Multiple Myeloma in 2017 – Making Sense of All of the Choices

TACOS

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Scottsdale, Arizona
Rochester, Minnesota
Jacksonville, Florida

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Financial Disclosure(s)

I currently have or have had the following relevant financial relations to disclose:

Contracted Research: Abbvie, Celgene, Sanofi
Off-Label Use Disclosure(s)

I do not intend to discuss an off label use of a product during this activity.
Objectives

• Review the plethora of options for frontline therapy
• Describe the benefit of combining multiple mechanisms of action in therapy
• Appreciate the ongoing importance of ASCT in MM
• Develop a strategy for treating relapsed MM
Important and Overall Themes in Myeloma Care in 2017

• Longer therapy with fewer “treatment holidays” – especially in older patients

• Combination therapy – A plus B can be superior to A then B

• Improved side effect profile and quality of life in patients treated with novel agents

• Immunotherapy – leveraging the immune system is HUGE in cancer, and has now arrived in myeloma also
The Immune System and Cancer

The Myeloma Microenvironment Is Key to Disease Pathophysiology

Improving Survival in MM

*Year ranges represent the year of diagnosis.

Note: By linking to the SSA Master Death File, survival was measured as time from diagnosis date to the date of death obtained from the SSA, time from diagnosis date to the date of inpatient death, or time from diagnosis date to September 30, 2015; Survival estimates were presented for multiple myeloma patients diagnosed and treated during 2006-2012 (n=9,521).
Outcomes in Myeloma; Continued Progress and Real Hope

FDA Approvals in MM

- 2006 Thalidomide
- 2007 Doxil + BTZ
- 2006, 2014 Lenalidomide
- 2012, 2015 Carfilzomib
- 2013, 2015 Pomalidomide
- 2015 Panobinostat
- 2015 Ixazomib
- 2015 Daratumumab
- 2015 Elotuzumab

How I Treat - Initial Therapy

- ASCT Eligible
  - Bortezomib-lenalidomide Dex for most
  - Cyclophosphamide-Bortezomib-Dex for some

- ASCT Ineligible
  - Lenalidomide-Dex for most
  - Add bortezomib in high risk disease
Initial Treatment of Myeloma

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

**Transplant Candidate**
- **VRd x 4 cycles**
  - **Auto SCT +/- Maintenance**
    - (Len for std risk; bortez for high risk)
  - **VRd x 4 cycles**
    - Len maintenance
    - Delayed Transplant

*Frailty Score; Palumbo A, *Blood*. 2015;125:2068-2074; VCD x 12 months is alternative

Rajkumar SV. 2016
### mSMART 2.0: Classification of Active MM

<table>
<thead>
<tr>
<th>High-Risk</th>
<th>Intermediate-Risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Standard-Risk&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| - FISH<sup>c</sup>  
  - Del 17p  
  - t(14;16)  
  - t(14;20)  
- GEP  
  - High risk signature | - FISH  
  - t(4;14)<sup>d</sup>  
  - 1q gain  
  - High PC S-phase<sup>f</sup> | - All others including:  
  - Trisomies  
  - t(11;14)<sup>e</sup>  
  - t(6;14) |

<sup>a</sup> Note that a subset of patients with these factors will be classified as high-risk by GEP

<sup>b</sup> LDH >ULN and beta-2 M > 5.5 may indicate worse prognosis;<sup>c</sup> Trisomies may ameliorate

<sup>d</sup> Prognosis is worse when associated with high beta-2 M and anemia

<sup>e</sup> t(11;14) may be associated with plasma cell leukemia;<sup>f</sup> Cut-offs vary

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mSMART – Off-Study

Transplant Eligible

**Standard-Risk**

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

**Intermediate-Risk**

- t(4;14)
  - 4 cycles of VRd
  - Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
  - Bortezomib-based maintenance for 2 years

**High-Risk**

- Del 17p, t(14;16), t(14;20)
  - 4 cycles of KRd
  - Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
  - Carfilzomib or Bortezomib-based maintenance for 2 years

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*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 2 years

*Continuing Rd for patients responding to Rd and with low toxicities

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Induction Regimens for Patients Eligible for ASCT

Increasing depth of response in myeloma with newer drugs

At least VGPR after 4 cycles induction in newly diagnosed MM

RD or CyBorD
$100,000 per year

VRD or KRD
$250,000 per year

KRD - Dytfield Haematologica 99(9) e162-4 2014
KCD – Bringhen Blood 124(1) 63-69 2014
VCD – Khan Br J Haematol 156(3) 326-333 2012
TD & VTD – Cavo Blood 2012
RD – Rajkumar Lancet Oncol 11(1) 29-37

K – Carfilzomib
C – Cyclophosphamide
V – Bortezomib
R – Lenalidomide
A – Doxorubicin
D – Dexamethasone
SWOG S0777: Study Design

- Randomized phase III trial of VRd vs Rd
  
  *Stratified by ISS stage I/II/III and intent to transplant at progression*

  Previously untreated active MM (CRAB criteria) with measurable disease (including FLC) and CrCl > 30 cc/min (N = 525)

  - Primary endpoint: PFS
  - Secondary endpoints: ORR, OS, safety

  - Median follow-up: 55 mos
  - Median time on maintenance: 385 days
  - All pts received aspirin 325 mg/day; bortezomib pts received HSV prophylaxis

  **VRd**

  - Lenalidomide 25 mg/day PO D1-21 + Dexamethasone 40 mg/day PO D1,8,15,22 for six 28-day cycles (eligible n = 230)

  - Bortezomib 1.3 mg/m^2 IV D1,4,8,11 + Lenalidomide 25 mg/day PO D1-14 + Dexamethasone 20 mg/day D1,2,4,5,8,9,11,12 for eight 21-day cycles (eligible n = 243)

  **Rd**

  Maintenance until PD, unacceptable toxicity, or withdrawal of consent

## SWOG S0777: Pt Characteristics

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>VRd (n = 264)</th>
<th>Rd (n = 261)</th>
<th>Overall (N = 525)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>63</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>65 yrs of age or older</td>
<td>38</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>SWOG PS &gt; 1</td>
<td>12</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Serum ß₂-m ≥ 4 mg/L</td>
<td>51</td>
<td>56</td>
<td>53</td>
</tr>
<tr>
<td>CRP ≥ 8 mg/L</td>
<td>21</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Creatinine ≥ 2 mg/dL</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>LDH ≥ 190 U/L</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Albumin &lt; 3.5 g/dL</td>
<td>41</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Hb &lt; 10 g/dL</td>
<td>33</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Platelets &lt; 150 x 10⁹/L</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ISS stage III</td>
<td>32</td>
<td>34</td>
<td>33</td>
</tr>
</tbody>
</table>

## SWOG S0777: Response

<table>
<thead>
<tr>
<th>Confirmed Response, %</th>
<th>VRd (n = 216*)</th>
<th>Rd (n = 214*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (PR or better)</td>
<td>81.5</td>
<td>71.5</td>
</tr>
<tr>
<td>- CR</td>
<td>15.7</td>
<td>8.4</td>
</tr>
<tr>
<td>- VGPR</td>
<td>27.8</td>
<td>23.4</td>
</tr>
<tr>
<td>- PR</td>
<td>38.0</td>
<td>39.7</td>
</tr>
<tr>
<td>SD or better</td>
<td>97.2</td>
<td>95.8</td>
</tr>
<tr>
<td>- SD</td>
<td>15.7</td>
<td>24.3</td>
</tr>
<tr>
<td>PD or death</td>
<td>2.8</td>
<td>4.2</td>
</tr>
</tbody>
</table>

*Assessable.

**SWOG S0777: Survival Outcomes**

<table>
<thead>
<tr>
<th>Survival, Mos</th>
<th>VRd (n = 242)</th>
<th>Rd (n = 229)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>43</td>
<td>30</td>
<td>0.712</td>
<td>.0018*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.560 - 0.906)</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>75</td>
<td>64</td>
<td>0.709</td>
<td>.025†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.516 - 0.973)</td>
<td></td>
</tr>
</tbody>
</table>

*1-sided P value.
†2-sided P value.

- PFS, OS increase remain significant when age-adjusted in multivariate analysis
- Other significant factors: ISS stage III, 65 yrs of age or older

# SWOG S0777: Safety

<table>
<thead>
<tr>
<th>Adverse Event, * %</th>
<th>VRd (n = 241†)</th>
<th>Rd (n = 226†)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Neurologic</td>
<td>33</td>
<td>11</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>- Pain</td>
<td>12</td>
<td>4</td>
<td>.0002</td>
</tr>
<tr>
<td>- Sensory</td>
<td>23</td>
<td>3</td>
<td>.004</td>
</tr>
<tr>
<td>- Gastrointestinal</td>
<td>22</td>
<td>8</td>
<td>NR</td>
</tr>
<tr>
<td>Secondary primary malignancies</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*Only AEs at least possibly attributed to protocol therapy. †Evaluable.

SWOG S0777: Conclusions

- Addition of bortezomib to Rd (VRd) induction with continuous Rd maintenance significantly improves outcomes in untreated pts with MM vs Rd alone
  - Significantly longer PFS, OS
  - Deeper responses

- Acceptable safety profile
  - Increased incidence of neuropathic, GI events with bortezomib (IV administration used)

- Investigators concluded that VRd induction followed by continuous Rd maintenance represents potential new standard of care for untreated MM

Phase III IFM 2009: RVD ± ASCT in Newly Diagnosed Younger MM Pts

Stratified by ISS stage and cytogenetics

Pts 65 yrs old of age or younger with symptomatic NDMM; ECOG PS < 2 with organ damage and measurable disease*; treated with 1 cycle RVD† (N = 700)

RVD† Cycles 2, 3
PBSC collection
Cyclophosphamide 3 g/m² + G-CSF
RVD† Cycles 4-8
(n = 350)

ASCT with MEL200
RVD† Cycles 4, 5
(n = 350)

Lenalidomide Maintenance 10-15 mg/day for 12 mos

*Serum M-protein > 10 g/L and/or urine M-protein > 200 mg/24 hrs and/or serum FLC > 100 mg/L if serum FLC ratio is abnormal.
†Lenalidomide 25 mg/day on Days 1-14; bortezomib 1.3 mg/m² on Days 1, 4, 8, 11; dexamethasone 20 mg/day on Days 1, 2, 4, 5, 8, 9, 11, 12.

At second interim analysis in June 2015 with median follow-up of 39 mos, the data and safety monitoring board for this trial recommended that the trial be stopped

### IFM 2009: Responses

<table>
<thead>
<tr>
<th>Response, %</th>
<th>RVD (n = 350)</th>
<th>Transplantation (n = 350)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>49</td>
<td>59</td>
<td>.02</td>
</tr>
<tr>
<td>VGPR</td>
<td>29</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>20</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>&lt; PR</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>78</td>
<td>88</td>
<td>.001</td>
</tr>
<tr>
<td>Negative MRD by FCM</td>
<td>65</td>
<td>80</td>
<td>.001</td>
</tr>
</tbody>
</table>

# IFM 2009: Pts Achieving ≥ VGPR by Treatment Phase

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>≥ VGPR Rate, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RVD (n = 350)</td>
<td>Transplantation (n = 350)</td>
<td></td>
</tr>
<tr>
<td>After induction</td>
<td>47</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>After transplant or cycle 4 of consolidation</td>
<td>55</td>
<td>73</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>After consolidation completed</td>
<td>71</td>
<td>81</td>
<td>&lt; .006</td>
</tr>
<tr>
<td>At end of maintenance phase</td>
<td>78</td>
<td>88</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

IFM 2009: PFS (Primary Endpoint)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RVD (n = 350)</th>
<th>Transplantation (n = 350)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, mos</td>
<td>41</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Progression or death, n</td>
<td>204</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>34</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>4-yr PFS, %</td>
<td>35</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
<td>0.69 (0.56-0.84)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

IFM 2009: PFS (9/2015)

The Kaplan-Meier survival curve shows the proportion of patients (in %) remaining free of disease progression over time. The curve for patients receiving high-dose therapy (HDT) is compared to those not receiving HDT (no HDT).

The graph displays a significant difference in progression-free survival (PFS) between the two groups, with a p-value of less than 0.001. The number of patients at risk at different months of follow-up is as follows:

- **HDT**:
  - 0 months: 350
  - 12 months: 309
  - 24 months: 261
  - 36 months: 153
  - 48 months: 27

- **no HDT**:
  - 0 months: 350
  - 12 months: 296
  - 24 months: 228
  - 36 months: 128
  - 48 months: 24

The curve indicates a higher proportion of patients remaining PFS in the HDT group compared to the no HDT group, especially in the later months of follow-up.
IFM 2009: Conclusions

ASCT vs RVD in pts with NDMM is associated with:
31% reduced risk of progression or death (P < .001)
Improved TTP and rate of MRD negativity
Similar, low rate of mortality

This analysis demonstrates that transplantation:
Is feasible: 93%
Is associated with an acceptable Transplant Related Mortality: 1.4%.
Is associated with an increased rate of neg MRD (80% vs 65%, p<0.01).
Is associated with an improved 4-year PFS (47% vs 35%, p<0.001).
Is associated with an improved 4-year TTP (49% vs 35%, p<0.001).

A longer follow up is required to draw any conclusion concerning OS,
Since the 4-year survival is high in both arms (81% vs 83%).
However, transplantation is already associated with a reduced risk of death due to myeloma.

In the era of new drugs, Transplantation should Remain “A Standard of Care”
ECOG E1A11 Trial: KRD vs. VRD
Newly Diagnosed, Standard Risk MM (N=756)

**Primary Endpoint:**
OS (maintenance)

**Secondary Endpoints:**
PFS (maintenance)
PFS (induction)
Response & MRD (induction)
Safety
HR-QoL

**STATISTICS FOR INDUCTION PFS COMPARISON:**
- Stratified logrank test will be used to compare PFS distributions.
- Median PFS on VRd (Arm A) is expected to be 3 years. With 756 patients randomized at induction, there is 80% power at a 1-sided 0.025 significance level to detect a 25% reduction in the hazard rate on the CRd arm (33% improvement in median PFS to 4 years; hazard ratio=0.75).

**KRD (28-day cycle x 9)**
- Carfilzomib: 20/36 mg/m² IV D1, 2, 8, 9, 15, 16
- Lenalidomide: 25 mg PO daily (days 1-21)
- Dexamethasone: 20/40 mg PO D1, 8, 15, 22

**VRd (21-day cycle x 12)**
- Bortezomib: 1.3 mg/m² SC or IV D1, 4, 8, 11
- Lenalidomide: 25 mg PO daily (days 1-14)
- Dexamethasone: 10/20 mg PO D1, 2, 4, 5, 8, 9, 11, 12

**LEN maintenance**
15 mg PO D1-21
- for 24 cycles
- until PD or intolerance

FPFV = August 2013
Enrollment period = 42 months

E1A11 Clinical Study Protocol. Available at: clinicaltrials.gov. NCT01863550.
European Myeloma Network (EMN) FORTE Study: Randomized Study of CFZ in Transplant-Eligible NDMM

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

N= 425

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

Arm A: KRd
- 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 A: KRd
- 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: KCyd
- 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

Arm B: KCyd
- 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

Arm C: KRd
- 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

Total 12 Cycles

Lenalidomide 10 mg Days 1-21

MRD (M0) MRD (M4) MRD (M12) MRD (q6Mo)
Daratumumab Trial in Transplant-Eligible NDMM
Hovon/IFM

Endpoints:
• sCR
• PFS, OS

Induction 4 cycles
- VTD
  + Dara

Consolidation 2 cycles
- VTD
  + Dara

Maintenance
- Dara
  Observation

Stratify by: dara treatment, response, MRD status

Courtesy P. Sonneveld
Effect of Pre-transplant Salvage Therapy Prior to Autologous Transplant (ASCT) in Patients Not Responding to Initial Induction for MM

Deepened response in 68%

Salvage Chemotherapy

Salvage Cohort

No Salvage Cohort

Diagnosis and Initial Induction

< PR to induction

< PR to induction

12 months from diagnosis to ASCT

ASCT

Vij et al, BBMT 2014
Outcomes with/without Pre-ASCT Salvage

**PFS**
- SALVAGE (n=324)
- NO SALVAGE (n=251)

**OS**
- SALVAGE (n=324)
- NO SALVAGE (n=251)

P = NS

(Source: Txz12_23 & _24) MM06-04-12_15.ppt

Vij et al, BBMT 2014
Conclusions in Transplant Eligible Patients

• RVD (Lenalidomide – Bortezomib – Dex) remains the standard of care

• Consideration should still be given to CyBorD or VTD in the right context and place

• Novel agents have not supplanted the need of transplants

• Carfilzomib is reasonable option, especially in high risk disease or patients with pre-existing neuropathy

• Watch for the addition of monoclonal antibodies soon…
Transplant Ineligible Patients

Summary (punchline before story!)

• Melphalan is no longer frontline standard

• Novel agent use with lenalidomide or bortezomib is feasible and effective

• Arbitrary 12-18 month length of therapy no longer necessary – can treat indefinitely

• Dose adjustment is critical in older patients
  • Weekly, subcutaneous bortezomib
  • Lower dose lenalidomide
  • Lower dose weekly dexamethasone

• More convenient and less toxic options on the way!
mSMART – Off-Study

Transplant Ineligible

<table>
<thead>
<tr>
<th>Standard-Risk</th>
<th>Intermediate-Risk</th>
<th>High-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;14), t(6;14), Trisomies</td>
<td>t(4;14)</td>
<td>Del 17p, t(14;16), t(14;20)</td>
</tr>
<tr>
<td>VRd for ~12 months; If age ≥75 or frail: Rd a</td>
<td>VRd for ~12 months</td>
<td>VRd c for ~12 months</td>
</tr>
<tr>
<td>Rd x 1 year a, b</td>
<td>Bortezomib-based maintenance for minimum of 1 year</td>
<td>Bortezomib-based maintenance for minimum of 1 year</td>
</tr>
</tbody>
</table>

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a In patients treated initially with Rd, continuing treatment until progression is an option for patients responding well with low toxicities;

b Dex is usually discontinued after first year

c Clinical trials strongly recommended as the first option

**FIRST (MM-020): Study Design**

- **Stratification:** Age (≤ 75 vs > 75 yrs), country, and ISS stage (I/II vs III)
- **Thromboprophylaxis** was mandatory
- **Data cutoff:** January 21, 2016

**Randomization 1:1:1** (N = 1623)

- **Arm A**
  - **Rd Continuous**
  - (n = 535)
  - LEN + LoDEX: Continuously
    - LENALIDOMIDE: 25 mg days 1-21/28
    - LoDEX: 40 mg days 1, 8, 15, 22/28

- **Arm B**
  - **Rd18**
  - (n = 541)
  - LEN + LoDEX: 18 Cycles (72 weeks)
    - LENALIDOMIDE: 25 mg days 1-21/28
    - LoDEX: 40 mg days 1, 8, 15, 22/28

- **Arm C**
  - **MPT**
  - (n = 547)
  - MEL + PRED + THAL 12 Cycles (72 weeks)
    - MELPHALAN: 0.25 mg/kg days 1-4/42
    - PREDNISONE: 2 mg/kg days 1-4/42
    - THALIDOMIDE: 200 mg days 1-42/42

**PD or Unacceptable Toxicity**

- **PD, OS, and** Subsequent anti-MM Tx

**LT Follow-Up**

- Pts aged > 75 yrs: LoDEX 20 mg days 1, 8, 15, 22/28; THAL 100 mg days 1-42/42; MEL 0.2 mg/kg days 1-4

Progression-Free Survival

- Updated PFS was prolonged with Rd continuous\(^a\)
  - Results remain consistent nearly 3 years after the original PFS analysis

![Graph showing progression-free survival probabilities over time.]

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mos</th>
<th>4-year PFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd continuous</td>
<td>26.0</td>
<td>32.6</td>
</tr>
<tr>
<td>Rd18</td>
<td>21.0</td>
<td>14.3</td>
</tr>
<tr>
<td>MPT</td>
<td>21.9</td>
<td>13.6</td>
</tr>
</tbody>
</table>

HR (95% CI)  
Rd continuous vs MPT:  
0.69 (0.59-0.79), \(P < .00001\)

\(^a\) PFS is based on investigator assessment of IMWG criteria; Data cutoff: January 21, 2016.
HR, hazard ratio; IMWG, International Myeloma Working Group; MPT, melphalan, prednisone, thalidomide; PFS, progression-free survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.
Overall Survival

- The pre-specified final OS analysis for the primary comparison showed that Rd continuous significantly extended OS vs MPT

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mos</th>
<th>4-yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd continuous</td>
<td>59.1</td>
<td>59.0</td>
</tr>
<tr>
<td>Rd18</td>
<td>62.3</td>
<td>58.0</td>
</tr>
<tr>
<td>MPT</td>
<td>49.1</td>
<td>51.7</td>
</tr>
</tbody>
</table>

HR (95% CI) Rd continuous vs MPT: 0.78 (0.67-0.92), P = .0023

Hazard ratio; MPT, melphalan, prednisone, thalidomide; OS, overall survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.
Second Primary Malignancies

- Hematologic SPM were more frequent with MPT than Rd continuous
- Incidence of solid tumor SPM was similar across treatment arms

<table>
<thead>
<tr>
<th>SPM, n (%)</th>
<th>Rd Continuous n = 532</th>
<th>Rd18 n = 540</th>
<th>MPT n = 541</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td>36 (6.8)</td>
<td>38 (7.0)</td>
<td>46 (8.5)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>4 (0.8)</td>
<td>2 (0.4)</td>
<td>14 (2.6)</td>
</tr>
<tr>
<td>AML</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>MDS</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>MDS to AML</td>
<td>0</td>
<td>0</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>B-cell leukemia</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Solid Tumor</td>
<td>32 (6.0)</td>
<td>37 (6.9)</td>
<td>32 (5.9)</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; MPT, melphalan, prednisone, thalidomide; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; SPM, second primary malignancies.
Conclusions

• Rd continuous significantly prolonged PFS compared with MPT in transplant-ineligible patients with NDMM, consistent with previously published analyses$^{1,2}$

• In this final analysis of OS, Rd continuous significantly improved OS compared with MPT

• No new safety signals were observed with long-term follow-up of Rd continuous

• The final analysis of this trial reaffirms Rd continuous as a standard of care for transplant-ineligible patients with NDMM

MPT, melphalan, prednisone, thalidomide; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression.

FIRST – Improved OS with Rd in good risk

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>3-yr, %</th>
<th>HR (95% CI) (Rd cont vs)</th>
<th>P Value (Rd cont vs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not High Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd cont</td>
<td>205</td>
<td>77.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rd18</td>
<td>209</td>
<td>71.0</td>
<td>0.85 (0.62-1.18)</td>
<td>.337</td>
</tr>
<tr>
<td>MPT</td>
<td>206</td>
<td>64.8</td>
<td>0.66 (0.48-0.91)</td>
<td>.009</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rd cont</td>
<td>43</td>
<td>40.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rd18</td>
<td>52</td>
<td>39.6</td>
<td>0.90 (0.55-1.47)</td>
<td>.676</td>
</tr>
<tr>
<td>MPT</td>
<td>47</td>
<td>46.8</td>
<td>0.95 (0.57-1.59)</td>
<td>.859</td>
</tr>
</tbody>
</table>

Overall Survival (mos)
Relapsed Myeloma
A Step-Wise Approach

• Overall approach must be:
  • Evidence based
  • Rational
  • Individualized to patient

• STRATEGY not a SCRIPT
  • No longer 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} line...etc, but a deliberate strategy based on several critical variables

• Ask yourself the following questions:
Question #1: Do I really need to treat this patient now?

- Spectrum of MGUS, Asymptomatic (smoldering) MM and true MM
  - Recall the importance of CRAB criteria
- This has been updated recently to include 3 more factors in newly diagnosed disease\(^1\)
  1. Plasmacytosis $\geq 60\%$
  2. Light chains Involved/Uninvolved $\geq 100$
  3. MRI 1 or more focal lesions

Ultra High Risk SMM = Active Myeloma

Not CRAB but now SLiM CRAB

- **S** (60% Plasmacytosis)
- **Li** (Light chains I/U >100)
- **M** (MRI 1 or more focal lesion)
- **C** (calcium elevation)
- **R** (renal insufficiency)
- **A** (anemia)
- **B** (bone disease)

Question #2: Should I retreat with a previous therapy?

- Depth of response
  - How rapidly and successfully did it work?\(^1\)
    - CR, VGPR, PR, MR, SD

- Duration of Response\(^2\)
  - How long did it last?

- If depth and duration (min 6 months) reasonable, consider retreating with same regimen – knowing it will be likely be less effective

- Bortezomib approval for re-treatment in 2014

CR= Complete Response; PR= Partial Response; MR= Minimal Response; SD= Stable Disease; VGPR= Very Good Partial Response

Question #3: Have I employed the Big Eight?

1. Thalidomide – often neglected in the US and dismissed due to other IMiDs – remains a very active and useful agent

- **PLUS** – minimal myelosuppression, combines well with traditional chemo and proteasome inhibitors, can be used in renal dysfunction

- **MINUS** - Neuropathy, fatigue, thrombosis, constipation

- **Best uses** – late in disease course, in patients who cannot tolerate myelosuppression, in combination (especially VTD and CyBorD-T)

VTD= combination bortezomib/thalidomide/dexamethasone; IMiD= immunomodulatory drugs
2. Bortezomib – extensively used in upfront and relapsed MM

- PLUS – highly effective, manageable cytopenias, can be used in renal dysfunction

- MINUS – Neuropathy (although mostly mitigated by SC route and weekly administration)

- Best uses – widely used alone, in combination with IMiDs and cyclophosphamide (CyBorD) and now with Daratumumab
The Big Eight

3. Lenalidomide – extensively used in relapsed setting, usually with dexamethasone

• PLUS - little neuropathy, can be dose adjusted for cytopenias, oral administration

• MINUS – Cytopenias, Fatigue, possible concern of MDS or SPMs, cramping, diarrhea

• Best Uses – widely used with dex alone, or with proteasome inhibitors, especially carfilzomib and ixazomib; most recently with Daratumumab
4. Carfilzomib – FDA approved agent in 2012 for pts refractory to last line with previous exposure to bortezomib and thal or len

- PLUS – highly effective, minimal neuropathy
- MINUS – possible tumor lysis, limited cardiac toxicity (mostly volume issue), twice weekly administration (but now more weekly)
- Best uses – wide use, even in bortezomib refractory disease, alone and in combination with other anti myeloma agents
The Big Eight

5. Pomalidomide – FDA approved agent in 2013 for pts refractory to last line with previous exposure to bortezomib and lenalidomide (very similar to carfilzomib)

- PLUS - Similar to lenalidomide with slightly less myelotoxicity and fatigue

- MINUS – Thromboprophylaxis necessary, some myelosuppression

- Best uses – highly active with dex, has been combined with bortezomib and carfilzomib effectively
6. Daratumumab – FDA approved Nov 2015 in patients with 3 or more lines of therapy of dual refractory to PI and IMiD; Nov 2016 in combination with bortezomib or lenalidomide

- PLUS – first monoclonal antibody with unique MOA, lack of overlapping toxicity, ideal partner for combinations

- MINUS – very long initial infusion (we plan on 9 hours) with at least 50% infusion reactions

- Best uses – monotherapy AND in combination, maybe even frontline soon
• CD38 is highly and ubiquitously expressed on myeloma cells\(^1,2\)
• DARA is a human IgG1 monoclonal antibody that binds CD38-expressing cells
• DARA binding to CD38 induces tumor cell death through direct and indirect mechanisms\(^3-5\)

Overall Response Rate

- ORR was 29% (95% CI, 21–39) in patients receiving 16 mg/kg DARA
- Stringent complete response (sCR) in 3% of patients (95% CI, 0.6–8.0)
- VGPR or better achieved in 12% (95% CI, 7–20) of patients
- Clinical benefit rate (ORR + MR) was 34% (95% CI, 25–44)

PR=partial response; VGPR=very good partial response.
CASTOR: Study Design

Multicenter, randomized, open-label, active-controlled phase 3 study

Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior bortezomib exposure, but not refractory

DVd (n = 251)

Daratumumab (16 mg/kg IV)
- Every week - cycle 1-3
- Every 3 weeks - cycle 4-8
- Every 4 weeks - cycles 9+

Vel: 1.3 mg/m² SC, days 1,4,8,11 - cycle 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycle 1-8

Vd (n = 247)

Vel: 1.3 mg/m² SC, days 1,4,8,11 - cycle 1-8
dex: 20 mg PO-IV, days 1,2,4,5,8,9,11,12 - cycle 1-8

1:1 RANDOMIZE

Primary Endpoint
- PFS

Secondary Endpoints
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.
## Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DVd (n = 251)</th>
<th>Vd (n = 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>64 (30-88)</td>
<td>64 (33-85)</td>
</tr>
<tr>
<td>≥75, n (%)</td>
<td>23 (9)</td>
<td>35 (14)</td>
</tr>
<tr>
<td>ISS staging, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>98 (39)</td>
<td>96 (39)</td>
</tr>
<tr>
<td>II</td>
<td>94 (38)</td>
<td>100 (41)</td>
</tr>
<tr>
<td>III</td>
<td>59 (24)</td>
<td>51 (21)</td>
</tr>
<tr>
<td>Cytogenetic profile, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del17p</td>
<td>28 (16)</td>
<td>21 (12)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>14 (8)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Time from diagnosis, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.87 (0.7-20.7)</td>
<td>3.72 (0.6-18.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DVd (n = 251)</th>
<th>Vd (n = 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior lines of therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>122 (49)</td>
<td>113 (46)</td>
</tr>
<tr>
<td>2</td>
<td>70 (28)</td>
<td>74 (30)</td>
</tr>
<tr>
<td>3</td>
<td>37 (15)</td>
<td>32 (13)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>22 (9)</td>
<td>28 (11)</td>
</tr>
<tr>
<td>Prior ASCT, n (%)</td>
<td>156 (62)</td>
<td>149 (60)</td>
</tr>
<tr>
<td>Prior PI, n (%)</td>
<td>169 (67)</td>
<td>172 (70)</td>
</tr>
<tr>
<td>Prior IMiD, n (%)</td>
<td>179 (71)</td>
<td>198 (80)</td>
</tr>
<tr>
<td>Prior PI + IMiD, n (%)</td>
<td>112 (45)</td>
<td>129 (52)</td>
</tr>
<tr>
<td>Refractory to IMiD, n (%)</td>
<td>74 (30)</td>
<td>90 (36)</td>
</tr>
<tr>
<td>Refractory to last line of therapy, n (%)</td>
<td>76 (30)</td>
<td>85 (34)</td>
</tr>
</tbody>
</table>
Progression-free Survival

Median : not reached

Median : 7.2 months

HR: 0.39 (95% CI, 0.28-0.53); \( P<0.0001 \)

61% reduction in the risk of disease progression or death for DVd vs Vd

*KM estimate; HR, hazard ratio.
**POLLUX: Study Design**

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study

---

**DRd (n = 286)**

- **Daratumumab** 16 mg/kg IV
  - Qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD
  - R 25 mg PO
  - Days 1-21 of each cycle until PD
  - 40 mg PO
  - 40 mg weekly until PD

**Rd (n = 283)**

- **R** 25 mg PO
  - Days 1-21 of each cycle until PD
  - 40 mg PO
  - 40 mg weekly until PD

---

**Key eligibility criteria**

- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Patients with creatinine clearance ≥30 mL/min

**Stratification factors**

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

**Primary endpoint**

- PFS

**Secondary endpoints**

- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

**Statistical analyses**

- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

---

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg\(^a\), paracetamol, and an antihistamine

---

\(^a\)On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.
Progression-free Survival

- 12-month PFS*: 83%
- 18-month PFS*: 78%

HR: 0.37 (95% CI, 0.27-0.52; P <0.0001)

Median PFS: 18.4 months

63% reduction in the risk of disease progression or death for DRd vs Rd

*KM estimate; HR, hazard ratio.
My Take - Daratumumab

- Will have the greatest impact of the drugs approved in 2015
- Ideal partner to combine with PIs or IMiDs due to lack of overlapping toxicity
- Single agent activity impressive ("rituximab" of myeloma)
- Infusional reactions are real and infusion is LONG…but maybe subcutaneous soon?
- Will likely see it first line soon
- Watch for the next CD38 MoAb = Isatuximab
The Big Eight

7. Ixazomib – FDA approved Nov 2015 for relapsed MM 1-3 prior lines in combination with lenalidomide

PLUS – first oral proteasome inhibitor, well tolerated, 3 pills/month, can be combined

MINUS – current use only with lenalidomide, appears to be less active than bortezomib

Best uses – in combination with lenalidomide, but emerging with pom also
TOURMALINE-MM1: Phase 3 Study of Weekly Oral Ixazomib Plus Lenalidomide-Dexamethasone

Global, double-blind, randomized, placebo-controlled study design

Randomization

1:1

N=722

Ixazomib + Lenalidomide + Dexamethasone
- Ixazomib: 4 mg on days 1, 8, and 15
- Lenalidomide: 25 mg* on days 1-21
- Dexamethasone: 40 mg on days 1, 8, 15, 22

Placebo + Lenalidomide + Dexamethasone
- Placebo: on days 1, 8, and 15
- Lenalidomide: 25 mg* on days 1-21
- Dexamethasone: 40 mg on days 1, 8, 15, 22

Repeat every 28 days until progression, or unacceptable toxicity

Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

Key secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

Final PFS Analysis: A Significant, 35% Improvement in PFS with IRd vs Placebo-Rd

- Median PFS:
  - IRd: 20.6 months
  - Placebo-Rd: 14.7 months

- Log-rank test: p=0.012
- Hazard ratio (95% CI): 0.742 (0.587, 0.939)
- Number of events: IRd 129; Placebo-Rd 157

Number of patients at risk:
- IRd: 362 340 325 308 288 274 254 237 218 208 188 157 130 101 88 85 71 58 46 31 22 15 5 3 0 0
- Placebo-Rd: 360 345 332 315 298 283 270 248 233 224 206 182 145 119 111 95 72 58 44 34 26 14 9 1 0

Median follow-up: ~15 months
My Take - Ixazomib

• Appears to be slightly less potent than bortezomib, but unique molecule with significant single agent activity
• Very attractive in older or less fit patients
• All oral regimen very convenient
• Lack of neuropathy is encouraging
8. Elotuzumab – FDA approved Dec 2015 in relapsed MM 1-3 prior lines in combination with lenalidomide

PLUS – novel mechanism of action with costimulatory immune effect, well tolerated (10% infusion reactions)

MINUS – no single agent activity, must be partnered with lenalidomide (bortezomib data less convincing)

Best uses – early relapse with lenalidomide, perhaps with pom soon
Dual Mechanism of Action of Elotuzumab

- Humanized IgG1 immunostimulatory monoclonal antibody targeted against SLAMF7, a glycoprotein highly expressed on myeloma and natural killer cells but not on normal tissues

- Direct activation: Binding to SLAMF7 directly activates natural killer cells, but not myeloma cells

- Tagging for recognition: Elotuzumab activates natural killer cells via CD16, enabling selective killing of myeloma cells via antibody-dependent cellular cytotoxicity (ADCC) with minimal effects on normal tissue

SLAMF7 = Signaling Lymphocyte Activation Molecule-F7

ELOQUENT-2 Study Design

- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)

**Key inclusion criteria**
- RRMM
- 1–3 prior lines of therapy
- Prior Len exposure permitted in 10% of study population (patients not refractory to Len)

**Elo plus Len/Dex (E-Ld) schedule (n=321)**
- Elo (10 mg/kg IV): Cycle 1 and 2: weekly; Cycles 3+: every other week
- Len (25 mg PO): days 1–21
- Dex: weekly equivalent, 40 mg

**Len/Dex (Ld) schedule (n=325)**
- Len (25 mg PO): days 1–21;
- Dex: 40 mg PO days 1, 8, 15, 22

**Assessment**
- Tumor response: every 4 wks until progressive disease
- Survival: every 12 wks after disease progression

- Endpoints:
  - Co-primary: PFS and ORR
  - Other: overall survival (data not yet mature); duration of response, quality of life, safety

- All patients received premedication to mitigate infusion reactions prior to Elo administration

Co-Primary Endpoint: Progression-Free Survival

E-Ld-treated patients had a 30% reduction in the risk of disease progression or death; treatment difference at 1 and 2 years was 11% and 14%, respectively.

PFS analysis used the primary definition of PFS
My Take - Elotuzumab

• No single agent activity, but unique mechanism of action

• True “immune effect” of tail of durable response yet to be fully proven

• Limited now by need of lenalidomide – future use with pomalidomide could be important

• Results with bortezomib less impressive
## Lenalidomide-based Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>POLLUX DRd vs Rd</th>
<th>ASPIRE KRd vs Rd&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ELOQUENT-2 ERd vs Rd&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>TOURMALINE-MM1 NRd vs Rd&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS HR (95% CI)</strong></td>
<td>0.37 (0.27-0.52)</td>
<td>0.69 (0.57-0.83)</td>
<td>0.73 (0.60-0.89)</td>
<td>0.74 (0.59-0.94)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>93%</td>
<td>87%</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>76%</td>
<td>70%</td>
<td>33%</td>
<td>48%</td>
</tr>
<tr>
<td>≥CR</td>
<td>43%</td>
<td>32%</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>Duration of response, mo</td>
<td>NE</td>
<td>28.6</td>
<td>20.7</td>
<td>20.5</td>
</tr>
<tr>
<td><strong>OS HR (95% CI)</strong></td>
<td>0.64 (0.40-1.01)</td>
<td>0.79 (0.63-0.99)</td>
<td>0.77 (0.61-0.97)</td>
<td>NE</td>
</tr>
</tbody>
</table>


K, carfilzomib; E, elotuzumab; N, ixazomib.
ASPIRE, TOURMALINE, ELOQUENT-2—Summary of PFS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>PFS Invest. arm</th>
<th>PFS Rd arm</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE</td>
<td>Rd vs KRd</td>
<td>26.3mo</td>
<td>17.6mo</td>
<td>0.69</td>
</tr>
<tr>
<td>ELOUQUENT-2</td>
<td>Rd vs IRd</td>
<td>19.4mo</td>
<td>14.9mo</td>
<td>0.70</td>
</tr>
<tr>
<td>TOURMALINE</td>
<td>Rd vs EloRd</td>
<td>20.6mo</td>
<td>14.7mo</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Relapsed/Refractory MM—Summary of Combination Therapy: ORR

**Median Lines of Tx:**

<table>
<thead>
<tr>
<th>Line</th>
<th>Therapy</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>RD*</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>KRd*</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>RVD*</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>PVd*</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>PanVd*</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>Vd*</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>CyBorD*</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>CRD*</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>CPd*</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Pd*</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Kd*</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>KPd*</td>
<td>70</td>
</tr>
</tbody>
</table>

*Data from phase III trials, all others from phase I or II trials

VGPR Rates/PFS with Triplet vs Doublet Regimens

### Odds of Achieving ≥VGPR in Early Relapse

<table>
<thead>
<tr>
<th>Trial</th>
<th>Odds Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANORAMA-1</td>
<td>2.044</td>
<td>1.435</td>
<td>2.914</td>
<td>.000</td>
</tr>
<tr>
<td>MM VAR/IFM 2005-004</td>
<td>2.330</td>
<td>1.391</td>
<td>3.903</td>
<td>.001</td>
</tr>
<tr>
<td>ELOQUENT</td>
<td>1.250</td>
<td>0.893</td>
<td>1.749</td>
<td>.193</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>3.433</td>
<td>2.559</td>
<td>4.606</td>
<td>.000</td>
</tr>
<tr>
<td>POOLED ODDS RATIO</td>
<td>2.185</td>
<td>1.832</td>
<td>2.606</td>
<td>.000</td>
</tr>
</tbody>
</table>

### Pooled Hazards Ratio: PFS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Hazard Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>z-Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANORAMA-1</td>
<td>0.630</td>
<td>0.521</td>
<td>0.762</td>
<td>-4.773</td>
<td>.000</td>
</tr>
<tr>
<td>MM VAR/IFM 2005-004</td>
<td>0.990</td>
<td>0.438</td>
<td>0.796</td>
<td>-3.460</td>
<td>.001</td>
</tr>
<tr>
<td>ELOQUENT</td>
<td>0.700</td>
<td>0.573</td>
<td>0.855</td>
<td>-3.499</td>
<td>.000</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>0.660</td>
<td>0.572</td>
<td>0.833</td>
<td>-3.87</td>
<td>.000</td>
</tr>
<tr>
<td>POOLED ODDS RATIO</td>
<td>0.661</td>
<td>0.596</td>
<td>0.734</td>
<td>-7.788</td>
<td>.000</td>
</tr>
</tbody>
</table>

Question #4 Have I Used the “add on” agents?

Usually combined with novel agents…

- **Panobinostat** (just FDA Approved!)
- **Corticosteroids**
  - Dexamethasone weekly (20-40mg)
  - Alternate day prednisone (25-100mg)
- **Alkylating agents**
  - Cyclophosphosphamide
  - Melphalan
- **Liposomal doxorubicin**

Also consider without novel agent (cyclo-pred)
Question #5 Have I considered an individualized, risk-stratified approach?
Factors in Selecting Relapsed Therapy

**PATIENT**
- Age
- Performance Status
- Renal Insufficiency
- Poor Marrow Reserve
- Neuropathy
- Other comorbidities
  - Cardiac
  - Diabetes

**DISEASE**
- Risk Status
- Rapidity of Relapse
  - Rate of rise
  - Organ damage
  - Extra-medullary
- Previous Therapy
  - Depth
  - Duration

**TREATMENT**
- Mode of Administration
- Single or Combination
- Cost
- Toxicity
  - Myelosuppression
  - Neuropathy
  - Thrombosis
- Risk of SPM
mSMART 2.0: Classification of Relapsed MM

**High-Risk**
- Relapse <12 months from transplant or progression within first year of diagnosis
- FISH
  - Del 17p
  - t(14;16)
  - t(14;20)
- High risk GEP

**Intermediate-Risk**
- FISH
  - t(4;14)
  - 1q gain
  - High PC S-phase

**Standard-Risk**
- All others including:
  - Trisomies
  - t(11;14)
  - t(6;14)


v4 //last reviewed Dec 2015
First Relapse Off-Study

**On maintenance**

- Fit Patients*
  - KPd or DVd if Rev maintenance
  - DRd if Vel maintenance

- Indolent Relapse* or Frail patients
  - DVd or ICd if Rev maintenance
  - IRd or DRd if Vel maintenance

**Off-therapy/ Unmaintained***

- Fit Patients*
  - KRd or DRd

- Indolent Relapse* or Frail patients
  - IRd or ERd

*Consider salvage auto SCT in patients eligible for ASCT who have not had transplant before; Consider 2nd auto SCT if eligible and >18 months unmaintained or >36 months maintained response to first auto

v5 //last reviewed July 2016
Second or later Relapse Off-Study

Not Plasma Cell Leukemia (PCL) or Similar extramedullary disease (EMD)

Single Refractory*
- Refractory to Imid or PI but not both

Dual Refractory*
- Bortezomib and/or Ixazomib
- Lenalidomide

Triple Refractory*
- Bortezomib and/or Ixazomib
- Lenalidomide
- Carfilzomib

• Pom-based regimen (Pom-Dex or Pom-Cyclo-Dex) plus daratumumab**
  Or
  KPd/KRd

• Pom-based regimen (Pom-Dex or Pom-Cyclo-Dex) plus daratumumab**

• Dara-based regimen;** or Alkylator-based regimen if alkylator naïve; or Proteasome inhibitor plus panobinostat

*Auto transplant is an option, if transplant candidate and feasible; **If known to be refractory to Daratumumab as single agent, use elotuzumab instead
Second or later Relapse – Off-Study

Quadruple-refractory (Lenalidomide, Pomalidomide, Bortezomib, and Carfilzomib)

VDT-PACE* x 2 cycles if possible.*
Auto transplant if transplant candidate; if not, treat with regimens that the patient is not known to be refractory to (eg., daratumumab-containing regimen; panobinostat-containing regimen; bendamustine; alkylator-containing combination if not alkylator refractory; or anthracycline containing regimen such as RAD, VDD, PAD, or CHOP)

*CVAD or similar regimen can be used in place of VDT-PACE in older patients or patients with poor functional status
Second or later Relapse – Off-Study

Secondary PCL or extensive EMD

VDT-PACE x 2 cycles;*
Auto transplant if transplant candidate; if not maintain with one of the regimens listed that the patient is not known to be refractory to (eg., daratumumab-containing regimen; alkylator-containing combination if not alkylator refractory; or anthracycline containing regimen such as RAD, VDD, PAD, or CHOP)

*CVAD or similar regimen can be used in place of VDT-PACE in older patients or patients with poor functional status
Pillars of Myeloma

- **Conventional Chemo**
  - Bendamustine
  - DPACE...
- **Others?**
- **Immunomodulatory**
  - Steroids
  - Elotuzumab
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
- **Proteasome Inhibitors**
  - Bortezomib
  - Carfilzomib
  - Ixazomib...
- **Monoclonal Antibodies**
  - Daratumumab
  - Elotuzumab
  - Isatuximab
- **Alkylators**
  - Melphalan, Cyclophosphamide
- **Others?**
  - Other Conventional Chemo
    - (Bendamustine, DPACE...)

Additional terms:
- **Alkylators**
  - Melphalan, Cyclophosphamide
- **Monoclonal Antibodies**
  - Daratumumab
  - Elotuzumab
  - Isatuximab
- **Proteasome Inhibitors**
  - Bortezomib
  - Carfilzomib
  - Ixazomib...
- **Immunomodulatory**
  - Steroids
  - Elotuzumab
Treatment sequence in Myeloma

**Now**

- VD
- Rev/Dex
- CyBorD
- VTD
- VRD
- KRD

**Front line treatment**

- Induction
- Consolidation

**Maintenance**

- ? More induction
- Nothing Thalidomide?
- Bortezomib Lenalidomide

**Relapsed**

- Bortezomib Lenalidomide
- Thalidomide
- Carfilzomib Pomalidomide
- Panobinostat
- Daratumumab
- Ixazomib Elotuzumab

**New**

- Carfilzomib Combos Adding Mono Abs
- “more” induction Lenalidomide 2 mths
- ? Ixazomib combinations

**Novel MoAbs:** Isatuximab...

**Newer HDACs**

PD/PDL-1 Inhibition

Multiple small molecules

++++++++++
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