD/NE | PR | VGPR | CR | sCR

**Efficacy: MRD (Flow Cytometry; 10^{-5})**

**P < 0.0001**

<table>
<thead>
<tr>
<th>MRD-negative rate, %</th>
<th>D-VTd (n = 543)</th>
<th>VTd (n = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>63%</td>
<td>43%</td>
</tr>
</tbody>
</table>

D-VTd superior across all subgroups including high-risk cytogenetics and ISS stage III

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>VTd</th>
<th>D-VTd</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>131 (41)</td>
<td>192 (61)</td>
<td>2.22 (1.62–3.05)</td>
</tr>
<tr>
<td>Female</td>
<td>105 (47)</td>
<td>154 (68)</td>
<td>2.37 (1.62–3.48)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>38 (42)</td>
<td>56 (68)</td>
<td>2.84 (1.53–5.28)</td>
</tr>
<tr>
<td>≥50 years</td>
<td>198 (44)</td>
<td>290 (63)</td>
<td>2.19 (1.68–2.85)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFM</td>
<td>204 (45)</td>
<td>287 (64)</td>
<td>2.16 (1.65–2.81)</td>
</tr>
<tr>
<td>HOVON</td>
<td>32 (38)</td>
<td>59 (65)</td>
<td>3.05 (1.65–5.65)</td>
</tr>
<tr>
<td><strong>ISS disease stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>103 (45)</td>
<td>137 (67)</td>
<td>2.48 (1.68–3.67)</td>
</tr>
<tr>
<td>II</td>
<td>96 (41)</td>
<td>155 (61)</td>
<td>2.21 (1.54–3.18)</td>
</tr>
<tr>
<td>III</td>
<td>37 (46)</td>
<td>54 (64)</td>
<td>2.14 (1.15–4.00)</td>
</tr>
<tr>
<td><strong>Cytogenetic profile at trial entry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>38 (44)</td>
<td>49 (60)</td>
<td>1.88 (1.02–3.46)</td>
</tr>
<tr>
<td>Standard risk</td>
<td>197 (43)</td>
<td>296 (64)</td>
<td>2.35 (1.80–3.07)</td>
</tr>
<tr>
<td><strong>Baseline creatinine clearance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90 ml/min</td>
<td>139 (44)</td>
<td>205 (62)</td>
<td>2.07 (1.51–2.84)</td>
</tr>
<tr>
<td>≤90 ml/min</td>
<td>97 (43)</td>
<td>141 (67)</td>
<td>2.64 (1.79–3.89)</td>
</tr>
<tr>
<td><strong>Baseline hepatic function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>216 (43)</td>
<td>310 (65)</td>
<td>2.40 (1.85–3.10)</td>
</tr>
<tr>
<td>Impaired</td>
<td>20 (48)</td>
<td>36 (57)</td>
<td>1.47 (0.67–3.21)</td>
</tr>
<tr>
<td><strong>Type of multiple myeloma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lgG</td>
<td>122 (39)</td>
<td>201 (61)</td>
<td>2.43 (1.77–3.34)</td>
</tr>
<tr>
<td>Non-lgG</td>
<td>59 (49)</td>
<td>61 (66)</td>
<td>2.00 (1.15–3.50)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>112 (44)</td>
<td>172 (65)</td>
<td>2.39 (1.68–3.41)</td>
</tr>
<tr>
<td>≥1</td>
<td>124 (44)</td>
<td>174 (63)</td>
<td>2.17 (1.55–3.04)</td>
</tr>
</tbody>
</table>

Efficacy: PFS From First Randomization

- Median (range) follow-up: 18.8 (0.0-32.2) months

53% reduction in the risk of progression or death in the D-VTd arm

Post-consolidation PFS by MRD Status (MFC; $10^{-5}$)

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>VTd MRD−</th>
<th>VTd MRD+</th>
<th>D-VTd MRD−</th>
<th>D-VTd MRD+</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-VTd MRD−</td>
<td>344</td>
<td>241</td>
<td>132</td>
<td>44</td>
</tr>
<tr>
<td>VTd MRD−</td>
<td>232</td>
<td>167</td>
<td>88</td>
<td>27</td>
</tr>
<tr>
<td>D-VTd MRD+</td>
<td>148</td>
<td>105</td>
<td>53</td>
<td>17</td>
</tr>
<tr>
<td>VTd MRD+</td>
<td>243</td>
<td>152</td>
<td>75</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MRD− vs MRD+</th>
<th>D-VTd vs VTd</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.31 (0.20-0.50)</td>
<td>0.48 (0.30-0.78)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>0.0028</td>
</tr>
</tbody>
</table>

PFS benefit for D-VTd versus VTd in patients achieving MRD negativity

Avet-Loiseau et al. EHA 2019
Randomized Phase 2 GRIFFIN Study: RVd + Daratumumab in ASCT-Eligible Patients

Key eligibility criteria:
- Transplant-eligible NDMM
- 18-70 years of age
- ECOG PS score 0-2
- CrCl ≥30 ml/min

Induction: Cycles 1-4
D-RVd
D: 16 mg/kg IV Days 1, 8, 15
R: 25 mg PO Days 1-14
V: 1.3 mg/m² SC Days 1, 4, 8, 11
d: 20 mg PO Days 1, 2, 8, 9, 15, 16

Consolidation: Cycles 5-6
D-RVd
D: 16 mg/kg IV Day 1
R: 25 mg PO Days 1-14
V: 1.3 mg/m² SC Days 1, 4, 8, 11
d: 20 mg PO Days 1, 2, 8, 9, 15, 16

Maintenance: Cycles 7-32
D-R
D: 16 mg/kg IV Day 1
R: 25 mg PO Days 1-14
V: 1.3 mg/m² SC Days 1, 4, 8, 11
d: 20 mg PO Days 1, 2, 8, 9, 15, 16

Stem cell mobilization with G-CSF ± plerixafor

Endpoints & statistical assumptions
Primary endpoint: sCR rate (by end of consolidation); 1-sided alpha of 0.1
80% power to detect 15% improvement (50% vs 35%), N = 200

Secondary endpoints:
- rates of MRD negativity (measured by clonoSEQ; NGS 10⁻⁵), CR, ORR, ≥VGPR

**GRiffin: Responses Deepened Over Time**

**D-RVd**

- End of induction: 52.5%
- End of ASCT: 59.6%
- End of consolidation: 39.4%
- Clinical cutoff: 17.2%

**RVd**

- End of induction: 7.2%
- End of ASCT: 43.3%
- End of consolidation: 35.1%

**Response rates and depths were greater for D-RVd at all time points**

# Post-Consolidation MRD Negativity

<table>
<thead>
<tr>
<th>MRD-Negative Status (10^{-5}),^a n (%)</th>
<th>D-RVd</th>
<th>RVd</th>
<th>Odds Ratio (95% CI)</th>
<th>( P ) value^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>In ITT population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRD negative regardless of response</td>
<td>46/104 (44.2)</td>
<td>15/103 (14.6)</td>
<td>4.70 (2.38-9.28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MRD negative with CR or better</td>
<td>30/104 (28.8)</td>
<td>10/103 (9.7)</td>
<td>3.73 (1.71-8.16)</td>
<td>0.0007</td>
</tr>
<tr>
<td>In patients achieving CR or better</td>
<td>30/51 (58.8)</td>
<td>10/41 (24.4)</td>
<td>4.65 (1.76-12.28)</td>
<td>0.0014</td>
</tr>
<tr>
<td>In patients who received ASCT</td>
<td>45/94 (47.9)</td>
<td>14/78 (17.9)</td>
<td>4.31 (2.10-8.85)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

^aThe threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on assessment of bone marrow aspirates by next-generation sequencing in accordance with International Myeloma Working Group criteria. MRD assessments occurred in patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken (D-RVd, n = 71; RVd, n = 55). Patients with a missing or inconclusive assessment were considered MRD positive. ^b\( P \) values were calculated from the Fisher’s exact test.

D-RVd improved MRD-negativity (10^{-5}) rates at the end of consolidation.
D-RVd: Estimated PFS and OS (>95%) at 2 Years…

… but impressive results also achieved in the RVd arm!!

- Median follow-up = 22.1 months

Role of tandem ASCT
5-year PFS
53.5% vs 44.9%

5-year OS
83.3% vs 72.6%

Cavo et al. EMN02 study
Maintenance with lenalidomide

![Graph showing OS (probability) over time with lenalidomide maintenance or placebo/observation.]

<table>
<thead>
<tr>
<th></th>
<th>No. of Events/No. of Patients</th>
<th>Median OS (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Len maintenance</td>
<td>215/605</td>
<td>NR (NR to NR)</td>
<td>0.75 (0.63 to 0.90)</td>
</tr>
<tr>
<td>Placebo/observation</td>
<td>275/603</td>
<td>86.0 months (79.8 to 96.0)</td>
<td></td>
</tr>
</tbody>
</table>

No. at risk:
- Len maintenance: 605 577 555 508 473 431 385 282 200 95 20 1 0
- Placebo/observation: 603 569 542 505 459 425 351 270 174 71 10 0

McCarthy. JCO. 2017;35:3279.
Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial

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

Maintenance trial after ASCT

Arm A
Lena/dexa

Arm B
Lena/dexa + Ixazomib
d 1,8,15

MRD assessment

MRD neg → Stop

MRD pos

Lena/dexa
X 3 years

MRD annual
Eligibility for ASCT

Yes

Induction: 3-drug regimens
VTD + CD38
RVD + CD38

200 mg/m2 Melphalan followed by ASCT
Tandem for high-risk disease?
Consolidation: Triplet + CD38?

Maintenance
Lenalidomide + Ixa / CD38

No

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

FRONTLINE THERAPY
ESMO guidelines, 2020?
Now, let’s return to our patient case
Patient Case Example: 73-Year-Old Male

Presents with:

- Bone pain
- Anemia Hb: 10.2 g/dL
- Serum electrophoresis: M-spike: 4.2 g/dL; IF: IgG K
- Bone marrow aspirate: 30% plasma cells
- Cytogenetics (FISH): $t(11;14)$
- Low-dose whole-body CT: diffuse bone lesions, spine
- Creatinine: 0.9 mg/dL; β2-M: 2.5 mg/L, albumin 3.8 g/dL, LDH < normal

→ symptomatic multiple myeloma, ISS1, R-ISS1
Assessment 2: Now, what would you recommend for this patient?

1. Rd until progression
2. VRD x 8 followed by Rd until PD
3. VRD lite followed by R until PD
4. VMP-daratumumab x 9 followed by daratumumab until PD
5. Rd + daratumumab, until PD
6. VRD x 4 → ASCT prepared by mel 200 → len maintenance until PD
7. Uncertain
Panel Discussion: Individualized Approaches to Frontline Treatment Selection